APPENDIX 10: ZRHR-PK-01-EU CLINICAL STUDY SUMMARY

The study was conducted in Northern Ireland from November to December 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 Ethics Committee (IEC) and the subjects received complete information about the study and signed an informed consent form (ICF).

Study ZRHR-PK-01-EU

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 nasal spray.

Principal Investigator and Study Center: Adrian Stewart, MD, MRCGP, MFPM
Celerion, 22-24 Lisburn Road, Belfast, BT9 6AD, Northern Ireland

Publication (reference): ClinicalTrials.gov ID: NCT01967732. Brief title: Nicotine Pharmacokinetic Profile and Safety of The Tobacco Heating System 2.2 (THS 2.2).

Period of Study:

First subject screened: 01 November 2013

Last subject last visit: 21 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 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:

   Primary nicotine pharmacokinetic (PK) parameters (THS 2.2 vs. CC):

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.

- 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 are higher relative to nicotine nasal spray (NNS) following single use of the THS 2.2 and NNS.

   Endpoints:

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

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

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

   Endpoints:

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

3. To evaluate the time to the maximum concentration (t_{max}) of 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 NNS.

   Endpoint:

   - t_{max}.

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

   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 NNS.

   Endpoint:

   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.

   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.

7. To describe the levels of carbon monoxide (CO) exposure for the THS 2.2, as compared to CC and NNS 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 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.
- CC.
- 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 and the NNS was performed by the study site staff during the Screening Visit.

Day -1 (Admission Day):

As the last procedure of the eligibility assessments, all subjects underwent a product test prior to enrollment: first THS 2.2 (using up to 3 THS Tobacco Sticks) and subsequently NNS (1 spray of 0.5 mg of nicotine per nostril). Product tests with either the THS 2.2 or the NNS were only performed in female subjects, with a negative urine pregnancy test. Only subjects willing and ready to use both the THS 2.2 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/CC/NNS).

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

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 → NNS (N=9).
- Sequence 4: NNS → THS 2.2 (N=9).

Subjects were discharged from the investigational site the morning of Day 4 following the completion of all examinations on 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:	137 subjects
Exposed to THS 2.2:	62 subjects
Enrolled:	62 subjects
Randomized:	62 subjects
Safety population:	62 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 PK (comparison between THS 2.2 and NNS) populations were composed of a different set of subjects.

Diagnosis and Main Criteria for Inclusion:

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

- Caucasian subject was aged from 21 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 non-menthol CC per day (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 NNS 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 (ISO 0.5 mg nicotine), Holder, Charger, a Cleaning Tool, a main power supply, and a USB cable.

Pack batch number of THS Tobacco Sticks: B-05874. Production date: 07 June 2013. Expiry date: 06 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, and CC or NNS.

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. Nicotine nasal spray (Nicorette® 10 mg/mL) was used as a 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 were back-transformed by exponentiation and tabulated together with the ratio (THS 2.2:CC) 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). The primary analysis was repeated for each level of the 2 sub-groups.

Nicotine plasma 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 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 - CC or THS 2.2 - 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: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 were higher relative to NNS.

The parameter t_{max} was analyzed to test if it was shorter with THS 2.2 than with NNS 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 (LLOQ) before the time point of first product use during study day (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 NNS analyses:

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

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 analysis of the exhaled CO during single use and log-transformed 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 versus CC and THS 2.2 versus NNS, using a 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 effect 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 were 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. 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.

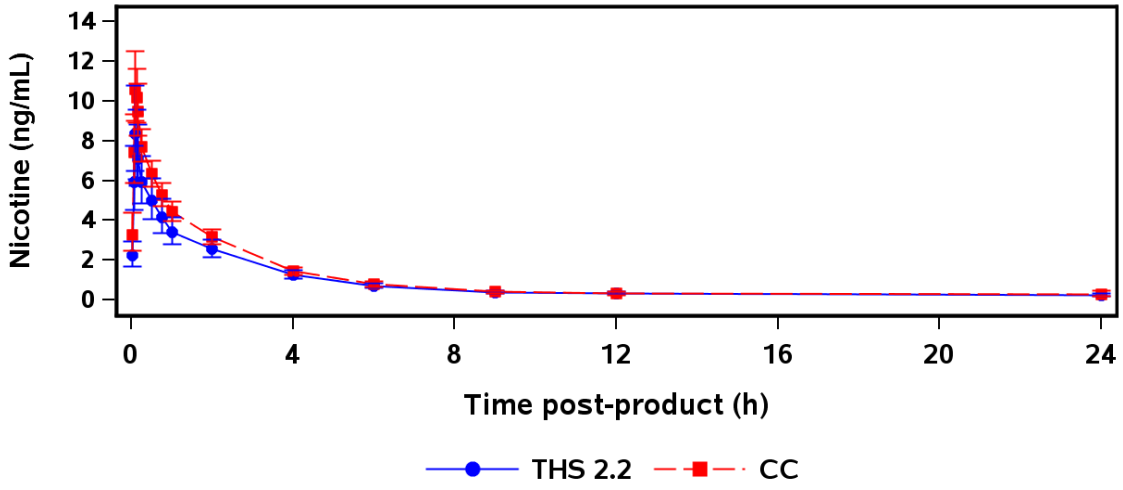
Medical history and concomitant disease were coded using MedDRA® Version 16.0 and listed separately by sequence, SOC, and PT within SOC.

