APPENDIX 15: ZRHM-REXA-07-JP CLINICAL STUDY SUMMARY

The study was conducted in Japan from August 2013 to July 2014. Principles as defined in the International Conference on Harmonization (ICH) Good Clinical Practice (GCP), and in the Declaration of Helsinki as well as additional applicable national regulations were followed. The protocol was approved by an Institutional Review Board (IRB) and the subjects received complete information about the study and signed an informed consent form (ICF).

Sponsor:

Philip Morris Products S.A

Study Title: A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting

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Publication (reference): ClinicalTrials.gov ID: NCT01970995. Reduced Exposure Study Using the Tobacco Heating System 2.2 (THS 2.2) Menthol for 90 Days in Confinement and Ambulatory

Period of Study:

First subject screened: 01 August 2013

Last subject last visit: 03 July 2014

This appendix to the Philip Morris Products S.A. Technical & Scientific Dossier For the Electrically Heated Tobacco Product (EHTP) as part of the Tobacco Heating System (THS), Version 2.0, dated 27 May 2016, has been reformatted for publication on pmiscience.com.

Objectives and Endpoints:

Primary Objective 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 [NNAL]) in a confinement setting in smokers switching from menthol conventional cigarette (mCC) to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoint:

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

1. 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.

   Endpoint:

   - 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 of this study were:

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

   Endpoint:

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

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

Endpoint:

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

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

   Endpoints:

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

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

   Endpoints:

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

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

   Endpoints:

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

6. To describe the change in cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and to SA.

   Endpoint:

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

7. To monitor the safety profiles during the study.

   Endpoints:

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

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

   Endpoints:

   - Systolic and diastolic blood pressure on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - High sensitive C-reactive protein (hs-CRP), homocysteine, blood glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TGs), total cholesterol (TC) in serum on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Fibrinogen in plasma on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Hemoglobin A1c (HbA1c) in blood on Day 90 Visit.
   - Soluble intercellular adhesion molecule-1 (sICAM-1) in serum on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - White blood cell (WBC) and platelet count in blood on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.

- 8-epi-prostaglandin F2 alpha (8-epi-$PGF_{2\alpha}$) and 11-dehydro-thromboxane B2 (11 DTX-B2) in 24-hour urine on Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine).
- Body weight and waist circumference on Day 90 Visit.

Exploratory Objectives and Endpoints:

The exploratory objectives and endpoints of this study were:

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

   Endpoints:

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

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

   Endpoints:

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

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

   Endpoints:

   - Product evaluation: Modified Cigarette Evaluation Questionnaire (MCEQ).

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

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

   Endpoints:

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

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

   Endpoint:

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

Methodology:

Study design:

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

Screening Period; Day -30 to Day -3:

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

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

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

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

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

The Baseline Period was defined as from 06:30 AM on Day -1 until 06:29 AM on Day 1. All subjects continued smoking their single preferred brand of mCC and baseline values were recorded. On Day 0, subjects were randomized to one of the 3 study arms in a 2:1:1 ratio using a stratified randomization by sex and average daily mCC consumption over the last 4 weeks as reported during the Screening Visit. Subjects were informed of their randomized study arm by the study collaborators on Day 1 prior to 06:30 AM.

Exposure Period:

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

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

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

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

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

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

Product use on Ambulatory Visits was unrestricted, and subjects in the THS 2.2 Menthol and mCC arms were allowed to use their assigned product from approximately 08:00 AM to

11:00 PM on Day 30, Day 60, and Day 90. On Day 31 and Day 61, product use was allowed from 06:30 AM. The last exposure to the allocated product was at Day 90, 11:00 PM. On Day 91, subjects were discharged from the investigational site after all safety examination procedures had been conducted.

