TABLE OF CONTENTS

6.2.1.1.1 Background and Overview 4
6.2.1.1.2 Summary of Results of Individual Studies 5
6.2.1.1.2.1. Study ZRHR-PK-01-EU 5
6.2.1.1.2.1.1. Methodology of the ZRHR-PK-01-EU Study 5
6.2.1.1.2.1.2. Pharmacokinetic Results 7
6.2.1.1.2.2. Study ZRHR-PK-02-JP 7
6.2.1.1.2.2.1. Methodology of the ZRHR-PK-02-JP Study 7
6.2.1.1.2.2.2. Pharmacokinetic Results 9
6.2.1.1.2.3. Study ZRHM-PK-05-JP 10
6.2.1.1.2.3.1. Methodology of the ZRHM-PK-05-JP Study 10
6.2.1.1.2.3.2. Pharmacokinetic Results 11
6.2.1.1.2.4. Study ZRHM-PK-06-US 12
6.2.1.1.2.4.1. Methodology of the ZRHM-PK-06-US Study 12
6.2.1.1.2.4.2. Pharmacokinetic Results 14
6.2.1.1.3 Analysis across studies 14
6.2.1.1.3.1. Pharmacokinetic Results across Studies 14
6.2.1.1.3.2. Model-based analysis 17
6.2.1.1.3.2.1. Objectives, data and methods 17
6.2.1.1.3.2.2. Results 21
6.2.1.1.3.2.3. Visual Predictive Checks 25
6.2.1.1.3.2.4. Goodness of fit 26
6.2.1.1.3.2.5. Exposure PK parameters 29
6.2.1.1.3.2.6. Conclusion 29
6.2.1.1.3.3. Pharmacodynamics Results across Studies 30
6.2.1.1.3.3.1. QSU brief 31
6.2.1.1.3.3.2. Results 31
6.2.1.1.3.3.2.1. MCEQ 33
6.2.1.1.3.3.2.2. Results 34
6.2.1.1.4 References 36

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TABLE OF FIGURES

Figure 1 Examples of individual nicotine plasma concentration over time data for the population PK analysis - Learning dataset 19
Figure 2 Schematic of the workflow of the nicotine population PK analysis 20
Figure 3 Compartmental representation of the population PK model and its two submodels-for product use and for nicotine background 22
Figure 4 Visual predictive checks using the final nicotine model (10%, 50% and 90% percentile) for period 1 (top) and period 2 (bottom)- semi-logarithmic scale - Learning dataset 26
Figure 5 Goodness of fit Plots on the Final Model for Nicotine-Validation dataset 27
Figure 6 Examples of individual observed concentrations (ng/mL) of nicotine and predictions derived from the final model-Validation dataset (REX studies) .. 28
Figure 7 Total score of the QSU brief–Group 1 (arithmetic mean and 95% confidence intervals) 32
Figure 8 mCEQ subscales brief–Group 1 (arithmetic mean and 95% confidence intervals) 35

TABLE OF TABLES

Table 1 Randomization Groups and Sequences 5
Table 2 Methodology of the ZRHR-PK-01-EU Study 6
Table 3 Results ZRHR-PK-01-EU: Noncompartmental analysis of pharmacokinetics after single product use THS Regular and CC Regular 7
Table 4 Results ZRHR-PK-01-EU: Noncompartmental analysis of pharmacokinetics after single product use THS Regular and NNS 7
Table 5 Methodology of the ZRHR-PK-02-JP Study 8
Table 6 Results ZRHR-PK-02-JP: Noncompartmental analysis of pharmacokinetics after single product use THS Regular and CC 9
Table 7 Results ZRHR-PK-02-JP: Noncompartmental analysis of pharmacokinetics after single product use THS Regular and NRT gum 10
Table 8 Methodology of the ZRHM-PK-05-JP Study 10
Table 9 Results ZRHM-PK-05-JP: Noncompartmental analysis of pharmacokinetics after single product use THS Menthol and mCC 12
Table 10 Results ZRHM-PK-05-JP: Noncompartmental analysis of pharmacokinetics after single product use THS Menthol and NRT gum 12
Table 11 Methodology of the ZRHM-PK-06-US Study 13

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Table 12 Results ZRHM-PK-06-US: Noncompartmental analysis of pharmacokinetics after single product use THS 2.2 Menthol and mCC 14

Table 13 Results ZRHM-PK-06-US: Noncompartmental analysis of pharmacokinetics after single product use THS 2.2 Menthol and NNS 14

Table 14 Single product use noncompartmental PK analysis. 95% confidence intervals for the ratio of means 15

Table 15 Methodology of the nicotine population PK model development 17

Table 16 Number of subjects in the full population PK dataset- by study and by Learning (PK studies) and Validation (REX studies) dataset 18

Table 17 Number of Measurable Observations Included in the Population PK Dataset by Study and Product — Learning Dataset (PK Studies) - Nicotine Concentration Assessments 18

Table 18 Number of Observations Included in the Population PK Dataset by Study and Product — Validation Dataset (PK Studies) - Nicotine Concentration Assessments 19

Table 19 Parameter Estimates of the Final Population PK Model for Nicotine 24

Table 20 Mean (CV%) of Population PK Predicted Nicotine Exposure Metrics by Product-Learning dataset 29

Table 21 Analysis of Urge to Smoke after Single Use by Study – THS vs CC 33

Table 22 Analysis of Urge to Smoke after Single Use by Study –THS vs NRT 33

Table 23 Product Evaluation after Single Use by Study – THS vs CC 35

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6.2.1.1.1 Background and Overview

The pharmacokinetics and metabolism of nicotine has been extensively analyzed and reviewed.

An average tobacco rod of a conventional cigarette contains 10 to 14 mg of nicotine. On average, about 1 to 1.5 mg of nicotine is absorbed systemically during smoking. Because of the large surface area of the alveoli and small airways, when tobacco smoke reaches the small airways and alveoli of the lung, nicotine is rapidly absorbed. The rapidity of rise in nicotine levels in blood permits the smoker to titrate the level of nicotine and related effects during smoking. CYP2A6 is the enzyme that is primarily responsible for the oxidation of nicotine and its main metabolite cotinine. The rate of clearance of nicotine is controlled by hepatic blood flow (Benowitz 2009, Hukkanen 2005).

The PMI candidate modified risk tobacco product proposed for marketing authorization, THS 2.2, is claimed to be a reduced risk product compared to combustible cigarettes. The overall clinical assessment program encompassed characterization of nicotine uptake, comparison of pharmacodynamics effects through subjective effects, demonstration of exposure reduction in smokers who switch to THS, change in clinical risk markers in subjects who use THS and confirmation of an acceptable safety profile.

A total of four PK studies have been completed to assess the rate and extent of nicotine uptake in subjects using THS compared with those using conventional cigarettes (CC) or nicotine replacement therapy (NRT). They compared the single use profiles of nicotine uptake, rate and extent of nicotine absorbed, in subjects who switched from CC to THS compared to subjects who used their own preferred brand of CC. In addition, THS was evaluated versus NRT, which was used as a reference point product in all four PK studies (Table 1). Subjective effects, such as urge to smoke, measures related to reinforcing or aversive effects, were part of the assessment. Since factors such as taste, flavor and sensory experience are important for adult smoker acceptance, they were recorded through self-administered questionnaires.

