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PMI RESEARCH & DEVELOPMENT

Clinical Study Report

ZRHR-REXC-03-EU

Study Title:	A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement
Short Title:	Reduced exposure study in smokers using Tobacco Heating System 2.2 (THS 2.2) with 5 days in a confinement setting
Study Number:	ZRHR-REXC-03-EU
Product Name:	Tobacco Heating System 2.2 (THS 2.2)
Study Initiated (first subject screened):	29 June 2013
Study Completed (last subject last visit):	26 September 2013
Principal Investigator and Affiliation:	Katarzyna Jarus-Dziedzic, MD, PhD BioVirtus Research Site Sp. z o.o., Mokra 7 05-830 Kajetany, Poland
Sponsor:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Sponsor Signatories:	Christelle Haziza, PhD, Manager P1 Clinical Program, Clinical Scientist Andrea Donelli, Clinical Scientist Guillaume de La Bourdonnaye, MEng, MSc, Biostatistician Patrick Picavet, MD, Medical Safety Officer
Version:	2.0
Date:	08 March 2016

This study was conducted in accordance with Good Clinical Practice.

Confidentiality Statement

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



SYNOPSIS

Sponsor: Philip Morris Products S.A	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Tobacco Heating System (THS) 2.2	Volume:	
Name of Active Ingredient: Not applicable	Page:	
Study Title: A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement.		
Principal Investigator and Study Center: Katarzyna Jarus-Dziedzic, MD, PhD BioVirtus Research Site Sp. z o.o., Mokra 7, 05-830 Kajetany, Poland.		
Publication (reference): ClinicalTrials.gov ID: NCT01959932. Brief title: Reduced exposure study in smokers using Tobacco Heating System 2.2 (THS 2.2) with 5 days in a confinement setting		
Period of Study: First subject screened: 29 June 2013 Last subject last visit: 26 September 2013		
Objectives and Endpoints: Primary Objective and Endpoints: The primary objective of this study was: <ol style="list-style-type: none">To demonstrate the reduction of primary biomarkers of exposure (BoExp) in smokers switching from conventional cigarettes (CC) to THS 2.2 as compared to smokers continuing to smoke CC. <u>Endpoints:</u><ul style="list-style-type: none">Monohydroxybutenylmercapturic 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 % saturation of hemoglobin) as measured on Day 5. Secondary Objectives and Endpoints: The secondary objectives of this study were: <ol style="list-style-type: none">To determine the reduction of secondary BoExp on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC. <u>Endpoints:</u><ul style="list-style-type: none">Quantity excreted in urine over 24 hours for MHBMA, S-PMA, and 3-HPMA.Carbon monoxide ([CO] expressed as ppm) in exhaled breathUrinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.To describe the levels of primary and secondary BoExp over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.		

Endpoints:

- CO (expressed as ppm) in exhaled breath.
- COHb in blood (expressed as % saturation of hemoglobin).
- Primary and secondary urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

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

Endpoints:

- Nicotine equivalent ([NEQ] expressed in quantity excreted and concentration adjusted to creatinine) in 24-hour urine on Day 5 and from Day 1 to Day 5.
- Plasma nicotine and cotinine concentrations.

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

Endpoints:

- COHb in blood (expressed as % saturation of hemoglobin).
- CO (expressed as ppm) in exhaled breath.
- Primary and secondary urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

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

Endpoints:

- Peak (highest concentration value along the day) on Day 5 in plasma.
- Time to peak (actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
- Weighted average concentration over 24 hours on Day 5.

6. To describe the changes in cytochrome P450 1A2 (CYP1A2) enzymatic activity on Day 5 in smokers switching from CC to THS 2.2, switching from CC to SA, and continuing to smoke CC.

Endpoint:

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

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

Endpoint:

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

8. To monitor the safety profile during the study.

Endpoints:

- Incidence of adverse events (AEs)/serious adverse events (SAEs) and device events, including THS 2.2 malfunction/misuse.
- Respiratory symptoms: cough assessment by visual analog scale (VAS), Likert scales, and one open question.
- Vital signs.
- Spirometry.



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

Exploratory Objectives and Endpoints:

The exploratory objectives of this study were:

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

Endpoints:

- Ames mutagenicity test (YG1024+S9).
- The total score, Factor 1 (relief) and Factor 2 (reward) from Questionnaire of Smoking Urges (brief version [QSU-brief]).
- The total scores from Minnesota Nicotine Withdrawal Scale (MNWS).
- Cytochrome P450 2A6 (CYP2A6 enzymatic activity as a molar ratio of 3-hydroxycotinine and cotinine
- Selected risk markers (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine: 8-epi-prostaglandine F2 α (8-epi-PGF_{2 α}) and 11-dehydrothromboxane B2 (11-DTX-B2).

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

Endpoints:

- Primary and secondary BoExp and NEQ*.
- Selected risk markers (8-epi-PGF_{2 α} and 11-DTX-B2) and NEQ.

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

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

Endpoints:Product evaluation as measure with the Modified Cigarette Evaluation Questionnaire (MCEQ):

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

Smoking pattern: human smoking topography (HST) parameters and HST questionnaire.

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

Endpoints:

- Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.
- Filter analysis: smoke nicotine in filter and UV absorbance at 310 nm.

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

This was a randomized, controlled, open-label, 3-arm, parallel group, single-center study to compare the use of THS 2.2 with continuing to smoke CC and SA. This was an *ad libitum* smoking study. In general, smoking during confinement was allowed between 06:30 AM and 11:00 PM.

Screening Visit; Day -30 to Day -3:

A Screening Visit was conducted within 4 weeks prior to Admission to the study site (Day -2). A demonstration of the THS 2.2 product (i.e., THS Tobacco Sticks, Charger, Holder, and accessories) was given by the study site staff 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 on that day, all subjects had a product test of THS 2.2 (using up to 3 THS Tobacco Sticks). In female subjects, the THS 2.2 product test was performed only after pregnancy was excluded by a negative urine pregnancy test. Only those who were willing and able to use the product participated in the study. Enrollment took place after all requested inclusion and exclusion criteria had been satisfactorily met.

Baseline period; Day -1, 06:30 AM until Day 1, 06:29 AM:

All subjects continued smoking their single preferred brand of CC and baseline values were recorded. On Day 0, subjects were randomized to 1 of the 3 study arms in a 2:1:1 ratio:

- THS 2.2 arm (80 subjects, *ad libitum* use of the THS 2.2 product).
- CC arm (40 subjects, *ad libitum* use of their preferred CC brand).
- SA arm (40 subjects who abstained from smoking).

Randomization was stratified by sex and average daily CC consumption (using average consumption reported during the Screening Visit in the previous 4 weeks: those smoking 10 to 19 CC and those smoking >19 CC per day). In each study arm, each sex and each of the smoking strata had a quota applied to ensure they represented at least 40% of the population. Subjects were informed of their randomized study arm by the study site staff on Day 1 prior to 06:30 AM.

Exposure period; Day 1, 06:30 AM until Day 5, 11:00 PM:

Five days of *ad libitum* use of the assigned product in the THS 2.2 and CC arms. Use of any tobacco/nicotine-containing product other than the assigned product was not allowed.

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

Day of Discharge (Day 6); Day 5, 11:01 PM to the time of Discharge:

Procedures of Discharge, including but not limited to laboratory parameters, were conducted to discharge the subject from the clinic after 9 days in a confined setting. Use of CC was allowed on Day 6, but only after spirometry had been performed.

Safety follow-up period (from Day 6, time of Discharge to Day 13):

After time of Discharge, subjects entered a 7-day safety follow-up during which there was recording of spontaneously reported new AEs/SAEs and the active follow-up of any ongoing AEs/SAEs by the study site. In general, all AEs were actively followed until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event had been found. The end of study was defined as the time of Discharge on Day 6 plus 7-day follow-up period.

Type of blinding: Not applicable as this was an open-label study.

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

Planned:	160 subjects
Screened:	329 subjects
Exposed to THS 2.2 (product test):	169 subjects
Enrolled:	169 subjects
Randomized:	160 subjects
Completed:	159 subjects
Safety population	169 subjects
Full analysis set (FAS) population	160 subjects
Per-protocol (PP) population:	160 subjects

Diagnosis and Main Criteria for Inclusion:

One hundred and sixty female or male smoking healthy Caucasian subjects, who met the following main inclusion criteria:

- 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 aged from 21 to 65 years (inclusive).
- Subject was of Caucasian origin.
- Subject was a smoking, but healthy subject, as judged by the Principal Investigator or designee, based on all available assessments from the Screening period/Day of Admission (e.g., safety laboratory, spirometry [forced expiratory volume in 1 second {FEV₁}/forced vital capacity {FVC} >0.7 at post-bronchodilator spirometry, post-bronchodilator FEV₁ >80% predicted value, and post-bronchodilator FVC >80% predicted value], vital signs, physical examination, ECG, chest X-ray, and medical history).
- Subject was a current smoker (based on self-reporting) who had smoked for the last 4 weeks at least 10 commercially available non-menthol CC per day (no brand restrictions) with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) per cigarette. Furthermore, the subject had smoked for at least the last 3 consecutive years. The smoking status was verified with a urinary cotinine test (cotinine ≥200 ng/mL).
- The subject was a current smoker who did not plan to quit smoking in the next 3 months.
- The subject was ready to accept 5 days of SA.
- The subject was ready to accept using the THS 2.2 product.

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

Test Product and Lot Numbers:

The THS 2.2 product was provided by the Sponsor and comprised the following components: THS Tobacco Stick, Holder, Charger, a Cleaning Tool, a main power supply, and a USB cable. Pack batch number of THS Tobacco Sticks: B-05875. Production date: 07 June 2013. Expiry date: 06 January 2014.

Duration of Exposure Period:

The exposure period was 5 days and was the period after the randomization in which the subject used the assigned product (THS 2.2 or CC), or abstained from smoking (Day 1, 06:30 AM until Day 5, 11:00 PM).

Reference Product:

The reference product to THS 2.2 during the randomized exposure period was the subject's own preferred commercially available single brand of non-menthol CC. Smoking abstinence was used as a reference point.

**Statistical Methods:****Primary Analyses:**

The primary endpoints, assessed on Day 5 for the comparison of THS 2.2 and CC, were MHBMA, 3-HPMA, S-PMA in 24-hour urine (concentration adjusted to creatinine), and COHb in blood (expressed as % saturation of hemoglobin).

Descriptive summary statistics including the number of subjects (n), number and percent of subjects with missing data, number of subjects with results below the limit of quantification (BLOQ), arithmetic mean, arithmetic standard deviation (SD), median, first and third quartiles, minimum, maximum, geometric mean and associated 95% confidence intervals (CI) and geometric coefficient of variation (CV) were presented for each study arm stratified by sex and CC consumption.

The values and percent changes for the primary endpoints were listed and summarized. In addition, line graphs were produced for means (and 95% CI) over all time points.

The primary endpoints were log-transformed (base_e) prior to analysis. An analysis of covariance (ANCOVA) model was used with terms for the log-transformed baseline value, sex, average daily CC consumption over the last 4 weeks as reported during Screening, and product.

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

The primary analysis was performed on the FAS.

Secondary Analyses:

As a secondary analysis, the quantity of MHBMA, 3-HPMA, and S-PMA excreted over 24 hours was analyzed. The primary endpoints were also examined to compare the reductions in THS 2.2 versus SA using the same methodology as for the primary analysis.

The secondary BoExp are exhaled CO and urinary Total 1-hydroxypyrene (1-OHP), Total N-nitrosonornicotine (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-hydroxy(a)benzopyrene (3-OH-B[a]P), S-benzylmercapturic acid (S-BMA), 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA), Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), and NEQ. The urine parameters were expressed as concentrations adjusted for creatinine and the quantity excreted over 24 hours.

Descriptive statistics, summarized by product, were produced separately for all time points for all visits applicable for exhaled CO. This was done on the FAS, stratified by sex and CC consumption.

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

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

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

The analysis compared the log-transformed urinary concentrations corrected for creatinine on Day 5, and the quantity excreted over 24-hours on Day 5 between the THS 2.2 and CC arms. An ANCOVA model was used with terms for the log-transformed baseline value, sex, average daily CC consumption over the last 4 weeks as reported during Screening, and product. Least squares means for each product along with the difference (THS 2.2 - CC) and 95% CI were presented in the tables.

The secondary BoExp were also examined to compare the reductions in THS 2.2 versus SA using the same methodology as above.



The concentrations of nicotine and cotinine were listed and summarized along with the change from Day 0 to Day 5. Line graphs of the nicotine and cotinine concentration profiles across all study days showing mean and 95% CI were produced.

For nicotine and cotinine plasma concentrations, the changes from baseline were analyzed using an ANCOVA model with terms for baseline concentration, sex, average daily CC consumption over the last 4 weeks as reported during Screening, and product.

Least squares means for each product along with the difference (THS 2.2 - CC) and 95% CI were presented. All figures, summaries, and analyses were performed on the FAS only.

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

The analysis compared C_{peak} and C_{avg} on Day 5 between the THS 2.2 and CC arms. An analysis of variance (ANOVA) model was used with terms for sex, average daily CC consumption over the last 4 weeks as reported during Screening, and product.

Least squares means for each product along with the difference (THS 2.2 - CC) and 95% CI were presented. For t_{peak} on Day 5, the comparison between the THS 2.2 and CC arms was made using the Wilcoxon Rank Sum test.

For CYP1A2 activity, descriptive statistics of the values and percent change on Day 5 from Day 0, and supportive listings were provided. The analysis compared the Day 5 values between the THS 2.2 and CC arms and between the THS 2.2 and SA arms. An ANOVA model was used with terms for sex, average daily CC consumption over the last 4 weeks as reported during Screening, and product. Least squares means for each product along with the difference (THS 2.2 - CC) and 95% CI were presented.

Study Hypotheses And Evaluation Criteria

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

The study was considered successful if the study demonstrated a 50% or more reduction in MHBMA, 3-HPMA, S-PMA, and COHb in the THS 2.2 arm compared to the CC arm (as measured on Day 5), using a one-sided test with 2.5% type I error probability.

Safety Analyses:

There was no formal statistical analysis of safety data. Adverse events (including SAEs and AEs that lead to discontinuation) were summarized and listed by study arm. Adverse events were categorized by system organ class (SOC) and preferred term (PT) and coded using the Medical Dictionary for Regulatory Activities (MedDRA[®], version 16.0). Respiratory symptoms (cough assessment), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), spirometry, ECG data, clinical laboratory safety parameters (clinical chemistry, hematology, and urine analysis), body mass index, physical examination, and device malfunction/misuse events were listed and summarized as appropriate.

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

**Summary of Results****Primary Endpoints**

The primary endpoints for this study were assessed on Day 5 (evening) for the BoExp COHb blood (% saturation of hemoglobin); MHBMA urinary concentration adjusted for creatinine (pg/mg creat); 3-HPMA urinary concentration adjusted for creatinine (ng/mg creat); and S-PMA urinary concentration adjusted for creatinine (pg/mg creat).

Reductions were seen in the level of each BoExp assessed as a primary endpoint for the THS 2.2 arm compared to the CC arm, with reductions of approximately 77% in COHb (whole blood), 92% in MHBMA urinary concentration adjusted for creatinine, 58% in 3-HPMA urinary concentration adjusted for creatinine, and 94% in S-PMA urinary concentration adjusted for creatinine.

These results were consistent with the study hypothesis and evaluation criteria in demonstrating a >50% reduction in COHb, MHBMA, 3-HPMA, and S-PMA in the THS 2.2 arm compared to the CC arm.

Secondary Endpoints*Carboxyhemoglobin in Whole Blood, MHBMA, 3-HPMA, and S-PMA (Concentrations Adjusted for Creatinine) versus Smoking Abstinence*

Differences were seen for levels of COHb and 3-HPMA in the THS 2.2 arm compared to the SA arm. Mean COHb was approximately 8% higher on Day 5 for the THS 2.2 arm compared to the SA arm, and 3-HPMA urinary concentration adjusted for creatinine was approximately 64% higher on Day 5 (although this was still considerably lower than compared to CC use). There were no notable differences observed between subjects who switched to THS 2.2 and subjects who abstained from smoking for urinary concentrations of MHBMA and S-PMA adjusted for creatinine on Day 5.

MHBMA, 3-HPMA, and S-PMA (Urinary Quantity Excreted Over 24 Hours) versus Conventional Cigarettes

The levels of MHBMA, 3-HPMA, and S-PMA in the THS 2.2 arm were reduced compared to the CC arm on Day 5, with reductions of approximately 92% in urinary quantity of MHBMA excreted over 24 hours, 60% in urinary quantity of 3-HPMA excreted over 24 hours, and 94% in the urinary quantity of S-PMA excreted over 24 hours.

MHBMA, 3-HPMA, and S-PMA (Urinary Quantity Excreted Over 24 Hours) versus Smoking Abstinence

A difference was observed in the THS 2.2 arm for levels of 3-HPMA compared to the SA arm, with mean urinary quantity of 3-HPMA excreted over 24 hours being approximately 50% higher on Day 5 (although this was still considerably lower than compared to CC use). There were no notable differences observed between subjects who switched to THS 2.2 and subjects who abstained from smoking for the urinary quantities of MHBMA and S-PMA excreted over 24 hours on Day 5.

Other Biomarkers of Exposure versus Conventional Cigarettes

Reductions were seen in the THS 2.2 arm compared to the CC arm of approximately 84% in exhaled CO, 56% in Total 1-OHP urinary concentration adjusted for creatinine, 76% in Total NNN urinary concentration adjusted for creatinine, 85% in 4-ABP urinary concentration adjusted for creatinine, 96% in 1-NA urinary concentration adjusted for creatinine, 88% in 2-NA urinary concentration adjusted for creatinine, 58% in o-toluidine urinary concentration adjusted for creatinine, 87% in CEMA urinary concentration adjusted for creatinine, 68% in HEMA urinary concentration adjusted for creatinine, 73% in 3-OH-B[a]P urinary concentration adjusted for creatinine, 77% in 3-HMPMA urinary concentration adjusted for creatinine, and 56% in Total NNAL urinary concentration adjusted for creatinine. There was no notable difference in the S-BMA urinary concentration adjusted for creatinine between the THS 2.2 and CC arms.

The reductions in the quantities excreted over 24 hours for each of the other biomarkers of exposure in



the THS 2.2 arm compared to the CC arm were consistent with the results obtained for the urinary concentrations adjusted for creatinine.

With the exception of S-BMA, the results are consistent with the study hypothesis in that the geometric mean level of each of the other BoExp was lower for the THS 2.2 arm relative to the CC arm on Day 5.

Other Biomarkers of Exposure versus Smoking Abstinence

Higher values were seen in the THS 2.2 arm compared to the SA arm on Day 5, with Total NNN urinary concentration adjusted for creatinine being 9.8-fold higher, 19% higher for 4-ABP urinary concentration adjusted for creatinine, 30% higher for 1-NA urinary concentration adjusted for creatinine, 17% higher for 2-NA urinary concentration adjusted for creatinine, 21% higher for o-toluidine urinary concentration adjusted for creatinine, 32% higher for 3-HMPMA urinary concentration adjusted for creatinine, and 27% higher for Total NNAL urinary concentration adjusted for creatinine. There were no notable differences observed in exhaled CO, Total 1-OHP, CEMA, HEMA, 3-OH-B[a]P, and S-BMA concentrations adjusted for creatinine on Day 5 between subjects who switched to THS 2.2 and subjects who abstained from smoking.

The results obtained for the quantity of each of the other biomarker of exposure excreted over 24 hours were consistent with the results for the concentrations adjusted for creatinine.

Exposure to Nicotine

On Day 5, both the NEQ urinary concentration adjusted for creatinine (mg/g creat) and the quantity excreted over 24 hours (mg) were comparable between subjects who switched to THS 2.2 and subjects who continued to smoke CC. Mean levels of NEQ urinary concentration adjusted for creatinine and quantity of NEQ excreted over 24 hours in subjects who switched to THS 2.2 use were higher (approximately 77-fold and 70-fold higher, respectively) than those of subjects who abstained from smoking.

Mean plasma nicotine concentrations taken between 08:00 and 10:00 PM increased from Day 0 to Day 5 for both the THS 2.2 and CC arms. There was no notable difference in the changes from Day 0 plasma nicotine concentrations to Day 5 between subjects who switched to THS 2.2 and subjects who continued to smoke CC. For cotinine, mean plasma concentrations increased from Day 0 to Day 5 in the THS 2.2 arm and decreased in the CC arm, resulting in an LS mean difference of 30.9 ng/mL (95% CI: 6.4, 55.5).

For both nicotine and cotinine exposure on Day 5, peak and weighted average plasma concentrations were similar for the THS 2.2 and CC arms. On average, the Day 5 peak and weighted average nicotine and cotinine concentrations were approximately 11% to 13% higher for THS 2.2 compared to CC. The time to peak concentration on Day 5 was identical for the THS 2.2 and CC arms for both nicotine and cotinine.

Cytochrome P450 1A2 Activity

At baseline, CYP1A2 activity was comparable between study arms (range of 110% to 113%). In the THS 2.2 and SA arms at Day 5, CYP1A2 activity had decreased by approximately 17% and 15%, respectively, while in the CC arm, CYP1A2 activity increased by approximately 13%. This resulted in differences in absolute and change from baseline CYP1A2 activity (THS 2.2 - CC) of -34% (95% CI: -41, -27). There was no notable difference in absolute CYP1A2 activity on Day 5 or change from baseline in CYP1A2 activity between subjects who switched to THS 2.2 use and subjects who abstained from smoking.

Tobacco Consumption

In the THS 2.2 arm, the mean number of THS Tobacco Sticks consumed daily initially decreased from the number of CC smoked at baseline (16 cigarettes/day) to Day 1 (15 sticks/day) before increasing again over Day 2 to Day 5 (17 to 21 sticks/day), with the number of THS Tobacco Sticks used from Day 2 onwards being greater than the number of CC smoked at baseline.

In the CC arm, the mean number of CC consumed daily initially decreased from baseline



(16 cigarettes/day) to Day 1, before increasing over Day 2 to Day 5 and was comparable to the baseline value at Day 5 (17 cigarettes/day).

On Day 1 to Day 5, subjects in the THS 2.2 arm consumed more THS Tobacco Sticks than the number of CC smoked in the CC arm.

Safety:

There were no SAEs reported in this study and no randomized subjects discontinued from the study due to an AE. Eight subjects were discontinued from the study prior to randomization following abnormal assessments on Day 0. A further subject was discontinued prior to randomization for having weak veins.

Overall, there were 227 AEs reported by 112 of the 169 subjects (66.3%) in the Safety population, most of which were mild or moderate in severity. Only 1 severe AE was reported which occurred in the CC arm, and was not considered to be related to investigational product (IP) use or study procedures. The incidence and frequency of AEs were comparable in the THS 2.2 (98 AEs in 50/80 subjects [62.5%]), the CC (63 AEs reported by 29/41 [70.7%] subjects), and the SA arms (49 AEs in 24/39 [61.5%] subjects).

The most frequent AEs after THS 2.2 or CC exposure were headache, oropharyngeal pain, syncope, polyuria, and spirometry abnormal. The most frequent AEs after SA were headache, back pain, influenza-like illness, spirometry abnormal, abdominal distension, hypertriglyceridemia, polyuria, hypertension, and vertigo. The incidence of headache and spirometry abnormal were comparable between the THS 2.2, CC, and SA arms, the incidence of polyuria was higher in the THS 2.2 and CC arms, while syncope and oropharyngeal pain were not experienced by any subject in the SA arm.

Only 26 of the 227 reported AEs were assessed as being related to THS 2.2 or CC use and were reported by 23 of the 130 subjects in the THS 2.2, CC, and enrolled not randomized arms (17.7%). The incidence of AEs assessed as related to IP use was comparable for the THS 2.2 (14/80 subjects [17.5%]) and CC arms (7/41 subjects [17.1%]). The most frequent AEs assessed as related to IP use were spirometry abnormal, syncope, COHb increased, cough, and vertigo. All other AEs assessed as related to IP use were reported by single subjects in the THS 2.2 arm only.

During THS 2.2 use, 12 subjects experienced a total of 19 major device events or malfunctions which led to the replacement of the THS Tobacco Stick Holder or Charger. None of these events led to an AE.

CONCLUSIONS

The study demonstrated that switching from CC smoking to THS 2.2 use resulted in substantial reductions in exposure to 15 selected harmful and potentially harmful constituents (HPHCs). The kinetics and the magnitude of decrease of BoExp levels observed in the THS 2.2 arm were approaching the levels observed in the SA arm. However, the exposure to nicotine was similar between the THS 2.2 and CC arms indicating that users adapt quickly to the new product and achieve their individual nicotine levels.

The combination of the results of nicotine-exposure and subjective effects measures indicated that THS 2.2 offers comparable satisfaction to what was observed in CC smokers. Different patterns observed for the corresponding domains in the SA arm tend to substantiate these observations.

No SAEs and 1 severe AE (occurring in the CC arm) were reported during this study, with the total number of AEs being evenly balanced across study arms.

In summary, this study demonstrated that THS 2.2 reduced exposure to HPHCs close to what was observed when abstaining from smoking, and was acceptable with regards to taste, ritual sensorial experience, and nicotine delivery to the users and therefore might be a suitable substitute for CC for adult smokers.



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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-HMPMA	3-hydroxy-1-methylpropylmercapturic acid
3-HPMA	3-hydroxypropylmercapturic acid
3-OH-B[a]P	3-hydroxy(a)benzopyrene
4-ABP	4-aminobiphenyl
8-epi-PGF _{2α}	8-epi-prostaglandine F2α
11-DTX-B2	11-dehydrothromboxane B2
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC _{0-24 h}	Area under the concentration-time curve from 0 to 24 hours
BLOQ	Below the limit of quantification
BMI	Body mass index
BoExp	Biomarker(s) of exposure
CAF	Caffeine
C _{avg}	Weighted average concentration over 24 hours
CC	Conventional cigarette
CEMA	2-cyanoethylmercapturic acid
CI	Confidence interval
CO	Carbon monoxide
COHb	Carboxyhemoglobin
C _{peak}	Peak nicotine and cotinine plasma concentration



CRA	Clinical Research Associate
CRF	Case report form
CRU	Clinical Research Unit
CTCAE	Common terminology criteria for adverse events and common toxicity criteria
CV	Coefficient of variation
CYP1A2	Cytochrome P450 1A2
CYP2A6	Cytochrome P450 2A6
DMP	Data management plan
ECG	Electrocardiogram
ePRO	Electronic patient reported outcome
FAS	Full analysis set
FDA	Food and Drug Administration
FEV ₁	Forced expiratory volume in 1 second
FTND	Fagerström Test for Nicotine Dependence
FVC	Forced vital capacity
GCP	Good Clinical Practice
GVP	Gas vapor phase
HAT	Hollow acetate tube
HbsAg	Hepatitis B surface antigen
HEMA	2-hydroxyethyl mercapturic acid
HIV	Human immunodeficiency virus
HPHCs	Harmful and potentially harmful constituents
HST	Human smoking topography
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation



IEC	Independent Ethics Committee
IP	Investigational product
ISO	International Organization for Standardization
LS	Least squares
MCEQ	Modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MHBMA	Monohydroxybutenylmercapturic acid
miRNA	Micro ribonucleic acid
MNWS	Minnesota Nicotine Withdrawal Scale
mRNA	Messenger ribonucleic acid
M RTP	Modified risk tobacco product
NEQ	Nicotine equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
NRT	Nicotine replacement therapy
NSAID	Non-steroidal anti-inflammatory drugs
OTC	Over-the-counter
PAH	polycyclic aromatic hydrocarbons
PK	Pharmacokinetic(s)
PLA	Polymer-film filter
PMI	Philip Morris International
PP	Per-protocol
PT	Preferred term
PX	Paraxanthine
QC	Quality control



QSU	Questionnaire of Smoking Urges
SA	Smoking abstinence
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
S-BMA	S-benzylmercapturic acid
SD	Standard deviation
SE	Standard error
SHM	Sample handling manual
SOC	System organ class
SOP	Standard operating procedures
S-PMA	S-phenylmercapturic acid
T ₀	Time point of first product use
THS 2.2	Tobacco Heating System 2.2
t _{peak}	Time to peak concentration
TPM	Total particulate matter
VAS	Visual analog scale
WBC	White blood cell
WHO	World Health Organization
WHO-DDE	World Health Organization - Drug Dictionary Enhanced



4 DEFINITION OF TERMS

The following special terms are used in this report.

Baseline period	06:30 AM at Day -1 until 06:29 AM of Day 1.
Charger	The function of the Charger (Model 4) was to recharge the Holder after use. It contained a battery with sufficient capacity to recharge the Holder approximately 20 times. It is a convenient size to carry around, and could itself be recharged from a main power source.
Conventional cigarette (CC)	The term 'conventional cigarette' refers to manufactured and commercially available cigarettes and excluded hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.
CC incompatible with the HST device	All CCs that were incompatible with the human smoking topography (HST) device (e.g., slim CC).
Day of Discharge	Day 6.
End of study	'End of study' was defined as the time of discharge on Day 6 plus 7-day safety follow-up period.
Enrollment	On Day -2 for eligible subjects after all application inclusion and exclusion criteria had been satisfactorily met and the subject was willing and ready to use Tobacco Heating System 2.2 (THS 2.2). The test of THS 2.2 was the last assessment prior to enrollment.
Exposure Period	06:30 AM of Day -1 until 11:00 PM of Day 5.
Randomization	Assignment of the subject randomization number in the Interactive Web and Voice Response System. This could have been done at any time on Day 0; however, subjects were not informed of their randomization group and number prior Day 1.
Run-in Period	Admission to site until 06:29 AM of Day -1.



Safety follow-up period	After the time of discharge, a 7-day safety follow-up was done for the recording of spontaneously reported new adverse events (AEs)/serious adverse events (SAEs) and the active follow-up of ongoing AEs/SAEs. In general, any AE was actively followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event had been found.
Screening failure	Subjects who did not meet the entry criteria from informed consent form (ICF) signature to the time of enrollment were considered a screening failure and were replaced by other subjects.
Screening Visit	Refers to the visit during which subjects signed the ICFs, underwent Screening procedures, and were reviewed for eligibility.
Sponsor	Refers to Philip Morris Products S.A.
Subject	Refers to an individual who participated in the clinical study.
Time of Discharge	The time of day the subject was discharged on Day of Discharge.
THS Tobacco Stick	The THS Tobacco Stick (product code C3) 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 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 Tobacco Stick).
Tobacco Heating Device	The Device comprises everything in THS 2.2 except the Tobacco Stick.
Tobacco Heating System 2.2 (THS 2.2)	THS 2.2 comprises the following components: Tobacco Stick, Holder, Charger, a Cleaning Tool, a main power supply, and a USB cable.



5 ETHICS

5.1 Independent Ethics Committee

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF] which included both subject information sheet and informed consent, subject recruitment procedures [e.g., advertisements], written information to be provided to the subjects, Investigator's Brochure [IB], available safety information, the Principal Investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the Independent Ethics Committee [IEC]), were submitted for review and approval to the relevant IEC. The IEC 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, a written confirmation of the IEC approval was provided to the Sponsor. This identified the study (Principal Investigator's name, study number, and title) and the documents that were approved by the IEC, with dates and version numbers, as well as the date of approval. The composition of the IEC, including the name and occupation of the chairperson, was supplied to the Sponsor together with a GCP compliance statement.

Independent Ethics Committee approval was granted on 23 May 2013. The written approval from the IEC was filed in the Investigator file, and another copy was filed in the Study Master File at Covance Clinical Research Unit (CRU) Ltd. The study did not start before the Sponsor had obtained written confirmation of favorable opinion/approval from the concerned IEC. No protocol amendments occurred during this study.

A copy of the final protocol (Final version dated 25 April 2013) is provided in [Appendix 16.1.1](#).

The name and address of the IEC are provided in [Appendix 16.1.3](#), together with IEC 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 are consistent with the applicable ICH/GCP, regulatory principles.

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



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

5.3 Subject Information and Consent

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

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

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

5.4 Sample Banking Informed Consent Form

Subjects were provided with information and were, on an ICF specific to transcriptomics bio-banking, asked for their consent to collect blood samples for bio-banking for transcriptomics (pharmacogenomics) in order to study the variation of the ribonucleic acid (messenger ribonucleic acid [mRNA] and micro ribonucleic acid [miRNA]) in smokers using Tobacco Heating System 2.2 (THS 2.2) as compared to smokers continuing to smoke conventional cigarettes (CC) or smokers switching to smoking abstinence (SA). The comparison was based on previously described biological networks. In-house data from an exploratory study to assess the reduction of exposure to harmful and potentially harmful constituents (HPHCs) (ClinicalTrials.gov: ID: NCT01780714) in smokers switching to THS 2.1 as compared to smokers continuing smoking CC showed that using THS 2.1, the earlier version of THS 2.2, resulted in significant variation of RNA characteristics as compared to smoking CC. A copy of the Subject Information and Informed Consent Form Optional Transcriptomic Research Study (version 1.0, 07 May 2013) is provided in [Appendix 16.1.3](#).

Subjects were also provided with separate subject information and ICF for samples (serum/plasma and urine) which were stored in a bio-bank for subsequent analysis of biomarkers of exposure (BoExp) and/or risk markers following completion of this study. The informed consent for these samples formed part of the ICF for the main study



(Consent for Collection and Long-term Storage of Blood and Urine Samples), provided in [Appendix 16.1.3](#).

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

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



6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

Study site (clinical conduct)	BioVirtus Research Site Sp. z o.o. Mokra 7 05-830 Kajetany Poland
Principal Investigator	Katarzyna Jarus-Dziedzic, MD, PhD
Sponsor	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Manager Zurich Clinical Program, Clinical Scientist	Christelle Haziza, PhD
Clinical Scientist	Andrea Donelli
Medical Safety Officer	Kausar Aamir, MD, PhD
Biostatistician	Guillaume de La Bourdonnaye, MEng, MSc
Clinical Study Manager	Dimitra Skiada
Study Data Manager	Sarah Merlet
Clinical laboratory and analytical sites	
Clinical Safety Laboratory and COHb	Synevo Central Lab Sp. z o.o. Al. Jerozolimskie 96 00-807 Warsaw Poland
Study Contact	Tomasz Anyszek, MD, PhD, EurClinChem
Plasma, urine, blood BoExp ¹ (MHBMA, 3-HPMA, S-PMA, 1-OHP [blood only], NNN, 4-ABP, 1-NA, 2-NA [blood only], o-toluidine [blood only], CEMA, HEMA, 3-hydroxy(a)benzopyrene, S-BMA, NNAL, NEQ, nicotine, and cotinine) and risk markers (8-epi-PGF _{2α} and 11-DTX-B2)	Celerion Inc. 621 Rose Street Lincoln Nebraska 68502 USA
¹ See Table 1 for definitions of BoExp	
Bioanalytical Principal Investigator	Kirk Newland, BSc
Quality Assurance Manager	Crystal Bickford, BA
Urine 4-ABP, 2-NA, Total 1-OHP, and o-toluidine ¹	Celerion Switzerland AG Allmendstrasse 32 CH-8320 Feraltorf (Zürich) Switzerland
¹ See Table 1 for definitions of BoExp	
Bioanalytical Principal Investigator	Matthias Jecklim, PhD
Quality Assurance Manager	Diana Buergin



Topography	Philip Morris International. Research and Development, Human Smoking Topography Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Human Smoking Topography Scientists	Valerie Poux, Anthony Bruchet
THS Filter Analysis	Labstat International ULC 262 Manitou Drive Kitchener, Ontario N2C 1L3 Canada
Technical Director	Pete Joza
Study monitoring	Covance (Polska) Sp. zo.o Ul. Wspolna 47/49 00-684 Warsaw Poland
Clinical Research Associate	Karolina Krysiuk
Randomization Interactive Web and Voice Response System	(b) (4)
Project Manager	(b) (4)
Electronic patient reported outcome (ePRO)	(b) (4)
Senior Project Manager	(b) (4)
Clinical Research Organization (Serious Adverse Event and Pregnancy Reporting)	United BioSource Corporation Safety 16, Chemin des Coquelicots 1214 Vernier/Geneva Switzerland
Safety Scientist	Alexandra Banderier
Clinical Research Organization (Data Management and Study Reporting)	Covance CRU Ltd. Springfield House, Hyde Street Leeds, LS2 9LH, UK
Project Manager	Alex Wilkinson, BSc
Medical Monitor	Katerina Bovtenko, MD MSc
Data Manager	Paul Hope, BSc
Pharmacokineticist	Stuart Hossack, BSc
Statistician	Andrew Hedge, BSc, MSc
Medical Writer	Andrew Senior, BSc, PhD



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

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



7 INTRODUCTION

Cigarette smoking causes pulmonary and cardiovascular diseases and other serious diseases in smokers [2], with smoking cessation being the only intervention proven to reduce the risk of smoking-related diseases in smokers. 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 to by the United States Food and Drug Administration (FDA) as modified risk tobacco products (MRTPs) [3]. The Institute of Medicine refers to smoking cessation as the “gold standard” for assessing risk reduction, and also that “the closer risks and exposures from the MRTP are to cessation products, the more confident a regulator can be of achieving a net public health benefit” [4].

More than 5,300 smoke constituents (the chemicals formed when tobacco is burned or combusted) have been identified [5], and more than 100 of them have been categorized as HPHCs [6]. 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 CC, but which limit pyrolysis and combustion by heating tobacco at significantly lower temperatures than CC. This is likely to offer a more acceptable alternative to CC 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 THS 2.2. 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 is composed of the ‘THS Tobacco Stick Holder’, dedicated special THS 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, the THS Tobacco Sticks do not burn down during their consumption and their lengths remain constant after use.

The non-clinical assessment of THS 2.2 and its predecessors, including THS 1.0 described in the IB [7], supports the initiation of the clinical studies. No new or increased toxicological hazard in the product’s aerosol was detected, compared with CC smoke. The aerosol was chemically analyzed confirming that none of the determined HPHCs in the THS 2.2 were increased compared to the CC. The biological activity was tested in a number of *in vitro* assays to assess the cytotoxicity and the genotoxicity of the aerosol fractions, total particulate matter (TPM), and gas vapor phase (GVP). *In vitro* and *in vivo* results corroborated the concept that absence of combustion when consuming tobacco substantially lowers toxic effects seen in these biological models. Further details are given in the IB [7].



Several clinical studies have been conducted on THS 1.0, in Europe, Asia, Africa, and the United States. All studies showed reductions in exposure to the majority of measured HPHCs from both aerosol fractions, TPM, and GVP, in subjects who used the THS 1.0 as compared to subjects continuing smoking CC, both in controlled and ambulatory conditions.

The previous version of THS 2.2, namely THS 2.1, was tested in 2 exploratory clinical studies to measure the nicotine plasma kinetic profile (ClinicalTrials.gov: ID: NCT01780688) and to assess the reduction of exposure to HPHCs (ClinicalTrials.gov: ID: NCT01780714) when switching from CC to THS 2.1. The observed nicotine plasma kinetic profile for THS 2.1 was similar to CC as well, with significant reductions in the exposure to the majority of selected HPHCs. Clinical studies conducted so far have revealed no safety concerns for either of the previous versions of THS 2.2 tested. Further details on the clinical data are provided in the IB [7].

The overall goal of the study was to show that the *ad libitum* use of THS 2.2 for 5 days by adult healthy smokers resulted in a reduction in selected BoExp to HPHCs (except BoExp to nicotine) in a well-controlled environment, and to obtain information about safety in subjects using the THS 2.2 product as compared to smokers who continued smoking their own preferred brand of CC. Smokers who were asked to abstain from using any nicotine/tobacco-containing products were used as a reference point to THS 2.2 to evaluate how similar the reduced exposure in the THS 2.2 arm was compared to SA. The subjects allocated to the THS 2.2 and CC arms were allowed to use their assigned product *ad libitum*.

Additional parameters were explored on selected variables (e.g., Cytochrome P450 2A6 [CYP2A6]/Cytochrome P450 1A2 [CYP1A2] enzymatic activity, pharmacokinetic [PK] profile of nicotine and cotinine, product evaluation, product use and related subjective effects, human smoking topography [HST], and selected risk markers).



8 STUDY OBJECTIVES

8.1 Primary Objective and Endpoints

The primary objective of this study was:

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

Endpoints:

- Monohydroxybutenylmercapturic 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 % saturation of hemoglobin) as measured on Day 5.

Primary BoExp are listed in [Table 1](#).

8.2 Secondary Objectives and Endpoints

The secondary objectives of this study were:

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

Endpoints:

- Quantity excreted in urine over 24 hours for MHBMA, S-PMA, and 3-HPMA.
- Carbon monoxide ([CO] expressed as ppm) in exhaled breath.
- Secondary urinary BoExp ([[Table 1](#)] expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

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

Endpoints:

- CO (expressed as ppm) in exhaled breath.
- COHb in blood (expressed as % saturation of hemoglobin).
- Primary and secondary urinary BoExp ([[Table 1](#)] expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

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

Endpoints:

- Nicotine equivalents ([NEQ] expressed in quantity excreted and concentration adjusted to creatinine [Table 1]) in 24-hour urine on Day 5 and from Day 1 to Day 5.
 - Plasma nicotine and cotinine concentrations.
4. To describe the levels of primary, secondary BoExp, and BoExp to nicotine over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers switching from CC to SA.

Endpoints:

- COHb in blood (expressed as % saturation of hemoglobin).
 - CO (expressed as ppm) in exhaled breath.
 - Primary and secondary urinary BoExp ([Table 1] expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.
5. To describe the PK profiles of the nicotine and cotinine in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

Endpoints:

- Peak (highest concentration value along the day) on Day 5 in plasma.
 - Time to peak (actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
 - Weighted average concentration over 24 hours on Day 5.
6. To describe the changes in CYP1A2 enzymatic activity on Day 5 in smokers switching from CC to THS 2.2, switching from CC to SA, and continuing to smoke CC.

Endpoint:

- Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5.
7. To describe the daily THS Tobacco Stick/CC consumption over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

Endpoint:

- Number of THS Tobacco Sticks and CC used each day for each subject from Day 1 to Day 5.
8. To monitor the safety profile during the study.

Endpoints:

- Incidence of adverse events (AEs)/serious adverse events (SAEs) and device events, including THS 2.2 malfunction/misuse.
- Respiratory symptoms: cough assessment by visual analog scale (VAS), Likert scales, and one open question.



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

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

	Biomarkers of Exposure (BoExp)	HPHCs	Matrix
Primary BoExp	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
Secondary BoExp	carbon monoxide (CO)	CO	Exhaled breath
	Total 1-hydroxypyrene (1-OHP)	pyrene	Urine
	Total N-nitrosonornicotine (NNN)	N-nitrosonornicotine	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-hydroxyethyl mercapturic acid (HEMA)	ethylene oxide	Urine
	3-hydroxy(a)benzopyrene (3-OH-B[a]P)	benzo(a)pyrene	Urine
	3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA)	crotonaldehyde	Urine
	S-benzylmercapturic acid (S-BMA)	toluene	Urine
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	Urine
BoExp to nicotine	Nicotine equivalents (NEQ)		
	free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide	nicotine	Urine
	nicotine	nicotine	Plasma
	cotinine	nicotine	Plasma



8.3 Exploratory Objectives and Endpoints

The exploratory objectives of this study were:

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

Endpoints:

- Ames mutagenicity test (YG1024+S9).
- The total score, Factor 1 (relief) and Factor 2 (reward) from Questionnaire of Smoking Urges (brief version [QSU-brief]) [8].
- The total scores from Minnesota Nicotine Withdrawal Scale (MNWS) [9].
- CYP2A6 enzymatic activity as a molar ratio of 3-hydroxycotinine and cotinine
- Selected risk markers (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine: 8-epi-prostaglandine F2 α (8-epi-PGF $_{2\alpha}$) and 11-dehydrothromboxane B2 (11-DTX-B2).

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

Endpoints:

- Primary and secondary BoExp and NEQ*.
- Selected risk markers (8-epi-PGF $_{2\alpha}$ and 11-DTX-B2) and NEQ.

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

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

Endpoints:

Product evaluation as measure with the Modified Cigarette Evaluation Questionnaire (MCEQ) [10]:

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

Smoking pattern: HST parameters (Table 15) and HST questionnaire.



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

Endpoints:

- Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.
- Filter analysis: smoke nicotine in filter and UV absorbance at 310 nm.

8.4 Study Hypotheses and Evaluation Criteria

8.4.1 Hypotheses

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

8.4.2 Evaluation Criteria

The study will be considered successful if the study demonstrated a 50% or more reduction in MHBMA, 3-HPMA, S-PMA, and COHb in the THS 2.2 arm compared to the CC arm (as measured on Day 5), using a one-sided test with 2.5% type I error probability.



9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This was a randomized, controlled, open-label, 3-arm, parallel group, single-center study to compare the use of THS 2.2 with continuing to smoke CC and SA.

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

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

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

The baseline period was defined as from 06:30 AM of Day -1 until 06:29 AM of Day 1. All subjects continued smoking their single preferred brand of CC and baseline values were recorded. On Day 0, subjects were randomized to 1 of the 3 study arms in a 2:1:1 ratio (Table 2).

Table 2 Definition of Study Arms

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

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

Randomization was stratified by sex and average daily CC consumption (using average consumption reported during the Screening Visit in the previous 4 weeks; those smoking 10 to 19 CC and those smoking >19 CC per day). In each study arm, each sex and each of the smoking strata had a quota applied to ensure they represented at least 40% of the population. Subjects were informed of their randomized study arm by the study site staff on Day 1 prior to 06:30 AM.



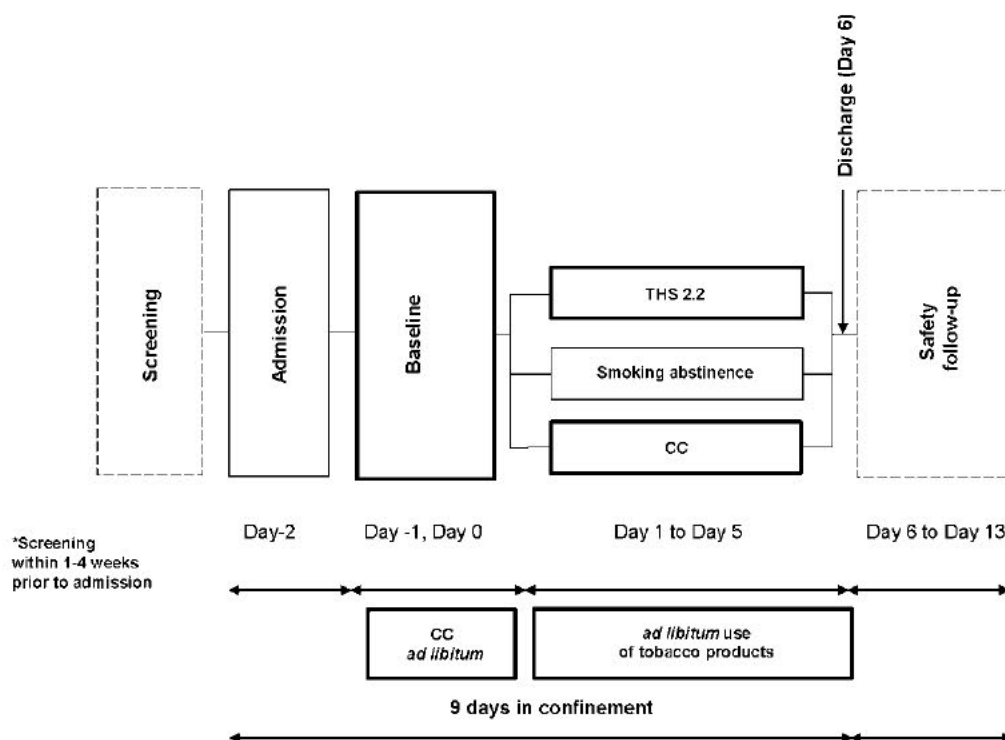
The exposure period (defined as the time from Day 1, 06:30 AM until Day 5, 11:00 PM) consisted of 5 days of *ad libitum* use of the assigned product in the THS 2.2 and CC arms. Use of any tobacco/nicotine-containing product other than the assigned product was not allowed.

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

The Day of Discharge (Day 6) was defined as from Day 5, 11:01 PM to the time of Discharge. Procedures of Discharge, including but not limited to laboratory parameters, were conducted to discharge the subject from the clinic after 9 days in a confined setting. Use of CC was allowed on Day 6, but only after spirometry had been performed.

After time of Discharge, subjects entered a 7-day safety follow-up during which there was recording of spontaneously reported new AEs/SAEs and the active follow-up of any ongoing AEs/SAEs by the study site. In general, all AEs were actively followed until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event had been found. The end of study was defined as the time of Discharge on Day 6 plus 7-day follow-up period.

During the study, subjects in the CC and THS 2.2 arms who wanted to quit smoking received appropriate medical advice and were referred to a smoking cessation counselor.

**Figure 1 Study Flow Chart**

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

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

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

The aim of this study was to demonstrate reduction in exposure to selected HPHCs (except nicotine) in smokers switching to the THS 2.2, a candidate MRTP.

The choice of HPHCs to be assessed in this study was derived from the World Health Organization (WHO) [\[11\]](#) and the draft guidance on Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke [\[6\]](#).

In the WHO list, 9 HPHCs (acrolein, CO, 1-3 butadiene, benzene, NNN, NNK, acetaldehyde, benzo[a]pyrene, and formaldehyde) with evidence of carcinogenicity, respiratory, and cardiac toxicity were recommended to be measured as priority in the smoke chemistry for mandated lowering [\[11\]](#). In addition to the 9 HPHCs recommended



to be measured by WHO list, the FDA has required that an additional 9 HPHCs are added for reporting (in total 18 HPHCs in cigarette smoke) [6].

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 [12].
- They are specific to the source of exposure with other sources being minor or non-existent.
- They are easily detectable using reliable, reproducible, and precise analytical methods.
- They ensure assessment of both gas and particulate phase of the THS 2.2 aerosol.
- They exhibit, on average, an elimination half-life of ≤ 24 hours. Therefore, the 5 days of exposure would be sufficient to reach the steady state with the THS 2.2 and SA arms (4 to 5 times the half-life was expected to lead to less than 5% of the original exposure levels of assessed biomarkers on Day 5).
- 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).

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, CC, 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.

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 [6]. 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 [11].

Cytochrome P450 1A2 activity, which is well known to be increased by smoking and to be decreased upon SA, was measured in this study to evaluate the effect of THS 2.2 use on the activity of this enzyme [13] and data from a previous study [14].

Selected risk markers (clinical risk endpoints) were assessed in this study as exploratory endpoints to understand if the reduced exposure resulted in biological changes. The risk



markers were chosen based on their changes shown in smoking cessation studies, as well as their believed association to health risks. The risk markers were:

- 8-epi-PGF_{2α} is a well-established marker of oxidative stress, a pathway which is involved in atherosclerosis. F2-isoprostanes are bioactive prostaglandin-like compounds that are produced from arachidonic acid through a non-enzymatic process of lipid peroxidation catalyzed by oxygen free-radicals. On smoking cessation, the level of 8-epi-PGF_{2α} decreases rapidly within 1 to 2 weeks to the levels seen in non-smoker plasma, serum, and urine [15].
- 11-DTX-B2, a major stable metabolite of thromboxane A2, which elicits mainly platelet aggregation. This risk marker was reported to decrease upon smoking cessation [16, 17].

The main reference product in this study was smokers who continued to smoke CC. Smokers who stopped smoking (the SA arm) were used as a reference point.

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

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

The exposure period in confinement provided information on exposure reductions in a well-controlled environment and allowed full control of daily CC consumption.

All subjects were asked to provide their own CC according to their anticipated needs for the whole confinement period. This was done to minimize any changes in their smoking behavior due to their participation in the study.

9.3 Selection of Study Population

One hundred and sixty female or male smoking healthy Caucasian subjects, who smoked at least 10 non-menthol CC for the last 4 weeks with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) per cigarette, were included in this study. Subjects had a smoking history of at least 3 years of consecutive smoking prior to the Screening Visit. There were no brand restrictions. Subjects could smoke different non-menthol brands until Admission to the clinic. From Admission to the clinic onwards, however, they were to restrict themselves to 1 preferred, non-menthol CC brand. The smoking status was verified with a urinary cotinine test (cotinine ≥ 200 ng/ml).



9.3.1 Inclusion Criteria

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

1. Subject had signed the ICF and was able to understand the information provided in the Subject Information Sheet and ICF.
2. Subject was aged from 21 to 65 years (inclusive).
3. Subject was of Caucasian origin.
4. Subject was a smoking, but healthy subject, as judged by the Principal Investigator or designee based on all available assessments from the Screening period/day of Admission (e.g., safety laboratory, spirometry [forced expiratory volume in 1 second {FEV₁}/forced vital capacity {FVC} >0.7 at post-bronchodilator spirometry, post-bronchodilator FEV₁ >80% predicted value, and post-bronchodilator FVC >80% predicted value], vital signs, physical examination, ECG, chest X-ray, and medical history).
5. Subject was a current smoker (based on self-reporting) who had smoked for the last 4 weeks at least 10 commercially available non-menthol CC per day (no brand restrictions) with a maximum yield of 1 mg nicotine ISO per cigarette. Furthermore, the subject had smoked for at least the last 3 consecutive years. The smoking status was verified with a urinary cotinine test (cotinine ≥ 200 ng/mL).
6. The subject was a current smoker who did not plan to quit smoking in the next 3 months.
7. The subject was ready to accept 5 days of SA.
8. The subject was ready to accept using the THS 2.2 product.

9.3.2 Exclusion Criteria

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

1. As per Principal Investigator or designee 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 were involuntarily incarcerated).
3. The subject had a medical condition requiring smoking cessation, or clinically relevant diseases (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease, or any other medical condition [including but not limited to clinically relevant abnormal laboratory parameters]) in the judgment of the Principal Investigator or designee.
4. The subject had a body mass index (BMI) <18.5 or ≥ 32.0 kg/m².



5. As per Principal Investigator or designee judgment, the subject had medical conditions which required or would have required in the course of the study, a medical intervention (e.g., start of treatment, surgery, hospitalization) which could have interfered with the study participation and/or study results.
6. The subject had used nicotine-containing products, other than commercially available CC (either tobacco-based products or nicotine replacement therapy [NRT]), as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment.
7. The subject had received medication (prescription or over-the-counter [OTC]) within 14 days or within 5 half-lives of the drug (whichever was longer) prior to the Admission Day (Day -2) which had an impact on CYP1A2 or CYP2A6 activity.
8. If the subject had received any medication (prescribed or OTC) within 14 days prior to Screening or prior to the Admission Day (Day -2), it was decided at the discretion of the Principal Investigator or designee if these could have potentially interfered with the study objectives and subject's safety.
9. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid.
10. The subject had a positive alcohol test and/or the subject had a history of alcohol abuse that could have interfered with subject's participation in study.
11. The subject had a positive urine drug test.
12. Positive serology test for human immunodeficiency virus (HIV) 1/2, hepatitis B surface antigen (HbsAg), or hepatitis C virus.
13. Donation or receipt of whole blood or blood products within 3 months prior to Admission.
14. The subject was a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling, child).
15. The subject was an employee of the investigational site or any other parties involved in the study or of their first-degree relatives (parent, sibling, child).
16. The subject had participated in a clinical study within 3 months prior to the Screening Visit.
17. The subject had previously participated in the same study at a different time (i.e., each subject could be included in the study population only once).

Additionally, women were excluded if:

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

*Intrauterine device, intrauterine system, established use of oral/injectable/implantable/transdermal hormonal methods, barrier methods of contraception (condoms, occlusive



caps) with spermicidal foam/gel/film/suppository, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal were not effective methods) from Screening until the end of the safety follow-up period.

9.3.3 Removal of Subjects from the Study

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

If a subject had withdrawn or was removed from the study, the whole examination procedure planned on Day 6 was performed as soon as possible after the time of their discontinuation, unless the subject had withdrawn their informed consent to do so. After the discontinuation, the subject was entered into the 7-day period of safety follow-up. For the subject who decided to withdraw from the study (Subject 0085), the samples were analyzed until the time point of withdrawal following confirmation by the Principal Investigator that the subject still agreed to have their sample analyzed and data used.

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

- Withdrawal of informed consent.
- Any AE or condition (including clinically relevant changes in a laboratory parameter), at the discretion of the Principal Investigator.
- Positive pregnancy testing (any invasive procedures, including the drawing of blood were not to be performed after diagnosis of pregnancy).
- The Sponsor, Principal Investigator, or designee terminated the study.
- 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 have been discussed with the Contract Research Organization Medical Monitor on an ongoing basis).
- If a subject used any CC or nicotine/tobacco-containing product other than the product/regimen he/she was assigned to, it was at the discretion of the Principal Investigator or designee to decide whether or not to withdraw the subject from the study.



- Non-compliance to the study procedures.

Subjects withdrawn prematurely after randomization were not replaced and were not allowed to re-enter the study. All subject withdrawals were documented properly in the source documentation and the CRF.

9.3.3.1 Violation of Selection Criteria

Subjects who were eligible at Screening, but did not meet the entry criteria at Admission Day (Day -2), were considered a screen failure and were replaced by other subjects.

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

9.3.3.2 Other Reasons for Removal of Subjects from Study

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

9.4 Investigational Products

9.4.1 THS 2.2 Product

THS 2.2 product was provided by the Sponsor and comprised the following components: Tobacco Stick, Holder, Charger, a Cleaning Tool, a main 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 is a convenient size to carry around, and could be recharged from a main power source.
Tobacco Stick Holder (Holder):	The function of the Holder (Model 4.2) was to heat the 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 Tobacco Stick).
THS Tobacco Stick (Tobacco Stick):	The Tobacco Stick (product code C3) contained tobacco which, when heated, generated an aerosol. It was custom-designed to be used with the Holder.

The overall objective of the product design was to provide an acceptable experience in which the HPHC levels in the aerosol were substantially reduced in comparison with CC.

The pack batch number of the THS Tobacco Sticks was B-05875; the production date was 07 June 2013, and the expiry date as 06 January 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 non-menthol CC. The CC were not provided by the Sponsor. Users of hand-rolled cigarettes were not allowed to participate in the study.

The reference product to the THS 2.2 during the randomized exposure period was the subject's own preferred commercially available single brand of non-menthol CC.

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

9.4.3 Packaging and Labeling

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

Each pack of CC provided by the subject was labeled to identify which subject the CCs belonged to (labels were to be affixed to the cellophane wrapper of the lower part of the pack). Each pack of CC was labeled to identify necessary information to match the subject with its suppliers.

For the THS Tobacco Sticks, the packs were printed with the necessary information including, but not limited to, subject number, health warning, tar/nicotine/CO ISO levels, and product code.

9.4.4 Storage and Accountability

The THS 2.2 and CC were stored in a secured storage site with access limited to authorized personnel only. Full accountability of the distributed products was ensured by designated staff. Subjects returned each butt of any used THS Tobacco Stick or CC immediately after use for documenting in an appropriate log.

The filters and tobacco plugs of all used THS Tobacco Sticks were collected from Day 1 to Day 5, using dedicated vials, for accountability and subsequent analysis of both nicotine and tar assessments in the filters and identification of potential combustion occurrences in the tobacco plugs.



9.4.5 Investigational Product Retention

Upon study completion, all unused THS Tobacco Sticks were returned to the Sponsor and destroyed. All components of the THS 2.2 Devices including accessories were returned to the Sponsor.

Irrespective of the study arm, the site staff returned any remaining CC to the subjects given by them on the Day of Admission.

9.4.6 Method of Assigning Subjects to Study Arms

When all the eligibility criteria were met, randomization was done through an Interactive Web and Voice Response System on Day 0. 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:CC:SA in a 2:1:1 ratio. Stratified randomization was conducted by sex and by average daily CC consumption in the 4 weeks prior to the Screening Visit, as reported by the subject (those smoking 10 to 19 CC and those smoking >19 CC per day). In each arm, each sex and each of the smoking strata had a quota applied to ensure they represented at least 40% of the population.

The randomization scheme and codes are provided in [Appendix 16.1.6](#).

9.4.7 Administration of Investigational Products

Subjects were never requested or forced to smoke and were free to stop smoking at any time during the study. The study was designed as an *ad libitum* use study. During the confinement period, smoking was generally allowed between 06:30 AM to 11:00 PM. 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 study procedures. All subjects were allowed to continue smoking *ad libitum* their single preferred brand of usual CC. All subjects underwent a THS 2.2 product test prior to enrollment.

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



9.4.7.2 Baseline Period

During the baseline period, all subjects were allowed to continue smoking *ad libitum* their single preferred usual brand of non-menthol CC.

9.4.7.3 Exposure Period

Subjects were not allowed to smoke any CC or use any nicotine/tobacco-containing products other than their assigned product/regimen.

9.4.7.3.1 THS 2.2 Arm

Subjects randomized to the THS 2.2 arm exclusively used THS 2.2 from Day 1, 06:30 AM onwards until Day 5, 11:00 PM.

9.4.7.3.2 Conventional Cigarette Arm

Subjects randomized to the CC arm continued smoking their CC from Day 1, 06:30 AM onwards until Day 5, 11:00 PM.

9.4.7.3.3 Smoking Abstinence Arm

Subjects randomized to the SA arm were instructed to abstain from smoking from Day 1, 06:30 AM onwards until Day 5, 11:00 PM. They were not provided with medication supportive for SA.

9.4.7.4 Safety Follow-up Period

During the safety follow-up period (after discharge at Day 6 until Day 13), all subjects were free to smoke their own CC *ad libitum*. Subjects in the SA arm, who wished to continue their SA, or any subject who wished to stop smoking 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 Stopping Rules for Investigational Product/Reference Point Product

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 or designee.



9.4.9 Selection and Timing of Investigational Product Use for Each Subject

Subjects did not have free access to their CC or THS 2.2, including the THS Tobacco Sticks. Both products were stored as described in [Section 9.4.4](#).

From Day -2 onwards, each CC was dispensed to the subjects. Subjects in the THS 2.2 arm were provided with THS Tobacco Sticks by the site personnel from Day 1 to Day 5. One CC/THS Tobacco Stick was allowed at a time and documented in an appropriate log.

On each day of the confinement period, the time of dispense and return for each product (CC/THS 2.2) use was documented from Day -1 for CC and from Day 1 for THS Tobacco Sticks onwards.

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

9.4.10 Blinding/Unblinding

This was an open-label study; therefore, the subjects and Investigators or designees were unblinded to subject's arm. However, there was a limited degree of blinding in the data review and data analysis process. In particular, PMI and Covance personnel were blinded to the randomized scheme as summarized in [Table 3](#).

Table 3 Blinding Scheme

Blinded Study Personnel	End of Blinding Period
PMI and Covance study statisticians	After the SAP finalization or PMI blind database review, whichever came last.
PMI data manager	After the finalization of PMI blind database review.
PMI safety and clinical scientists	After the finalization of PMI blind database review. Could be actively unblinded before that time point in case of the occurrence of any safety question, when appropriate.

As part of the PMI Quality Control (QC) activity, data were reviewed by Covance and PMI before database lock, with no access to the randomization scheme information. Full details including the definition of the blinded and unblinded PMI study teams are available in the data review plan (Version 1.0 date: 22 Mar 2014).

9.4.11 Prior and Concomitant Therapy

No medication was to be taken during the study without first informing the Principal Investigator or designee. However, the Principal Investigator was responsible for the medical care of the subjects during their participation in this study. Any decisions regarding the prescribing of medication was made in the best interest of the subject.



