Appendix 10: ZRHM-PK-05-JP Clinical Study Summary

PMI RESEARCH & DEVELOPMENT

Clinical Study Report

ZRHM-PK-05-JP

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 gum
Short Title:	Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Number:	ZRHM-PK-05-JP
Product Name:	Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Initiated (first subject screened):	01 August 2013
Study Completed (last subject last visit):	16 November 2013
Principal Investigator and Affiliation:	F. Nobuoka, MD Ageo Medical Clinic 3133 Haraichi, Ageo City Saitama 362-0021, Japan
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 Nicola Lama, PhD, Biostatistician Andrea Donelli, Clinical Scientist Patrick Picavet, MD, Medical Safety Officer
Version:	1.0
Date:	12 May 2015

This study was conducted in accordance with Good Clinical Practice.

SYNOPSIS

Sponsor: Phillip 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 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 gum.

Principal Investigator and Study Center: F. Nobuoka, MD, Ageo Medical Clinic, 3133 Haraichi, Ageo City, Saitama 362-0021, Japan

Publication (reference): ClinicalTrials.gov ID: NCT01967706. 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: 01 August 2013
Last subject completed: 16 November 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 the time of the 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.

   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 plasma nicotine of the THS 2.2 Menthol are higher relative to nicotine replacement therapy (NRT) gum following single use of the THS 2.2 Menthol and NRT gum.

   Endpoints:
   Primary nicotine PK parameters (THS 2.2 Menthol vs. NRT gum):
   - C_{max}.
   - $AUC_{0\text{-}last}$.

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

Endpoints:
Secondary nicotine PK parameters:
- $AUC_{(0-\infty)}$.
- Partial $AUC_{(0-t')}$.

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

   Endpoint:
   - t_{max}.

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

   Endpoint:
   - $t_{1/2.}$

5. 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 NRT gum.

   Endpoints:
   Urge-to-smoke questionnaire (Questionnaire of Smoking Urges-brief [QSU-brief]):
   - Total score
   - Factor 1
   - Factor 2

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

   Endpoints:
   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.

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

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

8. To monitor the safety during the study.

   Endpoints:
   - Incidence of 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 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 where each subject received 2 of the following 3 products:

- THS 2.2 Menthol.
- mCC.
- NRT gum.

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 NRT gum 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 Menthol Tobacco Sticks) and subsequently NRT gum. Product tests with either the THS 2.2 Menthol or the NRT gum were only performed in female subjects with a negative urine pregnancy test. Only subjects willing and ready to use both the THS 2.2 Menthol and NRT gum 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/NRT gum).

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

In total, 62 eligible, mCC-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→ NRT gum (N=9).
- Sequence 4: NRT gum → 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 adverse events (AEs)/serious adverse events (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:	147 subjects
Exposed to THS 2.2 Menthol:	73 subjects
Enrolled:	73 subjects
Randomized:	62 subjects
Safety population	73 subjects
Group-1 PK population:	43 subjects
Group-2 PK population	18 subjects

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

Diagnosis and Main Criteria for Inclusion:

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

- Subject was aged from 23 to 65 years (inclusive).
- Subject was Japanese.
- 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 smoking at least 10 commercially available mCC per day (no brand restrictions) with a maximum yield of 1 mg nicotine International Organization for 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 willing and able to accept interruptions of smoking for up to 4 days.
- The subject was willing and able to accept using both the THS 2.2 Menthol and NRT gum 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-05775. Production date: 12 June 2013. Expiry date: 11 January 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 THS 2.2 Menthol, and mCC or NRT gum.

Reference Products:

The subject's own supply of commercially available single-brand of mCC of up to 1 mg nicotine ISO per cigarette. Nicotine replacement therapy gum (Nicorette® 2 mg gum) 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 2 planned sub-groups: sex and nicotine levels (≤0.6 mg and >0.6 mg to ≤ 1mg). The primary analysis was repeated for each level of the 2 sub-groups.

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 and NRT gum (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 - NRT gum) 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 was 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 : NRT gum) 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 NRT gum.

The parameter t_{max} was analyzed to test if it was shorter with THS 2.2 Menthol than with NRT gum and was analyzed on the original scale using the Wilcoxon Signed-Rank Test

To support the interpretation of the PK analysis, the values of nicotine concentration greater than the lower limit of quantification before T_0 were listed together with any PK parameters excluded from the analysis. Listings were presented 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

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 $AUC_{(0-last)}$, therefore, 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 NRT gum analyses:

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

The study evaluation criteria were defined as 95% CI of the THS 2.2 Menthol:mCC ratio for the nicotine C_{max} and $AUC_{(0-last)}$ being estimated with a precision of ±20%, based on the level of variability expected from the previous study (ClinicalTrials.gov Identifier: NCT01780688).