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Table 1 Randomization Groups and Sequences

Study (ClinicalTrials.gov Identifier)	Subject Population	THS Variant	CC Type	NRT
ZRHR-PK-01-EU (NCT01967732)	Healthy Caucasian female or male smokers	Regular	Regular	NNS
ZRHR-PK-02-JP (NCT01959607)	Healthy Japanese female or male smokers	Regular	Regular	NRT gum (menthol)
ZRHM-PK-05-JP (NCT01967706)	Healthy Japanese female or male smokers	Menthol	Menthol	NRT gum (menthol)
ZRHM-PK-06-US (NCT01967719)	Healthy female or male smokers	Menthol	Menthol	NNS

Abbreviations: CC = conventional cigarette; NNS = nicotine nasal spray; NRT = nicotine replacement therapy; THS = Tobacco Heating System

This section 'Summary of Clinical Pharmacology Studies' (SCP) reports only the relevant features and outcomes of the PK/PD assessment of the four healthy smoker studies. Summaries of the individual studies are presented, and more details can be found in the synopses of individual studies (section 6.2.1.2 PKPD Overview of Studies) and [study reports ZRHR-PK-01-EU, ZRHR-PK-02-JP, ZRHM-PK-05-JP, and ZRHM-PK-06-US]. A detailed analysis across the four PK studies is provided in (section 6.2.1.1.3), including a population PK model and results of the pharmacodynamics aspects.

In brief, nicotine pharmacokinetic studies show that THS replicates the nicotine delivery profile of cigarettes, indicating that it has the potential to effectively substitute CC use.

6.2.1.1.2 Summary of Results of Individual Studies

6.2.1.1.2.1. Study ZRHR-PK-01-EU

The purpose of this study [Study ZRHR-PK-01-EU] was to compare THS Regular with conventional cigarettes in terms of PK, PD, and safety following single tobacco product use. A nicotine containing product for nicotine replacement therapy (nicotine nasal spray) was tested in a second group of study participants and compared to THS Regular. The primary objective of this study was to determine the point estimate of the nicotine relative bioavailability (ratio of THS :CC) for C_{max} and $AUC_{(0\text{-last})}$.

6.2.1.1.2.1.1. Methodology of the ZRHR-PK-01-EU Study

A brief description of study design, endpoints and methodology is given in Table 2.

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Table 2 Methodology of the ZRHR-PK-01-EU Study

PK/PD study to determine PK and PD of THS 2.2, CC and nicotine nasal spray (NNS) single product use

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

Study design: Single center, randomized, controlled, 2-period, 4-sequence, single use crossover study, in which each subject received 2 of the following 3 products: (a) THS Regular (b) CC Regular (c) NNS.
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.

Subjects: Randomized: 62; Data set for safety analysis: 62. Data set for pharmacokinetic comparison between THS Regular and CC Regular analysis (Group-1): 42. Data set for pharmacokinetic comparison THS Regular and NNS (Group-2): 18.

Main criteria for inclusion:

- Male and female Caucasians aged 21 to 65 years
- Considered in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening
- Smoking at least 10 CC per day with a maximum nicotine yield of 1 mg (ISO)
- Did not plan to quit smoking in the following 3 months
- Body mass index between 18.5 and 32.0 kg/m^2

Test Product: Tobacco Heating System 2.2 (THS 2.2) Regular

Reference Product: Commercially available CC Regular with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) as labeled on the cigarette package

Comparison Product: Commercially available nasal spray: Nicorette® 10 mg/mL

Duration of Use: Single product use. THS Regular: one Tobacco Stick, no fixed puffing regimen. CC Regular: One cigarette, no fixed puffing regimen. For NNS, one spray per nostril per product use

Analytical Method: Quantification limit used in this study: 0.2 ng/mL. Validation range: 0.200 to 10.0 ng/mL. Details on the bioanalytical method is provided in section 6.1.3.4 REX Overview of Studies.

Criteria for evaluation:

Pharmacokinetics:

Primary parameters: $AUC_{(0\rightarrow last)}$, C_{max},

Secondary parameters: $AUC_{(0\rightarrow\infty)}$, t_{max}

Pharmacodynamics:

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

Product evaluation questionnaire (Modified Cigarette Evaluation Questionnaire [mCEQ])

Safety:

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

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6.2.1.1.2.1.2. Pharmacokinetic Results

Nicotine plasma levels expressed as $AUC_{0\rightarrow last}$ and C_{max} were lower (26% and 23%, respectively) for THS Regular compared to CC Regular (Table 3). Peak concentration (t_{max}) of nicotine was reached after six minutes for both tobacco products. THS Regular peak concentration was 3 times higher than that of NNS with a comparable time to peak concentration (t_{max} of 7 minutes for THS Regular and 8 minutes for NNS).

Table 3 Results ZRHR-PK-01-EU: Noncompartmental analysis of pharmacokinetics after single product use THS Regular and CC Regular

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

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

Table 4 Results ZRHR-PK-01-EU: Noncompartmental analysis of pharmacokinetics after single product use THS Regular and NNS

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

Source: Appendix 15, Table 15.2.4.1. ZRHR-PK-01-EU

6.2.1.1.2.2. Study ZRHR-PK-02-JP

The purpose of this study [Study ZRHR-PK-02-JP] was to compare THS Regular with conventional cigarettes in terms of PK, PD, and safety following single tobacco product use. A nicotine containing product for nicotine replacement therapy (nicotine gum) was tested in a second group of study participants and compared to THS Regular. The primary objective of this study was to determine the point estimate of the nicotine relative bioavailability (ratio of THS:CC) for C_{max} and $AUC_{(0\text{-last})}$.

6.2.1.1.2.2.1. Methodology of the ZRHR-PK-02-JP Study

A brief description of study design, endpoints and methodology is given in Table 5.

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Table 5 Methodology of the ZRHR-PK-02-JP Study

PK/PD study to determine PK and PD of THS 2.2, CC and menthol nicotine gum (NRT Gum) single product use

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

Study design: Single center, randomized, controlled, 2-period, 4-sequence,single use crossover study, in which each subject received 2 of the following 3 products: (a) THS Regular (b) CC Regular (c) menthol nicotine gum (NRT Gum)

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

Subjects: Randomized: 62; Data set for safety analysis: 65. Data set for pharmacokinetic comparison between THS Regular and CC Regular analysis (Group-1): 42. Data set for pharmacokinetic comparison THS Regular and NRT gum (Group-2): 18.

Main criteria for inclusion:

- Male and female Japanese aged 23 to 65 years
- Considered in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening
- Smoking at least 10 CC per day with a maximum nicotine yield of 1 mg (ISO)
- Did not plan to quit smoking in the following 3 months
- Body mass index between 18.5 and 32.0 kg/m^2

Test Product: Tobacco Heating System 2.2 (THS 2.2) Regular

Reference Product: Commercially available CC Regular with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) as labeled on the cigarette package

Comparison Product: Commercially available nicotine gum: Nicorette ® 2 mg

Duration of Use: Single product use. THS Regular: one Tobacco Stick, no fixed puffing regimen. CC Regular: One cigarette, no fixed puffing regimen. NRT gum: one NRT gum was slowly chewed for 35 ± 5 minutes while spacing each chew.

Analytical Method: Quantification limit used in this study: 0.2 ng/mL. Validation range: 0.200 to 10.0 ng/mL. Details on the bioanalytical method is provided in section 6.1.3.4 REX Overview of Studies.

