Appendix 16: ZRHM-REXA-08-US Clinical Study Summary

PMI RESEARCH & DEVELOPMENT

Clinical Study Report

ZRHM-REXA-08-US

Study Title:	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting
Short Title:	Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting followed by 86 days in an ambulatory setting
Study Number:	ZRHM-REXA-08-US
Product Name:	Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Initiated (first subject screened):	17 December 2013
Study Completed (last subject last visit):	12 October 2014
Principal Investigators and Affiliations:	Dr William Lewis, Covance Dallas Site 1341 W. Mockingbird Ln., Suite 400E Dallas, TX 75247 Dr H. Frank Farmer, Covance Daytona Beach Site 1900 Mason Ave., Suite 140 Daytona Beach, FL 32117
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 Guillaume de La Bourdonnaye, MEng, MSc, Biostatistician Andrea Donelli, Clinical Scientist Ruben Rosoky, MD PhD MFPM, Medical Safety Officer
Version:	1.0
Date:	25 May 2016

This study was conducted in accordance with Good Clinical Practice.

SYNOPSIS

Sponsor: Philip Morris Products S.A.	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)	**Volume:**	
Name of Active Ingredient: Not applicable	**Page:**	

Study Title: A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting

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Publication (reference): ClinicalTrials.gov ID: NCT01989156. Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting followed by 86 days in an ambulatory setting

Period of Study:

First subject screened: 17 December 2013

Last subject last visit: 12 October 2014

Objectives and Endpoints:

Primary Objectives and Endpoints:

The primary objectives and endpoints of this study were:

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

Endpoints

- Monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA) (concentration adjusted for creatinine) in 24-hour urine, and carboxyhemoglobin (COHb) in blood (expressed as % of saturation of hemoglobin) as measured on Day 5.

2. To demonstrate the reduction of Total NNAL in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

Endpoints

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

Secondary Objectives and Endpoints:

The secondary objectives and endpoints of this study were:

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

   Endpoints

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

2. To determine the reduction of secondary BoExp in a confinement setting and in an ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoints

   - BoExp listed as secondary (expressed as quantity excreted or concentration adjusted for creatinine) as measured in 24-hour urine on Day 5 and on Day 90 Visit.

3. To describe the levels of primary and secondary BoExp over the entire Exposure Period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

   Endpoints

   - BoExp listed as primary and secondary from Day 1 to Day 5 and Day 30 Visit, Day 60 Visit and Day 90 Visit as follows:
     - Carbon monoxide (CO) (expressed as ppm) in exhaled breath.
     - COHb in blood (expressed as % saturation of hemoglobin).
     - Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine.

4. To determine the levels of nicotine over the entire Exposure Period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire Exposure Period.

   Endpoints

   - Nicotine equivalents (NEQ) (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine from Day 1 to Day 5 and on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Nicotine and cotinine in plasma from Day 1 to Day 5, and on Day 30 Visit, Day 60 Visit, and Day 90 Visit.

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

   Endpoints

   - Peak (highest concentration along the day) on Day 5.
   - Time to peak concentration (t_{peak}, actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
   - Weighted average concentration over 24 hours (C_{avg}) on Day 5.

6. To describe the change in cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching

from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

Endpoints

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

7. To determine the changes in lung functions in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoints

   - Full lung functions: Diffusion capacity for lung CO (DLCO), rate constant of CO (KCO), forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), vital capacity (VC) expressed as liters (L), total lung capacity (TLC), forced residual volume (FRV), inspiratory capacity (IC), mid expiratory flow (MEF 25-75).

8. To monitor the safety profiles during the study.

   Endpoints

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

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

   Endpoints

   - Systolic and diastolic blood pressure on Day 6/Discharge Confinement, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Highly sensitive C-reactive protein (hs-CRP), homocysteine, blood glucose, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), total cholesterol (TC) in serum on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Fibrinogen in plasma on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Hemoglobin A1c (HbA1c) in blood on Day 90 Visit.
   - Apolipoprotein A1 (Apo A1) and Apolipoprotein B (Apo B) in serum on Day 90 Visit.
   - Soluble inter-cellular adhesion molecule-1 (sICAM-1) in serum on Day 6/Discharge Confinement, on Day 30 Visit, Day 60 Visit and Day 90 Visit.
   - White blood cell (WBC; leukocytes) and platelet count in blood on Day 6/Discharge Confinement, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$) and 11-dehydro-thromboxane B2 (11-DTX-B2) in 24-hour urine on Day 5 and on Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine).
   - Body weight and waist circumference on Day 90 Visit.