Exhaled CO and Blood COHb Data

The exhaled CO and blood COHb 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 NRT gum, 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.

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 variance component 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), 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.

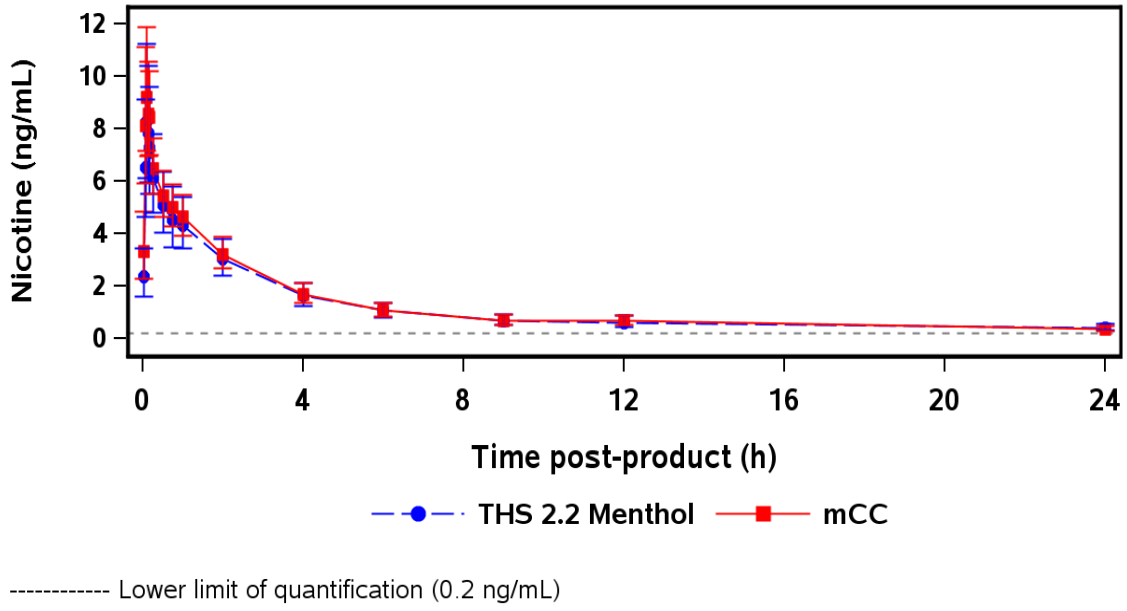
Medical History and concomitant disease were coded using MedDRA Version 16.0 and listed separately by sequence, SOC, and PT within SOC.

All medications were listed and summarized by sequence using PT and Anatomical, Therapeutic Chemical (ATC) codes (World Health Organisation Drug Dictionary, 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. 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 at the same time post-product use (6 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	43	10.7	88	64	69, 114	26
(ng/mL)	mCC	43	12.1				
$AUC_{(0\text{-last})}$	THS 2.2 Menthol	43	24.0	98	48	81, 119	21
(ng.h/mL)	mCC	43	24.50				

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

Following single use, there was no notable difference in the nicotine absorption between THS 2.2 Menthol and mCC as assessed by C_{max} (THS 2.2 Menthol:mCC geometric LS mean ratio: 88%) and $AUC_{(0\text{-last})}$ (THS 2.2 Menthol:mCC geometric LS mean ratio: 98%), with the 95% CIs for both parameters spanning 100%.

High between-subject variability was noted for both C_{max} and $AUC_{(0\text{-last})}$ for both products, with CV% values ranging from 88% to 117% and 83% to 110%, respectively. The within-subject variability was high for both C_{max} (64%) and $AUC_{(0\text{-last})}$ (48%).