Criteria for evaluation:

Pharmacokinetics:

Primary parameters: $AUC_{(0\rightarrow last)}$, C_{max},

Secondary parameters: $AUC_{(0\rightarrow\infty)}$, t_{max}

Pharmacodynamics:

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

Product evaluation questionnaire (Modified Cigarette Evaluation Questionnaire [mCEQ])

Safety:

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

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6.2.1.1.2.2.2. Pharmacokinetic Results

Nicotine plasma levels expressed as AUC and C_{max} were comparable for THS Regular and CC Regular (Table 6). Peak concentration of nicotine was reached after six minutes (t_{max}) for both tobacco products. The peak nicotine concentration was higher (Table 7) and the time to peak concentration was shorter (t_{max} of 6 vs 35 minutes, respectively) following THS Regular use compared to NRT gum, in line with the prescribed chewing duration of 35 ± 5 minutes.

Table 6 Results ZRHR-PK-02-JP: Noncompartmental analysis of pharmacokinetics after single product use THS Regular and CC

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

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

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Table 7 Results ZRHR-PK-02-JP: Noncompartmental analysis of pharmacokinetics after single product use THS Regular and NRT gum

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

Source: Appendix 15, Table 15.2.4.1. ZRHR-PK-02-JP

6.2.1.1.2.3. Study ZRHM-PK-05-JP

The purpose of this study [Study ZRHM-PK-05-JP] was to compare THS Menthol with menthol conventional cigarettes in terms of PK, PD, and safety following single tobacco product use. A nicotine containing product for nicotine replacement therapy (menthol nicotine gum) was tested in a second group of study participants and compared to THS Menthol. The primary objective of this study was to determine the point estimate of the nicotine relative bioavailability (ratio of THS Menthol:mCC) for C_{max} and $AUC_{(0\text{-last})}$.

6.2.1.1.2.3.1. Methodology of the ZRHM-PK-05-JP Study

A brief description of study design, endpoints and methodology is given in Table 8.

Table 8 Methodology of the ZRHM-PK-05-JP Study

PK/PD study to determine PK and PD of THS 2.2 Menthol, mCC and NRT Gum single product use
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 (mCC) and nicotine gum
Study design: Single center, randomized, controlled, 2-period, 4-sequence, single use crossover study, in which each subject received 2 of the following 3 products: (a) THS Menthol (b) mCC (c) menthol NRT gum. 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

(table continues)

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PK/PD study to determine PK and PD of THS 2.2 Menthol, mCC and NRT Gum single product use

Subjects: Randomized: 62; Data set for safety analysis: 73. Data set for pharmacokinetic comparison between THS Menthol and mCC analysis (Group-1): 43. Data set for pharmacokinetic comparison THS Menthol and NRT gum (Group-2): 18.

Main criteria for inclusion:

- Male and female Japanese aged 23 to 65 years
- Considered in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening.
- Smoking at least 10 mCC per day with a maximum nicotine yield of 1 mg (ISO)
- Did not plan to quit smoking in the following 3 months
- Body mass index between 18.5 and 32.0 kg/m^2

Test Product: Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)

Reference Product: Commercially available mCC with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) as labeled on the cigarette package

Comparison Product: Commercially available NRT Gum: Nicorette ® 2 mg

Duration of Use: Single product use. THS Menthol: one Tobacco Stick no fixed puffing regimen. mCC: One cigarette, no fixed puffing regimen. NRT gum: slowly chewed for 35 ± 5 minutes while spacing each chew

Analytical Method: Quantification limit used in this study: 0.2 ng/mL. Validation range: 0.200 to 10.0 ng/mL. Details on the bioanalytical method is provided in section 6.1.3.4 REX Overview of Studies.

Criteria for evaluation:

Pharmacokinetics:

Primary parameters: $AUC_{(0\rightarrow last)}$, C_{max},

Secondary parameters: $AUC_{(0\rightarrow\infty)}$, t_{max}

Pharmacodynamics:

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

Product evaluation questionnaire (Modified Cigarette Evaluation Questionnaire [mCEQ])

Safety:

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

6.2.1.1.2.3.2. Pharmacokinetic Results

Nicotine plasma levels expressed as AUC and C_{max} were similar for mCC and THS Menthol. Peak concentration (t_{max}) of nicotine was reached after six minutes for both tobacco products Table 9.

The t_{max} was significantly shorter for THS Menthol (8 minutes) compared to NRT gum (45 minutes), while the C_{max} did not differ between THS Menthol and NRT gum Table 10.

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As expected, the nicotine gum showed a slower input rate of nicotine than THS 2.2 and mCC, in line with the prescribed chewing duration of 35 ± 5 minutes.

Table 9 Results ZRHM-PK-05-JP: Noncompartmental analysis of pharmacokinetics after single product use THS Menthol and mCC

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

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

Table 10 Results ZRHM-PK-05-JP: Noncompartmental analysis of pharmacokinetics after single product use THS Menthol and NRT gum

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

Source: Appendix 15, Table 15.2.4.1. ZRHM-PK-05-JP

6.2.1.1.2.4. Study ZRHM-PK-06-US

The purpose of this study [Study ZRHM-PK-06-US] was to compare THS Menthol with menthol conventional cigarettes in terms of PK, PD, and safety following single tobacco product use. A non-tobacco nicotine containing product for nicotine replacement therapy (nicotine nasal spray) was tested in a second group of study participants and compared to THS Menthol. The primary objective of this study was to determine the point estimate of the nicotine relative bioavailability (ratio of THS Menthol:mCC) for C_{max} and $AUC_{(0\text{-last})}$.

Subjective effects were evaluated through the QSU and mCEQ.

6.2.1.1.2.4.1. Methodology of the ZRHM-PK-06-US Study

A brief description of study design, endpoints and methodology is given in Table 11.

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Table 11 Methodology of the ZRHM-PK-06-US Study

PK/PD study to determine PK and PD of THS 2.2 Menthol, mCC and nicotine nasal spray single product use
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
Study design: Single center, randomized, controlled, 2-period, 4-sequence, single use crossover study, in which each subject received 2 of the following 3 products: (a) THS Menthol (b) mCC (c) nicotine nasal spray (NNS). 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.
Subjects: Randomized: 62; Data set for safety analysis: 64. Data set for pharmacokinetic comparison between THS Menthol and mCC analysis (Group-1): 41. Data set for pharmacokinetic comparison THS Menthol and NNS (Group-2): 17.
Main criteria for inclusion: • Male and female smokers aged 22 to 65 years • Considered in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening • Smoking at least 10 mCC per day • Did not plan to quit smoking in the following 3 months • Body mass index between 18.5 and 35.0 kg/m^2
Test Product: Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Reference Product: Commercially available mCC
Comparison Product: Commercially available NNS: Nicotrol® 10 mg/ml
Duration of Use: Single product use. THS Menthol: one Tobacco Stick no fixed puffing regimen. mCC: One cigarette, no fixed puffing regimen. For NNS, one spray per nostril per product use
Analytical Method: Quantification limit used in this study: 0.2 ng/mL. Validation range: 0.200 to 10.0 ng/mL. Details on the bioanalytical method is provided in section 6.1.3.4 REX Overview of Studies.
Criteria for evaluation: Pharmacokinetics: Primary parameters: $AUC_{(0\rightarrow last)}$, C_{max}, Secondary parameters: $AUC_{(0\rightarrow\infty)}$, t_{max} Pharmacodynamics: Urge to smoke questionnaire (Questionnaire of Smoking Urges brief [QSU brief]) Product evaluation questionnaire (Modified Cigarette Evaluation Questionnaire [mCEQ]) Safety: Adverse events, assessments of physical condition, vital signs and body measurements, spirometry, respiratory symptoms, electrocardiogram, and monitoring of laboratory values

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6.2.1.1.2.4.2. Pharmacokinetic Results

Nicotine plasma levels expressed as AUC and C_{max} were approximately 44% and 43% lower for THS menthol compared to mCC, respectively (Table 12). Peak concentration (t_{max}) of nicotine was reached after seven minutes for THS Menthol and later for mCC (10 minutes).

