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6.2.1.2 PK/PD Overview of Studies

6.2.1.2.1 ZRHR-PK-01-EU

Study ZRHR-PK-01-EU	**Source: Section 7.3.1, Clinical Study Report ZRHR-PK-01-EU**

Title of the study:

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

Protocol-No.: ZRHR-PK-01-EU		
Date of final report: 25 March 2015		
Investigators:	Principal Investigator: Adrian Stewart, MD, MRCGP, MFPM	
Study center:	Celerion, 22-24 Lisburn Road, Belfast, BT9 6AD, Northern Ireland	
Time of clinical part:	November 2013 - December 2013	**Clinical Phase:** I (Product Performance)

Objective:
The purpose of this study was to compare the profile of nicotine uptake (rate and extent of nicotine absorbed) after single use of THS 2.2 and CC in smoking, healthy subjects. THS 2.2 was also compared with the nicotine nasal spray (NNS) product, used as a reference point.

Study design:

- Single center
- Single use
- Randomized
- Cross-over
- Open-label
- Two-way, four sequences
- At least a 24-hour nicotine wash-out (nicotine abstinence)

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Subjects:

- Planned: 62
- Enrolled: 62
- Randomized: 62
- Discontinuations: 2
- Data set for safety analysis: 62
- Group-1 (THS 2.2 / CC) data set for PK analysis: 42
- Group-2 (THS 2.2 / NRT) data set for PK analysis: 18

Main criteria for inclusion:

- Male or female Caucasians from 21 to 65 years of age and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening.
- Subjects were smoking at least 10 commercially available non- menthol CC (CC) per day with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) CC, as labeled on the cigarette package, for the last 4 weeks, and did not plan to quit smoking in the following 3 months. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
- Female subjects of child-bearing potential should had confirmed negative pregnancy test at enrollment and used effective methods of contraception without estrogen.
- Subjects had a body mass index between 18.5 and 32.0 (kg/m^2).
- Spirometry evaluation had to show forced expiratory volume in 1 second {FEV1}/forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV1 >80% predicted value, and post-bronchodilator FVC >0.8.
- Provide written informed consent prior to study participation.
- Able to communicate well with the investigator and comply with the requirements of the study.

THS 2.2:	Product:	Cigarette batch number of THS Tobacco Sticks B-05874 Production date: 07 June 2013. Expiry date: 06 January 2014
	ISO nicotine Content:	0.5 mg
	Use:	Single use
	Manufacturer:	PMI
Conventional Cigarette:	Product:	Own conventional cigarette brand.
	ISO nicotine Content:	Maximum yield of 1 mg per CC as labeled on the cigarette package

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	Use: Manufacturer:	Single use Commercially available non-menthol conventional cigarettes
Nicotine Nasal Spray:	Product: Nicotine content: Use: Manufacturer:	Nicorette® 10 mg/mL Single use (1 spray per nostril) Johnson & Johnson Ltd

Duration of use:	One inhalation experience of THS 2.2 consisted of one THS 2.2 heatstick. One inhalation experience of CC consisted of one cigarette. For NNS, one spray per nostril per product use. Each sampling period (Day 1 and Day 3) had a washout period (nicotine abstinence) of at least 24 hours prior to product use (Day 0 and Day 2).
Blood sampling points:	*Pharmacokinetics:* On Days 1 and 3, 16 blood samples were collected in blood with the first sample (T0) being drawn within 15 minutes prior to the single use and further samples taken (relative to T0, the time of first puff) after 2 (T1), 4 (T2), 6 (T3), 8 (T4), 10 (T5), 15 (T6), 30 (T7), 45 (T8), 60 (T9) minutes, T10 after 2 hours, 4 (T11), 6 (T12), 9 (T13), 12 (T14) and after 24 hours (T15) after T0. Plasma samples were used for bioanalysis.
Questionnaires:	*Pharmacodynamics (subjective effects) :* On Days 1 and 3, the QSU questionnaire was self-administered within 15 minutes prior to T0, then 15, 30, 45, 60 minutes, 2, 4, 6, 9 and 12 hours after T0. The MCEQ was filled out by the subjects who used the THS 2.2 or smoked CC only, on Days 1 and 3, between 8:00 and 11:00 PM.

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Analytical Method:	• Method:	LC-MS/MS
	• Specificity: retention nicotine	No significant interference at the time and mass transition of
	• Linearity (R^2)	0.9959
	• Accuracy:	
	Intra-batch:	-2.8 to 12.0%
	Inter-batch :	-0.9 to 5.5%
	• Precision:	
	Intra-batch (repeatability):	0.9 to 7.1%
	Inter-batch (intermediate precision):	2.6 to 6.2%
	• Calibration range:	0.200 to 10.0 ng/mL
	• Lower limit of quantification (LLOQ):	0.200 ng/mL

6.2.1.2.1.1 Safety

Adverse events, assessments of physical condition, vital signs and body measurements, spirometry, respiratory symptoms, electrocardiogram, and monitoring of laboratory values.

6.2.1.2.1.2 Statistical Methods

6.2.1.2.1.2.1 Pharmacokinetics

- Analysis of variance (ANOVA) on natural log-transformed values for $AUC_{0\rightarrow last}$, and C_{max}, including terms for sequence, subjects nested within sequence, period, and product as fixed effect factors. Adjusted geometric least square (LS) mean ratios and 95% confidence intervals (CIs) were calculated.
- Hodges–Lehmann estimates with 95% CIs were calculated for the median differences between THS 2.2 and CCs for t_{max}

6.2.1.2.1.2.2 Pharmacodynamics (Subjective Effects)

- The mean QSU-Brief scores and MCEQ sub-scales were calculated at each measurement time, and were compared using a mixed-effects model including terms for product, sequence, period, and subject nested within sequence as a random effect. The repeated measurements model for QSU-brief analysis also included terms for time and product*time accounting for the all post exposure assessment time-points. Adjusted LS mean differences and 95% CIs were calculated.

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6.2.1.2.1.3 Results

6.2.1.2.1.3.1 Pharmacokinetics

Group-1 (THS 2.2/CC)

Table 1 THS 2.2 Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	15.20	18.39	9.332	0.7; 49.3	18.77
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	18.34	20.51	9.373	4.3; 53.4	20.86
C_{max} [ng/mL]	9.60	12.15	8.282	1.3; 35.4	9.87

The median t_{max} was 6.18 minutes (min; max: 2.0; 30.1).

Data Source: Appendix 15, Table 15.2.4.5 ZRHR-PK-01-EU.

Table 2 Conventional Cigarette Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	20.13	21.87	9.429	9.5; 56.6	21.12
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	20.80	22.42	9.428	10.5; 58.5	22.11
C_{max} [ng/mL]	12.34	14.23	8.989	4.1; 57.1	12.85

The median t_{max} was 6.42 minutes (min; max: 2.2; 30.1).

Data Source: Appendix 15, Table 15.2.4.5 ZRHR-PK-01-EU.

Table 3 THS 2.2:CC Ratios of Geometric LS Means

Variable	Product Exposure	N	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2:CC) (%)	CV (%)	95% CI
$AUC_{0\rightarrow last}$ [ng•h/mL]	THS 2.2	42	15.10	74.47	45.34	61.52; 90.14
	CC	42	20.28			
C_{max} [ng/mL]	THS 2.2	42	9.62	77.43	50.67	62.69; 95.63
	CC	42	12.42			

Data Source: Appendix 15, Table 15.2.3.1 ZRHR-PK-01-EU

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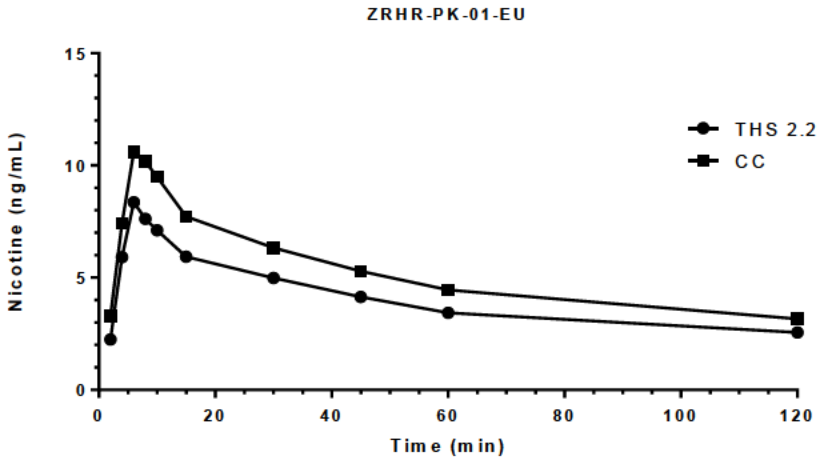


Figure 1 Geometric Means (n=42) of Plasma Concentrations of Nicotine After Single Use of THS 2.2 and CC

Data Source: Appendix 15, Figure 15.1.2.1.1 ZRHR-PK-01-EU

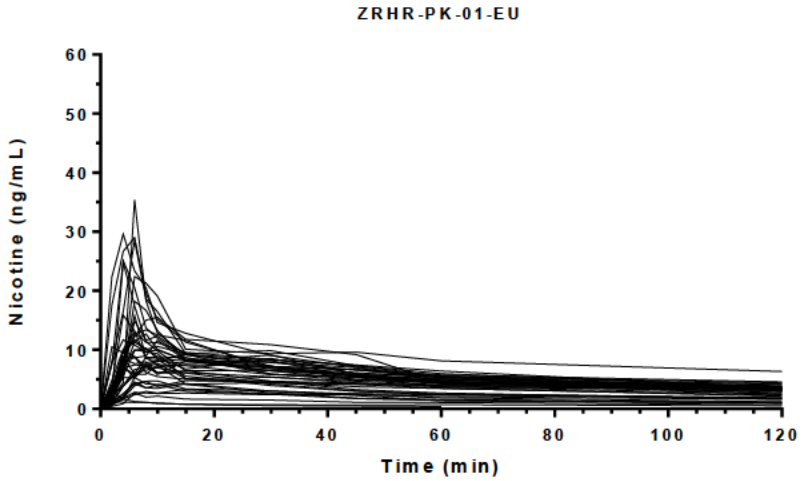


Figure 2 Individual Plasma Concentrations (N=42) of Nicotine After Single Use of THS 2.2

Data Source: Appendix 15, Listing 15.3.3.2 ZRHR-PK-01-EU

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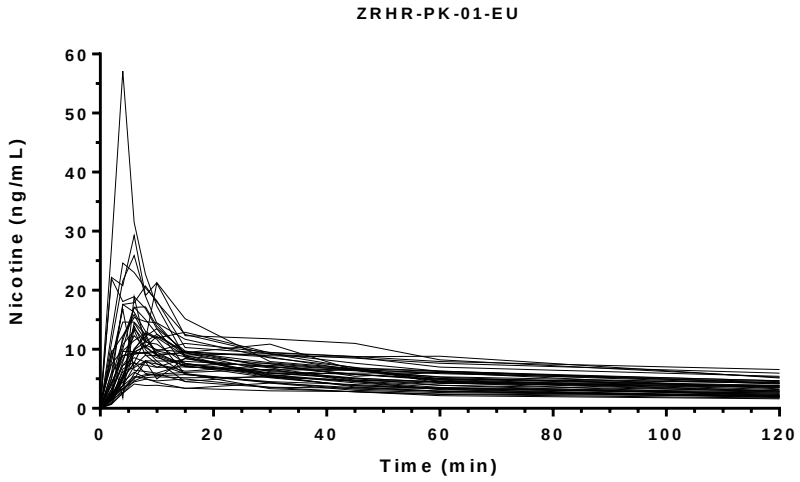


Figure 3 Individual Plasma Concentrations (N=42) of Nicotine After Single Use of CC

Data Source: Appendix 15, Listing 15.3.3.2 ZRHR-PK-01-EU

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Group-2 (THS 2.2/NNS)

Table 4 THS 2.2 Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	17.87	18.89	6.264	8.8; 30.4	19.00
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	19.61	20.46	6.069	10.9; 32.0	20.66
C_{max} [ng/mL]	10.52	12.35	7.720	3.5; 31.1	9.50

The median t_{max} was 7.13 minutes (min; max: 6.0; 60.0).