Concomitant use of NSAIDs and acetylsalicylic acid (including OTC products) was not allowed, as all of them could interfere with the levels of 11-DTX-B2 and possibly other risk markers. Paracetamol was allowed at a daily total dose of up to 1500 mg. Any medication with an impact on the CYP1A2 and CYP2A6 metabolism (prescription and OTC 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 CRF. Concomitant medications were followed-up with the Covance Medical Monitor on an ongoing basis.

The drugs and substances listed in [Table 4](#) and [Table 5](#) are a selection of drugs considered to have an impact on CYP1A2 and CYP2A6 activity, respectively [\[18\]](#). Prior to database lock, concomitant medications were assessed according to their potential impact on CYP1A2 and CYP2A6 activity and potential impact on the study results. The assessment indicated that no prior medications impacting CYP1A2 or CYP2A6 activity were administered ([Appendix 15, Listing 15.3.6.3.1](#)), while no randomized subject received concomitant medication, which could impact CYP1A2 or CYP2A6 activity ([Appendix 15, Listing 15.3.6.3.2](#)).

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

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

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

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

Data source: [18].

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

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

Data source: [18].

Concomitant medication use was first assessed at the Screening Visit. To be eligible for the study, any medication that impacted on CYP1A2 and CYP2A6 metabolism was discontinued at least 14 days prior to Admission to the study site or for at least 5 half-lives (whichever was longer). They were not to be used during the study until after Discharge. It was at the discretion of the Principal Investigator or designee to assess if the termination of such medication at Screening was medically justified and safe for the subject.

Estrogens for contraception and for hormone replacement therapy, even though known to be CYP1A2 inhibitors, were allowed in this study. The use of estrogens was documented in the CRF.

9.4.12 Compliance to Investigational Product/Reference Point Product

Compliance for all study arms was ensured by strict distribution of the products (product by product), and collection of THS Tobacco Sticks and CC butts were documented in an appropriate log.



In addition, in the SA arm, compliance was chemically verified using an exhaled CO breath test. The cut-off point for the CO breath test value to distinguish tobacco use versus no tobacco use was 10 ppm [19].

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 and Restrictions to the Smoking Abstinence Arm

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

In the THS 2.2 and SA arms, subjects were not allowed to smoke any CC or use any nicotine/tobacco-containing products (including NRT) from Day 1 (06:30 AM) until Day 5 (11:00 PM). In the CC arm, subjects were not allowed to use THS 2.2, any nicotine/tobacco-containing products, and CC other than those provided to the site by the subject.

During the confinement period, smoking was generally only allowed during the designated smoking times, from 06:30 AM to 11:00 PM. Subjects did not have free access to their CC or THS 2.2; these were dispensed by the study site staff individually as described in [Section 9.4.7](#).

Smoking was not allowed during assessments at Admission at the discretion of the study site. Smoking was also not allowed from Day 5, 11:01 PM until spirometry had been performed on Day 6.

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

9.4.13.2 Dietary Restrictions

A standard diet was designed by a dietician for the whole confinement period. For each meal, the caloric and fat content was controlled in order to avoid a “high-fat” diet. The



FDA guidance on food-effect studies for bioequivalency testing identifies a “high-fat” diet as a diet which maintains approximately 50% of total caloric content of the meal as fat and is high in calories (approximately 800 to 1000 calories) [20].

In order to avoid any effect on the assessment of BoExp, grilled or pan-fried meat, pre-cooked meats (e.g., tuna, ham, corned beef, and smoked meats), bacon, and sausage were not permitted [21]. 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 [13] except when the subject was asked to drink a cup of coffee 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 could have been distributed to the subjects, without restrictions, at any time during confinement as long as they fulfilled the above requirements described in this section. Consumption of water was allowed as desired. The same menu and meal schedule was administered uniformly for all subjects in all study arms. In addition, for the purpose of the Ames mutagenicity test planned on Day 0 and Day 5, the menus served on Day -1 and Day 4 were identical.

Fasting state was observed for at least 8 hours prior to blood draws for the safety laboratory (at the Screening Visit, on Day 0, and Day 6), for the serum/plasma bio-banking samples (on Day 0 and Day 6), and for blood bio-banking for transcriptomics (pharmacogenomics) on Day 0 and Day 6.

9.5 Study Variables Assessed and Schedule of Events

All study staff who conducted the study measurements or recordings had appropriate training. Quality and control measures were in place. An overview of all study procedures is shown in the Schedule of Events (see [Table 8](#) in [Section 9.5.7](#)).

Due to logistical reasons, it was not reasonable for all subjects to have study assessments/procedures at the same time. Therefore, adequate time windows were permitted for each study procedure at each time point (see Section 9 of the protocol [[Appendix 16.1.1](#)] and Section 6.1 of the SAP [[Appendix 16.1.8](#)]). Study site staff adhered to the study site’s standard operating procedures (SOPs) for all activities relevant to the quality of the study.



9.5.1 Biomarker Assessments

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

9.5.1.1 Biomarkers of Exposure

9.5.1.1.1 Urinary Biomarkers of Exposure

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

- BoExp for primary endpoints: MHBMA, 3-HPMA, S-PMA.
- Other BoExp: Total NNAL, 1-NA, Total 1-OHP, Total NNN, 3-hydroxy(a)benzopyrene, 4-ABP, 2-NA, o-toluidine, NEQ, CEMA, HEMA, S-BMA, and 3-HMPMA.

Primary and secondary urinary BoExp were measured in 24-hour urine samples from Day -1 to Day 5. In [Table 9](#), for the 24-hour urine collection samples, the dot corresponds to the day on which the 24-hour urine collection period started. For example, NEQ measured at Day 5 in the 24-hour urine collection started on Day 5 and ended later on Day 6. At time of Discharge on Day 6, subjects emptied their bladder shortly before 06:29 AM and this was the last urine portion for the 24-hour urine for the Day 5 dot mark in [Table 9](#).

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

9.5.1.1.2 Exhaled Carbon Monoxide and Carboxyhemoglobin

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

Carbon Monoxide Breath Test

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

On Day -1 to Day 5: for subjects in the THS 2.2 and CC arms, the CO breath test was conducted 4 times per day. The first test was conducted within 15 minutes prior to the first product use. The other 3 tests were conducted between 12:00 PM and 02:00 PM, 04:00 PM and 06:00 PM, and 08:00 PM and 10:00 PM.



On Days 1 to Day 5: for subjects in the SA arm, the first CO breath test was done between 08:00 AM and 10:00 AM. The other 3 tests were conducted between 12:00 PM and 02:00 PM, 04:00 PM and 06:00 PM, and 08:00 PM and 10:00 PM.

On Day -2 and Day 6: the CO breath tests were conducted once, and irrespective of the time of product use.

Carboxyhemoglobin

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

On Day -1 to Day 4: one blood sample was collected between 08:00 PM-10:00 PM.

On Day 5: for subjects in the THS 2.2 and CC arms, one blood sample was collected within 15 minutes prior to the first product use. The 3 other blood samples were collected between 12:00 PM and 02:00 PM, 04:00 PM and 06:00 PM, and 08:00 PM and 10:00 PM.

For subjects in the SA arm, the first COHb was collected between 08:00 AM and 10:00 AM. The three other blood samples were collected between 12:00 PM and 02:00 PM, 04:00 PM and 06:00 PM, and 08:00 PM and 10:00 PM.

9.5.1.1.3 Plasma Nicotine and Cotinine

Nicotine and cotinine concentrations were measured in plasma to evaluate the exposure to nicotine. For subjects in the SA arm, blood samples were collected on Day 0 to Day 4, at comparable time points to subjects in the THS 2.2 and CC arms. No nicotine PK samples were collected for subjects in the SA arm on Day 5 and Day 6.

On Day 0 to Day 4 (all study arms): one blood sample for nicotine and cotinine was drawn each day at 08:00 PM and 10:00 PM.

Nicotine/cotinine PK profiles on Day 5 and Day 6 (THS 2.2 and CC 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 time point of first product use (T_0). On Day 5, T_0 served as a reference for the time to peak concentration. An additional 8 blood samples were drawn in 2-hour intervals after T_0 . The last blood sample was drawn no later than 11:00 PM, corresponding to the end of the product use. At all time points, if the subject wanted to smoke around the time of the blood draw, he/she was allowed to smoke first and the blood was drawn after the product had been used. Depending on the time of the first product use, fewer than 8 blood samples could have been collected from a subject after T_0 .



9.5.1.2 Other Assessments

9.5.1.2.1 Risk Markers

The following risk markers were recorded/measured at the following time points:

- 8-epi-PGF_{2α}, measured in 24-hour urine on Day 0 and Day 5.
- 11-DTX-B2, measured in 24-hour urine on Day 0 and Day 5.

9.5.1.2.2 Cytochrome P450 1A2 Activity

Cytochrome P450 1A2 activity was measured at Day 0 and at Day 5. Measurement of enzyme activity was assessed through PX and CAF plasma molar concentrations approximately 6 hours (± 15 minutes) after the intake of a cup of coffee made from 4.2 g ($\pm 10\%$) regular instant coffee (Nescafé Gold Instant; Nestlé; Deutschland; CAF content: 72 mg/2 g) with 150 ml ± 10 ml water. The CAF content was approximately 150 mg CAF [13]. The exact time of the intake of the cup of coffee in the morning and of the blood sampling (taken 6 hours [± 15 minutes] after the intake of the coffee) was recorded.

9.5.1.2.3 Cytochrome P450 2A6 Activity

Cytochrome P450 2A6 activity was measured in plasma on Day 0, and on Day 6, using the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine [22]. Blood sampling for CYP2A6 activity was done prior to product use.

9.5.1.2.4 Ames Mutagenicity Test

Urine mutagenicity, a biomarker for measuring mutagen load, was measured on Day 0 and on Day 5 in 24-hour urine.

The urinary determination of each sample was done in one bacterial strain (*S. typhimurium* strain YG1024), using S9 metabolic activation and 4 doses for each of the urine extracts.

9.5.2 Safety Variables and Measurements

Safety variables were assessed in this study at the time points shown in Table 8 and included: AEs (including device malfunction or misuse), SAEs, vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), ECG data, spirometry, clinical laboratory safety panel (hematology, clinical chemistry, and urine analysis), concomitant medications, physical examination (including BMI), and respiratory symptoms (cough assessment).



9.5.2.1 Adverse Events

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

Full details of the definitions of AEs and the procedures relating to them are provided in Sections 8.1, 8.2, and 8.4 of the protocol ([Appendix 16.1.1](#)).

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

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

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

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

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

The Principal Investigator or designee was responsible for obtaining, assessing, and documenting all AEs during the study. Adverse event information was elicited throughout the study by the use of consistent, open, non-directive questions from the study site staff (e.g., "Have you had any health problems since the previous visit/How are you feeling since you were last asked?"). At the discretion of the Principal Investigator or designee, the collection of AE information was also triggered from his/her review of the subject questionnaires and the VAS used in this study. However, the main source for AE collection was the face-to-face interview with the subject.



Full details of the AE information that was recorded and the period of collection are provided in Sections 8.2.1 and 8.2.2 of the protocol ([Appendix 16.1.1](#)).

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

- Mild: The AE was easily tolerated and did not interfere with daily activity.
- Moderate: The AE interfered with daily activity, but the subject was still able to function.
- Severe: The AE was incapacitating and required medical intervention.

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

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

Full details of the assessment of AE intensity and relationship to IP administration or to the study procedures, and of the expectedness of an AE are provided in Sections 8.2.5, 8.2.6, and 8.2.7 of the protocol ([Appendix 16.1.1](#)).

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

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

Details of the reporting of pregnancies and AEs leading to withdrawal are provided in Sections 8.5 and 8.6 of the protocol ([Appendix 16.1.1](#)).

Any occurrences of malfunction or misuse of the THS Holder or Charger were documented by study site staff using a device issue log.



Furthermore, any malfunctions or misuse of the THS Holder or Charger that led to an AE/SAE, were to follow the processes for AEs/SAEs.

9.5.2.2 Physical examination

A physical examination was conducted at the Screening Visit, at Admission (Day -2), and at Day 6. Body weight was recorded at the same time points. Body height was measured only at the Screening Visit. Appropriate medical advice was provided to the subject in case of any medical findings that required health care. The BMI was calculated from the body weight and height using the following formula:

$$\text{BMI [kg/m}^2\text{]} = \text{weight [kg]} / (\text{height [m]})^2$$

9.5.2.3 Vital Signs

Systolic and diastolic blood pressure, pulse rate, and respiratory rate were measured at Screening, at Admission (Day -2), and on the morning of every day of the confinement period (Day -1 to Day 6). All parameters were recorded after the subject had rested for at least 5 minutes in a supine position.

For every measurement, it was documented as a deviation whether the subject had smoked a CC or used THS 2.2 within 15 minutes prior to the measurement.

9.5.2.4 Clinical Laboratory Parameters

Hematology, clinical chemistry, and urine analysis for the safety panel were measured at Screening, Day 0, and at Day 6. Blood was collected from the subject after at least 8 hours of fasting (see [Section 9.4.13.2](#)). The urine test was performed semi-quantitatively with a urine dipstick test at the study site. The parameters measured are listed in [Table 6](#).

**Table 6 Clinical Laboratory Parameters for Safety Panel**

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

9.5.2.5 Electrocardiogram

A standard 12-lead ECG was recorded at Screening and on Day 6. The ECG testing was performed as per the site's local practice and was recorded after the subject had rested for at least 10 minutes in a supine position.

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

9.5.2.6 Urine Drug Screen

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



9.5.2.7 Alcohol Breath Test

Subjects had a breath alcohol test at the Screening Visit and at Admission (Day -2), using an alcometer device.

9.5.2.8 Medical History and Previous Medications

Relevant medical history and concomitant disease were 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 at the Screening Visit.

Prior medication (prescription or OTC), considered as any pharmaceutical product used up to 4 weeks prior to the Screening Visit, were documented. Any medication usage which started prior to the Screening Visit and was still being taken by the subject was considered a concomitant medication; in addition, medication usage initiated after the Screening Visit was also considered as concomitant medication.

9.5.2.9 Urine Pregnancy Tests

At the Screening Visit, at Admission (Day -2), and at Day 6 urine pregnancy test were administered to all female subjects. Female subjects with a positive pregnancy test at the Screening Visit or at Day -2 were not to be enrolled and were to be considered a screening failure. The product test at Admission was only to be allowed for female subjects with a negative pregnancy test.

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

All pregnancies detected during the study were to be reported and handled as described in Section 8.5 of the protocol ([Appendix 16.1.1](#)).

9.5.2.10 Serological Tests

A test for HbsAg, hepatitis C virus, and HIV (anti-HIV 1/2 and p24 antigen) was done at Screening.



9.5.3 Other Clinical Assessments

9.5.3.1 Urine Cotinine Screening Test

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

9.5.3.2 Chest X-ray

A chest X-ray, with 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 had presented a chest X-ray with the requested views at the Screening Visit which was not older than 6 months.

9.5.3.3 Spirometry

Spirometry with and without a short-acting bronchodilator was done at the Screening Visit to evaluate inclusion/exclusion criteria (using the post-bronchodilator results). Spirometry without a bronchodilator was performed first, followed by spirometry with bronchodilator. Furthermore, spirometry without a bronchodilator was performed at Day 0 (baseline values) and at Day 6 for comparison with the baseline measures. Spirometry was performed prior to smoking the first CC of the day on Day 0 and Day 6.

All study site staff that performed lung function testing were appropriately trained. Quality control measures were put in place and were properly documented and filed at the pulmonary function laboratory (including any calibration records). The subject was submitted to a spirometry assessment with maximum voluntary ventilation measurement and the FEV₁ and FVC were recorded.

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

9.5.3.4 Demographic Data

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

9.5.3.5 Identification of the Current Cigarette Brand

Identification of the current CC brand(s) smoked by the subject was done at the Screening Visit and on Day -2. For the Screening Visit, subjects brought a packet of their own current CC brand(s) to the study site. The study site staff documented the brand name and yields.



On Day -2, subjects handed over their CC supply for the entire confinement period to the study site staff, who took a photograph of the front and the side (bearing the tar, nicotine, and CO yields) of the cigarette packages in addition to recording the brand name and yields. Photographs were considered as source documentation. A copy of the photographs was provided to, and received by, the Sponsor on Compact Discs.

9.5.3.6 Smoking History and Willingness to Quit Smoking

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

9.5.3.7 Demonstration and Trial of the Tobacco Heating System 2.2

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

9.5.4 Bioanalytical Methods

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

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

9.5.5 Sample Collection Storage and Shipping

Biomarkers of exposure in blood, selected BoExp in urine, and plasma samples were tested at Celerion's Lincoln, Nebraska laboratory, USA. The urine samples for the BoExp, 4-ABP, 2-NA, Total 1-OHP, and o-toluidine were analyzed at the Celerion Switzerland AG laboratory, Switzerland. All safety laboratory tests (including COHb blood sample) were performed at Synevo Central Lab Sp. Warsaw, Poland (see [Section 6](#)). The urine dipsticks for the safety laboratory tests, urine drug screen tests,



urine pregnancy tests and urine cotinine tests were performed by personnel at the study site. The tests were provided by the study site.

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

9.5.5.1 Blood Samples

Blood samples were collected by qualified and trained study site personnel. Subjects were in a seated position during blood collection. The maximum total volume of blood collected for each subject was approximately 170 mL, which included 20 mL for safety and repeated analysis, 20 mL of blood for long-term storage of the bio-banking samples for further analysis of BoExp and risk markers (only if additional consent was given, see [Section 5.4](#)), and 10 mL for long-term storage bio-banking samples for further transcriptomics analysis (only if additional consent was given, see [Section 5.4](#)).

The required aliquots and volumes for assessments of blood/plasma parameters and tests were summarized in the SHM.

9.5.5.2 Urine Samples

Spot urine samples were used for the urine drug screen, urine cotinine screen, urine pregnancy tests, and safety urinalysis. Detailed procedures were provided in a separate Celerion SHM.

For the 24-hour urine collection, subjects emptied their bladders shortly before 06:30 AM on the study day indicated in [Table 9](#). The collection period started at 06:30 AM and ended on the following day at 06:29 AM. Shortly before 06:29 AM, after nearly 24-hours of urine collection, subjects emptied their bladder again and this urine was used as the final portion of the 24-hour urine sample. During the sampling period, all urine passed was collected and put into the sampling bottle, with the exception of approximately 10 mL for the spot urine tests. The start and the end time of the 24-hour urine collection were recorded by the study site staff.

For assessment of urine BoExp, creatinine for normalization of urine BoExp, sample bio-banking, and urine mutagenicity, aliquots from the 24-hour urine collection were taken, as planned.

Details regarding the processing of the 24-hour urine samples are provided in a separate Celerion SHM.



9.5.5.3 Bio-banking

All samples collected for bio-banking were collected only when subjects had signed the ICF. If a subject gave consent for sample bio-banking for BoExp/risk markers, additional samples of urine (from the 24-hour urine collection) and serum/plasma (20 mL of blood total) were collected as follows:

- Samples from the 24-hour urine were collected from the urine collections that started on Day 0 and on Day 5.
- Serum/plasma was collected on Day 0 and Day 6.

These samples were intended for possible later analysis of additional BoExp/risk markers. No genetic or transcriptogenomics testing was to be performed on these samples.

The samples intended for sample bio-banking were kept frozen according to the SHM, separate from the other samples collected, and were shipped to a central storage facility. After the final clinical study report was signed, samples of plasma/serum were to be stored for a maximum of 5 years and samples of urine for a maximum of 2 years. The blood bio-banking for transcriptomics was to be stored for a maximum of 5 years.

The facility at which the samples were stored followed their procedures for destruction of banked samples if a subject withdrew their consent for sample bio-banking.

9.5.6 Other Study Procedures

9.5.6.1 Human Smoking Topography Assessment

Human smoking topography involved the measurement of each smoker's unique way of smoking CCs or using THS Tobacco Sticks. The HST SODIM[®] device, model SPA/M (SODIM[®] Instrumentation, Fleury les Aubrais, France) was used to measure smoking topography (see Appendix 4 of the protocol [[Appendix 16.1.1](#)]). It consisted of a special sample holder (containing a constriction in the middle) which was placed between the subject's mouth and the filter of the CC or THS Tobacco Stick. The sample holder was connected by 2 narrow tubes to a portable data recording system.

At Day 0, the HST SODIM[®] device was used for all CC smoked for all subjects. On Day 1 and Day 4 of the confinement period, the HST SODIM[®] device was used for every product use for all subjects in the CC and THS 2.2 arms.

Smoking topography with the HST SODIM[®] device was not performed for 51 subjects at Day 0, 15 subjects at Day 1, and 16 subjects at Day 4 because these were incompatible with the HST SODIM[®] device (e.g., slim CC).



There was a limited amount of 40 HST SODIM[®] devices available for each cohort, which were sufficient to perform all the assessments needed. For each subject, 1 HST SODIM[®] device was assigned at Day -1, which was used by that subject on all HST assessment days (in the case of malfunction, the device was exchanged). In the CC arm, HST SODIM[®] devices were assigned to all subjects smoking non-slim CC.

From Day 1, for subjects in the SA arm, no HST assessments were performed.

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

The HST SODIM[®] device measured and recorded the flow and other per-puff parameters listed in [Section 9.7.1.7.2](#), [Table 14](#). From the per-puff parameters, the per-cigarette parameters shown in [Table 15](#) were derived (representing average values or totals per cigarette).

9.5.6.2 THS Filter Analysis

All filters from used THS Tobacco Sticks were sent to a Labstat for analysis.

9.5.6.3 Visual Inspection of THS Tobacco Plugs

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

9.5.6.4 Questionnaires

In this study, questionnaires were used to assess nicotine dependence (Fagerström Test for Nicotine Dependence [FTND], revised version), assessment of cough (on a VAS), product evaluation (MCEQ), urge-to-smoke symptoms (QSU-brief), withdrawal symptoms (MNWS questionnaire, revised version), and the impact of using the HST device on smoking experience in terms of ritual disruption (HST questionnaire) (see [Appendix 16.1.2](#) for examples of all questionnaires).

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

9.5.6.4.1 Fagerström Test for Nicotine Dependence (Revised Version)

Potential nicotine dependence was assessed at Screening using the FTND in its revised version [\[23, 24\]](#), as updated in 2012 [\[25\]](#).



The questionnaire consisted of 6 questions, which were answered by the subject himself/herself. The scores obtained on the test permit the classification of nicotine dependence into 3 levels: Mild (0 to 3 points); Moderate (4 to 6 points); Severe (7 to 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. On each day, cough assessment was done prior to product use.

Subjects were asked if they had experienced a regular need to cough (e.g., coughing several times in the last 24 hours prior to assessment). If the answer was 'Yes', the subjects completed a VAS, 3 Likert scales, and the open question.

The VAS assessed how bothersome the cough was to the subject during the previous 24 hours, ranging from 'not bothering me at all' to 'extremely bothersome'.

Furthermore, subjects assessed the intensity and frequency of the cough and the amount of sputum production on Likert scales (Table 7).

Table 7 Cough Assessment Likert Scales

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

Finally, subjects were asked with an open question if there were any other important observations that they wanted to share with the 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 [10]. 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).

Only subjects who were randomized to the THS 2.2 and CC arms completed the MCEQ from Day -1 to Day 5; subjects in the SA arm completed the MCEQ up until their randomization was communicated to them. The subjects completed the questionnaire by themselves during the confinement period.

9.5.6.4.4 Questionnaire of Smoking Urges Brief Version

To assess the urge-to-smoke, all subjects were asked to fill-in a 10-item brief version of the QSU-brief [8]. The QSU-brief is a self-reported questionnaire with 10 items to be rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores in this questionnaire indicate a higher urge-to-smoke.

The QSU-brief was completed by the subject himself/herself on a daily basis, from Day -1 to Day 5.

9.5.6.4.5 Minnesota Nicotine Dependence/Withdrawal Scale (Revised Version)

The MNWS is a valid and reliable scale that has been used previously to examine signs and symptoms of withdrawal from cigarette smoking [9, 26]. It consists of 2 scales: a 'self-report scale' and an 'observer scale'.

For the purpose of this study, only the self-reporting scale was used and filled-in by the subject. Furthermore, the subject's weight was not recorded for the purpose of the MNWS. At the end of the assessment of the questionnaire, the subject's pulse rate was recorded.



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

The MNWS was completed on a daily basis from Day 0 to Day 6. On each day, MNWS was completed prior to product use.

9.5.6.4.6 Human Smoking Topography Questionnaire

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

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

- The end of the baseline period on Day 0 for all subjects smoking CC compatible with the HST SODIM[®] device (i.e., non-slim CC).
- On Day 4 for all subjects in the THS 2.2 and for all subjects smoking CC compatible with the HST SODIM[®] device (i.e., non-slim CC).

9.5.7 Schedule of Events

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



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Table 8 Schedule of Events[illegible]



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Table 8 **Schedule of Events (continued)**

[illegible]


Table 8 Schedule of Events (continued)

	Screening	Confinement Period									Safety Follow-up
Study Day	-30 to -3	-2	-1	0	1	2	3	4	5	6	6 to 13
MNWS (revised version) ^k				•	•	•	•	•	•	•	
MCEQ (modified version; THS 2.2 and CC arms) ^l			•	•	•	•	•	•	•		
HST (THS 2.2 and CC arms) ^m				•	•			•			
HST questionnaire (THS 2.2 and CC arms) ^m				•				•			
Assessment of cough				•	•	•	•	•	•	•	
AE/SAE recording	•	•	•	•	•	•	•	•	•	•	•
Collection of tobacco plugs and filters from all used Tobacco Sticks for analysis of combustion occurrences and filter analysis and for accountability					•	•	•	•	•		
Collection of used CC butts for accountability			•	•	•	•	•	•	•		
B: Bio-banking for biomarkers of exposure and risk markers ⁿ				•						•	
B: Bio-banking transcriptomics ⁿ				•						•	

Abbreviations: AE = adverse event; B = blood; BMI = body mass index; BoExp = biomarkers of exposure; CC = conventional cigarette(s); CO = carbon monoxide; COHb = carboxyhemoglobin; CYP1A2 = cytochrome P450 1A2; CYP2A6 = cytochrome P450 2A6; ECG = electrocardiogram; FTND = Fagerström Test for Nicotine Dependence (revised version); HIV = human immunodeficiency virus; HST = human smoking topography; MCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine



Withdrawal Scale (revised version); QSU-brief = Questionnaire of Smoking Urges (brief); SA = smoking abstinence; SAE = serious adverse event; T₀ = time point of first product use; THS 2.2 = Tobacco Heating System 2.2; U = urine.

- ^a Systolic and diastolic blood pressure, pulse rate, and respiratory rate.
- ^b Including height (only at Screening), body weight, and calculated BMI.
- ^c Spirometry had to be done prior to smoking on Day 0 and Day 6. At Screening, spirometry needed to be done prior at least 1 hour after smoking.
- ^d Pre-study chest X-ray (with anterior-posterior and left lateral views) could have been used, if performed within 6 months prior to Screening.
- ^e Subjects were asked if they planned to quit smoking within the next 3 months (at Screening only) and, in order to satisfy the protocol inclusion criteria, if they were ready to abstain from smoking for at least 5 days (at Screening and Day -2).
- ^f THS 2.2 product test to be conducted as the last procedure of eligibility check at Day -2 (and after urine pregnancy test was done in female subjects to exclude pregnancy).
- ^g On Day -1 to Day 5, the CO breath test was conducted 4 times per day. For subjects in the THS 2.2 and CC arms, the first test was conducted prior to the first product use. The other 3 tests were conducted as described in [Section 9.5.1.1.2](#).
On Day 1 to Day 5, the CO breath test was conducted 4 times per day. For subjects in the SA arm, the first CO breath test was done at 08:00 AM-10:00 AM. The other 3 tests were conducted as described in [Section 9.5.1.1.2](#).
On Day -2 and Day 6, the CO breath tests were conducted once.
- ^h COHb; Assessments were done in conjunction with CO breath tests, where applicable. Day -1 to Day 4: one blood sample in the evening as described in [Section 9.5.1.1.2](#).
Day 5: four blood samples were collected 4 times per day. One blood sample was collected prior to the first product use (for subjects in the THS 2.2 and CC arms) and at 08:00 to 10:00 AM for subjects in the SA arm, and the 3 remaining samples as described in [Section 9.5.1.1.2](#).
- ⁱ Nicotine/cotinine: Day 0 to Day 4 (all study arms): one blood sample at 08:00 PM-10:00 PM.
Day 5 and Day 6 (THS 2.2 and CC arms): one sample within 15 minutes prior to T₀; 8 blood samples after T₀ each at 2-hour intervals. On Day 6, two blood samples were drawn. The first sample was 20 hours after T₀ and the second blood sample was 24 hours after T₀ (with T₀ being the time of the first product use on Day 5).
Day 5 and Day 6 (SA arm): on Day 5, one blood sample in the evening at 08:00 PM to 10:00 PM. On Day 6, one blood sample was drawn at 08:00 AM to 10:00 AM.
- ^j QSU-brief: daily from Day -1 to Day 5.
- ^k MNWS: daily from Day 0 to Day 6.
- ^l MCEQ: daily from Day -1 to Day 5.
- ^m On Day 0, HST and the HST questionnaire were done in all subjects smoking CC compatible with the HST SODIM[®] device. On Day 1 and Day 4, HST and the HST questionnaire were done in all subjects in the THS 2.2 and CC arms. Smoking topography with the HST SODIM[®] device was not done in subjects smoking CC that were incompatible with the HST SODIM[®] device (e.g. slim CC). No HST assessments were done in subjects in the SA arm.
- ⁿ Samples were only taken if additional consent for BoExp bio-banking was given by the subject.

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

24-hour Urine Samples	Baseline Period		Confinement Exposure Period				
	Day -1 to Day 0	Day 0 to Day 1	Day 1 to Day 2	Day 2 to Day 3	Day 3 to Day 4	Day 4 to Day 5	Day 5 to Day 6
BoExp in urine	•	•	•	•	•	•	•
Creatinine	•	•	•	•	•	•	•
Ames mutagenicity test, 11-DTX-B2 and 8-epi-PGF _{2α}		•					•
Bio-banking		•					•

Abbreviations: 8-epi-PGF_{2α} = 8-epi-prostaglandine F_{2α}; 11-DTX-B2 = 11-dehydrothromboxane B2; BoExp = biomarkers of exposure



9.5.8 Appropriateness of Measurements

The laboratory measures used in this study were selected based on the following criteria: 1) the availability of a validated analytical method; 2) the measure is known to be directly or indirectly affected by smoking; 3) measure is readily reversible after smoking cessation; 4) timeframe of reversibility of measure in the perspective of the study duration; 5) practicality/acceptability by subjects; and 6) robustness (rapid, simple, accurate).

All questionnaires used in this study were either available as validated (except the VAS cough) or forward and back-translated with subsequent independent verification from the local language.

9.6 Data Quality Assurance

Details of the QC and quality assurance for this study are provided in Section 10 of the protocol ([Appendix 16.1.1](#)).

9.6.1 Monitoring

The Covance Clinical Research Associate (CRA) (“Monitor”) was responsible for the monitoring of the study. Monitoring was performed according to Covance’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 deemed necessary to ensure that data were being recorded in an adequate manner and that protocol adherence was satisfactory.

The Principal Investigator provided access to all medical records to the Monitor so that entries in the CRFs could be verified. The Principal Investigator, as part of their responsibilities, was responsible for ensuring that the study adhered to ICH GCP requirements.

9.6.1.1 Investigator Meeting

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



9.6.1.2 Pre-investigation (Site Initiation) Visits

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

- Meet with the Principal Investigator and applicable staff to review the protocol, study procedures, Principal Investigator obligations according to ICH GCP/other local regulations, and monitoring procedures.
- Determine the adequacy of the facilities.
- Inform the Principal Investigator of her responsibilities and the procedures for ensuring adequate and correct documentation.

9.6.1.3 Routine Monitoring Visits

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

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

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

The Principal Investigator, or a designated member of the Principal Investigator's 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

The close-out visit was conducted by a CRA from Covance in accordance with Covance SOPs.

The close-out visit occurred on 22 July 2014. All CRFs were to be completed and sent to Covance's Data Management department and all data clarification forms subsequently resolved before database lock (05 June 2014).



The purpose of the close-out visit was to:

- Ensure all CRF pages were monitored and frozen.
- Perform final IP accountability and ensure the return (or destruction) of remaining IP.
- Final checks to ensure all laboratory samples were shipped from the site.
- Final check that all e-diaries, devices, HST SODIM[®] devices, and butt/filter collectors were shipped back
- Review completion and accuracy of the Investigator File as per Study Site File checklist including Monitoring Visit Log, Site Responsibility Log, Subject Screening and Enrollment Log, and IP Shipment and Accountability Logs.
- Review procedure for record retention, IEC notification, and publication rights with Principal Investigator.
- Advise site to notify the IEC of study closure.

9.6.2 Training of Staff

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

The meeting included the following topics:

- Review of study organization and timelines.
- Review of the clinical study protocol and IB.
- Presentation of query process.
- Presentation of reporting of protocol deviations.
- Training on use of IP and devices.
- Training on HST and use of HST SODIM[®] device.
- Laboratory manuals, kits and labels, laboratory shipments.
- Presentation of safety reporting procedures, SAE form, and SAE handling.
- Pregnancy reporting procedures, pregnancy form, and pregnancy handling.
- Refresher training on ICH GCP requirements.
- IXRS[®] randomization procedure and training.
- Electronic data capture system training.
- ePRO system training.



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

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

9.6.3 Data Management

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

9.6.3.1 Data Capture

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

The Principal Investigator had ultimate responsibility for the collection and reporting of all data related to the clinical study and ensured that the data were accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. The CRF was signed by the Principal Investigator or designee to attest that the data contained in the CRF were true and accurate. Any corrections made to source documents were clearly recorded, without obscuring the original values, and were accompanied by the date of change, reason for change, and identification of the person making the change. The CRF for each subject was checked against the source documents at the study site by the CRA. Instances of missing or unclear data were discussed with the Principal Investigator for resolution. A CRF was generated for all subjects that signed the 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 Section 11.1.1 of the protocol ([Appendix 16.1.1](#)).



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

9.6.3.2 Data Handling

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

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

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

9.6.3.2.1 Data Validation

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

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

9.6.3.2.2 Coding

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

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

Adverse events: MedDRA[®], Version 16.0

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



9.6.3.2.3 Database Lock

After all outstanding data management issues had been resolved and all validation, quality review, and cleaning activities were completed the database was declared soft-locked. Access to change data in the soft-locked database at this time was limited to specified Data Management personnel.

After data review by the Sponsor, resolution of all raised queries, and QC of the changed data, the database was declared locked on 05 June 2014 and, following a database unlock on 20 June 2014, was re-locked on 22 June 2014.

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.

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

9.6.4 Audits and Inspections

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

Authorized representatives of the Sponsor, regulatory agencies, and/or an IEC could perform 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 they were contacted by a regulatory agency about an inspection at their study site.

The Principal Investigator or designee 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 the clinical study protocol, the Principal Investigator understood and agreed to provide access to the necessary documentation and files.



9.7 Planned Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 General Issues on Evaluation and Presentation of Data

All statistical evaluation and analyses were performed and validated using Statistical Analysis Software® (SAS®), version 9.3.

9.7.1.2 Data Sets for Analysis

The main population for non-safety analysis was the full analysis set (FAS). The per-protocol (PP) population was used only for the analysis of the primary endpoint to examine the robustness of the primary analysis. As there was not expected to be major differences between the FAS and PP population for this study, the PP population was only assessed if more than 10 subjects were excluded from the PP population.

Safety data were analyzed using the safety population.

9.7.1.2.1 Full Analysis Set

The FAS consisted of all the randomized subjects who had at least one post-randomization product use experience (if randomized to THS 2.2 or CC) and had at least 1 valid BoExp measurement (THS 2.2, CC, SA arms).

9.7.1.2.2 Per-protocol Population

The PP population was a subset of the FAS and included all randomized subjects who:

- Had no major protocol deviation to product compliance (as defined in Section 11 of the SAP [[Appendix 16.1.8](#)]) if randomized to THS 2.2 or SA.
- Had not been misrandomized.
- Had no other major protocol deviation.*

* Only subjects with major protocol deviations that impacted the validity of the evaluation of the results (see Section 11 of the SAP [[Appendix 16.1.8](#)]) were excluded from the PP population.



9.7.1.2.3 Safety Population

The Safety population consisted of all the subjects who had at least 1 exposure to THS 2.2 (product test at Admission Day). Subjects in the Safety population were analyzed according to actual exposure.

9.7.1.3 Stratification

Each sex and each of the current CC consumption levels (10 to 19 CC/day and >19 CC/day) had a quota applied to ensure they represented at least 40% of the total study population.

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

9.7.1.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics were summarized for the Safety population and FAS, and listed for all screened subjects.

The demographic variables age, sex, race, body weight, height, and BMI were summarized by actual exposure, and by the 2 stratification factors (sex, and CC consumption), using the following descriptive statistics: number of subjects (n), number and percentage of subjects with missing data, arithmetic mean, arithmetic standard deviation (SD), median, first and third quartiles, minimum, maximum, and number and/or counts and percentages within specified categories (see Section 12.1.3 of the SAP in [Appendix 16.1.8](#)).

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

9.7.1.4.1 Fagerström Test for Nicotine Dependence at Screening

The FTND used in its revised version [\[23\]](#), as updated in 2012 [\[25\]](#) was conducted at Screening to determine the subject's dependence on nicotine. The questionnaire consisted of 6 questions, which subjects answered themselves.

[Table 10](#) shows the 6 questions and the scores associated with each question.

**Table 10 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?	<ul style="list-style-type: none">• Within 5 minutes• 6 to 30 minutes• 31 to 60 minutes• After 60 minutes	<ul style="list-style-type: none">3210
2. Do you find it difficult to refrain from smoking in places where it is forbidden?	<ul style="list-style-type: none">• Yes• No	<ul style="list-style-type: none">10
3. Which cigarette would you hate most to give up?	<ul style="list-style-type: none">• The first one in the morning• Any other	<ul style="list-style-type: none">10
4. How many cigarettes per day do you smoke?	<ul style="list-style-type: none">• 10 or less• 11 to 20• 21 to 30• 31 or more	<ul style="list-style-type: none">0123
5. Do you smoke more frequently during the first hours after awakening than during the rest of the day?	<ul style="list-style-type: none">• Yes• No	<ul style="list-style-type: none">10
6. Do you smoke even if you are so ill that you are in bed most of the day?	<ul style="list-style-type: none">• Yes• No	<ul style="list-style-type: none">10

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

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

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

9.7.1.4.2 Current Conventional Cigarette Brand Consumption

Current CC brand(s) smoked by the subject, and recorded at the Screening Visit and Admission (Day -2), were summarized and/or listed by actual exposure and study day for the Safety population. This included brand name(s) and ISO nicotine, tar, and CO yields. Data at Screening were listed only.



ISO tar yields at Admission (Day -2) were categorized as: 1 to 5 mg, 6 to 8 mg, 9 to 10 mg, and >10 mg. ISO nicotine levels were categorized as: ≤ 0.6 mg and >0.6 to ≤ 1 mg. The number of CCs smoked on a daily basis during the previous 4 weeks was categorized as 10 to 19 cigarettes/day and >19 cigarettes/day.

9.7.1.4.3 Smoking History and Willingness to Quit Smoking

Smoking history, including whether subjects had smoked for at least the last 3 consecutive years, and whether the subject had smoked any menthol CC during the previous 4 weeks, were listed by actual exposure at Screening and Admission (Day -2), where applicable.

The subjects' responses to whether they "plan to quit smoking in next 3 months" were listed at Screening. Readiness to accept interruption of smoking for up to 5 days and the advice on the risks of smoking and debriefing were listed at Admission.

9.7.1.4.4 Other Baseline Data

The following data collected at Screening and/or at Admission were listed by actual exposure:

- Cotinine urine test.
- Urine pregnancy test.
- Chest X-ray.
- Urine drug screen.
- Serology.
- Alcohol breath test.
- Prior medication.
- Debriefing and risk of smoking.
- Willingness to use THS 2.2.

9.7.1.5 Primary Analyses

9.7.1.5.1 Primary Biomarkers of Exposure in 24-hour collection

The primary endpoints assessed on Day 5 for the comparison of THS 2.2 and CC were MHBMA, 3-HPMA, S-PMA (concentration adjusted to creatinine) in 24-hour urine, and COHb in blood (expressed as % saturation of hemoglobin).

Descriptive summary statistics, including the number of subjects (n), number, and percent of subjects with missing data, number of subjects with results below the limit of



quantification (BLOQ), arithmetic mean, arithmetic SD, median, first and third quartiles, minimum, maximum, geometric mean and associated 95% confidence intervals (CI), and geometric coefficient of variation (CV) were presented for each study arm stratified by sex and CC consumption.

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

The primary endpoints were log-transformed (base_e) prior to analysis. The analysis compared (1) last Day 5 values of COHb in blood and (2) urinary concentrations of MHBMA, 3-HPMA, and S-PMA corrected for creatinine on Day 5 between the THS 2.2 and CC arms. An analysis of covariance (ANCOVA) [27, 28] model was used with terms for the log-transformed baseline value, sex, average daily CC consumption over the last 4 weeks as reported during Screening, and product.

The least squares (LS) means and estimate of the difference along with its 95% CI were back-transformed before they were presented in the tables. The geometric LS means for each product along with the ratio (THS 2.2:CC) and 95% CI were presented in the tables.

The primary analysis was performed on the FAS, with the PP population used only to examine the robustness of the analysis of the primary endpoints.

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

Analysis was conducted on the natural log scale, in order to test the following hypothesis:

Null hypothesis (H_0): $m_1 \geq m_2$

Alternative hypothesis (H_1): $m_1 < m_2$

where m_1 and m_2 are the geometric means of the BoExp levels on Day 5 for THS 2.2 and CC, respectively.

The confirmatory analysis was performed on the FAS only.

9.7.1.6 Secondary Analyses

9.7.1.6.1 Biomarkers of Exposure

Additionally, the quantity of MHBMA, 3-HPMA, and S-PMA excreted over 24 hours was presented. The levels of MHBMA, 3-HPMA, and S-PMA were also examined to



compare the reductions in THS 2.2 versus SA using the same methodology as for the primary analysis.

The secondary BoExp are exhaled CO and urinary Total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, CEMA, HEMA, 3-OH-B[a]P, 3-HMPMA, S-BMA, Total NNAL and NEQ. The urine parameters were expressed as concentrations adjusted for creatinine and the quantity excreted over 24 hours.

The quantity of NEQ excreted over 24 hours was derived according to the formula below. The concentrations reported for free nicotine and its 5 major metabolites were not used as analysis variables.

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

The baseline of the exhaled CO was the time-matched measurements on Day 0, i.e. the first measurement on Days 1 to 5 was matched to the first measurement on Day 0 and similarly for the second, third, and fourth measurements. The baseline of the urinary biomarkers was the last assessment prior to 06:29 AM on Day 1.

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

Carbon monoxide in exhaled breath was measured using the Micro+™ Smokerlyzer® or similar device, conducted on Day -2 to Day 6. On Day -1 to Day 5 the first test per day was performed within 15 minutes prior to the first product use, and then between 12:00 and 02:00 PM, between 04:00 and 06:00 PM, and between 08:00 and 10:00 PM. On Day -2 and Day 6 the CO breath tests were conducted once.

Descriptive statistics, summarized by exposure, were produced separately for all time points for all visits applicable for exhaled CO. This was done on the FAS, stratified by sex and CC consumption.

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



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

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

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

The secondary BoExp were also examined to compare the reductions in THS 2.2 versus SA using the same methodology as above.

The hypothesis to be tested for each of the other BoExp was the same as that for the primary endpoint.

9.7.1.6.2 Nicotine and Cotinine Concentrations

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

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

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

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

9.7.1.6.3 Nicotine and Cotinine Pharmacokinetic Parameters

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



weighted average concentration over 24 hours (C_{avg}) on Day 5 was calculated by dividing the area under the concentration-time curve from 0 to 24 hours ($AUC_{0-24 h}$) by 24, where the $AUC_{0-24 h}$ was calculated using the linear trapezoidal rule.

Since the samples were taken whilst the subjects were smoking freely, all samples must be non-missing for the parameters to be calculated as C_{peak} (and t_{peak}) could have occurred at any time.

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

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

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

9.7.1.6.4 CYP1A2 Activity

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

A conversion factor was applied as follows:

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

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

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

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



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

9.7.1.7 Exploratory Analyses

9.7.1.7.1 Questionnaires

Questionnaire of Smoking Urges-brief

Details of the QSU-brief [8] and timings of the assessment are presented in Section 9.5.6.4.4. The QSU-brief consists of 10 items as presented in Table 11.

Table 11 Questionnaire of Smoking Urges Brief - Questions and Factors

Question	Factor
1 I have a desire for a cigarette right now	1
2 Nothing would be better than smoking a cigarette right now	2
3 If it were possible, I probably would smoke now	1
4 I could control things better right now if I could smoke	2
5 All I want right now is a cigarette	2
6 I have an urge for a cigarette	1
7 A cigarette would taste good now	1
8 I would do almost anything for a cigarette now	2
9 Smoking would make me less depressed	2
10 I am going to smoke as soon as possible	1

All items are rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores indicate a higher urge to smoke.

Two factor scores and a total score were derived [8]. Each factor was a subset that included 5 of the 10 questions as defined in Table 11. 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. All summaries, profiles, and analysis were presented for the THS 2.2, CC, and SA arms.

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 change from baseline were summarized. The answers to the individual questions, along with the domain scores, total scores, and changes from baseline were listed.



Profiles of the raw means from baseline to Day 5 for the total score and 2 domain scores were produced.

The analysis compared each post-baseline time point in the domain and total scores. A repeated measures ANCOVA model was used with terms for baseline QSU-brief score, sex, average daily CC consumption over the last 4 weeks as reported during Screening, product, time point, and the interaction between product and time point. No adjustment was made for multiple comparisons.

Least squares means for each product along with the difference (THS 2.2 - CC and THS 2.2 - SA) with 95% CI were presented. All figures, summaries, and analyses were performed on the FAS.

Modified Cigarette Evaluation Questionnaire

Details of the MCEQ [10] and timings of the assessment are presented in [Section 9.5.6.4.3](#). The MCEQ consists of 12 items as presented in [Table 12](#).

Table 12 Modified Cigarette Evaluation Questionnaire - Questions and Subscales

Question	Subscale
1 Was smoking satisfying?	Smoking Satisfaction
2 Did cigarettes taste good?	Smoking Satisfaction
3 Did you enjoy the sensation in your throat and chest?	Enjoyment of Respiratory Tract Sensations
4 Did smoking calm you down?	Psychological Reward
5 Did smoking make you feel more aware?	Psychological Reward
6 Did smoking make you feel less irritable?	Psychological Reward
7 Did smoking help you concentrate?	Psychological Reward
8 Did smoking reduce your hunger for food?	Psychological Reward
9 Did smoking make you dizzy?	Aversion
10 Did smoking make you nauseous?	Aversion
11 Did smoking immediately relieve your craving for a cigarette?	Craving Reduction
12 Did you enjoy smoking?	Smoking Satisfaction

Items are assessed on a 7-point scale, ranging from 1 (not at all) to 7 (extremely). Higher scores indicate greater intensity on that scale.

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



All summaries, profiles, and analysis were presented for the THS 2.2 and CC arms only; the MCEQ was not captured for the SA arm.

The change from baseline was calculated for the 5 domain scores. The domain scores, along with the change from baseline, were summarized. The answers to the individual questions, along with the domain scores and changes from baseline, were listed.

Profiles of the raw means from baseline to Day 5 for the 5 subscale scores were produced.

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

Least squares means for each product along with the difference (THS 2.2 - CC) with 95% CI were presented.

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

Minnesota Nicotine Withdrawal Scale (Revised Edition) Questionnaire

The MNWS [9] is a 24-hour recall that was completed by the subject him/herself daily on Day 0 to Day 6 prior to product use to reflect the previous day's experience. Therefore, although it was collected on Days 0 to 6, it was reported as Days -1 to 5. The baseline was the last assessment prior to 06:29 AM on Day 1. Only the self-reported part of the MNWS was used.

The self-reported part of the MNWS consists of the following 15 items, which were rated over the last 24 hours on a scale of 0 to 4 (see Table 13). Higher scores indicate greater intensity on that scale.

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

**Table 13 Minnesota Nicotine Withdrawal Scale (Revised Edition)
Questionnaire Scores**

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

If the baseline score was 0, the percent change from baseline was calculated using a value of 1 for the denominator.

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

The change from baseline was calculated for both scores. The 2 scores, along with the change from baseline were summarized. The answers to the individual questions, along with the 2 scores and changes from baseline, were listed.

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

The analysis compared each post-baseline time point for the 2 scores. A repeated measures ANCOVA model was used with terms for baseline score, sex, average daily CC consumption over the last 4 weeks as reported during Screening, product, time point, and the interaction between product and time point. No adjustment was made for multiple comparisons.

Least squares means for each product along with the difference (THS 2.2 - CC and THS 2.2 - SA) with 95% CI were presented.

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



9.7.1.7.2 Human Smoking Topography Assessment

The HST assessments took place on Day 0, Day 1, and Day 4 in the THS 2.2 and CC arms only, if CC were compatible with the HST SODIM[®] device.

The HST SODIM[®] device measured and recorded the flow and other per-puff parameters listed below (Table 14). From the per-puff parameters, the per-cigarette parameters shown below were derived (representing average values or totals per cigarette [Table 15]). Prior to calculation of the per-cigarette parameters, the Sponsor's 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.

The per-cigarette parameters derived from the HST assessments were summarized along with their changes from baseline. The per-puff and per-cigarette parameters were listed. In addition, the product mean and 95% CI per-cigarette parameters were presented graphically.

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

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

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

Table 14 Human Smoking Topography - Per-Puff Parameters

Description	Variable	Unit
Puff number	Ni	
Puff volume	Vi	mL
Puff duration	Di	S
Average flow [Vi/Di]	Qmi	mL/s
Peak flow	Qci	mL/s
Inter puff interval	li	S
Sum of li and Di	DFi	S
Work [INT Pmi*FinalFlow*dt]	Wi	mJ
Average pressure drop	Pmi	mmWG
Peak pressure drop	Pci	mmWG
Average resistance [Pmi/Qmi]	Rmi	mmWG/mL/s
Peak resistance [Pci/Qci]	Rci	mmWG/mL/s

**Table 15 Human Smoking Topography - Per-Cigarette Parameters**

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

9.7.1.7.3 Human Smoking Topography Questionnaire

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

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

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

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 FAS.



9.7.1.7.4 CYP2A6 Activity

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

A conversion factor was applied as follows:

Cotinine: The molecular weight is 176.215 g/mol. Therefore, to convert cotinine in ng/mL to nmol/L, the result in ng/mL was multiplied by 5.675.

Trans-3' hydroxycotinine: The molecular weight is 192.217 g/mol. Therefore, to convert trans-3' hydroxycotinine in ng/mL to nmol/L, the result in ng/mL was multiplied by 5.202.

CYP2A6 activity was measured in plasma on Day 0 and Day 6. Descriptive statistics of the values and change on Day 6 from Day 0 and supportive listings were provided.

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

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

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 is reported in a separate report, as stated in [Section 9.8.2](#).

9.7.1.7.6 Risk Markers

The risk markers were 8-epi-PGF_{2α} and 11-DTX-B2 in urine and were presented as quantity excreted over 24 hours and concentration adjusted for creatinine.

The quantity excreted over 24 hours, percent changes in the quantity excreted, and the concentration adjusted for creatinine in 24-hour urine were listed and summarized. In addition, line graphs were produced for product means (and 95% CI) over all time points.

The analysis compared the concentrations adjusted for creatinine and the quantity excreted over 24 hours on Day 5, between the THS 2.2 and CC arms and between the



THS 2.2 and SA arms. An ANCOVA model was used with terms for Day 0 concentration adjusted for creatinine or quantity excreted over 24 hours, sex, average daily CC consumption over the last 4 weeks as reported during Screening, and product. No adjustment was made for multiple comparisons.

If there was evidence of non-normality then the concentrations or quantity excreted were transformed prior to analysis.

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

Relationship Between Risk Markers, Biomarkers of Exposure and Nicotine Equivalents

The relationship between risk markers and NEQ was examined by fitting a general linear model with terms for baseline and Day 5 NEQ for each study arm separately.

The slope along with 95% CIs and the p-value were presented. In addition, scatterplots of each risk marker separately with NEQ, with the regression from the above model shown on the plot if there was a significant slope from the above model.

9.7.1.7.7 Ames Mutagenicity Test

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

9.7.1.7.8 Visual Inspection of the Tobacco Plugs

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

9.7.1.7.9 Filter Analysis

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

9.7.2 Post-hoc Analyses

Any post-hoc and additional exploratory analyses completed to support the planned study analyses, which were not identified in the protocol or SAP, were documented and



reported, as applicable. Any results from these unplanned analyses are described in [Section 9.8.2](#).

9.7.3 Safety Data Summary

The safety variables monitored in this study are described in [Section 9.5.2](#).

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

Adverse events reported from subjects that had a first product use, but were not randomized, were summarized in a separate study arm: “Exposed but not randomized”.

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

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

9.7.3.1 Adverse Events

All AE tables were presented by randomized arm. A general summary table of AEs was presented, including:

- The number of events and the number and percentage of subjects reporting at least 1 AE.
- The number of events and the number and percentage of subjects reporting at least 1 study product-related AE, broken down by product relatedness (related to THS 2.2/CC) and expectedness (expected for THS 2.2/CC).
- The number of events and the number and percentage of subjects reporting at least 1 AE broken down by severity including each subject only once with their worst severity.
- The number of events and the number and percentage of subjects reporting at least 1 SAE.



- The number of events and the number and percentage of subjects reporting at least 1 AE leading to any action taken, broken down by action taken related to the product (product use interrupted, product use reduced, product use stopped, not applicable, none), treatment given (yes, no), study discontinuation, other action taken.
- The number of events and the number and percentage of subjects reporting at least 1 AE related to study procedure.

Additional summary tables of AEs were presented with a breakdown of the number of events, as well as the number and percentage of subjects reporting each AE, categorized by system organ class (SOC) and preferred term (PT) coded according to MedDRA[®] (version 16.0):

- The number of events and the number and percentage of subjects reporting at least 1 AE.
- The number of events and the number and percentage of subjects with at least 1 AE related to product exposure and expectedness for IP (THS 2.2 or CC).
- The number of events and the number and percentage of subjects with at least 1 AE leading to product discontinuation or reduction.
- The number of events and the number and percentage of subjects with at least 1 AE leading to study discontinuation.
- The number of events and the number and percentage of subjects with at least 1 AE related to study procedure.
- The number of events and the number and percentage of subjects with at least 1 AE by severity (mild, moderate, severe).

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

9.7.3.2 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, which started on or after Screening. Medications that started prior to Screening and were ongoing at Screening were considered as concomitant.

All medications were listed by actual exposure using PT and ATC codes (WHO-DDE, Q1 2013). A flag was presented on the listing indicating whether the medication was prior or concomitant. Partial dates were not imputed, but assumptions were made as described in Section 12.6.4.5.1 of the SAP (see [Appendix 16.1.8](#)).



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

9.7.3.3 Laboratory Safety Parameters

Table 6 lists the hematology, clinical chemistry, and urine analysis parameters that were assessed in this study.

The grading scheme used in the common terminology criteria for adverse events and common toxicity criteria ([CTCAE], version 4.03) was used by the Principal Investigator to assess abnormal laboratory AEs. These CTCAE grades were derived programmatically in the creation of the datasets.

Laboratory data were summarized and listed at Screening, Day 0, and at Day of Discharge (Day 6 or day of withdrawal), together with changes from baseline. The number and percentage of subjects with normal results, high/low results, and abnormal clinical result (as defined by Principal Investigator comment) were tabulated for laboratory parameters.

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

9.7.3.4 Physical Examination

Physical examination data recorded at the Screening Visit, Admission (Day -2), and at the day of Discharge (Day 6 or at the day of withdrawal for withdrawn subjects) were listed by actual exposure. Subject's data with abnormal and abnormal clinically significant physical examination findings were flagged. Number of subjects (%) with normal, abnormal, and abnormal clinically significant results was tabulated by body systems at Screening, Admission, and day of Discharge.

Body weight (recorded at Admission and day of Discharge) and body height (recorded at the Screening Visit) were also listed together with BMI. Descriptive statistics of body weight, body height, and BMI, at Admission and day of Discharge, were presented.

The BMI was categorized into: underweight ($<18.5 \text{ kg/m}^2$), normal range (≥ 18.5 to $<25.0 \text{ kg/m}^2$), overweight (≥ 25.0 to $<30.0 \text{ kg/m}^2$), and obese ($\geq 30.0 \text{ kg/m}^2$).



9.7.3.5 Vital Signs

Details of the vital sign 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. Assessment after baseline included change from baseline. Descriptive statistics were presented for systolic and diastolic blood pressure, pulse rate, and respiratory rate at baseline, and on every subsequent day of the confinement period by actual exposure for each study day. Vital signs data were summarized together with changes from baseline.

9.7.3.6 Electrocardiogram

Details of the ECG assessment and timings are provided in [Section 9.5.2.5](#). Electrocardiogram data values and normality evaluations were listed by actual exposure and study day (Screening and Day 6) together with changes and shift in normality from baseline (Screening). 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 by actual exposure. Electrocardiogram data were summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal/abnormal clinically significant results.

9.7.3.7 Spirometry

The assessed spirometry parameters included:

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

The above data were collected at Screening, Day 0, and Day of Discharge (Day 6 or day of withdrawal for withdrawn subjects). At Screening, data were collected prior and post-bronchodilator, also including the brand (trade) name and dose of the bronchodilator.



Spirometry data values and normality evaluation were listed by actual exposure and study day. Assessments performed after baseline (Day 0) 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 FEV₁ (L), FEV₁ (% pred), FVC (L), FVC (% pred), and FEV₁/FVC at baseline, and Discharge by actual exposure, and overall. Spirometry data were summarized together with changes from baseline (pre-bronchodilator), and the number and percentage of subjects with normal/abnormal/abnormal clinically significant results. The post-bronchodilator data were not included in the summaries, only listed.

9.7.3.8 Medical and Surgical History

Medical history and concomitant diseases recorded at the Screening Visit were coded using MedDRA® (version 16.0) and listed separately by actual exposure, SOC, and PT within SOC.

9.7.3.9 Assessment of Cough

The cough questionnaire was completed from Day 0 to Day 6. Details of the cough assessment are provided in [Section 9.5.6.4.2](#).

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

9.7.3.10 Device Malfunction or Misuse

All events relating to the THS 2.2 device 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.

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

- Number of device events and the number and percentage of subjects reporting at least 1 device event.
- Number of device events and the number and percentage of subjects categorized by severity of device event (minor, major).
- Number of device events and the number and percentage of subjects categorized by AE relationship (related, not related).



- Number of device events and the number and percentage of subjects categorized by event description (Holder stops heating, Holder does not charge, Holder LED blinking red, smoking experience does not start, electronic malfunction, other).

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

9.7.3.11 Product Compliance

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

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

9.7.4 Interim Analyses

No interim analysis was planned or conducted for this study.

9.7.5 Determination of Sample Size

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

Sample size determination was based on the expected CV and mean ratio between THS 2.2 and the CC control arm in COHb, 3-HPMA, MHBMA, and S-PMA based on data from the YVD-CS01-EU (ClinicalTrials.gov: ID: NCT00812279) and ZRHX-EX-01 studies (ClinicalTrials.gov: ID: NCT01780714) sponsored by PMI. Based on these 2 studies, the power to demonstrate a reduction was computed ([Table 16](#)).

**Table 16 Expected Power (YVD-CS01-EU and ZRHX-EX-01 Studies Assumptions)**

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

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

9.8 Changes in the Conduct of the Study or Planned Analyses

The study was conducted according to the final protocol dated 25 April 2013. There were no protocol amendments for this study.

9.8.1 Changes in the Conduct of the Study

There were no changes in the conduct of the study.

9.8.2 Changes in the Planned Analyses

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

Shift tables for safety endpoints were not produced for this study, the relevant information was provided in listings.

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

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

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



now only investigated:

- The relationship between primary and secondary BoExp and NEQ, which will be reported in a separate report.
- The relationship between risk markers and NEQ (presented in this report).

The term “adjusted to creatinine” was replaced by “adjusted for creatinine” in all relevant endpoints and analyses.

While reviewing the values used in the graphs for BoExp in urine, it was identified that the values used as baseline in the figures were incorrect for 7 subjects. For Subjects ZRHR-REXC-03-EU-BIO-0051/0086/0123/0218/0252/0265 of the SA arm and Subjects ZRHR-REXC-03-EU-BIO-0055 of the THS 2.2 arm, the baseline value is the value on Day -1 given the following definition of baseline “Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.” Figures were drawn with Day 0 as the baseline value; whereas for these subjects Day -1 should have been used.

In addition, a minor error was noted for Listing 15.4.4.44 (Analysis of Change from Baseline QSU-brief Questionnaire Factors and Total Score - FAS) in that the listing was incorrectly numbered as Listing 15.2.4.44; however, the title of the listing was correct. Due to the minor nature of this error, the listing’s number was not corrected and is presented correctly in Section 15.4.



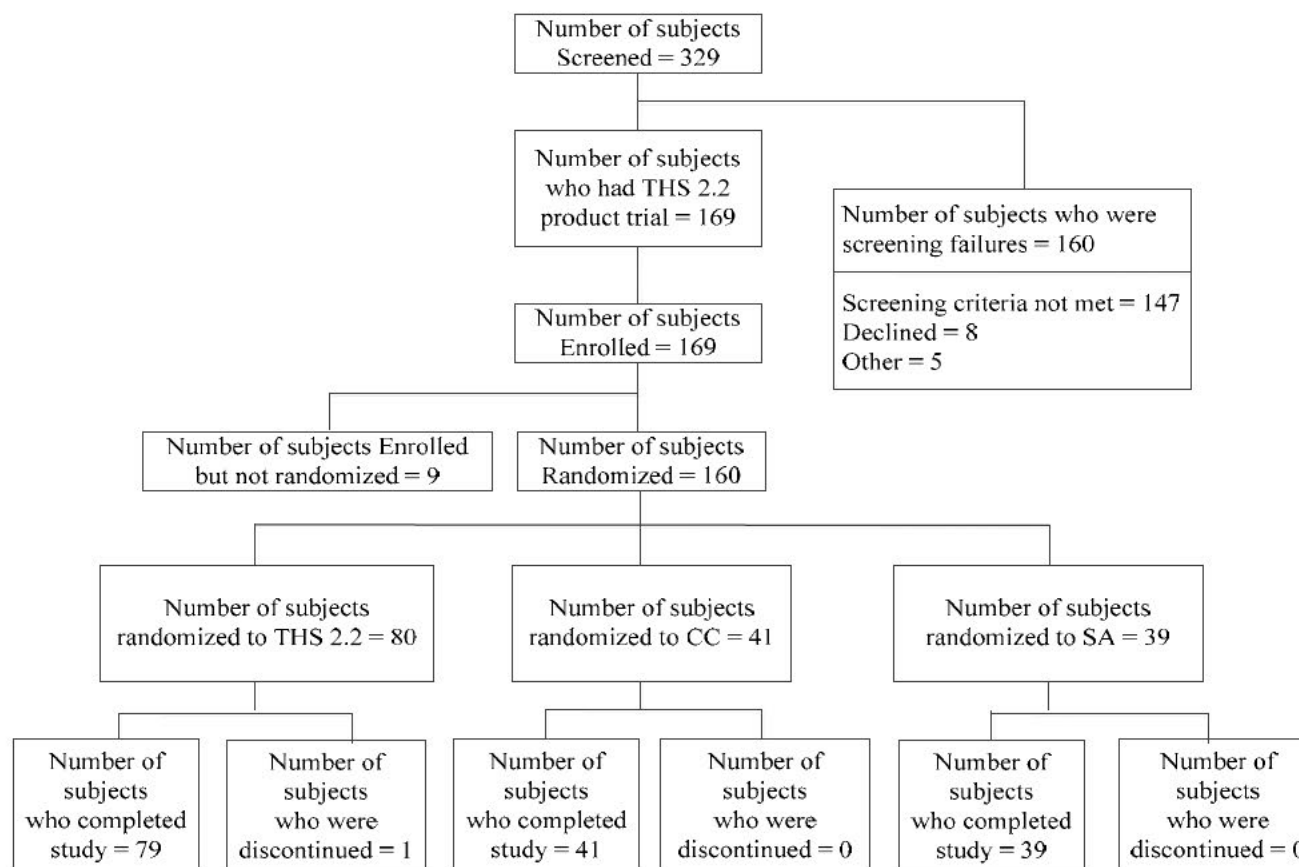
10 STUDY SUBJECTS

10.1 Disposition of Subjects

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

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

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

**Figure 2 Disposition of Subjects**

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

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



Reasons for subject discontinuation are summarized for all subjects in [Table 17](#).

