APPENDIX 11: ZRHM-PK-06-US CLINICAL STUDY SUMMARY

The study was conducted in the United States from October to December 2013. 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 single center, open label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine nasal spray.

Principal Investigator and Study Center: J. Borders, MD
CKRA, 3475 Richmond Road, Third Floor, Lexington, KY 40509 USA

Publication (reference): ClinicalTrials.gov ID: NCT01967719. Brief title: Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)

Period of Study:

First subject screened: 02 October 2013

Last subject last visit: 02 December 2013

Objectives and Endpoints:

Primary Objective and Endpoints:

The primary objective of this study was:

1. To evaluate the rate and the amount of nicotine absorbed (as assessed by maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve [AUC] from start of product use to time of last quantifiable concentration [$AUC_{(0\text{-last})}$]) from THS 2.2 Menthol relative to menthol conventional cigarettes (mCC), following single use of THS 2.2 Menthol and mCC.

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.

Endpoints:

Nicotine pharmacokinetic (PK) parameters (THS 2.2 Menthol vs. mCC):

- C_{max}.
- $AUC_{0\text{-last}}$.

Secondary Objectives and Endpoints:

The secondary objectives of this study were:

1. To determine if C_{max} and $AUC_{(0\text{-last})}$ of the THS 2.2 Menthol are higher relative to nicotine nasal spray (NNS) following single use of the THS 2.2 Menthol and NNS.

   Endpoints:

   Primary nicotine PK parameters (THS 2.2 Menthol vs. NNS).

   - C_{max}.
   - $AUC_{0\text{-last}}$.

1. To evaluate the difference on nicotine pharmacokinetic (PK) absorption parameters (AUC from start of product use extrapolated to infinity [$AUC_{(0\text{-}\infty)}$] and partial AUC, where t' is the subject-specific time of maximum nicotine concentration following single use of mCC or NNS product [$AUC_{(0\text{-t'})}$]) between the THS 2.2 Menthol and mCC, as well as the THS 2.2 Menthol and NNS.

   Endpoints:

   Secondary nicotine PK parameters

   - $AUC_{(0\text{-}\infty)}$.
   - Partial $AUC_{(0\text{-t'})}$.

2. To evaluate the time to maximum plasma concentration (t_{max}) of plasma nicotine for the THS 2.2 Menthol as compared to mCC and to determine if the tmax for THS 2.2 Menthol is shorter as compared to NNS.

   Endpoint:

   - t_{max}.

3. To describe the terminal half-life ($t_{1/2.}$) of nicotine for the THS 2.2 Menthol, mCC, and NNS.

   Endpoint:

   - $t_{1/2}$.

4. To describe the differences on urge-to-smoke over time between the THS 2.2 Menthol and mCC, as well as between the THS 2.2 Menthol and NNS.

Endpoint:

Urge-to-smoke questionnaire (Questionnaire of Smoking Urges-brief [QSU-brief]).

- Total score.
- Factor 1.
- Factor 2.

5. To describe product evaluation in the THS 2.2 Menthol and mCC users.

   Endpoint:

   Product evaluation questionnaire (Modified Cigarette Evaluation Questionnaire [MCEQ]).

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

6. To describe the levels of carbon monoxide (CO) exposure for the THS 2.2 Menthol users, as compared to mCC and NNS users.

   Endpoints:

   - Levels of exhaled CO.
   - Carboxyhemoglobin (COHb) in blood.

7. To describe the plasma levels of cotinine in the THS 2.2 Menthol, mCC, and NNS.

   Endpoint:

   - Cotinine levels in plasma prior T_0, T_0 + 12 hours (T_{14}), T_0 + 24 hours (T_{15}).

8. To monitor the safety during the study.

   Endpoints:

- Incidence of adverse events (AEs)/serious AEs (SAEs) and device events, including THS 2.2 Menthol malfunction/misuse.
- Respiratory symptoms: cough assessment by Visual Analog Scale (VAS) and Likert scales and 1 open question.
- Vital signs.
- Spirometry.
- Electrocardiogram (ECG).
- Clinical chemistry, hematology, and urine analysis safety panel.
- Physical examination.
- Concomitant medications.

Methodology:

Study design:

This was a randomized, controlled, 2-period, 4-sequence, single use crossover study with each subject using 2 of the following 3 products:

- THS 2.2 Menthol.
- mCC.
- NNS.