Methodology:

Study design:

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

restriction on product use in the THS 2.2 Menthol and mCC arms.

Screening Period; Day -30 to Day -3:

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

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

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

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

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

The Baseline Period was defined as from 06:30 AM on Day -1 until 06:29 AM on Day 1. All subjects continued smoking their preferred brand of mCC, and baseline values were recorded.

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

On Day 0, subjects were randomized to 1 of the 3 study arms in a 2:1:1 ratio using a stratified randomization by sex and average daily mCC consumption over the last 4 weeks, as reported during Screening Visit (stratification factors).

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

Exposure Period:

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

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

Subjects who were allocated to THS 2.2 Menthol and mCC used their assigned product *ad libitum*. Subjects allocated to the SA arm were asked to abstain from smoking. Subjects in the SA arm were provided psychological support but were not provided with smoking cessation medications. Product use from Day 1 to Day 5 was allowed between 06:30 AM and 11:00 PM. On Day 6, product use was allowed from 06:30 AM onwards. Use of any tobacco/nicotine-containing product other than the assigned product/regimen was not allowed during Confinement.

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

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

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

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

the collection of a 4-hour urine fraction.

Product use during Ambulatory Visits was unrestricted, and subjects in the THS 2.2 Menthol and mCC arms were allowed to use their assigned product from the time of check-in in the morning, prior to 08:30 AM, until around 11:00 PM on Day 30, Day 60, and Day 90. On Day 31 and Day 61, product use was allowed from 06:30 AM. On Day 91/Discharge Ambulatory, subjects were allowed to use their own mCCs after all safety examination procedures had been conducted. Subjects were then subsequently discharged from the investigational site.

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

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

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

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

Number of Subjects (Planned and Analyzed):

Planned:	160 subjects
Screened:	**659 subjects**
Subjects excluded and not exposed to THS 2.2 Menthol	494 subjects
Subjects exposed to THS 2.2 Menthol:	165 subjects
Safety Population:	**165 subjects**
Exposed and not enrolled	**1 subject**
Enrolled	**164 subjects**
Randomized	**160 subjects**
Full Analysis Set (FAS) population:	**160 subjects**
Per Protocol (PP) Set:	
PP Set Period 1:	134 subjects
PP Set Period 2:	87 subjects
PP Set Period 3:	86 subjects
PP Set Period 4:	88 subjects
Compliant populations:	
Compliant Population Period 1	134 subjects
Compliant Population Period 2:	74 subjects
Compliant Population Period 3:	77 subjects
Compliant Population Period 4:	79 subjects

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

- Subject had signed the informed consent form (ICF) and was able to understand the information provided in the Subject Information Sheet and ICF.
- Subject was at a minimum 22 years of age.
- Smoking, apparently healthy subject as judged by the Principal Investigator based on all available assessments from the Screening Period/Day of Admission (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG, chest X-ray, and medical history).

- Subject smoked at least 10 commercially available mCCs per day (no brand restrictions), for the last 4 weeks, based on self-reporting. Furthermore, the subject had been smoking for at least the last 3 consecutive years. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
- The subject did not plan to quit smoking within the next 6 months as assessed by the Prochaska 'Stage of Change' questionnaire.
- The subject was ready to comply with the study protocol (e.g., readiness to accept interruptions of smoking for up to 91 days and to use THS 2.2 Menthol). Readiness to use THS 2.2 Menthol was asked on Day of Admission after the product test.

Some specific exclusion criteria for the study were:

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

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

Test Product and Lot Numbers:

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

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

Duration of Exposure Period:

The randomized Exposure Period was approximately 91 days and was from Day 1, 06:30 AM until Discharge on Day 91. The Exposure Period included both exposure during the Confinement and the Ambulatory Setting. Product use periods were subsets of the Exposure Period and were defined as Period 1, Period 2, Period 3, and Period 4.