Table 17 Subject Discontinuations for All Subjects

	THS 2.2 (N=80)	CC (N=41)	SA (N=39)	Overall Randomized (N=160)
Total number of discontinuations – n (%)	1 (1.3%)	0	0	1 (0.6%)
Reason for discontinuation				
Adverse events – n (%)	0	0	0	0
Protocol violation – n (%)	0	0	0	0
Withdrawal by subject – n (%)	1 (1.3%)	0	0	1 (0.6%)
Lost to follow-up – n (%)	0	0	0	0
Other – n (%)	0	0	0	0

Abbreviations: CC = conventional cigarette; N = number of subjects randomized; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

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

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

Of the 329 subjects who were screened, 169 subjects tried the THS 2.2 product during the product test, and 160 subjects were screening failures. Of the 169 subjects that tried the THS 2.2 product, 9 subjects were enrolled but were not randomized (8 subjects following abnormal assessments on Day 0 and 1 subject had weak veins), and 160 subjects were randomized.

Of the 160 subjects randomized, 80 subjects were randomized to the THS 2.2 arm, 41 subjects were randomized to the CC arm, and 39 subjects were randomized to the SA arm.

One hundred and fifty nine subjects completed the study, with 1 subject (Subject 0085 from the THS 2.2 arm) voluntarily withdrawing on Day 3 ([Appendix 15, Table 15.2.1.2](#)).

10.2 Protocol Deviations

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

The number and percent of subjects with major and minor protocol deviations are summarized in [Appendix 15, Table 15.2.1.3](#) and shown in [Table 18](#).

**Table 18 Protocol Deviations**

	THS 2.2 (N=80)	CC (N=41)	SA (N=39)	Exposed Not Randomized (N=9)	Overall Safety (N=169)
Number (%) of subjects with:					
Major protocol deviations	1 (1.3%)	0	0	0	1 (0.6%)
Protocol violation	1 (1.3%)	0	0	0	1 (0.6%)
Minor protocol deviations	32 (40.0%)	18 (43.9%)	18 (46.2%)	8 (88.9%)	76 (45.0%)
Time schedule deviation	26 (32.5%)	14 (34.1%)	15 (38.5%)	1 (11.1%)	56 (33.1%)
Procedure violation	16 (20.0%)	9 (22.0%)	4 (10.3%)	8 (88.9%)	37 (21.9%)
Assessment missing	1 (1.3%)	0	4 (10.3%)	0	5 (3.0%)

Abbreviations: CC = conventional cigarette; N = number of subjects; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

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

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

One major protocol deviation was reported during the study. Subject 0153 (THS 2.2 arm) had a post-bronchodilator FEV₁ which was <80% predicted value (78%) at Screening, and therefore should have not been enrolled onto the study. It was decided that even though FEV₁ was marginally below 80%, the subject's FEV₁/FVC was >75%, which did not meet the criteria for obstruction. In addition, a reversibility test was negative and the result was assessed as normal. It was decided that this deviation would not impact the evaluability of the primary endpoints in this study, so subject was not excluded.

Minor protocol deviations relating to timing windows of assessments, minor procedure violations, or missing assessments were reported.

10.3 Data Sets Analyzed

The number of subjects in each analysis population are summarized in [Table 19](#).

**Table 19 Summary of Analysis Populations by Stratification Factors and Product**

	THS 2.2 (N=80)	CC (N=41)	SA (N=39)	FAS Population (N=160)	Overall Safety (N=169)
Sex					
Male, n (%)	39 (48.8%)	21 (51.2%)	20 (51.3%)	80 (50.0%)	85 (50.3%)
Female, n (%)	41 (51.3%)	20 (48.8%)	19 (48.7%)	80 (50.0%)	84 (49.7%)
Daily CC consumption at Screening					
10 to 19 cig/day, n (%)	41 (51.3%)	21 (51.2%)	19 (48.7%)	81 (50.6%)	84 (49.7%)
>19 cig/day, n (%)	39 (48.8%)	20 (48.8%)	20 (51.3%)	79 (49.4%)	85 (50.3%)

Abbreviations: CC = conventional cigarette; FAS = full analysis set; N = number of subjects; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

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

The FAS and PP populations both consisted of 160 subjects. As there was no difference between the FAS and PP population for this study, the PP population was not analyzed and the primary endpoints were analyzed using the FAS population only. The FAS population consisted of 80 subjects in the THS 2.2 arm, 41 subjects in the CC arm, and 39 subjects in the SA arm.

The safety endpoints were analyzed using the Safety population. The Safety population consisted of 169 subjects: 160 randomized subjects and 9 non-randomized subjects. The non-randomized subjects included into the Safety population consisted of the 9 enrolled but not randomized subjects who had the THS 2.2 product test on Day -2.

The distribution of male and female subjects and daily CC consumption of 10 to 19 and >19 cigarettes/day was comparable between the THS 2.2, CC, and SA arms. Within each of the male and female sub-populations, there were no major differences in the distribution of high and low CC consumers (see [Appendix 15, Table 15.2.1.4.2.1](#) and [Table 15.2.1.4.2.2](#)).

10.4 Demographics and Other Baseline Characteristics

10.4.1 Demographics

Subject demographic data are listed in [Appendix 15, Listing 15.3.1.6](#), and are summarized along with baseline characteristics data for the safety and FAS populations in [Appendix 15, Table 15.2.1.4.1](#) and [Table 15.2.1.4.2](#), respectively.

An overview of demography and baseline characteristics is shown for the safety and FAS populations in [Table 20](#).

**Table 20 Summary of Demographic Data**

Variable		THS 2.2 (N=80)	CC (N=41)	SA (N=39)	FAS Population (N=160)	Overall Safety (N=169)
Race						
White	n (%)	80 (100%)	41 (100%)	39 (100%)	160 (100%)	169 (100%)
Age (years)	Mean (SD)	35.4 (9.40)	32.6 (10.06)	33.6 (11.51)	34.3 (10.12)	34.8 (10.51)
	Median	32.5	29.0	29.0	31.5	32.0
	Min, Max	22, 59	21, 59	21, 60	21, 60	21, 60
Height (m)	Mean (SD)	1.722 (0.0918)	1.710 (0.0926)	1.707 (0.1060)	1.715 (0.0953)	1.713 (0.0948)
	Median	1.710	1.700	1.720	1.710	1.710
	Min, Max	1.57, 2.00	1.52, 1.87	1.51, 1.88	1.51, 2.00	1.51, 2.00
Weight (kg)	Mean (SD)	72.72 (11.708)	76.05 (14.579)	72.52 (11.614)	73.52 (12.491)	73.56 (12.627)
	Median	70.65	75.40	72.90	72.90	72.90
	Min, Max	49.7, 103.4	48.2, 106.0	52.3, 99.0	48.2, 106.0	48.2, 106.0
BMI (kg/m ²)	Mean (SD)	24.46 (3.034)	25.80 (3.228)	24.81 (2.505)	24.89 (3.001)	24.96 (3.055)
	Median	24.35	26.00	24.60	24.70	24.70
	Min, Max	18.9, 31.6	18.8, 31.8	20.3, 31.6	18.8, 31.8	18.8, 31.8

Abbreviations: BMI = body mass index; CC = conventional cigarette; FAS = full analysis set; Max = maximum; Min = minimum; N = number of subjects; SA = smoking abstinence; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

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

All subjects were White, with a comparable mean age, height, weight, and BMI between the THS 2.2, CC, and SA arms.

Baseline BMI data are further summarized in [Appendix 15, Table 15.2.1.4.1](#) and [Table 15.2.1.4.2](#) by the following categories: underweight (<18.5 kg/m²), normal range (≥18.5 to <25.0 kg/m²), overweight (≥25.0 to <30.0 kg/m²), and obese (≥30.0 kg/m²).

10.4.2 Medical and Surgical History

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

Seventy-three subjects (43.2%) had medical history findings at Screening; 33 subjects (41.3%) in the THS 2.2 arm, 17 subjects (41.5%) in the CC arm, 18 subjects (46.2%) in the SA arm, and 5 of the enrolled not randomized subjects (55.6%).

The most frequent medical history findings by SOC were injury, poisoning, and procedural complications (19 subjects [23.8%] in the THS 2.2 arm, 9 subjects [22.0%] in the CC arm, 5 subjects [12.8%] in the SA arm, and 2 of the enrolled not randomized subjects [22.2%]).



and surgical and medical procedures (14 subjects [17.5%] in the THS 2.2 arm, 8 subjects [19.5%] in the CC arm, 9 subjects [23.1%] in the SA arm, and 3 of the enrolled not randomized subjects [33.3%]).

The most frequent medical history findings by PT were appendicectomy (6 subjects [7.5%] in the THS 2.2 arm, 2 subjects [4.9%] in the CC arm, 4 subjects [10.3%] in the SA arm, and 1 enrolled not randomized subject [11.1%]); clavicle fracture (1 subject [1.3%] in the THS 2.2 arm, 3 subjects [7.3%] in the CC arm, and 1 subject [2.6%] in the SA arm); scar (4 subjects [5.0%] in the THS 2.2 arm and 1 subject [2.6%] in the SA arm); and caesarean section (3 subjects [3.8%] in the THS 2.2 arm and 2 subjects [4.9%] in the CC arm).

No notable differences were observed between study arms with regard to medical history and there were no medical history findings of clinical concern.

10.4.3 CYP2A6 Activity at Baseline

Cytochrome P450 2A6 activity in plasma at Day 0 is listed by subject in [Appendix 15, Listing 15.3.6.15](#) and summarized for the Safety and FAS populations in [Appendix 15, Table 15.2.1.4.1](#) and [Table 15.2.1.4.2](#).

No relevant differences were observed between the 3 study arms, with regard to baseline CYP2A6 activity.

Overall, the 160 randomized subjects in the FAS population had a mean baseline CYP2A6 activity of 42.096% (SD = 15.3945%; minimum = 6.68%; maximum = 79.21%). Furthermore, no relevant differences were observed between males and females or between subjects who smoked 10 to 19 CC/day and >19 CC/day.

10.4.4 Fagerström Test for Nicotine Dependence at Screening

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

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

The distribution of subjects in each classification category, and the mean total scores were comparable between study arms. Overall, the majority of enrolled subjects (49.7%) had an FTND overall classification of moderate. Forty-six subjects (27.2%) had an FTND overall classification of severe: 20 subjects in the THS 2.2 arm, 10 subjects in the CC arm, 12 subjects in the SA arm, and 4 enrolled not randomized subjects. Of the 42 randomized subjects with an FTND classification of severe, 20 were male and 22 were female and 13 subjects smoked 10 to 19 cigarettes/day and 29 subjects smoked >19 cigarettes/day.



10.4.5 Current Cigarette Brand Consumption

The current CC brand(s) smoked by the subject, including brand name, ISO tar, nicotine, and CO yields, as recorded at the Screening Visit and at Admission, are listed by study arm in [Appendix 15, Listing 15.3.1.2](#).

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

The current CC brand names recorded at Admission (Day -2) are summarized in [Appendix 15, Table 15.2.1.5](#).

The majority of enrolled subjects smoked cigarettes with an ISO tar yield of 6 to 8 mg (100 subjects, 59.2%). In general, the distribution of subjects in each ISO tar yield category was comparable between the THS 2.2, CC, and SA arms. However, the number of male subjects who smoked cigarettes with an ISO tar yield of 1 to 5 mg was lower than the number of female subjects for all study arms, with male subjects accounting for only 2 of the 17 randomized subjects in this category.

10.4.6 Smoking History and Willingness to Quit Smoking

Smoking history responses (including “plan to quit smoking in next 3 months” responses) at the Screening Visit and at Admission (Day -2), are listed by study arm in [Appendix 15, Listing 15.3.1.3](#).

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

The number of cigarettes smoked per day on average during the previous 4 weeks as reported during Screening, 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 19](#) in [Section 10.3](#).



10.4.7 Other Baseline Data

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

- Chest X-ray findings at the Screening Visit were normal for 164 subjects; 5 subjects had findings of abnormal, not clinically significant.
- Urine cotinine screen at the Screening Visit and at Admission (Day -2) were positive for all enrolled subjects.
- Urine drug screen and alcohol breath test at the Screening Visit and at Admission were negative for all enrolled subjects.
- Serology tests at the Screening Visit: tests for HbsAg, hepatitis C virus, and HIV 1/2 antibody were negative for all enrolled subjects.
- Urine pregnancy test results at the Screening Visit, Admission, and at the Day of Discharge were negative for all 84 enrolled female subjects.

10.4.8 Concomitant Diseases

Concomitant diseases are presented by subject in [Appendix 15, Listing 15.3.1.8.2](#) and summarized by SOC for the Safety population in [Appendix 15, Table 15.2.1.7](#) and in [Table 21](#).

**Table 21 Concomitant Diseases by System Organ Class (Safety Population)**

System Organ Class	Study Arm			Enrolled not Randomized (N=9)	Overall Safety (N=169)
	THS 2.2 (N=80)	CC (N=41)	SA (N=39)		
Number (%) subjects with any concomitant disease	27 (33.8%)	9 (22.0%)	13 (33.3%)	3 (33.3%)	52 (30.8%)
Eye disorders	14 (17.5%)	3 (7.3%)	3 (7.7%)	1 (11.1%)	21 (12.4%)
Immune system disorders	4 (5.0%)	3 (7.3%)	3 (7.7%)	1 (11.1%)	11 (6.5%)
Injury, poisoning, and procedural complications	3 (3.8%)	1 (2.4%)	5 (12.8%)	0	9 (5.3%)
Skin and subcutaneous tissue disorders	3 (3.8%)	0	1 (2.6%)	0	4 (2.4%)
Social circumstances	1 (1.3%)	1 (2.4%)	1 (2.6%)	0	3 (1.8%)
Respiratory, thoracic, and mediastinal disorders	1 (1.3%)	0	1 (2.6%)	1 (11.1%)	3 (1.8%)
Surgical and medical procedures	2 (2.5%)	0	0	0	2 (1.2%)
Blood and lymphatic system disorders	0	0	1 (2.6%)	0	1 (0.6%)
Gastrointestinal disorders	1 (1.3%)	0	0	0	1 (0.6%)
Infections and infestations	1 (1.3%)	0	0	0	1 (0.6%)
Musculoskeletal and connective tissue disorders	0	1 (2.4%)	0	0	1 (0.6%)
Neoplasms benign, malignant, unspecified	0	1 (2.4%)	0	0	1 (0.6%)

Abbreviations: CC = conventional cigarette; N = number of subjects; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

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

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

Fifty-two (30.8%) of the 169 enrolled subjects had concomitant disease findings at Screening (defined as any condition that started prior to the Screening Visit and was still ongoing at the Screening Visit).

The incidence of concomitant diseases was lower in the CC arm (9 subjects [22.0%]) than in the THS 2.2 or SA arms, however, the difference in prevalence of concomitant diseases was not of concern for the analysis of study results.

The most frequent concomitant disease by PT were hypermetropia (7 subjects [8.8%] in the THS 2.2 arm, 1 subject [2.4%] in the CC arm, and 1 subject [2.6%] in the SA arm); myopia (5 subjects [6.3%] in the THS 2.2 arm, 1 subject [2.4%] in the CC arm, 2 subjects [5.1%] in



the SA arm, and 1 enrolled not randomized subject [11.1%]); and scar (3 subjects [3.8%] in the THS 2.2 arm, 1 subject [2.4%] in the CC arm, and 3 subjects [7.7%] in the SA arm).

10.4.9 Prior and Concomitant Medications

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

Prior medications are summarized by ATC in [Appendix 15, Table 15.2.6.11.1](#) and [Table 22](#), and by preferred drug name in [Appendix 15, Table 15.2.6.11.2](#). Concomitant medications are summarized by ATC in [Appendix 15, Table 15.2.6.12.1](#) and by preferred drug name in [Appendix 15, Table 15.2.6.12.2](#).

**Table 22 Prior Medications (Safety Population)**

ATC1 ATC2	Study Arm			Exposed not Randomized (N=9)	Overall Safety (N=169)
	THS 2.2 (N=80)	CC (N=41)	SA (N=39)		
Number (%) subjects with any prior medication	7 (8.8%)	1 (2.4%)	4 (10.3%)	1 (11.1%)	13 (7.7%)
Musculoskeletal system	3 (3.8%)	1 (2.4%)	1 (2.6%)	0	5 (3.0%)
Anti-inflammatory and antirheumatic products	3 (3.8%)	1 (2.4%)	1 (2.6%)	0	5 (3.0%)
Nervous system	1 (1.3%)	0	2 (5.1%)	0	3 (1.8%)
Analgesics	1 (1.3%)	0	0	0	1 (0.6%)
Anesthetics	0	0	1 (2.6%)	0	1 (0.6%)
Psychoanaleptics	0	0	1 (2.6%)	0	1 (0.6%)
Respiratory system	2 (2.5%)	0	0	0	2 (1.2%)
Antihistamines for systemic use	1 (1.3%)	0	0	0	1 (0.6%)
Cough and cold preparations	1 (1.3%)	0	0	0	1 (0.6%)
Anti-infectives for systemic use	0	0	0	1 (11.1%)	1 (0.6%)
Antibacterials for systemic use	0	0	0	1 (11.1%)	1 (0.6%)
Genitourinary system and sex hormones	0	0	1 (2.6%)	0	1 (0.6%)
Sex hormones and modulators of the genital system	0	0	1 (2.6%)	0	1 (0.6%)
Various	1 (1.3%)	0	0	0	1 (0.6%)
Unspecified herbal and traditional medicine	1 (1.3%)	0	0	0	1 (0.6%)

Abbreviations: ATC = Anatomical Therapeutic Chemical; CC = conventional cigarette; N = number of subjects; SA = smoking abstinence THS 2.2 = Tobacco Heating System 2.2.

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

Data Source: [Appendix 15, Table 15.2.6.11.1](#).

The only prior medications taken by more than 1 subject were anti-inflammatory and antirheumatic products (ibuprofen) which were used for the treatment of headaches.

Concomitant medications taken are summarized in [Table 23](#).

**Table 23 Concomitant Medications (Safety Population)**

ATC1 ATC2	Study Arm			Exposed not Randomized (N=9)	Overall Safety (N=169)
	THS 2.2 (N=80)	CC (N=41)	SA (N=39)		
Number (%) subjects with any concomitant medication	11 (13.8%)	9 (22.0%)	10 (25.6%)	3 (33.3%)	33 (19.5%)
Nervous system	7 (8.8%)	7 (17.1%)	8 (20.5%)	3 (33.3%)	25 (14.8%)
Analgesics	7 (8.8%)	7 (17.1%)	8 (20.5%)	3 (33.3%)	25 (14.8%)
Alimentary tract and metabolism	2 (2.5%)	1 (2.4%)	1 (2.6%)	1 (11.1%)	5 (3.0%)
Drugs for constipation	1 (1.3%)	1 (2.4%)	0	1 (11.1%)	3 (1.8%)
Drugs for functional gastrointestinal disorders	1 (1.3%)	0	1 (2.6%)	0	2 (1.2%)
Cardiovascular system	0	1 (2.4%)	1 (2.6%)	1 (11.1%)	3 (1.8%)
Vasoprotectives	0	1 (2.4%)	1 (2.6%)	0	2 (1.2%)
Calcium channel blockers	0	0	0	1 (11.1%)	1 (0.6%)
Respiratory system	1 (1.3%)	1 (2.4%)	1 (2.6%)	0	3 (1.8%)
Cough and cold preparations	1 (1.3%)	1 (2.4%)	0	0	2 (1.2%)
Nasal preparations	0	0	1 (2.6%)	0	1 (0.6%)
Throat preparations	0	0	1 (2.6%)	0	1 (0.6%)
Musculoskeletal system	1 (1.3%)	1 (2.4%)	0	0	2 (1.2%)
Anti-inflammatory and antirheumatic products	1 (1.3%)	1 (2.4%)	0	0	2 (1.2%)
Dermatologicals	1 (1.3%)	0	0	0	1 (0.6%)
Antiseptics and disinfectants	1 (1.3%)	0	0	0	1 (0.6%)
Various	1 (1.3%)	0	0	0	1 (0.6%)
Unspecified herbal and traditional medicine	1 (1.3%)	0	0	0	1 (0.6%)

Abbreviations: ATC = Anatomical Therapeutic Chemical; CC = conventional cigarette; N = number of subjects; SA = smoking abstinence THS 2.2 = Tobacco Heating System 2.2.

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

Data Source: [Appendix 15, Table 15.2.6.12.1](#).

The most common concomitant medications were analgesics, which were taken by 25 subjects (7 subjects [8.8%] in the THS 2.2 arm, 7 subjects [17.1%] in the CC arm, 8 subjects [20.5%] in the SA arm, and 3 subjects [33.3%] who were enrolled but not randomized). None of the AEs that required treatment with analgesics were related to IP use.

All other concomitant medications were taken by a maximum of 1 subject in each study arm.



The assessment of prior and concomitant medication indicated that no medications were administered which had an impact on CYP2A6 activity, while 1 enrolled not randomized subject (Subject 0247) took amlodipine which is known to affect CYP1A2 activity ([Appendix 15, Listing 15.3.6.3.1](#) and [Listing 15.3.6.3.2](#)).

10.5 Extent of Exposure to Investigational Product

Details of the subjects' daily consumption of CC, including *ad libitum* use on Day -2 to Day 0 are presented in [Appendix 15, Listing 15.3.2.1.1](#). Details of subject's THS Tobacco Stick daily consumption, including the product test at Admission, are presented in [Appendix 15, Listing 15.3.2.1.2](#).

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

All randomized subjects completed the product test at Day -2. The majority of subjects (126 subjects, 74.6%) used only 1 THS Tobacco Stick, while 31 subjects (18.3%) used 2 THS Tobacco Sticks, and 12 subjects (7.1%) used 3 THS Tobacco Sticks.

All subjects received the IP according to the randomization schedule. The number of THS Tobacco Sticks and CC consumed during the study are summarized for the Safety population in [Table 24](#).

Table 24 Number of THS Tobacco Sticks and Conventional Cigarettes Consumed Daily (Safety Population)

Study Arm	Visit	Number of Subjects	Mean (SD)	Min	Median	Max
THS 2.2	Day 0 (baseline, CC use)	80	16.0 (3.45)	9	16.0	33
	Day 1	80	14.9 (6.14)	5	14.0	50
	Day 2	80	17.3 (6.25)	6	17.0	40
	Day 3	80	18.2 (5.94)	6	17.0	38
	Day 4	79	18.5 (6.69)	9	17.0	50
	Day 5	79	20.7 (8.09)	9	20.0	60
CC	Day 0 (baseline)	41	16.2 (4.05)	10	16.0	32
	Day 1	41	14.5 (3.63)	6	14.0	22
	Day 2	41	15.1 (3.79)	8	15.0	24
	Day 3	41	14.9 (3.49)	8	15.0	22
	Day 4	41	14.3 (3.43)	8	14.0	21
	Day 5	41	16.6 (3.79)	10	16.0	26

Abbreviations: CC = conventional cigarette; Max = maximum; Min = minimum; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

Data Source: [Appendix 15, Table 15.2.2.1](#).



In the THS 2.2 arm, the mean number of THS Tobacco Sticks consumed daily initially decreased from the number of CC smoked at baseline (16.0 cigarettes/day) to Day 1 (14.9 sticks/day) before increasing again over Day 2 to Day 5, with the number of THS Tobacco Sticks used from Day 2 onwards being greater than the number of CC smoked at baseline.

In the CC arm, the mean number of CC consumed daily initially decreased from baseline (16.2 cigarettes/day) to Day 1 before increasing again over Day 2 to Day 5, and was comparable to the baseline value at Day 5 (16.6 cigarettes/day).

On Day 1 to Day 5, subjects in the THS 2.2 arm consumed more THS Tobacco Sticks than the number of CC smoked in the CC arm.

10.6 Compliance to Investigational Product

Compliance was ensured by strict distribution of the products (product-by-product) and collection of THS Tobacco Sticks and CC butts during the entire confinement period. In addition, in the SA arm, compliance was chemically verified using an exhaled CO breath test.

The exhaled CO levels (ppm) for subjects in the SA arm on Days 1 to 5 are listed in [Appendix 15, Listing 15.3.3.2](#), with levels >10 ppm considered as non-compliant. Descriptive statistics of compliance are presented in [Appendix 15, Table 15.2.5.1](#).

In the SA arm, all subjects had exhaled levels of CO \leq 10 ppm by 04:00 PM to 06:00 PM on Day 1 and were compliant for the remainder of the study.



11 ENDPOINT EVALUATIONS AND ADDITIONAL ANALYSES

11.1 Analysis of Primary Endpoints

The primary endpoints for this study were assessed on Day 5 for the BoExp COHb in blood (% saturation of hemoglobin) in the evening between 08:00 PM and 10:00 PM; MHBMA urinary concentration adjusted for creatinine (pg/mg creat); 3-HPMA urinary concentration adjusted for creatinine (ng/mg creat); and S-PMA urinary concentration adjusted for creatinine (pg/mg creat).

As there was no difference between the FAS and PP population for this study, the PP population was not assessed.

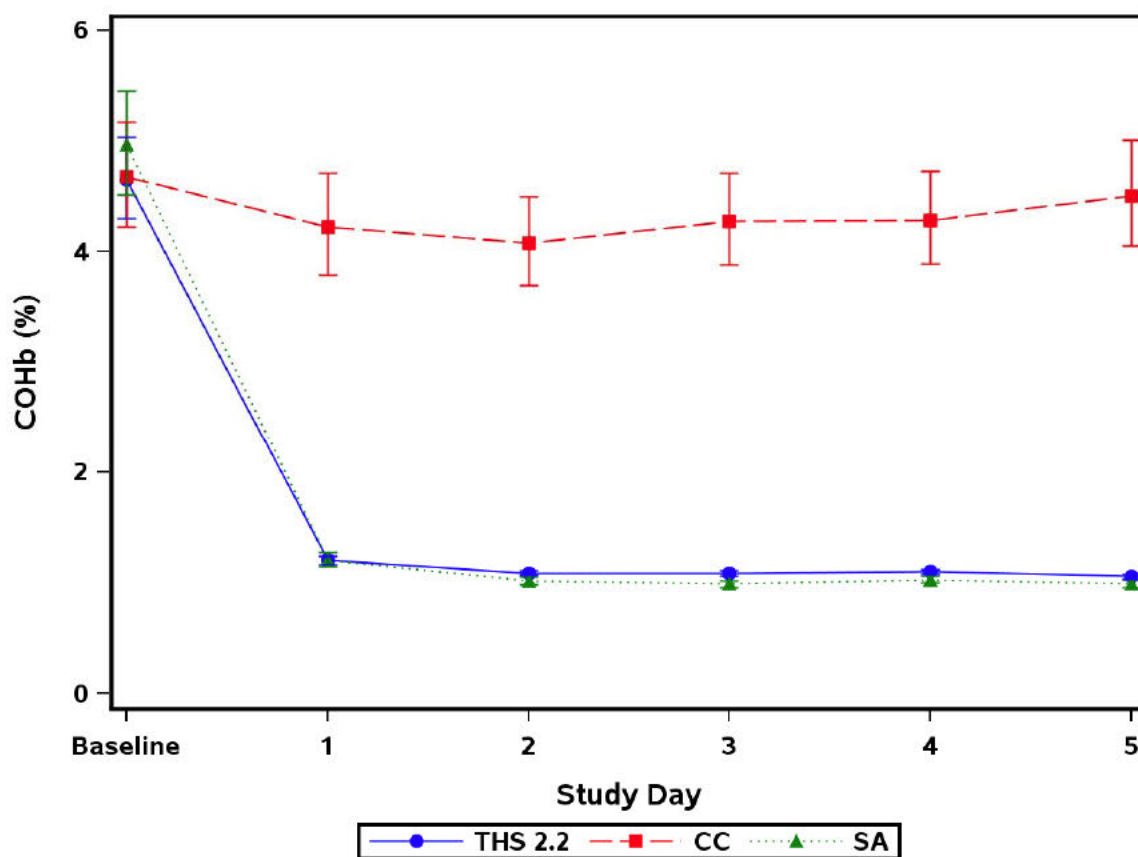
To assist with the interpretation, the profiles for SA for the primary endpoints are included with those of the THS 2.2 and CC arms, and are described the primary endpoint section. The statistical analysis of COHb, MHBMA, 3-HBMA, and S-PMA versus SA is described in [Section 11.2.1](#).

11.1.1 Carboxyhemoglobin in Whole Blood (% of Saturation of Hemoglobin)

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

Descriptive statistics of COHb assessment data during the course of the study are provided in [Appendix 15, Table 15.2.3.6](#) and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.6.1](#) and [Table 15.2.3.6.2](#), respectively. Geometric mean and 95% CIs for evening COHb are presented graphically in [Appendix 15, Figure 15.1.1.1](#) and [Figure 3](#).

Figure 3 Geometric Mean Evening COHb in Whole Blood (%) During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.1.1](#).

[Table 25](#) presents the result of the COHb assessments at each time point by study arm.

**Table 25 COHb in Whole Blood (%) Assessments by Study Arm During the Course of the Study (FAS Population)**

Study Arm	Visit	Number of	Geometric		Min	Median	Max
		Subjects	Mean	CV (%)			
THS 2.2	Baseline	80	4.65	36.82	1.6	4.55	9.3
	Day 1	80	1.20	14.65	0.9	1.20	1.9
	Day 2	80	1.09	9.51	0.8	1.10	1.4
	Day 3	79	1.08	10.15	0.8	1.10	1.3
	Day 4	79	1.10	8.42	0.9	1.10	1.3
	Day 5, 15 min < T ₀	79	1.11	10.62	0.9	1.10	1.4
	Day 5, 12:00-02:00 PM	79	1.11	10.47	0.9	1.10	1.5
	Day 5, 04:00-06:00 PM	79	1.07	10.38	0.8	1.10	1.4
	Day 5, 08:00-10:00 PM	79	1.06	9.44	0.9	1.10	1.4
CC	Baseline	41	4.68	33.09	2.6	4.70	11.2
	Day 1	40	4.22	35.05	2.7	3.90	10.8
	Day 2	41	4.08	31.99	2.3	4.10	7.7
	Day 3	41	4.28	31.49	2.6	4.30	10.2
	Day 4	41	4.29	31.56	2.7	4.20	8.1
	Day 5, 15 min < T ₀	41	2.65	30.15	1.8	2.50	5.8
	Day 5, 12:00-02:00 PM	41	4.24	36.43	2.4	4.40	9.4
	Day 5, 04:00-06:00 PM	41	4.55	29.88	2.7	4.70	8.9
	Day 5, 08:00-10:00 PM	41	4.51	34.27	2.7	4.80	10.1
SA	Baseline	39	4.96	29.60	2.5	5.00	8.8
	Day 1	39	1.21	15.87	0.8	1.20	1.6
	Day 2	39	1.01	11.08	0.7	1.00	1.2
	Day 3	39	0.99	9.39	0.7	1.00	1.2
	Day 4	39	1.03	9.28	0.8	1.00	1.2
	Day 5, 08:00-10:00 AM	39	1.08	9.67	0.8	1.10	1.2
	Day 5, 12:00-02:00 PM	39	1.03	10.81	0.8	1.00	1.3
	Day 5, 04:00-06:00 PM	39	1.02	9.67	0.7	1.00	1.2
	Day 5, 08:00-10:00 PM	39	0.99	10.39	0.7	1.00	1.2

Abbreviations: CC = conventional cigarette; CV = coefficient of variation; Max = maximum; Min = minimum; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.3.6](#).

The changes from baseline data throughout the study are summarized in [Appendix 15, Table 15.2.3.6](#), and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.6.1](#), and [Table 15.2.3.6.2](#), respectively. The change from baseline data on Day 5 for evening COHb are summarized in [Appendix 15, Table 15.2.3.5](#) and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.5.1](#), and [Table 15.2.3.5.2](#), respectively.

[Table 26](#) presents overall change from baseline in COHb assessment data by study arm.

**Table 26 Percent Change from Baseline in COHb in Whole Blood (%) by Study Arm During the Course of the Study (FAS Population)**

Study Arm	Visit	Number of Subjects	Arithmetic				
			Mean	SD	Min	Median	Max
THS 2.2	Day 1	80	-72.99	8.641	-87.5	-74.75	-37.5
	Day 2	80	-75.18	9.330	-88.6	-76.34	-37.5
	Day 3	79	-75.62	8.825	-88.6	-76.47	-42.9
	Day 4	79	-75.17	9.165	-88.6	-76.19	-37.5
	Day 5, 15 min < T ₀	79	-74.98	9.036	-89.2	-76.19	-38.1
	Day 5, 12:00-02:00 PM	79	-75.02	8.591	-89.2	-76.09	-42.9
	Day 5, 04:00-06:00 PM	79	-75.82	8.649	-89.2	-77.55	-43.8
	Day 5, 08:00-10:00 PM	79	-76.20	8.498	-90.3	-77.78	-42.9
CC	Day 1	40	-8.86	17.945	-44.9	-10.39	39.0
	Day 2	41	-11.13	17.306	-41.0	-14.58	30.8
	Day 3	41	-6.73	18.804	-41.9	-10.42	51.4
	Day 4	41	-7.02	15.513	-37.8	-8.00	37.1
	Day 5, 15 min < T ₀	41	-42.07	12.675	-63.5	-44.74	-5.7
	Day 5, 12:00-02:00 PM	41	-7.56	19.283	-40.0	-11.76	52.4
	Day 5, 04:00-06:00 PM	41	-0.98	19.661	-32.4	-5.26	51.4
	Day 5, 08:00-10:00 PM	41	-1.16	22.649	-42.9	-9.38	62.9
SA	Day 1	39	-74.94	6.434	-84.1	-76.00	-56.0
	Day 2	39	-78.76	6.140	-89.8	-79.59	-60.0
	Day 3	39	-79.29	5.928	-89.8	-79.59	-63.3
	Day 4	39	-78.39	6.307	-88.6	-79.07	-60.0
	Day 5, 08:00-10:00 AM	39	-77.37	6.523	-88.6	-77.78	-63.3
	Day 5, 12:00-02:00 PM	39	-78.36	6.148	-88.6	-78.43	-64.0
	Day 5, 04:00-06:00 PM	39	-78.74	5.867	-88.6	-79.59	-64.0
	Day 5, 08:00-10:00 PM	39	-79.24	5.676	-88.6	-79.07	-66.7

Abbreviations: CC = conventional cigarette; Max = maximum; Min = minimum; SA = smoking abstinence; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.3.6](#).

The profile of the mean evening COHb in the THS 2.2 arm was comparable to that of the SA arm.

Geometric mean COHb values decreased in the THS 2.2 arm from baseline (4.65%) to Day 5 (1.06%) compared to COHb values in the CC arm, which remained similar at baseline (4.68%) and Day 5 (4.51%). These values correspond to percent changes from baseline of -76.20% and -1.16% for the THS 2.2 and CC arms, respectively, with the majority of the decrease from baseline in the THS 2.2 arm achieved by Day 1 (-72.99%). In the SA arm, mean COHb values decreased from baseline (4.96%) to Day 5 (0.99%), as expected, which corresponded to a -79.24% change from baseline.



Mean COHb levels were higher for male subjects than female subjects in the CC arm and at baseline (*ad libitum* CC use) for the THS 2.2 and SA arms. Once THS 2.2 use or SA began, there were no notable differences between male and female subjects.

In the THS 2.2 and SA arms, mean COHb levels were higher for subjects who smoked >19 cigarettes than for subjects who smoked 10 to 19 cigarettes per day at baseline (*ad libitum* CC use) only. Once THS 2.2 use or SA began, there were no discernible differences between the 2 subgroups. For subjects in the CC arm, there was no discernible difference in mean COHb between the 10 to 19 cigarettes and the >19 cigarettes subgroups throughout the study.

Analysis of evening blood COHb (%) for THS 2.2 users versus CC on Day 5 is presented in [Appendix 15, Table 15.2.3.1](#) and [Table 27](#).

Table 27 Analysis of Evening Blood COHb (%) versus CC on Day 5 (FAS Population)

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean		CV (%)	95% CI	p-value
			Ratio (THS 2.2:CC) (%)				
THS 2.2	79	1.06	23.45		16.84	22.00, 24.99	<.001
CC	41	4.53					

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

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

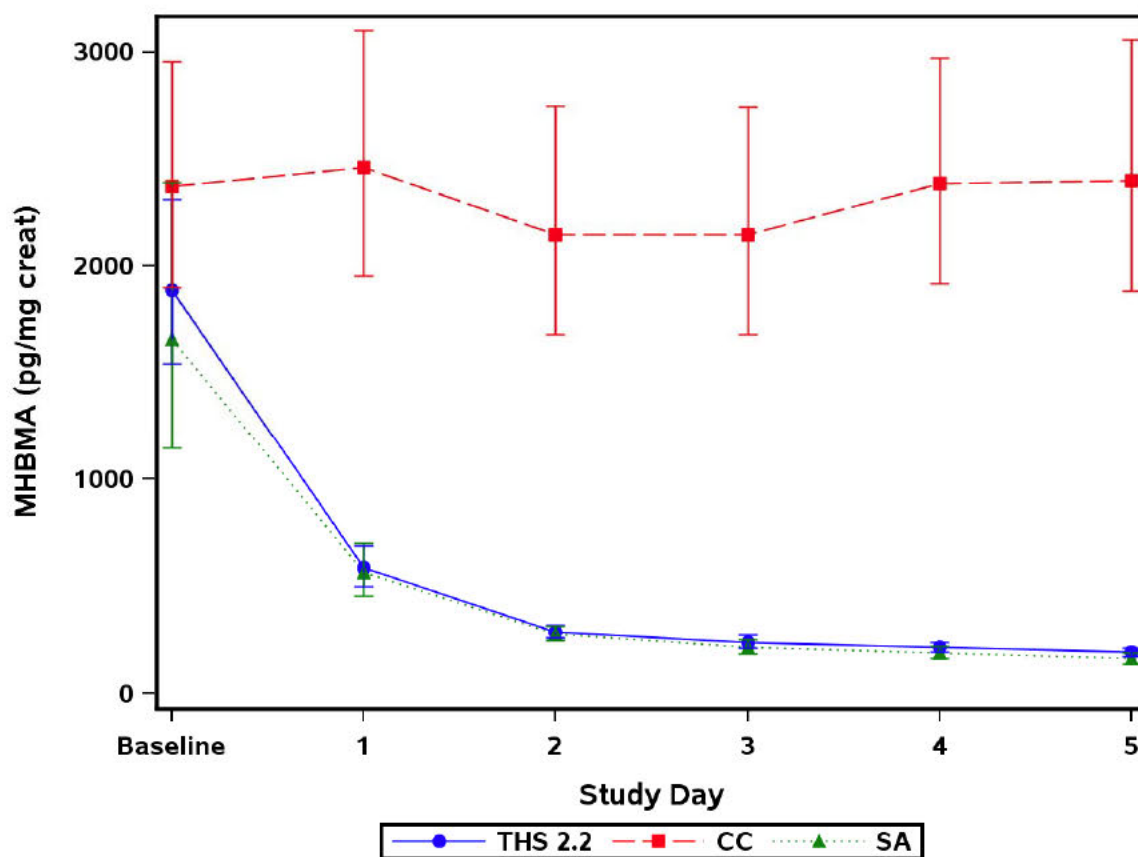
On Day 5 (evening), the LS mean level of COHb in subjects who switched to THS 2.2 use was 76.55% lower than that of subjects who continued to smoke CC ($p < .001$). This result is consistent with the study hypothesis in demonstrating a >50% reduction in COHb in the THS 2.2 arm compared to the CC arm.

11.1.2 Monohydroxybutenyl Mercapturic Acid in 24-hour Urine (Concentration Adjusted for Creatinine)

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 15.2.3.7](#) and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.7.1](#) and [Table 15.2.3.7.2](#), respectively. Geometric mean and 95% CIs for MHBMA concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.2](#) and [Figure 4](#).

Figure 4 Geometric Mean MHBMA Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

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

[Table 28](#) presents the absolute values for the MHBMA assessments by study arm.

**Table 28 Absolute Values of MHBMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm (FAS Population)**

Study Arm	Visit	Number of Geometric		CV (%)	Min	Median	Max
		Subjects	Mean				
THS 2.2	Baseline	80	1888.27	113.08	231.9	2310.34	7218.5
	Day 1	80	586.07	83.32	52.9	617.09	3777.4
	Day 2	80	288.75	48.27	84.9	297.32	2363.6
	Day 3	79	240.84	59.39	54.9	257.38	5461.0
	Day 4	79	215.96	47.00	61.3	250.61	412.2
	Day 5	79	192.93	46.00	62.8	203.08	384.6
CC	Baseline	41	2317.31	78.67	311.7	2500.00	7533.3
	Day 1	41	2459.59	84.32	327.9	2581.30	6974.4
	Day 2	41	2147.45	91.56	208.0	2413.79	6588.6
	Day 3	41	2147.10	90.66	141.2	2442.59	7064.1
	Day 4	41	2387.21	78.35	341.9	2551.96	7171.1
	Day 5	41	2399.40	89.21	155.8	2547.17	7163.6
SA	Baseline	39	1699.39	147.05	221.7	2455.66	6886.5
	Day 1	39	563.81	75.86	133.7	614.82	1677.1
	Day 2	39	278.79	36.08	106.6	278.11	517.1
	Day 3	39	216.01	48.38	79.2	223.88	571.8
	Day 4	39	189.81	51.44	71.9	202.03	439.1
	Day 5	39	163.17	54.22	68.7	183.12	431.1

Abbreviations: CC = conventional cigarette; CV = coefficient of variation; Max = maximum; Min = minimum; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.3.7](#).

The changes from baseline for MHBMA concentration adjusted for creatinine are summarized in [Appendix 15, Table 15.2.3.7](#) and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.7.1](#) and [Table 15.2.3.7.2](#), respectively. The change from baseline data on Day 5 for MHBMA concentration adjusted for creatinine are summarized in [Appendix 15, Table 15.2.3.5](#) and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.5.1](#) and [Table 15.2.3.5.2](#), respectively.

[Table 29](#) presents overall change from baseline in MHBMA concentration adjusted for creatinine data by study arm.

**Table 29 Percent Change from Baseline MHBMA Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm (FAS Population)**

Study Arm	Visit	Number of		SD	Min	Median	Max
		Subjects	Arithmetic Mean				
THS 2.2	Day 1	80	-66.19	15.575	-84.4	-70.95	-9.6
	Day 2	80	-79.01	19.183	-95.9	-87.39	-9.3
	Day 3	79	-80.74	20.935	-98.3	-89.97	13.4
	Day 4	79	-83.20	16.333	-98.6	-90.31	-32.5
	Day 5	79	-84.98	14.906	-98.1	-92.03	-41.6
CC	Day 1	41	9.20	27.237	-34.0	5.21	102.2
	Day 2	41	-1.07	31.864	-87.2	-2.26	97.4
	Day 3	41	2.35	31.773	-97.3	1.05	77.5
	Day 4	41	6.32	26.218	-51.9	1.86	54.4
	Day 5	41	6.89	26.158	-50.0	5.28	55.1
SA	Day 1	39	-61.84	24.692	-82.0	-70.64	35.8
	Day 2	39	-72.07	32.632	-97.2	-87.06	24.1
	Day 3	39	-76.13	29.126	-98.1	-90.22	11.0
	Day 4	39	-75.76	33.253	-98.0	-91.24	17.8
	Day 5	39	-79.56	27.037	-98.1	-92.83	-6.4

Abbreviations: CC = conventional cigarette; Max = maximum; Min = minimum; SA = smoking abstinence; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.3.7](#).

The profile of the mean MHBMA urinary concentration adjusted for creatinine in the THS 2.2 arm was comparable to that of the SA arm.

Geometric mean MHBMA values decreased in the THS 2.2 arm from baseline (1888.27 pg/mg creat) to Day 5 (192.93 pg/mg creat) compared to MHBMA in the CC arm, which remained comparable to baseline (2317.31 pg/mg creat) at Day 5 (2399.40 pg/mg creat). These values correspond to percent changes from baseline of -84.98% and 6.89% for the THS 2.2 and CC arms, respectively, with most of the decrease from baseline in the THS 2.2 arm achieved by Day 2 (-79.01%). In the SA arm, mean MHBMA values decreased from baseline (1699.39 pg/mg creat) to Day 5 (163.17 pg/mg creat), as expected, which corresponded to a -79.56% change from baseline. Most of the decrease from baseline was achieved by Day 2 (-72.07%).

In the THS 2.2 arm, mean MHBMA values were higher for female subjects at all time points. In the CC arm, MHBMA values tended to be greater for male subjects (a difference of $\leq 20\%$ at all time points). For the SA arm, MHBMA values were higher for female subjects but only up to Day 2 after which the values were comparable between males and females.



In the THS 2.2 arm, MHBMA values were higher throughout the study for subjects who smoked >19 cigarettes than for subjects who smoked 10 to 19 cigarettes per day. In the CC arm, there was no notable difference between the 10 to 19 cigarettes and the >19 cigarettes subgroups throughout the study. For the SA arm, there was no notable difference between the 10 to 19 cigarettes and the >19 cigarettes subgroups until Days 3 to 5, when MHBMA values were higher for the >19 cigarettes subgroup.

Analysis of MHBMA urinary concentration adjusted for creatinine for THS 2.2 use versus CC use on Day 5 is presented [Appendix 15, Table 15.2.3.2](#) and [Table 30](#).

Table 30 Analysis of MHBMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) versus CC on Day 5 (FAS Population)

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean		CV (%)	95% CI	p-value
			Ratio (THS 2.2:CC) (%)				
THS 2.2	79	194.05	8.38		54.57	6.89, 10.20	<.001
CC	41	2314.37					

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC 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](#).

On Day 5, the LS mean level of MHBMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 91.62% lower than that of subjects who continued to smoke CC ($p < .001$). This result is consistent with the study hypothesis in demonstrating a >50% reduction in MHBMA urinary concentration adjusted for creatinine in the THS 2.2 arm compared to the CC arm.

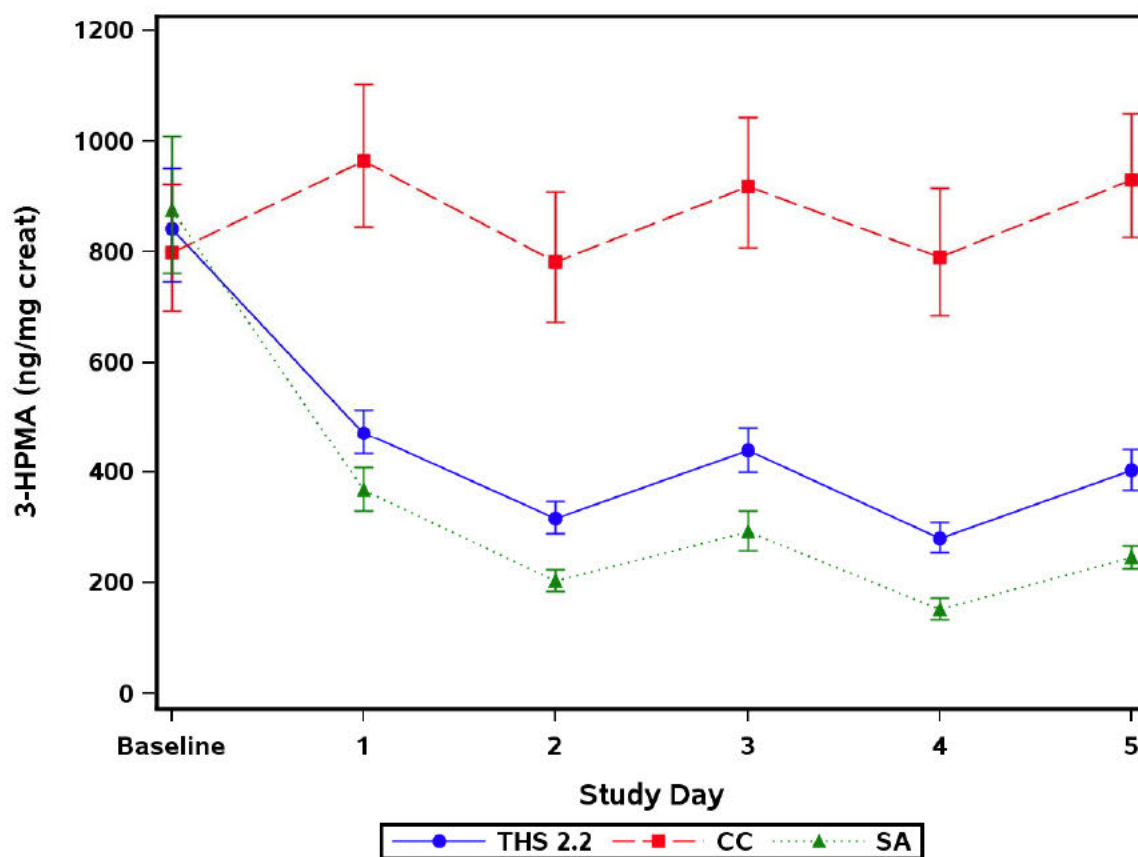
11.1.3 3-hydroxypropylmercapturic Acid 24-hour Urine (Concentration Adjusted for Creatinine)

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 15.2.3.8](#) and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.8.1](#), and [Table 15.2.3.8.2](#), respectively. Geometric mean and 95% CIs for 3-HPMA concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.3](#) and [Figure 5](#).



Figure 5 Geometric Mean 3-HPMA Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.1.3.](#)

[Table 31](#) presents the absolute values for the 3-HPMA assessments by study arm.

**Table 31 Absolute Values of 3-HPMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) by Study Arm (FAS Population)**

Study Arm	Visit	Number of Subjects	Geometric		Min	Median	Max
			Mean	CV (%)			
THS 2.2	Baseline	80	841.84	58.66	94.6	827.47	2495.7
	Day 1	80	472.09	39.66	82.2	489.90	953.7
	Day 2	80	316.19	44.03	53.7	335.41	730.6
	Day 3	79	438.42	43.74	38.8	442.88	1671.4
	Day 4	79	280.73	45.11	33.7	271.63	597.0
	Day 5	79	402.26	43.36	36.8	413.67	1261.8
CC	Baseline	41	799.37	47.28	287.9	837.67	2246.7
	Day 1	41	964.92	44.15	427.8	973.03	2102.3
	Day 2	41	781.80	50.32	191.2	818.53	1646.6
	Day 3	41	917.63	42.58	493.0	1001.95	1932.0
	Day 4	41	791.20	48.33	318.5	854.77	1806.9
	Day 5	41	931.01	39.44	451.6	941.04	1896.6
SA	Baseline	39	861.88	47.34	352.7	899.03	2530.7
	Day 1	39	367.06	33.84	174.5	380.74	794.7
	Day 2	39	202.82	29.97	66.1	198.10	351.1
	Day 3	39	292.06	39.26	74.1	304.24	532.2
	Day 4	39	152.31	41.31	67.2	152.17	354.1
	Day 5	39	245.69	25.98	126.9	240.26	436.5

Abbreviations: CC = conventional cigarette; CV = coefficient of variation; Max = maximum; Min = minimum; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.3.8](#).

The changes from baseline for 3-HPMA concentration adjusted for creatinine are summarized in [Appendix 15, Table 15.2.3.8](#) and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.8.1](#) and [Table 15.2.3.8.2](#), respectively. The change from baseline data on Day 5 for 3-HPMA concentration adjusted for creatinine are summarized in [Appendix 15, Table 15.2.3.5](#) and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.5.1](#) and [Table 15.2.3.5.2](#), respectively.

[Table 32](#) presents overall change from baseline in 3-HPMA concentration adjusted for creatinine data by study arm.

**Table 32 Percent Change from Baseline 3-HPMA Concentration Adjusted for Creatinine (ng/mg creat) by Study Arm (FAS Population)**

Study Arm	Visit	Number of		Arithmetic			
		Subjects	Mean	SD	Min	Median	Max
THS 2.2	Day 1	80	-39.99	25.202	-70.1	-47.28	77.1
	Day 2	80	-59.83	15.846	-86.3	-62.25	13.1
	Day 3	79	-44.78	24.495	-83.4	-49.14	83.6
	Day 4	79	-63.96	19.119	-84.1	-68.07	35.7
	Day 5	79	-49.68	20.696	-73.9	-54.93	44.6
CC	Day 1	41	24.37	32.093	-26.6	15.91	114.1
	Day 2	41	1.68	27.193	-67.8	-2.52	66.2
	Day 3	41	20.14	36.678	-57.9	15.50	132.4
	Day 4	41	2.12	25.821	-45.1	-0.67	62.3
	Day 5	41	20.28	31.247	-44.8	9.38	115.1
SA	Day 1	39	-55.29	13.894	-80.8	-57.06	-24.2
	Day 2	39	-74.40	9.906	-91.5	-75.16	-55.3
	Day 3	39	-63.74	12.889	-90.4	-65.40	-36.5
	Day 4	39	-81.04	6.873	-94.1	-81.89	-65.5
	Day 5	39	-69.45	11.761	-85.8	-72.54	-44.5

Abbreviations: CC = conventional cigarette; Max = maximum; Min = minimum; SA = smoking abstinence; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.3.8](#).

The profile of the mean 3-HPMA concentration adjusted for creatinine in the THS 2.2 arm followed a similar pattern to that of the SA arm, with an initial maximum decrease observed at Day 2 before fluctuating between Days 3, 4, and 5.

Geometric mean 3-HPMA values decreased in the THS 2.2 arm from baseline (841.84 ng/mg creat) to Day 5 (402.26 ng/mg creat) compared to 3-HPMA in the CC arm, which fluctuated from baseline (799.37 ng/mg creat) to Day 5 (931.01 ng/mg creat). These values correspond to percent changes from baseline of -49.68% and -20.28% for the THS 2.2 and CC arms, respectively, with the greatest decrease from baseline in the THS 2.2 arm achieved on Day 4 (-63.96%). In the SA arm, mean 3-HPMA values decreased from baseline (861.88 ng/mg creat) to Day 5 (245.69 ng/mg creat), as expected, which corresponded to a -69.45% change from baseline, although the greatest decrease was observed on Day 4 (-81.04%).

In the THS 2.2 arm, mean 3-HPMA values were comparable for male and female subjects. In the CC and SA arms, 3-HPMA values tended to be greater for female subjects.

In all study arms, 3-HPMA values were higher throughout the study for subjects who smoked >19 cigarettes than for subjects who smoked 10 to 19 cigarettes per day.



Analysis of 3-HPMA urinary concentration adjusted for creatinine for THS 2.2 use versus CC use on Day 5 is presented in [Appendix 15, Table 15.2.3.3](#) and [Table 33](#).

Table 33 Analysis of 3-HPMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) versus CC on Day 5 (FAS Population)

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean		CV (%)	95% CI	p-value
			Ratio (THS 2.2:CC) (%)				
THS 2.2	79	398.87	41.63		26.10	37.75, 45.91	<.001
CC	41	958.03					

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC 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 15.2.3.3](#).

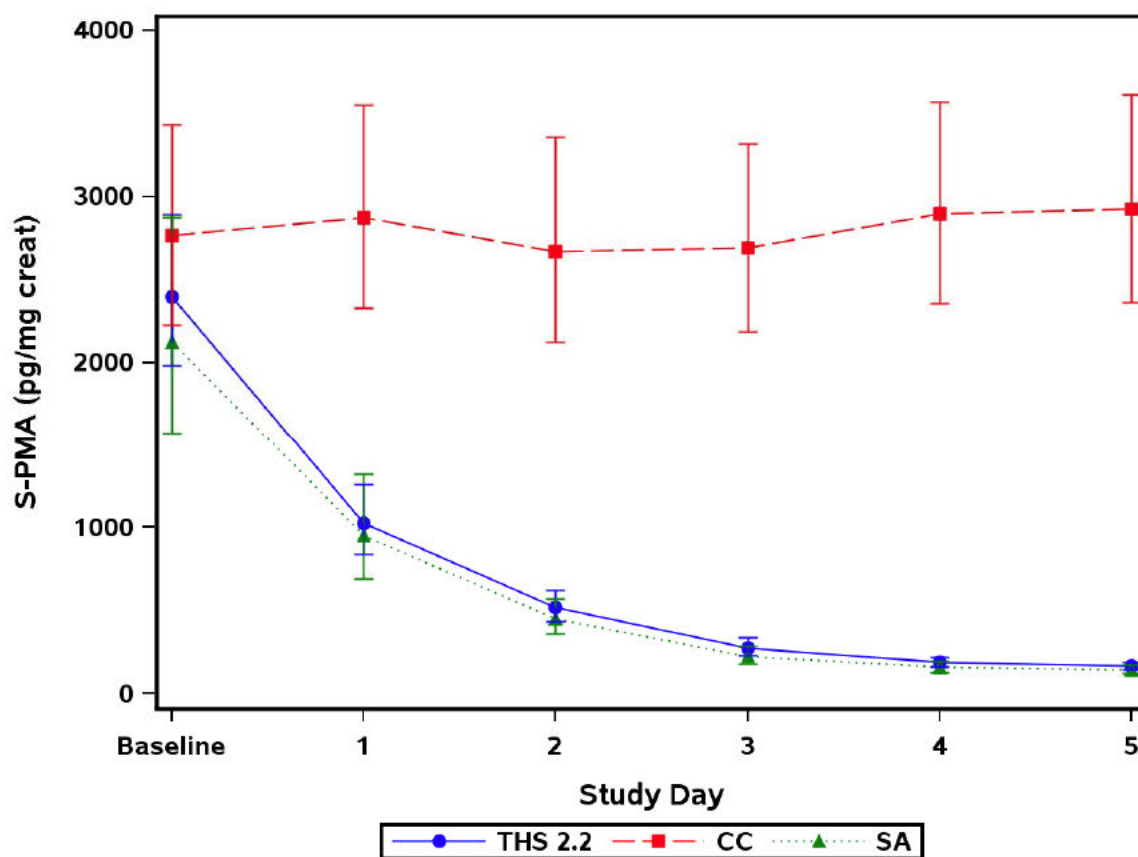
On Day 5, the LS mean level of 3-HPMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 58.37% lower than that of subjects who continued to smoke CC ($p < .001$). This result is consistent with the study hypothesis in demonstrating a >50% reduction in 3-HPMA urinary concentration adjusted for creatinine in the THS 2.2 arm compared to the CC arm.

11.1.4 S-phenylmercapturic Acid 24-hour Urine (Concentration Adjusted for Creatinine)

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 15.2.3.9](#) and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.9.1](#) and [Table 15.2.3.9.2](#), respectively. Geometric mean and 95% CIs for S-PMA concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.1.4](#) and [Figure 6](#).

Figure 6 Geometric Mean S-PMA Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.1.4](#).

[Table 34](#) presents the absolute values for the S-PMA assessments by study arm.

**Table 34 Absolute Values of S-PMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm (FAS Population)**

Study Arm	Visit	Number of Subjects	Geometric Mean	CV (%)	Min	Median	Max
THS 2.2	Baseline	80	2394.03	102.40	395.9	2582.08	11111.1
	Day 1	80	1024.34	114.28	130.5	1252.76	4554.9
	Day 2	80	518.55	93.26	96.5	597.58	3355.4
	Day 3	79	276.88	103.50	43.1	291.67	10732.9
	Day 4	79	188.72	74.72	36.3	203.43	1244.9
	Day 5	79	164.45	63.10	43.9	159.33	873.8
CC	Baseline	41	2765.20	77.42	357.1	2903.85	8830.3
	Day 1	41	2874.73	75.34	390.7	2934.58	10305.2
	Day 2	41	2667.74	83.51	299.8	2701.30	11642.4
	Day 3	41	2691.34	73.96	285.3	2877.25	9225.0
	Day 4	41	2897.36	73.70	340.5	2892.38	9258.1
	Day 5	41	2922.81	75.82	352.0	2981.82	9345.5
SA	Baseline	39	2153.82	116.41	336.7	2251.48	9539.9
	Day 1	39	953.37	132.83	161.0	1367.43	5357.1
	Day 2	39	450.61	82.26	104.7	443.62	1629.8
	Day 3	39	224.24	83.83	52.0	210.08	1149.4
	Day 4	39	158.09	75.09	54.2	142.35	690.5
	Day 5	39	143.70	53.43	67.2	142.29	509.0

Abbreviations: CC = conventional cigarette; CV = coefficient of variation; Max = maximum; Min = minimum; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.3.9](#).

The changes from baseline for S-PMA concentration adjusted for creatinine are summarized in [Appendix 15, Table 15.2.3.9](#) and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.9.1](#) and [Table 15.2.3.9.2](#), respectively. The change from baseline data on Day 5 for S-PMA concentration adjusted for creatinine are summarized in [Appendix 15, Table 15.2.3.5](#) and are summarized by sex and cigarette consumption in [Appendix 15, Table 15.2.3.5.1](#) and [Table 15.2.3.5.2](#), respectively.

[Table 35](#) presents overall change from baseline in S-PMA adjusted for creatinine data by study arm.

**Table 35 Percent Change from Baseline S-PMA Concentration Adjusted for Creatinine (pg/mg creat) by Study Arm (FAS Population)**

Study Arm	Visit	Number of	Arithmetic				
		Subjects	Mean	SD	Min	Median	Max
THS 2.2	Day 1	80	-55.62	11.952	-81.0	-57.86	-14.6
	Day 2	80	-75.73	14.618	-90.5	-79.31	-1.9
	Day 3	79	-86.71	13.679	-95.5	-89.71	25.7
	Day 4	79	-91.26	4.733	-97.3	-92.47	-76.2
	Day 5	79	-92.03	5.222	-97.7	-93.30	-75.3
CC	Day 1	41	6.93	27.319	-53.4	7.13	123.8
	Day 2	41	2.25	32.267	-78.0	-4.85	88.6
	Day 3	41	5.51	37.198	-89.2	4.63	139.1
	Day 4	41	9.62	33.161	-67.5	5.90	126.2
	Day 5	41	9.48	31.561	-46.4	4.24	127.5
SA	Day 1	39	-53.92	12.897	-79.3	-53.77	-26.6
	Day 2	39	-76.43	12.574	-91.5	-79.87	-42.1
	Day 3	39	-88.10	6.553	-96.2	-89.61	-66.5
	Day 4	39	-91.39	5.390	-97.7	-92.22	-70.5
	Day 5	39	-91.52	6.754	-97.9	-93.82	-70.9

Abbreviations: CC = conventional cigarette; Max = maximum; Min = minimum; SA = smoking abstinence; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.3.9](#).