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

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

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

Number of Subjects (Planned and Analyzed):

Planned:	160 subjects
Screened:	670 subjects
Enrolled:	231 subjects
Discontinued due to ICH/GCP non-compliance at Seishukai Clinic:	56 subjects
Safety Population (Tokyo Heart Center):	175 subjects
Subjects who were enrolled and not randomized:	15 subjects
Randomized (Tokyo Heart Center):	160 subjects
Safety Population (Tokyo Heart Center, post randomization):	160 subjects
Full Analysis Set (FAS) population:	160 subjects
Per Protocol (PP) Set Populations:	
PP Population Period 1:	157 subjects
PP Population Period 2:	154 subjects
PP Population Period 3:	150 subjects
PP Population Period 4:	148 subjects
Compliant Populations:	
Compliant Population Period 1:	157 subjects
Compliant Population Period 2:	142 subjects
Compliant Population Period 3:	144 subjects
Compliant Population Period 4	143 subjects

Diagnosis and Main Criteria for Inclusion:

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

- Subject has signed the informed consent form (ICF) and was able to understand the information provided in the Subject Information Sheet and ICF.
- Subject was aged from 23 to 65 years (inclusive).
- Subject was Japanese.
- Smoking, healthy subject as judged by the Principal Investigator based on all available assessments from the Screening Period/day of Admission (e.g., safety laboratory, spirometry [forced expiratory volume in 1 second {FEV_1}/forced vital capacity {FVC} >0.7 at post-bronchodilator spirometry, post-bronchodilator FEV_1 >80% pred value, and post-bronchodilator FVC >80% pred value], vital signs, physical examination, ECG, chest X-ray, and medical history).

- Subject smoked at least 10 commercially available mCCs per day (no brand restrictions) with a maximum yield of 1 mg nicotine International Organization of Standardization (ISO)/mCC, as labeled on the cigarette package, for the last 4 weeks, based on self-reporting. Furthermore, the subject had been smoking for at least the last 3 consecutive years. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
- The subject did not plan to quit smoking in the next 3 months.
- The subject was ready to accept interruptions of smoking for up to 90 days.
- The subject was ready to accept using the THS 2.2 Menthol.

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

Test Product and Lot Numbers:

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

Pack batch number of THS Menthol Tobacco Sticks: B-05775, Production date: 12-Jun-2013, Expiry date: 11-Mar-2014; and B 08544, Production date: 25-Oct-2013, Expiry date: 24-Jul-2014.

Duration of Exposure Period:

The Exposure Period was approximately 90 days and was from Day 1, 06:30 AM, until 11:00 PM on Day 90. Day of Discharge was defined as Day 90, 11:00 PM, until Discharge on Day 91. The Exposure Period included both the Exposure Period in Confinement and the Exposure Period in the Ambulatory Setting. Product use periods were subsets of the Exposure Period and were defined as Period 1, Period 2, Period 3, and Period 4.

Reference Products:

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

Statistical Methods:

Analysis Populations:

The PP Set was the primary analysis data set for BoExp, CREs, and questionnaire assessments. The FAS was the primary analysis data set for compliance to randomization arm. Subjects enrolled at the Seishukai Clinic were discontinued due to the site being found to be

non-compliant with ICH/GCP guidance and thus, were excluded from the FAS/PP and the Safety Population; however, they were reported within the Full Safety Population. The Compliant Population was a subset of subjects from the PP Set; for the THS 2.2 Menthol arm it included subjects who were exclusive THS 2.2 Menthol users, for the mCC arm it included subjects who were exclusive users of mCC, and for the SA arm it included subjects who were fully abstinent.

