APPENDIX 8: ZRHR-PK-02-JP CLINICAL STUDY SUMMARY

The study was conducted in Japan from July to November 2013. Principles as defined in 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 (THS 2.2) following single use in smoking, healthy subjects compared to conventional cigarettes and nicotine gum.

Principal Investigator and Study Center: M. Sugimoto, MD
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Publication (reference): ClinicalTrials.gov: ID: NCT01959607. Brief title: Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 (THS 2.2)

Period of Study:
First subject screened: 31 July 2013
Last subject last visit: 15 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 time of last quantifiable concentration [$AUC_{(0\text{-last})}$]) from THS 2.2 relative to conventional cigarettes (CC), following single use of THS 2.2 and CC.

   Endpoints:

   Nicotine pharmacokinetic (PK) parameters (THS 2.2 vs. CC):

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

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.

Secondary Objectives and Endpoints:

The secondary objectives of this study were:

1. To determine if Cmax and $AUC_{(0\text{-}last)}$ of plasma nicotine of the THS 2.2 are higher relative to nicotine replacement therapy (NRT) gum following single use of the THS 2.2 and NRT gum.

   Endpoints:

   Primary nicotine PK parameters (THS 2.2 vs. NRT gum):

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

2. To evaluate the difference on nicotine 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 CC or NRT gum [$AUC_{(0\text{-}t')}$] between the THS 2.2 and CC, as well as the THS 2.2 and NRT gum.

   Endpoints:

   Secondary nicotine PK parameters:

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

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

   Endpoint:

   - $t_{1/2}$.

5. To describe the differences on urge-to-smoke over time between the THS 2.2 and CC, as well as between the THS 2.2 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 and CC 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, as compared to CC 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 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 with each subject using 2 of the following 3 products:

- THS 2.2
- CC
- 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 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 (using up to 3 Tobacco Sticks) and subsequently NRT gum. Product tests with either the THS 2.2 or the NRT gum were only performed in female subjects after pregnancy had been excluded by a negative urine pregnancy test. Only subjects willing and ready to use both the THS 2.2 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 /CC/NRT gum).

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

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

- Sequence 1: THS 2.2 → CC (N=22).
- Sequence 2: CC → THS 2.2 (N=22).
- Sequence 3: THS 2.2 → NRT gum (N=9).
- Sequence 4: NRT gum → THS 2.2 (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, where the Sponsor and the Clinical Research Organization personnel were blinded to the randomized sequence.

Number of Subjects (Planned and Analyzed):

Planned:	62 subjects
Screened:	110 subjects
Exposed to THS 2.2:	65 subjects
Enrolled:	65 subjects
Randomized:	62 subjects
Safety population:	65 subjects
Group-1 PK population	42 subjects
Group-2 PK population:	18 subjects

The Group-1 (comparison between THS 2.2 and CC) and Group-2 (comparison between THS 2.2 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 a current smoker, based on self-reporting, who had smoked for the last 4 weeks at least 10 commercially available non-menthol CC per day (single brand use only; no brand restrictions) with a maximum yield of 1 mg nicotine International Organization for

Standardization (ISO) per CC, as labeled on the cigarette package. 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 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 product was provided by the Sponsor and comprised the following components: THS Tobacco Stick, Holder, Charger, a Cleaning Tool, a main power supply, and a USB cable.

Pack batch number of THS Tobacco Sticks: B-05771. Production date: 11 June 2013.

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, and CC or NRT gum.

Reference Products:

The subject's own supply of commercially available single-brand of non-menthol CC of up to 1 mg nicotine ISO per cigarette were used as a reference product in this study. 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:CC) and 95% confidence interval (CI). Carry-over effect was not tested, as it cannot be statistically distinguished from the interaction between product and period in a 2x2 crossover design.

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 to ≤ 1 mg). 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 and CC (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 - CC or THS 2.2 - 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 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:NRT gum) was > 1.0 in order to determine if the rate and the amount of nicotine absorbed from THS 2.2 were higher relative to NRT gum. P values were reported for two-tailed tests

The parameter t_{max} was analyzed to test if it was shorter with THS 2.2 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:CC) 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 versus NRT gum analyses:

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

The study evaluation criteria were defined as 95% CI of the THS 2.2:CC 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 (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 vs CC and THS 2.2 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 - CC differences of the MCEQ domain scores and variances, with a REML method, using a 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 by sequence.