All medications were listed and summarized by sequence using PT and Anatomical, Therapeutic 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, although the concentration of nicotine appeared to be lower throughout the 24 hours following single use for THS 2.2. 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 approximately 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:CC) (%)	CV (%)	95% CI	Precision (%)
C_{max} (ng/mL)	THS 2.2	42	9.6	77	51	63, 96	18
	CC	42	12.4				
$AUC_{(0\text{-last})}$ (ng.h/mL)	THS 2.2	42	15.1	74	45	62, 90	16
	CC	42	20.3				

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, the exposure to nicotine, as assessed by C_{max} and $AUC_{(0\text{-}last)}$, was lower for THS 2.2 compared to CC (THS 2.2:CC geometric LS mean ratios of 77% and 74%, 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 56% to 84% and 43% to 88%, respectively. The within-subject variability was high for both C_{max} (51%) and $AUC_{(0\text{-}last)}$ (45%).

The THS 2.2:CC ratio for C_{max} was estimated with a precision of 18%, while the precision for $AUC_{(0\text{-}last)}$ was 16%, with precision calculated as the largest difference between the 95% CI bounds and the mean.

Secondary Endpoints:

Secondary Pharmacokinetic Parameters - THS 2.2 versus CC

The exposure to nicotine was lower for THS 2.2 compared to CC as assessed by both $AUC_{(0\text{-}\infty)}$ (THS 2.2: 18.0 ng.h/mL; CC: 21.4 ng.h/mL; THS 2.2:CC ratio: 84%; 95% CI: 74, 95) and $AUC_{(0\text{-}t')}$ (THS 2.2: 0.6 ng.h/mL; CC: 0.8 ng.h/mL; THS 2.2:CC ratio: 71%; 95% CI: 57, 89).

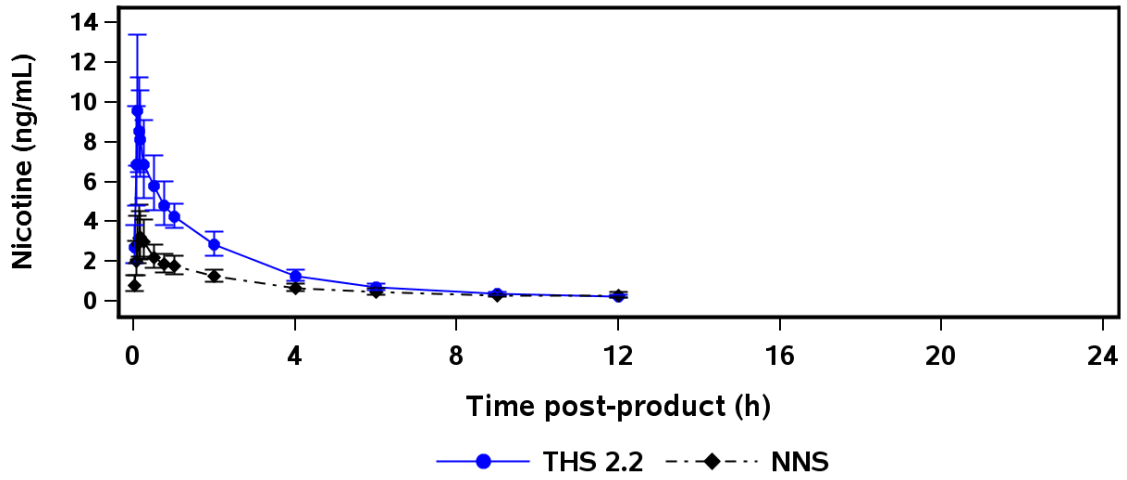
Between-subject variability was high for both $AUC_{(0\text{-}\infty)}$ and $AUC_{(0\text{-}t')}$ for both products, with CV% values ranging from 40% to 54% and 69% to 118%, respectively. The within-subject variability was moderate for $AUC_{(0\text{-}\infty)}$ (26%) and high for $AUC_{(0\text{-}t')}$ (53%).

The $t_{1/2}$ was similar for each product, with LS mean $t_{1/2}$ for THS 2.2 of 2.5 hours (95% CI: 2.4, 2.7) and 2.4 hours (95% CI: 2.2, 2.6) for CC, with a THS 2.2:CC ratio of 105% (95% CI: 96, 115).