The study was performed during a 6-day confinement period (5 overnight stays).

Day -29 to Day -2:

A Screening Visit was conducted within 4 weeks prior to Admission to the investigational site (Day -29 to Day -2). A demonstration of the THS 2.2 Menthol and the NNS was performed by the study site collaborator during the Screening Visit.

Day -1: Admission Day:

As the last procedure of the eligibility assessments, all subjects performed a product test prior to enrollment: first THS 2.2 Menthol (using up to 3 THS Menthol Tobacco Sticks) and subsequently NNS (1 spray of 0.5 mg per nostril as per label). In female subjects, product tests with either the THS 2.2 Menthol or the NNS were only performed after a negative urine pregnancy test. Only subjects willing and ready to use both the THS 2.2 Menthol and NNS were enrolled in order to minimize the dropout rate during the course of the study.

Day 0 to Day 3 Confinement Period:

The confinement consisted of 2 periods (Period 1, Period 2), with each period consisting of at least a 24-hour nicotine wash-out (nicotine abstinence) and 1 day of single product use.

Period 1: Day 0: Wash-out; Day 1: single product use (THS 2.2 Menthol/mCC/NNS).

Period 2: Day 2: Wash-out; Day 3: single product use (THS 2.2 Menthol/mCC/NNS).

In total, 62 eligible, smoking subjects were randomized into 1 of the 4 sequences:

- Sequence 1: THS 2.2 Menthol → mCC (N = 22).
- Sequence 2: mCC → THS 2.2 Menthol (N = 22).
- Sequence 3: THS 2.2 Menthol → NNS (N = 9).
- Sequence 4: NNS → THS 2.2 Menthol (N = 9).

Subjects were discharged from the investigational site the morning of the Day 4 following the completion of all examinations of the Day of Discharge.

Day 4 to Day 11 (Safety Follow-up Period):

After Discharge, there was a 7-day safety follow-up period to record spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the site. End of study was defined as the last day of the 7-day safety follow-up subsequent to discharge from the clinic.

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

Number of Subjects (Planned and Analyzed):

Planned:	62 subjects
Screened:	113 subjects
Exposed to THS 2.2 Menthol:	64 subjects
Enrolled:	64 subjects
Randomized:	62 subjects
Safety population:	64 subjects
Group-1 PK population:	41 subjects
Group-2 PK population:	17 subjects

The Group-1 (comparison between THS 2.2 Menthol and mCC) and Group-2 (comparison between THS 2.2 and NNS) PK populations were composed of a different set of subjects.

Diagnosis and Main Criteria for Inclusion:

Sixty-two smoking adult subjects who met the following main inclusion criteria:

- Subject was aged from 22 to 65 years (inclusive).
- Subject was a smoking, healthy subject, as judged by the Principal Investigator, based on all available assessments in 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 basal spirometry, post-bronchodilator FEV_1 >80% predicted value, and post-bronchodilator FVC >0.8], vital signs, physical examination, ECG, chest X-ray and medical history).
- Subject was a current smoker, based on self-reporting, who had smoked for the last 4 weeks at least 10 commercially available mCC per day (with brand restrictions). Furthermore, the subject had smoked 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 willing and able to accept interruptions of smoking for up to 4 days.
- The subject was willing and able to use both the THS 2.2 Menthol and NNS products.

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

Test Product and Lot Numbers:

The 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 main power supply, and a USB cable.

Pack batch number of THS Menthol Tobacco Sticks: B 06238. Production date: 04 July 2013. Expiry date: 03 February 2014

Duration of Exposure Period:

The exposure period was the period after randomization and consisted of 2 periods (Period 1, Period 2), with each period comprising of at least a 24 hour nicotine wash out (nicotine abstinence) and 1 day of single product use of THS 2.2 Menthol, and mCC or NNS.

Reference Products:

The subject's own supply of commercially available single brand mCC (restricted to Kool Mild, Kool, Newport Menthol Short, Newport Menthol, Newport Menthol 100, Camel Menthol Silver, Camel Menthol, Marlboro Menthol, and sub brands). NNS (Nicotrol® NS 10 mg/mL); 1 spray (resulting in the administration of 0.5 mg nicotine) per nostril was used as a non-investigational reference point product.