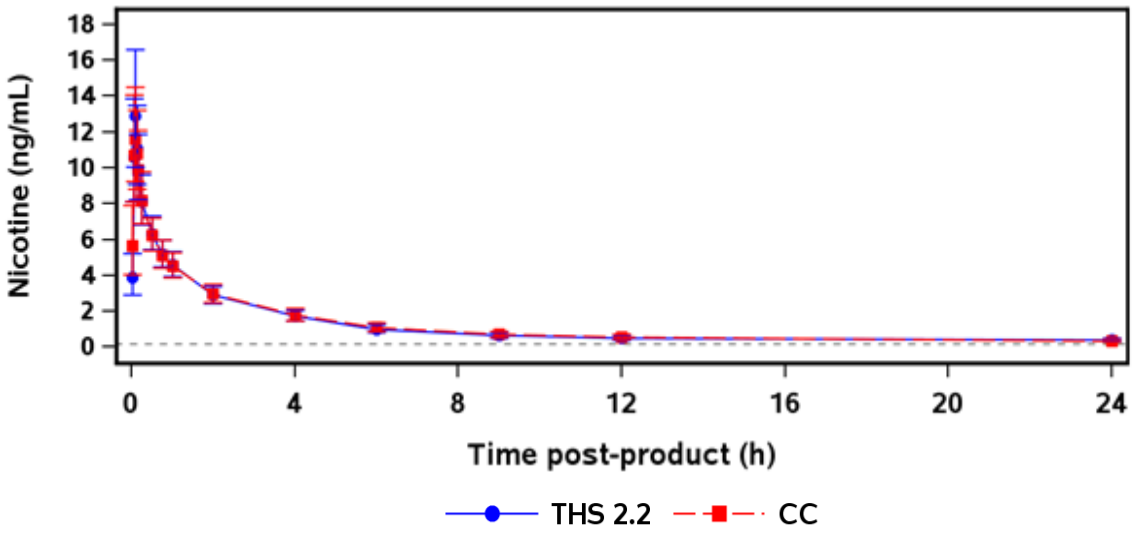
Medical History and concomitant disease were coded using MedDRA Version 16.0 and listed separately by sequence, SOC, and PT within SOC.

All medications were listed and summarized by sequence using PT and Anatomical Therapeutic and Chemical 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 and CC. The plasma concentration versus time profiles following single use of THS 2.2 and CC were characterized by a rapid absorption phase, with C_{max} reached at the same time post-product use (6 minutes).



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

Primary Pharmacokinetic Parameters:

PK Parameter (unit)	Product Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2:CC) (%)	CV (%)	95% CI	Precision (%)
C_{max}	THS 2.2	42	14.3	104	47	85, 126	23
(ng/mL)	CC	42	13.8				
$AUC_{(0\text{-last})}$	THS 2.2	42	23.8	96	29	85, 110	13
(ng.h/mL)	CC	42	24.7				

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; Cmax = 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 and CC as assessed by C_{max} (THS2.2:CC geometric LS mean ratio: 104%) and $AUC_{(0\text{-}last)}$ (THS2.2:CC geometric LS mean ratio: 96%), 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 83% to 84% and 65% to 70%, respectively. The within-subject variability was high for C_{max} (47%) and moderate for $AUC_{(0\text{-}last)}$ (29%).

The THS 2.2:CC ratio for $AUC_{(0\text{-}last)}$ was estimated with a precision of 13%, while the precision for C_{max} was 23%, with precision was calculated as the largest difference between the 95% CI bounds and the mean.

Secondary Endpoints:

Secondary Pharmacokinetic Parameters - THS 2.2 versus CC

There was no notable difference in exposure to nicotine between THS 2.2 and CC as assessed by $AUC_{(0\text{-}\infty)}$ (THS 2.2: 26.2 ng.h/mL; CC: 26.8 ng.h/mL; THS 2.2:CC ratio: 98%; 95% CI: 87, 110) and $AUC_{(0\text{-}t')}$ (THS 2.2: 0.8 ng.h/mL; CC: 0.9 ng.h/mL; THS 2.2:CC ratio: 88%; 95% CI: 70, 111).