Data Source: Appendix 15, Table 15.2.4.5 ZRHR-PK-01-EU

Table 5 NNS Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	8.02	9.61	7.327	2.9; 35.7	7.95
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	9.24	9.78	3.341	4.8 ; 15.4	9.10
C_{max} [ng/mL]	3.51	4.30	2.674	1.4; 9.7	3.45

The median t_{max} was 8.18 minutes (min; max: 2.0; 32.1).

Data Source: Appendix 15, Table 15.2.4.5 ZRHR-PK-01-EU

Table 6 THS 2.2:NNS Ratios of Geometric LS Means

Variable	Product Exposure	N	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2:NNS) (%)	CV (%)	95% CI
$AUC_{0\rightarrow last}$ [ng•h/mL]	THS 2.2	18	17.87	222.90	55.46	154.60; 321.39
	NNS	18	8.02			
C_{max} [ng/mL]	THS 2.2	18	10.52	299.96	61.75	200.74; 448.22
	NNS	18	3.51			

Data Source: Appendix 15, Table 15.2.4.2 ZRHR-PK-01-EU

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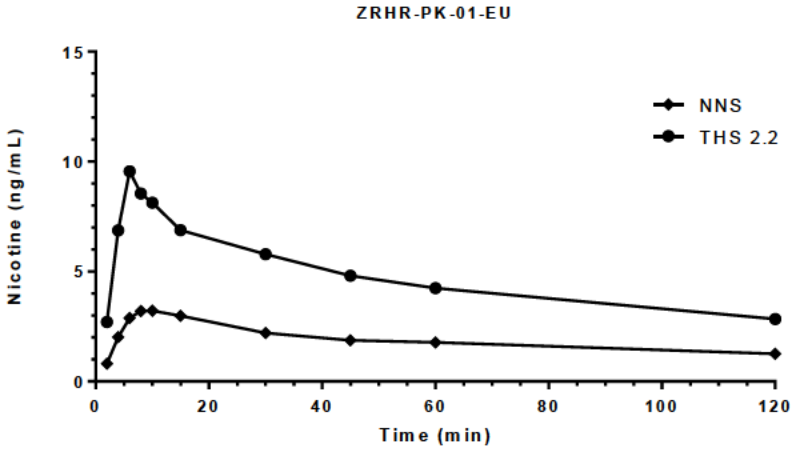


Figure 4 Geometric Means (n=18) of Plasma Concentrations of Nicotine After Single Use of THS 2.2 and NNS

Data Source: Appendix 15, Figure 15.1.2.1.2. ZRHR-PK-01-EU

6.2.1.2.1.3.2 Conclusion

- 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 two products. The results for CC were consistent with what has previously been reported in the literature.
- The maximal concentration reached with THS 2.2 was 3 times higher than that of NNS, with a similar time to peak concentration.

6.2.1.2.1.3.3 Pharmacodynamics (Subjective Effects)

Group-1 (THS/CC)

Table 7 Analysis of Urge-to-Smoke After Single Use – THS 2.2 vs CC (QSU-b Total Score)

QSU-b	Product Exposure	LS Mean	THS 2.2 - CC LS Mean Difference	LS Mean Difference 95% CI
Total Score	THS 2.2	4.47	0.17	-0.93; 1.26
	CC	4.30		

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model. QSU-brief total score items are rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores indicate a higher urge-to-smoke.

Data Source: Appendix 15, Table 15.2.4.12 ZRHR-PK-01-EU

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Group 2 (THS/NNS)

Table 8 Analysis of Urge-to-Smoke After Single Use – THS 2.2 vs NNS (QSU-b Total Score)

QSU-b	Product Exposure	LS Mean	THS 2.2 - NNS LS Mean Difference	LS Mean Difference 95% CI
Total Score	THS 2.2	3.92	-0.15	-1.35 ; 1.05
	NNS	4.07		

Data Source: Appendix 15, Table 15.2.4.12 ZRHR-PK-01-EU

Group-1 (THS/CC)

Table 9 Analysis of MCEQ After Single Use – THS vs CC

MCEQ Sub-Scale Domain	Product Exposure	LS Mean	THS 2.2 - CC LS Mean Difference	LS Mean Difference 95% CI
Aversion	THS 2.2	2.67	0.12	-0.38; 0.61
	CC	2.55		
Craving reduction	THS 2.2	4.73	-0.61	-1.18; -0.05
	CC	5.34		
Enjoyment of respiratory tract sensation	THS 2.2	4.13	-0.90	-1.48; -0.31
	CC	5.03		
Psychological reward	THS 2.2	3.68	-0.39	-0.91; 0.13
	CC	4.06		
Smoking satisfaction	THS 2.2	4.47	-1.03	-1.55; -0.50
	CC	5.49		

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model.

Data Source: Appendix 15, Table 15.2.4.15.

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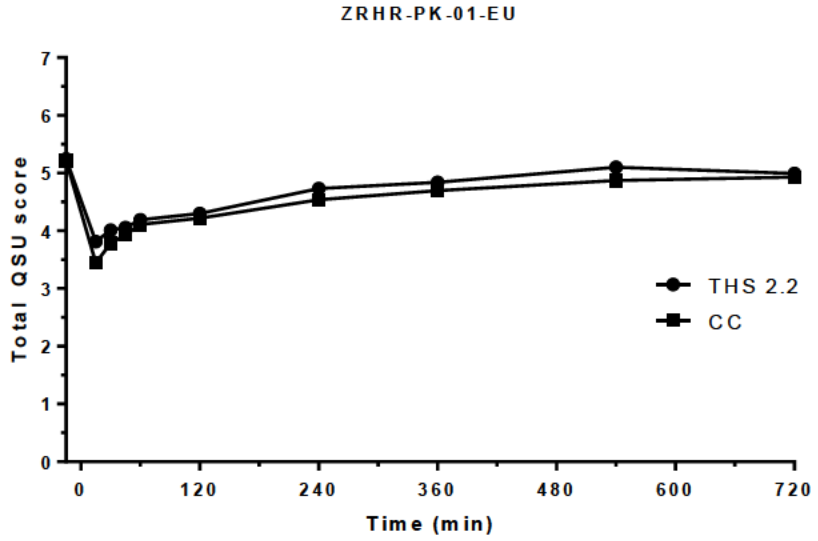


Figure 5 Arithmetic Mean of Total Scores for QSU-brief During Single Use of THS 2.2 and CC

Data Source: Appendix 15, Figure 15.1.2.10.1.

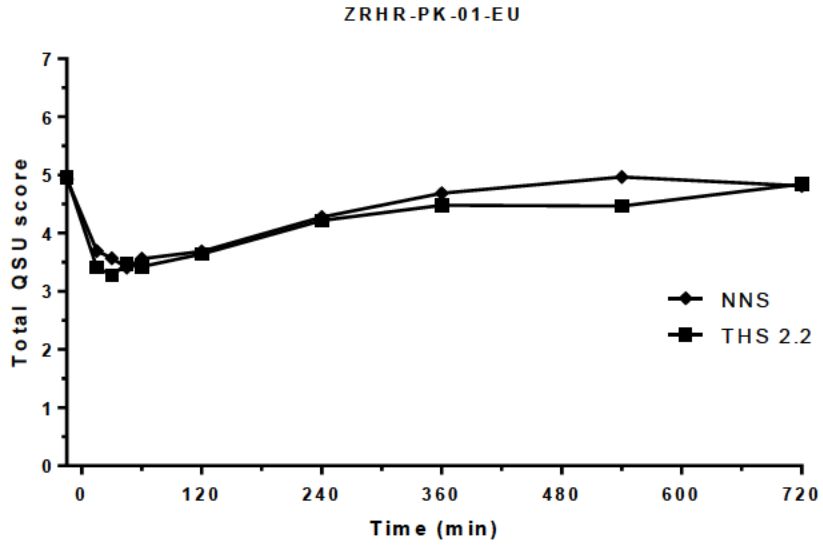


Figure 6 Arithmetic Mean of Total Scores for QSU-brief During Single Use of THS 2.2 and NNS

Data Source: Appendix 15, Figure 15.1.2.10.2.

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6.2.1.2.1.3.4 Conclusion

- THS 2.2 single use decreased the urge-to-smoke in a comparable fashion to CC single use at any time point post product use.
- There was no notable difference in mean QSU-brief total score for THS 2.2 compared to NNS.
- MCEQ subscales suggested that THS 2.2 use was less satisfying, reduced less the craving and provided a less enjoyable respiratory tract sensation compared to CC. No notable difference was observed between the two products in aversion and psychological reward.

6.2.1.2.1.4 Safety Findings

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

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 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.

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6.2.1.2.2 ZRHR-PK-02-JP

Study ZRHR-PK-02-JP	**Source: Section 7.3.1, Clinical Study Report ZRHR-PK-02-JP**

Title of the study:

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

Protocol-No.: ZRHR-PK-02-JP		
Date of final report: 19 February 2015		
Investigators:	Principal Investigator: M. Sugimoto	
Study center:	Koganeibashi Sakura Clinic, 2-11-25,Sakuracho, Koganei-shi Tokyo, Japan	
Time of clinical part:	July 2013 - November 2013	**Clinical Phase:** I (Product Performance)

Objective:

The purpose of this study was to evaluate the comparability of THS 2.2. relative to conventional cigarettes (CC) and nicotine replacement therapy (NRT) gum in terms of pharmacokinetics (PK), pharmacodynamics (PD), and safety following single product use in healthy adult Japanese subjects.