Statistical Methods:

Pharmacokinetic Data

The primary analysis was performed on the natural log-transformed PK parameters (C_{max} and $AUC_{(0\text{-last})}$) using an analysis of variance (ANOVA) model in the Group-1-PK population. The model included terms for sequence, subject nested within sequence, period, and product as fixed-effect factors. The least squares (LS) means for each product was back-transformed by exponentiation and tabulated together with the ratio (THS 2.2 Menthol:mCC) and 95% confidence interval (CI).

Exploratory sub-group analyses were conducted for the primary endpoints in the following planned strata: sex (male or female), mCC nicotine yield at Admission (International Organization for Standardization [ISO] nicotine yield ≤1.0 mg and >1.0 mg) provided there were greater than 4 subjects in each category.

Plasma nicotine concentrations were summarized in a similar manner to the PK parameters but were also split out by sample time point. Geometric mean (95% CI) profiles, spaghetti plots of all subjects, and individual PK profiles for each subject were also generated.

The analyses of $AUC_{(0-\infty)}$, $AUC_{(0-t')}$, and $t_{1/2}$ for the comparison between THS 2.2 Menthol and mCC (Group-1 PK population) and the comparison between THS 2.2 Menthol and NNS (Group-2 PK population) (plus C_{max} and AUC_{0-last} for the Group-2 PK population) were performed on the natural log-transformed parameters using the same ANOVA model as used for the primary analysis.

The analysis of t_{max} was performed by calculating the difference for each subject (THS 2.2 Menthol − mCC or THS 2.2 Menthol − NNS) and obtaining the Hodges-Lehmann 95% CI estimates. The median t_{max} for each product and the median difference between the products along with the 95% CI were calculated.

The analysis of C_{max} and $AUC_{(0-last)}$ tested if the lower bound of the 95% CI for the ratio (THS 2.2 Menthol : NNS) was >1.0 with a one-sided significance level of 2.5% in order to determine if the rate and the amount of nicotine absorbed from THS 2.2 Menthol were higher relative to NNS.

The parameter t_{max} was analyzed to test if it was shorter with THS 2.2 Menthol than with NNS and was analyzed on the original scale using the Wilcoxon signed-rank test with a type I error $\alpha = 0.025$ (one-sided test).

To support the interpretation of the PK analysis, the values of nicotine concentration greater than below the limit of quantification (BLOQ) before T_0 were listed together with any PK parameters excluded from the analysis. Listing were generated by PK parameter impact, sequence, period, and study date.

To better understand the impact of the T_0 value >5% of their C_{max} values, an analysis of the PK parameters excluding these subjects was performed as described above for the primary analysis.

Study Hypotheses and Evaluation Criteria

Given that the primary objective of this study was to determine the point estimate and precision of the nicotine relative bioavailability (ratio of THS 2.2 Menthol:mCC) for C_{max} and $AUC_{(0\ last)}$, there was no statistical hypothesis to be tested for the primary objective.

For the secondary objectives the following hypotheses were examined for THS 2.2 Menthol versus NNS analyses:

- The geometric mean C_{max} in THS 2.2 Menthol was higher relative to NNS.
- The $AUC_{(0-last)}$ in THS 2.2 Menthol was larger relative to NNS.
- The median t_{max} in THS 2.2 Menthol was shorter than in NNS.

The study evaluation criteria were defined as 95% CI of the THS 2.2 Menthol:mCC ratio for the nicotine C_{max} and $AUC_{(0\text{-last})}$ being estimated with a precision of ±20%, based on the level of variability expected from the previous study.

Exhaled CO and Blood COHb Data

The exhaled CO and blood COHb levels were analyzed using a mixed-effects ANOVA with a restricted maximum likelihood (REML) method to estimate mean differences and variances separately for THS 2.2 Menthol vs mCC and THS 2.2 Menthol vs NNS, using heterogeneous compound symmetry covariance structure in order to allow unequal variances at the different time points. Subject nested within sequence was used as a random effects, and sequence, period, product, and product*time point as fixed-effect factors. The model was evaluated, including all of the different assessment time points, excluding the assessment prior to T_0. In addition, time point was treated as a repeated measurement.