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

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

The overall shape of the mean nicotine concentration-time curves was similar for THS 2.2 and NNS, although the mean plasma nicotine concentrations following single use of THS 2.2 were higher than for NNS. The plasma concentration versus time profiles following single use of THS 2.2 and NNS were characterized by a rapid absorption phase, with C_{max} reached at similar times post-product use. The 24 hours post-product use time point is not displayed as all values were below the LLOQ at this time (no sampling was done at 16 and 20-hours post exposure).



Following single use, C_{max} was significantly higher for THS 2.2 compared to NNS (THS 2.2: 10.5 ng/mL; NNS: 3.5 ng/mL; THS 2.2:NNS ratio: 300%; 95% CI: 201, 448; P < 0.001). Exposure to nicotine as assessed by $AUC_{(0\text{-last})}$ was significantly higher for THS 2.2 compared to NNS (THS 2.2: 17.9 ng.h/mL; NNS: 8.0 ng.h/mL; THS 2.2:NNS ratio: 223%; 95% CI: 155, 321; P < 0.001). The results observed for C_{max} and $AUC_{(0\text{-last})}$ support the study hypotheses regarding the PK parameters following THS 2.2 and NNS use.

Exposure to nicotine as assessed by $AUC_{(0\text{-t'})}$ and $AUC_{(0\text{-}\infty)}$ was significantly higher for THS 2.2 compared to NNS ($AUC_{(0\text{-t'})}$ THS 2.2: 0.8 ng.h/mL; NNS: 0.3 ng.h/mL; THS 2.2:NNS ratio: 268%; 95% CI: 170, 421; P < 0.001. $AUC_{(0\text{-}\infty)}$ THS 2.2: 19.7 ng.h/mL; NNS: 9.1 ng.h/mL; THS 2.2:NNS ratio: 217%; 95% CI: 168, 280; P < 0.001).

High between-subject variability was reported for C_{max}, and $AUC_{(0\text{-t'})}$ for both THS 2.2 and NNS and for $AUC_{(0\text{-last})}$ for NNS, with CV% values ranging from 62% to 189% for THS 2.2 and 64% to 107% for NNS. Moderate between-subject variability was reported for $AUC_{(0\text{-}\infty)}$ for both THS 2.2 and NNS (31% and 37%, respectively), and $AUC_{(0\text{-last})}$ (36%) for THS 2.2. The within-subject variability was moderate for $AUC_{(0\text{-}\infty)}$ (32%) and high for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-t'})}$ (55% to 71%).

The $t_{1/2}$ was significantly shorter for THS 2.2 (2.1 hours; 95% CI: 1.9, 2.3) compared to NNS (2.8 hours; 95% CI: 2.5, 3.1) with a THS 2.2:NNS ratio of 74% (95% CI: 64, 86). The t_{max} was comparable for THS 2.2 and NNS (7 minutes and 8 minutes, respectively; P = 0.261).

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 27% and 34% following THS 2.2 and CC use, respectively, at T_0 + 15 minutes, corresponding to maximum reductions of 1.4 and 1.8 point decreases from baseline, respectively. For both THS 2.2 and CC, the average total score had not returned to their respective baseline values by the last assessment time point at 12 hours post-product use (95% and 94% of baseline, respectively).

The QSU-brief total scores were comparable for THS 2.2 and CC with an LS mean difference over all time points of 0.2 points for THS 2.2 - CC following single use (95% CI: -0.9, 1.3). 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 of 0.1; 95% CI: -1.1, 1.4), and Factor 2 reflecting anticipation of relief from negative effects of not smoking (THS 2.2 - CC difference of 0.2; 95% CI: -0.9, 1.3). The difference between THS 2.2 and CC for the total score was greatest at T_0 + 15 minutes with a THS 2.2 - CC difference of 0.4 (95% CI -1.1, 1.8).

In the Group-2 PK population, the average urge-to-smoke total score dropped by a maximum of approximately 34% and 31%, respectively. For THS 2.2, the maximum decrease was observed at T_0 + 30 minutes and at T_0 + 45 minutes for NNS, with maximum reductions corresponding to a 1.7 and 1.5 point decreases from baseline for THS 2.2 and NNS use, respectively. THS 2.2 total score was close to baseline value at 12 hours post-product use (98%) and NNS total score returned to baseline value at 9 hours post-product use (101%).

There was no notable difference in mean QSU-brief total score for THS 2.2 compared to NNS, with an LS mean difference over all time points of -0.2 points for THS 2.2 − NNS following single use (95% CI: -1.4, 1.2). Consistent results were obtained for the 2 factors, Factor 1 THS 2.2 − NNS difference of -0.2 (95% CI: -1.3, 0.9), and Factor 2 THS 2.2 − NNS difference of -0.1 (95% CI: -1.3, 1.2). The difference between THS 2.2 and NNS for the total score was greatest at T_0 + 9 hours with a THS 2.2 − NNS difference of 0.5 (95% CI -2.3, 1.3).