Study design:

- Single center
- Single use
- Randomized
- Cross-over
- Open-label
- Two-way, four sequences
- At least a 24-hour nicotine wash-out (nicotine abstinence)

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Subjects:	
• Planned:	62
• Enrolled:	65
• Randomized:	62
• Discontinuations:	2
• Data set for safety analysis:	65
• Group-1 (THS 2.2 / CC) data set for PK analysis:	42
• Group-2 (THS 2.2 / NRT Gum) data set for PK analysis:	18

Main criteria for inclusion:

- Male or female Japanese from 23 to 65 years of age and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening.
- Subjects were smoking at least 10 commercially available non-menthol CC (CC) per day 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, and did not plan to quit smoking in the following 3 months. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
- Female subjects of child-bearing potential should had confirmed negative pregnancy test at enrollment and used effective methods of contraception without estrogen.
- Subjects had a body mass index between 18.5 and 32.0 (kg/m^2).
- Spirometry evaluation had to show forced expiratory volume in 1 second {FEV1}/forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV1 >80% predicted value, and post-bronchodilator FVC >0.8.
- Provide written informed consent prior to study participation.
- Able to communicate well with the investigator and comply with the requirements of the study.

THS 2.2:	Product:	Cigarette batch number of THS Tobacco Sticks: B-05771 Production date: 11 June 2013. Expiry date: 10 January 2014
	ISO nicotine Content:	0.5 mg
	Use:	Single use
	Manufacturer:	PMI
Conventional Cigarette:	Product:	Own conventional cigarette brand
	ISO nicotine Content:	Maximum yield of 1 mg per CC as labeled on the cigarette package

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	Use: Manufacturer:	Single use Commercially available non-mentholated conventional cigarettes in Japan
Nicotine Gum:	Product Nicotine content: Use: Manufacturer:	Nicorette® 2 mg Single use Johnson and Johnson

Duration of use:	One inhalation experience of THS 2.2 consisted of one THS 2.2 heatstick. One inhalation experience of CC consisted of one cigarette. One NRT gum was slowly chewed for 35 ± 5 minutes while spacing each chew. Each sampling period (Day 1 and Day 3) had a washout period (nicotine abstinence) of at least 24 hours prior to product use (Day 0 and Day 2).
Blood sampling points:	*Pharmacokinetics:* On Days 1 and 3, 16 blood samples were collected in blood with the first sample (T0) being drawn within 15 minutes prior to the single use and further samples taken (relative to T0, the time of first puff) after 2 (T1), 4 (T2), 6 (T3), 8 (T4), 10 (T5), 15 (T6), 30 (T7), 45 (T8), 60 (T9) minutes, T10 after 2 hours, 4 (T11), 6 (T12), 9 (T13), 12 (T14) and after 24 hours (T15) after T0. Plasma samples were used for bioanalysis. For NRT on Day 1 and Day 3 only: 16 blood samples were collected in blood with the first sample (T0) being drawn within 15 minutes prior to the single use and further samples taken (relative to T0, the time of first puff) after 10 (T1), 20 (T2), 25 (T3), 30 (T4), 35 (T5), 40 (T6), 45 (T7), 60 (T8) minutes, T9 after 2 hours, 3 (T10), 4 (T11), 6 (T12), 9 (T13), 12 (T14) and after 24 hours (T15) after T0.
Questionnaires:	*Pharmacodynamics (subjective effects) :* On Days 1 and 3, the QSU questionnaire was self-administered within 15 minutes prior to T0, then 15, 30, 45, 60 minutes, 2, 4, 6, 9 and 12 hours after T0. For subjects on NRT gum: within 15 minutes prior to T0, then 20, 30, 45, 60 minutes, 2, 4, 6, 9 and 12 hours after T0. The MCEQ was filled out by the subjects who used the THS 2.2 or smoked mCC only, on Days 1 and 3, between 8:00 and 11:00 PM.

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Analytical Method:	• Method:	LC-MS/MS
	• Specificity: retention	No significant interference at the time and mass transition of nicotine
	• Linearity (R^2)	0.9969
	• Accuracy:	
	Intra-batch:	-2.8 to 12.0%
	Inter-batch :	-0.9 to 5.5%
	• Precision:	
	Intra-batch (repeatability):	0.9 to 7.1%
	Inter-batch (intermediate precision):	2.6 to 6.2%
	• Calibration range:	0.200 to 10.0 ng/mL
	• Lower limit of quantification (LLOQ):	0.200 ng/mL

6.2.1.2.2.1 Safety

Adverse events, assessments of physical condition, vital signs and body measurements, spirometry, respiratory symptoms, electrocardiogram, and monitoring of laboratory values.

6.2.1.2.2.2 Statistical methods

6.2.1.2.2.2.1 Pharmacokinetics

- Analysis of variance (ANOVA) on natural log-transformed values for $AUC_{0\rightarrow last}$, and C_{max}, including terms for sequence, subjects nested within sequence, period, and product as fixed-effect factors. Adjusted geometric least square (LS) mean ratios and 95% confidence intervals (CIs) were calculated.
- Hodges–Lehmann estimates with 95% CIs were calculated for the median differences between THS 2.2 and CCs for t_{max}

6.2.1.2.2.2.2 Pharmacodynamics (Subjective Effects)

The mean QSU-Brief scores and MCEQ sub-scales were calculated at each measurement time, and were compared using a mixed-effects model including terms for product, sequence, period, and subject nested within sequence as a random effect. The repeated measurements model for QSU-brief analysis also included terms for time and product*time accounting for the all post exposure assessment time-points. Adjusted LS mean differences and 95% CIs were calculated.

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6.2.1.2.2.3 Results

6.2.1.2.2.3.1 Pharmacokinetics

Group-1 (THS/CC)

Table 10 THS 2.2 Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	23.75	28.03	16.470	5.3; 70.6	22.07
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	26.07	30.70	18.012	6.2; 80.1	23.76
C_{max} [ng/mL]	14.30	18.19	12.358	3.4; 46.1	15.90

The median t_{max} was 6.00 minutes (min; max: 3.5; 30.0).

Data Source: Appendix 15, Table 15.2.4.5 ZRHR-PK-02-JP

Table 11 Conventional Cigarette Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	24.66	29.89	19.884	8.6; 110.7	27.02
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	26.81	32.59	21.873	9.5; 121.7	28.43
C_{max} [ng/mL]	13.82	17.57	11.595	4.2; 45.5	14.35

The median t_{max} was 6.00 minutes (min; max: 3.4; 29.5).

Data Source: Appendix 15, Table 15.2.4.5 ZRHR-PK-02-JP

Table 12 THS 2.2:CC Ratios of Geometric LS Means

Variable	Product Exposure	N	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2:CC) (%)	CV (%)	95% CI
$AUC_{0\rightarrow last}$ [ng•h/mL]	THS 2.2	42	23.75	96.34	28.68	85.10; 109.07
	CC	42	24.66			
C_{max} [ng/mL]	THS 2.2	42	14.30	103.50	47.14	84.94; 126.11
	CC	42	13.82			

Data Source: Appendix 15, Table 15.2.3.1 ZRHR-PK-02-JP

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Group-2 (THS/Gum)

Table 13 THS 2.2 Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	18.92	25.12	17.748	4.3; 64.8	24.61
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	23.99	30.29	19.813	6.8; 70.5	27.15
C_{max} [ng/mL]	11.53	17.01	13.066	0.7; 50.2	13.40

The median t_{max} was 6.00 minutes (min; max: 3.4; 29.5).

Data Source: Appendix 15, Table 15.2.4.5 ZRHR-PK-02-JP

Table 14 Gum Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	14.88	16.03	6.991	9.4; 35.3	13.54
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	17.66	19.16	8.718	11.2; 39.9	15.54
C_{max} [ng/mL]	4.80	5.36	2.886	2.0; 13.9	4.51

The median t_{max} was 35.38 minutes (min; max: 25.0; 60.0).

Data Source: Appendix 15, Table 15.2.4.5 ZRHR-PK-02-JP

Table 15 THS 2.2:Gum Ratios of Geometric LS Means

Variable	Product Exposure	N	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2:Gum) (%)	CV (%)	95% CI
$AUC_{0\rightarrow last}$ [ng•h/mL]	THS 2.2	18	18.92	127.15	80.22	77.26; 209.24
	Gum	18	14.88			
C_{max} [ng/mL]	THS 2.2	18	11.53	240.23	105.08	130.60; 441.90
	Gum	18	4.80			

Data Source: Appendix 15, Table 15.2.4.2 ZRHR-PK-02-JP

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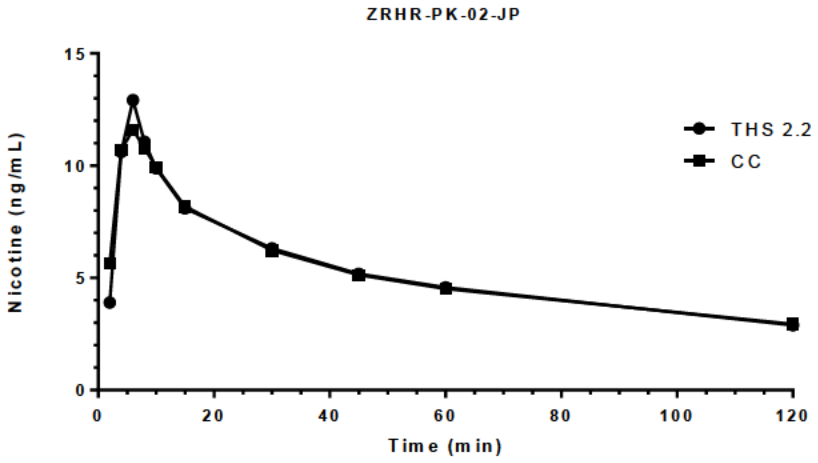


Figure 7 Geometric Means (n=42) of Plasma Concentrations of Nicotine After Single Use of THS 2.2 and CC