The THS 2.2 Menthol:mCC ratio for $AUC_{(0\text{-last})}$ was estimated with a precision of 21%, while the precision for C_{max} was 26%, 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

There was no notable difference in the amount of nicotine absorbed between THS 2.2 Menthol and mCC as assessed by $AUC_{(0\text{-}\infty)}$ (THS 2.2 Menthol: 26.3 ng.h/mL; mCC: 27.7 ng.h/mL; THS 2.2 Menthol:mCC ratio: 95%; 95% CI: 78, 116). The amount of nicotine absorbed as assessed by $AUC_{(0\text{-t'})}$ was lower for THS 2.2 Menthol compared to mCC (THS 2.2 Menthol: 0.6 ng.h/mL; mCC: 0.8 ng.h/mL; THS 2.2 Menthol:mCC ratio: 74%; 95% CI: 57, 97).

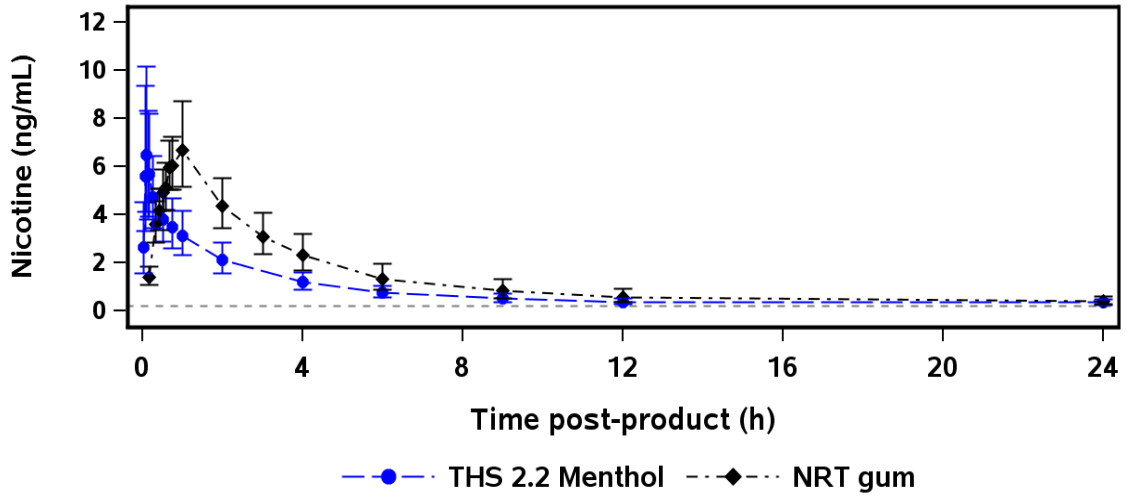
High between-subject variability was noted for both $AUC_{(0\text{-}\infty)}$ and $AUC_{(0\text{-t'})}$ for both products, with CV% values ranging from 85% to 86% and 98% to 160%, respectively. The within-subject variability was high for both $AUC_{(0\text{-}\infty)}$ (42%) and $AUC_{(0\text{-t'})}$ (67%).

The $t_{1/2}$ was similar for each product, with LS mean $t_{1/2}$ for THS 2.2 Menthol of 4.1 hours (95% CI: 3.6, 4.7) and 4.0 hours (95% CI: 3.5, 4.6) for mCC, with a THS 2.2 Menthol:mCC ratio of 102% (95% CI: 85, 123).

For t_{max}, there was no notable difference between THS 2.2 Menthol and mCC, with a median value of 6 minutes for both products.

Nicotine Pharmacokinetic Endpoints Following Single Use of THS 2.2 Menthol and NRT Gum

The overall shape of the mean nicotine concentration-time curves was different for THS 2.2 menthol and NRT gum. The plasma concentration versus time profile following single use was characterized by a rapid absorption phase for THS 2.2 Menthol, while C_{max} was comparable but attained later following NRT gum use.



---------- Lower limit of quantification (0.2 ng/mL)

Following single use, the maximum exposure to nicotine as assessed by C_{max} was comparable between THS 2.2 Menthol and NRT gum (THS 2.2 Menthol: 7.6 ng/mL; NRT gum: 7.5 ng/mL; THS 2.2 Menthol:NRT gum ratio: 102%; 95% CI: 62, 166; P = 0.47). The amount of nicotine absorbed as assessed by $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-}\infty)}$ were significantly lower for THS 2.2 Menthol compared to NRT gum ($AUC_{(0\text{-last})}$ THS 2.2 Menthol: 15.6 ng.h/mL; NRT gum: 27.9 ng.h/mL; THS 2.2 Menthol:NRT gum ratio: 56%; 95% CI: 38, 81. $AUC_{(0\text{-}\infty)}$ THS 2.2 Menthol: 15.8 ng.h/mL; NRT gum: 31.1 ng.h/mL; THS 2.2 Menthol:NRT gum ratio: 51%; 95% CI: 35, 74. P values were >0.99 for both $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-}\infty)}$ for the one-sided tests that the exposure was greater for THS 2.2 Menthol compared to NRT gum). The amount of nicotine absorbed as assessed by $AUC_{(0\text{-t'})}$ was higher for THS 2.2 Menthol compared to NRT gum but did not achieve statistical significance (THS 2.2 Menthol: 3.4 ng.h/mL; NRT gum: 3.0 ng.h/mL; THS 2.2 Menthol:NRT gum ratio: 114%; 95% CI: 79, 163; P = 0.23).