Cotinine

Cotinine plasma concentrations were summarized in a similar manner to the nicotine PK parameters but were also split out by sample time point. Cotinine levels were also summarized by race.

Subjective Effects Questionnaire Data

The QSU-brief questionnaire scores were analyzed using the same mixed-effects ANOVA adopted for the analysis of CO breath test.

A mixed-effects ANOVA model was used to estimate mean THS 2.2 Menthol − mCC differences of the MCEQ domain scores and variances, with a REML method, using heterogeneous compound symmetry covariance structure. Subjects within sequence were used as random effects and fixed effects were period, sequence, and product exposure.

Safety Data

There was no formal statistical analysis of safety data. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®, Version 16.0). Adverse events were listed by sequence and summarized by sequence, severity, relationship, and expectedness to product or study procedures. Serious AEs were listed separately. Adverse events were categorized by system organ class (SOC) and preferred term (PT). Respiratory symptoms (cough assessment questionnaire), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), spirometry, ECG data, clinical laboratory safety panel (clinical chemistry, hematology, and urine analysis), body mass index, physical examination, and device malfunction/misuse events were listed and summarized by sequence.

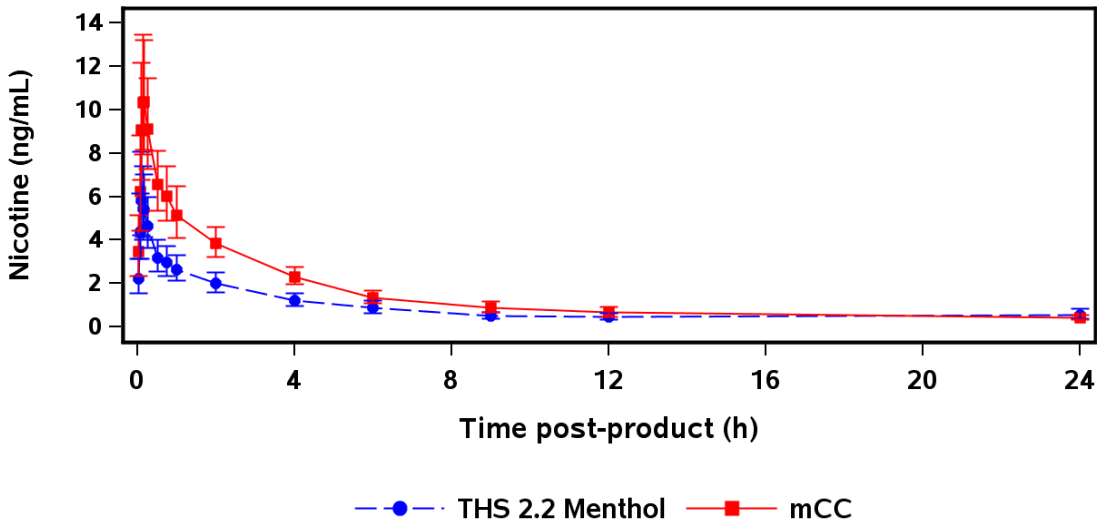
Medical History and concomitant disease were coded using MedDRA Version 16.0 and listed separately by sequence, SOC, and PT within SOC.

All medications were listed and summarized by sequence using PT and Anatomical Therapeutic Chemical (ATC) codes (World Health Organization Drug Dictionary Enhanced, Q1 2013) for the safety population.

Summary of Results:

Primary Endpoints:

The overall shape of the mean nicotine concentration-time curves was similar for THS 2.2 Menthol and mCC, although the nicotine concentrations appeared to be lower throughout the 24 hours following single use for THS 2.2 Menthol. The plasma concentration versus time profiles following single use of THS 2.2 Menthol and mCC were characterized by a rapid absorption phase, with C_{max} reached earlier following THS 2.2 Menthol (7 minutes) compared to mCC use (10 minutes).



Primary Pharmacokinetic Parameters

PK Parameter (unit)	Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2 Menthol:mCC) (%)	CV (%)	95% CI	Precision (%)
C_{max}	THS 2.2 Menthol	41	7.4	57	60	44, 72	16
(ng/mL)	mCC	41	13.1				
$AUC_{(0\text{-last})}$	THS 2.2 Menthol	41	16.5	56	61	43, 72	16
(ng.h/mL)	mCC	41	29.7				

Abbreviations: $AUC_{(0\text{-last})}$ = area under plasma concentration-time curve from start of product use to time of last quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; LS = least squares; mCC = menthol conventional cigarette; THS 2.2 = Tobacco Heating System 2.2.