Data Source: Appendix 15, Figure 15.1.2.1.1 ZRHR-PK-02-JP

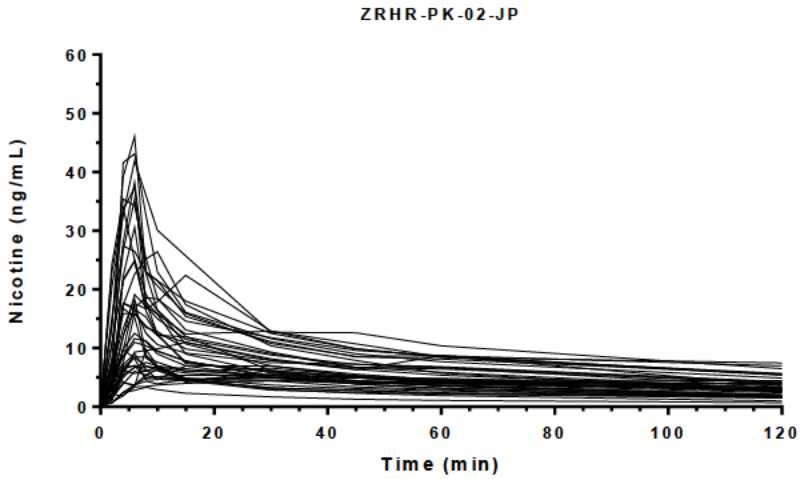


Figure 8 Individual Plasma Concentrations (N=42) of Nicotine After Single Use of THS 2.2

Data Source: Appendix 15, Listing 15.3.3.2 ZRHR-PK-02-JP

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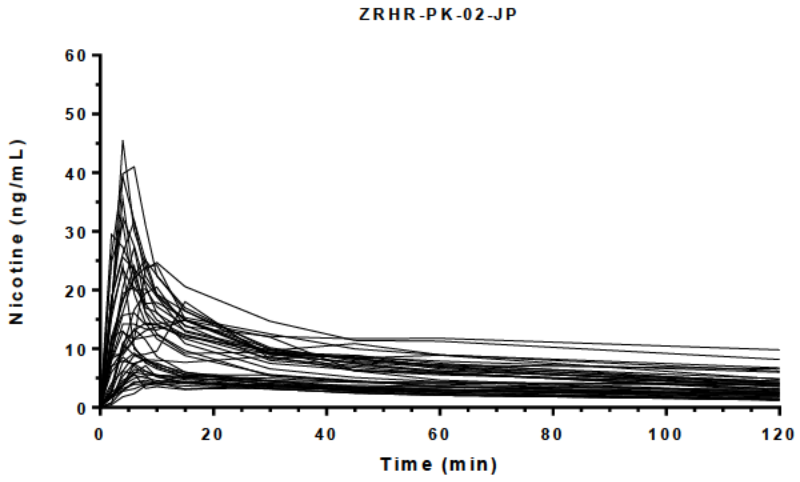


Figure 9 Individual Plasma Concentrations (N=43) of Nicotine After Single Use of CC

Data Source: Appendix 15, Listing 15.3.3.2 ZRHR-PK-02-JP

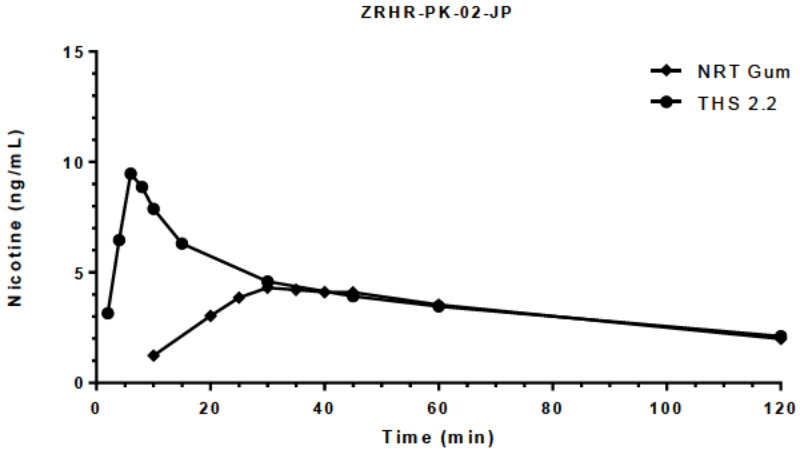


Figure 10 Geometric Means (n=18) of Plasma Concentrations of Nicotine After Single Use of THS 2.2 and NRT Gum

Data Source: Appendix 15, Figure 15.1.2.1.2 ZRHR-PK-02-JP

6.2.1.2.2.3.2 Conclusion

- In this study it has been demonstrated that the rate and the amount of nicotine absorbed, as assessed by C_{max}, $AUC_{(0\rightarrow last)}$ and $AUC_{(0\rightarrow\infty)}$, were all comparable following THS 2.2 single use when compared to CC single use. The t_{max} values obtained were also comparable following THS 2.2 and CC single use.
- This study demonstrated that nicotine absorption was higher and faster following THS 2.2 compared to NRT gum.

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6.2.1.2.2.3.3 Pharmacodynamics (Subjective Effects)

Group-1 (THS/CC)

Table 16 Analysis of Urge-to-Smoke After Single Use – THS 2.2 vs CC (QSU-b Total Score)

QSU-b	Product Exposure	LS Mean	THS 2.2 - CC LS Mean Difference	LS Mean Difference 95% CI
Total Score	THS 2.2	3.24	0.04	-0.70; 0.79
	CC	3.19		

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model. QSU-brief total score items are rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores indicate a higher urge-to-smoke.

Data Source: Appendix 15, Table 15.2.4.12 ZRHR-PK-02-JP

Group-2 (THS/Gum)

Table 17 Analysis of Urge-to-Smoke After Single Use – THS 2.2 vs Gum (QSU-b Total Score)

QSU-b	Product Exposure	LS Mean	THS 2.2 - Gum LS Mean Difference	LS Mean Difference 95% CI
Total Score	THS 2.2	3.00	-0.20	-0.87; 0.48
	Gum	3.20		

Data Source: Appendix 15, Table 15.2.4.12 ZRHR-PK-02-JP

Group-1 (THS/CC)

Table 18 Analysis of MCEQ After Single Use – THS 2.2 vs CC

MCEQ Sub-Scale Domain	Product Exposure	LS Mean	THS 2.2 - CC LS Mean Difference	LS Mean Difference 95% CI
Aversion	THS 2.2	3.11	0.35	-0.12; 0.81
	CC	2.76		
Craving reduction	THS 2.2	3.67	-0.31	-0.88; 0.27
	CC	3.98		

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Enjoyment of respiratory tract sensation	THS 2.2	3.10	-0.64	-1.21; -0.08
	CC	3.74		
Psychological reward	THS 2.2	2.70	-0.47	-0.72; -0.23
	CC	3.17		
Smoking satisfaction	THS 2.2	2.91	-1.29	-1.71; -0.87
	CC	4.20		

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model.

Data Source: Appendix 15, Table 15.2.4.15 ZRHR-PK-02-JP

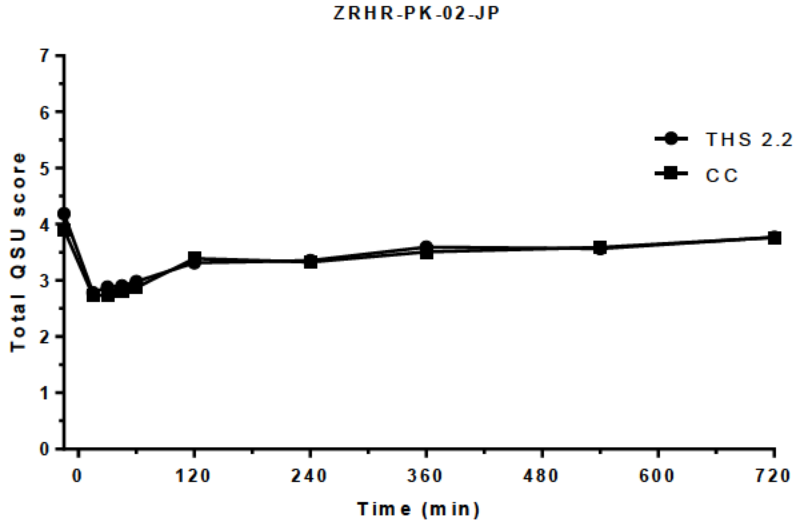


Figure 11 Arithmetic Means of Total Scores for QSU-brief During Single Use of THS 2.2 and CC

Data Source: Appendix 15, Figure 15.1.2.10.1 ZRHR-PK-02-JP

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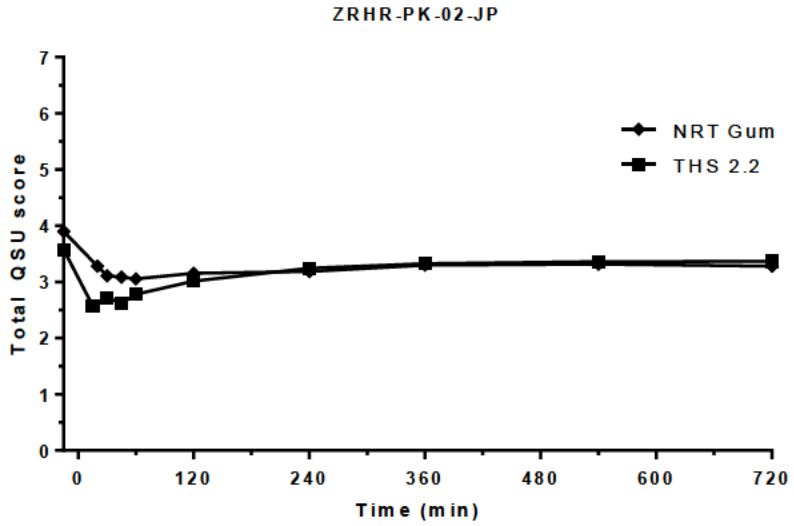


Figure 12 Arithmetic Means of Total Scores for QSU-brief During Single Use of THS 2.2 and NRT Gum

Data Source: Appendix 15, Figure 15.1.2.10.2 ZRHR-PK-02-JP

6.2.1.2.2.3.4 Conclusion

- THS 2.2 decreased the urge-to-smoke in a comparable fashion to CC single use, with no notable difference between the two products at any time point.
- THS 2.2 use decreased the urge-to-smoke more than NRT gum use, particularly for the first 2 hours post-product use.
- 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 two 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.
- THS 2.2 use reduced craving faster than NRT gum, but the overall time profile showed no notable difference in urge-to-smoke between THS 2.2 and NRT gum use.

6.2.1.2.2.4 Safety Findings

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

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 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.

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6.2.1.2.3 ZRHM-PK-05-JP

Study ZRHM-PK-05-JP	**Source: Section 7.3.1, Clinical Study Report ZRHM-PK-05-JP**

Title of the study:

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

Protocol-No.: ZRHM-PK-05-JP		
Date of final report: 12 May 2015		
Investigators:	Principal Investigator: F. Nobuoka, MD	
Study center:	Ageo Medical Clinic, 3133 Haraichi, Ageo City, Saitama 362-0021, Japan	
Time of clinical part:	August 2013 - November 2013	**Clinical Phase:** I (Product Performance)

Objective:

The purpose of this clinical study was to compare the profile of nicotine uptake (rate and amount of nicotine absorbed) after single use of switching from menthol conventional cigarettes (mCC) to THS 2.2 Menthol and mCC in smoking Japanese healthy subjects. THS 2.2 Menthol was also compared with the nicotine replacement therapy (NRT) gum.