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 NRT gum, with CV% values ranging from 75% to 109% for THS 2.2 Menthol and 51% to 75% for NRT gum. The within-subject variability was high for C_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-t'})}$, and $AUC_{(0\text{-}\infty)}$ (51% to 79%).

The $t_{1/2}$ was comparable for each product, with LS mean $t_{1/2}$ for THS 2.2 Menthol of 3.2 hours (95% CI: 2.7, 3.8) and 3.5 hours (95% CI: 3.0, 4.1) for NRT gum and a geometric mean ratio of 92% (95% CI: 74, 115).

The t_{max} was significantly shorter for THS 2.2 Menthol (8 minutes) compared to NRT gum (45 minutes), with a median difference of -38 minutes (95% CI: -45, -32, P <0.01).

Subjective Effects of Smoking Endpoints:

Urge-to-Smoke Symptoms (QSU-brief)

The average Group-1 PK population urge-to-smoke total score dropped by a maximum of approximately 35% at T_0 + 15 minutes and 29% at T_0 + 30 minutes following THS 2.2 Menthol and mCC use, respectively, corresponding to maximum reductions of 1.52 and 1.28 point decreases from baseline, respectively. For both THS 2.2 Menthol and mCC, the average total score had not returned to baseline values by the last assessment time point at 12 hours post-product use (90% and 93% of baseline, respectively).

There was no notable difference in QSU-brief total for THS 2.2 Menthol compared to mCC, with an LS mean difference over all time points of -0.3 points for THS 2.2 Menthol - mCC following single use (95% CI: -0.8, 0.2). 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 -0.3 (95% CI: -0.9, 0.3); and Factor 2 reflecting anticipation of relief from negative effects of not smoking (THS 2.2 Menthol - mCC difference of -0.2 (95% CI: -0.8, 0.3). 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 -0.4 (95% CI -1.1, 0.3).

In the Group-2 PK population, the average urge-to-smoke total score dropped by approximately 28% and 22% following THS 2.2 Menthol and NRT gum use, respectively. For THS 2.2 Menthol, the maximum decrease was observed at T_0 + 30 minutes and at T_0 + 45 minutes for NRT gum, with maximum reductions corresponding to a 1.1 and 0.9 point decrease from baseline, respectively. The average total scores for both products were below their respective baseline values at 12 hours post-product use (95% and 90% for THS 2.2 Menthol and NRT gum, respectively).

There was no notable difference in QSU-brief total score for THS 2.2 Menthol compared to NRT gum, with an LS mean difference over all time points of -0.3 points for THS 2.2 Menthol – NRT gum following single use (95% CI: -0.9, 0.2). Consistent results were obtained for the 2 factors, Factor 1 THS 2.2 Menthol - NRT gum difference of -0.3 (95% CI: -1.0, 0.4), and Factor 2 THS 2.2 Menthol - NRT gum difference of -0.4 (95% CI: -0.7, -0.1). The difference between THS 2.2 Menthol and NRT gum for the total score was greatest at T_0 + 15 and 20 minutes, where the applicable assessment time points apply for the products, with a THS 2.2 Menthol - NRT gum difference of -0.8 (95% CI -1.7, 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 two subscales, with enjoyment of respiratory tract sensation being 0.6 points (95% CI: 0.1, 1.1) lower and smoking satisfaction being 1.1 points (95% CI: 0.7, 1.5) lower for THS 2.2 Menthol compared to mCC.

There was no notable difference in aversion, craving reduction, and psychological reward between THS 2.2 Menthol and mCC following single use, with aversion being 0.1 points (95% CI: -0.4, 0.6) lower, craving reduction being 0.1 points (95% CI: -0.3, 0.5) lower, and psychological reward being 0.2 points lower (95% CI: 0.0, 0.4) for THS 2.2 Menthol than mCC.