Following single use, the exposure to nicotine, as assessed by C_{max} and $AUC_{(0\text{-last})}$, was lower for THS 2.2 Menthol compared to mCC (THS2.2:mCC geometric LS mean ratios of 57% and 56%, respectively), with the 95% CIs for both parameters being below 100%.

High between-subject variability was noted for both C_{max} and $AUC_{(0\text{-last})}$ for both products, with CV% values ranging from 97% to 100% and 112% to 135%, respectively. The within-subject variability was high for both C_{max} (60%) and $AUC_{(0\text{-last})}$ (61%).

The THS 2.2 Menthol:mCC ratio for C_{max} and $AUC_{(0\text{-last})}$ were both estimated with a precision of 16%, with precision calculated as the largest difference between the 95% CI bounds and the mean.

Secondary Endpoints:

Secondary Pharmacokinetic Parameters - THS 2.2 Menthol versus mCC

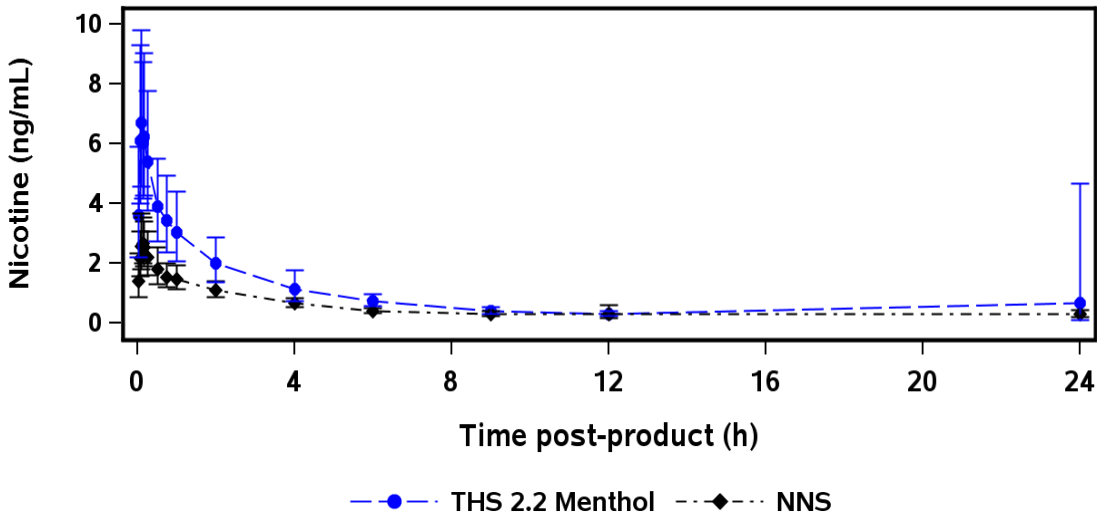
Exposure to nicotine was lower for THS 2.2 Menthol compared to mCC use, as assessed by both $AUC_{(0\text{-}\infty)}$ (THS 2.2 Menthol: 19.2 ng.h/mL; mCC: 33.8 ng.h/mL; THS 2.2 Menthol:mCC ratio: 57%; 95% CI: 41, 79) and $AUC_{(0\text{-t'})}$ (THS 2.2 Menthol: 0.7 ng.h/mL; mCC: 1.3 ng.h/mL; THS 2.2 Menthol:mCC ratio: 56%; 95% CI: 43, 74). Between-subject variability was high for both $AUC_{(0\text{-}\infty)}$ and $AUC_{(0\text{-t'})}$ for both products, with CV% values ranging from 53% to 82% and 144% to 159%, respectively. The within-subject variability was high for both $AUC_{(0\text{-}\infty)}$ (53%) and $AUC_{(0\text{-t'})}$ (68%).

The $t_{1/2}$ was comparable for each product, with LS mean $t_{1/2}$ for THS 2.2 Menthol of 3.4 hours (95% CI: 3.0, 3.9) and 3.8 hours (95% CI: 3.4, 4.4) for mCC, with a THS 2.2 Menthol:mCC ratio of 88% (95% CI: 74, 105).