The exposure to nicotine was higher for THS Menthol use compared to NNS use (Table 13). The time of maximum nicotine concentration was comparable between the 2 products (t_{max} of 9 minutes for THS Menthol and 8 minutes for NNS).

Table 12 Results ZRHM-PK-06-US: Noncompartmental analysis of pharmacokinetics after single product use THS 2.2 Menthol and mCC

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

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

Table 13 Results ZRHM-PK-06-US: Noncompartmental analysis of pharmacokinetics after single product use THS 2.2 Menthol and NNS

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

Source: Appendix 15, Table 15.2.4.1. ZRHM-PK-06-US

6.2.1.1.3 Analysis across studies

6.2.1.1.3.1. Pharmacokinetic Results across Studies

The data provided in this submission allow to combine single use PK results with the information on product consumption and nicotine exposure from longer term studies such

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as the one-week and three-month reduced exposure studies. These longer term studies include evaluation of changing smoking and consumption patterns and the adaptation of nicotine exposure over time in more real world settings. Also, possible changes in puffing behavior over time, were assessed in the 1 week and 3 month Reduced Exposure studies [Section 6.2.2 Product Usage].

Four single use clinical PK/PD studies compared nicotine PK for THS with those for CC and NRT. The studies did not apply a fixed puffing regimen, but instead the subjects controlled their own puffing behavior, which allows for a more realistic evaluation of a tobacco consumer product. Smokers can modulate their nicotine intake by controlling their puffing behavior including duration and volume of puffs, or the depth/intensity of inhalation. The standardization of product use by setting the number of puffs and the intervals between the puffs might have resulted in a decreased intra - and/or inter-subject variability, but the large sample size of 42 subjects allowed for an adequate precision of the C_{max} and AUC between 15 and 26% (Table 14).

Table 14 Single product use noncompartmental PK analysis. 95% confidence intervals for the ratio of means

Variable	Study	THS Geometric Mean	CC Geometric Mean	Ratio	95% CI Lower bound	95% CI Upper bound	Precision (%)
C_{max} [ng/mL]	PK-01-EU	9.62	12.42	77.43	62.69	95.63	18.20
	PK-02-JP	14.30	13.82	103.50	84.94	126.11	22.61
	PK-05-JP	10.70	12.09	88.47	68.64	114.03	25.55
	PK-06-US	7.40	13.08	56.57	44.21	72.39	15.81
$AUC_{(0\text{-last})}$ [ng/mL]	PK-01-EU	15.10	20.28	74.47	61.52	90.14	15.67
	PK-02-JP	23.75	24.66	96.34	85.10	109.07	12.72
	PK-05-JP	23.99	24.45	98.13	80.61	119.46	21.33
	PK-06-US	16.53	29.71	55.64	43.30	71.50	15.86

Source: Appendix 15, Table 15.2.3.1 ZRHR-PK-01-EU, Appendix 15, Table 15.2.3.1 ZRHR-PK-02-JP, Appendix 15, Table 15.2.3.1 ZRHM-PK-05-JP, Appendix 15, Table 15.2.3.1 ZRHM-PK-06-US.

In order to evaluate THS with non-tobacco nicotine containing products, the comparison to NRT was done for the nicotine nasal spray and the nicotine gum. The nasal spray was expected to be the NRT product closest to the rapid absorption of nicotine, while by study design the gum was reported having a longer time to reach maximum concentration. The studies included important product variants for THS and CC for consumer preferences such as Menthol and Regular. Populations known to vary in their CYP2A6 enzymatic activity (e.g., Japanese) due to genetic background were also part of the PMI PK/PD program.

For each study, subjects were stratified based on the International Organization for Standardization (ISO) nicotine level of the subjects preferred brand of CC smoked at Admission. ISO nicotine levels were ≤0.6 mg and >0.6 to ≤1 mg for the

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[ZRHR-PK-01-EU], [ZRHR-PK-02-JP], and [ZRHM-PK-05-JP] studies, and ≤1.0 mg and >1.0 mg for the [ZRHM-PK-06-US] study. Gender and nicotine level had a quota applied to ensure they represented at least 40% of the total study population. The confinement period consisted of two periods, with each period consisting of a nicotine abstinence period (24 hours minimum) which is considered long enough wash-out for a compound with a half-life of approximately two hours. The methods for the primary and secondary analysis are based on the FDA 2001 recommendations for non-replicated crossover 2x2 study designs. In compliance with these guidelines, the general linear model procedure was used. The model included factors accounting for sequence, subjects nested in sequences, period and exposure (FDA (Food and Drug Administration) 2001).

AUC and C_{max} calculated by noncompartmental analysis show very close similarity between THS and CC in the two studies in the Japanese smokers (THS:CC ratio 96.3% and 98.1% for AUC). Single use of the THS Tobacco Stick in the studies done in Europe [ZRHR-PK-01-EU] and in smokers from the US [ZRHM-PK-06-US] did not reach the same level of nicotine peak concentration and exposure compared to single CC use.

Smokers in the [ZRHM-PK-06-US] study were able to extract the most nicotine out from a single CC compared to the three other studies and, compared to the other PK studies, they also exhibited a later nicotine peak concentration reached with CC (6 to 6.7 minutes for THS and CC in [ZRHR-PK-01-EU], [ZRHR-PK-02-JP], and [ZRHM-PK-05-JP], and 10.1 minutes in CC in the [ZRHM-PK-06-US] study (6.7 and 8.9 minutes in group 1 and 2, respectively, for THS). This indicates a longer total smoking duration for CC compared to the THS. A similar difference of up to 1.5min in total smoking duration was observed in the [ZRHM-REXA-08-US] study as measured by Human puffing topography (section 6.2.2 Product Usage).

In conclusion, puffing behavior and the fact that in the [ZRHM-PK-06-US] study there was no ceiling of nicotine ISO levels at 1.0 mg as inclusion criteria could explain the significantly less nicotine levels the subjects reached with THS (i.e., average nicotine ISO level in group 1 for mCC was approximately 1 mg in [ZRHM-PK-06-US] while it was below 0.75 mg in all other studies, while the nicotine ISO level of THS Menthol and Regular is 0.5 mg).

Compared to the NRT product nasal spray, THS achieved higher nicotine exposure than NNS in studies [ZRHR-PK-01-EU] and [ZRHM-PK-06-US] (THS:NNS ratio of AUC 222.9% and 178.8%, respectively). Single product use resulted in earlier (0.8 to 1.2 minutes) and higher maximal nicotine concentration (2.6 to 3.0 fold) with THS compared to NNS (Table 4; Table 13).