Reference Products:

The reference product during the randomized Exposure Period was the subject's own preferred commercially available brand of mCC. Smoking abstinence was included in this study as a reference point.

Statistical Methods:

Data Set Populations:

The PP Set was the primary analysis set for BoExp, CREs, and questionnaire assessments. The FAS was the primary analysis set for compliance to randomization arm. The Compliant Population was a subset of subjects from the PP Set. For the THS 2.2 Menthol arm it included subjects who were exclusive THS 2.2 Menthol users, for the mCC arm it included subjects who were exclusive users of mCC, and for the SA arm it included subjects who were fully abstinent. Summaries of the extent of exposure were produced for the FAS and PP Set.

Primary Analyses:

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

The endpoints included in the primary objectives were log-transformed ($base_e$) prior to analysis. An analysis of covariance (ANCOVA) model was used, with terms for the log-transformed baseline value, stratification factors, and randomization arm.

The least squares (LS) means, estimate of the difference, and its 2-sided 95% confidence intervals (CI) were back-transformed. The geometric LS means for each randomization arm along with the ratio (THS 2.2 Menthol : mCC), two-sided 95% CI, and one-sided p-value, were reported in the tables. These analyses were performed on the PP Set, the FAS, and the Compliant Population.

A sensitivity analysis was also performed on the PP Set using a mixed model approach (conducted with baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors).

Descriptive summary statistics including the number of subjects (n), the number and percentage of subjects with missing data, the arithmetic mean, arithmetic standard deviation, 95% CI, median, first and third quartiles, minimum, and maximum; for log-normal data the geometric mean, geometric 95% CI, and geometric coefficient of variation were also presented for each study arm. In addition, BoExp for the endpoints related to the primary objectives were summarized, stratified by sex and mCC consumption, for the PP Set.

Secondary Analyses:

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

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

Biomarkers of exposure were analyzed using the same model as for the primary analyses. Carbon monoxide was analyzed on the linear scale and arithmetic means were calculated; whereas other BoExp were analyzed to calculate geometric means from the logarithmic scale. For all BoExp, if the results from the Day 5 analysis were significant (one-sided p-value $\leq$0.025) then the statistical significance was evaluated for the results of the Day 90 analysis. Least squares means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were presented in the tables (for exhaled CO, the difference in LS means and 95% CI were presented).

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

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

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

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

and 95% CI were generated.

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

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

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

For CYP1A2 activity, the analysis compared the log-transformed Day 5 values between the THS 2.2 Menthol and mCC arms and between the THS 2.2 Menthol and SA arms. An ANOVA model was used as described above for the nicotine and cotinine PK parameters. No adjustments were made for multiple comparisons. If the results from the Day 5 analysis were significant (one-sided p-value ≤ 0.025) then the analysis was repeated for the Day 90 values. Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were presented in the tables. All CYP1A2 summaries and analyses were performed on the FAS and PP Set as above.

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

The analysis compared the results on Day 90 between the THS 2.2 Menthol and mCC arms, and between the THS 2.2 Menthol and SA arms. An ANCOVA model was used with terms for baseline result, stratification factors, and randomization arm. If there was evidence of non-normality, the results were log-transformed prior to analysis. Least squares means for each product along with the difference (THS 2.2 Menthol - mCC) or ratio (THS 2.2 Menthol : mCC) and 95% CI were presented. All CRE summaries and analyses were performed on the PP Set and the FAS.

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

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

Study Hypotheses and Evaluation Criteria:

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

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

Safety Analyses:

Adverse events (including SAEs and AEs that lead to discontinuation) were summarized by study arm and product exposure for the Safety Population. Adverse events were categorized by system organ class and

preferred term (PT) and coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 16.0). Respiratory symptoms (cough assessment questionnaire), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), full lung function, ECG data, clinical laboratory safety parameters (clinical chemistry, hematology, and urinalysis), body mass index, physical examination, and device malfunction/misuse events were summarized.

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

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

Summary of Results

Primary Objectives and Endpoint Analyses

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

Reductions were observed in the level of each BoExp assessed for the THS 2.2 Menthol arm compared to the mCC arm on Day 5, with reductions of 62% (95% CI: 57.5, 65.8) in COHb, 87% (95% CI: 83.0, 90.7) in MHBMA, 54% (95% CI: 46.6, 60.8) in 3-HPMA, and 87% (95% CI: 83.4, 90.5) in S-PMA. In addition, on Day 90, a reduction of 74% (95% CI: 59.7, 82.7) was observed in the level of Total NNAL.