The t_{max} was shorter for THS 2.2 Menthol (6.7 minutes) compared to mCC (10.1 minutes).

Nicotine Pharmacokinetic Endpoints Following Single Use of THS 2.2 Menthol and NNS

The overall shape of the mean nicotine concentration-time curves was similar for THS 2.2 Menthol and NNS, although the mean plasma nicotine concentrations following single use of THS 2.2 Menthol were higher than for NNS. The plasma concentration versus time profiles following single use of THS 2.2 Menthol and NNS were characterized by a rapid absorption phase, with C_{max} reached at similar times post-product use.



Following single use, the exposure to nicotine as assessed by C_{max} and $AUC_{(0\text{-last})}$ was significantly higher for THS 2.2 Menthol compared to NNS (C_{max} THS 2.2 Menthol: 8.4 ng/mL; NNS: 3.2 ng/mL; THS 2.2 Menthol:NNS ratio: 260%; 95% CI: 168, 402; P <0.001. $AUC_{(0\text{-last})}$ THS 2.2 Menthol: 15.6 ng.h/mL; NNS: 8.7 ng.h/mL; THS 2.2 Menthol:NNS ratio: 179%; 95% CI: 106, 300; P = 0.015). The results observed for C_{max} and $AUC_{(0\text{-last})}$ support the study hypotheses regarding the PK parameters following THS 2.2 Menthol and NNS use.

Exposure to nicotine as assessed by $AUC_{(0\text{-t'})}$ was significantly higher for THS 2.2 Menthol compared to NNS (THS 2.2 Menthol: 0.7 ng.h/mL; NNS: 0.3 ng.h/mL; THS 2.2 Menthol:NNS ratio: 219%; 95% CI: 153, 315; P <0.001). $AUC_{(0\text{-}\infty)}$ was higher for THS 2.2 Menthol compared

to NNS, but did not achieve statistical significance (THS 2.2 Menthol: 15.7 ng.h/mL; NNS: 11.8 ng.h/mL; THS 2.2 Menthol:NNS ratio: 133%; 95% CI: 90, 196; P = 0.067).

High between-subject variability was reported for C_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\infty)}$, and $AUC_{(0\text{-t'})}$ for both THS 2.2 Menthol and NNS, with CV% values ranging from 81% to 156% for THS 2.2 Menthol and 66% to 143% for NNS. The within-subject variability was moderate for $AUC_{(0\text{-}\infty)}$ (38%) and high for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-t'})}$ (53% to 81%).

The $t_{1/2}$ was significantly shorter for THS 2.2 Menthol (2.9 hours; 95% CI: 2.3, 3.7) compared to NNS (4.1 hours; 95% CI: 3.2, 5.2) with a THS 2.2 Menthol:NNS ratio of 70% (95% CI: 50, 99).

The t_{max} was comparable for THS 2.2 Menthol and NNS (9 minutes and 8 minutes, respectively; P = 0.253).

Subjective Effects of Smoking Endpoints:

Urge-to-Smoke Symptoms (QSU-brief)

The average Group-1 PK population urge-to-smoke total scores dropped by a maximum of approximately 21% and 36%, following THS 2.2 Menthol and mCC use, respectively, at T_0 + 15 minutes, corresponding to maximum reductions 1.0 and 1.7 point decreases from baseline, respectively. For both THS 2.2 Menthol and mCC, the average total scores had not returned to baseline values by the last assessment time point at 12 hours post-product use (93% and 94% of baseline, respectively).

The QSU-brief total score was higher for THS 2.2 Menthol compared to mCC, with an LS mean difference over all time points of 0.4 points for THS 2.2 Menthol - mCC following single use (95% CI: 0.0, 0.8). Consistent results were obtained for the 2 factors, Factor 1 reflecting the desire and intention to smoke with smoking perceived as rewarding (THS 2.2 Menthol - mCC difference of 0.4 (95% CI: 0.0, 1.0); and Factor 2 reflecting anticipation of relief from negative effects of not smoking (THS 2.2 Menthol - mCC difference of 0.3 (95% CI: 0.0, 0.7). The difference between THS 2.2 Menthol and mCC for the total score was greatest at T_0 + 15 minutes with a THS 2.2 Menthol - mCC difference of 0.8 (95% CI: 0.1, 1.5).