In study [ZRHM-PK-05-JP] showed a higher nicotine exposure during the 12 hours observation period (AUC_{last}) for NRT gum than THS, while the maximal concentration (C_{max}) showed little difference between both products. In study [ZRHR-PK-02-JP], nicotine exposure was 20% lower for the NRT gum compared to THS (Table 7, Table 10). Considerable variability in the PK parameters of the nicotine gum was noted and is in line with published reports (Lunell 2011, Lunell 2005).

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6.2.1.1.3.2. Model-based analysis

In the previously reported noncompartmental PK analysis, the determination of PK parameters was occasionally complicated by the occurrence of unexplained rebounds in some concentration-time profiles, and by the presence of a measurable nicotine background (*i.e.,* pre-dose plasma concentration above the lower limit of quantification), suggesting that nicotine half-life might be longer than initially considered while defining the duration of the washout periods. This finding formed part of the rationale for conducting a population PK modeling of nicotine data.

This section summarizes the development and the results of the population PK modeling of nicotine following use of nicotine-containing products (i.e., THS and its comparators [CC, nicotine gum and nicotine nasal spray]) in subjects enrolled in the development program of THS (studies [ZRHR-PK-01-EU], [ZRHR-PK-02-JP], [ZRHM-PK-05-JP], [ZRHM-PK-06-US], [ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP], [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US]). This population PK-based analysis was initiated after the completion of the clinical studies. The main objectives of this modeling were to describe concentration-time profiles of nicotine based on rich data collected in a large population of healthy adult subjects enrolled in the THS clinical studies and to evaluate the covariates to assess sources of variability in nicotine PK parameters.

6.2.1.1.3.2.1. Objectives, data and methods

A brief description of the methodology is given in Table 15.

Table 15 Methodology of the nicotine population PK model development

Population pharmacokinetic modeling of nicotine in healthy adult smokers
Objectives: • Develop a population PK model to describe concentration-time profiles of nicotine in subjects enrolled in the development program of THS. • Assess sources of variability in nicotine PK parameters. • Assess the predictive performance of the nicotine population PK model based on data collected in the development program of THS. • Estimate plasma exposure to nicotine in subjects, distinguishing between the exposure due to product use and background exposure.
Software: SAS V9 for dataset building (SAS Institute), R® Version 3.2.0 (population PK, The R Foundation for statistical Computing) for exploratory data analyses and Phoenix ® NLME ™ 1.3 and FOCE ELS estimation method for population PK analysis (Pharsight Corporation).
Data source: A full population PK dataset was built by pooling the nicotine plasma concentrations and additional clinical studies from the ADaM datasets of 4 PK studies ([ZRHR-PK-01-EU], [ZRHR-PK-02-JP], [ZRHM-PK-05-JP], [ZRHM-PK-06-US]) and 4 REX studies ([ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP], [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US]). The full PK dataset included information

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on events (e.g., nicotine yield of allocated product, time of product use, and time of blood sample collection), concentration values (nicotine) and relevant covariates. It was split between a Learning dataset (4 PK studies) and a Validation dataset (4 REX studies). An overview of the studies are provided in section 6.2.1.2 PKPD Overview of studies, and for the REX studies in section 6.1.3.4 REX Overview of Studies. For the REX studies, only the nicotine samples from Day 5 to Day 6 were used, as only 1 blood sample was taken daily between Day 1 and Day 4.

Plasma samples were analyzed by a validated LC/MS/MS method with a lower limit of quantification of 0.2 ng/mL for the PK studies and 1 ng/mL for the REX studies section 6.1.3.3 Bioanalytical Methods).

The total number of subjects and plasma concentrations included in the Learning and Validation datasets are provided in Table 16, Table 17 and Table 18, respectively.

For the dose input to the model, the dose described in the product information leaflet was used for the NRT, while for THS and CC the nicotine ISO level was used.

Table 16 Number of subjects in the full population PK dataset- by study and by Learning (PK studies) and Validation (REX studies) dataset

Dataset	Study	N
Learning	ZRHR-PK-01-EU	60
	ZRHR-PK-02-JP	62
	ZRHM-PK-05-JP	62
	ZRHM-PK-06-US	62
	Overall	246
Validation	ZRHR-REXC-03-EU	120
	ZRHR-REXC-04-JP	119
	ZRHM-REXA-07-JP	118
	ZRHM-REXA-08-US	99
	Overall	456

N: Sample size
Source: Table 1 Population PK Report

Table 17 Number of Measurable Observations Included in the Population PK Dataset by Study and Product — Learning Dataset (PK Studies) - Nicotine Concentration Assessments

Product	ZRHR-PK-01-EU	ZRHR-PK-02-JP	ZRHM-PK-05-JP	ZRHM-PK-06-US	Overall
CC or mCC	573	622	626	635	2456
NNS	227	-	-	252	479
NRT GUM	-	261	266	-	527
THS or mTHS	801	875	890	815	3381
Total	1601	1758	1782	1702	6843

mTHS=Menthol Tobacco Heating System, THS=Tobacco Heating System, mCC=Menthol Conventional cigarette, CC=Conventional cigarette, NNS=Nicotine nasal spray, NRT=Nicotine replacement therapy
Source: Table A 8-6 Population PK Report

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Table 18 Number of Observations Included in the Population PK Dataset by Study and Product — Validation Dataset (PK Studies) - Nicotine Concentration Assessments

Product	ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US	Overall
CC or mCC	450	400	451	231	1532
THS or mTHS	869	800	847	858	3374
Total	1319	1200	1298	1089	4906

mTHS=Menthol Tobacco Heating System, THS=Tobacco Heating System, mCC=Menthol Conventional cigarette, CC=Conventional cigarette
Source: Table A 8-7 Population PK Report

Handling of missing data:

Subjects with missing actual time of product use were excluded from the analysis. No substitution was made for missing concentration. For missing covariates, the last observation was carried forward and if not available, the subject was excluded. In total, 2 out of 246 subjects (0.8%) were excluded from the Learning dataset due to missing CYP2A6 activity. In the Validation dataset, 20 out of 476 subjects (4.2%) were excluded (1 due to missing CYP2A6 activity and 19 due to missing ISO nicotine yield).

Handling of outlier data:

A graphical exploratory analysis of the nicotine concentration-time profiles resulted in the exclusion of 53 PK samples out of 6896 measurements (>0.8%) from the Learning dataset due to unexpectedly high nicotine values during (see Figure 1). No nicotine concentration was excluded from the Validation dataset.

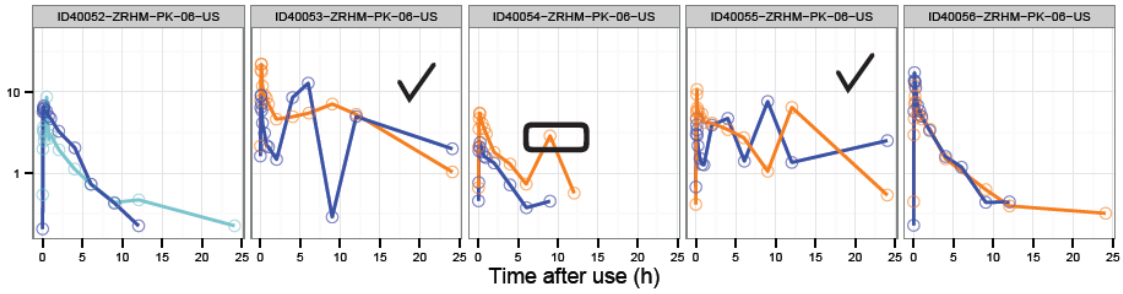


Figure 1 Examples of individual nicotine plasma concentration over time data for the population PK analysis - Learning dataset

The rectangle indicates a single nicotine concentration exclusion and the tick indicates profiles for which at least 2 data points were excluded from the Learning dataset.