Study design:

- Single center
- Single use
- Randomized
- Cross-over
- Open-label
- Two-way, four sequences
- At least a 24-hour nicotine wash-out (nicotine abstinence)

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Subjects:

- Planned: 62
- Enrolled: 73
- Randomized: 62
- Discontinuations: 1
- Data set for safety analysis: 73
- Group-1 (THS 2.2 Menthol / mCC) data set for PK analysis: 43
- Group-2 (THS 2.2 Menthol / NRT) data set for PK analysis: 18

Main criteria for inclusion:

- Male or female Japanese from 23 to 65 years of age and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening.
- Subjects were smoking at least 10 commercially available menthol CC (mCC) per day 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, and did not plan to quit smoking in the following 3 months. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
- Female subjects of child-bearing potential should had confirmed negative pregnancy test at enrollment and used effective methods of contraception without estrogen.
- Subjects had a body mass index between 18.5 and 32.0 (kg/m^2).
- Spirometry evaluation had to show forced expiratory volume in 1 second {FEV1}/forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV1 >80% predicted value, and post-bronchodilator FVC >0.8.
- Provide written informed consent prior to study participation.
- Able to communicate well with the investigator and comply with the requirements of the study.

THS 2.2:	Product:	Cigarette batch number of THS 2.2 Menthol Tobacco Sticks: B-05775 Production date: 12 June 2013. Expiry date: 11 January 2014
	ISO nicotine Content:	0.5 mg
	Use:	Single use
	Manufacturer:	PMI

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Conventional Cigarette Menthol:	Product: ISO nicotine Content: Use: Manufacturer:	Own menthol conventional cigarette brand Maximum yield of 1 mg per mCC as labeled on the cigarette package. Single use Commercially available mCC in Japan
Nicotine Gum:	Product: Nicotine content: Use: Manufacturer:	Nicorette® 2 mg Single use Johnson and Johnson

Duration of use:	One inhalation experience of THS 2.2 Menthol consisted of one THS 2.2 Menthol heatstick. One inhalation experience of mCC consisted of one cigarette. One NRT gum was slowly chewed for 35 ± 5 minutes while spacing each chew. Each sampling period (Day 1 and Day 3) had a washout period (nicotine abstinence) of at least 24 hours prior to product use (Day 0 and Day 2).
Blood sampling points:	*Pharmacokinetics* On Days 1 and 3, 16 blood samples were collected in blood with the first sample (T0) being drawn within 15 minutes prior to the single use and further samples taken (relative to T0, the time of first puff) after 2 (T1), 4 (T2), 6 (T3), 8 (T4), 10 (T5), 15 (T6), 30 (T7), 45 (T8), 60 (T9) minutes, T10 after 2 hours, 4 (T11), 6 (T12), 9 (T13), 12 (T14) and after 24 hours (T15) after T0. Plasma samples were used for bioanalysis. For NRT on Day 1 and Day 3 only: 16 blood samples were collected in blood with the first sample (T0) being drawn within 15 minutes prior to the single use and further samples taken (relative to T0, the time of first puff) after 10 (T1), 20 (T2), 25 (T3), 30 (T4), 35 (T5), 40 (T6), 45 (T7), 60 (T8) minutes, T9 after 2 hours, 3 (T10), 4 (T11), 6 (T12), 9 (T13), 12 (T14) and after 24 hours (T15) after T0.
Questionnaires:	*Pharmacodynamics (subjective effects) :* On Days 1 and 3, the QSU questionnaire was self-administered within 15 minutes prior to T0, then 15, 30, 45, 60 minutes, 2, 4, 6, 9 and 12 hours after T0. For subjects on NRT gum: within 15 minutes prior to T0, then 20, 30, 45, 60 minutes, 2, 4, 6, 9 and 12 hours after T0. The MCEQ was filled out by the subjects who used the THS 2.2 Menthol or smoked mCC only, on Day 1 and 3, between 8:00 and 11:00 PM.

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Analytical Method:	• Method: LC-MS/MS • Specificity: retention: No significant interference at the time and mass transition of nicotine • Linearity (R^2): 0.9973 • Accuracy: Intra-batch: -2.8 to 12.0% Inter-batch : -0.9 to 5.5% • Precision: Intra-batch (repeatability): 0.9 to 7.1% Inter-batch (intermediate precision): 2.6 to 6.2% • Calibration range: 0.200 to 10.0 ng/mL • Lower limit of quantification (LLOQ): 0.200 ng/mL

6.2.1.2.3.1 Safety

Adverse events, assessments of physical condition, vital signs and body measurements, spirometry, respiratory symptoms, electrocardiogram, and monitoring of laboratory values.

6.2.1.2.3.2 Statistical Methods

6.2.1.2.3.2.1 Pharmacokinetics

- Analysis of variance (ANOVA) on natural log-transformed values for $AUC_{0\rightarrow last}$, and C_{max}, including terms for sequence, subjects nested within sequence, period, and product as fixed-effect factors. Adjusted geometric least square (LS) mean ratios and 95% confidence intervals (CIs) were calculated.
- Hodges–Lehmann estimates with 95% CIs were calculated for the median differences between THS 2.2 Menthol and mCCs for t_{max}

6.2.1.2.3.2.2 Pharmacodynamics (Subjective Effects)

The mean QSU-Brief scores and MCEQ sub-scales were calculated at each measurement time, and were compared using a mixed-effects model including terms for product, sequence, period, and subject nested within sequence as a random effect. The repeated measurements model for QSU-brief analysis also included terms for time and product*time accounting for the all post exposure assessment time-points. Adjusted LS mean differences and 95% CIs were calculated.

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6.2.1.2.3.3 Results

6.2.1.2.3.3.1 Pharmacokinetics

Group-1 (THS Menthol/mCC)

Table 19 THS 2.2 Menthol Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	23.84	33.12	26.797	1.2; 117.7	21.53
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	26.03	33.81	25.607	5.7; 111.0	22.91
C_{max} [ng/mL]	10.65	14.38	9.996	0.4; 43.8	12.70

The median t_{max} was 6.00 minutes (min; max: 4.0; 720.0).

Data Source: Appendix 15, Table 15.2.4.5 ZRHM-PK-05-JP

Table 20 Menthol Conventional Cigarette Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	24.50	31.21	22.622	4.9; 100.9	24.46
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	26.97	34.82	25.973	5.4; 117.1	27.31
C_{max} [ng/mL]	12.12	15.63	11.349	2.3; 58.1	12.20

The median t_{max} was 6.00 minutes (min; max: 4.0; 30.0).

Data Source: Appendix 15, Table 15.2.4.5 ZRHM-PK-05-JP

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Table 21 THS 2.2 Menthol:mCC Ratios of Geometric LS Means

Variable	Product Exposure	N	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2 Menthol:mCC) (%)	CV (%)	95% CI
$AUC_{0\rightarrow last}$ [ng•h/mL]	THS 2.2 Menthol	43	23.99	98.13	47.55	80.61; 119.46
	mCC	43	24.45			
C_{max} [ng/mL]	THS 2.2 Menthol	43	10.70	88.47	63.54	68.64; 114.03
	mCC	43	12.09			

Data Source: Appendix 15, Table 15.2.3.1 ZRHM-PK-05-JP

Group 2 (THS Menthol/Gum)

Table 22 THS 2.2 Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	15.61	19.41	13.557	3.9; 48.3	16.02
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	16.78	20.94	15.235	4.9; 53.3	15.50
C_{max} [ng/mL]	7.64	10.92	10.568	1.3; 45.8	8.29

The median t_{max} was 8.00 minutes (min; max: 4.0; 30.0).

Data Source: Appendix 15, Table 15.2.4.5 ZRHM-PK-05-JP

Table 23 Gum Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	27.94	34.15	23.041	9.6; 86.4	25.44
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	29.71	36.78	25.574	11.0; 91.7	27.55
C_{max} [ng/mL]	7.52	8.76	6.702	2.7; 34.1	7.36

The median t_{max} was 45.00 minutes (min; max: 25.0; 60.0).

Data Source: Appendix 15, Table 15.2.4.5 ZRHM-PK-05-JP

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Table 24 THS 2.2 Menthol:Nicotine Gum Ratios of Geometric LS Means

Variable	Product Exposure	N	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2 Menthol:Gum) (%)	CV (%)	95% CI
$AUC_{0\rightarrow last}$ [ng•h/mL]	THS 2.2 Menthol	18	15.61	55.87	57.19	38.36; 81.36
	Gum	18	27.94			
C_{max} [ng/mL]	THS 2.2 Menthol	18	7.64	101.63	78.75	62.21; 166.04
	Gum	18	7.52			

Data Source: Appendix 15, Table 15.2.4.2 ZRHM-PK-05-JP

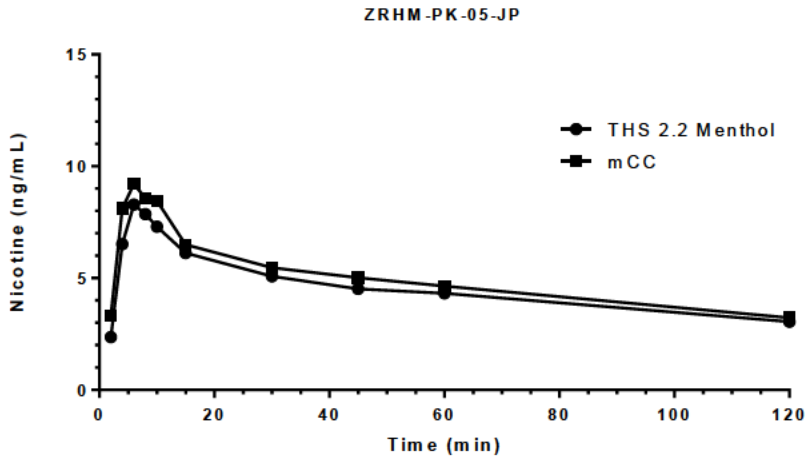


Figure 13 Geometric Means (n=43) of Plasma Concentrations of Nicotine After Single Use of THS 2.2 Menthol and mCC