Primary Analyses:

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

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

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

Secondary Analyses:

The BoExp included as endpoints in the primary objective were analyzed in the secondary objectives at Day 5 for Total NNAL and Day 90 for COHb, MHBMA, 3-HPMA, and S-PMA, for the PP Set and FAS using the same methodology as for the primary analysis, including the

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

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

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

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

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

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

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

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

For the MCEQ, each item was assessed on a 7-point scale, ranging from 1 (not at all) to 7 (extremely). The subscales scores were derived by averaging the individual non-missing item scores if at least 50% of the items within a subscale were non-missing, otherwise the subscale score was set to missing. As the questionnaire is intended to evaluate use of tobacco products (THS 2.2 or mCC), summaries, profiles, and analysis only included the THS 2.2 Menthol and mCC arms. The change from baseline was calculated for the 5 subscale scores. The subscale scores, along with the change from baseline were summarized. Profiles of the raw means from

baseline to Day 90 for the 5 subscale scores were produced. Least squares means for each product along with the difference (THS 2.2 Menthol - mCC) with 95% CI were presented.

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

Study Hypotheses and Evaluation Criteria

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

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

Safety Analyses:

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

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

All data for the Full Safety Population were listed.

Summary of Results:

Primary Objectives and Endpoints Analyses

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

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

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

Secondary Objectives and Endpoints Analyses

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

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

Biomarker/ Time point	Ratio THS m2.2:mCC		Ratio THS m2.2:SA	
	%	95% CI	%	95% CI
Evening COHb (%)				
Day 5	44.94	42.11, 47.97	99.31	92.91, 106.15
Day 90	51.72	48.07, 55.65	97.10	90.03, 104.72
Urinary MHBMA (pg/mg creat)				
Day 5	13.49	10.96, 16.60	99.57	80.56, 123.06
Day 90	19.01	14.68, 24.61	101.34	77.68, 132.20
Urinary 3-HPMA (ng/mg creat)				
Day 5	50.67	44.88, 57.20	165.87	146.50, 187.81
Day 90	54.08	46.94, 62.32	138.52	119.70, 160.30
Urinary S-PMA (pg/mg creat)				
Day 5	10.97	9.26, 12.99	113.70	95.67, 135.12
Day 90	12.80	9.88, 16.58	98.78	75.68, 128.94
Urinary Total NNAL (pg/mg creat)				
Day 5	43.69	39.62, 48.17	119.61	108.23, 132.19
Day 90	23.25	17.38, 31.11	150.85	111.62, 203.87

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

The reductions in COHb, 3-HPMA, MHBMA, and S-PMA observed on Day 5 during the Confinement Period for the THS 2.2 Menthol arm compared to the mCC arm were sustained during the Ambulatory Period, with decreases of 48% in COHb, 81% in MHBMA, 46% in 3-HPMA, and 87% in S-PMA, evident on Day 90. In addition, the reductions observed on Day 90

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

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

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

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

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

Biomarker/ Time point	Ratio THS m2.2:mCC		Ratio THS m2.2:SA	
	%	95% CI	%	95% CI
Urinary Total 1-OHP (pg/mg creat)				
Day 5	39.18	34.82, 44.07	109.65	97.23, 123.66
Day 90	52.02	44.83, 60.38	94.78	81.31, 110.48
Urinary Total NNN (pg/mg creat)				
Day 5	27.02	21.75, 33.55	786.46	630.18, 981.50
Day 90	29.31	21.48, 39.98	488.54	354.58, 673.12
Urinary 4-ABP (pg/mg creat)				
Day 5	20.10	17.08, 23.64	86.22	72.93, 101.94
Day 90	21.00	17.02, 25.89	85.76	69.00, 106.60
Urinary 1-NA (pg/mg creat)				
Day 5	5.70	4.93, 6.59	104.70	90.26, 121.44
Day 90	6.22	4.70, 8.22	81.26	60.87, 108.47
Urinary 2-NA (pg/mg creat)				