Handling of values below the limit of quantification:

Values below the limit of quantification (BLQ) were ignored during the development of the PK model. Once the final PK model has been selected, every BLQ (n=831) was reinserted and model parameters were re-estimated using the likelihood-based method available in the Phoenix NLME module.

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Model building steps:

The analysis started by omitting nicotine observations below the lower limit of quantification and by splitting the full dataset into a Learning and a Validation datasets. After an exploratory data analysis, the population PK model of nicotine was developed sequentially, with a stepwise inclusion of covariates until a final model was obtained. Sensitivity analyses were conducted to assess the impact of outlier and BLQ data. Model evaluation was performed on the base and final model, and was completed by an external validation using the Validation dataset. Following a successful evaluation of the final model, individual exposure metrics were derived in the Learning dataset. This process is illustrated in Figure 2.

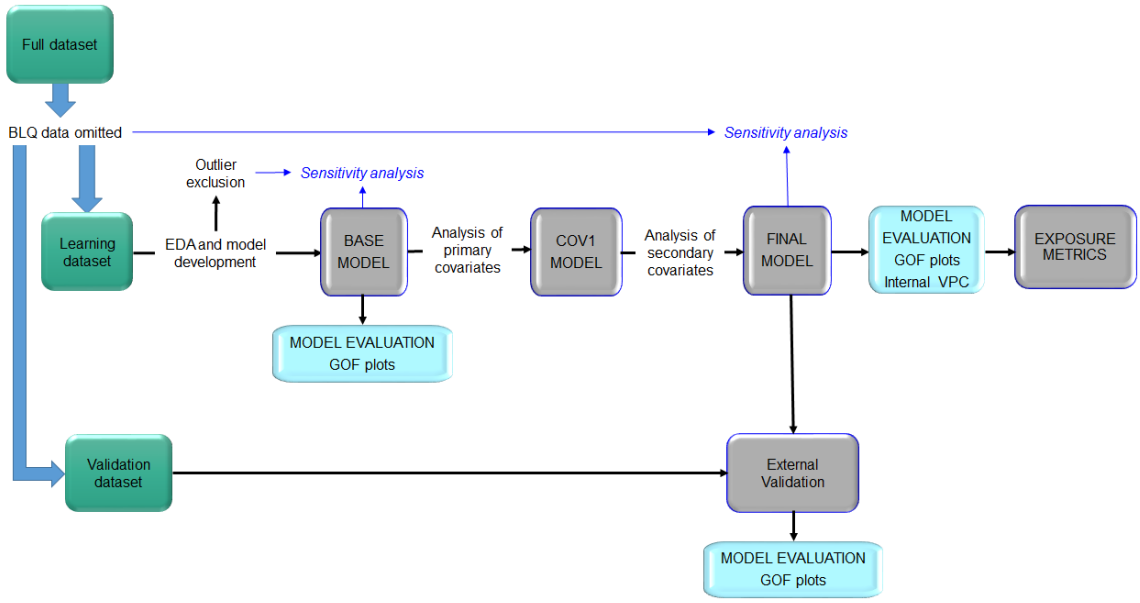


Figure 2 Schematic of the workflow of the nicotine population PK analysis

BLQ: below the limit of quantification; COV1 model: primary covariate model; EDA: exploratory data analysis; GOF: goodness of fit; VPC: visual predictive check.

Structural model:

Based on the observed nicotine concentration-time profiles of the Learning dataset (the 4 PK studies, [ZRHR-PK-01-EU], [ZRHR-PK-02-JP], [ZRHM-PK-05-JP], [ZRHM-PK-06-US]), two submodels were selected: 1) a 2-compartment linear disposition and zero order absorption to describe the nicotine plasma concentration after product use and 2) a mono-exponential decrease to describe the time-course of the background nicotine exposure. No covariates were included in the structural model.

The model evaluation and selection was based on the known pharmacological and physico-chemical properties of nicotine and diagnostic plots after completion of a Bayesian posthoc step (estimation of empirical Bayesian estimates with population parameters fixed to final estimates obtained from the PK dataset). Finally, a sensitivity analysis was performed by introducing the previously excluded 53 nicotine observations. The population PK parameters estimates were close to the estimates including all previously excluded values.

Covariates analysis:

The covariate analysis was conducted in a sequential manner. The two main steps were:

1) Selection of potential "primary" covariates by visual evaluation and physiological plausibility, followed by forward addition (with a threshold of $p < 0.05$) and backward elimination (with a threshold

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of p<0.01) procedure (Wahlby 2002).

2) Selection of potential "secondary" covariates after inclusion of the primary covariates, using the same procedure as for 1).

A total of 6 potential covariates were selected for the primary analysis (body weight, creatinine clearance, cytochrome P450 2A6 isoform (CYP2A6) activity, sex, nature of product, and nicotine ISO yield) and 13 for the secondary analysis (menthol, race, age, alanine transaminase, aspartate transaminase, total bilirubin, body height, body mass index, ethnicity, region, daily use of CC, total Fagerström test for nicotine dependence (FTND) score, and score of the first item from the FTND questionnaire. Collinearity between covariates was evaluated by evaluation of scatter-matrix plots.

Model evaluation:

After the covariate screening, GOF and visual predictive checks were used. More specifically, simulations of 1000 replicates of the Learning dataset were performed, the median, 10^{th} and 90% percentile calculated and overlaid with the observed data. The performance of the final model developed on the Learning dataset to predict the REX studies (Validation dataset) was based on standard diagnostic plots (European Medicines Agency (EMA) 2007, Karlsson 2007):

- Observed dependent variable (DV) versus population predicted (PRED) and individual predicted (IPRED) concentrations with a line of unity and a trend line;
- Conditional weighted residuals (CWRES) versus PRED;
- CWRES versus Time;
- Individual weighted residuals (IWRES) versus IPRED;
- Quantile-Quantile plot of CWRES and of CWRES (QQ plot).

Simulated exposure: The final population PK model was used to simulate nicotine concentration-time profiles, with a granularity of 1 minute and the individual exposure PK parameters (i.e., AUC, C_{max}, t_{max} and $t_{1/2}$) calculated by non-compartmental analysis in a post-hoc step. ParametersAUC and Cmax were derived both with and without background-adjustment.

6.2.1.1.3.2.2. Results

The population PK model for nicotine is presented in Figure 3 and the final PK parameters for the final 2-compartment submodel for product and the monoexponential decline for the nicotine background are provided in Table 19.