Data Source: Appendix 15, Figure 15.1.2.1.1 ZRHM-PK-05-JP

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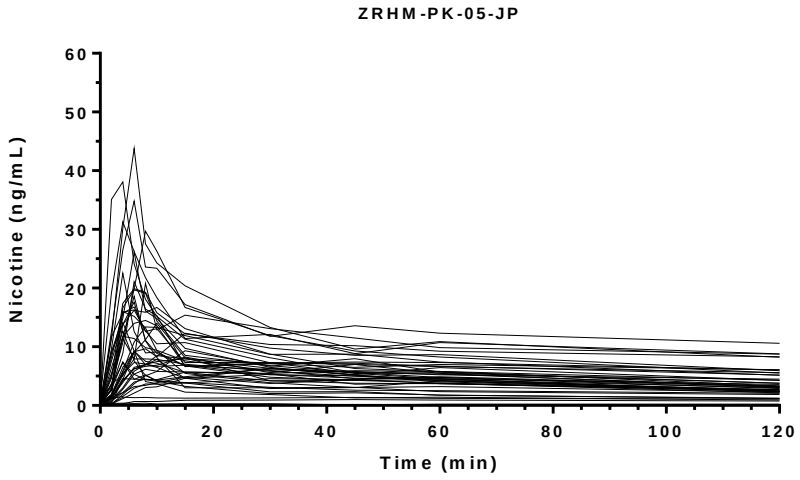


Figure 14 Individual Plasma Concentrations (N=44) of Nicotine After Single Use of THS 2.2 Menthol

Data Source: Appendix 15, Listing 15.3.3.2 ZRHM-PK-05-JP

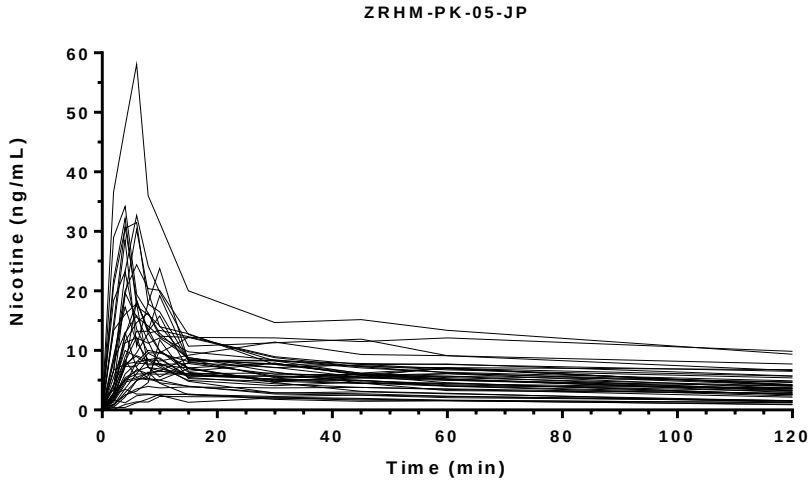


Figure 15 Individual Plasma Concentrations (N=43) of Nicotine after Single Use of mCC

Data Source: Appendix 15, Listing 15.3.3.2 ZRHM-PK-05-JP

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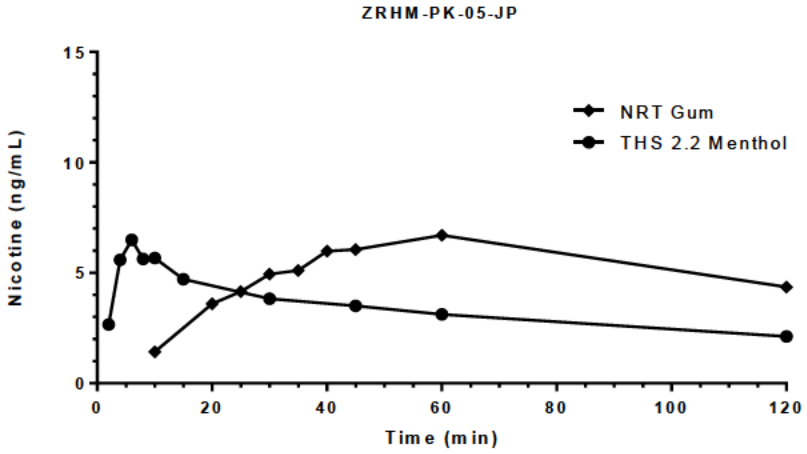


Figure 16 Geometric Means (n=18) of Plasma Concentrations of Nicotine After Single Use of THS 2.2 Menthol and NRT Gum

Data Source: Appendix 15, Figure 15.1.2.1.2 ZRHM-PK-05-JP

6.2.1.2.3.3.2 Conclusion

- 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 two products. The results for mCC were consistent with what has previously been reported in the literature.
- This study demonstrated that nicotine was absorbed more rapidly following THS 2.2 Menthol compared to NRT gum.

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6.2.1.2.3.3.3 Pharmacodynamics (Subjective Effects)

Group-1 (THS menthol/mCC)

Table 25 Analysis of Urge-to-Smoke After Single Use – THS 2.2 Menthol vs mCC (QSU-b Total Score)

QSU-b	Product Exposure	LS Mean	THS 2.2 Menthol - mCC LS Mean Difference	LS Mean Difference 95% CI
Total Score	THS 2.2 Menthol	3.36	-0.28	-0.79; 0.22
	mCC	3.64		

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model. QSU-brief total score items are rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores indicate a higher urge-to-smoke.

Data Source: Appendix 15, Table 15.2.4.12 ZRHM-PK-05-JP

Group 2 (THS Menthol/Gum)

Table 26 Analysis of Urge-to-Smoke After Single Use – THS 2.2 Menthol vs Gum (QSU-b Total Score)

QSU-b	Product Exposure	LS Mean	THS 2.2 Menthol - Gum LS Mean Difference	LS Mean Difference 95% CI
Total Score	THS 2.2 Menthol	3.33	-0.34	-0.87; 0.19
	Gum	3.66		

Data Source: Appendix 15, Table 15.2.4.12 ZRHM-PK-05-JP

Group-1 (THS menthol/mCC)

Table 27 Analysis of MCEQ After Single Use – THS 2.2 Menthol vs mCC

MCEQ Sub-Scale Domain	Product Exposure	LS Mean	THS 2.2 Menthol - mCC LS Mean Difference	LS Mean Difference 95% CI
Aversion	THS 2.2 Menthol	2.37	-0.10	-0.60; 0.41
	mCC	2.46		
Craving reduction	THS 2.2 Menthol	3.30	-0.14	-0.54; 0.26
	mCC	3.44		

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Enjoyment of respiratory tract sensation	THS 2.2 Menthol	3.34	-0.59	-1.05; -0.14
	mCC	3.94		
Psychological reward	THS 2.2 Menthol	2.77	-0.19	-0.40; 0.03
	mCC	2.96		
Smoking satisfaction	THS 2.2 Menthol	3.19	-1.12	-1.53; -0.72
	mCC	4.31		

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model.

Data Source: Appendix 15, Table 15.2.4.15 ZRHM-PK-05-JP

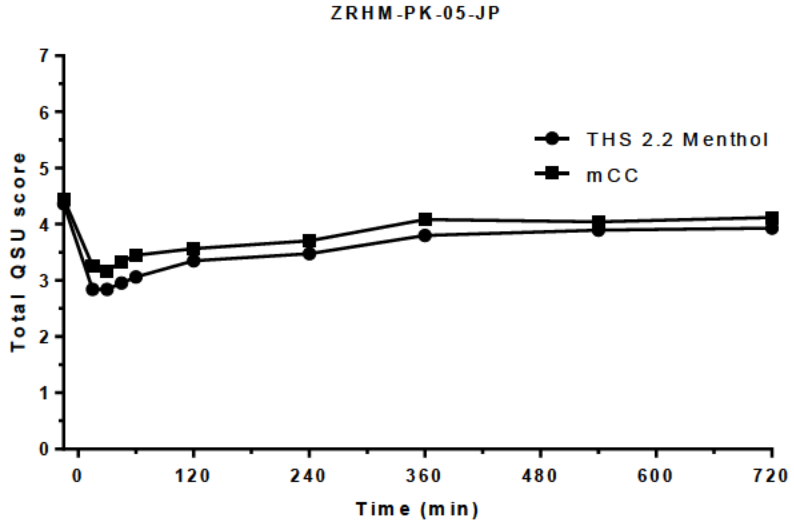


Figure 17 Arithmetic Means of Total Scores for QSU-brief During Single Use of THS 2.2 Menthol and mCC

Data Source: Appendix 15, Figure 15.1.2.10.1 ZRHM-PK-05-JP

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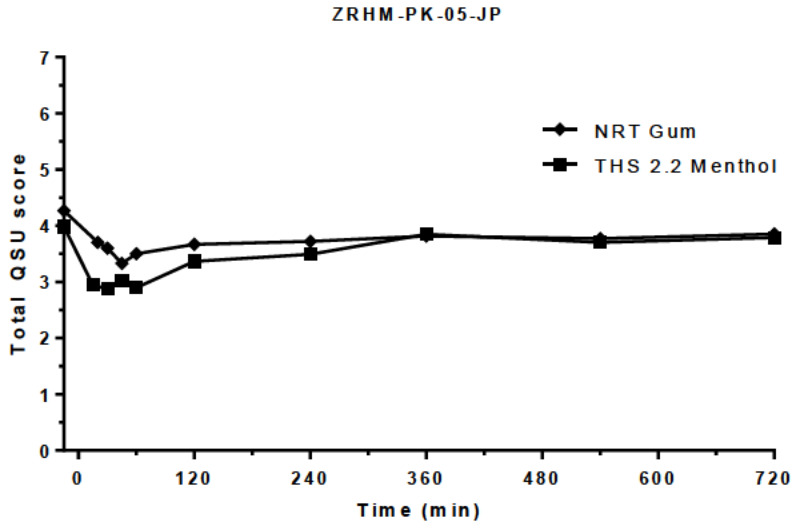


Figure 18 Arithmetic Means of Total Scores for QSU-brief During Single Use of THS 2.2 Menthol and NRT Gum

Data Source: Appendix 15, Figure 15.1.2.10.2 ZRHM-PK-05-JP

6.2.1.2.3.3.4 Conclusion

- 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.
- 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.

MCEQ subscales 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 two products in aversion and psychological reward.

6.2.1.2.3.4 Safety Findings

There were no SAEs or severe AEs reported in this study and no subjects discontinued from the study due to an AE. No AEs were assessed as being related to investigational product (THS 2.2 Menthol or mCC), NRT gum, or study procedures.

There were 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 adverse event.