For all of the BoExp included in the analysis of the primary objective at their respective time points, the study showed a greater than 50% reduction in smokers that switched to THS 2.2 Menthol compared to smokers that continued to smoke mCC.

Secondary Objectives and Endpoints Analyses

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

Analysis of COHb, MHBMA, 3-HPMA, S-PMA and Total NNAL on Day 5 and on Day 90 versus mCC and versus SA (PP Set)

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

Day 5	12.58	9.54, 16.58	102.34	74.82, 139.37
Day 90	22.08	13.52, 36.06	117.51	55.32, 249.57
Urinary Total NNAL (pg/mg creat)				
Day 5	43.81	36.92, 51.97	99.99	82.32, 121.44
Day 90	26.41	17.31, 40.26	75.98	39.92, 144.61

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid; CI = confidence interval; COHb = carboxyhemoglobin; LS = least squares; mCC = Menthol conventional cigarettes; MHBMA = monohydroxybutenyl mercapturic acid; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; PP = per protocol; SA = smoking abstinence; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol.

The reductions in COHb, 3-HPMA, MHBMA, and S-PMA observed on Day 5 during the Confinement Period for the THS 2.2 Menthol arm compared to the mCC arm were maintained during the Ambulatory Period, with decreases of 53% in COHb, 81% in MHBMA, 48% in 3-HPMA, and 78% in S-PMA, evident on Day 90. In addition, the initial reductions in levels of Total NNAL observed on Day 5 (56%) further decreased until Day 90 (74%) in the THS 2.2 Menthol arm compared to the mCC arm.

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

The level of 3-HPMA was 83% higher on Day 5 and 47% higher on Day 90 for the THS 2.2 Menthol arm compared to the SA arm. However, most of the reduction observed in the SA arm compared to the mCC arm, was also observed in the THS 2.2 Menthol arm.

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

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

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

Urinary o-toluidine (pg/mg creat)				
Day 5	48.72	39.70, 59.79	128.72	102.10, 162.28
Day 90	43.29	32.00, 58.55	112.05	70.79, 177.37
Urinary CEMA (ng/mg creat)				
Day 5	17.23	14.44, 20.55	105.84	86.65, 129.27
Day 90	14.29	9.01, 22.67	82.18	40.63, 166.22
Urinary HEMA (pg/mg creat)				
Day 5	39.19	31.22, 49.20	104.63	80.79, 135.51
Day 90	38.49	28.28, 52.38	77.74	48.68, 124.14
Urinary B[a]P (fg/mg creat)				
Day 5	28.94	23.14, 36.20	152.32	116.94, 198.39
Day 90	43.33	31.52, 59.57	92.93	57.11, 151.22
Urinary HMPMA (ng/mg creat)				
Day 5	38.26	30.73, 47.64	120.95	94.28, 155.18
Day 90	49.63	37.25, 66.13	102.41	66.08, 158.69
Urinary S-BMA (pg/mg creat)				
Day 5	116.05	90.29, 149.14	81.01	60.97, 107.63
Day 90	109.86	75.25, 160.39	88.13	49.39, 157.24

Abbreviations: 1-NA = 1-aminonaphthalene; 1-OHP = 1-hydroxypyrene; 2-NA = 2-aminonaphthalene; 4-ABP = 4-aminobiphenyl; B[a]P = 3-hydroxybenzo(a)pyrene; CEMA = 2-cyanoethylmercapturic acid; CI = confidence interval; CO = carbon monoxide; HEMA = 2-hydroxyethyl mercapturic acid; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; LS = least squares; mCC = Menthol conventional cigarettes; NNN = N-nitrosonornicotine; PP = per protocol; SA = smoking abstinence; S-BMA = S-benzylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol

Note: The difference in exhaled CO was calculated for THS 2.2 Menthol versus mCC or SA rather than the geometric LS mean ratio: Day 5 -19.96 (-21.62, -18.31) versus mCC and 0.17 (-1.72, 2.07) versus SA; Day 90 -14.62 (-17.67, -11.57) versus mCC and -0.10 (-4.99, 4.78) versus SA.