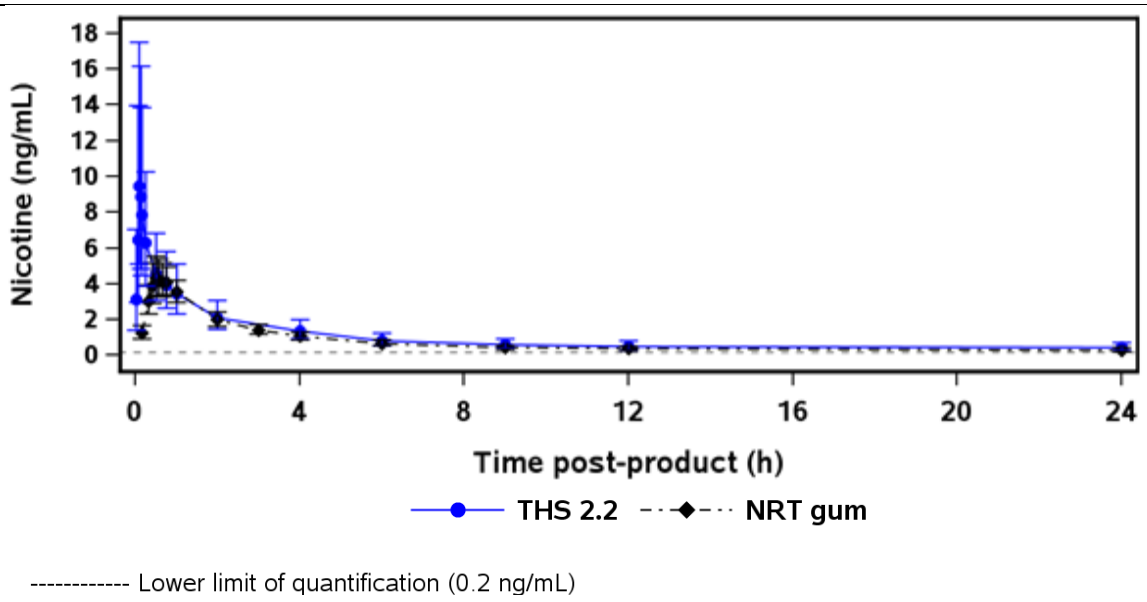
High between-subject variability was noted for both $AUC_{(0\text{-}\infty)}$ and $AUC_{(0\text{-}t')}$ for both products, with CV% values ranging from 64% to 71% and 86% to 100%, respectively. The within-subject variability was high for $AUC_{(0\text{-}t')}$ (55%) and moderate for $AUC_{(0\text{-}\infty)}$ (27%).

The $t_{1/2}$ was similar for each product, with mean $t_{1/2}$ for THS 2.2 of 3.8 hours (95% CI: 3.6, 4.1) and 4.1 hours (95% CI: 3.8, 4.4) for CC, and a THS 2.2:CC ratio of 93% (95% CI: 85, 102).

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

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

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



Following single use, the maximum exposure to nicotine as assessed by C_{max} was significantly higher for THS 2.2 compared to NRT gum (THS 2.2: 11.5 ng/mL; NRT gum: 4.8 ng/mL; THS 2.2:NRT gum ratio: 240%; 95% CI: 131, 442; P <0.01). Exposure to nicotine as assessed by $AUC_{(0\text{-last})}$ was approximately 1.3-fold higher for THS 2.2 compared to NRT gum, however this difference was not statistically significant (THS 2.2: 18.9 ng.h/mL; NRT gum: 14.9 ng.h/mL; THS 2.2:NRT gum ratio: 127%; 95% CI: 77, 209; P = 0.32). The result observed for C_{max} is consistent with the study hypotheses regarding the PK parameters following THS 2.2 and NRT gum use. The exposure to nicotine as assessed by $AUC_{(0\text{-last})}$ was higher for THS 2.2 compared to NRT gum, although a significant difference could not be detected.

Exposure to nicotine as assessed by $AUC_{(0\text{-t'})}$ and $AUC_{(0\text{-}\infty)}$ were significantly higher for THS 2.2 compared to NRT gum ($AUC_{(0\text{-t'})}$ THS 2.2: 3. 9 ng.h/mL; NRT gum: 1.7 ng.h/mL; THS 2.2:NRT gum ratio: 229%; 95% CI: 128, 407; P <0.01. $AUC_{(0\text{-}\infty)}$ THS 2.2: 28.9 ng.h/mL; NRT gum: 16.6 ng.h/mL; THS 2.2:NRT gum mean ratio: 174%; 95% CI: 110, 274; P = 0.02).