The profile of the mean S-PMA urinary concentration adjusted for creatinine in the THS 2.2 arm was comparable to that of the SA arm.

Geometric mean S-PMA values decreased in the THS 2.2 arm from baseline (2394.03 pg/mg creat) to Day 5 (164.45 pg/mg creat) compared to S-PMA in the CC arm, which remained comparable to baseline (2765.20 pg/mg creat) at Day 5 (2922.81 pg/mg creat). These values correspond to percent changes from baseline of -92.03% and 9.48% for the THS 2.2 and CC arms, respectively. In the SA arm, mean S-PMA values decreased from baseline (2153.82 pg/mg creat) to Day 5 (143.70 pg/mg creat). For both THS 2.2 and SA arms, the decrease in S-PMA values was seen across Days 1 to 5, with the magnitude of decrease becoming less with successive days.

In the THS 2.2 and SA arms, mean S-PMA values were higher for female subjects than for male subjects. In the CC arm, S-PMA values tended to be greater for female subjects (a difference of $\leq 20\%$ at all time points).

In the THS 2.2 and SA arms, S-PMA values were higher throughout the study for subjects who smoked >19 cigarettes than for subjects who smoked 10 to 19 cigarettes per day. In the



CC arm, S-PMA values were higher throughout the study for subjects who smoked 10 to 19 cigarettes than for subjects who smoked >19 cigarettes per day..

Analysis of S-PMA urinary concentration adjusted for creatinine for THS 2.2 use versus CC use on Day 5 is presented in [Appendix 15, Table 15.2.3.4](#) and [Table 36](#).

Table 36 Analysis of S-PMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) versus CC on Day 5 (FAS Population)

Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean	CV (%)	95% CI	p-value
			Ratio (THS 2.2:CC) (%)			
THS 2.2	79	164.51	5.99	37.30	5.21, 6.87	<.001
CC	41	2748.16				

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC 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 level of S-PMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 94.01% lower than that of subjects who continued to smoke CC ($p < .001$). This result is consistent with the study hypothesis in demonstrating a >50% reduction in S-PMA urinary concentration adjusted for creatinine in the THS 2.2 arm compared to the CC arm.

11.2 Analysis of Secondary Endpoints

11.2.1 Analysis of COHb, MHBMA, 3-HPMA, and S-PMA versus Smoking Abstinence

Analyses of evening COHb and urinary concentrations of MHBMA, 3-HPMA, and S-PMA adjusted for creatinine for THS 2.2 use versus SA on Day 5 are presented in [Appendix 15, Table 15.2.4.1](#) and [Table 37](#).

**Table 37 Analysis of COHb, MHBMA, 3-HPMA, and S-PMA versus SA on Day 5 (FAS Population)**

Biomarker	Exposure	Number of Subjects	Geometric LS Mean	Geometric Mean Ratio (THS 2.2:SA) (%)	CV (%)	95% CI
Evening COHb	THS 2.2	79	1.06	108.16	16.84	101.37, 115.41
	SA	39	0.98			
Urinary MHBMA (pg/mg creat)	THS 2.2	79	194.05	115.51	54.57	94.78, 140.76
	SA	39	168.01			
Urinary 3-HPMA (ng/mg creat)	THS 2.2	79	398.87	164.44	26.10	148.90, 181.60
	SA	39	242.56			
Urinary S-PMA (pg/mg creat)	THS 2.2	79	164.51	107.06	37.30	93.08, 123.13
	SA	39	153.66			

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CI = confidence interval; COHb = carboxyhemoglobin; CV = coefficient of variation; LS = least squares; MHBMA = monohydroxy butenyl mercapturic acid; SA = smoking abstinence; S-PMA = S-phenylmercapturic acid; THS 2.2 = Tobacco Heating System 2.2.

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC 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 15.2.4.1](#).

For evening COHb on Day 5, the LS mean level in subjects who switched to THS 2.2 use was 8.16% higher than that of subjects who abstained from smoking, although the lower limit of the 95% CI was close to 100% (95% CI: 101.37, 115.41). For urinary 3-HPMA concentration adjusted for creatinine on Day 5, the LS mean level in subjects who switched to THS 2.2 use was 64.44% higher than that of subjects who abstained from smoking, with the lower limit of the 95% CI greater than 100% (95% CI: 148.90, 181.60).

There were no notable differences observed between subjects who switched to THS 2.2 and subjects who abstained from smoking for urinary concentrations of MHBMA and S-PMA adjusted for creatinine on Day 5, with the 95% CIs for both parameters spanning 100%.



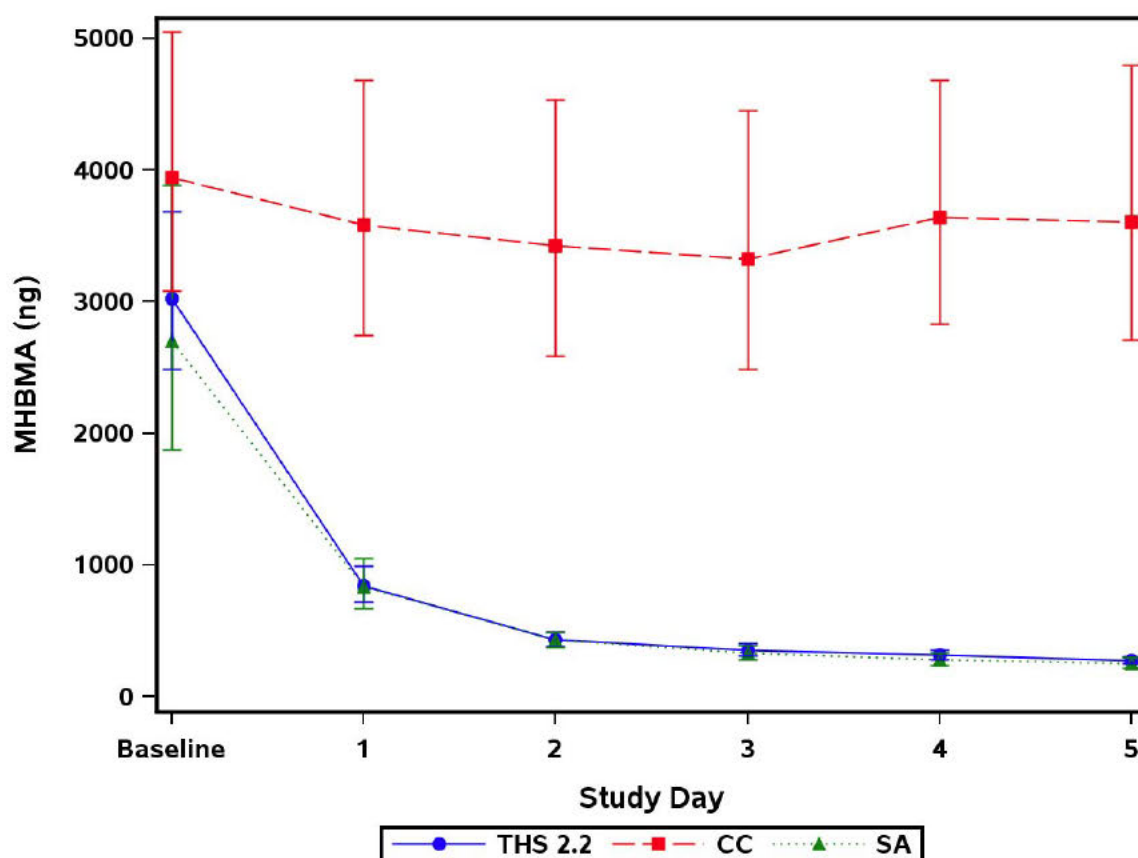
11.2.2 Urinary Quantity of MHBMA, 3-HPMA, and S-PMA Excreted Over 24 Hours

11.2.2.1 Urinary Quantity of MHBMA Excreted over 24 hours

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

Descriptive statistics of the urinary quantity of MHBMA excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.3](#). Geometric mean and 95% CIs for MHBMA (quantity excreted over 24 hours) are presented graphically in [Appendix 15, Figure 15.1.2.1](#) and [Figure 7](#).

Figure 7 Geometric Mean Urinary MHBMA Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.1](#).



Table 38 presents the absolute values for the urinary quantity of MHBMA excreted over 24 hours by study arm.

Table 38 Absolute Values of Urinary MHBMA Quantity Excreted Over 24 Hours (ng) by Study Arm (FAS Population)

Study Arm	Visit	Number of Subjects	Geometric		Min	Median	Max
			Mean	CV (%)			
THS 2.2	Baseline	80	3027.75	108.31	352.0	3974.13	13158.0
	Day 1	80	843.01	83.58	77.5	957.56	8176.0
	Day 2	80	431.84	59.44	105.0	447.53	8008.0
	Day 3	79	356.09	62.09	80.0	373.33	6930.0
	Day 4	79	315.48	48.52	90.0	351.53	690.2
	Day 5	79	277.00	44.49	112.5	301.30	647.5
CC	Baseline	41	3814.21	93.34	340.8	3760.00	15529.5
	Day 1	41	3586.22	102.47	348.3	3961.50	15060.3
	Day 2	41	3424.95	109.68	322.0	3680.00	18124.0
	Day 3	41	3324.73	116.09	132.5	3630.00	14832.0
	Day 4	41	3640.03	94.63	443.7	3726.00	17821.5
	Day 5	41	3603.43	112.80	140.0	3687.45	16351.0
SA	Baseline	39	2685.41	151.00	262.6	3078.00	13517.8
	Day 1	39	837.60	79.03	142.5	846.80	2727.0
	Day 2	39	428.89	44.78	147.5	457.30	977.6
	Day 3	39	331.38	54.55	116.3	364.00	712.4
	Day 4	39	279.30	54.17	100.0	305.10	777.8
	Day 5	39	255.97	50.13	105.0	292.60	573.2

Abbreviations: CC = conventional cigarette; CV = coefficient of variation; Max = maximum; Min = minimum; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.3](#).

The changes from baseline for the urinary quantity of MHBMA excreted over 24 hours are summarized in [Appendix 15, Table 15.2.4.3](#) and [Table 39](#).

**Table 39 Percent Change from Baseline Urinary MHBMA Quantity Excreted Over 24 Hours (ng) by Study Arm (FAS Population)**

Study Arm	Visit	Number of Subjects	Arithmetic Mean	SD	Min	Median	Max
THS 2.2	Day 1	80	-69.42	15.032	-86.1	-74.60	-6.9
	Day 2	80	-79.47	21.842	-96.4	-88.79	37.9
	Day 3	79	-81.80	20.999	-98.6	-90.53	28.4
	Day 4	79	-84.62	15.317	-98.9	-91.71	-36.5
	Day 5	79	-86.42	14.000	-97.7	-92.38	-39.8
CC	Day 1	41	-1.86	31.508	-46.3	-5.72	121.3
	Day 2	41	-0.04	44.404	-92.8	-10.01	179.8
	Day 3	41	-3.06	31.705	-97.7	-2.87	57.7
	Day 4	41	0.26	36.860	-43.0	-4.80	175.2
	Day 5	41	-0.39	34.033	-58.9	-2.70	126.0
SA	Day 1	39	-63.60	23.419	-85.6	-73.00	23.6
	Day 2	39	-71.70	33.342	-97.9	-86.84	31.3
	Day 3	39	-76.22	28.587	-98.4	-90.70	2.2
	Day 4	39	-76.73	31.183	-98.2	-93.33	7.0
	Day 5	39	-79.91	25.476	-98.2	-93.64	-16.0

Abbreviations: CC = conventional cigarette; Max = maximum; Min = minimum; SA = smoking abstinence; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.3](#).

Profiles of the mean urinary MHBMA quantity excreted over 24 hours were comparable to those of the concentrations adjusted for creatinine measured in 24 hour urine. In the THS 2.2 arm, the quantity of MHBMA excreted decreased from baseline (3027.75 ng) to Day 5 (277.00 ng) compared to MHBMA in the CC arm, which remained comparable to baseline (3814.21 ng) at Day 5 (3603.43 ng). These values correspond to percent changes from baseline of -86.42% and -0.39% for the THS 2.2 and CC arms, respectively. In the SA arm, the quantity of MHBMA excreted over 24-hours decreased from baseline (2685.41 ng) to Day 5 (255.97 ng), as expected, which corresponded to a -79.91% change from baseline.

Analyses of urinary quantity of MHBMA excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15, Table 15.2.4.2](#) and [Table 40](#).

**Table 40 Analysis of Urinary Quantity of MHBMA Excreted Over 24 Hours versus CC and SA on Day 5 (FAS Population)**

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
THS 2.2	79	279.67	8.17	0.100	6.70, 9.96
CC	41	3424.15			

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:SA) (%)	SE	95% CI
THS 2.2	79	279.67	105.95	0.102	86.73, 129.42
SA	39	263.97			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

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

As observed with the concentration adjusted for creatinine parameter measured in 24-hour urine, the LS mean level of the urinary quantity of MHBMA excreted over 24 hours on Day 5 in subjects who switched to THS 2.2 use was 91.83% lower than that of subjects who continued to smoke CC (95% CI: 90.04, 93.30).

On Day 5, the urinary quantity of MHBMA excreted over 24 hours between subjects who switched to THS 2.2 use and subjects who abstained from smoking was comparable, with the 95% CIs spanning 100%.

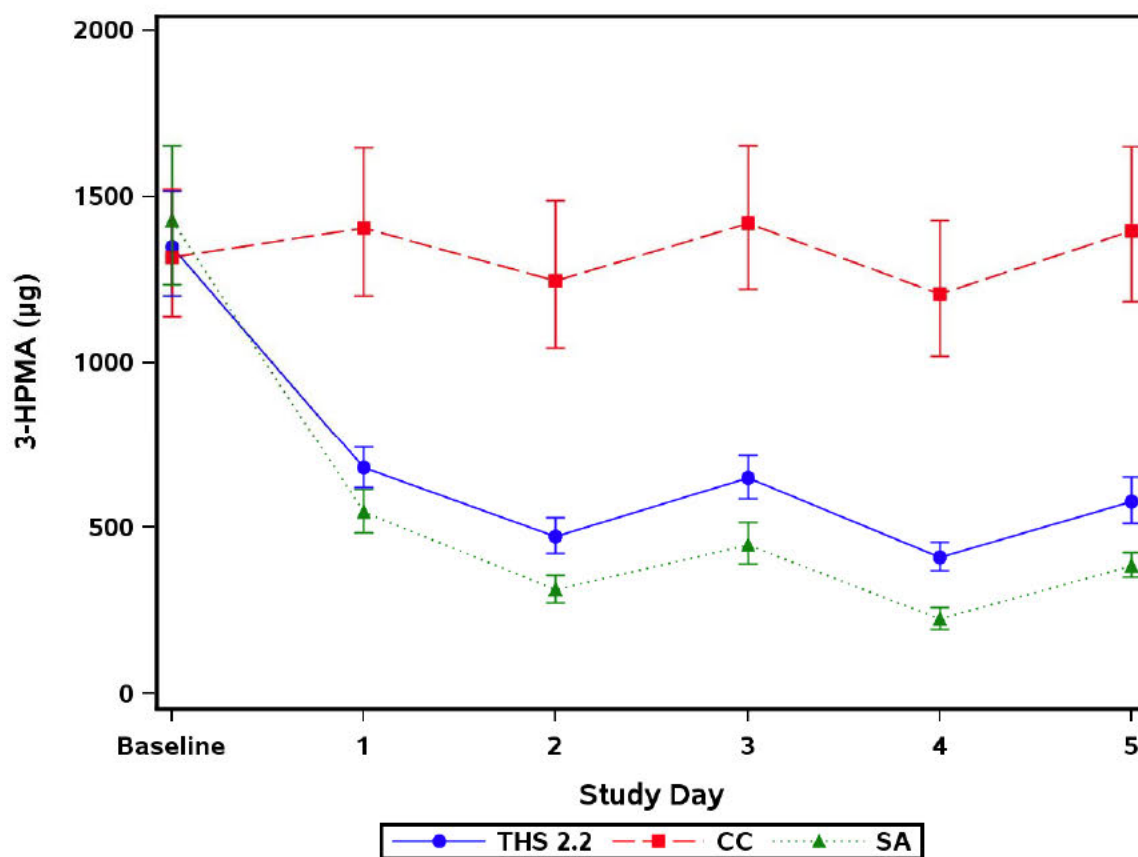
11.2.2.2 Urinary Quantity of 3-HPMA Quantity Excreted over 24 hours

Subject listings of 3-HPMA data are provided in [Appendix 15, Listing 15.3.3.1](#).

Descriptive statistics of the urinary quantity of 3-HPMA excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.4](#). Geometric mean and 95% CIs for 3-HPMA quantity excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.2](#) and [Figure 8](#).



Figure 8 Geometric Mean Urinary 3-HPMA Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.2](#).

[Table 41](#) presents the absolute values for the urinary quantity of 3-HPMA excreted over 24 hours by study arm.

**Table 41 Absolute Values of Urinary 3-HPMA Quantity Excreted Over 24 Hours (µg) by Study Arm (FAS Population)**

Study Arm	Visit	Number of Subjects	Geometric		Min	Median	Max
			Mean	CV (%)			
THS 2.2	Baseline	80	1349.85	56.09	144	1481.33	3680
	Day 1	80	679.06	41.55	102	685.90	1606
	Day 2	80	472.89	54.26	74	479.45	2475
	Day 3	79	648.21	46.89	46	679.40	2121
	Day 4	79	410.09	48.74	43	389.20	974
	Day 5	79	577.54	58.00	45	636.00	1264
CC	Baseline	41	1317.25	48.59	545	1309.38	3977
	Day 1	41	1406.91	53.32	464	1236.90	4292
	Day 2	41	1246.88	60.70	296	1086.40	3718
	Day 3	41	1420.92	50.78	485	1275.00	3875
	Day 4	41	1206.43	57.92	490	1073.50	3692
	Day 5	41	1398.20	56.32	548	1271.90	3963
SA	Baseline	39	1361.96	47.69	641	1305.50	3788
	Day 1	39	545.30	37.68	253	574.75	1159
	Day 2	39	312.02	41.30	82	318.60	596
	Day 3	39	448.05	45.32	111	491.40	1163
	Day 4	39	224.12	46.87	97	246.05	564
	Day 5	39	385.41	31.04	209	399.30	680

Abbreviations: CC = conventional cigarette; CV = coefficient of variation; Max = maximum; Min = minimum; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.4](#).

The changes from baseline for the urinary quantity of 3-HPMA excreted over 24 hours are summarized in [Appendix 15, Table 15.2.4.4](#) and [Table 42](#).

**Table 42 Percent Change from Baseline Urinary 3-HPMA Quantity Excreted Over 24 Hours (μg) by Study Arm (FAS Population)**

Study Arm	Visit	Number of Subjects	Arithmetic				
			Mean	SD	Min	Median	Max
THS 2.2	Day 1	80	-46.13	21.376	-75	-50.66	33
	Day 2	80	-61.62	20.343	-89	-64.17	72
	Day 3	79	-49.24	21.426	-84	-52.48	64
	Day 4	79	-67.07	17.144	-88	-70.38	15
	Day 5	79	-54.63	17.490	-86	-55.99	21
CC	Day 1	41	10.66	30.534	-44	3.49	96
	Day 2	41	1.88	38.960	-82	-6.48	124
	Day 3	41	12.81	33.815	-65	8.76	111
	Day 4	41	-4.65	29.949	-48	-10.39	122
	Day 5	41	10.22	32.754	-34	0.53	117
SA	Day 1	39	-57.81	14.357	-80	-60.35	-8
	Day 2	39	-74.80	10.380	-94	-75.96	-54
	Day 3	39	-64.29	14.146	-91	-64.48	-26
	Day 4	39	-82.07	7.610	-93	-82.67	-61
	Day 5	39	-69.49	11.844	-87	-72.37	-47

Abbreviations: CC = conventional cigarette; Max = maximum; Min = minimum; SA = smoking abstinence; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.4](#).

Profiles of the mean urinary 3-HPMA quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine measured in 24-hour urine. In the THS 2.2 arm, the quantity of 3-HPMA excreted over 24 hours decreased from baseline (1349.85 μg) to Day 5 (577.54 μg) compared to 3-HPMA in the CC arm, which fluctuated between baseline (1317.25 μg) and Day 5 (1398.20 μg). These values correspond to percent changes from baseline of -54.63% and 10.22% for the THS 2.2 and CC arms, respectively. In the SA arm, the quantity of 3-HPMA excreted over 24 hours decreased from baseline (1361.96 μg) to Day 5 (385.41 μg), as expected, which corresponded to a -69.49% change from baseline.

Analyses of urinary quantity of 3-HPMA excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15, Table 15.2.4.2](#) and [Table 43](#).

**Table 43 Analysis of Urinary Quantity of 3-HPMA Excreted Over 24 Hours versus CC and SA on Day 5 (FAS Population)**

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
THS 2.2	79	574.08	40.49	0.062	35.84, 45.74
CC	41	1417.81			

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:SA) (%)	SE	95% CI
THS 2.2	79	574.08	149.91	0.063	132.45, 169.66
SA	39	382.96			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

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

The LS mean of the urinary quantity of 3-HPMA excreted over 24 hours on Day 5 in subjects who switched to THS 2.2 use was 59.51% lower than that of subjects who continued to smoke CC (95% CI: 54.26, 64.16).

On Day 5, the LS mean level of the urinary quantity of 3-HPMA excreted over 24 hours in subjects who switched to THS 2.2 use was 49.91% higher than that of subjects who abstained from smoking (95% CI: 132.45, 169.66).

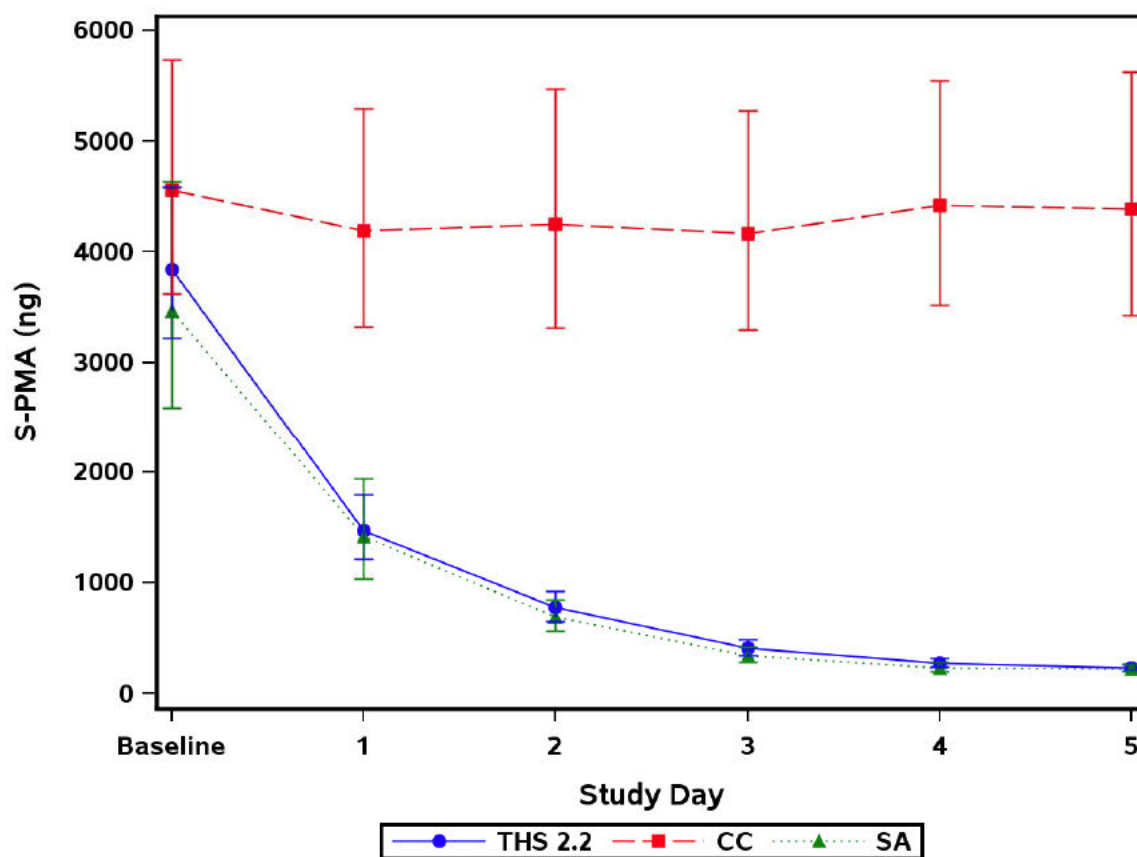
11.2.2.3 Urinary Quantity of S-PMA Quantity Excreted over 24 hours

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

Descriptive statistics of the urinary quantity of S-PMA excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.5](#). Geometric mean and 95% CIs for S-PMA quantity excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.3](#) and [Figure 9](#).



Figure 9 Geometric Mean Urinary S-PMA Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.3](#).

[Table 44](#) presents the absolute values for the urinary quantity of S-PMA excreted over 24 hours by study arm.

**Table 44 Absolute Values of Urinary S-PMA Quantity Excreted Over 24 Hours (ng) by Study Arm (FAS Population)**

Study Arm	Visit	Number of Subjects	Geometric Mean	CV (%)	Min	Median	Max
THS 2.2	Baseline	80	3838.72	94.24	552.2	4346.25	14792.0
	Day 1	80	1473.42	108.24	140.1	1639.65	6160.0
	Day 2	80	775.53	91.82	144.7	868.05	11368.0
	Day 3	79	409.37	94.75	65.0	439.20	13620.0
	Day 4	79	275.68	66.17	60.0	294.10	1197.0
	Day 5	79	236.11	60.35	35.6	249.75	1085.4
CC	Baseline	41	4556.63	83.71	390.5	5049.00	20438.3
	Day 1	41	4191.52	84.93	415.0	3892.00	17632.0
	Day 2	41	4254.75	93.92	309.0	4462.50	17755.5
	Day 3	41	4167.47	86.44	445.2	4320.00	18105.8
	Day 4	41	4417.91	82.43	442.2	4521.00	19838.0
	Day 5	41	4389.49	92.62	316.4	4216.00	21331.0
SA	Baseline	39	3403.50	115.28	467.1	4104.00	18904.0
	Day 1	39	1416.33	123.80	191.2	1717.00	5355.0
	Day 2	39	693.22	68.19	217.3	718.40	2018.8
	Day 3	39	344.02	66.61	103.1	298.80	1060.8
	Day 4	39	232.61	61.24	113.2	195.80	690.3
	Day 5	39	225.42	43.24	119.5	220.63	507.5

Abbreviations: CC = conventional cigarette; CV = coefficient of variation; Max = maximum; Min = minimum; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

The changes from baseline for the urinary quantity of S-PMA excreted over 24 hours are summarized in [Appendix 15, Table 15.2.4.5](#) and [Table 45](#).

**Table 45 Percent Change from Baseline Urinary S-PMA Quantity Excreted Over 24 Hours (ng) by Study Arm (FAS Population)**

Study Arm	Visit	Number of Arithmetic					
		Subjects	Mean	SD	Min	Median	Max
THS 2.2	Day 1	80	-59.86	12.335	-82.9	-62.03	-22.4
	Day 2	80	-76.46	17.422	-92.3	-80.14	15.1
	Day 3	79	-87.41	15.418	-96.0	-90.13	42.4
	Day 4	79	-92.03	4.354	-96.9	-93.26	-75.9
	Day 5	79	-92.84	4.598	-98.2	-94.19	-77.2
CC	Day 1	41	-4.60	27.756	-44.0	-8.65	79.3
	Day 2	41	3.52	47.697	-87.7	-7.92	186.1
	Day 3	41	-0.41	36.701	-91.1	-4.92	112.4
	Day 4	41	3.20	46.086	-50.0	-7.10	224.9
	Day 5	41	1.59	43.292	-41.7	-5.14	237.0
SA	Day 1	39	-56.15	14.131	-80.6	-59.44	-24.1
	Day 2	39	-76.65	12.685	-95.5	-80.22	-42.9
	Day 3	39	-88.47	6.128	-96.4	-89.41	-68.8
	Day 4	39	-91.89	5.132	-97.9	-92.92	-71.7
	Day 5	39	-91.65	6.187	-98.6	-93.71	-72.3

Abbreviations: CC = conventional cigarette; Max = maximum; Min = minimum; SA = smoking abstinence; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Profiles of the mean urinary S-PMA quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine measured in 24 hour urine, with the decrease in S-PMA values observed in the THS 2.2 and SA arms observed across Days 1 to 5 and the magnitude of decrease becoming less with successive days.

In the THS 2.2 arm, the quantity of S-PMA excreted over 24 hours decreased from baseline (3838.72 ng) to Day 5 (236.11 ng) compared to S-PMA in the CC arm, which remained comparable to baseline (4556.63 ng) at Day 5 (4389.49 ng). These values correspond to percent changes from baseline of -92.84% and 1.59% for the THS 2.2 and CC arms, respectively. In the SA arm, the quantity of S-PMA excreted over 24 hours decreased from baseline (3403.50 ng) to Day 5 (225.42 ng), as expected, which corresponded to a -91.65% change from baseline.

Analyses of urinary quantity of S-PMA excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15, Table 15.2.4.2](#) and [Table 46](#).

**Table 46 Analysis of Urinary Quantity of S-PMA Excreted Over 24 Hours versus CC and SA on Day 5 (FAS Population)**

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
THS 2.2	79	237.17	5.87	0.078	5.03, 6.85
CC	41	4039.58			

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:SA) (%)	SE	95% CI
THS 2.2	79	237.17	97.43	0.080	83.34, 113.89
SA	39	243.42			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

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

The LS mean of the urinary quantity of S-PMA excreted over 24 hours on Day 5 in subjects who switched to THS 2.2 use was 94.13% lower than that of subjects who continued to smoke CC (95% CI: 93.15, 94.97).

On Day 5, the urinary quantity of S-PMA excreted over 24 hours between subjects who switched to THS 2.2 use and subjects who abstained from smoking was comparable, with the 95% CIs spanning 100%.

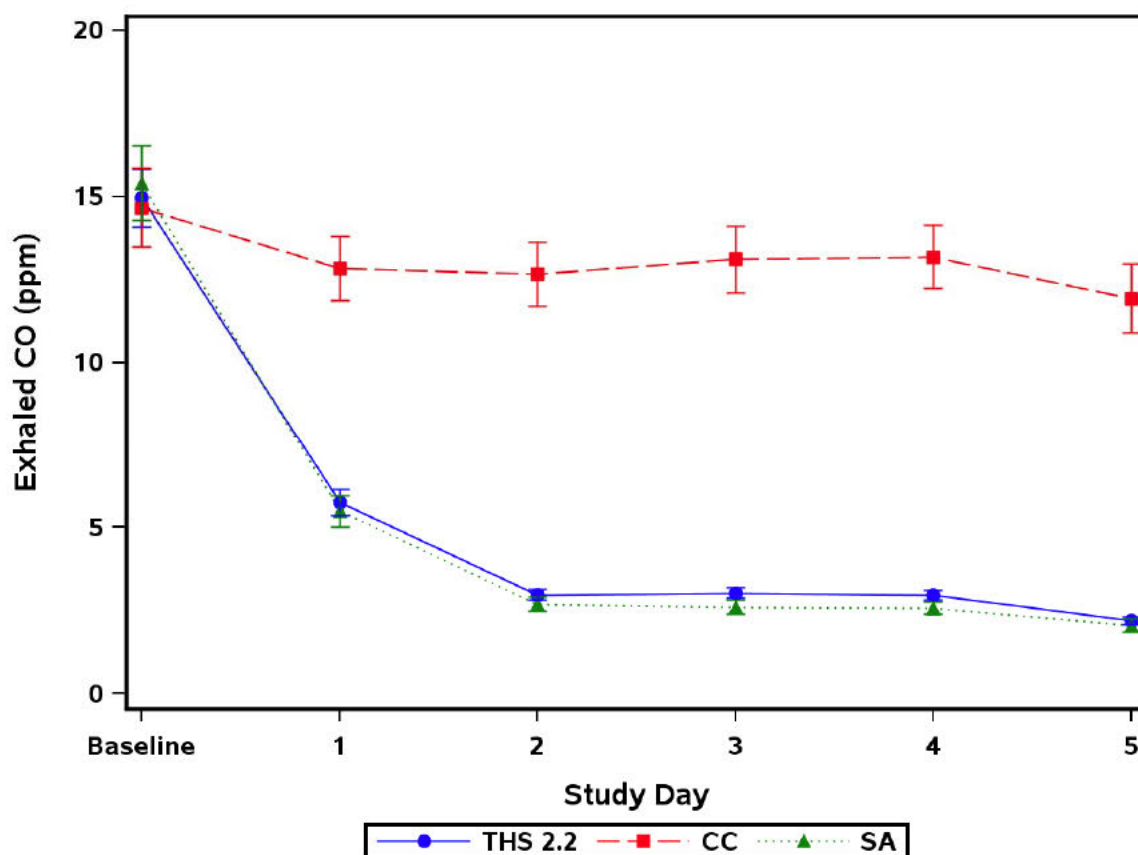
11.2.3 Other Biomarkers of Exposure

11.2.3.1 Exhaled Carbon Monoxide

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 are provided in [Appendix 15, Table 15.2.4.7](#). Descriptive statistics of time matched changes in exhaled CO are provided in [Appendix 15, Table 15.2.4.8](#). Arithmetic mean and 95% CIs for exhaled CO are presented graphically in [Appendix 15, Figure 15.1.2.4](#) and [Figure 10](#).

Figure 10 Arithmetic Mean Exhaled CO During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.4](#).

Exhaled CO values from the evening assessment (between 08:00 and 10:00 PM) are compared in the following paragraph.

The exhaled CO profiles were comparable for both THS 2.2 and SA arms, with most of the reduction in exhaled CO being achieved by Day 2 and the results plateauing thereafter. Geometric mean exhaled CO values decreased in the THS 2.2 arm from the evening of Day 0 (15.4 ppm) to the evening of Day 5 (2.0 ppm) while exhaled CO values in the CC arm remained comparable between Day 0 and Day 5 (15.6 ppm on the evening of Day 0 and 12.3 ppm on the evening of Day 5). These values correspond to percent changes from baseline of -85.48% and -16.59% for the THS 2.2 and CC arms, respectively. In the SA



arm, exhaled CO values also decreased from Day 0 (16.9 ppm) to Day 5 (2.2 ppm), as expected, which corresponded to a -88.22% change from baseline.

Analyses of exhaled CO for THS 2.2 use versus CC use and versus SA on Day 5 are presented in [Appendix 15](#), [Table 15.2.4.6](#) and [Table 47](#).

Table 47 Analysis of Exhaled CO versus CC and SA on Day 5 (FAS Population)

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
THS 2.2	73	2.03	16.48	0.085	13.95, 19.47
CC	41	12.33			

Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:SA) (%)	SE	95% CI
THS 2.2	73	2.03	96.38	0.093	80.34, 115.61
SA	32	2.11			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15](#), [Table 15.2.4.6](#).

On Day 5, the LS mean level of exhaled CO in subjects who switched to THS 2.2 use was 83.52% lower than that of subjects who continued to smoke CC (95% CI: 80.53, 86.05).

On Day 5, the levels of exhaled CO between subjects who switched to THS 2.2 and subjects who abstained from smoking were comparable, with the 95% CIs spanning 100%.

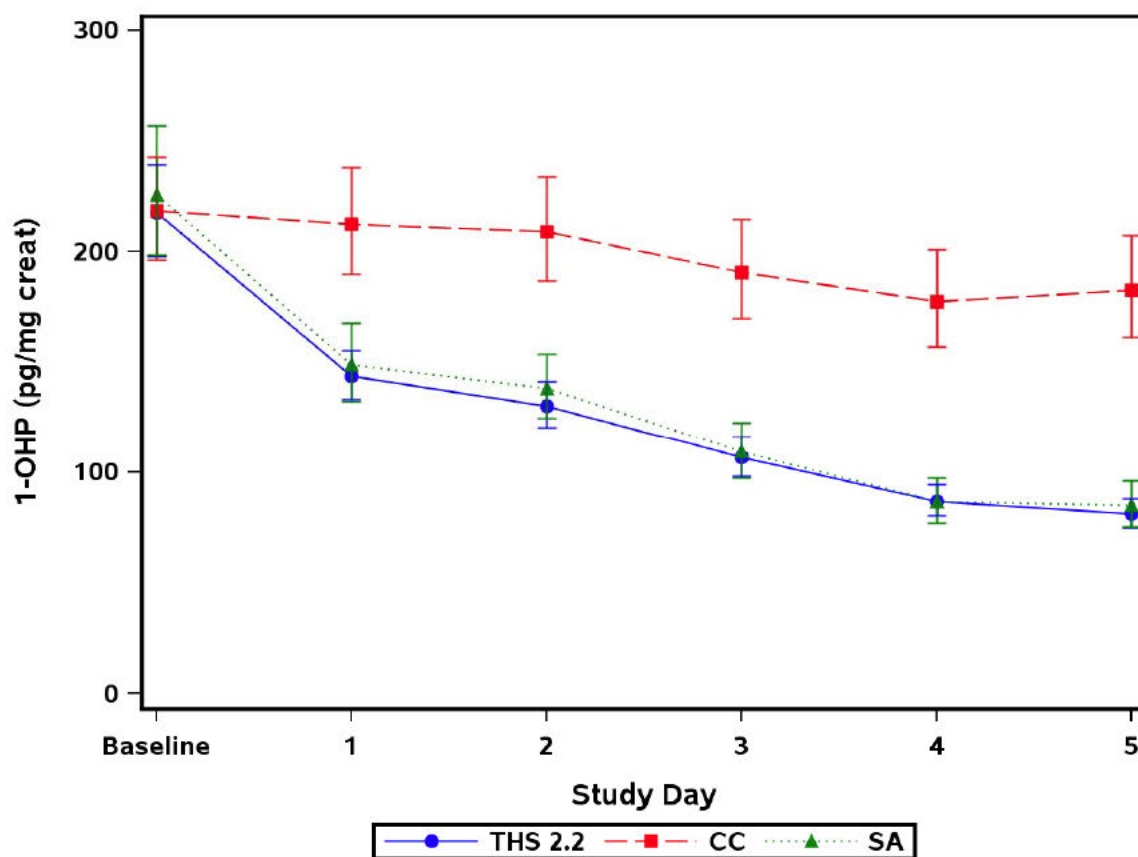
11.2.3.2 Total 1-hydroxypyrene in 24-hour Urine

Subject listings of Total 1-OHP data are provided in [Appendix 15](#), [Listing 15.3.3.2](#).

Descriptive statistics of the concentration of Total 1-OHP adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15](#), [Table 15.2.4.10](#), together with changes from baseline. Geometric mean and 95% CIs for Total 1-OHP urinary concentration adjusted for creatinine are presented graphically in [Appendix 15](#), [Figure 15.1.2.5](#) and [Figure 11](#). Geometric mean and 95% CIs for urinary quantity of Total 1-OHP excreted over 24 hours are presented graphically in [Appendix 15](#), [Figure 15.1.2.6](#) and [Figure 12](#).



Figure 11 Geometric Mean Total 1-OHP Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)



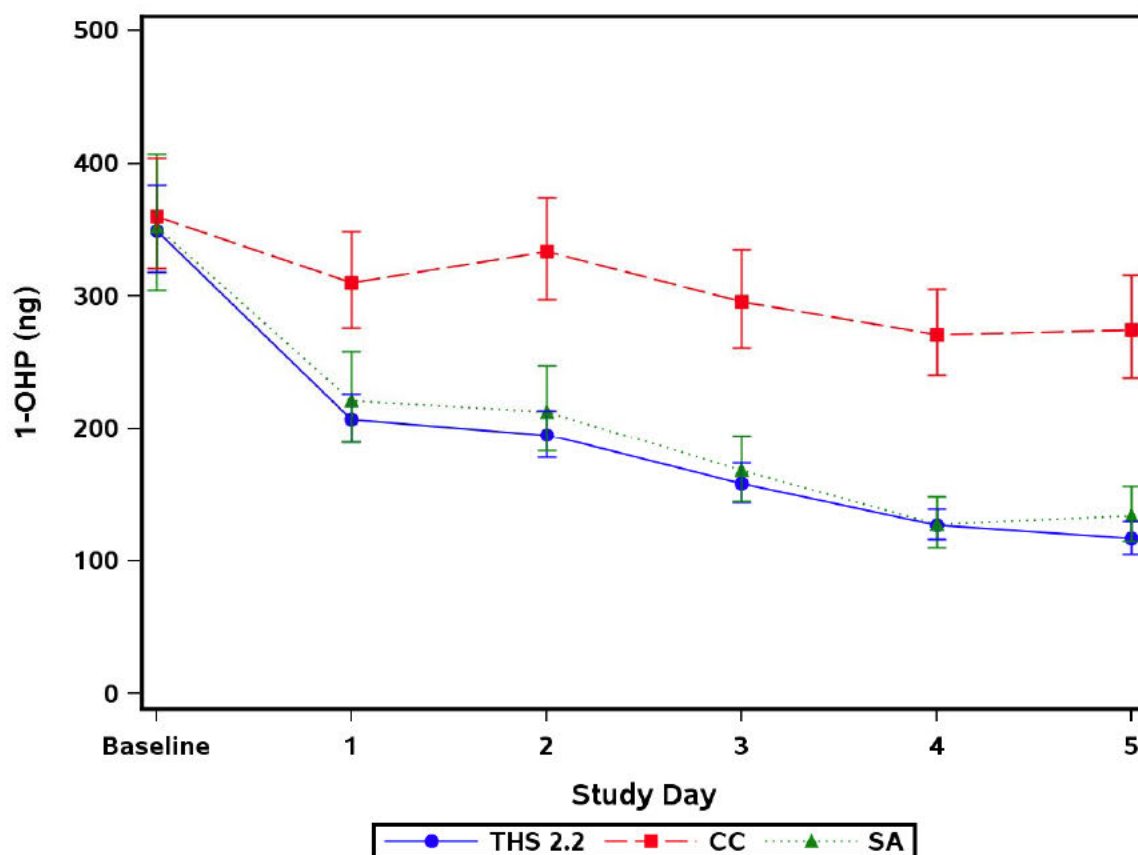
Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.5](#).



Figure 12 Geometric Mean Urinary Total 1-OHP Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.6](#).

The profiles were comparable for both THS 2.2 and SA, with the decrease in Total 1-OHP values achieved steadily over Days 1 to 5. Geometric mean Total 1-OHP values decreased in the THS 2.2 arm from baseline (217.69 pg/mg creat) to Day 5 (81.22 pg/mg creat) compared to Total 1-OHP in the CC arm, which was comparable to baseline (218.41 pg/mg creat) at Day 5 (182.85 pg/mg creat). These values correspond to percent changes from baseline of -60.17% and -13.52% for the THS 2.2 and CC arms, respectively. In the SA arm, Total 1-OHP values also decreased from baseline (223.95 pg/mg creat) to Day 5 (85.13 pg/mg creat), as expected, which corresponded to a -59.94% change from baseline.



The profiles for mean Total 1-OHP quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

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 use versus CC use, and versus SA on Day 5 are presented in [Appendix 15](#), [Table 15.2.4.9](#) and [Table 48](#).

Table 48 Analysis of Total 1-OHP versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	117.52	43.43	0.072	37.67, 50.06
	CC	41	270.63			
Concentration adjusted for creatinine	THS 2.2	79	81.48	44.35	0.054	39.88, 49.33
	CC	41	183.70			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	117.52	88.21	0.074	76.33, 101.93
	SA	39	133.23			
Concentration adjusted for creatinine	THS 2.2	79	81.48	96.63	0.055	86.73, 107.65
	SA	39	84.32			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15](#), [Table 15.2.4.9](#).

On Day 5, the LS mean level of Total 1-OHP urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 55.65% lower than that of subjects who continued to smoke CC (95% CI: 50.67, 60.12). 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 levels of Total 1-OHP urinary concentration adjusted for creatinine and quantity excreted over 24 hours between subjects who switched to THS 2.2 and subjects who abstained from smoking were comparable, with the 95% CIs for both assessments spanning 100%.

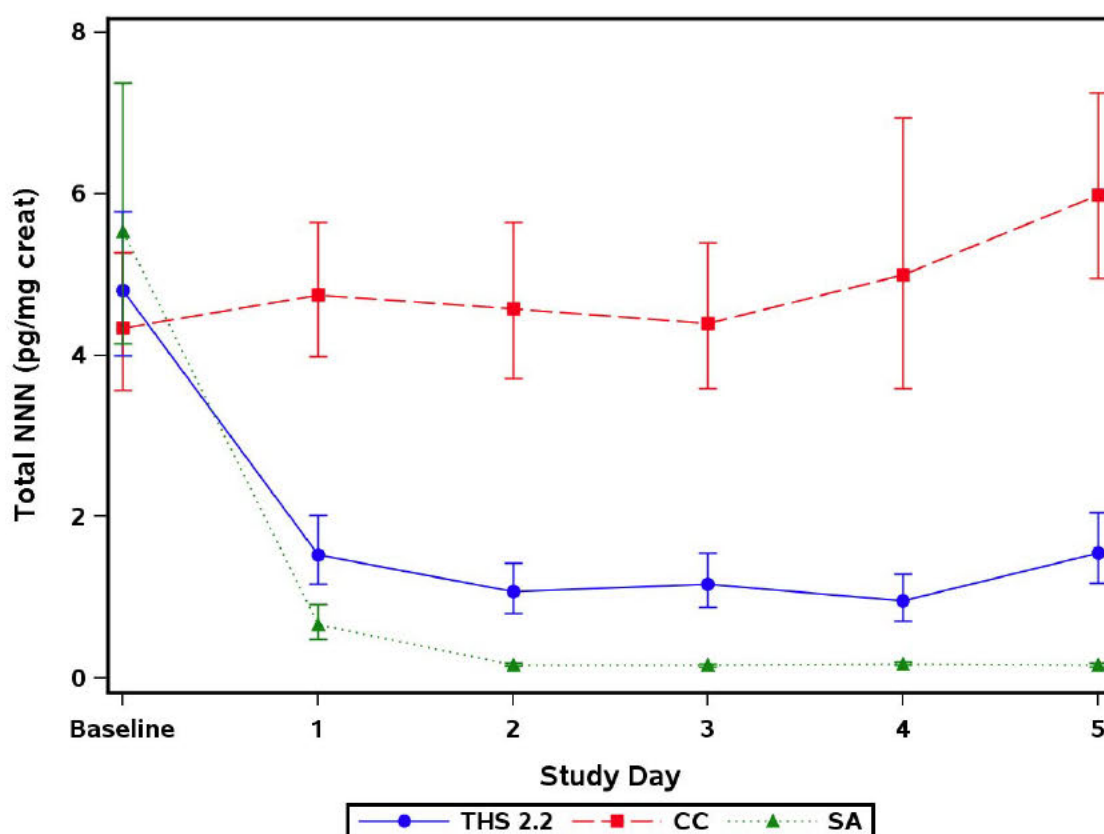


11.2.3.3 Total N-nitrosornicotine in 24-hour Urine

Subject listings of Total NNN data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of Total NNN concentration adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.12](#), together with changes from baseline. Geometric mean and 95% CIs for Total NNN urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.7](#) and [Figure 13](#). Geometric mean and 95% CIs for urinary quantity of Total NNN excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.8](#) and [Figure 14](#).

Figure 13 Geometric Mean Total NNN Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)

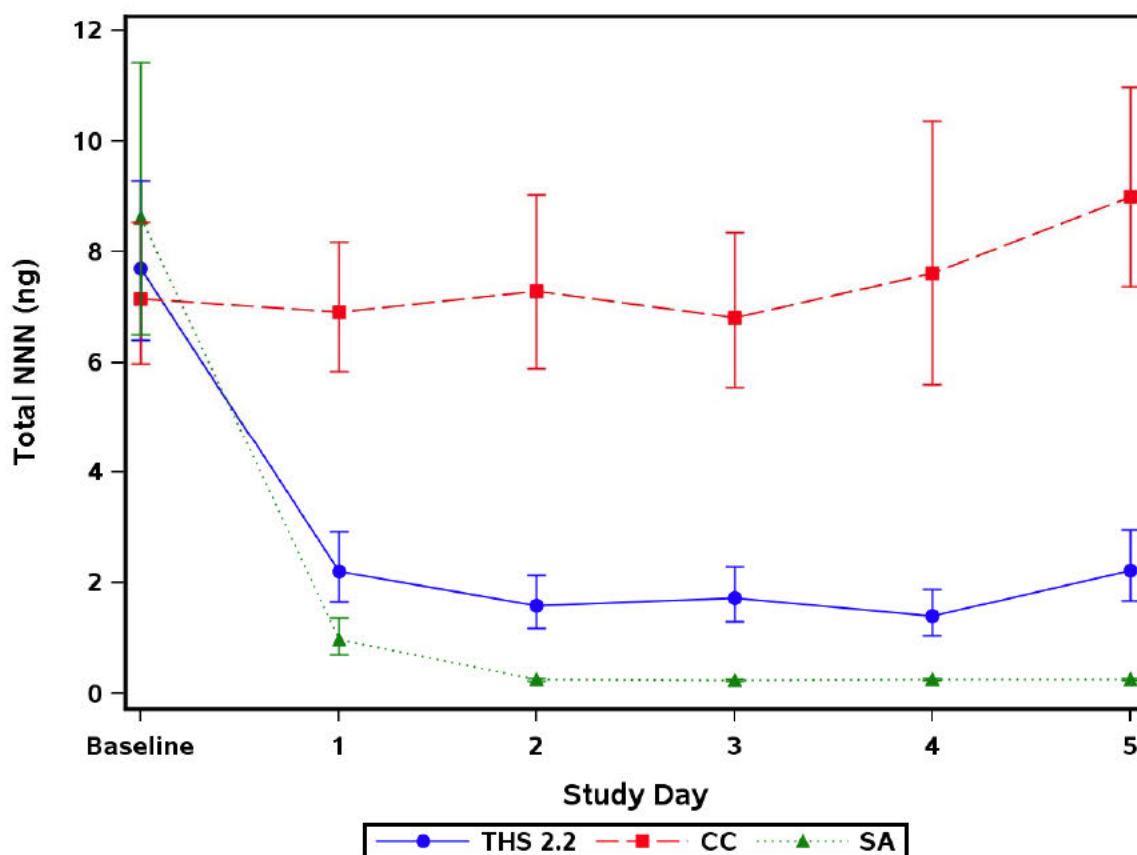


Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.7](#).

Figure 14 Geometric Mean Urinary Total NNN Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.8](#).

For the THS 2.2 and SA arms, most of the decrease in Total NNN was achieved by Day 1, with a greater decrease in Total NNN observed in the SA arm compared to the THS 2.2 arm on all study days. Geometric mean Total NNN values decreased in the THS 2.2 arm from baseline (4.81 pg/mg creat) to Day 4 (0.96 pg/mg creat) before increasing on Day 5 (1.55 pg/mg creat) compared to Total NNN in the CC arm, which increased from baseline (4.34 pg/mg creat) to Day 5 (5.99 pg/mg creat). These Day 5 values correspond to percent changes from baseline of 69.60% and 53.83% for the THS 2.2 and CC arms, respectively. The arithmetic mean change from baseline value on Day 5 following THS 2.2 use was skewed by 1 subject with outlying data (Subject 0147), whose Day 5 value (5125.3 pg/mg creat) was considerably larger than the median value in the THS 2.2 arm on Day 5



(1.42 pg/mg creat). Consequently, the median change from baseline value of -69.75% in the THS 2.2 arm is a more reliable assessment.

In the SA arm, geometric mean Total NNN values decreased from baseline (5.14 pg/mg creat) to Day 5 (0.16 pg/mg creat), as expected, which corresponded to a -95.31% change from baseline.

The profiles for mean Total NNN quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

Analyses of Total NNN urinary concentration adjusted for creatinine and urinary quantity of Total NNN excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15](#), [Table 15.2.4.11](#) and [Table 49](#).

Table 49 Analysis of Total NNN versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	2.21	23.45	0.160	17.12, 32.12
	CC	41	9.44			
Concentration adjusted for creatinine	THS 2.2	79	1.54	24.12	0.155	17.76, 32.75
	CC	41	6.37			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	2.21	896.44	0.162	651.32, 1233.82
	SA	39	0.25			
Concentration adjusted for creatinine	THS 2.2	79	1.54	980.18	0.158	718.45, 1337.25
	SA	39	0.16			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15](#), [Table 15.2.4.11](#).

On Day 5, the LS mean level of Total NNN urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 75.88% lower than that of subjects who continued to smoke CC (95% CI: 67.25, 82.24). 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 level of Total NNN urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 9.8-fold higher than that of subjects who abstained from smoking (95% CI: 718.45, 1337.25). The results for the quantity of Total NNN excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

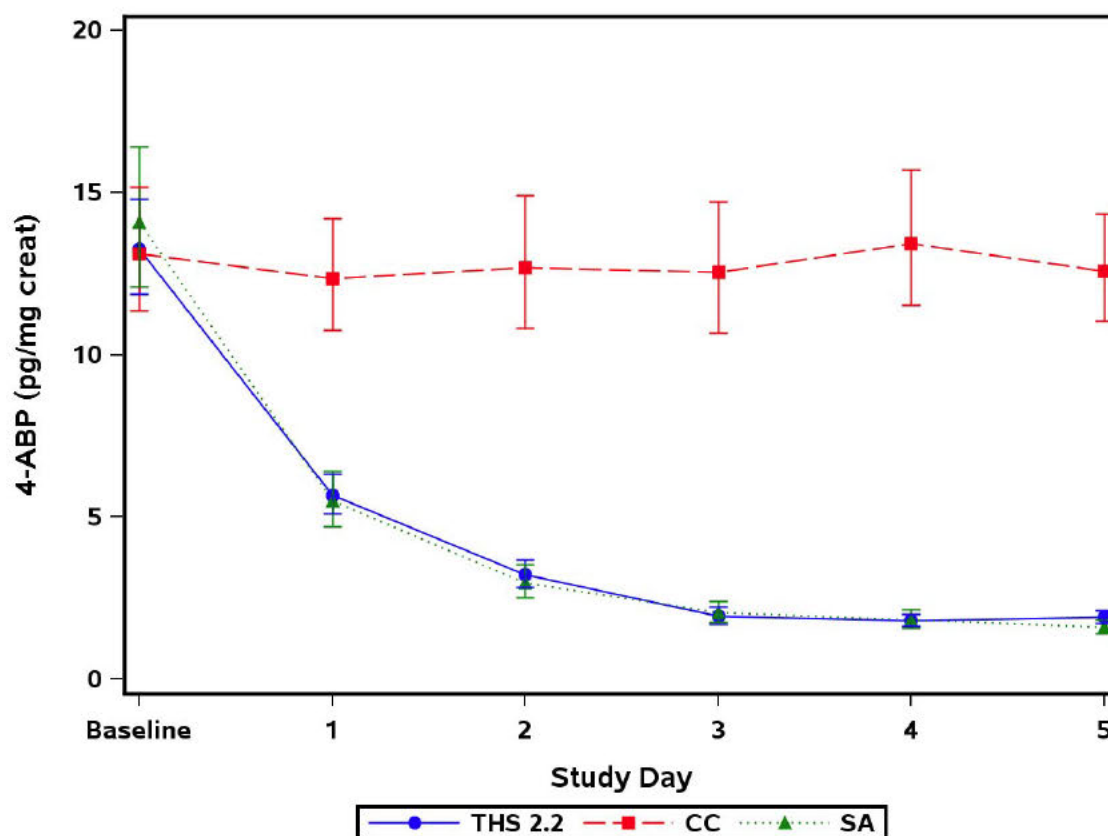
11.2.3.4 4-aminobiphenyl in 24-hour Urine

Subject listings of 4-ABP data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of the concentration of 4-ABP adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.14](#), together with changes from baseline. Geometric mean and 95% CIs for 4-ABP urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.9](#) and [Figure 15](#). Geometric mean and 95% CIs for urinary quantity of 4-ABP excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.10](#) and [Figure 16](#).



Figure 15 Geometric Mean 4-ABP Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)

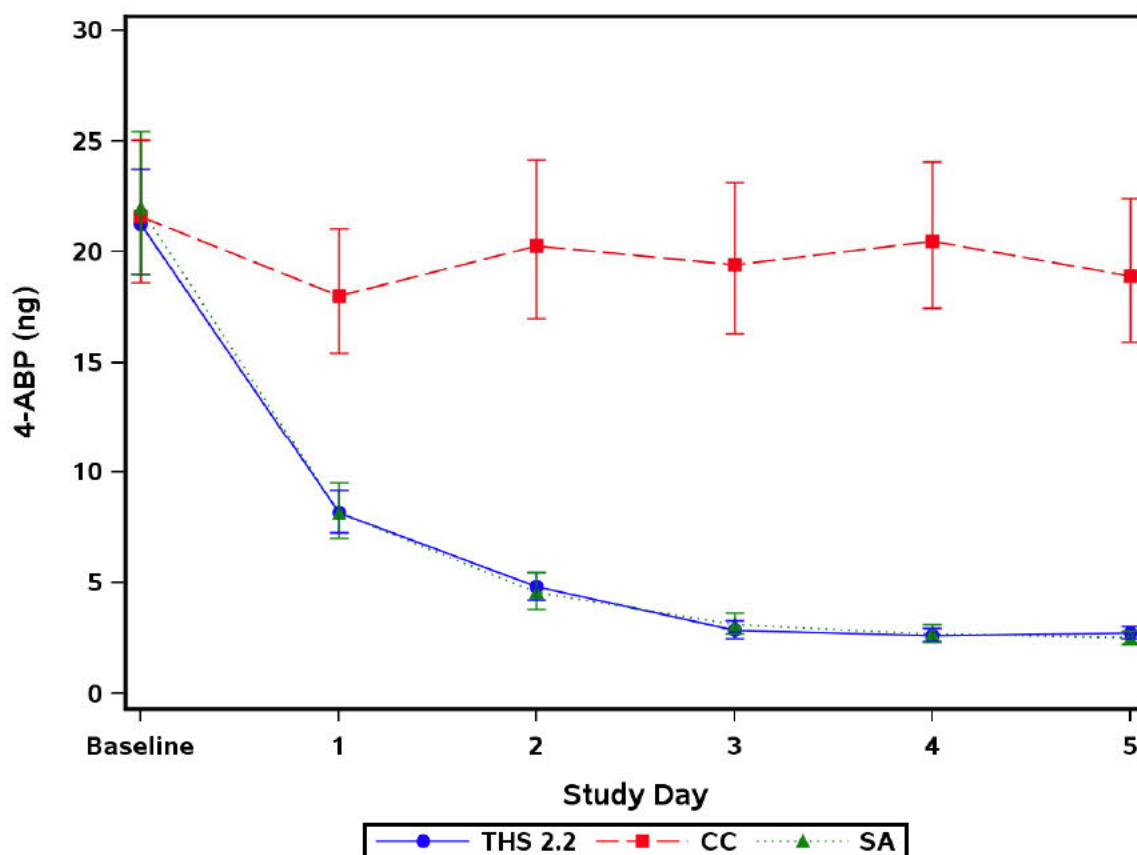


Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.9](#).

Figure 16 Geometric Mean Urinary 4-ABP Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.10](#).

The profiles were comparable for the THS 2.2 and SA arms, with most of the reduction in 4-ABP being achieved by Day 3 and the results plateauing thereafter. Geometric mean 4-ABP values decreased in the THS 2.2 arm from baseline (13.25 pg/mg creat) to Day 5 (1.90 pg/mg creat) compared to 4-ABP in the CC arm, which remained comparable to baseline (13.11 pg/mg creat) on Day 5 (12.58 pg/mg creat). These values correspond to percent changes from baseline of -82.12% and -1.66% for the THS 2.2 and CC arms, respectively. In the SA arm, 4-ABP values also decreased from baseline (13.53 pg/mg creat) to Day 5 (1.60 pg/mg creat), as expected, which corresponded to a -86.99% change from baseline.



The profiles for mean 4-ABP quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

Analyses of 4-ABP urinary concentration adjusted for creatinine and urinary quantity of 4-ABP excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15](#), [Table 15.2.4.13](#) and [Table 50](#).

Table 50 Analysis of 4-ABP versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	2.73	14.55	0.077	12.51, 16.92
	CC	41	18.77			
Concentration adjusted for creatinine	THS 2.2	79	1.90	14.94	0.075	12.89, 17.33
	CC	41	12.69			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	2.73	108.54	0.078	93.11, 126.53
	SA	39	2.52			
Concentration adjusted for creatinine	THS 2.2	79	1.90	118.51	0.077	101.96, 137.75
	SA	39	1.60			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15](#), [Table 15.2.4.13](#).

On Day 5, the LS mean level of 4-ABP urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 85.06% lower than that of subjects who continued to smoke CC (95% CI: 82.67, 87.11). The results for the quantity of 4-ABP excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS mean level of 4-ABP urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 18.51% higher than that of subjects who abstained from smoking, with the lower bound of the 95% CI just greater than 100% (95% CI: 101.96, 137.75). There was no notable difference observed in 4-ABP quantity excreted over 24 hours, with the 95% CIs spanning 100%.

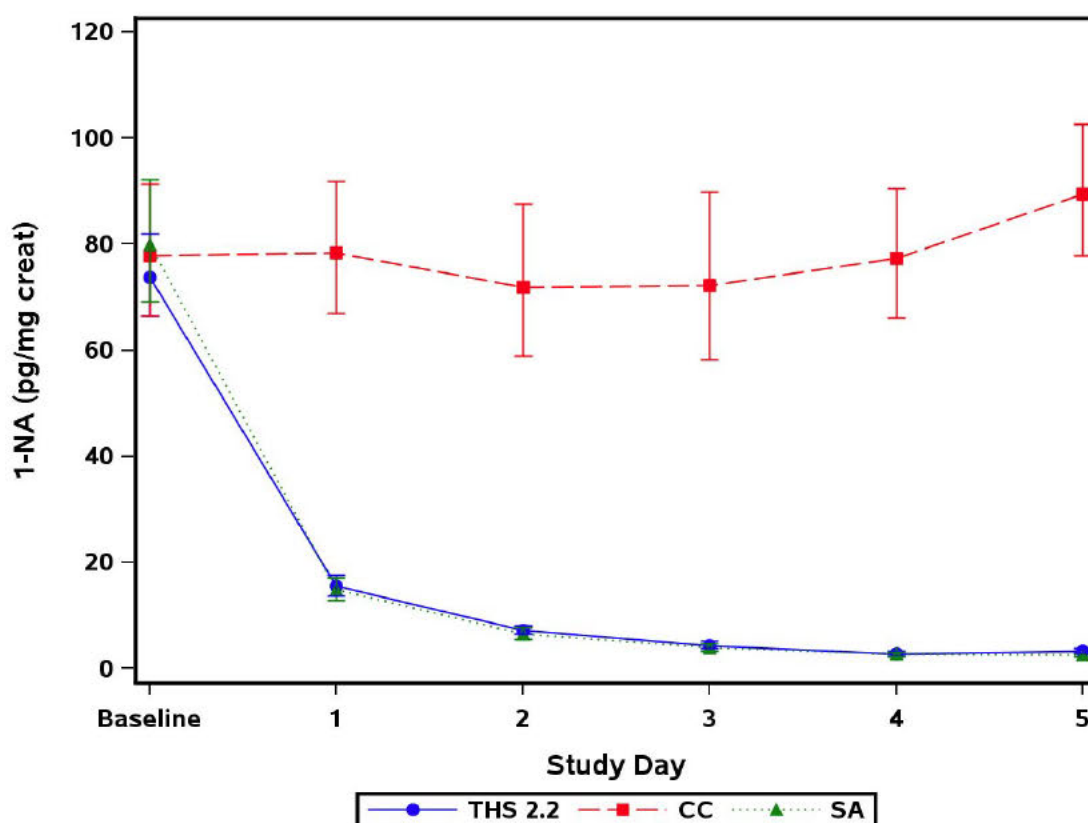


11.2.3.5 1-aminonaphthalene in 24-hour Urine

Subject listings of 1-NA data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of the concentration of 1-NA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.16](#), together with changes from baseline. Geometric mean and 95% CIs for 1-NA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.11](#) and [Figure 17](#). Geometric mean and 95% CIs for urinary quantity of 1-NA excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.12](#) and [Figure 18](#).