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6.2.1.2.4 ZRHM-PK-06-US

Study ZRHM-PK-06-US	**Source: Section 7.3.1, Clinical Study Report ZRHM-PK-06-US**

Title of the study:

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

Protocol-No.: ZRHM-PK-06-US		
Date of final report: 15 February 2016		
Investigators:	Principal Investigator: J. Borders, MD	
Study center:	CKRA, 3475 Richmond Road, Third Floor, Lexington, KY 40509 USA	
Time of clinical part:	October - December 2013	**Clinical Phase:** I (Product Performance)

Objective:

The purpose of this clinical study was to compare the profile of nicotine uptake (rate and extent of nicotine absorbed) after single use of THS 2.2 Menthol and mCC in healthy smokers. THS 2.2 Menthol was also to be compared with the nicotine nasal spray (NNS) product, used as a reference point.

Study design:

- Single center
- Single use
- Randomized
- Cross-over
- Open-label
- Two-way, four sequences
- At least a 24-hour nicotine wash-out (nicotine abstinence)

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Subjects:

- Planned: 62
- Enrolled: 64
- Randomized: 62
- Discontinuations: 3
- Data set for safety analysis: 64
- Group-1 (THS 2.2 Menthol / mCC) data set for PK analysis: 41
- Group-2 (THS 2.2 Menthol / NRT) data set for PK analysis: 17

Main criteria for inclusion:

- Male or female smokers from 22 to 65 years of age and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening.
- Subjects were smoking at least 10 commercially available menthol CC (mCC) per day for the last 4 weeks, and did not plan to quit smoking in the following 3 months. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
- Female subjects of child-bearing potential should had confirmed negative pregnancy test at enrollment and used effective methods of contraception without estrogen.
- Subjects had a body mass index between 18.5 and 35.0 (kg/m^2).
- Spirometry evaluation had to show forced expiratory volume in 1 second {FEV1}/forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV1 >80% predicted value, and post-bronchodilator FVC >0.8.
- Provide written informed consent prior to study participation.
- Able to communicate well with the investigator and comply with the requirements of the study.

THS 2.2:	Product:	Cigarette batch number of THS Menthol Tobacco Sticks: B 06238 Production date: 04 July 2013. Expiry date: 03 February 2014
	ISO nicotine Content:	0.5 mg
	Use:	Single use
	Manufacturer:	PMI

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Conventional Cigarette Menthol:	Product: ISO nicotine Content: Use: Manufacturer:	Own menthol conventional cigarette brand No restrictions Single use Commercially available mCC in USA (restricted list of brands)
Nicotine Nasal Spray:	Product: Nicotine content: Use: Manufacturer:	Nicotrol® NS 10 mg/ml Single use (1 spray per nostril) Pfizer inc

Duration of use:	One inhalation experience of THS 2.2 Menthol consisted of one THS 2.2 Menthol heatstick. One inhalation experience of mCC consisted of one cigarette. For NNS, one spray per nostril per product use. Each sampling period (Day 1 and Day 3) had a washout period (nicotine abstinence) of at least 24 hours prior to product use (Day 0 and Day 2).
Blood sampling points:	*Pharmacokinetics:* On Days 1 and 3, 16 blood samples were collected in blood with the first sample (T0) being drawn within 15 minutes prior to the single use and further samples taken (relative to T0, the time of first puff) after 2 (T1), 4 (T2), 6 (T3), 8 (T4), 10 (T5), 15 (T6), 30 (T7), 45 (T8), 60 (T9) minutes, T10 after 2 hours, 4 (T11), 6 (T12), 9 (T13), 12 (T14) and after 24 hours (T15) after T0. Plasma samples were used for bioanalysis.
Questionnaires:	*Pharmacodynamics (subjective effects) :* On Days 1 and 3, the QSU questionnaire was self-administered within 15 minutes prior to T0, then 15, 30, 45, 60 minutes, 2, 4, 6, 9 and 12 hours after T0. The MCEQ was filled out by the subjects who used the THS 2.2 Menthol or smoked mCC only, on Days 1 and 3, between 8:00 and 11:00 PM.

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Analytical Method:	• Method:	LC-MS/MS
	• Specificity: retention	No significant interference at the time and mass transition of nicotine
	• Linearity (R^2)	0.9963
	• Accuracy:	
	Intra-batch:	-2.8 to 12.0%
	Inter-batch :	-0.9 to 5.5%
	• Precision:	
	Intra-batch (repeatability):	0.9 to 7.1%
	Inter-batch (intermediate precision):	2.6 to 6.2%
	• Calibration range:	0.200 to 10.0 ng/mL
	• Lower limit of quantification (LLOQ):	0.200 ng/mL

6.2.1.2.4.1 Safety

Adverse events, assessments of physical condition, vital signs and body measurements, spirometry, respiratory symptoms, electrocardiogram, and monitoring of laboratory values.

6.2.1.2.4.2 Statistical Methods

6.2.1.2.4.2.1 Pharmacokinetics

- Analysis of variance (ANOVA) on natural log-transformed values for $AUC_{0\rightarrow last}$, and C_{max}, including terms for sequence, subjects nested within sequence, period, and product as fixed-effect factors. Adjusted geometric least square (LS) mean ratios and 95% confidence intervals (CIs) were calculated.
- Hodges–Lehmann estimates with 95% CIs were calculated for the median differences between THS 2.2 Menthol and mCCs for t_{max}

6.2.1.2.4.2.2 Pharmacodynamics (Subjective Effects)

The mean QSU-Brief scores and MCEQ sub-scales were calculated at each measurement time, and were compared using a mixed-effects model including terms for product, sequence, period, and subject nested within sequence as a random effect. The repeated measurements model for QSU-brief analysis also included terms for time and product*time accounting for the all post exposure assessment time-points. Adjusted LS mean differences and 95% CIs were calculated.

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6.2.1.2.4.3 Results

6.2.1.2.4.3.1 Pharmacokinetics

Group-1 (THS Menthol/mCC)

Table 28 THS 2.2 Menthol Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	16.56	23.21	20.315	1.3; 105.9	20.01
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	17.74	22.12	15.332	2.6; 78.9	20.41
C_{max} [ng/mL]	7.39	9.66	6.578	0.5; 29.1	8.55

The median t_{max} was 6.70 minutes (min; max: 2.5; 540.1).

Data Source: Appendix 15, Table 15.2.4.5 ZRHM-PK-06-US

Table 29 Menthol Conventional Cigarette Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	29.47	41.86	41.574	0.4; 265.8	32.47
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	37.94	42.54	21.151	11.8; 119.9	42.77
C_{max} [ng/mL]	13.02	16.63	10.720	0.6; 47.2	13.00

The median t_{max} was 10.10 minutes (min; max: 4.3; 720.3).

Data Source: Appendix 15, Table 15.2.4.5 ZRHM-PK-06-US

Table 30 THS 2.2 Menthol:mCC Ratios of Geometric LS Means

Variable	Product Exposure	N	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2 Menthol:mCC) (%)	CV (%)	95% CI
$AUC_{0\rightarrow last}$ [ng•h/mL]	THS 2.2 Menthol	41	16.53	55.64	60.83	43.30; 71.50
	mCC	41	29.71			
C_{max} [ng/mL]	THS 2.2 Menthol	41	7.40	56.57	59.62	44.21; 72.39
	mCC	41	13.08			

Data Source: Appendix 15, Table 15.2.3.1 ZRHM-PK-06-US

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Group-2 (THS Mnethol/NNS)

Table 31 THS 2.2 Menthol Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	15.87	22.18	19.201	2.2; 79.3	18.89
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	14.21	17.60	10.191	2.9; 41.7	20.28
C_{max} [ng/mL]	8.50	10.79	8.229	2.7; 34.7	8.84

The median t_{max} was 8.92 minutes (min; max: 2.4; 15.8).

Data Source: Appendix 15, Table 15.2.4.5 ZRHM-PK-06-US

Table 32 NNS Descriptive Statistics of Pharmacokinetic Parameters of Nicotine

Variable	Geom. Mean	Arith. Mean	Std. Dev.	Range	Median
$AUC_{0\rightarrow last}$ [ng•h/mL]	8.61	10.22	6.299	2.1; 25.0	7.73
$AUC_{0\rightarrow\infty}$ [ng•h/mL]	11.34	13.64	9.596	6.0; 33.6	8.78
C_{max} [ng/mL]	3.24	3.98	2.922	0.8; 12.7	3.02

The median tmax was 8.05 minutes (min; max: 2.9; 60.1).

Data Source: Appendix 15, Table 15.2.4.5 ZRHM-PK-06-US

Table 33 THS 2.2 Menthol:NNS Ratios of Geometric LS Means

Variable	Product Exposure	N	Geometric LS Mean	Geometric LS Means Ratio (THS 2.2 Menthol:NNS) (%)	CV (%)	95% CI
$AUC_{0\rightarrow last}$ [ng•h/mL]	THS 2.2 Menthol	17	15.59	178.78	80.66	106.45; 300.25
	NNS	17	8.72			
C_{max} [ng/mL]	THS 2.2 Menthol	17	8.40	259.75	65.18	168.00; 401.60
	NNS	17	3.23			

Data Source: Appendix 15, Table 15.2.4.2 ZRHM-PK-06-US

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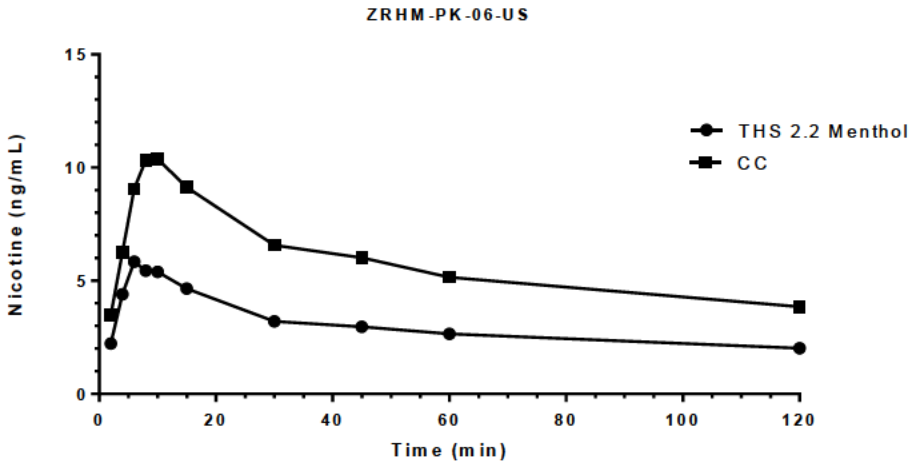


Figure 19 Geometric Means (n=41) of Plasma Concentrations of Nicotine After Single Use of THS 2.2 Menthol and mCC