High between-subject variability was reported for C_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-t'})}$, and $AUC_{(0\text{-}\infty)}$ for THS 2.2 and moderate to high between-subject variability for NRT gum, with CV% values ranging from 86% to 146% for THS 2.2 and 30% to 50% for NRT gum. The within-subject variability was high for C_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-t'})}$, and $AUC_{(0\text{-}\infty)}$ (52% to 105%).

The $t_{1/2}$ was similar for each product, with LS mean $t_{1/2}$ for THS 2.2 of 4.2 hours (95% CI: 3.4, 5.1) and 4.8 hours (95% CI: 3.9, 5.8) for NRT gum and a THS 2.2:NRT gum ratio of 87% (95% CI: 66, 116).

The median t_{max} was significantly shorter for THS 2.2 (6 minutes) compared to NRT gum (35 minutes), with a median difference of -29 minutes (95% CI: -36, -24, P <0.01), which is consistent with the study hypothesis concerning t_{max}.

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 34% and 30% following THS 2.2 and CC use, respectively, at T_0 + 15 minutes, corresponding to maximum reductions of 1.4 and 1.2 point decreases from baseline, respectively. For both THS 2.2 and CC, the average total scores had not returned to their respective baseline values by the last assessment time point at 12 hours post-product use (90% and 96% of baseline, respectively).

The QSU-brief total scores were comparable for THS 2.2 and CC with an LS mean difference mean over all time points of 0.0 points for THS 2.2 - CC following single use (95% CI: -0.7, 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 - CC difference: 0.1; 95% CI: -0.6, 0.8), and Factor 2 reflecting anticipation of relief from negative effects of not smoking (THS 2.2 – CC difference: 0.0; 95% CI: -0.5, 0.6). The difference between THS 2.2 and CC for the total score was greatest at T_0 + 30 minutes with a THS 2.2 - CC difference of 0.1 (95% CI -0.5, 0.7).

In the Group-2 PK population, the average urge-to-smoke total score dropped by a maximum of approximately 28% and 22% following THS 2.2 and NRT gum use, respectively. For THS 2.2, the maximum decrease was observed at T_0 + 15 minutes and at T_0 + 60 minutes for NRT gum, with maximum reductions corresponding to a 1.0 and 0.8 point decrease from baseline, respectively. The average total scores for both products were below their respective baseline values at 12 hours post-product use (94% and 84% for THS 2.2 and NRT gum, respectively).

There was no notable difference in mean QSU-brief total score for THS 2.2 compared to NRT gum, with an LS mean difference mean over all time points of -0.2 points for THS 2.2 – NRT gum following single use (95% CI: -0.9, 0.5). Consistent results were obtained for the 2 factors, Factor 1 THS 2.2 – NRT gum difference of -0.3 (95% CI: -1.0, 0.4), and Factor 2 THS 2.2 – NRT gum difference of -0.1 (95% CI: -0.6, 0.3). The difference between THS 2.2 and NRT gum for the total score was greatest at T_0 + 15/20 minutes with a THS 2.2 – NRT gum difference of -0.7 (95% CI -1.6, 0.2).

Product Evaluation Questionnaire (MCEQ)

Based on the results from the product comparison using the MCEQ subscale scores following single use, differences were observed for a number of subscales, with enjoyment of respiratory

tract sensation being 0.6 points (95% CI: 0.1, 1.2) lower for THS 2.2 than CC. Differences were also observed for psychological reward, with THS 2.2 being 0.5 points (95% CI: 0.2, 0.7) lower than CC, and smoking satisfaction for THS 2.2 being 1.3 points (95% CI: 0.9, 1.7) lower than CC.

There was no notable difference in aversion or craving reduction between THS 2.2 and CC following single use, with aversion being 0.4 points (95% CI: -0.1, 0.8) higher, and craving reduction being 0.3 points (95% CI: -0.3, 0.9) lower for THS 2.2 than CC.

Biomarker Endpoints:

Blood COHb

Mean COHb values following at least 24 hours of smoking abstinence and prior to product use were 2.3% for THS 2.2 and 2.4% for CC. Fifteen minutes after product use, the mean COHb value had increased for CC users, reaching a maximum of 3.3% at T_0 + 60 minutes, while COHb remained stable for the 12 hour post-product evaluation period for THS 2.2 users (within the range of 2.3% 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:CC ratio for COHb was 82% (95% CI: 79, 85) after single use.