Day 5	13.66	12.04, 15.49	91.67	80.53, 104.33
Day 90	15.45	12.98, 18.39	85.50	71.35, 102.45
Urinary o-tol (pg/mg creat)				
Day 5	43.80	36.31, 52.83	102.80	85.37, 123.79
Day 90	59.16	42.02, 83.29	87.24	61.98, 122.80
Urinary CEMA (ng/mg creat)				
Day 5	18.23	16.16, 20.56	107.03	94.63, 121.05
Day 90	9.17	7.01, 12.00	91.93	69.65, 121.33
Urinary HEMA (pg/mg creat)				
Day 5	50.14	44.09, 57.02	102.15	89.55, 116.51
Day 90	44.96	37.17, 54.37	102.01	83.82, 124.15
Urinary B[a]P (fg/mg creat)				
Day 5	27.19	23.17, 31.91	110.59	93.84, 130.33
Day 90	33.02	25.92, 42.08	95.92	74.58,123.38
Urinary HMPMA (ng/mg creat)				
Day 5	43.06	37.75, 49.10	109.54	95.76, 125.30
Day 90	50.31	42.96, 58.91	95.90	81.47, 112.89
Urinary S-BMA (pg/mg creat)				
Day 5	85.83	76.49, 96.31	94.56	84.06, 106.38
Day 90	111.27	88.65, 139.67	91.73	72.53, 116.01

Abbreviations: 1-NA = 1-aminonaphthalene; 1-OHP = 1-hydroxypyrene; 2-NA = 2-aminonaphthalene; 4-ABP = 4-aminobiphenyl; B[a]P = 3-hydroxybenzo(a)pyrene; CEMA = 2-cyanoethylmercapturic acid; CI = confidence interval; CO = carbon monoxide; HEMA = 2-hydroxyethyl mercapturic acid; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; LS = least squares; mCC = menthol conventional cigarettes; NNN = N-nitrosonornicotine; o-tol = o-toluidine; PP = per protocol; SA = smoking abstinence; S-BMA = S-benzylmercapturic acid; S-PMA = S-phenylmercapturic acid; THS m2.2 = Tobacco Heating System 2.2 Menthol
Note: The difference in exhaled CO was calculated for THS 2.2 Menthol versus mCC or SA rather than the geometric LS mean ratio: Day 5 -13.10 (-14.70, -11.50) versus mCC and -0.85 (-2.49, 0.79) versus SA; Day 90 -9.28 (-10.75, -7.81) versus mCC and -0.23 (-1.75, 1.29) versus SA.

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

Levels of the BoExp observed in subjects who switched to THS 2.2 Menthol use approached levels measured in subjects who abstained from smoking, except for Total NNN, which was 8-fold and 5-fold higher in the THS 2.2 Menthol arm compared to the SA arm on Day 5 and Day

90, respectively. Although, the numerical difference between the THS 2.2 Menthol and SA arms appeared substantial, when analyzed in the context of the reduction from mCC, THS 2.2 Menthol preserved most of the effect observed in the SA arm.

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

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

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

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

Cytochrome P450 1A2 Activity

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

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

Extent of Exposure – Product Use Consumption

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

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

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

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

Compliance to Product Use (FAS Population)

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

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

Risk Markers (Clinical Risk Markers)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

  Monocyte counts in subjects who switched to THS 2.2 Menthol use were 0.1 GI/L (95% CI: 0.01, 0.10) lower than that observed in subjects who continued to smoke mCC. There

were no notable differences observed in the monocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking.

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

- *Cardiovascular Risk: Homocysteine, hs-CRP, and Fibrinogen (Day 90)*
  For homocysteine and fibrinogen, there were no notable differences observed between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, and subjects who abstained from smoking.

  There was no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC for hs-CRP (93.6%; 95% CI: 62.23, 140.75). The levels of hs-CRP in subjects who switched to THS 2.2 Menthol use was 10.7% (95% CI: -27.33, 68.76) higher than that observed in subjects who abstained from smoking.

- *Risk Markers for Blood Pressure Monitoring: Systolic and Diastolic Blood Pressure (Day of Discharge from Ambulatory Period)*
  There were no notable differences observed in the systolic and diastolic blood pressure for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCCs, and compared to subjects who abstained from smoking.