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

Levels of the BoExp observed in subjects who switched to THS 2.2 Menthol use approached levels measured in subjects who abstained from smoking, except for Total NNN, which was higher in the THS 2.2 Menthol arm compared to the SA arm on Day 5 and Day 90. However, the numerical values for both the THS 2.2 Menthol and SA arms were very low, i.e., within the range of 0.91 and 0.13 pg/mg creat respectively, and the majority of the decrease of the SA arms was preserved in THS 2.2 Menthol.

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

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

The NEQ urinary concentration adjusted for creatinine in the THS 2.2 Menthol arm initially decreased from baseline to Day 2 (-21.27%), and then increased from Day 3 to Day 5, up to Day 30 (6.60%), with NEQ levels similar to baseline on Days 60 and 90 (-1.39% and -3.86%, respectively).

On Day 5, NEQ urinary concentration adjusted for creatinine was 13% lower in the THS 2.2 Menthol arm compared to subjects who continued to smoke mCC (95% CI: -8.2, 29.5). This difference progressively reduced over time and on Day 90, the NEQ was comparable between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC (96% geometric mean ratio; 95% CI: 66.4, 139.6).

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

Cytochrome P450 1A2 Activity

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

The CYP1A2 activity in subjects who switched to THS 2.2 Menthol use was 36% (95% CI: 30.8, 41.7) lower than subjects who continued to smoke mCC on Day 5 and 21% lower (95% CI: 7.0, 33.6) on Day 90. There was no notable difference in CYP1A2 activity between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (102%; 95% CI: 92.1, 111.9 on Day 5; 105%; 95% CI: 80.5, 137.9 on Day 90).

Extent of Exposure – Product Use Consumption

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

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

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

Compliance to Investigational Product and Product Use

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

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

Risk markers (Clinical Risk Markers; CREs)

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

The levels of 8-epi-$PGF_{2\alpha}$ in subjects who switched to THS 2.2 Menthol were 14% (95% CI: 2.0, 23.6) lower than that observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (geometric mean ratio: 95%; 95% CI: 77.7, 115.1).

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

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

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

The levels of sICAM-1 in subjects who switched to THS 2.2 Menthol were 11% (95% CI: 4.0, 16.7) lower than those observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (geometric mean ratio 99%; 95% CI: 88.7, 111.1).

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

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

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

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

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

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

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

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

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

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

- *Risk Markers for Blood Pressure Monitoring: Systolic and Diastolic Blood Pressure (Day 91/Day of Discharge from the Ambulatory Period)*

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

- *Risk Markers of Metabolic Syndrome: Blood Glucose, Hemoglobin A1c, Body Weight, and Waist Circumference (Day 90 or Day 91/Day of Discharge from the Ambulatory Period)*

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

- *Risk Markers for Respiratory Diseases: Lung Function*

In the PP Set (Period 4), there were no notable differences on Day 91/Discharge Ambulatory in gas transfer parameter (DLCO and KCO), lung volume parameters (FRV, TLC, and IC), or spirometry parameters (FEV_1, FVC, FEV_1/FVC, and MEF 25-75) between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC. On Day 91/Discharge Ambulatory, VC was 0.1 L higher in subjects who switched to THS 2.2 Menthol compared to subjects who continued to smoke mCC (95% CI: 0.0, 0.2).

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

Exploratory Endpoint: *Product Evaluation Questionnaire (MCEQ)*

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

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

Abbreviations: mCC = Menthol conventional cigarette; CI = confidence interval; MCEQ = Modified Cigarette Evaluation Questionnaire; PP = per protocol; THS 2.2 Menthol = Tobacco Heating System 2.2 Menthol.

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

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

Exploratory Endpoint: *Human Smoking Topography (HST)*

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

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

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

Safety:

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

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

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

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

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

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

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

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

CONCLUSIONS

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

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

Most likely driven by the initial decrease in nicotine exposure, product use consumption initially increased in average unit consumption from baseline to Day 5, followed by a subsequent reduction of product use between Day 5 and Day 30, and only limited change between Day 30 and the end of the Exposure Period.

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

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

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

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

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

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