Figure 17 Geometric Mean 1-NA Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)

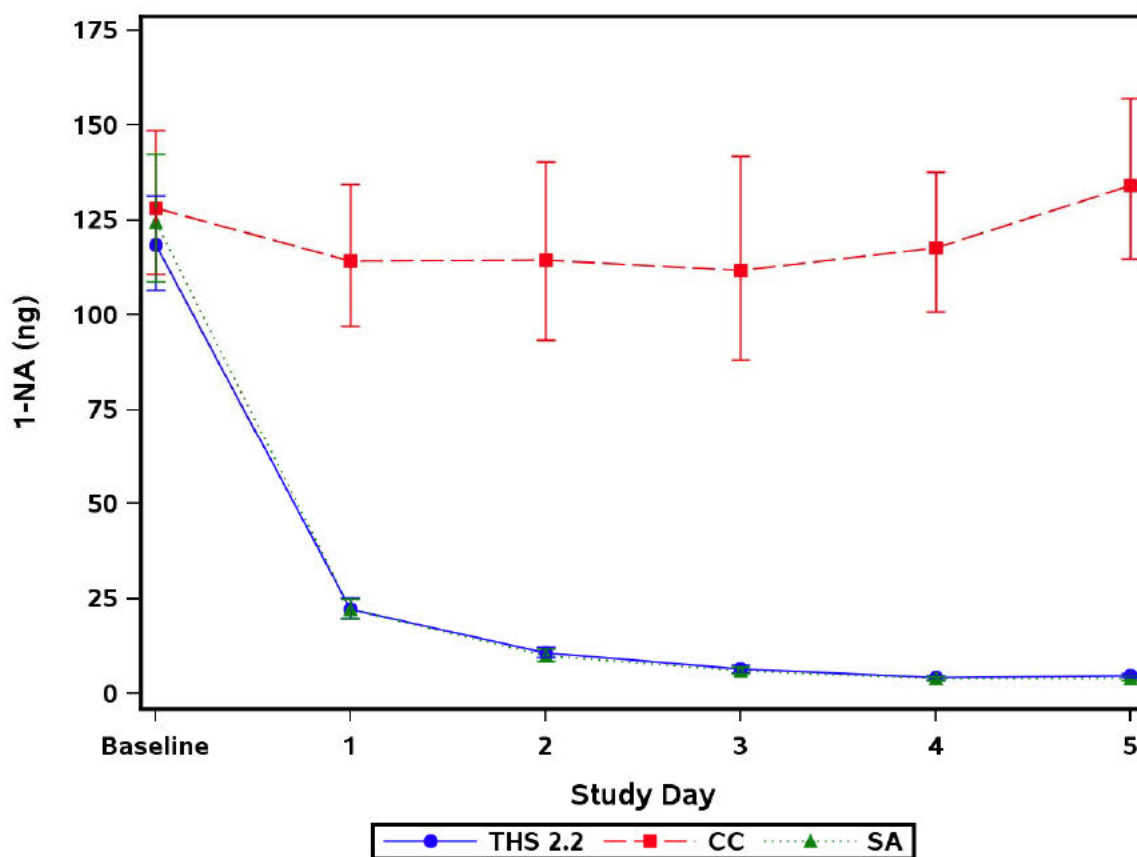


Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.11](#).

Figure 18 Geometric Mean Urinary 1-NA Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.12](#).

The profiles were comparable for the THS 2.2 and SA arms, with most of the reduction in 1-NA achieved by Day 1 and plateauing thereafter. Geometric mean 1-NA values decreased in the THS 2.2 arm from baseline (73.83 pg/mg creat) to Day 5 (3.30 pg/mg creat) compared to 1-NA in the CC arm, which increased from baseline (77.84 pg/mg creat) to Day 5 (89.37 pg/mg creat). These values correspond to percent changes from baseline of -94.16% and 19.17% for the THS 2.2 and CC arms, respectively. In the SA arm, 1-NA values also decreased from baseline (77.31 pg/mg creat) to Day 5 (2.56 pg/mg creat), as expected, which corresponded to a -96.41% change from baseline.



The profiles for mean 1-NA quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

Analyses of 1-NA urinary concentration adjusted for creatinine and urinary quantity of 1-NA excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15, Table 15.2.4.15](#) and [Table 51](#).

Table 51 Analysis of 1-NA versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	4.80	3.66	0.090	3.06, 4.37
	CC	41	131.10			
Concentration adjusted for creatinine	THS 2.2	79	3.32	3.73	0.085	3.15, 4.42
	CC	41	88.98			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	4.80	119.46	0.091	99.88, 142.87
	SA	39	4.02			
Concentration adjusted for creatinine	THS 2.2	79	3.32	130.03	0.087	109.64, 154.21
	SA	39	2.55			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

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

On Day 5, the LS mean level of 1-NA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 96.27% lower than that of subjects who continued to smoke CC (95% CI: 95.58, 96.85). 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 mean level of 1-NA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 30.03% higher than that of subjects who abstained from smoking (95% CI: 109.64, 154.21). The results for the quantity of 1-NA excreted over 24 hours showed 1-NA was 19.46% higher in subjects who switched to THS 2.2 compared to SA (95% CI: 99.88, 142.87).

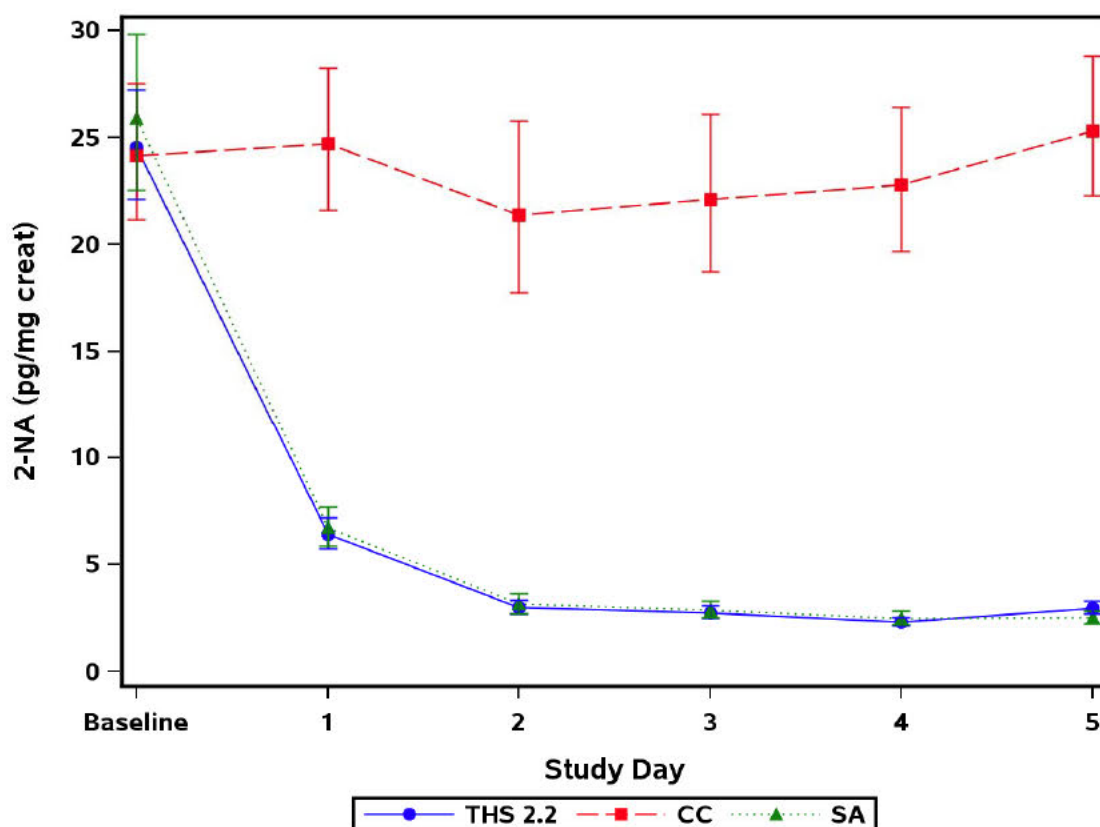


11.2.3.6 2-aminonaphthalene in 24-hour Urine

Subject listings of 2-NA data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of the concentration of 2-NA 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](#), together with changes from baseline. Geometric mean and 95% CIs for 2-NA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.13](#) and [Figure 19](#). Geometric mean and 95% CIs for urinary quantity of 2-NA excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.14](#) and [Figure 20](#).

Figure 19 Geometric Mean 2-NA Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)



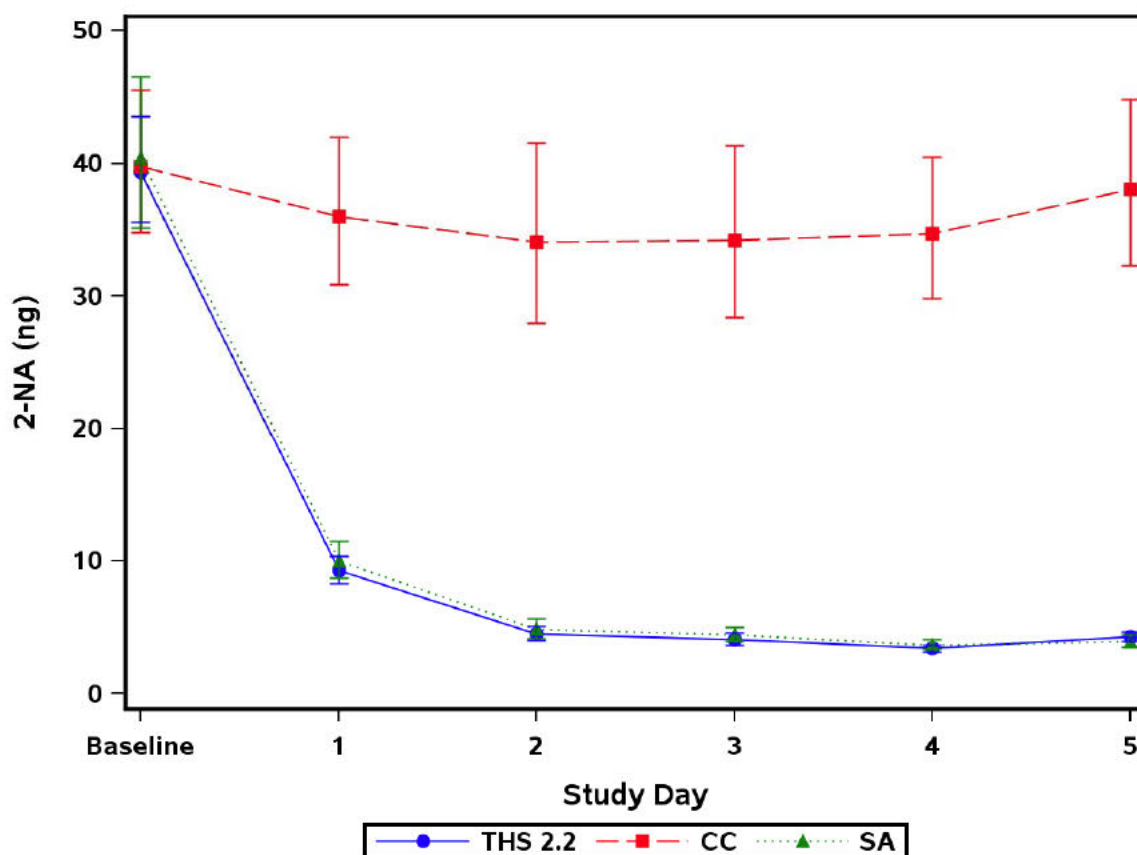
Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.13](#).



Figure 20 Geometric Mean Urinary 2-NA Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.14](#).

The profiles were comparable for the THS 2.2 and SA arms, with most of the reduction in 2-NA achieved by Day 2 and plateauing thereafter. Geometric mean 2-NA values decreased in the THS 2.2 arm from baseline (24.54 pg/mg creat) to Day 5 (2.96 pg/mg creat) compared to 2-NA in the CC arm, which was comparable to baseline (24.14 pg/mg creat) at Day 5 (25.32 pg/mg creat). These values correspond to percent changes from baseline of -85.39% and 7.19% for the THS 2.2 and CC arms, respectively. In the SA arm, 2-NA values also decreased from baseline (24.59 pg/mg creat) to Day 5 (2.52 pg/mg creat), as expected, which corresponded to a -88.93% change from baseline.



The profiles for mean 2-NA quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

Analyses of 2-NA urinary concentration adjusted for creatinine and urinary quantity of 2-NA excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15, Table 15.2.4.17](#) and [Table 52](#).

Table 52 Analysis of 2-NA versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	4.24	11.22	0.071	9.75, 12.91
	CC	41	37.84			
Concentration adjusted for creatinine	THS 2.2	79	2.95	11.54	0.069	10.08, 13.21
	CC	41	25.55			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	4.24	106.71	0.072	92.57, 123.02
	SA	39	3.98			
Concentration adjusted for creatinine	THS 2.2	79	2.95	116.65	0.070	101.73, 133.76
	SA	39	2.53			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15, Table 15.2.4.17](#).

On Day 5, the LS mean level of 2-NA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 88.46% lower than that of subjects who continued to smoke CC (95% CI: 86.79, 89.92). 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 mean level of 2-NA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 16.65% higher than that of subjects who abstained from smoking, with the lower bound of the 95% CI just greater than 100% (95% CI: 101.73, 133.76). There was no notable difference observed in 2-NA quantity excreted over 24 hours, with the 95% CIs spanning 100%.

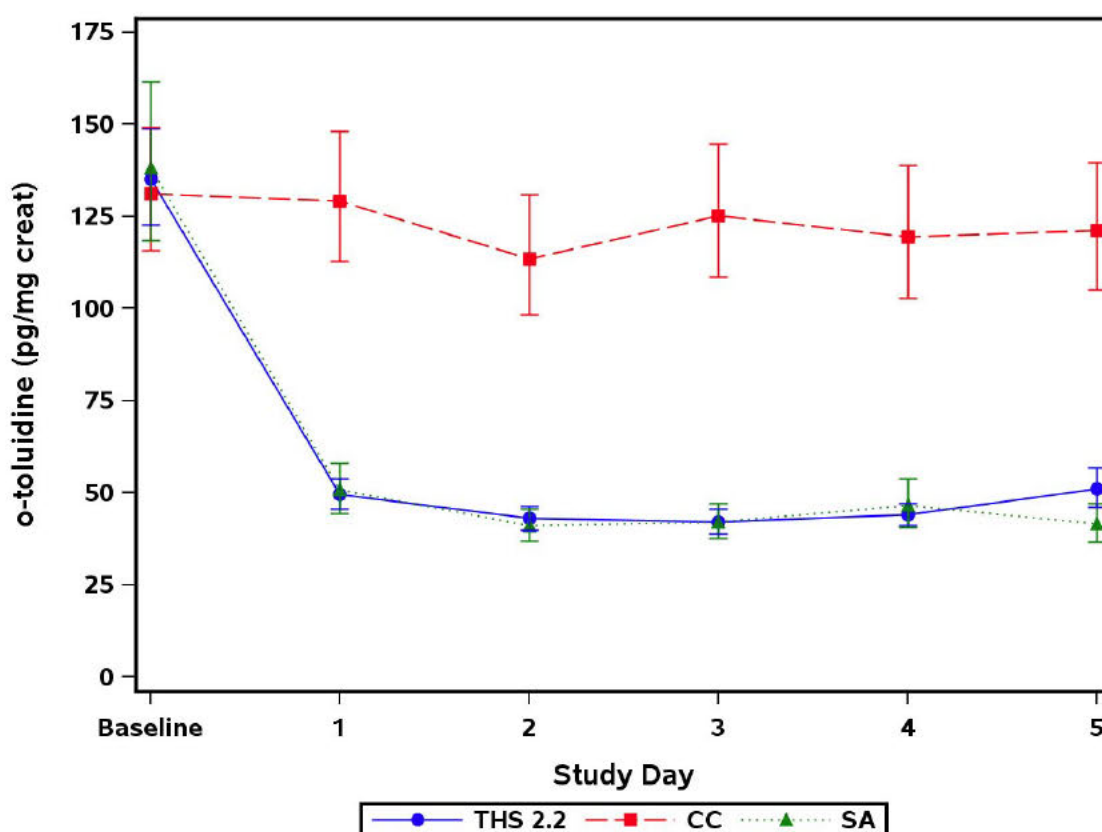


11.2.3.7 o-toluidine in 24-hour Urine

Subject listings of o-toluidine data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of the concentration of o-toluidine adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.20](#) together with changes from baseline. Geometric mean and 95% CIs for o-toluidine urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.15](#) and [Figure 21](#). Geometric mean and 95% CIs for urinary quantity of o-toluidine excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.16](#) and [Figure 22](#).

Figure 21 Geometric Mean o-toluidine Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)

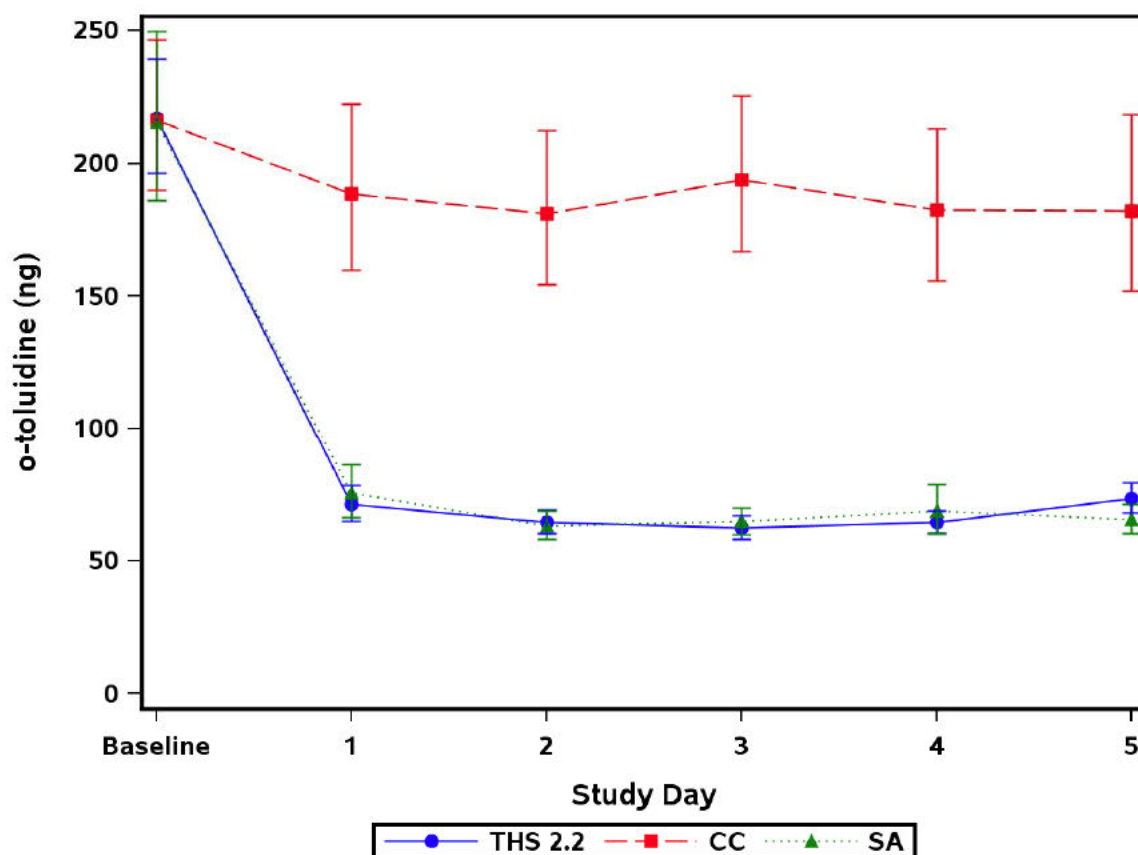


Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.15](#).

Figure 22 Geometric Mean Urinary o-toluidine Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.16](#).

The profiles were comparable for the THS 2.2 and SA arms, with most of the reduction in o-toluidine achieved by Day 1 and plateauing thereafter. Geometric mean o-toluidine values decreased in the THS 2.2 arm from baseline (135.20 pg/mg creat) to Day 5 (51.15 pg/mg creat) compared to o-toluidine in the CC arm, which was comparable to baseline (131.32 pg/mg creat) at Day 5 (121.16 pg/mg creat). These values correspond to percent changes from baseline of -50.96% and -3.08% for the THS 2.2 and CC arms, respectively. In the SA arm, o-toluidine values also decreased from baseline (132.49 pg/mg creat) to Day 5 (41.64 pg/mg creat), as expected, which corresponded to a -64.96% change from baseline.



The profiles for mean o-toluidine quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

Analyses of o-toluidine urinary concentration adjusted for creatinine and urinary quantity of o-toluidine excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15](#), [Table 15.2.4.19](#) and [Table 53](#).

Table 53 Analysis of o-toluidine versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	73.19	40.38	0.074	34.92, 46.68
	CC	41	181.28			
Concentration adjusted for creatinine	THS 2.2	79	50.89	41.70	0.075	36.01, 48.29
	CC	41	122.03			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	73.19	111.12	0.075	95.86, 128.80
	SA	39	65.87			
Concentration adjusted for creatinine	THS 2.2	79	50.89	121.31	0.076	104.50, 140.81
	SA	39	41.95			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15](#), [Table 15.2.4.19](#).

On Day 5, the LS mean level of o-toluidine urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 58.30% lower than that of subjects who continued to smoke CC (95% CI: 51.71, 63.99). 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 level of o-toluidine urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 21.31% higher than that of subjects who abstained from smoking, with the lower bound of the 95% CI greater than 100% (95% CI:



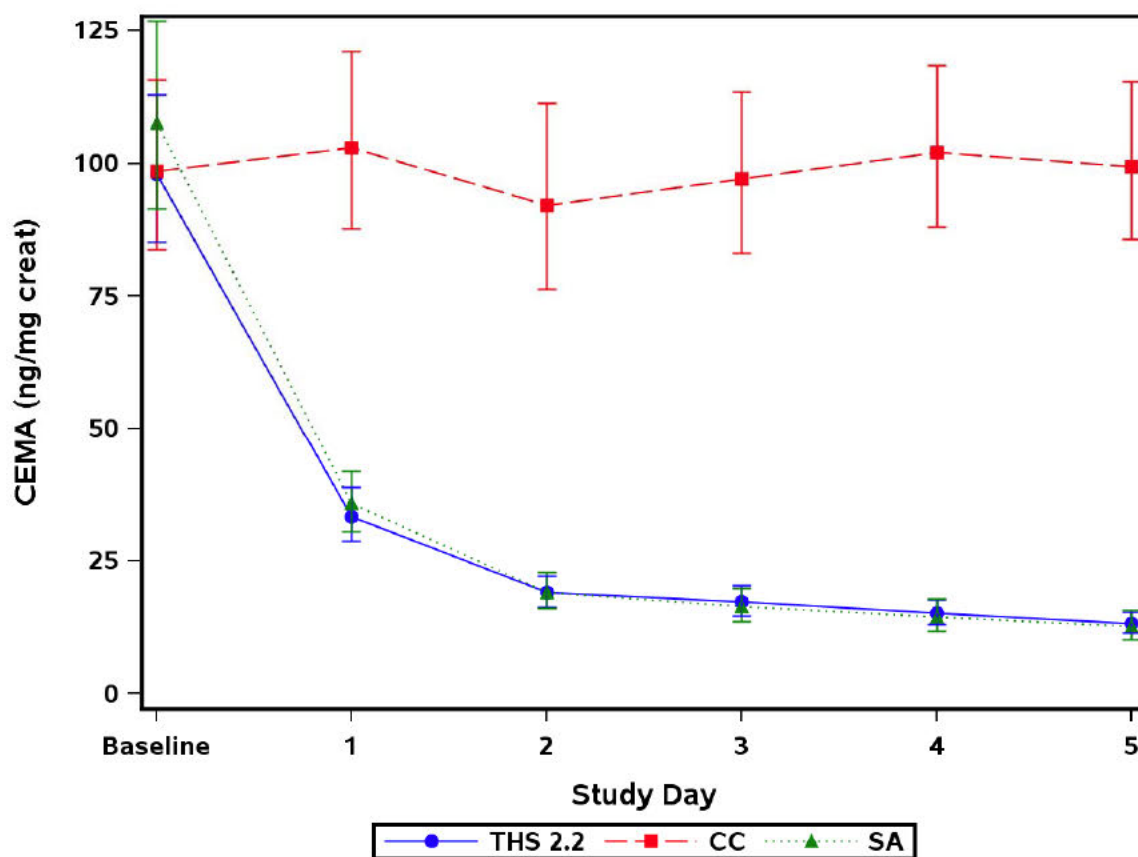
104.50, 140.81). There was no notable difference observed in o-toluidine quantity excreted over 24 hours, with the 95% CIs spanning 100%.

11.2.3.8 2-cyanoethylmercapturic acid in 24-hour Urine

Subject listings of CEMA data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of the concentration of CEMA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.22](#), together with changes from baseline. Geometric mean and 95% CIs for CEMA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.17](#) and [Figure 23](#). Geometric mean and 95% CIs for urinary quantity of CEMA excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.18](#) and [Figure 24](#).

Figure 23 Geometric Mean CEMA Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)

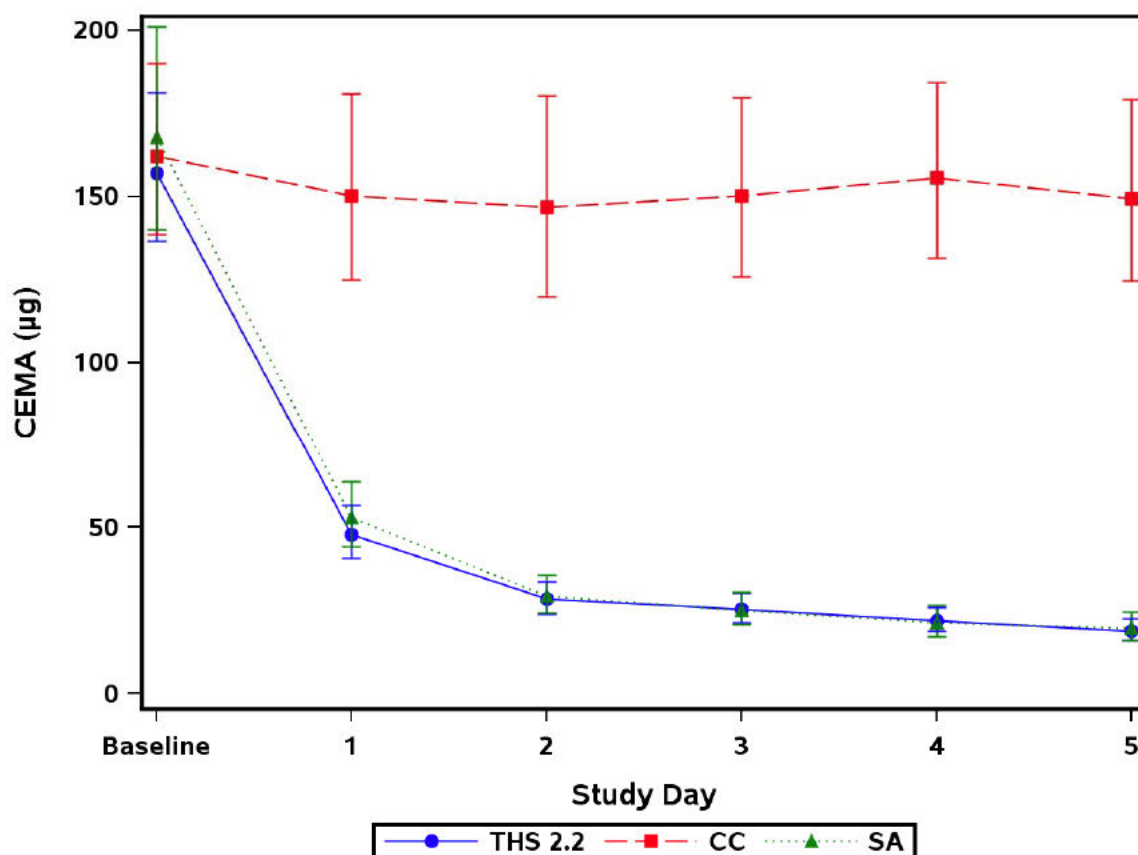


Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.17](#).

Figure 24 Geometric Mean Urinary CEMA Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.18](#).

The profiles were comparable for the THS 2.2 and SA arms, with most of the decrease in CEMA achieved by Day 2 and plateauing thereafter. Geometric mean CEMA values decreased in the THS 2.2 arm from baseline (98.03 ng/mg creat) to Day 5 (13.18 ng/mg creat) compared to CEMA in the CC arm, which was comparable to baseline (98.46 ng/mg creat) at Day 5 (99.48 ng/mg creat). These values correspond to percent changes from baseline of -86.10% and 4.21% for the THS 2.2 and CC arms, respectively. In the SA arm, CEMA values also decreased from baseline (103.51 ng/mg creat) to Day 5 (12.60 ng/mg creat), as expected, which corresponded to a -86.74% change from baseline.

The profiles for mean CEMA quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.



Analyses of CEMA urinary concentration adjusted for creatinine and urinary quantity of CEMA excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15, Table 15.2.4.21](#) and [Table 54](#).

Table 54 Analysis of CEMA versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)		
				SE	95% CI	
Quantity excreted over 24 hours	THS 2.2	79	19.19	12.96	0.076	11.15, 15.06
	CC	41	148.07			
Concentration adjusted for creatinine	THS 2.2	79	13.29	13.16	0.065	11.58, 14.95
	CC	41	101.03			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:SA) (%)		
				SE	95% CI	
Quantity excreted over 24 hours	THS 2.2	79	19.19	98.95	0.078	84.98, 115.23
	SA	39	19.39			
Concentration adjusted for creatinine	THS 2.2	79	13.29	108.96	0.066	95.73, 124.02
	SA	39	12.20			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15, Table 15.2.4.21](#).

On Day 5, the LS mean level of CEMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 86.84% lower than that of subjects who continued to smoke CC (95% CI: 85.05, 88.42). The results for the quantity of CEMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

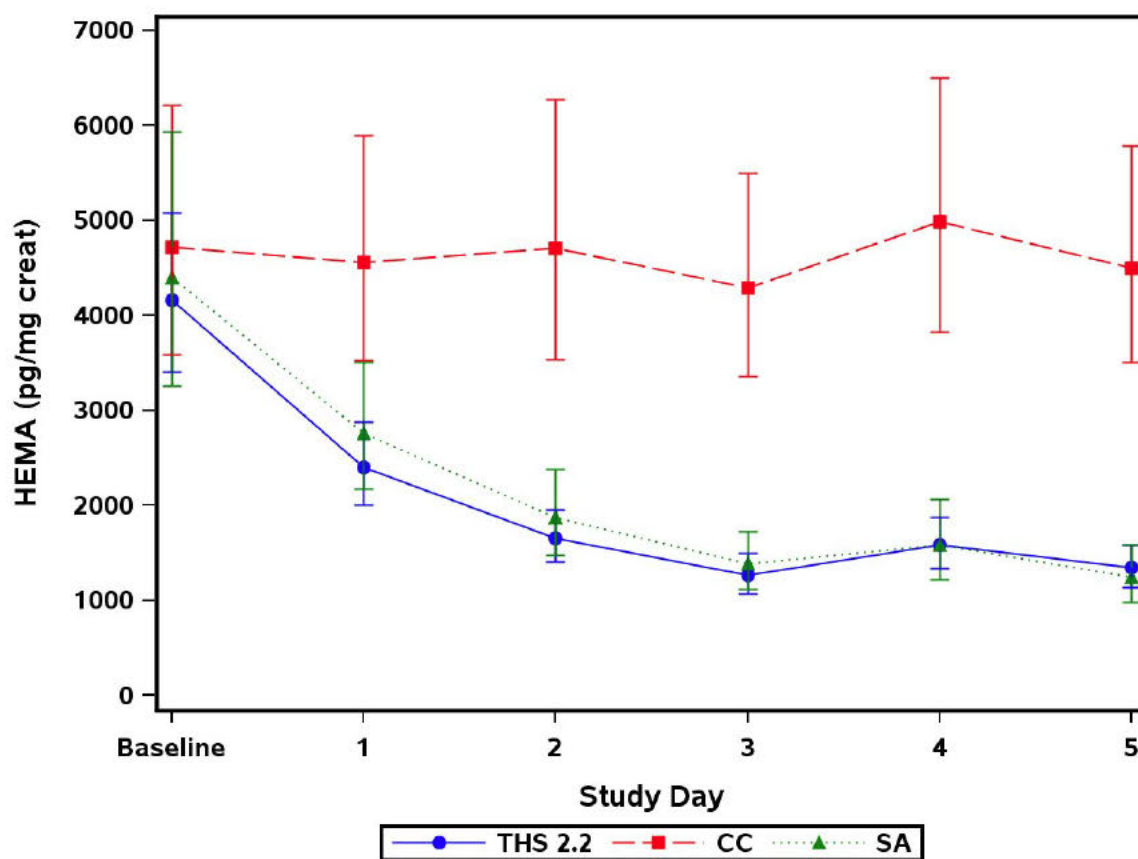
On Day 5, both CEMA urinary concentration adjusted for creatinine and quantity excreted over 24 hours between subjects who switched to THS 2.2 and subjects who abstained from smoking were comparable, with the 95% CIs for both assessments spanning 100%.

11.2.3.9 2-hydroxyethyl mercapturic acid in 24-hour Urine

Subject listings of HEMA data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of the concentration of HEMA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.24](#) together with changes from baseline. Geometric mean and 95% CIs for HEMA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.19](#) and [Figure 25](#). Geometric mean and 95% CIs for urinary quantity of HEMA excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.20](#) and [Figure 26](#).

Figure 25 Geometric Mean HEMA Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)



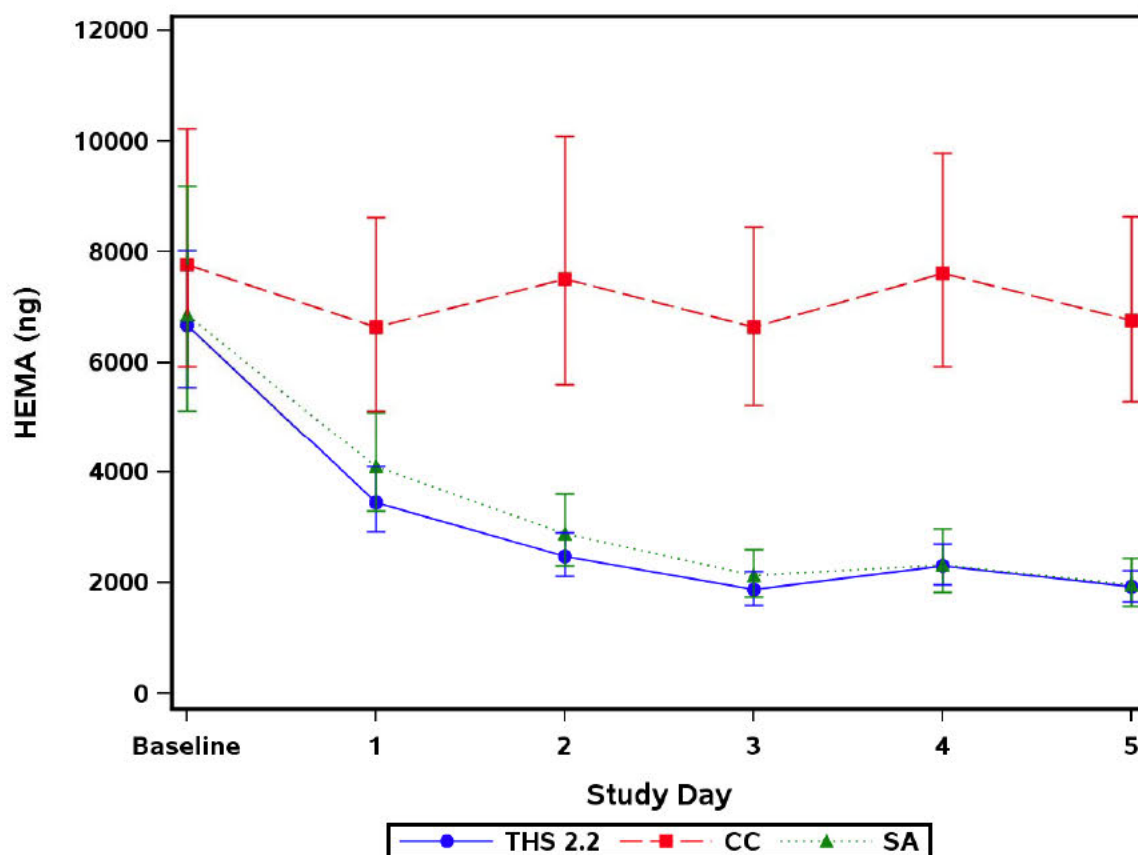
Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.19](#).



Figure 26 Geometric Mean Urinary HEMA Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.20](#).

The profiles were comparable for the THS 2.2 and SA arms, with most of the decrease in HEMA being achieved by Day 3 and the results plateauing thereafter. Geometric mean HEMA values decreased in the THS 2.2 arm from baseline (4161.66 pg/mg creat) to Day 5 (1342.40 pg/mg creat) compared to HEMA in the CC arm, which remained comparable to baseline (4718.48 pg/mg creat) on Day 5 (4504.00 pg/mg creat). These values correspond to percent changes from baseline of -60.71% and 0.74% for the THS 2.2 and CC arms, respectively. In the SA arm, HEMA values also decreased from baseline (4114.78 pg/mg creat) to Day 5 (1248.27 pg/mg creat), as expected, which corresponded to a -64.48% change from baseline.



The profiles for mean HEMA quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

Analyses of HEMA urinary concentration adjusted for creatinine and urinary quantity of HEMA excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15](#), [Table 15.2.4.23](#) and [Table 55](#).

Table 55 Analysis of HEMA versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	1966.21	31.37	0.086	26.51, 37.11
	CC	41	6268.43			
Concentration adjusted for creatinine	THS 2.2	79	1363.28	32.00	0.085	27.10, 37.79
	CC	41	4260.11			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	1966.21	96.55	0.087	81.43, 114.49
	SA	39	2036.38			
Concentration adjusted for creatinine	THS 2.2	79	1363.28	105.93	0.086	89.49, 125.38
	SA	39	1286.99			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15](#), [Table 15.2.4.23](#).

On Day 5, the LS mean level of HEMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 68.00% lower than that of subjects who continued to smoke CC (95% CI: 62.21, 72.90). 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, both HEMA urinary concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.



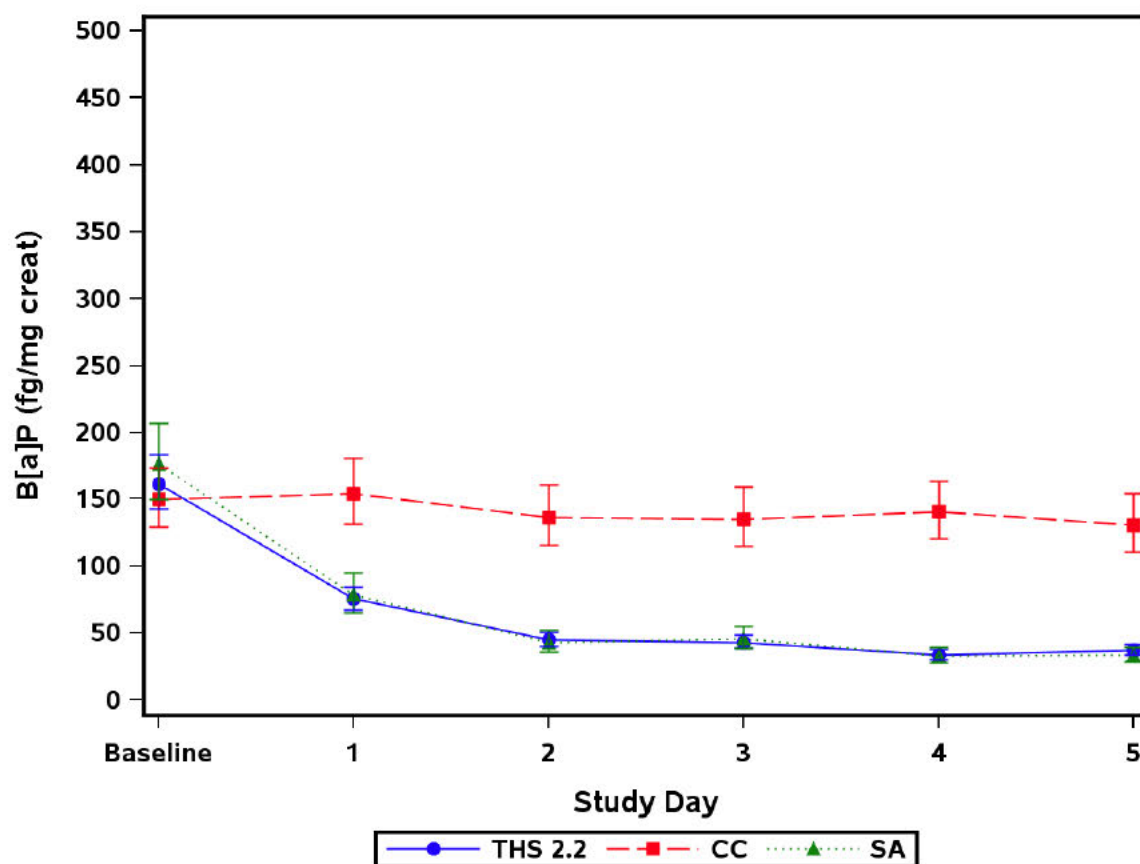
11.2.3.10 3-hydroxy(a)benzopyrene in 24-hour Urine

Subject listings of 3-OH-B[a]P data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of the concentration of 3-OH-B[a]P adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.26](#), together with changes from baseline. Geometric mean and 95% CIs for 3-OH-B[a]P urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.21](#) and [Figure 27](#). Geometric mean and 95% CIs for urinary quantity of 3-OH-B[a]P excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.22](#) and [Figure 28](#).



Figure 27 Geometric Mean 3-OH-B[a]P Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)

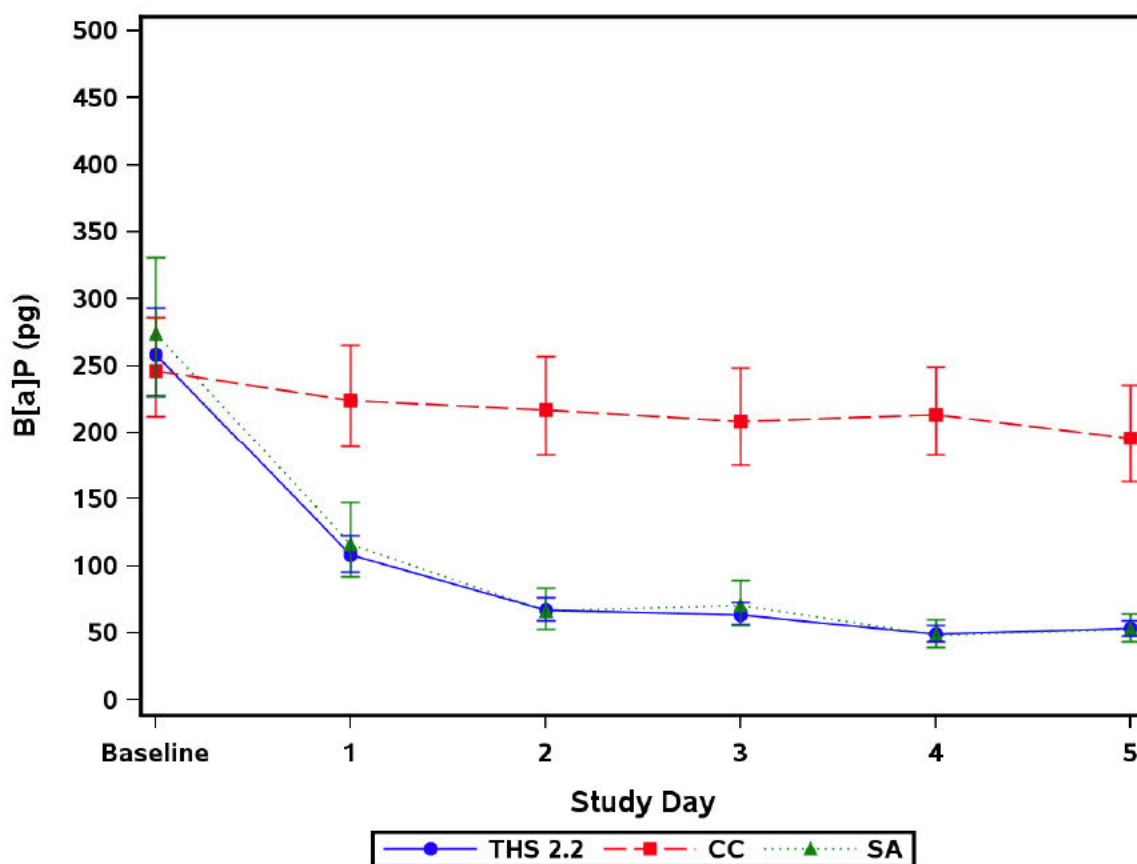


Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.21](#).

Figure 28 Geometric Mean Urinary 3-OH-B[a]P Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.22](#).

The profiles were comparable for the THS 2.2 and SA arms, with most of the decrease in 3-OH-B[a]P achieved by Day 2 and plateauing thereafter. Geometric mean 3-OH-B[a]P values decreased in the THS 2.2 arm from baseline (161.17 fg/mg creat) to Day 5 (37.07 fg/mg creat) compared to 3-OH-B[a]P in the CC arm, which was comparable to baseline (149.47 ng/mg creat) at Day 5 (130.29 ng/mg creat). These values correspond to percent changes from baseline of -71.43% and -8.92% for the THS 2.2 and CC arms, respectively. In the SA arm, 3-OH-B[a]P values also decreased from baseline (169.58 ng/mg creat) to Day 5 (33.64 ng/mg creat), as expected, which corresponded to a -77.24% change from baseline.



The profiles for mean 3-OH-B[a]P quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

Analyses of 3-OH-B[a]P urinary concentration adjusted for creatinine and urinary quantity of 3-OH-B[a]P excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15](#), [Table 15.2.4.25](#) and [Table 56](#).

Table 56 Analysis of 3-OH-B[a]P versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	53.12	26.62	0.089	22.33, 31.74
	CC	41	199.50			
Concentration adjusted for creatinine	THS 2.2	79	36.89	27.50	0.085	23.25, 32.52
	CC	41	134.13			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric Mean Ratio (THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	53.12	102.54	0.091	85.80, 122.56
	SA	39	51.80			
Concentration adjusted for creatinine	THS 2.2	79	36.89	111.62	0.087	94.16, 132.32
	SA	39	33.05			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15](#), [Table 15.2.4.25](#).

On Day 5, the LS mean level of 3-OH-B[a]P urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 72.50% lower than that of subjects who continued to smoke CC (95% CI: 67.48, 76.75). The results for the quantity of 3-OH-B[a]P excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, both 3-OH-B[a]P urinary concentration adjusted for creatinine and quantity excreted over 24 hours between subjects who switched to THS 2.2 and subjects who abstained from smoking were comparable, with the 95% CIs for both assessments spanning 100%.

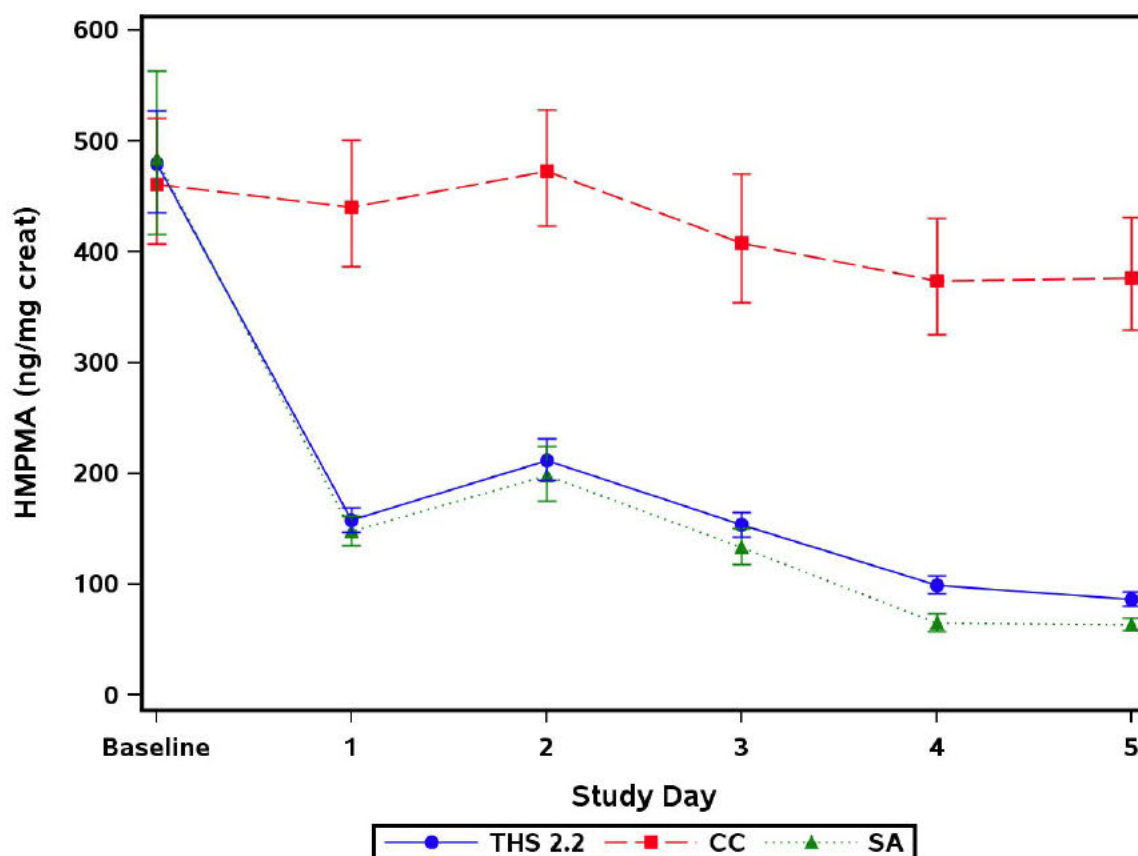


11.2.3.11 3-hydroxy-1-methylpropylmercapturic acid in 24-hour Urine

Subject listings of 3-HMPMA data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of the concentration of 3-HMPMA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.28](#), together with changes from baseline. Geometric mean and 95% CIs for 3-HMPMA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.23](#) and [Figure 29](#). Geometric mean and 95% CIs for urinary quantity of 3-HMPMA excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.24](#) and [Figure 30](#).

Figure 29 Geometric Mean 3-HMPMA Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)

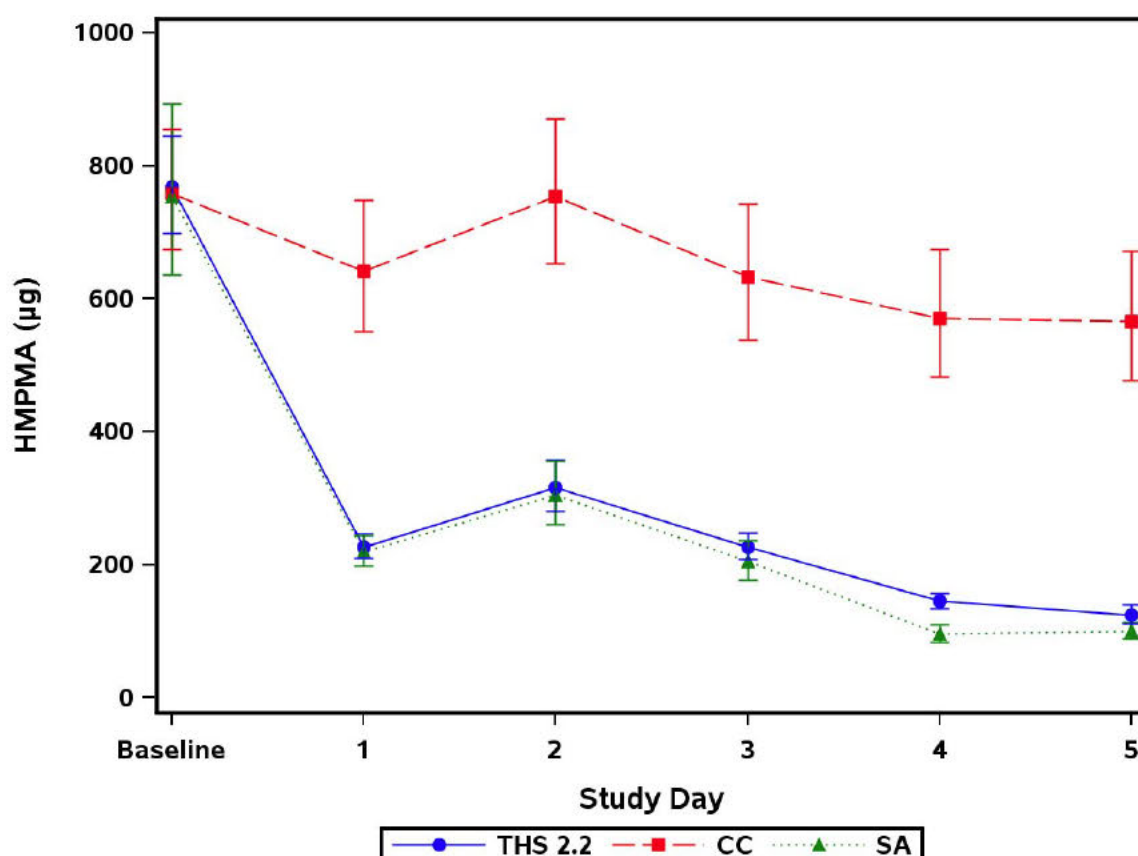


Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.23](#).

Figure 30 Geometric Mean Urinary 3-HMPMA Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.24](#).

The profiles were comparable for the THS 2.2 and SA arms, with an initial sharp decrease achieved on Day 1 before 3-HMPMA values increased slightly on Day 2 and then decreased steadily thereafter. Geometric mean 3-HMPMA values decreased in the THS 2.2 arm from baseline (479.34 ng/mg creat) to Day 5 (86.65 ng/mg creat) compared to 3-HMPMA in the CC arm, which decreased from baseline (460.52 ng/mg creat) to Day 5 (376.78 ng/mg creat). These values correspond to percent changes from baseline of -80.58% and -14.53% for the THS 2.2 and CC arms, respectively. In the SA arm, 3-HMPMA values also decreased from baseline (443.71 ng/mg creat) to Day 5 (63.25 ng/mg creat), as expected, which corresponded to a -84.39% change from baseline.



The profiles for mean 3-HMPMA quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

Analyses of 3-HMPMA urinary concentration adjusted for creatinine and urinary quantity of 3-HMPMA excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15](#), [Table 15.2.4.27](#) and [Table 57](#).

Table 57 Analysis of 3-HMPMA versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	78	122.82	21.85	0.076	18.83, 25.36
	CC	41	562.07			
Concentration adjusted for creatinine	THS 2.2	78	85.52	22.54	0.059	20.10, 25.29
	CC	41	379.36			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric Mean Ratio (THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	78	122.82	120.28	0.077	103.31, 140.02
	SA	39	102.12			
Concentration adjusted for creatinine	THS 2.2	78	85.52	132.46	0.060	117.83, 148.90
	SA	39	64.57			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15](#), [Table 15.2.4.27](#).

On Day 5, the LS mean level of 3-HMPMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 77.46% lower than that of subjects who continued to smoke CC (95% CI: 74.71, 79.90). The results for the quantity of 3-HMPMA excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS mean level of 3-HMPMA urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 32.46% higher than that of subjects who abstained from smoking (95% CI: 117.83, 148.90). The results for the quantity of 3-HMPMA excreted over 24 hours were consistent with the results of the urinary



concentration adjusted for creatinine, with 3-HMPMA 20.28% higher in subjects who switched to THS 2.2 compared to SA.

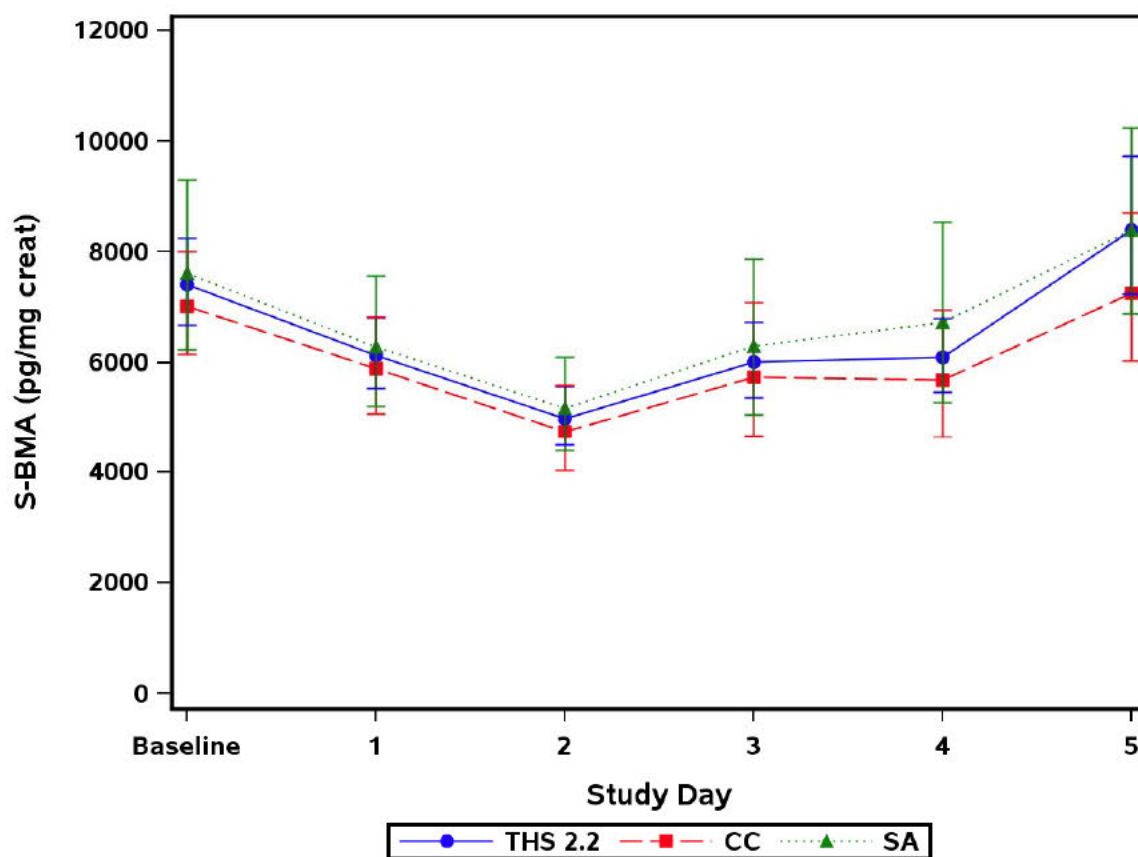
11.2.3.12 S-benzylmercapturic acid in 24-hour Urine

Subject listings of S-BMA data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of the concentration of S-BMA adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.30](#), together with changes from baseline. Geometric mean and 95% CIs for S-BMA urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.25](#) and [Figure 31](#). Geometric mean and 95% CIs for urinary quantity of S-BMA excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.26](#) and [Figure 32](#).



Figure 31 Geometric Mean S-BMA Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)



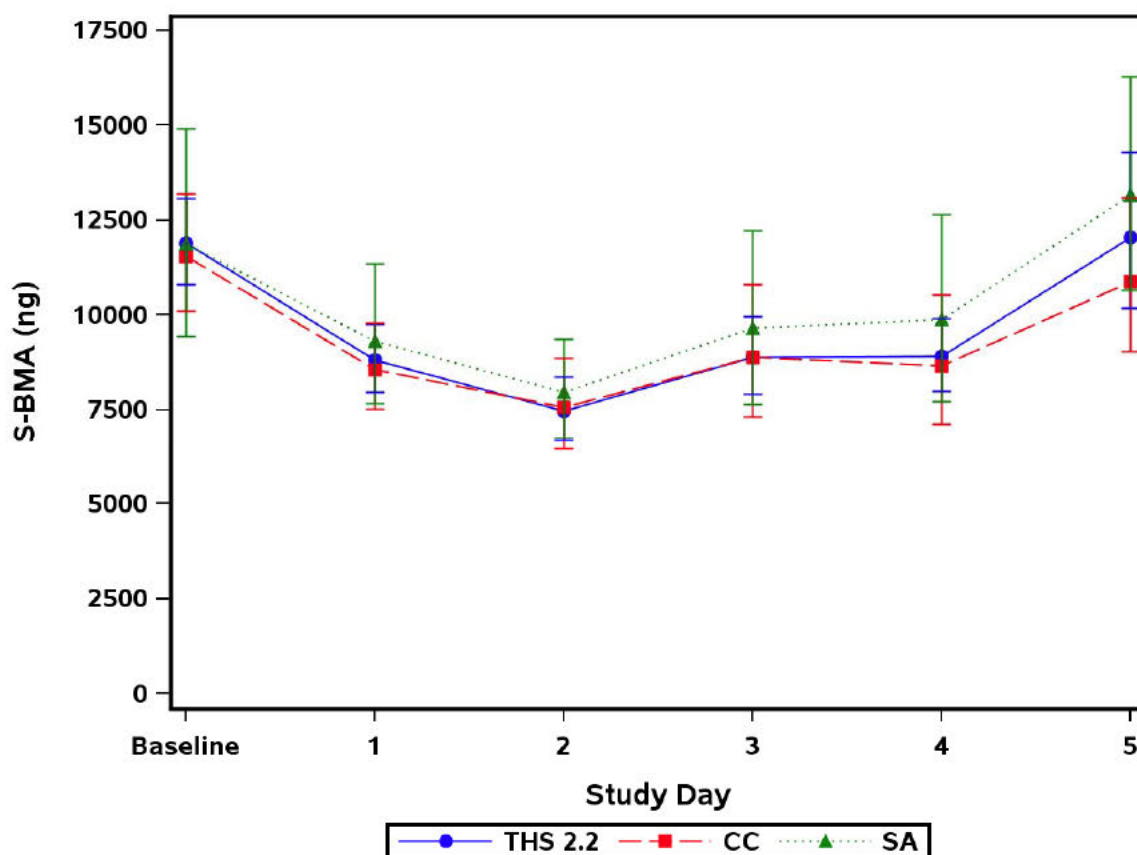
Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.25](#).