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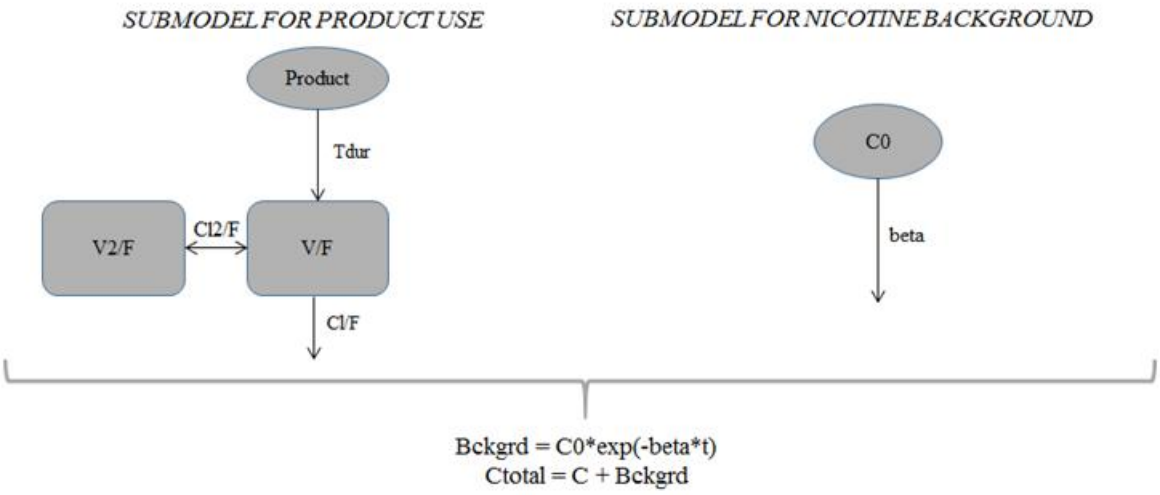


Figure 3 Compartmental representation of the population PK model and its two submodels-for product use and for nicotine background

Bckgrd: background; C0: baseline nicotine concentration prior to first product use; Cl/F: apparent clearance; Cl2/F: apparent inter-compartmental clearance; Frel: bioavailability relative to THS; T_{dur}: duration of zero-order absorption; V/F: apparent central volume of distribution; V2/F: apparent peripheral volume of distribution.
Date source: Figure 4 Population PK Report

The final model included the following covariate effects:

- Effects on bioavailability relative to THS (Frel): the bioavailability of CC, NNS and gum relative to THS was 102%, 24%, and 61%, respectively (i.e., e0.0189, e-1.42, and e-0.489, respectively). Frel was found to decrease with increasing nicotine ISO yield according to a power function with an exponent of -0.573. In other words, any doubling in nicotine ISO yield would result in a 33% relative decrease in Frel (2-0.573 = 0.67). Similarly, Frel decreased with increasing body weight according to a power function with an exponent of -0.715, meaning that any 10% increase in body weight would decrease Frel by 6.6% (1.10-0.715 = 0.934).
- Effects on Cl/F: Cl/F in female subjects is 26% higher than Cl/F in males. In addition, Cl/F was positively correlated with baseline CYP2A6 activity according to a power function with an exponent of 0.322. Any doubling in CYP2A6 activity would increase Cl/F by 25% ($2^{0.322} = 1.25$).
- Effects on V/F: V/F was found to be 9.5% larger ($e^{0.0912} = 1.095$) with mentholated than with regular products.
- Effects on C0: C0 decreased with increasing CYP2A6 activity according to a power function with an exponent of -0.401. This translated into a 24% decrease in C0 for any doubling in CYP2A6 activity ($2^{-0.401} = 0.76$). In addition, the effect of being black increased C0 by 50% ($e^{0.408} = 1.50$).
- Effects on T_{dur}: absorption duration from the nicotine gum lasted 45 minutes ($5.30\ e^{2.14} = 45$) versus 5.3 minutes for other products. In addition, menthol

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variants marginally but significantly increased T_{dur} by 5% compared to regular variants ($e^{0.0530} = 1.05$).

The equations of the final model are presented below:

$$Frel_{THS} = 1 * (\text{nicotine ISO yield}/0.5\ \text{mg})^{-0.573} * (\text{Weight}/69.1\ \text{kg})^{-0.715}$$

$$Frel_{CC} = Frel_{THS} * e^{0.0189}$$

$$Frel_{NNS} = Frel_{THS} * e^{-1.42}$$

$$Frel_{GUM} = Frel_{THS} * e^{-0.489}$$

$$\text{Typical Cl/F (L/min)} = 0.407 * e^{0.235\ (\text{if female})} * (\text{CYP2A6}/29.2\%)^{0.322}$$

$$\text{Typical C0 (ng/mL)} = 0.358 * (\text{CYP2A6}/29.2\%)^{-0.401} * e^{0.408\ (\text{if Black})}$$

$$\text{Typical V/F (L)} = 70.0 * e^{0.0912\ (\text{if Menthol})}$$

$$\text{Typical } T_{dur}\ (\text{min}) = 5.30 * e^{0.0530\ (\text{if mentholated})} * e^{2.14\ (\text{if Gum})}$$

All fixed effect parameters were well estimated, with a relative standard error consistently within 4%.

Menthol had no effect on parameters Frel and Cl/F, which are the determinants of plasma exposure (AUC) at a given nicotine ISO yield. The final population PK model did not include any effect of age, alanine aminotransferase, aspartate aminotransferase, body height, body mass index, creatinine clearance, daily use of conventional cigarettes, region (i.e., Japanese versus non-Japanese), total bilirubin, total Fagerström test for nicotine dependence (FTND) score, or score of the first item from the FTND questionnaire.

The typical initial and terminal half-lives were 1.35 hours and 17 hours, respectively.

Absence of residual effects by graphical exploration suggested that the covariates effects in the Learning data set have been captured by the final PK model.

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Table 19 Parameter Estimates of the Final Population PK Model for Nicotine

	Fixed effects		Random effects			
Parameter (unit)	**Estimate**	**RSE %**	**Variance**	**RSE%**	**IIV%**	**Shrinkage (%)**
V/F (L)	70.0	2.8	0.641	4.1	80	1.9
Cl/F (L/min)	0.407	3.0	0.467	4.2	68	2.5
V2/F (L)	171	3.3	0.715	4.4	85	29.4
Cl2/F (L/min)	0.171	3.5	1.93	4.4	139	14.3
T_{dur} (min)	5.30	1.2	0.141	4.1	38	12.4
Frel –THS	1	fixed				
C0 (ng/mL)	0.358	1.5	0.233	4.5	48	22.6
dTdurd- GUM	2.14	1.2				
dFreld – CC	0.0189	1.6	0.489	4.3	70	5.2
dFreld – NNS	-1.42	1.5	0.489	4.3	70	5.2
dFreld – GUM	-0.489	1.6	0.489	4.3	70	5.2
dCldCYP2A6	0.322	1.6				
dCldSEX (female)	0.235	1.6				
dFreldDOSE	-0.573	1.6				
dC0dCYP2A6	-0.401	1.6				
dFreldWT	-0.715	1.6				
dVdMENTH	0.0912	1.6				
dC0dBLACK	0.408	1.6				
dTdurdMENTH	0.0530	1.6				
Residual (log domain)	0.289	0.9				
Secondary parameters						
Alpha (1/min)	0.00858					
Initial half-life (h)	1.35					
Beta (1/min)	0.000678					
Terminal half-life (h)	17.0					
-2LL	6954					
AIC	7006					
BIC	7184					
#parameters	26					
# observations	6803					
# subjects	244					