Product Evaluation Questionnaire (MCEQ)

Based on the results from the product comparison using the MCEQ subscale scores following single use, differences were observed for all subscales, with the exceptions of aversion and psychological reward. Craving reduction was 0.6 points (95% CI: 0.1, 1.2) lower, enjoyment of respiratory tract sensation was 0.9 points (95% CI: 0.3, 1.5) lower, and smoking satisfaction was 1.0 points (95% CI: 0.5, 1.6) lower for THS 2.2 compared to CC.

There was no notable difference in aversion or psychological reward between THS 2.2 and CC following single use, with aversion being 0.1 points (95% CI: -0.4, 0.6) higher and psychological reward being 0.4 points (95% CI: -0.1, 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 both THS 2.2 and CC. Fifteen minutes after CC use, the mean COHb value had increased to a maximum of 3.2%, while COHb remained stable for the 12 hour post-product evaluation period for THS 2.2 users (within the range of 2.1% to 2.4%, with the maximum achieved at T_0 + 15 minutes). Across the full 12 hour post-product evaluation period, the THS 2.2:CC ratio for COHb was 79% (95% CI: 76, 82).

Following THS 2.2 and NNS use, there was no notable difference in overall mean COHb levels between THS 2.2 and NNS users. Mean COHb levels remained relatively unchanged throughout the assessment day (2.3% to 2.4% for THS 2.2 and 2.2% to 2.5% for NNS), with the maximum COHb value observed at T_0 + 60 minutes for THS 2.2 and T_0 + 4 hours for NNS.

Exhaled CO

Mean exhaled CO values following 24 hours of smoking abstinence and prior to product use were 3.7 ppm for THS 2.2 and 4.0 ppm for CC. Following single CC use, mean exhaled CO levels initially increased, reaching a peak of 5.4 ppm at 12:00-01:30 PM (the first post-product use assessment); thereafter levels decreased to 4.9 ppm for the remaining assessments (04:00-05:30 PM and 08:00-09:30 PM). Following single THS 2.2 use, mean CO levels remained relatively steady throughout the evaluation period (within the range of 3.5 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 use was 1.4 ppm lower than that determined following single CC use (95% CI: 1.1, 1.7).

Following THS 2.2 and NNS use, there was no notable difference in overall exhaled CO levels. Mean exhaled CO values remained relatively unchanged throughout the assessment day (3.7 to 4.1 ppm for THS 2.2 and 3.7 to 4.2 ppm for NNS) with the maximum mean level attained at 08:00-09:30 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 39 AEs reported by 23 of the 62 subjects (37%) in the safety population, the majority of which were mild in severity. The frequency of AEs was greater for the THS 2.2 − CC sequence (21 AEs) compared to the CC − THS 2.2 (10 AEs), THS 2.2 – NNS (4 AEs), and NNS − THS 2.2 (4 AEs) sequences. The greater number of AEs in the THS 2.2 − CC sequence was partly due to 7 study procedure related AEs in 3 subjects which were not observed in any of the other sequences. The incidence of subjects reporting AEs was comparable between the

THS 2.2 – CC and THS 2.2 – NNS sequences (44.4% to 45.5%) and was lower in the CC − THS 2.2 (31.8%) and NNS − THS 2.2 (22.2%) sequences.

The most frequent AEs were dizziness (8 AEs), headache (6 AEs), presyncope (6 AEs), nausea (3 AEs), and vomiting (3 AEs). All other AEs were reported by 2 or fewer subjects and a maximum of 1 subject per sequence.

During the study, 12 subjects experienced 14 AEs that were considered to be related to the investigational product ([IP] THS 2.2 or CC) and none of the events were considered unexpected. No AEs were considered to be related to NNS use.

No device events or malfunctions occurred during the study for any subject.

Conclusions:

In this study, the amount of nicotine absorbed was lower following single use of THS 2.2 compared to CC. However, nicotine was absorbed as rapidly for THS 2.2 as for CC, and eliminated at a similar rate for the 2 products. The results for CC were consistent with what has previously been reported in the literature. Despite the lower exposure compared to CC use, THS 2.2 single use reduced urge-to-smoke similarly to CC, with no notable difference observed. The MCEQ results also suggested that single THS 2.2 use was less satisfying than CC.

The maximal concentration reached with THS 2.2 was 3 times higher than that of NNS, with a similar time to peak concentration and urge-to-smoke relief.

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

No SAEs or severe AEs were reported during this study, with the number of AEs related to IP use being low.

Final Report Date: Version 1.0 / 25 March 2015