Figure 32 Geometric Mean Urinary S-BMA Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.26](#).

The profiles were comparable for all study arms, with mean values falling slightly from baseline to Day 2 before increasing over Days 3, 4, and 5. By Day 5, geometric mean S-BMA values in the THS 2.2, CC, and SA arms (8394.71, 7248.99, and 8397.62 pg/mg creat, respectively) had returned to approximate baseline values (7416.70, 7011.99, and 7254.96 pg/mg creat respectively). These values correspond to percent changes from baseline of 32.22%, 18.26%, and 30.80% for the THS 2.2, CC, and SA arms, respectively.

The profiles for mean S-BMA quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for all study arms.



Analyses of S-BMA urinary concentration adjusted for creatinine and urinary quantity of S-BMA excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15, Table 15.2.4.29](#) and [Table 58](#).

Table 58 Analysis of S-BMA versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	11888.39	108.37	0.113	86.78, 135.33
	CC	41	10970.22			
Concentration adjusted for creatinine	THS 2.2	79	8241.59	110.44	0.099	90.88, 134.20
	CC	41	7462.65			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	11888.39	88.79	0.115	70.83, 111.30
	SA	39	13389.43			
Concentration adjusted for creatinine	THS 2.2	79	8241.59	97.54	0.101	80.02, 118.89
	SA	39	8449.62			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15, Table 15.2.4.29](#).

On Day 5, both S-BMA urinary concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 and subjects who continued to smoke CC, with the 95% CIs for both assessments spanning 100%. Both S-BMA urinary concentration adjusted for creatinine and quantity excreted over 24 hours were also comparable between subjects who switched to THS 2.2 and subjects who abstained from smoking.

11.2.3.13 Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in 24-hour Urine

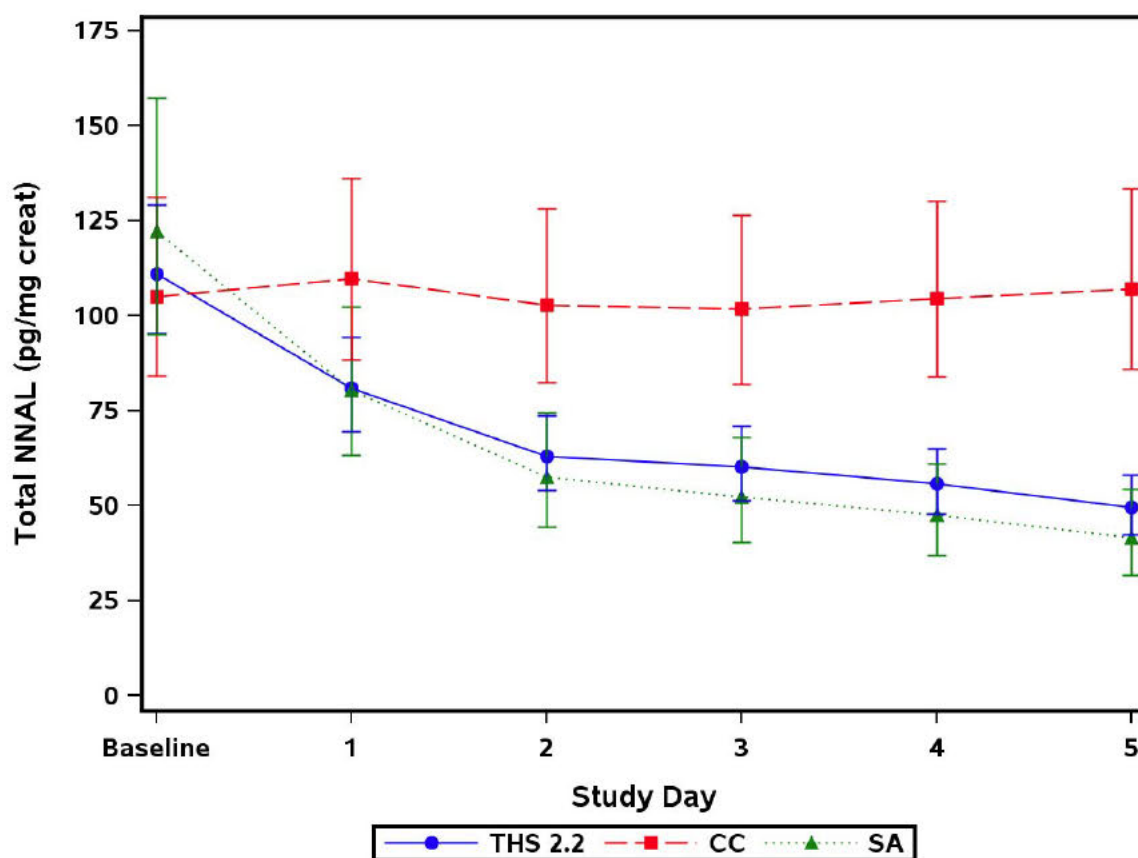
Subject listings of Total NNAL data are provided in [Appendix 15, Listing 15.3.3.2](#).

Descriptive statistics of the concentration of Total NNAL adjusted for creatinine and urinary quantity excreted over 24 hours during the course of the study are provided in [Appendix 15, Table 15.2.4.32](#) together with changes from baseline. Geometric mean and



95% CIs for Total NNAL urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.27](#) and [Figure 33](#). Geometric mean and 95% CIs for urinary quantity of Total NNAL excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.28](#) and [Figure 34](#).

Figure 33 Geometric Mean Total NNAL Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)

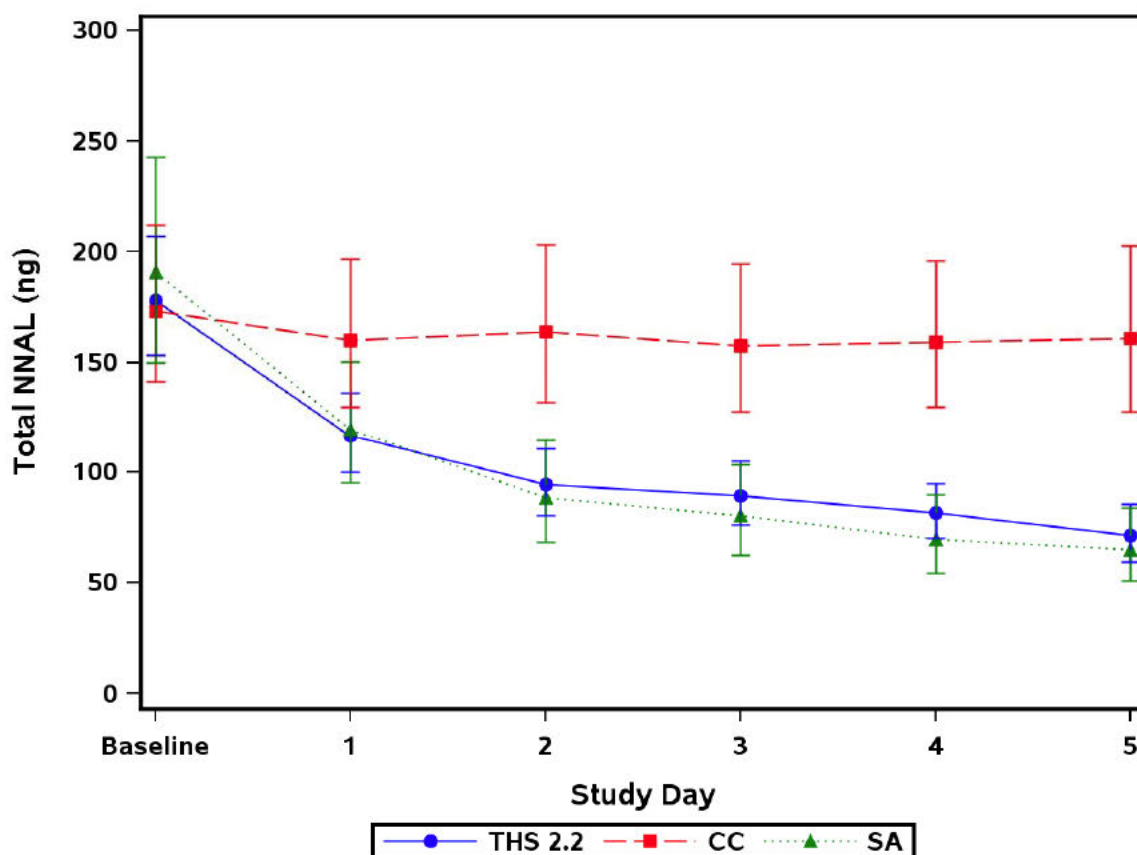


Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.27](#).

Figure 34 Geometric Mean Urinary Total NNAL Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.28](#).

The profiles were comparable for the THS 2.2 and SA arms, with a gradual decrease in Total NNAL observed from baseline to Day 5. Geometric mean Total NNAL values decreased in the THS 2.2 arm from baseline (111.01 pg/mg creat) to Day 5 (49.65 pg/mg creat) compared to Total NNAL in the CC arm, which remained comparable to baseline (105.05 pg/mg creat) on Day 5 (107.04 pg/mg creat). These values correspond to percent changes from baseline of -53.98% and 3.85% for the THS 2.2 and CC arms, respectively. In the SA arm, Total NNAL values also decreased from baseline (119.40 pg/mg creat) to Day 5 (41.51 pg/mg creat), as expected, which corresponded to a -63.95% change from baseline.



The profiles for mean Total NNAL quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

Analyses of Total NNAL urinary concentration adjusted for creatinine and urinary quantity of Total NNAL excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15, Table 15.2.4.31](#) and [Table 59](#).

Table 59 Analysis of Total NNAL versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	71.56	42.79	0.069	37.40, 48.95
	CC	41	167.25			
Concentration adjusted for creatinine	THS 2.2	79	49.61	43.54	0.052	39.34, 48.19
	CC	41	113.93			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio		
				(THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	71.56	115.49	0.070	100.73, 132.41
	SA	39	61.96			
Concentration adjusted for creatinine	THS 2.2	79	49.61	127.25	0.053	114.77, 141.08
	SA	39	38.99			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15, Table 15.2.4.31](#).

On Day 5, the LS mean level of Total NNAL urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 56.46% lower than that of subjects who continued to smoke CC (95% CI: 51.81, 60.66). The results for the quantity of Total NNAL excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS mean level of Total NNAL urinary concentration adjusted for creatinine in subjects who switched to THS 2.2 use was 27.25% higher than that of subjects who abstained from smoking, with the lower bound of the 95% CI greater than 100% (95% CI:



114.77, 141.08). The results for the quantity of Total NNAL excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine, with Total NNAL 15.49% higher in subjects who switched to THS 2.2 compared to SA.

11.2.4 Biomarkers of Exposure to Nicotine

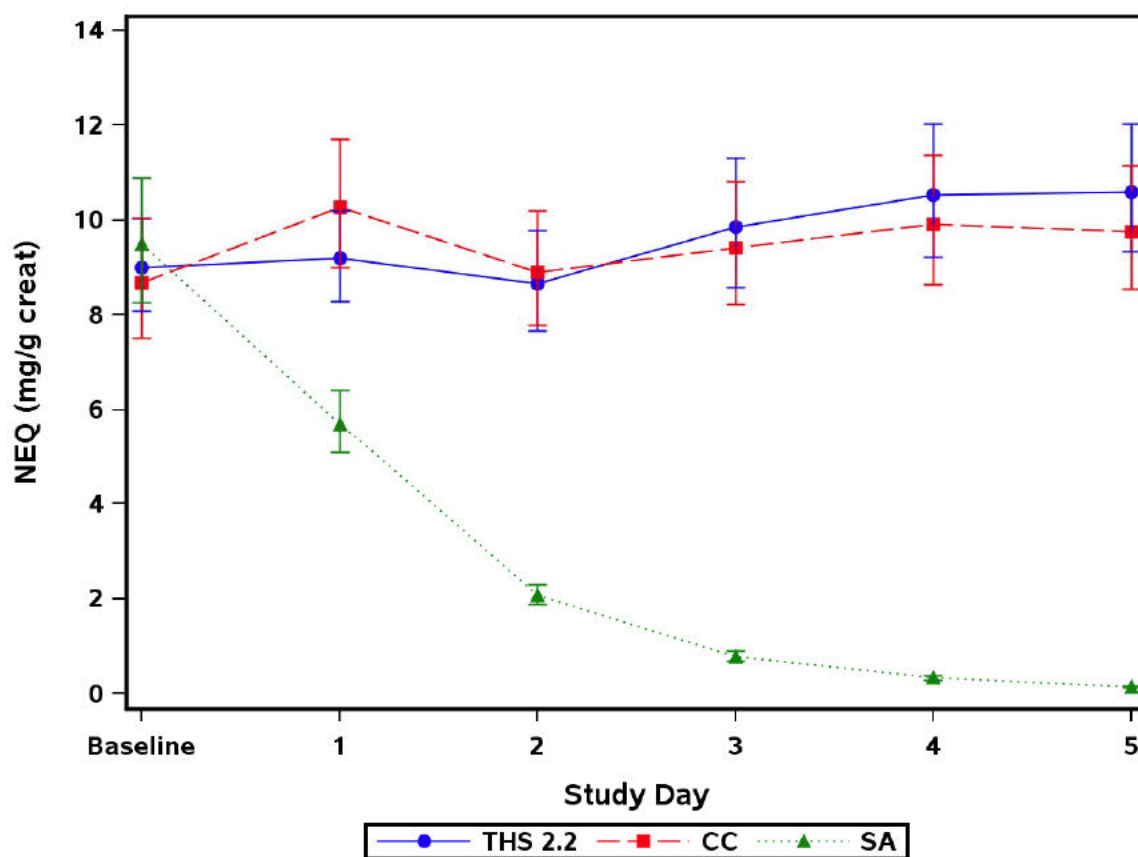
11.2.4.1 Nicotine Equivalents in 24-hour Urine

Subject listings of NEQ data are provided in [Appendix 15, Listing 15.3.3.2](#).

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 15.2.4.34](#) together with changes from baseline. Geometric mean and 95% CIs for NEQ urinary concentration adjusted for creatinine are presented graphically in [Appendix 15, Figure 15.1.2.29](#) and [Figure 35](#). Geometric mean and 95% CIs for urinary quantity of NEQ excreted over 24 hours are presented graphically in [Appendix 15, Figure 15.1.2.30](#) and [Figure 36](#).



Figure 35 Geometric Mean NEQ Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)



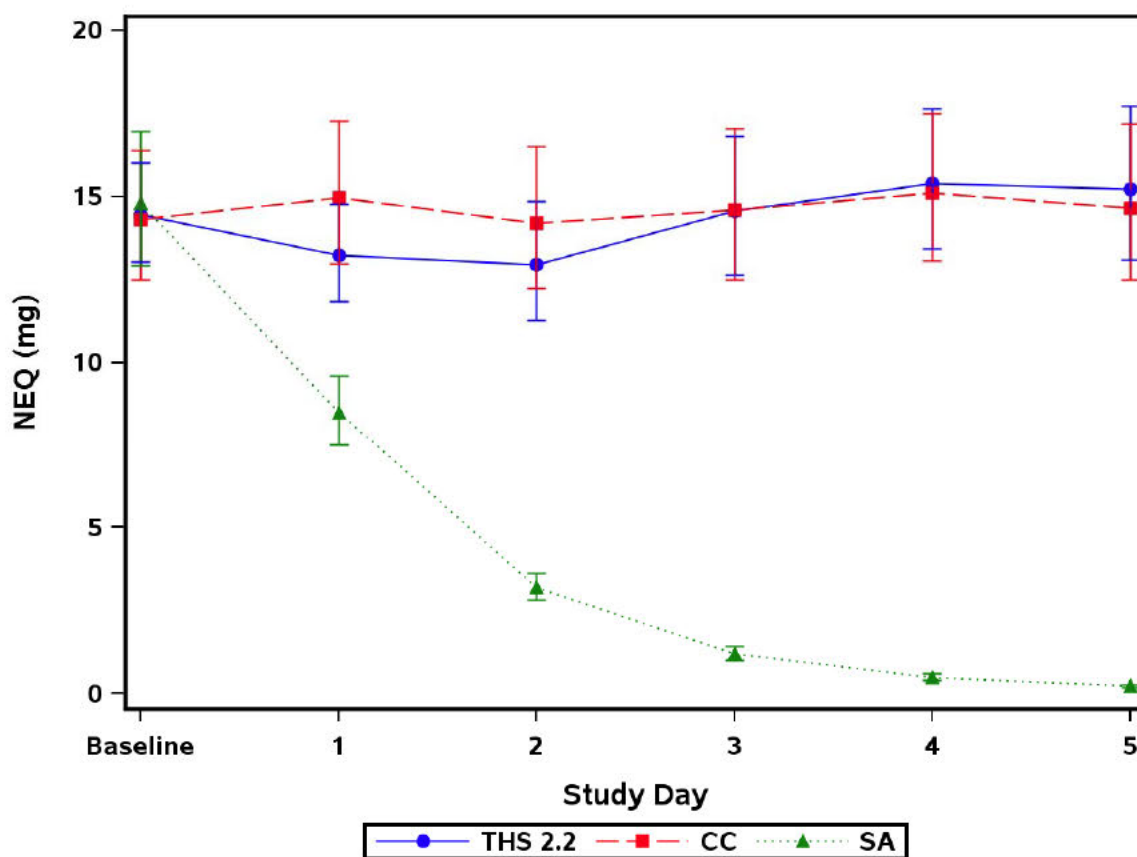
Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.29](#).



Figure 36 Geometric Mean Urinary NEQ Quantity Excreted Over 24 Hours During the Course of the Study (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

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

Data Source: [Appendix 15, Figure 15.1.2.30](#).

The profiles were comparable for the THS 2.2 and CC arms, with the exception of a decrease in NEQ levels on Days 1 and 2 in the THS 2.2 arm. In the THS 2.2 arm, geometric mean NEQ values increased from baseline (9.01 mg/g creat) to Day 5 (10.60 mg/g creat) while the results from the CC arm were comparable with those of the THS 2.2 arm, and showed an increase in NEQ from baseline (8.69 mg/g creat) to Day 5 (9.76 mg/g creat). These values correspond to percent changes from baseline of 22.95% and 14.78% for the THS 2.2 and CC arms, respectively. In the SA arm, NEQ values decreased from baseline (9.53 mg/g creat) to Day 5 (0.14 mg/g creat), as expected, which corresponded to a -98.25% change from baseline.



The profiles for mean NEQ quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

Analyses of NEQ urinary concentration adjusted for creatinine and urinary quantity of NEQ excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15, Table 15.2.4.33](#) and [Table 60](#).

Table 60 Analysis of NEQ versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC)		
				(%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	15.30	102.80	0.082	87.50, 120.78
	CC	41	14.89			
Concentration adjusted for creatinine	THS 2.2	79	10.61	104.89	0.067	92.03, 119.55
	CC	41	10.12			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:SA)		
				(%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	15.30	7043.21	0.083	5978.67, 8297.29
	SA	39	0.22			
Concentration adjusted for creatinine	THS 2.2	79	10.61	7737.73	0.068	6773.93, 8838.66
	SA	39	0.14			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15, Table 15.2.4.33](#).

On Day 5, both NEQ urinary concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 and subjects who continued to smoke CC, with the 95% CIs for both assessments spanning 100%.

On Day 5, the LS mean level of NEQ concentration adjusted for creatinine in subjects who switched to THS 2.2 use was higher than that of subjects who abstained from smoking, as expected (approximately 77-fold; 95% CI: 6773.93, 8838.66). The results for the quantity of NEQ excreted over 24 hours were consistent with the results of the urinary concentration



adjusted for creatinine, with a 70-fold higher level of NEQ in subjects who switched to THS 2.2 compared to SA.

11.2.4.2 Nicotine and Cotinine Concentrations in Plasma

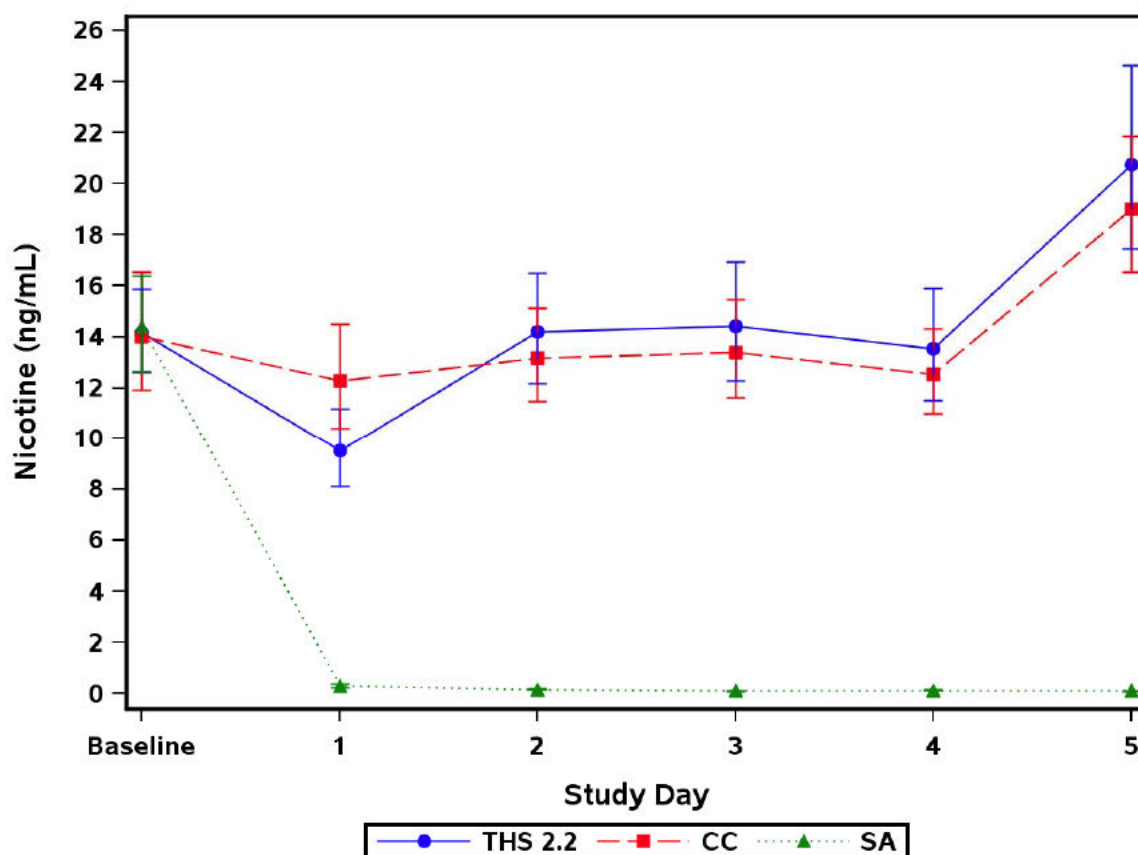
11.2.4.2.1 Plasma Nicotine Concentrations

Plasma nicotine concentrations (ng/mL) and sampling times are listed by subject in [Appendix 15, Listing 15.3.3.4](#). Plasma nicotine concentrations are summarized by study arm in [Appendix 15, Table 15.2.4.35](#).

Mean plasma nicotine concentrations taken between 08:00 and 10:00 PM are shown by study arm in [Appendix 15, Figure 15.1.2.31](#) and [Figure 37](#).



Figure 37 Geometric Mean Plasma Nicotine Concentrations (ng/mL) (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1. Evening result is presented for Day 5.

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

Data Source: [Appendix 15, Figure 15.1.2.31](#).

The profiles were comparable for the THS 2.2 and CC arms, with similar mean nicotine concentrations reported on all days except on Day 1 when the nicotine plasma concentration in the THS 2.2 arm was lower than that of the CC arm by 2.76 ng/mL. In the THS 2.2 arm, mean plasma nicotine concentration increased from baseline (14.16 ng/mL) to Day 5 (20.74 ng/mL) while the results from the CC arm showed an increase in mean nicotine plasma concentration from baseline (14.03 ng/mL) to Day 5 (19.01 ng/mL). There was an increase in use of approximately 2 Tobacco Sticks/CC between Day 4 and Day 5 in the THS 2.2 and CC arms, which could account for the increase in mean plasma nicotine concentration from Day 4 to Day 5.



In the SA arm, mean nicotine concentrations were comparable to those of the other study arms at baseline (14.39 ng/mL) before decreasing to 0.29 ng/mL at Day 1 following one day of SA and remained low for the remainder of the study (range of 0.17 to 0.10 ng/mL), with the majority of subjects nicotine concentrations BLOQ from Day 3 onwards.

Analysis of the change from Day 0 plasma nicotine concentration taken between 08:00 and 10:00 PM on Day 5 is presented in [Appendix 15, Table 15.2.4.41](#) and in [Table 61](#).

Table 61 Analysis of Change from Day 0 Plasma Nicotine Concentration at 08:00 PM on Day 5 (FAS Population)

Variable (unit)	Exposure	Number of Subjects	LS Mean	THS 2.2-CC	95% CI
Nicotine (ng/mL)	THS 2.2	79	3.54	2.55	-0.19, 5.29
	CC	41	0.99		

Abbreviations: CC = conventional cigarette; CI = confidence interval; LS = least squares; THS 2.2 = Tobacco Heating System 2.2.

Adjusted LS means and CIs from an ANCOVA model conducted on the change from Day 0 in Day 5 (result closest to 08:00 PM) values, with log-transformed Day 0 value, study arm, sex, and CC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.41](#).

Mean plasma nicotine concentrations increased from Day 0 to Day 5 for both the THS 2.2 and CC arms. There was a difference of 2.55 ng/mL in the changes from Day 0 plasma nicotine concentrations to Day 5 between subjects who switched to THS 2.2 and subjects who continued to smoke CC, although the 95% CIs spanned 0 (-0.19, 5.29).

Subject listings of plasma nicotine concentration parameters on Day 5 are provided in [Appendix 15, Listing 15.3.3.5](#) and are summarized by study arm in [Appendix 15, Table 15.2.4.37](#) and [Table 62](#).

**Table 62 Summary of Plasma Nicotine Concentration Parameters (FAS Population)**

Parameter (unit)	THS 2.2 (N=80)	CC (N=41)
C_{peak} (ng/mL)		
Number of subjects	79	40
Geometric mean	23.39	20.87
95% CI	20.44, 26.76	18.49, 23.56
Min, Max	2.2, 73.0	7.7, 41.6
CV (%)	65.82	39.25
t_{peak} (h)		
Number of subjects	79	40
Median	15.93	15.93
Min, Max	2.0, 16.2	4.0, 16.0
C_{avg} (ng/mL)		
Number of subjects	79	40
Geometric mean	12.40	11.08
95% CI	10.75, 14.31	9.81, 12.51
Min, Max	0.8, 29.9	4.6, 24.6
CV (%)	70.89	39.31

Abbreviations: C_{avg} = weighted average concentration over 24 hours; CC = conventional cigarette; CI = confidence interval; C_{peak} = peak plasma concentration; CV = coefficient of variation; Max = maximum; Min = minimum; N = number of subjects; THS 2.2 = Tobacco Heating System 2.2; t_{peak} = time to peak concentration

The parameters C_{peak} and C_{avg} were obtained directly from the plasma nicotine concentrations obtained on Day 5.

Data Source: [Appendix 15, Table 15.2.4.37](#).

Analysis of the plasma nicotine concentration parameters on Day 5 is presented in [Appendix 15, Table 15.2.4.39](#) and in [Table 63](#).

**Table 63 Analysis of Plasma Nicotine Concentration Parameters on Day 5 (FAS Population)**

Parameter (unit)	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2:CC) (%)	CV (%)	95% CI
C_{avg}^1 (ng/mL)	THS 2.2	79	12.44	112.91	59.51	91.36, 139.54
	CC	40	11.01			
C_{peak}^1 (ng/mL)	THS 2.2	79	23.44	112.80	56.42	92.15, 138.07
	CC	40	20.78			

Parameter (unit)	Exposure	Number of Subjects	Median	Median Difference	95% CI
t_{peak}^2 (h)	THS 2.2	79	15.93	0.00	0.00, 0.00
	CC	40	15.93		

Abbreviations: C_{avg} = weighted average concentration over 24 hours; CC = conventional cigarette; CI = confidence interval; C_{peak} = peak plasma concentration; CV = coefficient of variation; LS = least squares; THS 2.2 = Tobacco Heating System 2.2; t_{peak} = time to peak concentration.

¹ Geometric LS mean and 95% CI are the adjusted geometric least squares means based on an ANOVA model conducted on log-transformed values with study arm, sex, and CC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

² 95% CI are estimated only for the median difference based on the Hodges-Lehmann estimate
Data Source: [Appendix 15, Table 15.2.4.39](#).

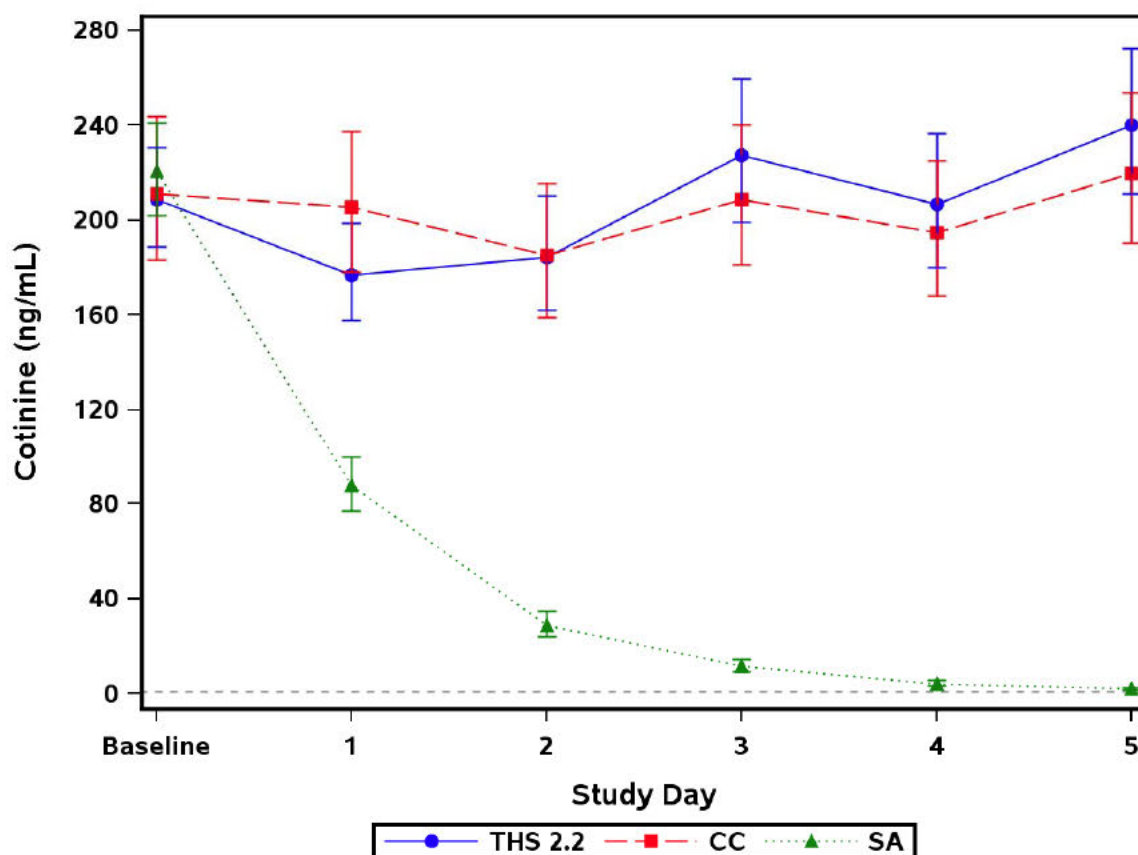
For nicotine exposure on Day 5, peak and weighted average plasma concentrations were comparable for the THS 2.2 and CC arms. On average, the Day 5 peak and weighted average nicotine concentrations were approximately 13% higher for THS 2.2 compared to CC, although the differences were not notable. The time to peak concentration on Day 5 was identical for the THS 2.2 and CC arms.

11.2.4.2.2 Plasma Cotinine Concentrations

Plasma cotinine concentrations (ng/mL) and sampling times are listed by subject in [Appendix 15, Listing 15.3.3.6](#). Plasma cotinine concentrations are summarized by study arm in [Appendix 15, Table 15.2.4.36](#).

Mean plasma cotinine concentrations taken between 08:00 and 10:00 PM are shown by study arm in [Appendix 15, Figure 15.1.2.32](#) and [Figure 38](#).

Figure 38 Geometric Mean Plasma Cotinine Concentrations (ng/mL) (FAS Population)



Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1. Evening result is presented for Day 5.

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

Data Source: [Appendix 15, Figure 15.1.2.32](#).

The profiles were comparable for the THS 2.2 and CC arms, although cotinine levels appeared to be higher for subjects in the THS 2.2 arm from Days 3 onwards. In the THS 2.2 arm, mean plasma cotinine concentration increased from baseline (208.54 ng/mL) to Day 5 (239.99 ng/mL) while the results from the CC arm showed comparable levels of mean cotinine plasma concentration at baseline (211.26 ng/mL) and Day 5 (219.73 ng/mL). In the SA arm, mean cotinine concentrations were comparable to those of the other study arms at baseline (220.60 ng/mL) and steadily decreased from Day 1 to Day 5 (2.05 ng/mL).

Analysis of the change from Day 0 plasma cotinine concentration at 08:00 PM taken between 08:00 and 10:00 PM on Day 5 is presented in [Appendix 15, Table 15.2.4.41](#) and in [Table 64](#).

**Table 64 Analysis of Change from Day 0 Plasma Cotinine Concentration at 08:00 PM on Day 5 (FAS Population)**

Variable (unit)	Exposure	Number of Subjects	LS Mean	THS 2.2 - CC	95% CI
Cotinine (ng/mL)	THS 2.2	79	25.20	30.91	6.36, 55.45
	CC	41	-5.70		

Abbreviations: CC = conventional cigarette; CI = confidence interval; LS = least squares; THS 2.2 = Tobacco Heating System 2.2.

Adjusted LS means and CIs from an ANCOVA model conducted on the change from Day 0 in Day 5 (result closest to 08:00 PM) values, with log-transformed Day 0 value, study arm, sex, and CC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.41](#).

Mean plasma cotinine concentrations increased from Day 0 to Day 5 in the THS 2.2 arm and decreased in the CC arm. The difference in the changes from Day 0 plasma cotinine concentrations to Day 5 between subjects who switched to THS 2.2 and subjects who continued to smoke CC was 30.91 ng/mL (95% CI: 6.36, 55.45).

Subject listings of plasma cotinine concentration parameters are provided in [Appendix 15, Listing 15.3.3.7](#), and are summarized by study arm in [Appendix 15, Table 15.2.4.38](#) and [Table 65](#).

**Table 65 Summary of Plasma Cotinine Concentration Parameters (FAS Population)**

Parameter (unit)	THS 2.2 (N=80)	CC (N=41)
C_{peak} (ng/mL)		
Number of subjects	79	41
Geometric mean	259.22	227.79
95% CI	228.21, 294.43	197.11, 263.25
Min, Max	25.4, 646.0	92.4, 641.0
CV (%)	61.79	48.35
t_{peak} (h)		
Number of subjects	79	41
Median	16.03	16.00
Min, Max	0.0, 24.0	0.0, 24.0
C_{avg} (ng/mL)		
Number of subjects	79	41
Geometric mean	219.58	197.98
95% CI	193.13, 249.66	171.50, 228.55
Min, Max	17.8, 479.1	82.4, 570.8
CV (%)	62.34	47.94

Abbreviations: C_{avg} = weighted average concentration over 24 hours; CC = conventional cigarette; CI = confidence interval; C_{peak} = peak plasma concentration; CV = coefficient of variation; Max = maximum; Min = minimum; N = number of subjects; THS 2.2 = Tobacco Heating System 2.2; t_{peak} = time to peak concentration.

The parameters C_{peak} and C_{avg} were obtained directly from the plasma cotinine concentrations obtained on Day 5.

Data Source: [Appendix 15, Table 15.2.4.38](#).

Analysis of the plasma cotinine concentration parameters on Day 5 is presented in [Appendix 15, Table 15.2.4.40](#) and in [Table 66](#).

**Table 66 Analysis of Plasma Cotinine Concentration Parameters on Day 5 (FAS Population)**

Parameter (unit)	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2:CC) (%)	CV (%)	95% CI
C_{avg}^1 (ng/mL)	THS 2.2	79	220.07	111.03	56.37	90.87, 135.65
	CC	41	198.21			
C_{peak}^1 (ng/mL)	THS 2.2	79	259.79	113.83	55.86	93.31, 138.85
	CC	41	228.23			

Parameter (unit)	Exposure	Number of Subjects	Median	Median Difference	95% CI
t_{peak}^2 (h)	THS 2.2	79	16.03	0.00	0.00, 0.07
	CC	41	16.00		

Abbreviations: C_{avg} = weighted average concentration over 24 hours; CC = conventional cigarette; CI = confidence interval; C_{peak} = peak plasma concentration; CV = coefficient of variation; LS = least squares; THS 2.2 = Tobacco Heating System 2.2; t_{peak} = time to peak concentration.

¹ Geometric LS mean and 95% CI are the adjusted geometric least squares means based on an ANOVA model conducted on log-transformed values with study arm, sex, and CC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

² 95% CI are estimated only for the median difference based on the Hodges-Lehmann estimate.

Data Source: [Appendix 15, Table 15.2.4.40](#).

For cotinine exposure on Day 5, peak and weighted average plasma concentrations were similar for the THS 2.2 and CC arms. On average, the Day 5 peak and weighted average cotinine concentrations were approximately 11% to 13% higher for THS 2.2 compared to CC, although the differences were not notable. The time to peak concentration on Day 5 was identical for the THS 2.2 and CC arms.

11.2.5 Cytochrome P450 1A2 Activity

Cytochrome P450 1A2 activity was calculated in plasma as the metabolic ratio of PX/CAF.

Individual subject listings of CYP1A2 activity and changes from baseline data are provided in [Appendix 15, Listing 15.3.4.1](#). Descriptive statistics of CYP1A2 activity including change from baseline are summarized by study arm in [Appendix 15, Table 15.2.4.49](#) and [Table 67](#).

**Table 67 Descriptive Statistics and Percent Change from Baseline in CYP1A2 Activity (FAS Population)**

Study Arm	Time Point	Number of Subjects	Mean	SD	Min	Median	Max
THS 2.2	Baseline	80	112.426	36.0013	32.10	111.142	204.80
	Day 5	79	91.710	29.1658	29.37	90.420	186.18
	% change from baseline	79	-16.509	17.9780	-48.87	-18.491	54.20
CC	Baseline	40	110.260	29.9344	49.54	112.561	177.59
	Day 5	41	123.009	34.6639	49.98	121.947	186.55
	% change from baseline	40	12.714	15.6626	-20.96	11.200	48.70
SA	Baseline	38	113.141	44.8515	40.02	104.343	204.40
	Day 5	39	94.450	36.5866	30.63	86.408	190.61
	% change from baseline	38	-14.860	15.7985	-45.71	-16.514	26.84

Abbreviations: CC = conventional cigarette; Max = maximum; Min = minimum; SA = smoking abstinence; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.49](#).

At baseline, CYP1A2 activity was comparable between study arms (range of 110.260% to 113.141%). In the THS 2.2 and SA arms, CYP1A2 activity had decreased by approximately 17% and 15%, respectively, at Day 5. In the CC arm, CYP1A2 activity increased by approximately 13%.

Analyses of CYP1A2 activity (absolute and change from baseline) on Day 5 for THS 2.2 use versus CC use, and versus SA, are presented in [Appendix 15, Table 15.2.4.50](#) and [Table 68](#).

**Table 68 Analysis of CYP1A2 Activity versus CC and SA on Day 5 (FAS Population)**

Parameter	Exposure	Number of Subjects	LS Mean	THS 2.2 - CC	SE	95% CI
Absolute	THS 2.2	79	91.35	-33.60	3.537	-40.59, -26.61
	CC	41	124.95			
Change from baseline	THS 2.2	79	-20.81	-33.60	3.537	-40.59, -26.61
	CC	40	12.79			

Parameter	Exposure	Number of Subjects	LS Mean	THS 2.2 - SA	SE	95% CI
Absolute	THS 2.2	79	91.35	-1.99	3.597	-9.10, 5.12
	SA	39	93.34			
Change from baseline	THS 2.2	79	-20.81	-1.99	3.597	-9.10, 5.12
	SA	38	-18.83			

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

Adjusted LS means and CIs from an ANOVA model with baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.50](#).

On Day 5, the LS mean levels of absolute and change from baseline CYP1A2 activity following THS 2.2 use was 33.60% lower than that determined following CC use (95% CI: 26.61, 40.59).

There was no notable difference in absolute CYP1A2 activity on Day 5 or change from baseline in CYP1A2 activity between subjects who switched to THS 2.2 use and subjects who abstained from smoking.

11.2.6 Tobacco Consumption

Subject listings of product usage are provided in [Appendix 15, Listing 15.3.2.1.1](#) and [Listing 15.3.2.1.2](#), and are summarized for the Safety population by study arm in [Appendix 15, Table 15.2.2.1](#).

Details of subject's tobacco consumption are presented in [Section 10.5](#).



11.3 Analysis of Exploratory Endpoints

11.3.1 Ames Mutagenicity Test

Individual subject listings of mutagenicity results and percent changes from baseline data are provided in [Appendix 15, Listing 15.3.5.1](#). Descriptive statistics of Ames Mutagenicity Test (YG1024+S9) including change from baseline are summarized by study arm in [Appendix 15, Table 15.2.4.42](#) and [Table 69](#).

Table 69 Descriptive Statistics and Percent Change from Baseline in Ames Mutagenicity Test (YG1024+S9) (REV/24h) (FAS Population)

Study Arm	Time Point	Number of		SD	Min	Median	Max
		Subjects	Arithmetic Mean				
THS 2.2	Baseline	64	23199.26	21054.119	0.0	19681.50	107250.0
	Day 5	52	10670.52	8155.693	0.0	8822.75	39600.0
	% change from baseline	42	52997.96	273527.662	-100.0	-56.93	1707300.0
CC	Baseline	28	16914.76	14336.658	0.0	15775.00	72216.0
	Day 5	31	26975.64	15866.931	0.0	21689.00	63840.0
	% change from baseline	23	370667.73	1348543.061	-64.5	29.29	6111000.0
SA	Baseline	23	30212.25	29347.944	3060.0	22540.00	113620.0
	Day 5	26	10609.63	12918.414	0.0	7437.00	65400.0
	% change from baseline	17	-3.67	203.176	-100.0	-62.44	768.6

Abbreviations: CC = conventional cigarette; Max = maximum; Min = minimum; SA = smoking abstinence; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.42](#).

The mean Ames mutagenicity test values and changes from baseline appear to be skewed higher due to a number of subjects with outlying data, therefore the median values are probably more reliable for interpretation of the data. The following subjects had outlying mean change from baseline data:

In the THS 2.2 arm:

- Subject 0282: 0.0 REV/24h at baseline and 17073 REV/24h at Day 5; change from baseline of 1707300%.
- Subject 0308: 0.0 REV/24h at baseline and 5202 REV/24h at Day 5; change from baseline of 520200%.



In the CC arm:

- Subject 0224: 5831 REV/24h at baseline and 32240 REV/24h at Day 5; change from baseline of 452.91%.
- Subject 0283: 0.0 REV/24h at baseline and 24133.5 REV/24h at Day 5; change from baseline of 2413350%.
- Subject 0285: 0.0 REV/24h at baseline and 61110 REV/24h at Day 5; change from baseline of 6111000%.

In the SA arm:

- Subject 0145: 3060 REV/24h at baseline and 26580 REV/24h at Day 5; change from baseline of 768.63%.

At baseline, median Ames mutagenicity test values were comparable between the THS 2.2 and SA arms (19681.5 and 22540.0 Rev/24h, respectively) and slightly lower in the CC arm (15775.0 Rev/24h). On Day 5, in the THS 2.2 and SA arms, median Ames mutagenicity test values had decreased by approximately 57% and 62%, respectively, while in the CC arm, median Ames mutagenicity test values increased by approximately 29%.

11.3.2 Cytochrome P450 2A6 Activity

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 15.3.6.15](#). Descriptive statistics of CYP2A6 activity including change from baseline are summarized by study arm in [Appendix 15, Table 15.2.4.51](#) and [Table 70](#).

**Table 70 Descriptive Statistics and Percent Change from Baseline in CYP2A6 Activity (FAS Population)**

Study Arm	Time Point	Number of Subjects	Mean	SD	Min	Median	Max
THS 2.2	Baseline	80	41.556	15.3968	6.68	40.501	73.00
	Day 6	79	26.794	8.7966	7.86	27.583	49.57
	% change from baseline	79	-32.377	14.8052	-66.98	-34.700	17.72
CC	Baseline	41	44.313	15.2036	16.00	40.794	73.57
	Day 6	41	27.927	8.6240	13.49	27.125	51.77
	% change from baseline	41	-33.581	20.6722	-61.84	-39.634	39.05
SA	Baseline	39	40.874	15.7486	14.65	38.310	79.21
	Day 6	30	98.652	46.3961	24.57	92.381	191.30
	% change from baseline	30	166.984	107.3340	23.67	150.270	456.62

Abbreviations: CC = conventional cigarette; Max = maximum; Min = minimum; SA = smoking abstinence; SD = standard deviation; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Table 15.2.4.51](#).

At baseline, CYP2A6 activity was comparable between study arms (range of 40.874% to 44.313%). In the THS 2.2 and CC arms, CYP2A6 activity had decreased by approximately 32% and 34%, respectively, at Day 6. In the SA arm, CYP2A6 activity increased by approximately 167%.

Analyses of CYP2A6 activity (absolute and change from baseline) on Day 6 for THS 2.2 use versus CC use, and versus SA, are presented in [Appendix 15, Table 15.2.4.52](#) and [Table 71](#).

**Table 71 Analysis of CYP2A6 Activity versus CC and SA on Day 6 (FAS Population)**

Parameter	Exposure	Number of Subjects	LS Mean	THS 2.2 - CC	SE	95% CI
Absolute	THS 2.2	79	26.63	0.48	3.671	-6.78, 7.74
	CC	41	26.15			
Change from baseline	THS 2.2	79	-14.86	0.48	3.671	-6.78, 7.74
	CC	41	-15.34			

Parameter	Exposure	Number of Subjects	LS Mean	THS 2.2 - SA	SE	95% CI
Absolute	THS 2.2	79	26.63	-75.50	4.125	-83.66, -67.34
	SA	30	102.13			
Change from baseline	THS 2.2	79	-14.86	-75.50	4.125	-83.66, -67.34
	SA	30	60.64			

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

Adjusted LS means and CIs from an ANOVA model with baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors.

Data Source: [Appendix 15, Table 15.2.4.52](#).

There was no notable difference in absolute CYP2A6 activity on Day 6 or change from baseline in CYP2A6 activity between subjects who switched to THS 2.2 use and subjects who continued to smoke CC.

On Day 6, the absolute and change from baseline CYP2A6 activity following THS 2.2 use were 75.50% lower than that determined following SA (95% CI: 67.34, 83.66).

11.3.3 Risk Markers

11.3.3.1 8-epi-prostaglandine F2 α in Urine

Subject listings of 8-epi-PGF_{2 α} data are provided in [Appendix 15, Listing 15.3.3.3](#).

Descriptive statistics of the urinary quantity of 8-epi-PGF_{2 α} excreted over 24 hours and the urinary concentration adjusted for creatinine and at baseline and on Day 5 are provided in [Appendix 15, Table 15.2.4.54](#), together with changes from baseline.

At baseline, the concentration of 8-epi-PGF_{2 α} adjusted for creatinine was comparable between study arms (geometric mean range of 189.93 to 209.01 pg/mg creat). At Day 5, the levels of 8-epi-PGF_{2 α} concentration adjusted for creatinine were 236.11, 232.76, and



241.95 pg/mg creat (an increase from baseline of approximately 15%, 25%, and 28%) in the THS 2.2, CC, and SA arms, respectively.

Results for the quantity of 8-epi-PGF_{2α} excreted over 24 hours showed a comparable trend. At baseline, the quantity of 8-epi-PGF_{2α} excreted over 24 hours was comparable between study arms (geometric mean range of 312.98 to 335.13 ng). At Day 5, the quantity of 8-epi-PGF_{2α} excreted over 24 hours were 338.99, 349.57, and 379.54 ng (an increase from baseline of approximately 5%, 16%, and 26%) in the THS 2.2, CC, and SA arms, respectively.

Analyses of 8-epi-PGF_{2α} urinary concentration adjusted for creatinine and urinary quantity of 8-epi-PGF_{2α} excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15, Table 15.2.4.53](#) and [Table 72](#).

Table 72 Analysis of 8-epi-PGF_{2α} versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)		
				SE	95% CI	
Quantity excreted over 24 hours	THS 2.2	79	330.82	91.96	0.054	82.67, 102.30
	CC	41	359.73			
Concentration adjusted for creatinine	THS 2.2	79	230.45	94.40	0.041	87.16, 102.23
	CC	41	244.13			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:SA) (%)		
				SE	95% CI	
Quantity excreted over 24 hours	THS 2.2	79	330.82	84.45	0.058	75.31, 94.68
	SA	39	391.76			
Concentration adjusted for creatinine	THS 2.2	79	230.45	92.40	0.044	84.84, 100.62
	SA	39	249.42			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15, Table 15.2.4.53](#).

On Day 5, there were no notable differences observed in both the urinary concentration of 8-epi-PGF_{2α} adjusted for creatinine and the quantity excreted over 24 hours between



subjects who switched to THS 2.2 and subjects who continued to smoke CC, with the 95% CIs for both assessments spanning 100%.

On Day 5, there was no notable difference observed in the concentration of 8-epi-PGF_{2α} adjusted for creatinine between subjects who switched to THS 2.2 use and that of subjects who abstained from smoking, with the 95% CIs spanning 100%. The LS mean level of 8-epi-PGF_{2α} excreted over 24 hours in subjects who switched to THS 2.2 use was 15.55% lower than that of subjects who abstained from smoking (95% CI: 5.32, 24.69)

11.3.3.2 11-dehydrothromboxane B2 in Urine

Subject listings of 11-DTX-B2 data are provided in [Appendix 15, Listing 15.3.3.3](#).

Descriptive statistics of the urinary concentration of 11-DTX-B2 adjusted for creatinine and urinary quantity excreted over 24 hours at baseline and on Day 5 are provided in [Appendix 15, Table 15.2.4.56](#), together with changes from baseline.

At baseline, the concentration of 11-DTX-B2 adjusted for creatinine was comparable in the CC and SA arms (geometric mean values of 467.88 and 468.61 pg/mg creat, respectively) and was higher in the THS 2.2 arm (536.12 pg/mg creat). At Day 5, the 11-DTX-B2 adjusted for creatinine was comparable to the baseline value in the THS 2.2 and SA arms (approximate 1% increase and 3% decrease, respectively), and had increased to 565.18 pg/mg creat (an increase from baseline of approximately 30%) in the CC arm.

At baseline, the quantity of 11-DTX-B2 excreted over 24 hours was comparable in the CC and SA arms (geometric mean values of 764.90 and 730.60 ng, respectively) and was higher in the THS 2.2 arm (859.64 ng). In the THS 2.2 and SA arms at Day 5, the quantity of 11-DTX-B2 excreted over 24 hours was comparable to baseline (approximately 7% and 2% decrease, respectively), and had increased to 848.79 ng (an increase from baseline of approximately 21%) in the CC arm.

Analyses of 11-DTX-B2 urinary concentration adjusted for creatinine and urinary quantity of 11-DTX-B2 excreted over 24 hours for THS 2.2 use versus CC use and SA on Day 5 are presented in [Appendix 15, Table 15.2.4.55](#) and [Table 73](#).

**Table 73 Analysis of 11-DTX-B2 versus CC and SA on Day 5 (FAS Population)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	727.62	81.26	0.056	72.83, 90.66
	CC	41	895.44			
Concentration adjusted for creatinine	THS 2.2	79	506.02	83.63	0.040	77.31, 90.46
	CC	41	605.09			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:SA) (%)	SE	95% CI
Quantity excreted over 24 hours	THS 2.2	79	727.62	101.44	0.060	90.19, 114.09
	SA	39	717.31			
Concentration adjusted for creatinine	THS 2.2	79	506.02	110.07	0.043	101.22, 119.70
	SA	39	459.73			

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

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed Day 5 values with log-transformed baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Standard errors presented from analysis performed on the log_e scale.

Data Source: [Appendix 15, Table 15.2.4.55](#).

On Day 5, the LS mean level of the concentration of 11-DTX-B2 adjusted for creatinine in subjects who switched to THS 2.2 use was 16.37% lower than that of subjects who continued to smoke CC (95% CI: 9.54, 22.69). The results for the quantity of 11-DTX-B2 excreted over 24 hours were consistent with the results of the concentration adjusted for creatinine, with a 18.74% decrease in subjects who switched to THS 2.2 compared to subjects who continued to smoke CC (95% CI: 9.34, 27.17).

On Day 5, the LS mean concentration of 11-DTX-B2 adjusted for creatinine in subjects who switched to THS 2.2 use was 10.07% higher than that of subjects who abstained from smoking (95% CI: 101.22, 119.70). There was no notable difference observed in the quantity of 11-DTX-B2 excreted over 24 hours between subjects who switched to THS 2.2 and subjects who abstained from smoking, with the 95% CIs spanning 100%.

11.3.3.3 Analysis of the Relationship between Risk Markers and Nicotine Equivalents

A scatterplot of 8-epi-PGF_{2α} urinary concentration adjusted for creatinine versus NEQ urinary concentration adjusted for creatinine is presented in [Appendix 15, Figure 15.1.2.40](#).



A scatterplot of 8-epi-PGF_{2α} urinary quantity excreted over 24 hours versus NEQ urinary quantity excreted over 24 hours is presented in [Appendix 15, Figure 15.1.2.41](#).

Analysis of the relationship between 8-epi-PGF_{2α} (urinary concentration adjusted for creatinine and quantity excreted over 24 hours) and NEQ are presented in [Appendix 15, Table 15.2.4.57](#) and [Table 74](#).

Table 74 Analysis of Relationship Between NEQ and 8-epi-PGF_{2α} on Day 5 (FAS Population)

Relationship	Randomization Arm	Slope	P-value
NEQ (mg/g creat) vs. 8-epi-PGF _{2α} (pg/mg creat)	THS 2.2	2.84	0.127
	CC	6.19	0.014
	SA	507.12	0.038
	THS 2.2 vs. CC	-3.34	0.314
NEQ (mg/24h) vs. 8-epi-PGF _{2α} (ng/24h)	THS 2.2	9.68	<0.001
	CC	9.09	<0.001
	SA	795.44	<0.001
	THS 2.2 vs. CC	0.58	0.848

Abbreviations: 8-epi-PGF_{2α} = 8-epi-prostaglandine F_{2α}; CC = conventional cigarette; NEQ = nicotine equivalents; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Model for each arm separately was: Biomarker = NEQ for each arm separately. P-value for test of R² = 0. Model for THS 2.2 vs CC was: Biomarker = NEQ + randomization arm + NEQ*randomization arm. P-value for significance of NEQ*randomization arm. Slope estimate was the difference in slopes.

Data Source: [Appendix 15, Table 15.2.4.57](#).

There was no correlation between the concentration of NEQ adjusted for creatinine and the concentration of 8-epi-PGF_{2α} adjusted for creatinine for subjects in the THS 2.2 arm, whereas for subjects in the CC and SA arms, a correlation was observed. There was no correlation between the slopes for the THS 2.2 and the CC arms.

There was a correlation between the urinary quantity of NEQ excreted over 24 hours versus the urinary quantity of 8-epi-PGF_{2α} for all study arms. However, there was no correlation between the slopes for the THS 2.2 and the CC arms.

A scatterplot of 11-DTX-B2 urinary concentration adjusted for creatinine versus NEQ urinary concentration adjusted for creatinine is presented in [Appendix 15, Figure 15.1.2.42](#). A scatterplot of 11-DTX-B2 urinary quantity excreted over 24 hours versus NEQ urinary quantity excreted over 24 hours is presented in [Appendix 15, Figure 15.1.2.43](#).

Analysis of the relationship between 11-DTX-B2 (urinary concentration adjusted for creatinine and quantity excreted over 24 hours) and NEQ are presented in [Appendix 15, Table 15.2.4.57](#) and [Table 75](#).

**Table 75 Analysis of Relationship Between NEQ and 11-DTX-B2 on Day 5 (FAS Population)**

Relationship	Randomization Arm	Slope	P-value
NEQ (mg/g creat) vs. 11-DTX-B2 (pg/mg creat)	THS 2.2	12.13	<0.001
	CC	27.52	0.003
	SA	-721.77	0.130
	THS 2.2 vs. CC	-15.39	0.058
NEQ (mg/24h) vs. 11-DTX-B2 (ng/24h)	THS 2.2	16.95	<0.001
	CC	18.69	0.004
	SA	-85.58	0.789
	THS 2.2 vs. CC	-1.73	0.771

Abbreviations: 11-DTX-B2 = 11-dehydrothromboxane B2; CC = conventional cigarette; NEQ = nicotine equivalents; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Model for each arm separately was: Biomarker = NEQ for each arm separately. P-value for test of $R^2 = 0$. Model for THS 2.2 vs CC was: Biomarker = NEQ + randomization arm + NEQ*randomization arm. P-value for significance of NEQ*randomization arm. Slope estimate was the difference in slopes.

Data Source: [Appendix 15, Table 15.2.4.57](#).

There was a correlation between the concentration of NEQ adjusted for creatinine and the concentration of 11-DTX-B2 adjusted for creatinine for subjects in the THS 2.2 and CC arms, whereas for subjects in the SA arm, there was no correlation. There was also no correlation between the slopes for the THS 2.2 and the CC arms.

There was a correlation between the urinary quantity of NEQ excreted over 24 hours versus the urinary quantity of 11-DTX-B2 for the THS 2.2 and CC arms; however, there was no correlation for subjects in the SA arm. There was also no correlation between the slopes for the THS 2.2 and the CC arms.

11.3.4 Subjective Effects of Smoking Endpoints

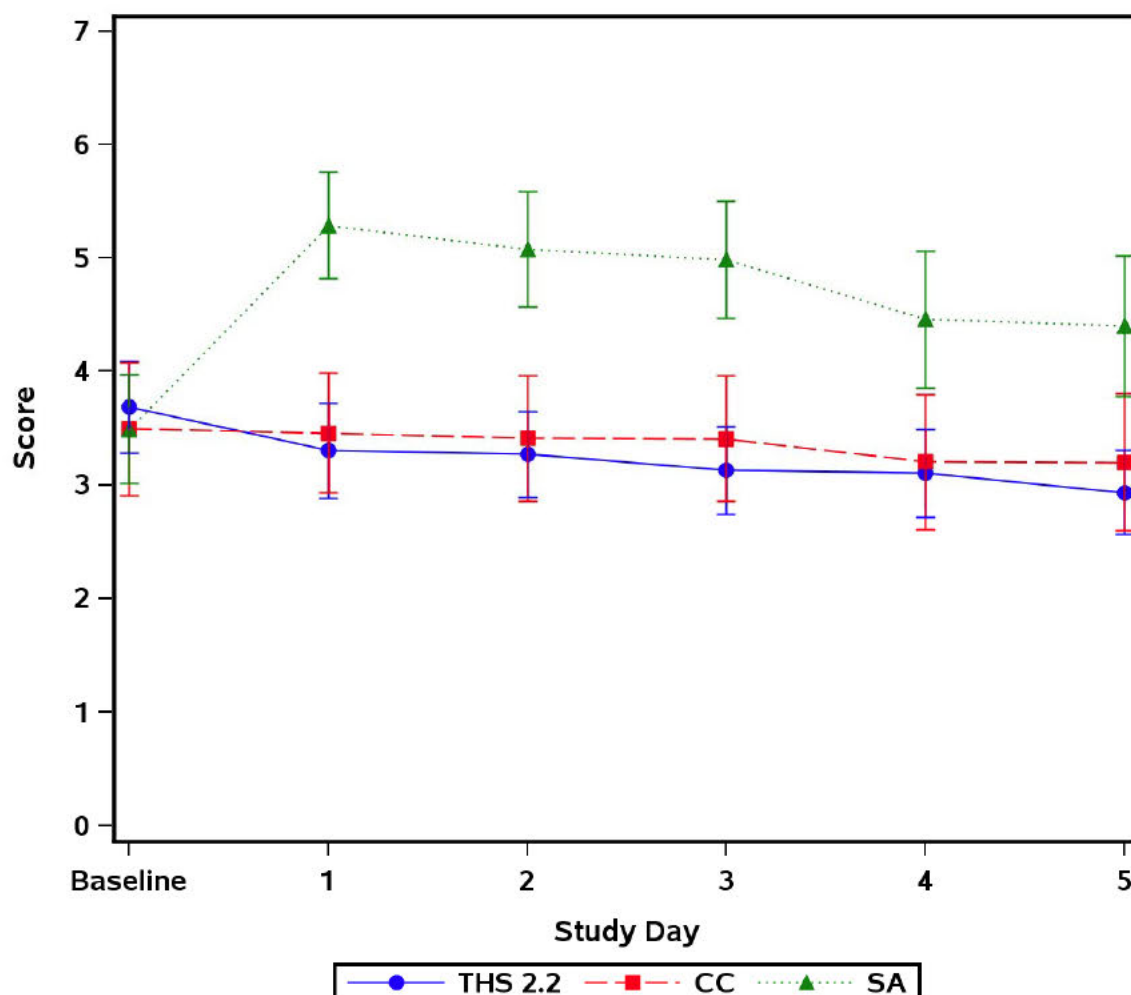
11.3.4.1 Urge-to-Smoke Symptoms (QSU-brief)

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 15.3.6.11](#), and are summarized by study arm in [Appendix 15, Table 15.2.4.43](#).

Line graphs showing the mean scores for the QSU-brief over the course of the study are presented in [Appendix 15, Figure 15.1.2.33](#) (Factor 1, Factor 2, and total scores) and in [Figure 39](#) (total score).



Figure 39 Mean Total Scores for QSU-Brief During the Course of the Study (FAS Population)



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

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

QSU-brief scores were reported on a 7-point scale. Higher scores indicate greater intensity of urge.

Data Source: [Appendix 15, Figure 15.1.2.33](#).

The average urge-to-smoke total scores were 3.69 for the THS 2.2 arm, 3.49 for the CC arm, and 3.49 for the SA arm at baseline. For the THS 2.2 and CC arms, the average urge-to-smoke total score remained stable and were comparable throughout the study (ranges of 2.93 to 3.30 and 3.20 to 3.46, respectively). In the SA arm, the urge-to-smoke total score increased from baseline to Day 1 (score of 5.29, corresponding to an increase of 1.8 points). Total score values then decreased from 5.29 at Day 1 to 4.40 at Day 5.



The results from the statistical analysis of the QSU-brief questionnaire factors and total score are presented in [Appendix 15, Table 15.2.4.44](#) and [Table 76](#). Profiles of the LS mean differences (THS 2.2 – CC and THS 2.2 – SA) over time are presented in [Appendix 15, Figure 15.1.2.34](#) (Factor 1, Factor 2, and total scores).