In the Group-2 PK population, the average urge-to-smoke total score dropped by approximately 33% and 21% following THS 2.2 Menthol and NNS use, respectively. For THS 2.2 Menthol, the maximum decrease was observed at T_0 + 45 minutes and at T_0 + 30 minutes for NNS, with maximum reductions corresponding to a 1.5 and 1.0 point decrease from baseline, respectively. The average total scores for both products were below their respective baseline values at 12 hours post-product use (93% for both THS 2.2 Menthol and NNS).

The QSU-brief total score was lower for THS 2.2 Menthol compared to NNS with an LS mean difference over all time points of -0.4 points for THS 2.2 Menthol - NNS following single use (95% CI: -0.8, 0.1). Consistent results were obtained for the 2 factors, Factor 1 THS 2.2 Menthol - NNS difference of -0.6 (95% CI: -1.1, 0.0), and Factor 2 THS 2.2 Menthol - NNS difference of -0.2 (95% CI: -0.6, 0.3). The difference between THS 2.2 Menthol and NNS for the total score was greatest at T_0 + 45 minutes, with a THS 2.2 Menthol - NNS mean difference of -0.7 points (95% CI: -1.3, -0.1).

Product evaluation questionnaire (MCEQ)

Based on the results from the product comparison using the MCEQ subscale scores following single use, differences were observed for 4 of the 5 subscales. Craving reduction was 1.2 points lower (95% CI: 0.6, 1.8), enjoyment of respiratory tract sensation was 0.8 points lower (95% CI: 0.1, 1.5), psychological reward was 0.6 points lower (95% CI: 0.2, 1.0), and smoking satisfaction was 1.2 points lower (95% CI: 0.6, 1.8) for THS 2.2 Menthol compared to mCC.

There was no notable difference in aversion between THS 2.2 Menthol and mCC following single use, with THS 2.2 Menthol being 0.0 points higher (95% CI: -0.6, 0.6) than mCC.

Biomarker Endpoints:

Blood COHb

Mean COHb values following at least 24 hours of smoking abstinence and prior to product use were 2.6% for THS 2.2 Menthol and 2.5% for mCC. Fifteen minutes after product use, the mean COHb value had increased to a maximum of 3.5% for mCC users, while COHb remained stable for the 12 hour post-product evaluation period for THS 2.2 Menthol users (within the range of 2.3% to 2.5%, with the maximum observed at T_0 + 12 hours). Across the full 12 hour post-product evaluation period, the THS 2.2 Menthol:mCC ratio for COHb was 76% (95% CI: 72, 80) after single use.

Following THS 2.2 Menthol and NNS use, there was no notable difference in overall mean COHb levels between THS 2.2 Menthol and NNS users. Mean COHb levels remained relatively unchanged throughout the assessment day (2.2% to 2.3% for THS 2.2 Menthol and 2.1% to 2.2% for NNS), with the maximum COHb value achieved at T_0 + 60 minutes for both products.

Exhaled CO

Mean exhaled CO values following 24 hours of smoking abstinence and prior to product use were 1.5 ppm for THS 2.2 Menthol and 1.3 ppm for mCC. Following single mCC use, the mean exhaled CO levels initially increased, reaching a peak of 2.6 ppm at 12:00-01:30 PM; thereafter levels decreased and were below baseline levels at 08:00-09:30 PM (0.8 ppm). Following single

THS 2.2 Menthol use, mean CO levels declined throughout the evaluation period (from 1.5 ppm at baseline to 0.5 ppm at 08:00-09:30 PM). Across the full post-product evaluation period, the LS mean level for exhaled CO following single THS 2.2 Menthol use was 0.8 ppm lower than that determined following single mCC use (95% CI: 0.5, 1.1).

Plasma Cotinine

Mean plasma cotinine levels following at least 24 hours of smoking abstinence and prior to product use were 38.0 ng/mL for THS 2.2 Menthol and 29.4 ng/mL for mCC. Following single use of THS 2.2 Menthol and mCC, mean plasma cotinine values were comparable at both the T_0 + 12 hours and T_0 + 24 hours time points, with mean values at T_0 + 12 hours being 29.8 ng/mL and 35.5 ng/mL, and 20.8 ng/mL and 25.7 ng/mL T_0 + 24 hours following THS 2.2 Menthol and mCC use, respectively. High between-subject variability was observed for both products at all assessment time points. Plasma cotinine levels were consistently higher in Black or African American subjects (maximum concentrations range of 8.8 to 318 ng/mL) compared with White subjects (maximum concentrations range of 12.0 to 174 ng/mL) for both products.