- *Risk Markers of Metabolic Syndrome: Blood Glucose, Body Weight and Waist Circumference, and Hb1Ac (Day 90/Day of Discharge from Ambulatory Period)*
  For glucose, there were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (98.98% ratio; 95% CI: 96.42, 101.60). The levels of glucose in subjects who switched to THS 2.2 Menthol use was 2.80% (95% CI: 0.06, 5.61) higher than that observed in subjects who abstained from smoking.

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

  For assessment of weight, there was no notable difference for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC (-0.09

difference; 95% CI: -0.75, 0.57). The values in subjects who switched to THS 2.2 Menthol use were 1.24 kg (95% CI: 0.56, 1.92) lower than in subjects who abstained from smoking.

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

- *Risk Markers Associated with Respiratory Diseases*

  The value of FEV_1 (without bronchodilator) in subjects who switched to THS 2.2 Menthol use were 1.92 %pred (95% CI: -0.14, 3.97) higher than that observed in subjects who continued to smoke mCC. There were no notable differences observed in FEV_1 between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-0.02 difference; 95% CI: -2.15, 2.11).

Exploratory Endpoint

Product Evaluation Questionnaire (MCEQ)

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

Difference Between THS m2.2 and mCC Scores for MCEQ Subscales – PP Set		
MCEQ Subscale/ Time point	**Difference THS m2.2 - mCC**	
	Difference	**95% CI**
Aversion		
Day 1	0.07	-0.24, 0.37
Day 5	0.07	-0.23, 0.37
Day 90	-0.16	-0.49, 0.18
Craving reduction		
Day 1	-0.54	-1.05, -0.03
Day 5	-0.02	-0.55, 0.50
Day 90	-0.15	-0.62, 0.32
Enjoyment of respiratory tract sensation		
Day 1	-0.56	-0.96, -0.16
Day 5	-0.13	-0.55, 0.29
Day 90	0.30	-0.18, 0.78
Psychological reward		
Day 1	-0.41	-0.72, -0.10
Day 5	-0.21	-0.51, 0.10
Day 90	0.00	-0.37, 0.36
Smoking satisfaction		
Day 1	-0.86	-1.26, -0.47
Day 5	-0.39	-0.81, 0.03
Day 90	0.01	-0.39, 0.41
Abbreviations: mCC = Menthol conventional cigarette; CI = confidence interval; MCEQ = Modified Cigarette Evaluation Questionnaire; PP = per protocol; THS m2.2 = Tobacco Heating System 2.2 Menthol.		

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

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

Human Smoking Topography (Day 90)

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

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

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

Safety:

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

Overall, there were 93 AEs reported post-randomization by 60 of the 160 subjects (37.5%) in the Safety Population, most of which were mild in severity. Only 2 AEs were considered

moderate, with 1 moderate AE reported in the Confinement Period for the SA arm and 1 moderate AE reported in the Ambulatory Period for the mCC arm. The number of subjects reporting AEs in each study arm were 32/78 (41.0%) for the THS 2.2 Menthol arm, 14/42 (33.3%) for the mCC arm, and 14/40 (35.0%) for the SA arm.

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

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

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

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

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

Conclusions

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

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

and consequently the overall number of puffs over time, correlated well with the changes in product use and nicotine exposure.

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

In conclusion, the observed kinetics of nicotine exposure, the number of THS 2.2 Menthol Tobacco Sticks used over time, the observed changes in puffing topography parameters and the results of subjective effect measures showed comparable results for the THS 2.2 Menthol and the mCC arms from Day 30 onwards. These data suggested that subjects are able to quickly adapt to the THS 2.2 Menthol product, despite the different characteristics respective to their own preferred brand of mCC, by titrating and controlling their desired level of nicotine exposure, and consequently achieving similar satisfaction with the use of THS 2.2 Menthol compared to mCC.

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

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

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

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