Table 76 Analysis of Change from Baseline QSU-brief Questionnaire Factors and Total Score (FAS Population)

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS 2.2 – CC)	
					LS Mean	95% CI
Total	Overall	THS 2.2	80	-0.52	-0.31	-0.75, 0.12
		CC	41	-0.20		
Factor 1	Overall	THS 2.2	80	-0.56	-0.36	-0.85, 0.13
		CC	41	-0.20		
Factor 2	Overall	THS 2.2	80	-0.46	-0.23	-0.66, 0.20
		CC	41	-0.23		
Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS 2.2 – SA)	
					LS Mean	95% CI
Total	Overall	THS 2.2	80	-0.52	-1.83	-2.27, -1.39
		SA	39	1.31		
Factor 1	Overall	THS 2.2	80	-0.56	-1.94	-2.44, -1.45
		SA	39	1.38		
Factor 2	Overall	THS 2.2	80	-0.46	-1.71	-2.15, -1.28
		SA	39	1.26		

Abbreviations: CC = conventional cigarette; CI = confidence interval; LS = least squares; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Adjusted LS means and CIs from an ANCOVA model with study arm, sex, CC consumption reported at Screening, day, and study arm*day fitted as fixed effect factors with baseline fitted as a covariate. Day fitted as a repeated factor.

Data Source: [Appendix 15, Table 15.2.4.44](#).

Considering the overall time points, the decrease from baseline in LS mean QSU-brief total score was 0.31 points greater for subjects who switched to THS 2.2 use than for subjects who continued to smoke CC (95% CI: -0.75, 0.12). Consistent results were obtained for the change from baseline for the 2 factors, Factor 1 reflecting the desire and intention to smoke with smoking perceived as rewarding (mean difference: -0.36; 95% CI: -0.85, 0.13), and Factor 2 reflecting anticipation of relief from negative effects of not smoking (mean difference: -0.23; 95% CI: -0.66, 0.20). There were also no notable differences in urge-to-



smoke between the THS 2.2 and CC arms in factor and total scores for the QSU-brief questionnaire on any of the study days.

For the comparison of subjects who switched to THS 2.2 with subjects who abstained from smoking, there was an LS mean difference in QSU-brief total score of -1.83 points for THS 2.2 - SA (95% CI: -2.27, -1.39). Consistent results were obtained for the change from baseline for the 2 factors, Factor 1 mean difference of -1.94 (95% CI: -2.44, -1.45) and Factor 2 mean difference of -1.71 (95% CI: -2.15, -1.28). Urge-to-smoke was also lower for subjects who switched to THS 2.2 compared to subjects who abstained from smoking on all study days.

11.3.4.2 Minnesota Nicotine Withdrawal Scale

Responses to the MNWS questionnaire results are listed by subject in [Appendix 15, Listing 15.3.6.12](#) and are summarized by study arm in [Appendix 15, Table 15.2.4.45](#).

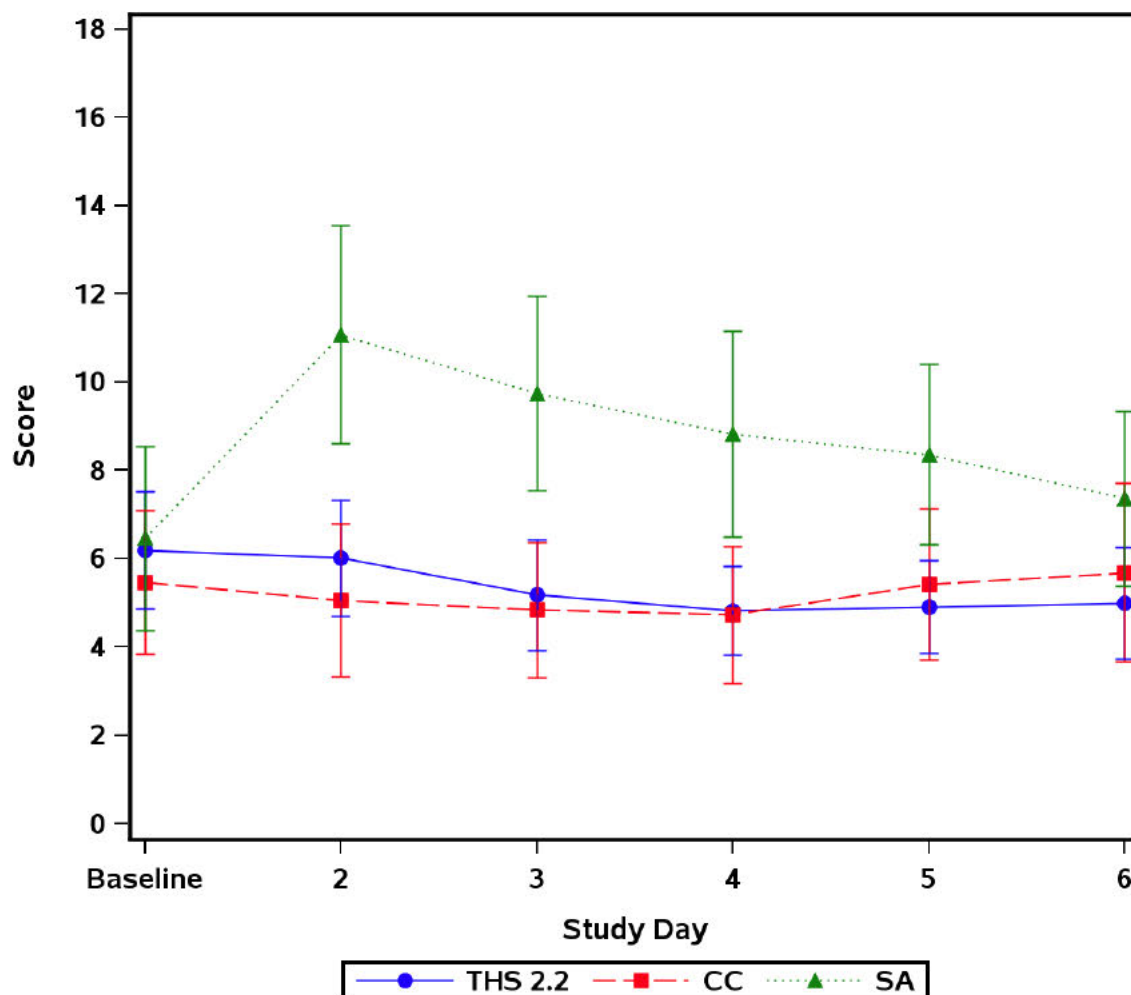
The MNWS is a 24 hour recall that was completed by the subject themselves daily on Day 0 to Day 6, prior to product use, to reflect the previous days experience. Therefore, although the data was collected on Days 0 to 6 and presented as such in the tables, figures, and listings, the responses reflect the subject's experience on Days -1 to 5.

Line graphs showing the mean scores for total score 1 and total score 2 for the MNWS questionnaire over the course of the study are presented in [Appendix 15, Figure 15.1.2.35](#) and in [Figure 40](#) and [Figure 41](#).

The total score 1 was calculated by summing the results of the first 9 responses on the MNWS questionnaire and are based on validated items, total score 2 was based on 6 additional items on the MNWS questionnaire, which are thought to have an impact on withdrawal but have not been validated.



Figure 40 Mean MNWS Total Score 1 During the Course of the Study (FAS Population)

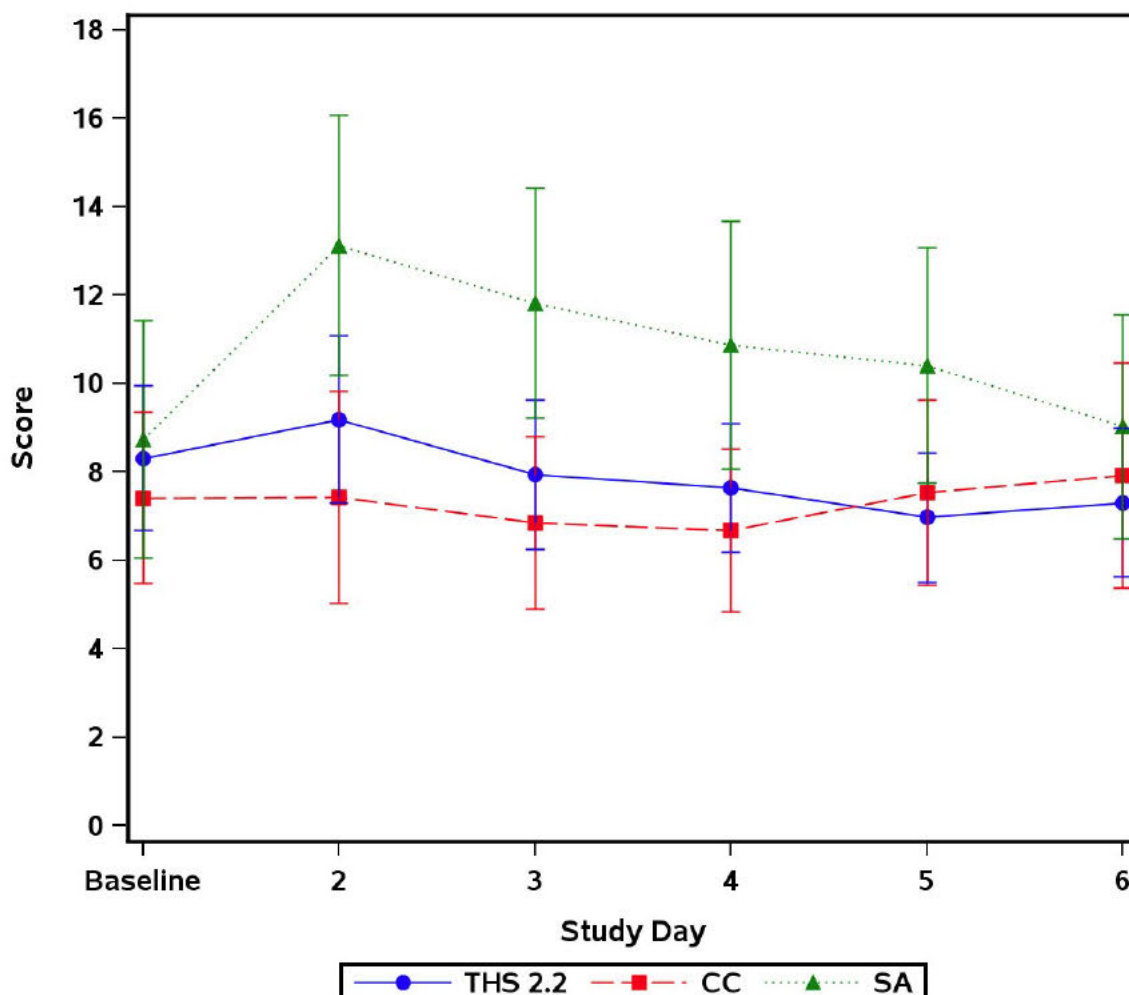


Abbreviations: CC = conventional cigarette; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Figure 15.1.2.35](#).

Figure 41 Mean MNWS Total Score 2 During the Course of the Study (FAS Population)



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

Baseline was defined as the last assessment prior to first product use in CC/THS 2.2 arms on Day 1 or last assessment prior to 06:29 AM in SA arm on Day 1.

Data Source: [Appendix 15, Figure 15.1.2.35](#).

The average MNWS total score 1 values were 6.2 for the THS 2.2 arm, 5.5 for the CC arm, and 6.5 for the SA arm at baseline. For the THS 2.2 and CC arms, the average MNWS total score 1 values remained stable (with in the ranges of 4.8 to 6.0 and 4.7 to 5.7, respectively) throughout the study. In the SA arm, the MNWS total score 1 increased from baseline to Day 2 (11.1, corresponding to an increase of 4.6 points). The total score 1 value then decreased from Day 2 to Day 6, and was approaching the scores of the THS 2.2 and CC arms by Day 6 (a total score 1 value of 7.4).



Total score 2 was based on 6 additional items on the MNWS questionnaire which are thought to have an impact on withdrawal but have not been validated. The average MNWS total score 2 values were 8.3 for the THS 2.2 arm, 7.4 for the CC arm, and 8.7 for the SA arm at baseline. For the THS 2.2 arm, the average MNWS total score 2 increased from baseline to Day 2 (increase of 0.9 points) before gradually decreasing over the course of the study. For the CC arm, the average MNWS total score 2 value remained stable throughout the study (range of 6.7 to 7.9) and was comparable to the THS 2.2 arm on Days 3 to 6. In the SA arm, the MNWS total score 2 increased from baseline to Day 2 (13.1, corresponding to an increase of 4.4 points). The total score 2 value then decreased from Day 2 to Day 6, and was approaching the score of the THS 2.2 and CC arms by Day 6.

The results from the statistical analysis of the MNWS questionnaire total scores are presented in [Appendix 15, Table 15.2.4.46](#) and [Table 77](#). Profiles of the LS mean differences (THS 2.2 – CC and THS 2.2 – SA) over time are presented in [Appendix 15, Figure 15.1.2.36](#).

Table 77 Analysis of Change from Baseline MNWS Questionnaire Total Scores (FAS Population)

Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS 2.2 – CC)	
					LS Mean	95% CI
Total score 1	Overall	THS 2.2	80	-1.15	-1.01	-2.61, 0.58
		CC	41	-0.13		
Total score 2	Overall	THS 2.2	80	-0.52	-0.48	-2.45, 1.50
		CC	41	-0.04		
Score	Time Point	Exposure	Number of Subjects	LS Mean	Difference (THS 2.2 – SA)	
					LS Mean	95% CI
Total score 1	Overall	THS 2.2	80	-1.15	-3.69	-5.24, -2.13
		SA	39	2.54		
Total score 2	Overall	THS 2.2	80	-0.52	-2.76	-4.71, -0.82
		SA	39	2.25		

Abbreviations: CC = conventional cigarette; CI = confidence interval; LS = least squares; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Adjusted LS means and CIs from an ANCOVA model with study arm, sex, CC consumption reported at Screening, day, and study arm*day fitted as fixed effect factors with baseline fitted as a covariate. Day fitted as a repeated factor.

Data Source: [Appendix 15, Table 15.2.4.46](#).

Considering the overall time points, the decrease from baseline in LS mean MNWS total score 1 was 1.01 points greater for subjects who switched to THS 2.2 use than for subjects who continued to smoke CC (95% CI: -2.61, 0.58). A similar result was obtained for the change from baseline for total score 2 although the mean difference was smaller (-0.48;



95% CI: -2.45, 1.50). There were also no notable differences between the THS 2.2 and CC arms in MNWS total scores on any of the individual study days.

For the comparison of subjects who switched to THS 2.2 with subjects who abstained from smoking, there was an LS mean difference in MNWS total score 1 of -3.69 points for THS 2.2 - SA (95% CI: -5.24, -2.13). Consistent results were obtained for the change from baseline for MNWS total score 2, with a mean difference of -2.76 (95% CI: -4.71, -0.82). MNWS total scores were also lower for subjects who switched to THS 2.2 compared to subjects who abstained from smoking on all study days, with the exception of Day 1 for both total scores, and Day 6 for total score 2.

11.3.4.3 Modified Cigarette Evaluation Questionnaire

Responses to the individual items of the MCEQ used to assess product evaluation and the subscale scores for the MCEQ are listed in [Appendix 15, Listing 15.3.6.13](#). The subscale scores for the MCEQ are summarized in [Appendix 15, Table 15.2.4.47](#).

The results from the statistical analysis of the MCEQ subscales score are presented in [Appendix 15, Table 15.2.4.48](#) and [Table 78](#).

**Table 78 Analysis of Change from Baseline in MCEQ Subscales (FAS Population)**

Subscale	Time Point	Product Exposure	Number of Subjects	Difference (THS 2.2 – CC)		
				LS Mean	LS Mean	95% CI
Aversion	Overall	THS 2.2	79	0.15	0.25	0.04, 0.46
		CC	41	-0.10		
Craving reduction	Overall	THS 2.2	79	-1.53	-1.12	-1.58, -0.66
		CC	41	-0.41		
Enjoyment of respiratory tract sensation	Overall	THS 2.2	79	-1.23	-1.00	-1.36, -0.64
		CC	41	-0.23		
Psychological reward	Overall	THS 2.2	79	-1.13	-0.72	-1.06, -0.39
		CC	41	-0.41		
Smoking satisfaction	Overall	THS 2.2	79	-1.51	-1.26	-1.68, -0.85
		CC	41	-0.25		

Abbreviations: CC = conventional cigarette; CI = confidence interval; LS = least squares; THS 2.2 = Tobacco Heating System 2.2.

Adjusted LS means and CIs from an ANCOVA model with study arm, sex, CC consumption reported at Screening, day, and study arm*day fitted as fixed effect factors with baseline fitted as a covariate. Day fitted as a repeated factor.

Data Source: [Appendix 15, Table 15.2.4.48](#).

On Day 5, reductions from baseline in craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction were all greater for subjects who switched to THS 2.2 compared to subjects who continued to smoke CC. Greater decreases from baseline were reported in the THS 2.2 arm compared to the CC arm both overall and on all individual study days. Overall, aversion was increased from baseline in the THS 2.2 arm while there was a decrease from baseline in the CC arm, with the greatest differences between the 2 arms reported on Day 1 and Day 2.

11.3.5 Human Smoking Topography

11.3.5.1 Human Smoking Topography Questionnaire

Responses to the HST questionnaire are listed in [Appendix 15, Listing 15.3.7.2](#), and are summarized by product use in [Appendix 15, Table 15.2.4.60](#).

On both Day 0 and Day 4, the majority of subjects in the THS 2.2 arm found that use of the THS 2.2 product was different with the HST device, whereas less than half of the subjects



found their cigarettes were different with the HST device in the CC arm. The majority of subjects in both the THS 2.2 and CC arms found that the taste of the CC /THS 2.2 Tobacco Sticks was not different with the device and that the device was easy to use on both Day 0 and Day 4. Responses to the other questions tended to be relatively evenly distributed in both the THS 2.2 and CC arms on Day 0 and Day 4. There was a substantial increase in subjects having their smoking disturbed by the HST device at Day 4, in comparison with Day 0, for both THS 2.2 and CC arms.

11.3.5.2 Human Smoking Topography Device

The individual parameters collected from the HST SODIM[®] device and changes from baseline are listed in [Appendix 15, Listing 15.3.7.1](#). Descriptive statistics are summarized for the per-cigarette parameters collected from the HST SODIM[®] device on Days 0, 1, and 4, together with changes from baseline in [Appendix 15, Table 15.2.4.58](#). Mean HST per-cigarette parameters are presented graphically in [Appendix 15, Figure 15.1.2.39](#).

[Appendix 15, Figure 15.1.2.39](#) showed that the baseline values for each assessed parameter were comparable between the THS 2.2 and the CC arms while subjects were using their usual brand of CC. In the CC arm, the values for all parameters were stable between baseline and Day 1, and between Day 1 and Day 4. In the THS 2.2 arm, values for total number of puffs, total puff volume, average puff volume, total work, average work, average pressure drop, and average peak pressure drop were stable from baseline (CC use) to Day 4. Average puff duration, total puff duration, smoking intensity, puffing time index, and puff frequency all increased from baseline to Day 1 once the subjects began using the THS 2.2 device and were stable between Day 1 and Day 4. Average flow, average peak flow, total inter puff interval, average inter puff interval, and total smoking duration all decreased from baseline to Day 1 once the subjects began using the THS 2.2 device and were stable between Day 1 and Day 4.

The results from the statistical analysis of the HST per-cigarette parameters are presented in [Appendix 15, Table 15.2.4.59](#) and [Table 79](#).



Table 79 Analysis of HST Parameters (Averaged over All Cigarettes per Day) (FAS Population)

Variable (units)	Time Point	Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)			95% CI
						CV (%)		
Total number of puffs	Day 1	THS 2.2	55	16.53	103.06	18.49	94.26, 112.70	
		CC	27	16.04				
	Day 4	THS 2.2	55	16.06	97.14	17.08	89.42, 105.53	
		CC	27	16.53				
Total puff volume (mL)	Day 1	THS 2.2	55	766.65	109.53	30.67	94.73, 126.64	
		CC	27	699.95				
	Day 4	THS 2.2	55	791.70	105.26	27.10	92.59, 119.65	
		CC	27	752.16				
Average puff volume (mL)	Day 1	THS 2.2	55	46.29	101.55	24.54	90.61, 113.80	
		CC	27	45.59				
	Day 4	THS 2.2	55	49.44	105.50	21.22	95.55, 116.48	
		CC	27	46.87				
Average puff duration (s)	Day 1	THS 2.2	55	1.89	126.07	19.04	115.33, 137.81	
		CC	27	1.50				
	Day 4	THS 2.2	55	1.98	132.25	20.38	120.24, 145.46	
		CC	27	1.49				
Total puff duration (s)	Day 1	THS 2.2	55	31.55	136.09	26.96	119.89, 154.47	
		CC	27	23.19				
	Day 4	THS 2.2	55	32.21	137.33	29.94	119.35, 158.03	
		CC	27	23.45				
Average flow (mL/s)	Day 1	THS 2.2	55	25.48	81.64	18.77	74.78, 89.12	
		CC	27	31.22				
	Day 4	THS 2.2	55	25.98	79.95	19.91	72.86, 87.73	
		CC	27	32.49				
Average peak flow (mL/s)	Day 1	THS 2.2	55	39.14	82.61	18.51	75.72, 90.12	
		CC	27	47.37				
	Day 4	THS 2.2	55	39.45	80.44	19.73	73.28, 88.29	
		CC	27	49.05				



Table 79 Analysis of HST Parameters (Averaged over All Cigarettes per Day) (FAS Population) (continued)

Variable (units)	Time Point	Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio	CV (%)	95% CI
					(THS 2.2:CC) (%)		
Total inter puff interval (s)	Day 1	THS 2.2	55	169.83	73.66	25.63	65.32, 83.07
		CC	27	230.55			
	Day 4	THS 2.2	55	159.35	70.75	26.00	62.63, 79.93
		CC	27	225.22			
Average inter puff interval (s)	Day 1	THS 2.2	55	10.26	68.24	29.37	59.20, 78.68
		CC	27	15.03			
	Day 4	THS 2.2	55	9.85	67.83	26.88	59.51, 77.31
		CC	27	14.52			
Total smoking duration (s)	Day 1	THS 2.2	55	205.27	80.39	21.10	72.80, 88.77
		CC	27	255.35			
	Day 4	THS 2.2	55	194.84	77.64	22.79	69.77, 86.41
		CC	27	250.94			
Total work (mJ)	Day 1	THS 2.2	55	1838.31	108.46	44.74	88.69, 132.64
		CC	27	1694.92			
	Day 4	THS 2.2	55	1845.35	99.74	36.40	84.47, 117.75
		CC	27	1850.25			
Average work (mJ)	Day 1	THS 2.2	55	109.38	96.23	40.89	79.86, 115.95
		CC	27	113.66			
	Day 4	THS 2.2	55	115.07	96.76	35.16	82.22, 113.86
		CC	27	118.93			
Average pressure drop (mmWg)	Day 1	THS 2.2	55	205.60	98.55	24.33	88.00, 110.36
		CC	27	208.63			
	Day 4	THS 2.2	55	202.90	93.74	24.24	83.72, 104.95
		CC	27	216.45			

**Table 79 Analysis of HST Parameters (Averaged over All Cigarettes per Day) (FAS Population) (continued)**

Variable (units)	Time Point	Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio	CV (%)	95% CI
					(THS 2.2:CC) (%)		
Average peak pressure drop (mmWg)	Day 1	THS 2.2	55	341.98	100.66	25.16	89.40, 113.34
		CC	27	339.74			
	Day 4	THS 2.2	55	333.20	94.20	25.55	83.45, 106.34
		CC	27	353.72			
Smoking intensity (mL/s)	Day 1	THS 2.2	55	3.96	138.25	37.18	116.16, 164.55
		CC	27	2.87			
	Day 4	THS 2.2	55	4.36	139.82	33.78	119.31, 163.84
		CC	27	3.12			
Puffing time index (%)	Day 1	THS 2.2	55	16.07	166.45	32.05	143.21, 193.45
		CC	27	9.66			
	Day 4	THS 2.2	55	17.54	176.78	32.18	151.99, 205.62
		CC	27	9.92			
Puff frequency (puffs/min)	Day 1	THS 2.2	55	5.08	131.32	23.76	116.97, 147.43
		CC	27	3.87			
	Day 4	THS 2.2	55	5.29	132.33	23.04	118.25, 148.09
		CC	27	4.00			

Abbreviations: CC = conventional cigarette; CI = confidence interval; CV = coefficient of variation; LS = least squares; 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 CC 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 15.2.4.59](#).

For each study arm, the majority of mean values for each smoking parameter were comparable on Day 1 and Day 4. There were no apparent differences between THS 2.2 and CC use in the total number of puffs, total puff volume, average puff volume, total work, average work, average pressure drop, and average peak pressure drop on both Day 1 and Day 4.

Average puff duration, total puff duration, smoking intensity, puffing time index, and puff frequency were all greater for THS 2.2 use compared to CC use on both Day 1 and Day 4. Average flow, average peak flow, total inter puff interval, average inter puff interval, and total smoking duration were all lower for THS 2.2 use compared to CC use.



11.3.6 Visual Inspection of the THS Tobacco Plugs

Results from the inspection of individual THS Tobacco Plugs are listed in [Appendix 15, Listing 15.3.6.16](#) and are summarized in [Appendix 15, Table 15.2.4.61](#) and [Table 80](#).

Table 80 Summary of Visual Inspection of the THS 2.2 Tobacco Plug (FAS Population)

Evaluation	THS 2.2 (N=80)				
	Day 1 n = 1191	Day 2 n = 1384	Day 3 n = 1457	Day 4 n = 1459	Day 5 n = 1639
0	1142 (98.9%)	1343 (98.2%)	1408 (98.3%)	1375 (97.9%)	1569 (98.4%)
1	13 (1.1%)	24 (1.8%)	25 (1.7%)	29 (2.1%)	25 (1.6%)
2	0	0	0	0	0
Missing	36	17	24	55	45

Abbreviations: n = number of THS 2.2 products used; N = number of subjects; THS 2.2 = Tobacco Heating System 2.2.

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 15.2.4.61](#).

Visual inspection of THS Tobacco Plugs was possible for the majority of plugs on Days 1 to 5. 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 (grade 1) was similar across all study days (range 1.1% to 2.1%). No THS Tobacco plugs were reported as showing ashes inside the tobacco plug and burnt paper (grade 2) following visual inspection (i.e., no combustion occurred).

11.3.7 Filter Analysis

Results from the filter analysis are listed in [Appendix 15, Listing 15.3.6.17](#), and are summarized in [Appendix 15, Table 15.2.4.62](#).

All 80 subjects in the THS 2.2 arm had the full filter analyzed, while the mouthpiece and polymer-film filter (PLA) + hollow acetate tube (HAT) were only analyzed for 49 of the 80 subjects ([Appendix 15, Table 15.2.4.62](#)).

Mean values for all THS Tobacco Plug filter analysis parameters assessed on the full filter, mouthpiece, and PLA + HAT (nicotine amount, absolute UV TAR absorbance and normalized UV absorbance) appeared to increase between Day 1 and Day 2 before stabilising between Day 2 and Day 4, and then increasing between Day 4 and Day 5.



11.4 Statistical and Analytical Issues

11.4.1 Sample Size

One hundred and sixty smokers were randomized into this study as planned (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 CC consumption were included in the model and a baseline value was included, except for the analysis of the PK parameters of nicotine and cotinine.

11.4.3 Handling of Dropouts or Missing Data

In general, missing data were not imputed in this study, due to the nature of the measurements and the short periods of exposure and use. However, for questionnaire data, total scores and domain or subscale scores could have used a certain degree of imputation (by averaging across individual item scores).

11.4.4 Interim Analysis and Data Analysis

No interim analysis was planned or conducted for this study.

11.4.5 Multicenter Studies

Not applicable as this was a single-center 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

Primary Endpoints

The primary endpoints for this study were assessed on Day 5 (evening) for the BoExp COHb blood (% saturation of hemoglobin); MHBMA urinary concentration adjusted for creatinine (pg/mg creat); 3-HPMA urinary concentration adjusted for creatinine (ng/mg creat); and S-PMA urinary concentration adjusted for creatinine (pg/mg creat).

Reductions were seen in the level of each BoExp assessed as a primary endpoint for the THS 2.2 arm compared to the CC arm, with reductions of approximately 77% in COHb (whole blood), 92% in MHBMA urinary concentration adjusted for creatinine, 58% in 3-HPMA urinary concentration adjusted for creatinine, and 94% in S-PMA urinary concentration adjusted for creatinine.

These results were consistent with the study hypothesis and evaluation criteria (see [Section 8.4.1](#) and [Section 8.4.2](#)) in demonstrating a >50% reduction in COHb, MHBMA, 3-HPMA, and S-PMA in the THS 2.2 arm compared to the CC arm.

Secondary Endpoints

Carboxyhemoglobin in Whole Blood, MHBMA, 3-HPMA, and S-PMA (Concentrations Adjusted for Creatinine) versus Smoking Abstinence

Differences were seen for levels of COHb and 3-HPMA in the THS 2.2 arm compared to the SA arm. Mean COHb was approximately 8% higher on Day 5 for the THS 2.2 arm compared to the SA arm, and 3-HPMA urinary concentration adjusted for creatinine was approximately 64% higher on Day 5 (although this was still considerably lower than compared to CC use). There were no notable differences observed between subjects who switched to THS 2.2 and subjects who abstained from smoking for urinary concentrations of MHBMA and S-PMA adjusted for creatinine on Day 5.

MHBMA, 3-HPMA, and S-PMA (Urinary Quantity Excreted Over 24 Hours) versus Conventional Cigarettes

The levels of MHBMA, 3-HPMA, and S-PMA in the THS 2.2 arm were reduced compared to the CC arm on Day 5, with reductions of approximately 92% in urinary quantity of MHBMA excreted over 24 hours, 60% in urinary quantity of 3-HPMA excreted over 24 hours, and 94% in the urinary quantity of S-PMA excreted over 24 hours.



MHBMA, 3-HPMA, and S-PMA (Urinary Quantity Excreted Over 24 Hours) versus Smoking Abstinence

A difference was observed in the THS 2.2 arm for levels of 3-HPMA compared to the SA arm, with mean urinary quantity of 3-HPMA excreted over 24 hours being approximately 50% higher on Day 5 (although this was still considerably lower than compared to CC use). There were no notable differences observed between subjects who switched to THS 2.2 and subjects who abstained from smoking for the urinary quantities of MHBMA and S-PMA excreted over 24 hours on Day 5.

Other Biomarkers of Exposure versus Conventional Cigarettes

Reductions were seen in the THS 2.2 arm compared to the CC arm of approximately 84% in exhaled CO, 56% in Total 1-OHP urinary concentration adjusted for creatinine, 76% in Total NNN urinary concentration adjusted for creatinine, 85% in 4-ABP urinary concentration adjusted for creatinine, 96% in 1-NA urinary concentration adjusted for creatinine, 88% in 2-NA urinary concentration adjusted for creatinine, 58% in o-toluidine urinary concentration adjusted for creatinine, 87% in CEMA urinary concentration adjusted for creatinine, 68% in HEMA urinary concentration adjusted for creatinine, 73% in 3-OH-B[a]P urinary concentration adjusted for creatinine, 77% in 3-HMPMA urinary concentration adjusted for creatinine, and 56% in Total NNAL urinary concentration adjusted for creatinine. There was no notable difference in the S-BMA urinary concentration adjusted for creatinine between the THS 2.2 and CC arms.

The reductions in the quantities excreted over 24 hours for each of the other biomarkers of exposure in the THS 2.2 arm compared to the CC arm were consistent with the results obtained for the urinary concentrations adjusted for creatinine.

With the exception of S-BMA, the results are consistent with the study hypothesis (see [Section 8.4.1](#)) in that the geometric mean level of each of the other BoExp was lower for the THS 2.2 arm relative to the CC arm on Day 5.

Other Biomarkers of Exposure versus Smoking Abstinence

Higher values were seen in the THS 2.2 arm compared to the SA arm on Day 5, with Total NNN urinary concentration adjusted for creatinine being 9.8-fold higher, 19% higher for 4-ABP urinary concentration adjusted for creatinine, 30% higher for 1-NA urinary concentration adjusted for creatinine, 17% higher for 2-NA urinary concentration adjusted for creatinine, 21% higher for o-toluidine urinary concentration adjusted for creatinine, 32% higher for 3-HMPMA urinary concentration adjusted for creatinine, and 27% higher for Total NNAL urinary concentration adjusted for creatinine. There were no notable differences observed in exhaled CO, Total 1-OHP, CEMA, HEMA, 3-OH-B[a]P, and



S-BMA concentrations adjusted for creatinine on Day 5 between subjects who switched to THS 2.2 and subjects who abstained from smoking.

The results obtained for the quantity of each of the other biomarker of exposure excreted over 24 hours were consistent with the results for the concentrations adjusted for creatinine.

Exposure to Nicotine

On Day 5, both the NEQ urinary concentration adjusted for creatinine (mg/g creat) and the quantity excreted over 24 hours (mg) were comparable between subjects who switched to THS 2.2 and subjects who continued to smoke CC. Mean levels of NEQ urinary concentration adjusted for creatinine and quantity of NEQ excreted over 24 hours in subjects who switched to THS 2.2 use were higher (approximately 77-fold and 70-fold higher, respectively) than those of subjects who abstained from smoking.

Mean plasma nicotine concentrations taken between 08:00 and 10:00 PM increased from Day 0 to Day 5 for both the THS 2.2 and CC arms. There was no notable difference in the changes from Day 0 plasma nicotine concentrations to Day 5 between subjects who switched to THS 2.2 and subjects who continued to smoke CC. For cotinine, mean plasma concentrations increased from Day 0 to Day 5 in the THS 2.2 arm and decreased in the CC arm, resulting in an LS mean difference of 30.9 ng/mL (95% CI: 6.4, 55.5).

For both nicotine and cotinine exposure on Day 5, peak and weighted average plasma concentrations were similar for the THS 2.2 and CC arms. On average, the Day 5 peak and weighted average nicotine and cotinine concentrations were approximately 11% to 13% higher for THS 2.2 compared to CC. The time to peak concentration on Day 5 was identical for the THS 2.2 and CC arms for both nicotine and cotinine.

Cytochrome P450 1A2 Activity

At baseline, CYP1A2 activity was comparable between study arms (range of 110% to 113%). In the THS 2.2 and SA arms at Day 5, CYP1A2 activity had decreased by approximately 17% and 15%, respectively, while in the CC arm, CYP1A2 activity increased by approximately 13%. This resulted in differences in absolute and change from baseline CYP1A2 activity (THS 2.2 - CC) of -34% (95% CI: -41, -27). There was no notable difference in absolute CYP1A2 activity on Day 5 or change from baseline in CYP1A2 activity between subjects who switched to THS 2.2 use and subjects who abstained from smoking.

Tobacco Consumption

In the THS 2.2 arm, the mean number of THS Tobacco Sticks consumed daily initially decreased from the number of CC smoked at baseline (16 cigarettes/day) to Day 1 (15 sticks/day) before increasing again over Day 2 to Day 5 (17 to 21 sticks/day), with the



number of THS Tobacco Sticks used from Day 2 onwards being greater than the number of CC smoked at baseline.

In the CC arm, the mean number of CC consumed daily initially decreased from baseline (16 cigarettes/day) to Day 1, before increasing over Day 2 to Day 5 and was comparable to the baseline value at Day 5 (17 cigarettes/day).

On Day 1 to Day 5, subjects in the THS 2.2 arm consumed more THS Tobacco Sticks than the number of CC smoked in the CC arm.

Exploratory Endpoints

Ames Mutagenicity Test

At baseline, median Ames mutagenicity test values were comparable between the THS 2.2 and SA arms (19681.5 and 22540.0 Rev/24h, respectively) and slightly lower in the CC arm (15775.0 Rev/24h). On Day 5, in the THS 2.2 and SA arms, median Ames mutagenicity test values had decreased by approximately 57% and 62%, respectively, while in the CC arm, median Ames mutagenicity test values increased by approximately 29%.

Cytochrome P450 2A6 Activity

At baseline, CYP2A6 activity was comparable between study arms (range of 41% to 44%). In the THS 2.2 and CC arms at Day 6, CYP2A6 activity had decreased by approximately 32% and 34%, respectively. In the SA arm, CYP2A6 activity increased by approximately 167%. There was no notable difference in absolute CYP2A6 activity on Day 6 or change from baseline in CYP2A6 activity between subjects who switched to THS 2.2 use and subjects who continued to smoke CC. The LS mean levels of absolute and change from baseline CYP2A6 activity were lower by 76% (95% CI: 67, 84) in subjects who switched to THS 2.2 use compared to subjects who abstained from smoking.

Risk Markers

At baseline, the concentration of 8-epi-PGF_{2α} adjusted for creatinine was comparable between study arms (geometric mean range of 189.9 to 209.0 pg/mg creat). At Day 5, the levels of 8-epi-PGF_{2α} concentration adjusted for creatinine increased from baseline by approximately 15%, 25%, and 28% in the THS 2.2, CC, and SA arms, respectively. Results for the quantity of 8-epi-PGF_{2α} excreted over 24 hours showed a comparable trend.

There were no notable differences observed on Day 5 in both the concentration of 8-epi-PGF_{2α} adjusted for creatinine and the urinary quantity excreted over 24 hours between subjects who switched to THS 2.2 and subjects who continued to smoke CC. There was no notable difference observed in the concentration of 8-epi-PGF_{2α} adjusted for creatinine between that of subjects who switched to THS 2.2 use and that of subjects who



abstained from smoking. Mean 8-epi-PGF_{2α} excreted over 24 hours in subjects who switched to THS 2.2 use was approximately 16% lower on Day 5 than that of subjects who abstained from smoking (95% CI: 5, 25).

The concentration of 11-DTX-B2 adjusted for creatinine was comparable in the CC and SA arms at baseline (geometric mean values of 467.9 and 468.6 pg/mg creat, respectively) and was higher in the THS 2.2 arm (536.1 pg/mg creat). At Day 5, the 11-DTX-B2 adjusted for creatinine was comparable to the baseline value in the THS 2.2 and SA arms (approximate 1% increase and 3% decrease, respectively), and had increased by approximately 30% in the CC arm. The quantity of 11-DTX-B2 excreted over 24 hours at baseline was comparable in the CC and SA arms (geometric mean values of 764.9 and 730.6 ng, respectively) and was higher in the THS 2.2 arm (859.6 ng). In the THS 2.2 and SA arms at Day 5, the quantity of 11-DTX-B2 excreted over 24 hours was comparable to baseline (approximately 7% and 2% decrease, respectively), and had increased from baseline by approximately 21% in the CC arm.

On Day 5, the LS mean level of 11-DTX-B2 concentration adjusted for creatinine in subjects who switched to THS 2.2 use was approximately 16% lower than that of subjects who continued to smoke CC (95% CI: 10, 23). The results for the quantity of 11-DTX-B2 excreted over 24 hours were consistent with the results of the concentration adjusted for creatinine, with a 19% decrease (95% CI: 9, 27) in subjects who switched to THS 2.2 compared to subjects who continued to smoke CC.

On Day 5, the LS mean concentration of 11-DTX-B2 adjusted for creatinine in subjects who switched to THS 2.2 use was approximately 10% higher than that of subjects who abstained from smoking (95% CI: 101, 120). There was no notable difference observed in the quantity of 11-DTX-B2 excreted over 24 hours between subjects who switched to THS 2.2 and subjects who abstained from smoking.

Relationship between Risk Markers and Nicotine Equivalents

There was no correlation between the concentration of NEQ adjusted for creatinine and the concentration of 8-epi-PGF_{2α} adjusted for creatinine for subjects in the THS 2.2 arm, whereas for subjects in the CC and SA arms, a correlation was observed. There was no correlation between the slopes for the THS 2.2 and the CC arms. There was a correlation between the urinary quantity of NEQ excreted over 24 hours versus the urinary quantity of 8-epi-PGF_{2α} for all study arms. However, there was no correlation between the slopes for the THS 2.2 and the CC arms which suggests that even though adjusting for NEQ, there was no difference between the THS 2.2 and CC arms for this risk marker.

There was a correlation between the concentration of NEQ adjusted for creatinine and the concentration of 11-DTX-B2 adjusted for creatinine for subjects in the THS 2.2 and CC arms, whereas for subjects in the SA arm there was no correlation. There was also no



correlation between the slopes for the THS 2.2 and the CC arms. There was a correlation between the urinary quantity of NEQ excreted over 24 hours versus the urinary quantity of 11-DTX-B2, for the THS 2.2 and CC arms, however, there was no correlation for subjects in the SA arm. There also was no correlation between the slopes for the THS 2.2 and the CC arms, which again suggests that even though adjusting for NEQ, there was no difference between the THS 2.2 and CC arms for this risk marker.

Urge-to-Smoke Symptoms (QSU-brief)

The average urge-to-smoke total scores were comparable between study arms at baseline. For the THS 2.2 and CC arms, the average urge-to-smoke total score remained stable and were comparable throughout the study (ranges of 2.9 to 3.3 and 3.2 to 3.5, respectively). Considering the overall time points, there was an LS mean difference in QSU-brief total score of -0.3 points for THS 2.2 - CC (95% CI: -0.75, 0.12). Consistent results were obtained for the change from baseline for the 2 factors, Factor 1 reflecting the desire and intention to smoke with smoking perceived as rewarding (mean difference: -0.4; 95% CI: -0.9, 0.1) and Factor 2 reflecting anticipation of relief from negative effects of not smoking (mean difference: -0.2; 95% CI: -0.7, 0.2).

In the SA arm, the urge-to-smoke total score increased from baseline to Day 1 (score of 5.3, corresponding to an increase of 1.8 points). Total score values then decreased from Day 1 to Day 5 (total score of 4.4). Considering the overall time points, there was an LS mean difference in QSU-brief total score of -1.8 points for THS 2.2 - SA (95% CI: -2.3, -1.4). Consistent results were obtained for the change from baseline for the 2 factors.

Minnesota Nicotine Withdrawal Scale

Average MNWS total score 1 values remained relatively stable for the THS 2.2 and CC arms, and were comparable throughout the study (ranges of 4.8 to 6.0 and 4.7 to 5.7, respectively). Average MNWS total score 2 increased from baseline to Day 2 (increase of 0.9 points) for the THS 2.2 arm, before decreasing over the course of the study. For the CC arm, the average MNWS total score 2 value remained relatively stable throughout the study (range of 6.7 to 7.9) and was comparable to the THS 2.2 arm on Days 3 to 6. Considering the overall time points, mean MNWS total score 1 decreased from baseline by 1.0 points more for subjects who switched to THS 2.2 use than for subjects who continued to smoke CC (95% CI: -2.6, 0.6). A similar result was obtained for the change from baseline for total score 2 although the mean difference was smaller (-0.5; 95% CI: -2.5, 1.5).

In the SA arm, the MNWS total score 1 increased from baseline to Day 2 (11.1, corresponding to an increase of 4.6 points) before decreasing from Day 2 to Day 6. The MNWS total score 2 also increased from baseline to Day 2 (13.1, corresponding to an increase of 4.4 points) before decreasing from Day 2 to Day 6. Both total score 1 and 2 were approaching the respective scores of the THS 2.2 and CC arms by Day 6. Considering



the overall time points, there was an LS mean difference in MNWS total score 1 of -3.69 points for THS 2.2 - SA (95% CI: -5.24, -2.13). Consistent results were obtained for the change from baseline for MNWS total score 2, with a mean difference of -2.76 (95% CI: -4.71, -0.82).

Product Evaluation Questionnaire (MCEO)

On Day 5, differences were observed for a number of subscales, with the change from baseline in craving reduction being 1.1 points lower (95% CI: 0.7, 1.6), change from baseline in enjoyment of respiratory tract sensation being 1.0 point lower (95% CI: 0.6, 1.4), change from baseline in psychological reward being 0.7 points lower (95% CI: 0.4, 1.1), and change from baseline smoking satisfaction being 1.3 points lower (95% CI: 0.9, 1.7) for THS 2.2 compared to CC.

Overall, the change from baseline in aversion was greater in the THS 2.2 arm compared to the CC arm, with an LS mean difference of 0.3 points for THS 2.2 – CC (95% CI: 0.0, 0.5).

Human Smoking Topography Device

Values were comparable at baseline between the THS 2.2 and the CC arms for each assessed parameter while subjects were using their usual brand of CC. In the CC arm, the values for all parameters were stable between baseline and Day 4. In the THS 2.2 arm, values for total number of puffs, total puff volume, average puff volume, total work, average work, average pressure drop, and average peak pressure drop were stable from baseline (CC use) to Day 4. Average puff duration, total puff duration, smoking intensity, puffing time index, and puff frequency all increased from baseline to Day 1 once the subjects began using the THS 2.2 device and were stable between Day 1 and Day 4. Average flow, average peak flow, total inter puff interval, average inter puff interval, and total smoking duration all decreased from baseline to Day 1 once the subjects began using the THS 2.2 device and were stable between Day 1 and Day 4.

For each study arm, the majority of smoking parameters were comparable on Day 1 and Day 4. There were no apparent differences between THS 2.2 and CC use in the total number of puffs, total puff volume, average puff volume, total work, average work, average pressure drop, and average peak pressure drop on both Day 1 and Day 4. Average puff duration, total puff duration, smoking intensity, puffing time index, and puff frequency were all greater for THS 2.2 use compared to CC use on both Day 1 and Day 4. Average flow, average peak flow, total inter puff interval, average inter puff interval, and total smoking duration were all lower for THS 2.2 use compared to CC use.



Visual Inspection of the THS Tobacco Plugs

Visual inspection of THS Tobacco Plugs was possible for the majority of plugs on Days 1 to 5 (>96%). 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 (grade 1) was similar across all study days (range 1.1% to 2.1%). No THS Tobacco Plugs were reported as showing ashes inside the tobacco plug and burnt paper (grade 2) following visual inspection (i.e., no combustion occurred).

Filter Analysis

Mean values for all THS 2.2 filter analysis parameters assessed on the full filter, mouthpiece, and PLA + HAT (nicotine amount, absolute UV TAR absorbance and normalized UV absorbance) appeared to increase between Day 1 and Day 2 before stabilising between Day 2 and Day 4, and then increasing between Day 4 and Day 5.

Summary

Primary Objective

- In smokers who switched from CC to THS 2.2, levels of COHb in blood and MHBMA, 3-HPMA, and S-PMA concentrations adjusted for creatinine were approximately 58% to 94% lower on Day 5 compared to those of smokers who continued to smoke CC.

Secondary Objectives

- On Day 5, in smokers who switched from CC to THS 2.2:
 - Quantities of MHBMA, 3-HPMA, and S-PMA excreted in urine over 24 hours were approximately 60% to 94% lower compared to smokers who continued to smoke CC.
 - Levels of exhaled CO were approximately 84% lower compared to smokers who continued to smoke CC.
 - Other BoExp, expressed as concentrations adjusted for creatinine and quantities excreted over 24 hours, were approximately 56% to 96% lower compared to smokers who continued to smoke CC, with the exception of S-BMA.
- The levels of BoExp remained comparable to their baseline values for smokers who continued to smoke CC. Levels of BoExp for smokers who switched from CC to THS 2.2 decreased rapidly for a number of BoExp (e.g., COHb, MHBMA), with the maximum decrease obtained 1 or 2 days after switching. For other BoExp, such as S-PMA and Total 1-OHP, the decrease was observed steadily over 5 days.



- On Day 5, there were no notable differences between smokers who switched from CC to THS 2.2 and smokers who continued to smoke CC in the NEQ expressed as urinary concentration adjusted for creatinine and the quantity excreted over 24 hours.
- On Day 5, in smokers who switched from CC to THS 2.2:
 - Mean COHb was approximately 8% higher compared to SA.
 - Exhaled CO levels were comparable to SA.
 - Concentrations of Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, 3-HMPMA, and Total NNAL adjusted for creatinine were higher compared to SA. There were no notable differences observed in Total 1-OHP, CEMA, HEMA, B[a]P, and S-BMA concentrations adjusted for creatinine compared to SA. The results obtained for the quantity of each biomarker excreted over 24 hours were consistent with the results for the concentrations adjusted for creatinine for the most part.
- For both nicotine and cotinine on Day 5, there were no notable differences in the peak and weighted average plasma concentrations and the time to peak concentration between smokers who switched from CC to THS 2.2 and smokers who continued to smoke CC.
- CYP1A2 activity decreased in the THS 2.2 and SA arms at Day 5, whereas activity increased in the CC arm. CYP1A2 activity (absolute and change from baseline) was lower in smokers who switched from CC to THS 2.2 compared to subjects who continued to smoke CC. There was no notable difference in absolute CYP1A2 activity or change from baseline in CYP1A2 activity between smokers who switched from CC to THS 2.2 and SA.
- Cigarette consumption at baseline was comparable between the THS 2.2 and CC study arms. In the THS 2.2 arm, the number of THS Tobacco Sticks consumed daily increased from Day 1 to Day 5. In the CC arm, the mean number of CC consumed daily initially decreased from the baseline value but had increased back to approximate baseline values by Day 5.

Exploratory Objectives

- Median Ames mutagenicity test values had decreased by approximately 57% and 62% on Day 5 in the THS 2.2 and SA arms, respectively, whereas median values increased by approximately 29% in the CC arm.
- There was a greater decrease in the urge-to-smoke for smokers who switched to THS 2.2 compared to smokers who continued to smoke CC, although the difference was not notable. The urge-to-smoke score in smokers who switched to THS 2.2 was lower compared with subjects who abstained from smoking.
- The decrease from baseline in MNWS total score 1 and 2 were greater for subjects who switched to THS 2.2 use than for subjects who continued to smoke CC. MNWS total score 1 and 2 in smokers who switched to THS 2.2 were lower compared with subjects who abstained from smoking.



- CYP2A6 activity decreased in the THS 2.2 and CC arms at Day 6, whereas activity increased in the SA arm. There was no notable difference in absolute CYP2A6 activity or change from baseline in CYP2A6 activity between smokers who switched from CC to THS 2.2 and smokers who continued to smoke CC. CYP2A6 activity (absolute and change from baseline) was lower in smokers who switched from CC to THS 2.2 compared to subjects who abstained from smoking.
- For the biomarker of risk, 8-epi-PGF_{2α}:
 - There were no notable differences in both the urinary concentration adjusted for creatinine and the urinary quantity excreted over 24 hours between smokers who switched from CC to THS 2.2 and smokers who continued to smoke CC.
 - There was no notable difference in the urinary concentration adjusted for creatinine between smokers who switched from CC to THS 2.2 compared with subjects who abstained from smoking. The quantity excreted over 24 hours was lower in smokers who switched from CC to THS 2.2 compared with subjects who abstained from smoking.
- For the biomarker of risk, 11-DTX-B2:
 - The concentration adjusted for creatinine and urinary quantity excreted over 24 hours were lower in smokers who switched from CC to THS 2.2 compared with smokers who continued to smoke CC.
 - The urinary concentration adjusted for creatinine in smokers who switched from CC to THS 2.2 use was higher than that of subjects who abstained from smoking. There was no notable difference in the quantity excreted over 24 hours between smokers who switched from CC to THS 2.2 and subjects who abstained from smoking.
- For the relationship between risk markers and NEQ:
 - There was no statistical difference in 8-epi-PGF_{2α} (urinary concentration adjusted for creatinine and quantity excreted over 24 hours) between THS 2.2 and CC when adjusting for NEQ.
 - There was no statistical difference in 11-DTX-B2 (urinary concentration adjusted for creatinine and quantity excreted over 24 hours) between THS 2.2 and CC when adjusting for NEQ.
- On Day 5, craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction were all lower for smokers who switched to THS 2.2 compared to smokers who continued to smoke CC, while aversion was higher.
- The total number of puffs, total puff volume, average puff volume, total work, average work, average pressure drop, and average peak pressure drop were not notably different between THS 2.2 use and CC use on both Day 1 and Day 4. Average puff duration, total puff duration, smoking intensity, puffing time index, and puff frequency were all greater for THS 2.2 use compared to CC use on both Day 1 and Day 4. Average flow, average peak flow, total inter puff interval, average inter puff interval, and total smoking duration were all lower for THS 2.2 use compared to CC use.



- On all study days, the majority of THS Tobacco Plugs showed no overheating. The proportion of THS Tobacco Plugs found to have white spot(s) inside the tobacco plug was low on all study days (1.1% to 2.1%).
- Mean values for all THS 2.2 filter analysis parameters appeared to increase between Day 1 and Day 2 before stabilising between Day 2 and Day 4, and then increasing again between Day 4 and Day 5.



12 SAFETY EVALUATIONS

The safety endpoints were analyzed using the Safety population. The Safety population consisted of 169 subjects: 160 randomized subjects (80 subjects in the THS 2.2 arm, 41 subjects in the CC arm, and 39 subjects in the SA arm) and 9 subjects who were exposed to THS 2.2 from the product test on Day -2. Unless otherwise stated, 169 was the denominator used for the calculation of percentages, including all events that occurred from after the product test of THS 2.2 at Day -2.

12.1 Adverse Events

12.1.1 Brief Summary of Adverse Events

Adverse events are listed by subject in [Appendix 15, Listing 15.3.6.1.1](#).

An overall summary of AEs is presented for the Safety population by study arm in [Appendix 15, Table 15.2.6.1](#) and [Table 81](#).

Table 81 Summary of Adverse Events (Safety Population)

	Study Arm				Overall Safety (N=169)
	THS 2.2 (N=80)	CC (N=41)	SA (N=39)	Exposed not Randomized (N=9)	
Number of:					
AEs	98	63	49	17	227
SAEs	0	0	0	0	0
Severe AEs	0	1	0	0	1
AEs leading to discontinuation	0	0	0	8	8
AEs related to IP	15	9	0	2	26
AEs related to study procedures	11	8	1	2	22

Number (%) of subjects with

AEs	50 (62.5%)	29 (70.7%)	24 (61.5%)	9 (100%)	112 (66.3%)
AEs related to IP	14 (17.5%)	7 (17.1%)	0	2 (22.2%)	23 (13.6%)
AEs related to study procedures	11 (13.8%)	6 (14.6%)	1 (2.6%)	2 (22.2%)	20 (11.8%)

Abbreviations: AE = adverse event; CC = conventional cigarette; IP = investigational product; N = number of subjects; SA = smoking abstinence; SAE = serious adverse event; THS 2.2 = Tobacco Heating System 2.2.

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

Data Source: [Appendix 15, Table 15.2.6.1](#) and [Table 15.2.6.5](#).

There were no SAEs reported during the study and all discontinuations due to AEs (8 subjects) occurred prior to randomization and were due to abnormal assessments (see [Section 12.2.1.3.1](#)). Further details of the individual AEs which led to 8 enrolled subjects



not being randomized on to the study can be found in the clinical chemistry ([Section 12.3.1](#)), hematology ([Section 12.3.2](#)), vital signs ([Section 12.4.1](#)), and spirometry sections ([Section 12.4.4](#)). The majority of AEs were mild or moderate in severity, with only 1 severe AE reported in the CC arm (see [Section 12.1.3.1](#)). Overall, there were 227 AEs reported in 112 of the 169 subjects (66.3%) in the Safety population.

The incidence and frequency of AEs were comparable in the THS 2.2 (98 AEs in 50/80 subjects [62.5%]), the CC (63 AEs reported by 29/41 [70.7%] subjects), and the SA arms (49 AEs in 24/39 [61.5%] subjects). All 9 subjects who were exposed but not randomized reported at least 1 AE.

Of the 227 AEs reported during the study, only 26 AEs in 23 subjects (13.6%) were assessed as being related to either THS 2.2 or CC (15 AEs in 14/80 subjects [17.5%] in the THS 2.2 arm, 9 AEs in 7/41 subjects [17.1%] in the CC arm, and 2 AEs in 2/9 exposed not randomized subjects [22.2%]).

Twenty-two AEs reported by 20 subjects (11.8%) were assessed as being related to study procedures (11 AEs in 11/80 subjects [13.8%] in the THS 2.2 arm, 8 AEs in 6/41 subjects [14.6%] in the CC arm, 1 AE in 1/39 subjects [2.6%] in the SA arm, and 2 AEs in 2/9 exposed not randomized subjects [22.2%]).

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 15.2.6.2.1](#) and [Table 82](#), by SOC in [Appendix 15, Table 15.2.6.2.2](#), and by PT in [Appendix 15, Table 15.2.6.2.3](#).

**Table 82 Summary of Adverse Events by System Organ Class and Preferred Term (Safety Population)**

System Organ Class Preferred Term	Study Arm				Overall Safety (N=169)
	THS 2.2 (N=80)	CC (N=41)	SA (N=39)	Exposed not Randomized (N=9)	
Number (%) subjects with any AEs	50 (62.5%)	29 (70.7%)	24 (61.5%)	9 (100%)	112 (66.3%)
Nervous system disorders	27 (33.8%)	19 (46.3%)	13 (33.3%)	3 (33.3%)	62 (36.7%)
Headache	24 (30.0%)	16 (39.0%)	13 (33.3%)	3 (33.3%)	56 (33.1%)
Syncope	6 (7.5%)	4 (9.8%)	0	0	10 (5.9%)
Investigations	7 (8.8%)	6 (14.6%)	3 (7.7%)	3 (33.3%)	19 (11.2%)
Spirometry abnormal	4 (5.0%)	3 (7.3%)	2 (5.1%)	3 (33.3%)	12 (7.1%)
Lymphocyte count increased	1 (1.3%)	0	1 (2.6%)	1 (11.1%)	3 (1.8%)
Carboxyhaemoglobin increased	0	2 (4.9%)	0	0	2 (1.2%)
Blood bilirubin increased	1 (1.3%)	0	0	0	1 (0.6%)
Eosinophil count increased	1 (1.3%)	0	0	0	1 (0.6%)
Neutrophil count decreased	0	1 (2.4%)	0	0	1 (0.6%)
Gastrointestinal disorders	7 (8.8%)	5 (12.2%)	3 (7.7%)	2 (22.2%)	17 (10.1%)
Constipation	3 (3.8%)	2 (4.9%)	0	1 (11.1%)	6 (3.6%)
Toothache	1 (1.3%)	1 (2.4%)	0	1 (11.1%)	3 (1.8%)
Abdominal distension	0	0	2 (5.1%)	0	2 (1.2%)
Gastrooesophageal reflux disease	0	2 (4.9%)	0	0	2 (1.2%)
Mouth ulceration	2 (2.5%)	0	0	0	2 (1.2%)
Abdominal pain upper	0	0	1 (2.6%)	0	1 (0.6%)
Nausea	0	0	1 (2.6%)	0	1 (0.6%)
Oral pain	1 (1.3%)	0	0	0	1 (0.6%)
Vomiting	0	0	1 (2.6%)	0	1 (0.6%)
Respiratory, thoracic, and mediastinal disorders	10 (12.5%)	4 (9.8%)	0	1 (11.1%)	15 (8.9%)
Oropharyngeal pain	7 (8.8%)	3 (7.3%)	0	0	10 (5.9%)
Cough	3 (3.8%)	0	0	1 (11.1%)	4 (2.4%)
Epistaxis	0	1 (2.4%)	0	0	1 (0.6%)

**Table 82 Summary of Adverse Events by System Organ Class and Preferred Term (Safety Population) (continued)**

System Organ Class Preferred Term	Study Arm				Overall Safety (N=169)
	THS 2.2 (N=80)	CC (N=41)	SA (N=39)	Exposed not Randomized (N=9)	
Metabolism and nutrition disorders	4 (5.0%)	3 (7.3%)	4 (10.3%)	2 (22.2%)	13 (7.7%)
Hypertriglyceridaemia	3 (3.8%)	2 (4.9%)	2 (5.1%)	0	7 (4.1%)
Hypercholesterolaemia	0	1 (2.4%)	1 (2.6%)	0	2 (1.2%)
Hyperglycaemia	0	0	1 (2.6%)	1 (11.1%)	2 (1.2%)
Hyperkalaemia	1 (1.3%)	0	0	1 (11.1%)	2 (1.2%)
Renal and urinary disorders	7 (8.8%)	4 (9.8%)	2 (5.1%)	0	13 (7.7%)
Polyuria	6 (7.5%)	4 (9.8%)	2 (5.1%)	0	12 (7.1%)
Leukocyturia	1 (1.3%)	0	0	0	1 (0.6%)
Musculoskeletal and connective tissue disorders	6 (7.5%)	2 (4.9%)	4 (10.3%)	0	12 (7.1%)
Back pain	3 (3.8%)	2 (4.9%)	3 (7.7%)	0	8 (4.7%)
Arthralgia	1 (1.3%)	0	0	0	1 (0.6%)
Musculoskeletal chest pain	1 (1.3%)	0	0	0	1 (0.6%)
Myalgia	0	0	1 (2.6%)	0	1 (0.6%)
Pain in extremity	1 (1.3%)	0	0	0	1 (0.6%)
Vascular disorders	3 (3.8%)	2 (4.9%)	3 (7.7%)	2 (22.2%)	10 (5.9%)
Hypertension	1 (1.3%)	1 (2.4%)	2 (5.1%)	2 (22.2%)	6 (3.6%)
Hypotension	2 (2.5%)	1 (2.4%)	1 (2.6%)	0	4 (2.4%)
Infections and infestations	4 (5.0%)	2 (4.9%)	1 (2.6%)	0	7 (4.1%)
Nasopharyngitis	3 (3.8%)	1 (2.4%)	1 (2.6%)	0	5 (3.0%)
Herpes virus infection	0	1 (2.4%)	0	0	1 (0.6%)
Urinary tract infection	1 (1.3%)	0	0	0	1 (0.6%)
General disorders and administration site conditions	2 (2.5%)	1 (2.4%)	3 (7.7%)	0	6 (3.6%)
Influenza like illness	0	1 (2.4%)	3 (7.7%)	0	4 (2.4%)
Vessel puncture site reaction	2 (2.5%)	0	0	0	2 (1.2%)

**Table 82 Summary of Adverse Events by System Organ Class and Preferred Term (Safety Population) (continued)**

System Organ Class Preferred Term	Study Arm				Overall Safety (N=169)
	THS 2.2 (N=80)	CC (N=41)	SA (N=39)	Exposed not Randomized (N=9)	
Ear and labyrinth disorders	3 (3.8%)	0	2 (5.1%)	0	5 (3.0%)
Vertigo	3 (3.8%)	0	2 (5.1%)	0	5 (3.0%)
Reproductive system and breast disorders	3 (3.8%)	1 (2.4%)	1 (2.6%)	0	5 (3.0%)
Dysmenorrhoea	3 (3.8%)	1 (2.4%)	1 (2.6%)	0	5 (3.0%)
Cardiac disorders	1 (1.3%)	2 (4.9%)	0	1 (11.1%)	4 (2.4%)
Tachycardia	0	2 (4.9%)	0	0	2 (1.2%)
Myocardial ischaemia	1 (1.3%)	0	0	0	1 (0.6%)
Ventricular extrasystoles	0	0	0	1 (11.1%)	1 (0.6%)
Blood and lymphatic disorders	0	0	0	2 (22.2%)	2 (1.2%)
Leukocytosis	0	0	0	2 (22.2%)	2 (1.2%)
Eye disorders	0	0	1 (2.6%)	0	1 (0.6%)
Conjunctivitis	0	0	1 (2.6%)	0	1 (0.6%)
Hepatobiliary disorders	1 (1.3%)	0	0	0	1 (0.6%)
Hyperbilirubinaemia	1 (1.3%)	0	0	0	1 (0.6%)
Psychiatric disorders	0	0	1 (2.6%)	0	1 (0.6%)
Nicotine dependence	0	0	1 (2.6%)	0	1 (0.6%)
Skin and subcutaneous tissue disorders	1 (1.3%)	0	0	0	1 (0.6%)
Hyperhidrosis	1 (1.3%)	0	0	0	1 (0.6%)

Abbreviations: AE = adverse event; CC = conventional cigarette; N = number of subjects; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Terms coded using MedDRA® version 16.0.