Mean plasma cotinine levels following at least 24 hours of smoking abstinence and prior to product use were 28.2 ng/mL for THS 2.2 Menthol and 27.3 ng/mL for NNS. Following single use of THS 2.2 Menthol and NNS, mean plasma cotinine values had declined at T_0 + 12 hours to 24.3 ng/mL for THS 2.2 Menthol and 21.2 ng/mL for NNS. Cotinine values had decreased further at T_0 + 24 hours, to 17.1 ng/mL for THS 2.2 Menthol and 14.2 ng/mL for NNS. Plasma cotinine levels were consistently higher in Black or African American subjects (maximum concentrations range of 30.2 to 212 ng/mL) compared with White subjects (maximum concentrations range of 15.0 to 68.8 ng/mL) for both products.

Safety:

There were no SAEs reported during the study and no subjects discontinued from the study due to an AE.

Overall, there were 28 AEs reported in 19 of the 64 subjects (30%) in the safety population, the majority of which were mild or moderate in severity. Two severe AEs were reported by 1 subject. The incidence of AEs was comparable in the THS 2.2 Menthol – mCC sequence (10 AEs in 7 out of 22 subjects [31.8%]), the mCC – THS 2.2 Menthol sequence (9 AEs in 7 out of 22 subjects [31.8%]), and the THS 2.2 Menthol – NNS sequence (7 AEs reported in 3 out of 9 subjects [33.3%]). Only 2 subjects reported 2 AEs from the 9 subjects in the NNS – THS 2.2 Menthol sequence (22.2%).

The most frequent AEs were headache (7 AEs), vomiting (3 AEs), nasal congestion (3 AEs), and spirometry abnormal (2 AEs). All other AEs were reported by 2 or fewer subjects only and a maximum of 1 subject per sequence.

During the study, 4 subjects experienced 5 AEs that were considered to be related to the investigational product (IP). Vomiting and nausea were each reported by 2 subjects, and headache was reported by 1 subject. An AE of sneezing was also considered to be related to NNS use.

During THS 2.2 Menthol use, 3 subjects experienced 6 device events or malfunctions which led to the replacement of both the Tobacco Stick Holder and the Charger. None of these events led to an AE.

Conclusions

In this study, the amount of nicotine absorbed was lower following THS 2.2 Menthol when compared to mCC. The elimination was comparable following THS 2.2 Menthol use compared to mCC while t_{max} occurred at 7 and 10 minutes following THS 2.2 Menthol and mCC use, respectively. THS 2.2 Menthol also decreased the urge-to-smoke less than mCC use, most noticeably for the first 2 hours post-product use. The MCEQ results also showed that single THS 2.2 use was less satisfying than mCC.

This study has also indicated that exposure to nicotine as assessed by C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-t'})}$ were higher for THS 2.2 Menthol use compared to NNS use, and that $AUC_{(0\text{-}\infty)}$,while higher following THS 2.2 Menthol use compared to NNS, was not statistically significantly greater. The time of maximum nicotine concentration was comparable between the 2 products, while the $t_{1/2}$ values obtained were shorter following THS 2.2 Menthol use compared with NNS use. THS 2.2 Menthol also decreased the urge-to-smoke more than NNS use, particularly for the first 2 hours post-product use, but the overall time profile showed no notable difference in urge-to-smoke between THS 2.2 Menthol and NNS use.

In contrast to mCC single use, where CO exposure increased rapidly, no increase in CO exposure was observed following THS 2.2 Menthol or NNS single use.

No notable differences were observed in plasma cotinine levels between THS 2.2 Menthol and mCC or THS 2.2 Menthol and NNS. However, consistent with previously published literature, plasma cotinine levels were consistently higher in Black or African American subjects compared with White subjects for both products.

No SAEs were reported during this study, while 2 severe AEs were reported by 1 subject and were not considered to be related to the IP, NNS, or study procedures.

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