Biomarker Endpoints:

Blood COHb

Mean COHb values following at least 24 hours of smoking abstinence and prior to product use were 2.5% for both THS 2.2 Menthol and mCC. Fifteen minutes after product use, the mean value had increased to 3.5% for mCC, while COHb remained stable for the 12 hour post-product evaluation period for THS 2.2 Menthol users (within the range of 2.4% to 2.6%, with the maximum achieved at T_0 + 60 minutes). Across the full 12 hour post-product evaluation period, the THS 2.2 Menthol:mCC ratio for COHb was 81% (95% CI: 79, 84) after single use.

Mean COHb values following at least 24 hours of smoking abstinence and prior to product use were 2.4% for both THS 2.2 Menthol and NRT gum. Following THS 2.2 Menthol and NRT gum use, there was no

notable difference in overall mean COHb levels between THS 2.2 Menthol and NRT gum users. Mean COHb levels remained relatively unchanged throughout the assessment day (2.4% to 2.5% for THS 2.2 Menthol and 2.4% to 2.5% for NRT gum), with the maximum COHb value achieved at T_0 + 4 hours for both products.

Exhaled CO

Mean exhaled CO values following 24 hours of smoking abstinence and prior to product use were 3.5 ppm for THS 2.2 Menthol and 3.7 ppm for mCC. Following single mCC use, the mean exhaled CO levels initially increased, reaching a peak of 5.8 ppm at 12:00-01:30 pm (the first post-product use assessment). Following single THS 2.2 Menthol use, mean CO levels remained relatively steady throughout the evaluation period (within the range of 3.2 to 3.7 ppm with the maximum mean level attained at 04:00-05:30 PM). Across the full post-product evaluation period, the LS mean level for exhaled CO following single THS 2.2 Menthol use was 1.6 ppm lower than that determined following single mCC use (95% CI: 1.3, 1.9).

Mean exhaled CO values following at least 24 hours of smoking abstinence and prior to product use were 3.7 ppm for both THS 2.2 Menthol and NRT gum. Following THS 2.2 Menthol and NRT gum use, there was no notable difference in overall exhaled CO levels. For both products, mean exhaled CO values remained relatively steady throughout the evaluation period (2.9 to 3.7 ppm for THS 2.2 Menthol and 2.7 to 3.3 ppm for NRT gum) with values comparable to baseline observed at 08:00-09:30 PM (3.7 ppm for THS 2.2 Menthol and 3.3 ppm for NRT gum).

Safety:

There were no SAEs or severe AEs reported in this study and no subjects discontinued from the study due to an AE.

Overall, there were only 4 AEs (lymphocyte count increased, bilirubin conjugated increased, blood bilirubin increased, and hemoglobin decreased) reported by 4 of the 73 subjects (5.5%) in the safety population (which included 11 subjects who were enrolled but not randomized). All 4 AEs were mild in severity. None of the subjects who were exposed but not randomized reported an AE. No AEs were assessed as being related to investigational product (THS 2.2 Menthol or mCC), NRT gum, or study procedures.

None of the subjects experienced a device event or malfunction.

CONCLUSIONS

In this study, the amount of nicotine absorbed was comparable following THS 2.2 Menthol single use when compared to mCC single use. Nicotine was absorbed and eliminated at a similar rate for the 2 products. The results for mCC were consistent with what has previously been reported in the literature. THS 2.2 Menthol single use decreased the urge-to-smoke in a comparable fashion to mCC single use at any time point post-product use. Results from other subjective effects of smoking suggested that THS 2.2 Menthol use was less satisfying and provided a less enjoyable respiratory tract sensation compared to mCC. No notable difference was observed between the 2 products in aversion and psychological reward.

This study demonstrated that nicotine was absorbed more rapidly following THS 2.2 Menthol compared to NRT gum. However, it was also observed that the amount of nicotine absorbed was significantly lower following THS 2.2 Menthol compared to NRT gum, while the elimination rate was comparable for the 2 products. THS 2.2 Menthol use reduced craving faster than NRT gum, but the overall time profile showed no notable difference in urge-to-smoke between THS 2.2 Menthol and NRT gum use. However, THS 2.2 Menthol use decreased the urge-to-smoke more than NRT gum use for the first 4 hours post-product 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 NRT gum single use.

No SAEs or severe AEs were reported during this study, with no AEs related to investigational product use.

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