Data Source: Appendix 15, Figure 15.1.2.1.1 ZRHM-PK-06-US

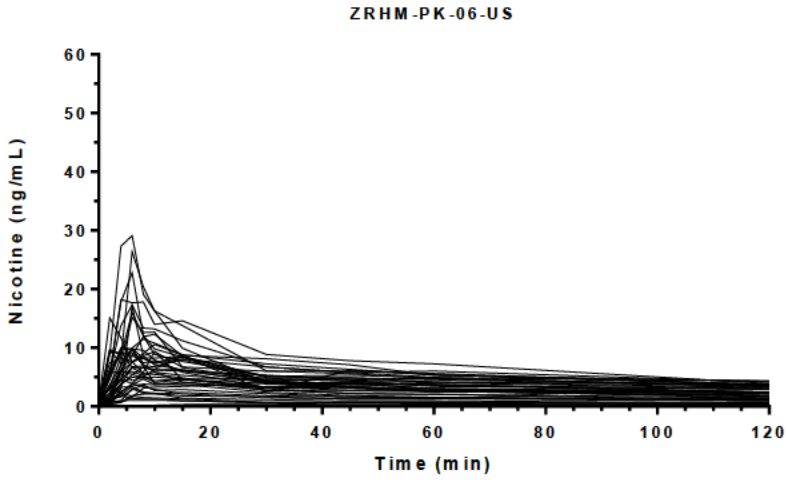


Figure 20 Individual Plasma Concentrations (N=41) of Nicotine After Single Use of THS 2.2 Menthol

Data Source: Appendix 15, Listing 15.3.3.2 ZRHM-PK-06-US

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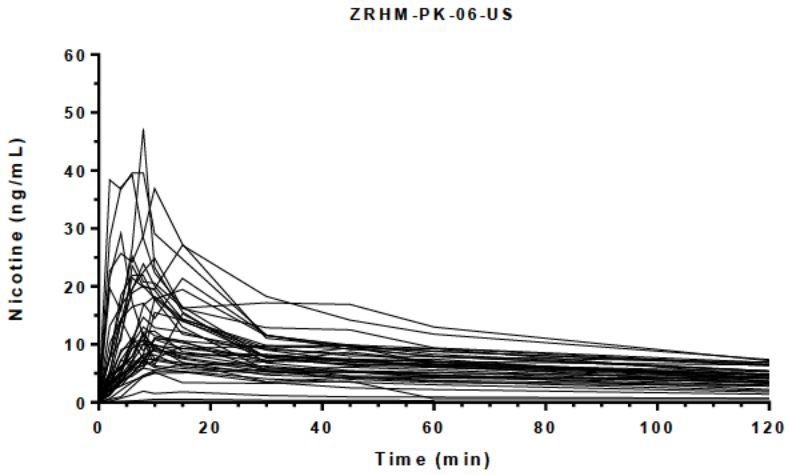


Figure 21 Individual Plasma Concentrations (N=41) of Nicotine After Single Use of mCC

Data Source: Appendix 15, Listing 15.3.3.2 ZRHM-PK-06-US

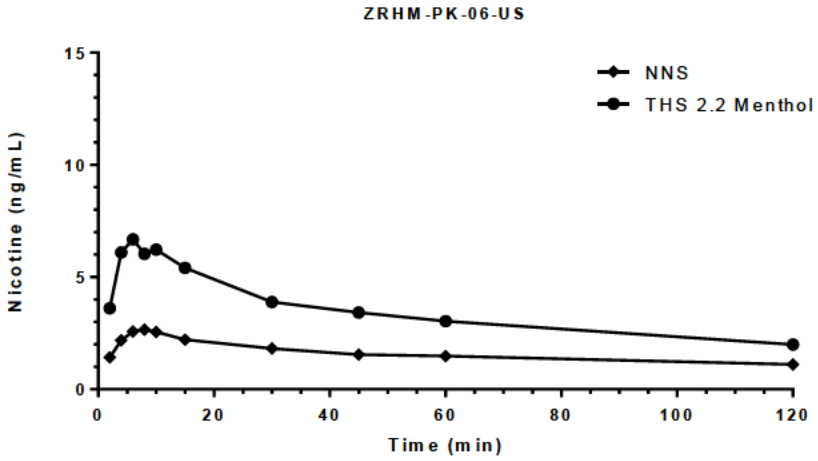


Figure 22 Geometric Mean (n=17) Plasma Concentrations of Nicotine After Single Use of THS 2.2 Menthol and NNS

Data Source: Appendix 15, Figure 15.1.2.1.2 ZRHM-PK-06-US

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6.2.1.2.4.3.2 Conclusion

- 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 tmax occurred at 7 and 10 minutes following THS 2.2 Menthol and mCC use, respectively.
- This study has also indicated that exposure to nicotine was higher for THS 2.2 Menthol use compared to NNS use. The time of maximum nicotine concentration was comparable between the 2 products.

6.2.1.2.4.3.3 Pharmacodynamics (Subjective Effects)

Group-1 (THS Menthol/mCC)

Table 34 Analysis of Urge-to-Smoke After Single Use – THS 2.2 Menthol vs mCC (QSU-b Total Score)

QSU-b	Product Exposure	LS Mean	THS 2.2 Menthol - mCC LS Mean Difference	LS Mean Difference 95% CI
Total Score	THS 2.2 Menthol	4.28	0.37	-0.02; 0.77
	mCC	3.91		

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model. QSU-brief total score items are rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores indicate a higher urge-to-smoke.

Data Source: Appendix 15, Table 15.2.4.12 ZRHM-PK-06-US

Group-2 (THS Menthol/NNS)

Table 35 Analysis of Urge-to-Smoke After Single Use – THS 2.2 Menthol vs NNS (QSU-b Total Score)

QSU-b	Product Exposure	LS Mean	THS 2.2 Menthol - mCC LS Mean Difference	LS Mean Difference 95% CI
Total Score	THS 2.2 Menthol	3.34	-0.35	-0.79; 0.09
	NNS	3.70		

Data Source: Appendix 15, Table 15.2.4.12 ZRHM-PK-06-US

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Group-1 (THS Menthol/mCC)

Table 36 Analysis of MCEQ After Single Use – THS 2.2 Menthol vs mCC

MCEQ Sub-Scale Domain	Product Exposure	LS Mean	THS 2.2 Menthol - mCC LS Mean Difference	LS Mean Difference 95% CI
Aversion	THS 2.2 Menthol	2.44	0.02	-0.56; 0.59
	mCC	2.42		
Craving reduction	THS 2.2 Menthol	3.71	-1.21	-1.79; -0.63
	mCC	4.92		
Enjoyment of respiratory tract sensation	THS 2.2 Menthol	3.24	-0.80	-1.52; -0.08
	mCC	4.04		
Psychological reward	THS 2.2 Menthol	3.18	-0.60	-1.04; -0.16
	mCC	3.78		
Smoking satisfaction	THS 2.2 Menthol	3.78	-1.20	-1.79; -0.60
	mCC	4.97		

Means and 95% CI are the adjusted LS means and CIs from an ANOVA model.

Data Source: Appendix 15, Table 15.2.4.15 ZRHM-PK-06-US

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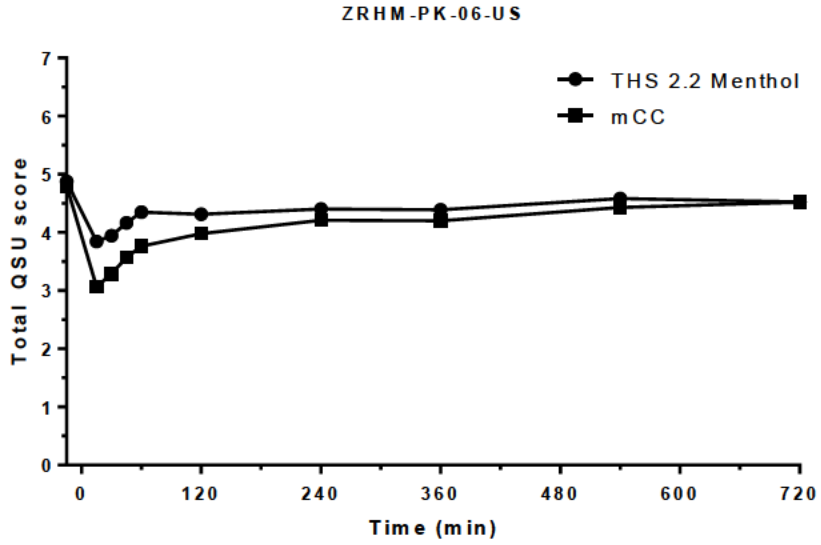


Figure 23 Arithmetic Means of Total Scores for QSU-brief During Single Use of THS 2.2 Menthol and mCC

Data Source: Appendix 15, Figure 15.1.2.10.1 ZRHM-PK-06-US

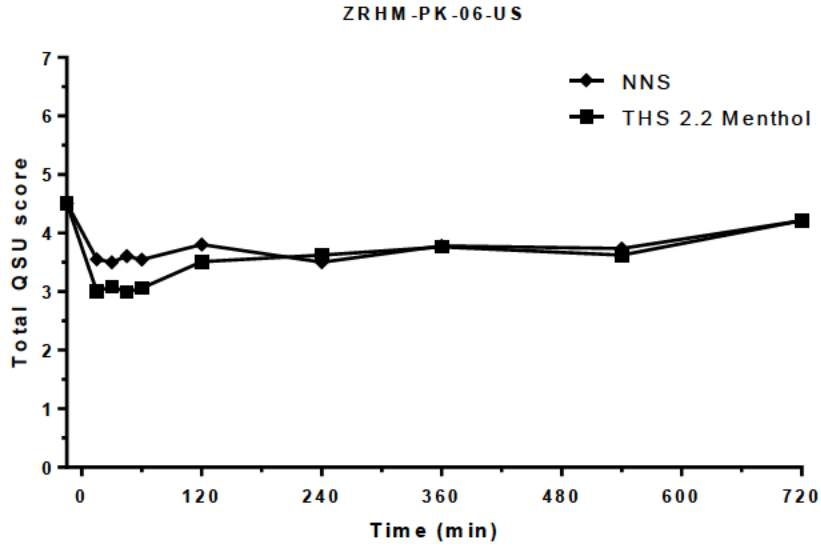


Figure 24 Arithmetic Means of Total Scores for QSU-brief During Single Use of THS 2.2 Menthol and NNS

Data Source: Appendix 15, Figure 15.1.2.10.2 ZRHM-PK-06-US

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6.2.1.2.4.3.4 Conclusion

- THS 2.2 Menthol single use decreased the urge-to-smoke less than mCC use, most noticeably for the first 2 hours post-product use.
- MCEQ subscales suggested that THS 2.2 Menthol use was less satisfying than mCC

THS 2.2 Menthol 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.

6.2.1.2.4.4 Safety Findings

No SAEs were reported during this study, while 2 severe AEs were reported by 1 subject and were not considered to be related to THS 2.2 Menthol, NNS, or study procedures.

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.

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