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

Data Source: [Appendix 15, Table 15.2.6.2.1](#).

***Adverse Events by System Organ Class***

The most frequent AEs by SOC after THS 2.2 exposure were nervous system disorders, experienced by 27 subjects (33.8%); respiratory, thoracic, and mediastinal disorders experienced by 10 subjects (12.5%); investigations, gastrointestinal disorders, and renal and urinary disorders each experienced by 7 subjects (8.8%); and musculoskeletal and connective tissue disorders experienced by 6 subjects (7.5%).

The most frequent AEs by SOC after CC exposure were nervous system disorders, experienced by 19 subjects (46.3%); investigations experienced by 6 subjects (14.6%); gastrointestinal disorders experienced by 5 subjects (12.2%); respiratory, thoracic, and mediastinal disorders and renal and urinary disorders each experienced by 4 subjects (9.8%); and metabolism and nutrition disorders experienced by 3 subjects (7.3%).

The most frequent AEs by SOC after SA were nervous system disorders, experienced by 13 subjects (33.3%); metabolism and nutrition disorders and musculoskeletal and connective tissue disorders each experienced by 4 subjects (10.3%); investigations, gastrointestinal disorders, and vascular disorders each experienced by 3 subjects (7.7%); and renal and urinary disorders and ear and labyrinth disorders each experienced by 2 subjects (5.1%).

All other AEs by SOC were experienced by $\leq 5\%$ of subjects in each study arm.

Adverse Events by Preferred Term

The most frequent AEs after THS 2.2 exposure were headache, experienced by 24 subjects (30.0%); oropharyngeal pain experienced by 7 subjects (8.8%); syncope and polyuria each experienced by 6 subjects (7.5%); and spirometry abnormal experienced by 4 subjects (5.0%).

The most frequent AEs after CC exposure were headache, experienced by 16 subjects (39.0%); syncope and polyuria each experienced by 4 subjects (9.8%); and spirometry abnormal and oropharyngeal pain each experienced by 3 subjects (7.3%).

The most frequent AEs after SA were headache, experienced by 13 subjects (33.3%); back pain and influenza like illness each experienced by 3 subjects (7.7%); and spirometry abnormal, abdominal distension, hypertriglyceridemia, polyuria, hypertension, and vertigo each experienced by 2 subjects (5.1%).

The incidence of headache and spirometry abnormal were comparable between the THS 2.2, CC, and SA arms, the incidence of polyuria was higher in the THS 2.2 and CC arms, while syncope and oropharyngeal pain were not experienced by any subject in the SA arm.



All other AEs were experienced by <5% of subjects in each study arm.

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 15.2.6.7](#).

An overview of AE severity is shown in [Table 83](#).

Table 83 Overview of Adverse Event Severity (Safety Population)

System Organ Class Preferred Term	Study Arm			Exposed not Randomized (N=9)	Overall Safety (N=169)
	THS 2.2 (N=80)	CC (N=41)	SA (N=39)		
Number (%) subjects with any AEs	50 (62.5%)	29 (70.7%)	24 (61.5%)	9 (100%)	112 (66.3%)
Mild	28 (35.0%)	13 (31.7%)	11 (28.2%)	3 (33.3%)	55 (32.5%)
Moderate	22 (27.5%)	15 (36.6%)	13 (33.3%)	6 (66.7%)	56 (33.1%)
Severe	0	1 (2.4%)	0	0	1 (0.6%)

Abbreviations: AE = adverse event; CC = conventional cigarette; N = number of subjects; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Terms coded using MedDRA® version 16.0.

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

Data Source: [Appendix 15, Table 15.2.6.7](#).

The majority of AEs were mild or moderate in severity, with only 1 severe AE reported. Subject 0029 (CC arm) reported a severe AE of hypertriglyceridemia (see [Section 12.3.1](#)). The incidence of subjects who reported only mild AEs, and the incidence of subjects who reported at least one moderate intensity AE were comparable between the THS 2.2, CC, and SA arms.

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 or CC) are summarized by SOC and PT for the Safety population by study arm in [Appendix 15, Table 15.2.6.3](#) and by PT in [Table 84](#).

**Table 84 Summary of Adverse Events Related to Investigational Product by Preferred Term (Safety Population)**

Preferred Term	Study Arm			Exposed not Randomized (N=9)	Overall Safety (N=169)
	THS 2.2 (N=80)	CC (N=41)	SA (N=39)		
Number (%) subjects with any AEs related to IP	14 (17.5%)	7 (17.1%)	0	2 (22.2%)	23 (13.6%)
Spirometry abnormal	4 (5.0%)	3 (7.3%)	0	2 (22.2%)	9 (5.3%)
Syncope	1 (1.3%)	2 (4.9%)	0	0	3 (1.8%)
Carboxyhaemoglobin increased	0	2 (4.9%)	0	0	2 (1.2%)
Cough	2 (2.5%)	0	0	0	2 (1.2%)
Vertigo	2 (2.5%)	0	0	0	2 (1.2%)
Oral pain	1 (1.3%)	0	0	0	1 (0.6%)
Oropharyngeal pain	1 (1.3%)	0	0	0	1 (0.6%)
Hypertriglyceridaemia	1 (1.3%)	0	0	0	1 (0.6%)
Musculoskeletal chest pain	1 (1.3%)	0	0	0	1 (0.6%)
Myocardial ischaemia	1 (1.3%)	0	0	0	1 (0.6%)
Hyperhidrosis	1 (1.3%)	0	0	0	1 (0.6%)

Abbreviations: AE = adverse event; CC = conventional cigarette; IP = investigational product; N = number of subjects; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Terms coded using MedDRA® version 16.0.

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

Data Source: [Appendix 15, Table 15.2.6.3](#).

Twenty-six AEs assessed as related to IP use were reported by 23 of the 130 subjects in the THS 2.2, CC, and enrolled not randomized arms (17.7%). The incidence of AEs assessed as related to IP use was comparable for the THS 2.2 (14/80 subjects [17.5%]) and CC arms (7/41 subjects [17.1%]). The most frequent AEs assessed as related to IP use were spirometry abnormal, experienced by 9 subjects (5.3%; 4/80 subjects [5.0%] in the THS 2.2 arm, 3/41 subjects [7.3%] in the CC arm, and 2/9 enrolled not randomized subjects [22.2%]); syncope, experienced by 3 subjects (1.8%; 1/80 subjects [1.3%] in the THS 2.2 arm and 2/41 subjects [4.9%] in the CC arm); COHb increased, experienced by 2 subjects (1.2%), both in the CC arm (2/41 [4.9%]); cough, experienced by 2 subjects (1.2%), both in the THS 2.2 arm (2/80 [2.5%]); and vertigo, experienced by 2 subjects (1.2%), both in the THS 2.2 arm (2/80 [2.5%]). All other AEs assessed as related to IP use were reported by single subjects in the THS 2.2 arm only.

Of the 26 AEs assessed as related to IP, 23 were mild in severity. Adverse events of hypertriglyceridemia (Subject 0014) and cough (Subject 0216) which were moderate in severity were reported following IP use in the THS 2.2 arm. An AE of syncope which was



moderate in severity was reported by Subject 0160 in the CC arm; this event was also considered related to study procedures (see [Section 12.1.3.2.2](#)).

Of the 23 subjects with AEs assessed as related to IP use, expected AEs were reported by 12 subjects (7.1%; 3 subjects [3.8%] in the THS 2.2 arm, 7 subjects [17.1%] in the CC arm, and 2 enrolled not randomized subjects [22.2%]); all other AEs assessed as related to IP use were therefore unexpected. Expected AEs included spirometry abnormal experienced by 8 subjects (4.7%; 3 subjects [3.8%] in the THS 2.2 arm, 3 subjects in the CC arm [7.3%], and 2 enrolled not randomized subjects [22.2%]); syncope experienced by 2 subjects (1.2%; both in the CC arm [4.9%]); and COHb increased experienced by 2 subjects (1.2%; both in the CC arm [4.9%]). All unexpected AEs occurred in the THS 2.2 arm. Unexpected AEs included cough and vertigo which were each experienced by 2 subjects; all other unexpected AEs were only experienced by 1 subject.

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 by study arm in [Appendix 15, Table 15.2.6.6](#) and by PT in [Table 85](#).

Table 85 Summary of Adverse Events Related to Study Procedure by Preferred Term (Safety Population)

Preferred Term	Study Arm			Exposed not Randomized (N=9)	Overall Safety (N=169)
	THS 2.2 (N=80)	CC (N=41)	SA (N=39)		
Number (%) subjects with any AEs related to study procedure	11 (13.8%)	6 (14.6%)	1 (2.6%)	2 (22.2%)	20 (11.8%)
Syncope	4 (5.0%)	3 (7.3%)	0	0	7 (4.1%)
Spirometry abnormal	2 (2.5%)	1 (2.4%)	0	2 (22.2%)	5 (3.0%)
Carboxyhaemoglobin increased	0	2 (4.9%)	0	0	2 (1.2%)
Vessel puncture site reaction	2 (2.5%)	0	0	0	2 (1.2%)
Vertigo	1 (1.3%)	0	0	0	1 (0.6%)
Musculoskeletal chest pain	1 (1.3%)	0	0	0	1 (0.6%)
Nicotine dependence	0	0	1 (2.6%)	0	1 (0.6%)
Oropharyngeal pain	1 (1.3%)	0	0	0	1 (0.6%)

Abbreviations: AE = adverse event; CC = conventional cigarette; N = number of subjects; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.

Terms coded using MedDRA® version 16.0.

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

Data Source: [Appendix 15, Table 15.2.6.6](#).



The incidence of AEs assessed as related to study procedures was comparable for subjects in the THS 2.2 (13.8%) and CC arms (14.6%), and was considerably lower for subjects in the SA arm (2.6%).

The most frequent AEs related to study procedure after THS 2.2 exposure were syncope, experienced by 4 subjects (5.0%); and spirometry abnormal and vessel puncture site reaction, each experienced by 2 subjects (2.5%). Other AEs related to study procedure after THS 2.2 exposure were only reported by individual subjects.

The most frequent AEs related to study procedure after CC exposure were syncope, experienced by 3 subjects (7.3%) and COHb increased, experienced by 2 subjects (4.9%). Other AEs were only reported by individual subjects

The only AE related to study procedures reported after SA was nicotine withdrawal, reported by 1 subject. Spirometry abnormal was reported by 2 subjects who were enrolled but not randomized.

Of the 22 AEs assessed as related to study procedures, 20 were mild in severity. Adverse events of syncope which were moderate in severity were reported following IP use in the THS 2.2 arm (Subject 0232) and CC arm (Subject 0160); the latter event was also considered related to IP administration (see [Section 12.1.3.2.1](#)).

12.1.4 Listing of Adverse Events by Subject

Adverse events are listed by subject in [Appendix 15, Listing 15.3.6.1.1](#).

12.1.5 Investigational Device Malfunction or Misuse Events

Device events and malfunctions, including an assessment of whether the event was related to an AE, are listed by subject in [Appendix 15, Listing 15.3.6.2](#). Device events and malfunctions are summarized by study arm for the Safety population in [Appendix 15, Table 15.2.6.10](#), and are summarized for the THS 2.2 arm in [Table 86](#).

**Table 86 Summary of THS 2.2 Device Events and Malfunctions (THS 2.2 Arm)**

	THS 2.2 (N=80)
Number (%) subjects with any device events and malfunctions	12 (15.0%)
Is not related to adverse event	12 (15.0%)
Major	12 (15.0%)
Charging issue	8 (10.0%)
Device inoperable	3 (3.8%)
Device stops intermittently	2 (2.5%)
Device operates differently than expected	2 (2.5%)
Device difficult to set up or prepare	1 (1.3%)
Output issue	1 (1.3%)

Abbreviations: N = number of subjects; THS 2.2 = Tobacco Heating System 2.2.

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

Data Source: [Appendix 15, Table 15.2.6.10](#).

During THS 2.2 use, 12 subjects (15.0%) reported a total of 19 major device events or malfunctions. None of these events led to an AE.

12.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.2.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Serious AEs and AEs that led to withdrawal from the study are listed by subject in [Appendix 15, Listing 15.3.6.1.2](#) and [Listing 15.3.6.1.3](#), respectively.

12.2.1.1 Deaths

No deaths occurred in this study.

12.2.1.2 Other Serious Adverse Events

No SAEs occurred during the study for any subject.

12.2.1.3 Other Significant Adverse Events

12.2.1.3.1 Adverse Events Leading to Study Discontinuation

Adverse events leading to study discontinuation are summarized by SOC and PT for the Safety population by study arm in [Appendix 15, Table 15.2.6.5](#). There were no AEs leading to study discontinuation in any randomized subject. Eight of the exposed but not



randomized subjects were discontinued due to abnormal assessments which were performed after the product test at Day -2 and before randomization. Adverse events which led to discontinuation are summarized in [Table 87](#).

Table 87 Summary of Adverse Events Leading to Study Discontinuation by Preferred Term (Exposed Not Randomized Subjects)

	Exposed Not Randomized (N=9)
Number (%) subjects with any adverse event leading to study discontinuation	8 (88.9%)
Spirometry abnormal	3 (33.3%)
Leukocytosis	2 (22.2%)
Hypertension	2 (22.2%)
Hyperglycaemia	1 (11.1%)

Abbreviations: N = number of subjects.

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

Data Source: [Appendix 15, Table 15.2.6.5](#).

All AEs were mild in severity and only the 2 of the 3 AEs of spirometry abnormal (an expected AE) were considered to be related to both the IP and study procedures. Further details of the individual AEs which led to discontinuation can be found in the clinical chemistry ([Section 12.3.1](#)), hematology ([Section 12.3.2](#)), vital signs ([Section 12.4.1](#)), and spirometry sections ([Section 12.4.4](#)).

12.2.1.3.2 Adverse Events Leading to Product Discontinuation or Reduction

Adverse events leading to product discontinuation or reduction are summarized by SOC and PT for the Safety population by study arm in [Appendix 15, Table 15.2.6.4](#).

Only a single subject (0.6%) experienced an AE that led to product reduction. Subject 0318 from the CC arm (1/41 [2.4%]) experienced a mild AE of COHb increased which lasted for 2 days. Carboxyhemoglobin values for the 2 days were 9.1% and 8.4%. The event was considered related to CC consumption and product use was reduced for the duration of the event.

12.2.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths, SAEs, or other significant AEs occurred in this study.

12.2.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths, SAEs, or other significant AEs during the study.



12.3 Clinical Laboratory Evaluation

12.3.1 Clinical Chemistry

Clinical chemistry data are presented by subject in [Appendix 15, Listing 15.3.6.4](#) including individual changes and shifts from baseline (Day 0) to Discharge and toxicity grading (1 = mild, 2 = moderate, 3 = severe).

Clinical chemistry data are summarized for the Safety population in [Appendix 15, Table 15.2.6.13](#), including summaries of low, normal, high, and abnormal clinically relevant results.

A total of 28 results from 21 subjects which were deemed to be clinically relevant by the Investigator were reported for the clinical chemistry values during the study. Of these, 15 results from 14 subjects were reported after the product test at Day -2. The majority of subjects in all study arms had normal clinical chemistry values at Screening, Day 0, and Day of Discharge (the lowest number of normal values was 57%, which was observed for cholesterol at the Day of Discharge). In general, mean changes from baseline in clinical chemistry parameters were small and comparable between study arms.

Shifts in clinical chemistry parameters in which ≥ 2 subjects in any study arm had a shift from normal to low included triglycerides, LDH, glucose, creatinine, and protein. There was no apparent trend in the distribution of subjects who had clinical chemistry results which shifted from normal to low between the THS 2.2, CC, and SA arms.

Shifts from baseline in which ≥ 2 subjects in any study arm had a shift from normal to high included alanine aminotransferase, cholesterol, glucose, triglycerides, albumin, direct bilirubin, bilirubin, aspartate aminotransferase, and potassium. For each of these parameters, normal-to-high shifts were seen across all study arms, except for bilirubin and direct bilirubin (THS 2.2 arm only), potassium (THS 2.2 arm only), and albumin (THS 2.2 and SA arms only).

The majority of clinical chemistry variables were normal or classified as grade 1 (mild) on the toxicity grading. The following subjects reported clinical chemistry variables classified as grade 2 (moderate) or grade 3 (severe) on the toxicity grading, after the time of the product test on Day -2:

In the THS 2.2 arm:

- Subject 0014: Triglycerides of 333 mg/dL (grade 2) at Day of Discharge.
- Subject 0020: Bilirubin of 1.5 mg/dL (grade 1) at Screening, 1.1 mg/dL (grade 1) at Day 0, and 1.7 mg/dL (grade 2) at Day of Discharge.



- Subject 0057: Triglycerides of 180 mg/dL (grade 1) at Day 0 and 358 mg/dL (grade 2) at Day of Discharge.
- Subject 0134: Triglycerides of 240 mg/dL (grade 1), 308 mg/dL (grade 2), and 346 mg/dL (grade 2) at Screening, Day 0, and Day of Discharge, respectively.
- Subject 0162: Potassium of 5.8 mmol/L (grade 2) at Day of Discharge.
- Subject 0181: Bilirubin of 1.2 mg/dL at Screening (grade 1) and 1.7 mg/dL (grade 2) at Day of Discharge.

In the CC arm:

- Subject 0029: Triglycerides of 181 mg/dL (grade 1), 273 mg/dL (grade 1), and 552 mg/dL (grade 3) at Screening, Day 0, and Day of Discharge, respectively.
- Subject 0072: Potassium of 5.7 mmol/L (grade 2) at Day of Discharge.
- Subject 0118: Triglycerides of 193 mg/dL (grade 1), 195 mg/dL (grade 1), and 303 mg/dL (grade 2) at Screening, Day 0, and Day of Discharge, respectively.
- Subject 0328: Cholesterol of 286 mg/dL (grade 1), 278 mg/dL (grade 1), and 331 mg/dL (grade 2) at Screening, Day 0, and Day of Discharge, respectively.

In the SA arm:

- Subject 0028: Triglycerides of 183 mg/dL (grade 1), 166 mg/dL (grade 1), and 316 mg/dL (grade 2) at Screening, Day 0, and Day of Discharge, respectively.
- Subject 0128: Triglycerides of 209 mg/dL (grade 1), 254 mg/dL (grade 1), and 345 mg/dL (grade 2) at Screening, Day 0, and Day of Discharge, respectively.
- Subject 0249: Cholesterol of 285 mg/dL (grade 1), 327 mg/dL (grade 2), and 285 mg/dL (grade 1) at Screening, Day 0, and Day of Discharge, respectively.

Enrolled not randomized

- Subject 0299: Potassium of 5.8 mmol/L (grade 2) at Day 0.

For Subjects 0014, 0028, 0057, 0128, and 0134; increased triglycerides were reported as AEs (hypertriglyceridemia). The events began on Day 0 for Subject 0134 and at Day of Discharge for all other subjects. Each event was considered moderate in severity and not related to study procedures; hypertriglyceridemia in Subject 0014 was considered related to IP. No action was taken, each AE was ongoing at the end of the study but was not considered to require further follow-up. For Subject 0029, increased triglycerides was also reported as an AE (hypertriglyceridemia), beginning at Day of Discharge. The event was severe, but was not considered related to IP or study procedures. No action was taken, the AE was ongoing at the end of the study but was not considered to require further follow-up.



For Subjects 0020 and 0181, increases in bilirubin were reported as AEs (hyperbilirubinemia and blood bilirubin increased, respectively) beginning at Day of Discharge. Both events were moderate in severity and were not considered to be related to IP or study procedures. No action was taken, the AE was ongoing at the end of the study but was not considered to require further follow-up.

For Subjects 0162 and 0299, increases in potassium were reported as AEs (hyperkalemia), beginning at Day of Discharge and Day 0, respectively. Both events were moderate and were not considered related to IP or study procedures. No action was taken with Subject 0162, the AE was ongoing at the end of the study but was not considered to require further follow-up. Subject 0299 was not randomized onto the study.

For Subjects 0249 and 0328, increases in cholesterol were reported as AEs (hypercholesterolemia), beginning at Day 0 and Day of Discharge, respectively. Both events were moderate, not considered related to IP or study procedures, and no action was taken. Hypercholesterolemia in Subject 0249 resolved after 7 days at Day of Discharge; for Subject 0328, the AE was ongoing at the end of the study but was not considered to require further follow-up.

One further subject was disqualified from the study due to a clinical chemistry result on Day 0. Subject 0312 had a glucose level of 127 mg/dL (grade 1) at Screening which had increased to 145 mg/dL at Day 0. The increased blood glucose was reported as an AE (hyperglycemia) which began on Day 0, was mild in severity, was not considered to be related to IP use or study procedures, and was ongoing at the end of the study but was not considered to require further follow-up.

12.3.2 Hematology

Hematology data are presented by subject in [Appendix 15, Listing 15.3.6.5](#) including individual changes and shifts from baseline (Day 0) to Discharge and toxicity grading (1 = mild, 2 = moderate, 3 = severe).

Hematology data are summarized for the Safety population in [Appendix 15, Table 15.2.6.14](#), including summaries of low, normal, high, and abnormal clinically relevant results.

A total of 12 results from 6 subjects which were deemed to be clinically relevant by the Investigator were reported for the hematology values during the study. Of these, 11 results from 5 subjects were reported after the product test at Day -2. The majority of subjects in all study arms had normal hematology values at Screening, Day 0, and Day of Discharge (the lowest number of normal values was 70%, which was observed for mean corpuscular hemoglobin concentration at Screening and the Day of Discharge). In general, mean



changes from baseline in hematology parameters were small and comparable between study arms.

Shifts in hematology parameters in which ≥ 2 subjects in any study arm displayed a shift from normal to low included neutrophil/leukocyte, lymphocyte/leukocyte, hemoglobin, and hematocrit. There was no apparent trend in the distribution of subjects who had hematology results which shifted from normal to low between the THS 2.2, CC, and SA arms.

Shifts in hematology parameters in which a number of subjects displayed a shift from normal to high included monocyte count, monocyte/leukocyte, leukocyte count, and mean corpuscular hemoglobin concentration. All other normal-to-high shifts at Day of Discharge when compared with baseline, occurred in fewer than 5 subjects across all study arms. There was no apparent trend in the distribution of subjects who had hematology results which shifted from normal to high between the THS 2.2, CC, and SA arms.

The majority of hematology results were normal or classified as grade 1 (mild) on the toxicity grading. The following subjects reported hematology results classified as grade 2 (moderate) or grade 3 (severe) on the toxicity grading after the time of the product test on Day -2:

In the THS 2.2 arm:

- Subject 0031: Hemoglobin of 21.8 g/dL (grade 3) at Day 0.
- Subject 0088: Lymphocytes of 4.24 G/L (grade 2) at Day of Discharge.
- Subject 0090: Lymphocytes of 4.44 G/L (grade 2) at Day 0.

In the CC arm:

- Subject 0313: Neutrophils of 1.24 G/L (grade 2) at Day 0.

In the SA arm:

- Subject 0049: Lymphocytes of 4.49 G/L (grade 2) at Day 0.

Enrolled not randomized:

- Subject 0269: Lymphocytes of 4.10 G/L (grade 2) at Day 0.

For Subjects 0049 and 0090, increases in lymphocytes were reported as AEs (lymphocyte count increased), beginning at Day 0. Both events were moderate, not considered related to IP or study procedures, no action was taken, and the AEs resolved 7 days later at the Day of Discharge.



For Subject 0313, decreased neutrophil level was reported as an AE (neutrophil count decreased) which began on Day 0. The AE was considered moderate in severity, and was not related to IP or study procedure. No action was taken and the AE resolved after 7 days at Day of Discharge.

Three other AEs were reported relating to changes in hematology parameters. Subject 0256 (THS 2.2 arm) reported an AE of eosinophil count increased which began at Day 0. The event was mild in severity, not considered to be related to IP or study procedures, no action was taken, and the AE resolved 7 days later at the Day of Discharge.

Subjects 0242 and 0245 (enrolled not randomized) were discontinued from the study due to increased leukocyte levels at Day 0 (11.66 and 13.22 G/L, respectively, both Grade 1). The increases in leukocytes were reported as AEs (leukocytosis) which began on Day 0, were mild in severity, were not considered to be related to IP use or study procedures, and was ongoing at the end of the study for Subject 0242 but was not considered to require further follow-up, and resolved 6 days later for Subject 0245.

12.3.3 Urinalysis

Urinalysis data are presented by subject in [Appendix 15, Listing 15.3.6.6](#), including individual changes and shifts from baseline (Day 0) to Discharge and toxicity grading (1 = mild, 2 = moderate, 3 = severe).

Urinalysis data are summarized for the Safety population in [Appendix 15, Table 15.2.6.15](#), including summaries of low, normal, high, and abnormal clinically relevant results.

The majority of subjects ($\geq 87\%$) in all study arms had normal urinalysis results at Screening, Day 0, and Day of Discharge. Occult blood (negative) exhibited the lowest percentage of normal values (87% of subjects at Day of Discharge). 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. A number of clinically relevant urinalysis results were observed at Screening; the majority of these were positive occult blood results in female subjects.

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

12.4.1 Vital Signs

Vital signs data are presented by subject in [Appendix 15, Listing 15.3.6.7](#), including individual changes from baseline.



Vital signs data are summarized for the Safety population in [Appendix 15, Table 15.2.6.16](#) 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. Eighteen clinically relevant vital signs results were observed and reported as AEs. Hypertension was experienced on 10 occasions by 6 subjects (3.6%; 2 events in 1 subject in the THS 2.2 arm [1.3%], 1 event in 1 subject in the CC arm [2.4%], 5 events in 2 subjects in the SA arm [5.1%], and 2 events in 2 enrolled not randomized subjects [22.2%]). Hypotension was experienced on 5 occasions in 4 subjects (2.4%; 2 events in 2 subjects in the THS 2.2 arm [2.5%], 1 event in 1 subject in the CC arm [2.4%], and 2 events in 1 subject in the SA arm [2.6%]), and tachycardia was observed on 3 occasions in 2 subjects (1.2%; both subjects [4.9%] in the CC arm).

The 2 enrolled not randomized subjects who experienced hypertension (Subjects 0211 and 0247) were disqualified from the study on Day 0. Both events were recored as mild AEs and was ongoing at Discharge but not considered to require further follow-up for Subject 0211 and resolved 10 days later for Subject 0247.

In addition, some AEs were temporally associated with vital signs changes. Ten events of syncope were observed in 10 subjects (5.9%; 6 subjects in the THS 2.2 arm [7.5%] and 4 subjects in the CC arm [9.8%]); 3 of these (all from the CC group) were temporally related to substantial changes in vital signs, of which 2 were considered to be related to the IP. Summaries of AEs related to, and associated with vital signs changes that were considered to be related to IP are detailed below.

Subject 0160 (CC arm) experienced moderate syncope on Day 5, which lasted for 1 day and was concurrent with vital signs changes. At an unscheduled evaluation approximately 3.5 hours prior to the scheduled Day 5 evaluation, the subject was bradycardic, with a pulse rate of 56 bpm (decrease of 20 bpm from baseline). Heart rate had recovered by the time of the scheduled Day 5 evaluation, with a pulse rate of 70 bpm (decrease of 6 bpm from baseline). The event of syncope was considered related to IP and study procedures.

Subject 0200 (CC arm) experienced mild syncope on Day 5, which lasted for 1 day and was concurrent with vital signs changes. At an unscheduled evaluation approximately 3.5 hours prior to the scheduled Day 5 evaluation, the subject experienced an increase from baseline of 18 bpm in pulse rate to 96 bpm. At the scheduled Day 5 evaluation, the subjects pulse rate value had moved closer to baseline at 76 bpm (decrease of 2 bpm from baseline). Syncope was considered related to IP and study procedures.

The mean and median data for all vital signs parameters analyzed were unremarkable and comparable between study arms. In general, mean changes from baseline in vital signs parameters were small and comparable between study arms.



12.4.2 Physical Examinations

Physical examination findings (including height, weight, and BMI) are presented by subject in [Appendix 15, Listing 15.3.6.10](#).

Weight and BMI data are summarized for the Safety population in [Appendix 15, Table 15.2.6.19](#), including summaries of changes from Day -2 to Day of Discharge.

In all study arms, no clinically significant physical examination findings were recorded at Screening, Day -2, or Day of Discharge.

Mean body weight and BMI were comparable between study arms and changes from baseline were small and comparable between study arms.

12.4.3 ECG

The ECG data are presented by subject in [Appendix 15, Listing 15.3.6.9](#), including individual changes from baseline, shifts from baseline in overall ECG interpretation, and a description of clinical relevance.

The ECG data are summarized for the Safety population in [Appendix 15, Table 15.2.6.17](#) 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. Overall, 31 subjects (18.3%) had at least 1 abnormal ECG interpretation (16 subjects in the THS 2.2 arm [20.0%], 6 subjects in the CC arm [14.6%], 7 subjects in the SA arm [18.0%], and 2 enrolled not randomized subjects [22.2%]), however, only 13 of these (6 subjects in the THS 2.2 arm [7.5%], 2 subjects in the CC arm [4.9%], 4 subjects in the SA arm [10.3%], and 1 enrolled not randomized subject [11.1%]) shifted from normal to abnormal ECG interpretations during the study.

Two subjects (1.2%) had clinically significant abnormalities in ECG interpretations (1 in the THS 2.2 arm [1.3%], and 1 enrolled not randomized subject [11.1%]) that were recorded as AEs.

At Day of Discharge, interpretation of ECG data for Subject 0031 (THS 2.2 arm) indicated myocardial ischemia of the anterior wall, which was not present at Screening. The AE was considered related to IP and was mild in severity; no concomitant treatment or intervention was required and the ECG was otherwise normal. However, the subject's history of a family/genetic predisposition to cardiovascular illness was not considered while reconciling this AE by the study site. Additionally, this 38 year old subject had a history of smoking >19 cigarettes/day for over 20 years, prior attending this particular study.



At Day of Discharge, interpretation of ECG data for Subject 0211 (enrolled not randomized) indicated ventricular extrasystoles, which was not present at Screening. The AE was not considered related to IP or study procedure, and was mild in severity; no concomitant treatment was required and the ECG was otherwise normal. At the time of diagnosis the subject had already experienced hypertension for which they were disqualified.

12.4.4 Spirometry

Spirometry data are presented by subject in [Appendix 15, Listing 15.3.6.8](#).

Spirometry results for the Safety population are summarized in [Appendix 15, Table 15.2.6.18](#), including summaries of changes from baseline to Discharge.

In all study arms all subjects had post-bronchodilator $FEV_1/FVC > 0.7$. However, 2 subjects had post-bronchodilator FEV_1 , $< 80\%$ of predicted, or post-bronchodilator $FVC < 80\%$ of predicted at Screening and therefore failed the inclusion/exclusion criteria for this study. Subject 0153 (THS 2.2 arm) had $FEV_1 < 80\%$ (78%) but was still randomized onto the study (see [Section 10.2](#)). Subject 0288 (enrolled not randomized) had $FVC < 80\%$ (79%) of predicted at Screening, and was not randomized onto the study due to worsening of spirometry 13 days later.

For all sequences, no notable changes from baseline in spirometry parameters were observed at Day of Discharge. No clinically relevant differences in spirometry parameters or in changes from baseline were observed between study arms.

Overall, 10 subjects (5.9%) had at least 1 clinically significant abnormal spirometry interpretation (3 subjects in the THS 2.2 arm [3.8%], 3 subjects in the CC arm [7.3%], 1 subject in the SA arm [2.6%], and 3 enrolled not randomized subjects [33.3%]). These events were recorded as mild AEs.

In the THS 2.2 arm:

- Subject 0149: FEV_1/FVC of 0.76, 0.71, and 0.69 at Screening, Day 0, and Day of Discharge, respectively.
- Subject 0177: FEV_1/FVC of 0.72, 0.68, and 0.72 at Screening, Day 0, and Day of Discharge, respectively.
- Subject 0206: FEV_1/FVC of 0.72, 0.65, and 0.66 at Screening, Day 0, and Day of Discharge, respectively.



In the CC arm:

- Subject 0042: FEV₁/FVC of 0.73, 0.69, and 0.69 at Screening, Day 0, and Day of Discharge, respectively.
- Subject 0080: FEV₁/FVC of 0.77, 0.78, and 0.63 at Screening, Day 0, and Day of Discharge, respectively.
- Subject 0148: FEV₁/FVC of 0.77, 0.76, and 0.75 at Screening, Day 0, and Day of Discharge, respectively.

In the SA arm:

- Subject 0203: FEV₁/FVC of 0.76, 0.75, and 0.71 at Screening, Day 0, and Day of Discharge, respectively.

With the exception of Subject 0203, each AE was considered to be related to IP. For Subjects 0042, 0149 and 0177, the AEs were also considered related to study procedures. All clinically significant results were observed on the Day of Discharge, with the exception of Subject 0177. Consequently the corresponding AEs were ongoing at the end of the study but were not considered to require further follow-up. For Subject 0177, abnormal spirometry was only recorded on Day 0, and consequently the corresponding AE had resolved by Day of Discharge.

Three enrolled but not randomized subjects (Subjects 0269, 0288, and 0309) were discontinued due to AEs of abnormal spirometry. Each had clinically significant results at Day 0 which were recorded as ongoing mild AEs.

- Subject 0269: FEV₁/FVC of 0.78 and 0.76 at Screening and Day 0, respectively.
- Subject 0288: FEV₁/FVC of 0.76 and 0.72 at Screening and Day 0, respectively.
- Subject 0309: FEV₁/FVC of 0.85 and 0.77 at Screening and Day 0, respectively.

For Subjects 0269 and 0288, the AE was considered related to IP and study procedures. For Subject 0309, the AE was not considered related to IP or study procedures.

A further 2 subjects reported mild AEs of abnormal spirometry, although the spirometry results were not interpreted as being clinically significant. Subjects 0155 (THS 2.2 arm) and 0185 (SA arm) reported AEs which began at Day of Discharge and Day 0, respectively. Neither of these AEs were deemed to be related to study procedures and only the AE for Subject 0155 was considered to be related to IP.



12.4.5 Assessment of Cough

Subject listings for the assessment of cough are presented by subject in [Appendix 15, Listing 15.3.6.14](#).

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 15.2.6.20](#). 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 15.2.6.20.1](#).

Overall, the number of subjects who experienced a cough during the study period was high (107 subjects, 63.3%). Cough was not experienced by any of the enrolled not randomized subjects. The incidence of cough was similar between the THS 2.2 and CC arms (73.8% and 65.9%, respectively), with incidence in the SA arm being marginally lower (53.8%).

Cough intensity and frequency of cough were comparable between the THS 2.2 and CC arms, with the most commonly reported cough intensity overall being mild (32.5% and 24.4%, respectively) and the most common frequency being sometimes (35.0% and 29.3%, respectively). In the SA arm the most commonly reported cough intensity overall was very mild (20.5%) and the most commonly reported frequency was rarely (28.2%). The highest intensity of cough experienced during the study was severe, which was reported at a similar incidence in the THS 2.2 (5.0%) and CC (4.9%) study arms; no severe coughing events were reported in SA subjects. The highest frequency of cough experienced during the study was often, which was reported by 1 subject in the THS 2.2 arm (1 event in 1 subject [1.3%]), and 1 subject in the CC arm (1 event in 1 subject [2.4%]).

In each study arm, the most frequently reported amount of sputum was a moderate amount of sputum, reported by 34 subjects in the THS 2.2 arm (42.5%), 18 subjects in the CC arm (43.9%), and 11 subjects in the SA arm (28.2%). The number of subjects who experienced a cough with no sputum was marginally higher in the THS 2.2 arm (30.0%) than the CC and SA arms (19.5% and 23.1%, respectively). The highest value for amount of sputum reported during the study was a large amount of sputum, which was reported by 1 subject each in the THS 2.2, CC, and SA arms (1.3%, 2.4%, and 2.6%, respectively).

Analysis of cough impact scale data (VAS) shows mean increases in how bothersome cough was perceived to be in each study arm. The mean VAS score was marginally higher for subjects in the SA arm who experienced a cough on Day -1, compared with subjects in the THS 2.2 and CC arms; however, at all other time points the mean VAS score was comparable across the 3 study arms. There were no other remarkable differences in the cough assessment in the study arms on individual study days.



There were no remarkable differences between reported intensity of cough between the THS 2.2 and CC arms throughout the study.

There were 2 subjects (both THS 2.2 arm [2.5%]) who had AEs of cough during the study that were considered to be related to the IP.

Subject 0216 (THS 2.2) reported moderate cough throughout the study from Day 2, and described a regular need to cough at each day of the study exempting Day 1 (Day 0 VAS value was very low at 6). The VAS scores for cough during the AE were between 36 and 60. Intensity, frequency of cough, and sputum produced were assessed as moderate, sometimes, and a moderate amount of sputum, respectively on each day during the AE exempting Day 5 (frequency increased to fairly often, and no sputum produced), and Day of Discharge (intensity decreased to mild). The AE was considered related to IP and recovered without intervention after 5 days.

Subject 0316 (THS 2.2) reported mild cough on Days 2 and 3, and described a regular need to cough on both of these days only. The VAS scores for cough during the AE were low at 3 and 7 on Days 2 and 3, respectively. Frequency of cough was sometimes, and no sputum was present on either occasion; cough intensity was moderate at Day 2 and mild at Day 3. The AE was considered related to IP and recovered without intervention after 2 days.

12.5 Safety Conclusions

There were no SAEs reported in this study and no randomized subjects discontinued from the study due to an AE. Eight subjects were discontinued from the study prior to randomization following abnormal assessments on Day 0. A further subject was discontinued prior to randomization for having weak veins.

Overall, there were 227 AEs reported by 112 of the 169 subjects (66.3%) in the Safety population, most of which were mild or moderate in severity. Only 1 severe AE was reported which occurred in the CC arm, and was not considered to be related to IP use or study procedures. The incidence and frequency of AEs were comparable in the THS 2.2 (98 AEs in 50/80 subjects [62.5%]), the CC (63 AEs reported by 29/41 [70.7%] subjects), and the SA arms (49 AEs in 24/39 [61.5%] subjects).

The most frequent AEs after THS 2.2 or CC exposure were headache, oropharyngeal pain, syncope, polyuria, and spirometry abnormal. The most frequent AEs after SA were headache, back pain, influenza-like illness, spirometry abnormal, abdominal distension, hypertriglyceridemia, polyuria, hypertension, and vertigo. The incidence of headache and spirometry abnormal were comparable between the THS 2.2, CC, and SA arms, the incidence of polyuria was higher in the THS 2.2 and CC arms, while syncope and oropharyngeal pain were not experienced by any subject in the SA arm.



Only 26 of the 227 reported AEs were assessed as being related to THS 2.2 or CC use and were reported by 23 of the 130 subjects in the THS 2.2, CC, and enrolled not randomized arms (17.7%). The incidence of AEs assessed as related to IP use was comparable for the THS 2.2 (14/80 subjects [17.5%]) and CC arms (7/41 subjects [17.1%]). The most frequent AEs assessed as related to IP use were spirometry abnormal, syncope, COHb increased, cough, and vertigo. All other AEs assessed as related to IP use were reported by single subjects in the THS 2.2 arm only.

During THS 2.2 use, 12 subjects experienced a total of 19 major device events or malfunctions which led to the replacement of the THS Tobacco Stick Holder or Charger. None of these events led to an AE.



13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

The study reported was designed to demonstrate exposure reduction to HPHCs when switching from CC to THS 2.2 use in a controlled setting, compared to those who continued to smoke CC, and those who abstained from smoking. Product distribution and use was controlled to ensure 5 days of exclusive use of THS 2.2 or CC and 5 days continuous abstinence from smoking in the SA arm. Compliance in the SA arm throughout the study was verified by the CO breath test <10 ppm. Such a controlled setting allowed the investigation of the maximum exposure reduction to HPHCs possible after 5 days of THS 2.2 use compared to CC smoking using SA as a benchmark. Furthermore, this study included endpoints to investigate the acceptance of THS 2.2 as a substitute to CC through the assessment of subjective effects.

In 2012, the US FDA's Center for Tobacco Products established a list of 18 HPHCs to be measured in smoke [6]. The present study assessed 17 HPHCs, including 15 of the HPHCs requested by the FDA for reporting, and found a significant reduction of 56% to 96% of levels of corresponding BoExp (except S-BMA) from baseline to Day 5 in subjects who switched from CC to THS 2.2. Similarly, the mutagenic potential of urine as assessed by the Ames mutagenicity test was 57% lower in THS 2.2 users and increased by approximately 29% in CC smokers at the end of the 5-day exposure period.

The Institute of Medicine refers to smoking cessation as the "gold standard" for assessing risk reduction, and 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" [4]. This study showed that for most of the BoExp assessed, the magnitude of reduction after THS 2.2 use was comparable or close to levels of BoExp observed in the SA arm. The differences observed for 3-HPMA, Total NNN, Total NNAL, 1-NA, and 3-HMPMA compared to SA might be best explained by the residual levels of the corresponding HPHCs in the aerosol of THS 2.2 as evaluated by the smoke chemistry [7]. The mutagenic potential of urine was similar in the THS 2.2 users and SA.

Overall, the study results demonstrated the potential of THS 2.2 to significantly reduce exposure to HPHCs close to levels reported in the literature after 5 days of smoking abstinence [29].

Moreover, this reduction of exposure to HPHCs measured in THS 2.2 users was achieved despite an observed increase in THS Tobacco Stick consumption and adaptation in puffing behavior associated with THS 2.2 use.

The average daily product use between baseline and the end of the exposure period increased by approximately 30% in the THS 2.2 arm, and remained in the same range in the



CC arm. Despite differences in product use, the exposure to nicotine was similar between the THS 2.2 and CC arms throughout the exposure period. These results 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 user.

This adaptation was also observed in HST parameters, which showed a change of the product use behavior. The HST parameters indicated that THS 2.2 users were taking a similar number of puffs and puff volume, using the same amount of work compared to CC, but adapted to the product by taking longer puffs, thus shortening the interpuff interval, and increasing the puffing time index.

The study evaluated the impact of using THS 2.2 for 5 days on CYP proteins, i.e., CYP1A2 and CYP2A6. The CYP1A2 enzymes are monooxygenases, which are involved in the activation of carcinogenic heterocyclic and aromatic amines, strong carcinogens associated with colon and bladder cancer [30, 31]. CYP1A2 also catalyzes many of the reactions involved in the metabolism of low therapeutic-index drugs and synthesis of cholesterol, steroids, and other lipids [32]. The CYP1A2 expression itself is induced to a large extent by polycyclic aromatic hydrocarbons (PAH) which are found in cigarette smoke [33].

In this study, CYP1A2 activity in subjects who switched to THS 2.2 was reduced to similar levels observed in subjects who abstained from smoking. The results obtained following 5 days of SA are in line with what is reported in the literature [13] and are likely to be linked to the overall reduction of exposure to PAH.

Overall, the results are indicative of a reduction of harmful metabolites resulting in reduced CYP1A2 activity after THS 2.2 use and SA.

The ratio of another nicotine metabolite, trans-3'-hydroxycotinine, to cotinine in biofluids is highly correlated with the rate of nicotine metabolism, which is catalyzed mainly by cytochrome CYP2A6. In our study, CYP2A6 activity was reduced in smokers who switched to THS 2.2 use and in those who maintained CC use, while activity increased in those who abstained from smoking. There was no notable difference in absolute CYP2A6 activity and change from baseline between THS 2.2 use and CC use, suggesting that CC smoking and THS 2.2 use are affecting CYP2A6 activity. The results obtained are in agreement with what was reported in other studies where the clearance of nicotine was significantly higher in non-smokers than in cigarette smokers [34] or in smokers who were abstinent from smoking for 4 to 7 days [35, 36]. The comparable levels of CYP2A6 activity observed in THS 2.2 users and CC smokers are plausibly explained by the nicotine contained in both products. Nicotine itself reduces the rate of its own metabolism by inhibiting CYP2A6 activity [37]. However, the reason why CYP2A6 activity was slightly reduced in THS 2.2 users and CC smokers at the end of the study compared to baseline is unknown.



Levels of 8-epi-PGF_{2α} and 11-DTX-B2 were assessed as clinical risk endpoints as these markers are associated with smoking-related disease pathways; oxidative stress and platelet coagulation, respectively. Both markers are known to be sensitive and reversible to levels observed in non-smokers after smoking cessation. Thereby, favorable changes in 8-epi-PGF_{2α} and 11-DTX-B2, in the THS 2.2 arm if similar to the changes observed in the SA arm, would indicate a sign of potential short-term health benefit.

Levels of 11-DTX-B2 were unchanged in the THS 2.2 and SA arms, when expressed both as concentration adjusted to creatinine or quantity excreted over 24 hours. Therefore, results obtained in this study are in contrast with the literature where decreases are reported following short period of SA [38].

No difference was found in the levels of 8-epi-PGF_{2α} in the THS 2.2 arm as compared to CC, whereas the 8-epi-PGF_{2α} levels were higher in the SA arm, against what was expected [39].

There was no statistical difference in 8-epi-PGF_{2α} and 11-DTX-B2 between THS 2.2 arm and CC when adjusting for NEQ

Possible explanations for these results are that changes of the clinical risk endpoints discussed will likely need a longer period of SA or switching to THS 2.2 than the duration of this study allowed. Literature reports at least 2 weeks for 8-epi-PGF_{2α} [15, 39] and for 11-DTX-B2 [38, 40]. Natural variability and factors such as age, gender, smoking intensity, or concomitant medication may add to the explanation of these results but will need further investigation. It is not excluded that the nicotine delivered by THS 2.2 may interfere and minimize the favorable changes.

Subjective effects:

The present study included endpoints to assess the overall satisfaction, to evaluate if THS 2.2 could be an acceptable substitute to CC. The results of the QSU-brief showed a similar reduction in urge-to smoke for THS 2.2 compared to CC and clearly different from what was observed during SA, where the urge-to-smoke increased from baseline to Day 1 before decreasing slowly from Day 1 to Day 5. Similar results were observed for withdrawal symptoms in the different study arms, where the MNWS showed no apparent difference between subjects who switched to THS 2.2 and smokers who continued to smoke CC. The MCEQ scale evaluated the overall satisfaction of THS 2.2 users compared to CC smokers, and showed that craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction were all lower; while aversion was higher for subjects who switched to THS 2.2 compared to subjects who continued to smoke CC.



The change in taste, sensorial experience, ritual, and differences in the ISO tar and nicotine yield of THS 2.2, are additional likely reasons for the observed differences in overall satisfaction. Nevertheless, overall subjective appreciation measures illustrate that THS 2.2 offered a close experience to what was observed in CC smokers. Different patterns observed for the corresponding domains in the SA arm tend to substantiate these observations. Further studies will determine if a longer time for adapting to THS 2.2 will further close the gap in perceived smoking effects.

Safety:

There were no SAEs reported in this study and no randomized subjects discontinued due to an AE. Only 1 severe AE (hypertriglyceridemia) was reported in the CC arm, and was not considered to be related to IP use or study procedures. There were no clinically relevant trends in safety laboratory parameters, vital signs, physical examination, ECG, spirometry findings, or assessment of cough.

Strength and Weaknesses of the Study:

A strength of the study was that all the BoExp were measured in 24-hour urine collection 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 when expressed as concentration adjusted to creatinine. These results showed that differences of urinary flow between subjects plays a minor role in the excretion of the selected BoExp measured in this study.

Another strength of this study was the number and variety of BoExp assessed. Cigarette smoke is a complex mixture containing more than 5,300 chemical compounds. The assessment of changes of BoExp to selected HPHCs as chosen for this study therefore acknowledges the fact that the aerosol/smoke matrix is not amenable to full analytical characterization due to its chemical complexity. The selected BoExp measured in this study represent HPHCs endorsed by public health advocates as a priority for being reduced in CC smoke and considered by the Institute of Medicine to provide a realistic assessment of human uptake of a variety of toxicants and carcinogens in tobacco-product.

The BoExp measured in this study 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) detectable using validated methods, (c) reflecting a specific toxic exposure or be a reliable surrogate of exposure to HPHCs, (d) representing a set of HPHCs as listed by the FDA, (e) represent assessment of both gas and particulate phase of the THS 2.2 aerosol, (f) cover a broad variety of chemical classes and organ toxicity classes (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, addiction potential).



The observed results are a consequence of the heat versus burn product design by which combustion is minimized or eliminated, and provide reasonable confidence that THS 2.2 reduces the exposure to HPHCs beyond the toxicants measured in this study, particularly as the levels of BoExp after THS 2.2 use are approaching those observed upon SA.

The results for S-BMA, a BoExp to toluene, were similar across all 3 study arms throughout the study without any discrimination. Despite the fact that S-BMA is a suitable BoExp to toluene in environmental and occupational studies [41], its suitability to discriminate between smokers and non-smokers seems therefore questionable and needs further evaluation. Various studies reported overlapping ranges in S-BMA levels with only subtle increase levels between smokers and non-smokers [41-43] which are in agreement with the findings of this study.

The interpretation of subjective effects related to THS 2.2 has limitation in this study. Based on PMI experience, the adaptation of smokers to a new tobacco product usually occurs within 1 to 2 months. A more robust understanding of these parameters would necessitate further studies including ambulatory setting and longer duration of product use.

13.2 Overall Conclusions

The study demonstrated that switching from CC smoking to THS 2.2 use resulted in substantial reductions in exposure to 15 selected HPHCs. The kinetics and the magnitude of decrease of BoExp levels observed in the THS 2.2 arm were approaching the levels observed in the SA arm. However, the exposure to nicotine was similar between the THS 2.2 and CC arms, indicating that users adapt quickly to the new product and achieve their individual nicotine levels.

The combination of the results of nicotine-exposure and subjective effects measures indicated that THS 2.2 offers comparable satisfaction to what was observed in CC smokers. Different patterns observed for the corresponding domains in the SA arm tend to substantiate these observations.

No SAEs and 1 severe AE (occurring in the CC arm) were reported during this study, with the total number of AEs being evenly balanced across study arms.

In summary, this study demonstrated that THS 2.2 reduced exposure to HPHCs close to what was observed when abstaining from smoking, and was acceptable with regards to taste, ritual sensorial experience, and nicotine delivery to the users, and therefore might be a suitable substitute for CC for adult smokers.



14 REFERENCE LIST

1. World Medical Association (WMA). WMA Declaration of Helsinki - Ethical principles for medical research involving human subjects. 2013.
2. U.S. Department of Health and Human Services. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. 2010.
3. FDA (Food and Drug Administration). Guidance for industry - Modified risk tobacco product applications - Draft Guidance. 2012.
4. IOM (Institute of Medicine). Scientific standards for studies on modified risk tobacco products. Washington, DC: The National Academies Press. 2012. doi: ISBN 978-0-309-22398-0.
5. Rodgman A, Perfetti TA. The chemical components of tobacco and tobacco smoke. 2nd ed: CRC Press, Taylor & Francis Inc (United States); 2013.
6. FDA (Food and Drug Administration). Guidance for industry - Reporting harmful and potentially harmful constituents in tobacco products and tobacco smoke under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act - Draft guidance. 2012.
7. Philip Morris Products S.A. *Unpublished on file data*: Investigator's Brochure for Tobacco Heating System 2.2 Menthol. Edition 2. 2013.
8. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res.* 2001;3:7-16.
9. Hughes JR, Hatsukami D. Background on the Minnesota Withdrawal Scale-Revised (MNWS-R). 2008;Available from: <http://www.uvm.edu/~hbpl/?Page=minnesota/default.html> (Accessed on 23 July 2014).
10. Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. *Addict Behav.* 2007;32:912-23. doi: 10.1016/j.addbeh.2006.06.028.
11. WHO Study Group, Ashley DL, Burns D, Djordjevic M, Dybing E, Gray N, et al. The scientific basis of tobacco product regulation: second report of a WHO study group. *World Health Organ Tech Rep Ser.* 2008(951):1-277, 1 p following Epub 2008/01/01. PubMed PMID: 19522165.
12. Lindner D, Smith S, Leroy CM, Tricker AR. Comparison of exposure to selected cigarette smoke constituents in adult smokers and nonsmokers in a European, multicenter, observational study. *Cancer Epidemiol Biomarkers Prev.* 2011;20(7):1524-36. Epub 2011/05/27. doi: 10.1158/1055-9965.epi-10-1186. PubMed PMID: 21613391.
13. Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. *Clin Pharmacol Ther.* 2004;76(2):178-84. Epub 2004/08/04. doi: 10.1016/j.clpt.2004.04.003. PubMed PMID: 15289794.
14. Philip Morris Products S.A. A controlled, randomised, open-label, 3-arm parallel single-centre confinement study to investigate exposure to selected smoke constituents in



smokers switching from conventional cigarettes to SMAR cigarettes for 5 days [YVD-CS01-EU]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2008-2009 [cited 2013 Dec 02]. Available from: <http://clinicaltrials.gov/show/NCT00812279> NLM Identifier: NCT00812279.

15. Pilz H, Oguogho A, Chehne F, Lupattelli G, Palumbo B, Sinzinger H. Quitting cigarette smoking results in a fast improvement of in vivo oxidation injury (determined via plasma, serum and urinary isoprostane). *Thromb Res.* 2000;99(3):209-21. Epub 2000/08/16. PubMed PMID: 10944241.

16. Morita H, Ikeda H, Haramaki N, Eguchi H, Imaizumi T. Only two-week smoking cessation improves platelet aggregability and intraplatelet redox imbalance of long-term smokers. *J Am Coll Cardiol.* 2005;45(4):589-94. Epub 2005/02/15. doi: 10.1016/j.jacc.2004.10.061. PubMed PMID: 15708708.

17. Benowitz NL, Fitzgerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. *J Am Coll Cardiol.* 1993;22(4):1159-67. Epub 1993/10/01. PubMed PMID: 7691912.

18. American Pharmacists Association. Cytochrome P450 enzymes: substrates, inhibitors, and inducers. *Drug information handbook.* 23rd ed 2014. p. 2316-24.

19. Society for Research on Nicotine and Tobacco Subcommittee on Biochemical Verification, Benowitz NL, III PJ, Ahijevych K, Jarvis MJ, Hall S, et al. Biochemical verification of tobacco use and cessation. *Nicotine & Tobacco Research.* 2002;4:149-59.

20. FDA (Food and Drug Administration). Food-effect bioavailability and fed bioequivalence studies. 2002.

21. Smith CJ, McKarns SC, Davis RA, Livingston SD, Bombick BR, Avalos JT, et al. Human urine mutagenicity study comparing cigarettes which burn or primarily heat tobacco. *Mutat Res.* 1996;361(1):1-9. Epub 1996/09/26. PubMed PMID: 8816936.

22. Jacob P, 3rd, Yu L, Duan M, Ramos L, Yturalde O, Benowitz NL. Determination of the nicotine metabolites cotinine and trans-3'-hydroxycotinine in biologic fluids of smokers and non-smokers using liquid chromatography-tandem mass spectrometry: biomarkers for tobacco smoke exposure and for phenotyping cytochrome P450 2A6 activity. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2011;879(3-4):267-76. Epub 2011/01/07. doi: 10.1016/j.jchromb.2010.12.012. PubMed PMID: 21208832.

23. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict.* 1991;86(9):1119-27. PubMed PMID: 1932883.

24. Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. *J Behav Med.* 1989;12(2):159-82. PubMed PMID: 2668531.

25. Fagerstrom K, Russ C, Yu CR, Yunis C, Foulds J. The Fagerstrom Test for Nicotine Dependence as a predictor of smoking abstinence: a pooled analysis of varenicline clinical trial data. *Nicotine Tob Res.* 2012;14(12):1467-73. Epub 2012/04/03. doi: 10.1093/ntr/nts018. PubMed PMID: 22467778.



26. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry*. 1986;43(3):289-94. Epub 1986/03/01. PubMed PMID: 3954551.
27. Snedecor GW, Cochran WG. One-way classifications: analysis of variance. *Statistical Methods*. 8th ed: Iowa: Iowa State Univ Press; 1989. p. 217-36.
28. Snedecor GW, Cochran WG. Analysis of variance: the random effects model. *Statistical Methods*. 8th ed: Iowa: Iowa State Univ Press; 1989. p. 237-53.
29. Carmella SG, Chen M, Han S, Briggs A, Jensen J, Hatsukami DK, et al. Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers *Chem Res Toxicol*. 2009;22(4):734-41. Erratum in *Chem Res Toxicol*. 2012 Mar 19;25(3):763. Epub 2009/03/26. doi: 10.1021/tx800479s. PubMed PMID: 19317515; PubMed Central PMCID: PMC2704054.
30. Gunes A, Dahl ML. Variation in CYP1A2 activity and its clinical implications: influence of environmental factors and genetic polymorphisms. *Pharmacogenomics*. 2008;9(5):625-37. Epub 2008/05/10. doi: 10.2217/14622416.9.5.625. PubMed PMID: 18466106.
31. MacLeod S, Sinha R, Kadlubar FF, Lang NP. Polymorphisms of CYP1A1 and GSTM1 influence the in vivo function of CYP1A2. *Mutat Res*. 1997;376(1-2):135-42. Epub 1997/05/12. PubMed PMID: 9202749.
32. Kroon LA. Drug interactions with smoking. *Am J Health Syst Pharm*. 2007;64(18):1917-21. Epub 2007/09/08. doi: 10.2146/ajhp060414. PubMed PMID: 17823102.
33. Benowitz NL. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. *Clinical pharmacology & Therapeutics*. 2008;83(4). doi: 10.1038/clpt.2008.3.
34. Benowitz NL, Jacob P, 3rd. Nicotine and cotinine elimination pharmacokinetics in smokers and nonsmokers. *Clin Pharmacol Ther*. 1993;53(3):316-23. PubMed Central PMCID: PMC[PubMed: 8453850].
35. Lee BL, Benowitz NL, Jacob P, 3rd. Influence of tobacco abstinence on the disposition kinetics and effects of nicotine. *Clin Pharmacol Ther*. 1987;41(4).
36. Benowitz NL, Jacob P, 3rd. Effects of cigarette smoking and carbon monoxide on nicotine and cotinine metabolism. *Clin Pharmacol Ther*. 2000;67:653-9.
37. Malaiyandi V, Goodz SD, Sellers EM, Tyndale RF. CYP2A6 genotype, phenotype, and the use of nicotine metabolites as biomarkers during ad libitum smoking. *Cancer Epidemiol Biomarkers Prev*. 2006;10:1812-9. doi: 10.1158/1055-9965.EPI-05-0723 PubMed Central PMCID: PMC17035386 [PubMed - indexed for MEDLINE].
38. Saareks V, Ylitalo P, Alanko J, Mucha I, Riutta A. Effects of smoking cessation and nicotine substitution on systemic eicosanoid production in man. *Naunyn Schmiedeberg's Arch Pharmacol*. 2001;363(5):556-61. Epub 2001/06/01. PubMed PMID: 11383717.
39. Oguogho A, Lupattelli G, Palumbo B, Sinzinger H. Isoprostanes quickly normalize after quitting cigarette smoking in healthy adults. *Vasa*. 2000;29(2):103-5. Epub 2000/07/20. PubMed PMID: 10901086.



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40. Fisher SD, Zareba W, Moss AJ, Marder VJ, Sparks CE, Hochman J, et al. Effect of smoking on lipid and thrombogenic factors two months after acute myocardial infarction. *Am J Cardiol*. 2000;86(8):813-8. Epub 2000/10/12. PubMed PMID: 11024393.
41. Lovreglio P, Barbieri A, Carrieri M, Sabatini L, Fracasso ME, Doria D, et al. Validity of new biomarkers of internal dose for use in the biological monitoring of occupational and environmental exposure to low concentrations of benzene and toluene. *Int Arch Occup Environ Health*. 2010;83(3):341-56. Epub Epub 2009 Oct 14. doi: doi: 10.1007/s00420-009-0469-7.
42. Imbriani M, Ghittori S, Cavalleri A. [Significance of urinary concentrations of S-benzyl-N-acetylcysteine (S-BMA) in subjects exposed to toluene] Italian. *G Ital Med Lav Ergon*. 1999;21(4):329-33. Epub 2000/04/20. PubMed PMID: 10771747.
43. Schettgen T, Musiol A, Alt A, Kraus T. Fast determination of urinary S-phenylmercapturic acid (S-PMA) and S-benzylmercapturic acid (S-BMA) by column-switching liquid chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2008;863(2):283-92. Epub 2008/02/09. doi: 10.1016/j.jchromb.2008.01.024. PubMed PMID: 18258494.



15 ADDITIONAL SUMMARIES NOT INCLUDED IN THE TEXT

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Not applicable.

15.4.2 Product Use

Not applicable.

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16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

- 16.1.1.1 Study Protocol
- 16.1.1.2 Protocol Amendments
- 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
- 16.1.2.3 Subject Questionnaire Local Language
- 16.1.2.4 Subject Smoking Diary English
- 16.1.2.5 Subject Smoking Diary Local Language

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- 16.1.3.1 IEC Information
- 16.1.3.2 IEC Study Submission Letter English
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- 16.1.3.6 IEC Protocol Amendment Submission Letter English
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- 16.1.3.8 IEC Protocol Amendment Approval Letter English
- 16.1.3.9 IEC Protocol Amendment Approval Letter Polish
- 16.1.3.10 IEC Subject Information and Informed Consent Form Version 1.0 Submission Letter English
- 16.1.3.11 IEC Subject Information and Informed Consent Form Version 1.0 Submission Letter Polish
- 16.1.3.12 IEC Subject Information and Informed Consent Form Version 1.0 Approval Letter English
- 16.1.3.13 IEC Subject Information and Informed Consent Form Version 1.0 Approval Letter Polish
- 16.1.3.14 IEC Subject Information and Informed Consent Form Version 2.0 Submission Letter English
- 16.1.3.15 IEC Subject Information and Informed Consent Form Version 2.0 Submission Letter Polish



- 16.1.3.16 IEC Subject Information and Informed Consent Form Version 2.0
Approval Letter English
- 16.1.3.17 IEC Subject Information and Informed Consent Form Version 2.0
Approval Letter Polish
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- 16.1.4 List of Investigators and Other Important Participants and Descriptions of
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 - 16.1.4.1 Site 1
 - 16.1.4.2 Site 2
 - 16.1.4.3 CV of Key CRO Staff
- 16.1.5 List of Subjects Receiving Investigational Products from Specific Batches,
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- 16.1.6 Randomization Scheme and Codes
 - 16.1.6.1 Randomization Scheme and Codes
 - 16.1.6.2 Biostatistical Addendum to IXRS
- 16.1.7 Audit Certificates
- 16.1.8 Documentation of Statistical Methods
- 16.1.9 Bioanalytical Documentation
 - 16.1.9.1 Standardization and Laboratory Reference Ranges
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 - 16.1.9.3 Bioanalytical Reports
 - 16.1.9.4 Bioanalytical References
- 16.1.10 Publications Based on the Clinical Study
- 16.1.11 All Publications Referenced in the Report

16.2 CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

Not applicable.



16.3 CRFs of All Study Participants

16.3.1 Screen Failures

16.3.2 Enrolled and Not Randomized

16.3.3 Randomized

16.4 Individual Subject Data Listings (US Archival Listings)

Not applicable.