Following THS 2.2 and NRT gum use, there was no notable difference in overall mean COHb levels between THS 2.2 and NRT gum users. Mean COHb levels remained relatively unchanged throughout the assessment day (2.3% to 2.6% for both THS 2.2 and 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 3.0 ppm for THS 2.2 and 2.9 ppm for CC. Following single CC use, the mean exhaled CO levels initially increased, reaching a peak of 5.1 ppm at 12:00-01:30 PM. Following single THS 2.2 use, mean CO levels remained relatively steady throughout the evaluation period (within the range of 2.5 to 2.8 ppm with the maximum mean level attained at 12:00-01:30 PM and 04:00-05:30 PM). Across the full post-product evaluation period, the LS mean level for exhaled CO following single THS 2.2 use was 1.4 ppm lower than that determined following single CC use (95% CI: 1.1, 1.7).

Following THS 2.2 and NRT gum use, there was no notable difference in overall exhaled CO levels. Mean exhaled CO values remained relatively unchanged throughout the assessment day (2.5 to 2.8 ppm for THS 2.2 and 2.6 to 2.9 ppm for NRT gum with the maximum mean level attained at 04:00-05:30 PM for both products).

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 14 AEs reported by 11 of the 65 subjects (17%) in the safety population (which included 3 subjects who were enrolled but not randomized), the majority of which were mild in severity. The incidence of AEs in the THS 2.2 – CC, CC - THS 2.2, and NRT gum – THS 2.2 sequences were comparable (11% to 14%), while the incidence of AEs was higher in the THS 2.2 – NRT gum sequence (4 out of 9 subjects [44%]) than in the other sequences. This difference was mostly due to study procedure AEs (2 out of 9 subjects [22%]) whereas investigational product (IP) related AEs (1 subject [11%]) were in line with that seen in other sequences.

The most frequent AEs were related to investigations and included blood triglycerides increased, hemoglobin decreased, and dysphoria which were each reported by 2 subjects. All other AEs were reported by only 1 subject.

During the study, 3 subjects experienced 3 AEs that were considered as related to IP. No AEs were considered to be related to NRT gum.

During THS 2.2 use, 2 subjects each experienced 1 device event or malfunction (a broken heater and a charging issue) which led to the replacement of the Tobacco Stick Holder. Neither of these events led to an AE.

Conclusions

In this study it has been demonstrated that the rate and the amount of nicotine absorbed, as assessed by C_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}\infty)}$, and $AUC_{(0\text{-}t')}$, were all comparable following THS 2.2 single use when compared to CC single use. The t_{max} and $t_{1/2}$ values obtained were also comparable following THS 2.2 and CC single use. THS 2.2 single use also decreased the urge-to-smoke in a comparable fashion to CC single use, with no notable difference between the 2 products at any time point. The results from the product comparison using the MCEQ subscales also showed no notable difference in craving reduction (urge-to-smoke) between THS 2.2 and CC single use and there was also no notable difference between the 2 products in aversion. The MCEQ results did suggest that CC use was psychologically more rewarding, smoking was more satisfying, and also provided a more enjoyable respiratory tract sensation compared to THS 2.2. The exposure to CO, as assessed by the measurement of the levels of blood COHb and exhaled CO, was not increased following THS 2.2 single use in contrast to CC single use.

This study has also demonstrated that exposure to nicotine as assessed by C_{max}, $AUC_{(0\text{-}\infty)}$, and $AUC_{(0\text{-}t')}$ were all higher following THS 2.2 use compared to NRT gum use, although $AUC_{(0\text{-}last)}$ was not notably higher. The time of maximum nicotine concentration was shorter following THS 2.2 use, while the $t_{1/2}$ values obtained were comparable between the 2 products. THS 2.2

use decreased the urge-to-smoke more than NRT gum use, particularly for the first 2 hours post-product use. THS 2.2 use reduced craving faster than NRT gum, but the profile over all time points showed no notable difference in urge-to-smoke between THS 2.2 and NRT gum use. Neither THS 2.2 nor NRT gum use increased blood COHb or exhaled CO levels, resulting in no notable differences following use of each product.

No SAEs or severe AEs were reported during this study, with the number of AEs being low and balanced across study sequences.

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