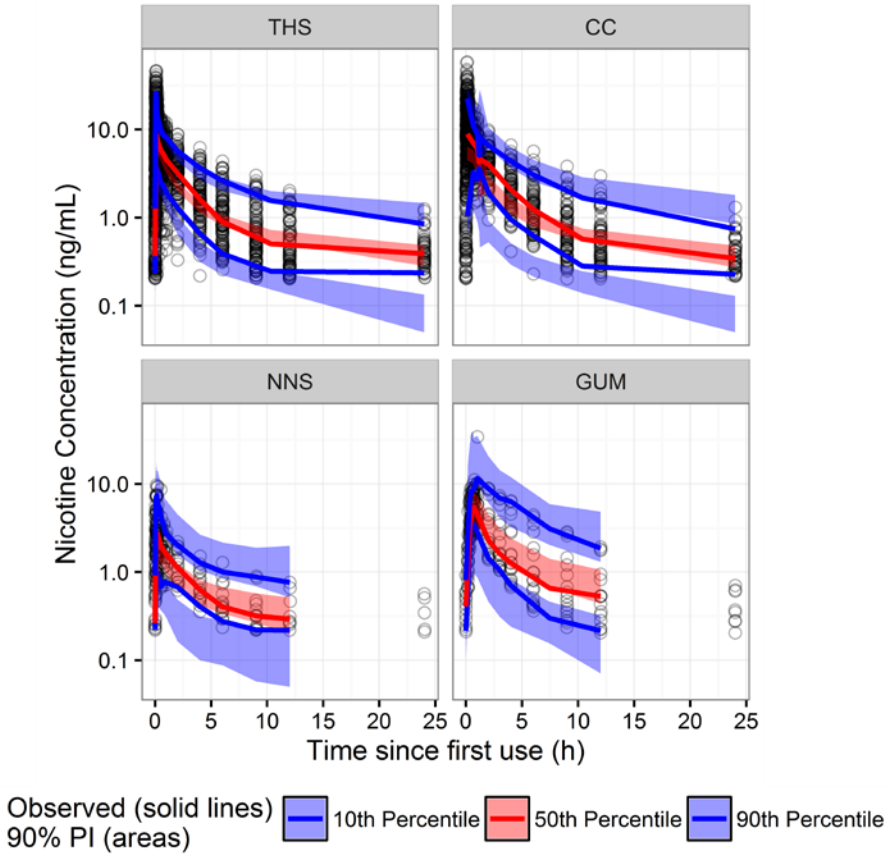
Alpha: initial rate constant; Beta: terminal rate constant; C0: baseline nicotine concentration prior to first product use; CC: conventional cigarette; Cl/F: apparent clearance; Cl2/F: apparent inter-compartmental clearance; dC0dBLACK: effect of being black on C0 (log scale); dC0dCYP2A6: effect of CYP2A6 on C0 (log scale); dCldCYP2A6: effect of CYP2A6 activity on Cl/F (log scale); dCldSEX (female): effect of sex on Cl/F (log scale); dFreldDOSE: effect of nicotine ISO yield on Frel (log scale); dFreldWT: effect of body weight on Frel (log scale); dTdurd- GUM: difference in gum; T_{dur} compared to other products (log scale); dTdurdMENTH: effect of being a menthol variant on T_{dur} (log scale); dFreld: difference in Frel compared to THS (log scale); dVdMENTH: effect of being a menthol variant on V/F (log scale);Frel: bioavailability relative to THS; IIV: inter-individual variability; NNS: nicotine nasal spray; RSE: relative standard error; T_{dur}: duration of zero-order absorption; V/F: apparent central volume of distribution; V2/F: apparent peripheral volume of distribution.
Source: Table 3 Population PK Report

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6.2.1.1.3.2.3. Visual Predictive Checks

Internal visual predictive checks using final population PK model (see Figure 4) revealed that the model captured adequately the median PK profile for every product in both periods. The observed 90th percentile was generally within the prediction interval. The model performance was hard to evaluate in a lower nicotine concentration range. Specifically, the 10th percentile was inconsistently captured by the simulations, possibly due to observations below the limit of quantification being censored whereas simulated concentrations were not.



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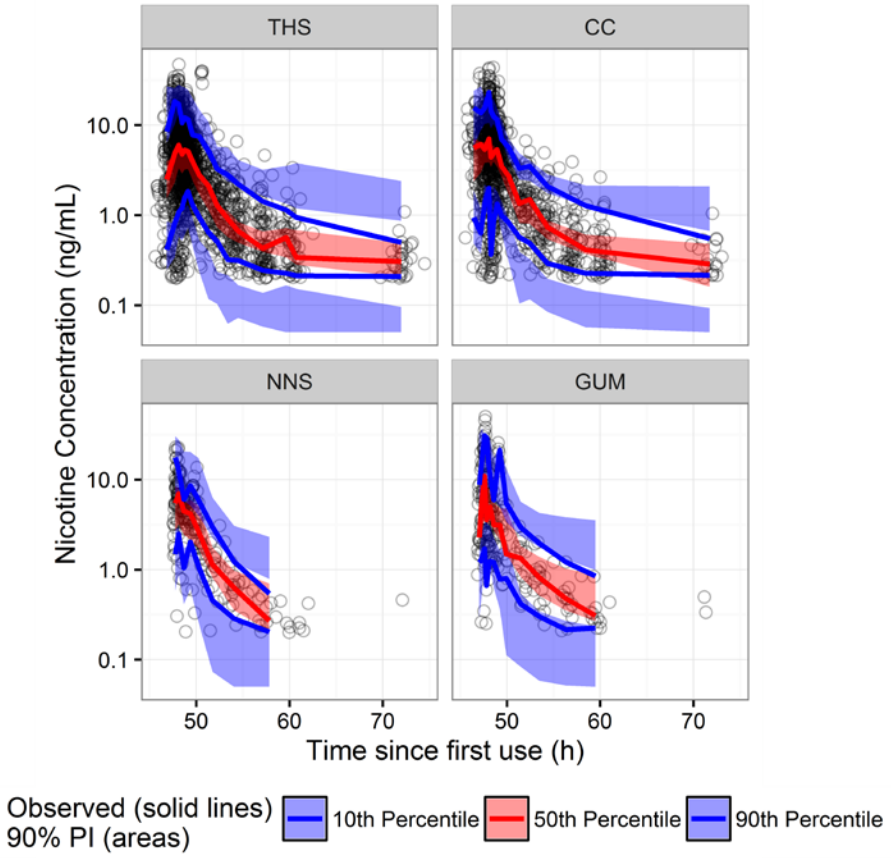


Figure 4 Visual predictive checks using the final nicotine model (10%, 50% and 90% percentile) for period 1 (top) and period 2 (bottom)- semi-logarithmic scale -Learning dataset

The product use at period 2 started nominally 48 h after first product use.
CC: Conventional cigarette; NNS: Nicotine nasal spray; PI: Prediction interval; THS: Tobacco Heating System
Given the small number of observations at 72 hours, simulations were not displayed beyond 60 hours for NNS and the gum.
Source: Figure 11 and Figure 12 Population PK Report

6.2.1.1.3.2.4. Goodness of fit

Goodness of fit plots appeared adequate even for population predictions of REX data (Figure 5) when the population model was not fit to the data (only post-hoc estimation). The individual weighted residual were homogeneously distributed around 0, suggesting no bias in the predicted concentrations of nicotine. The model fitted well the individual subjects, from both the Learning and Validation datasets (Figure 6).

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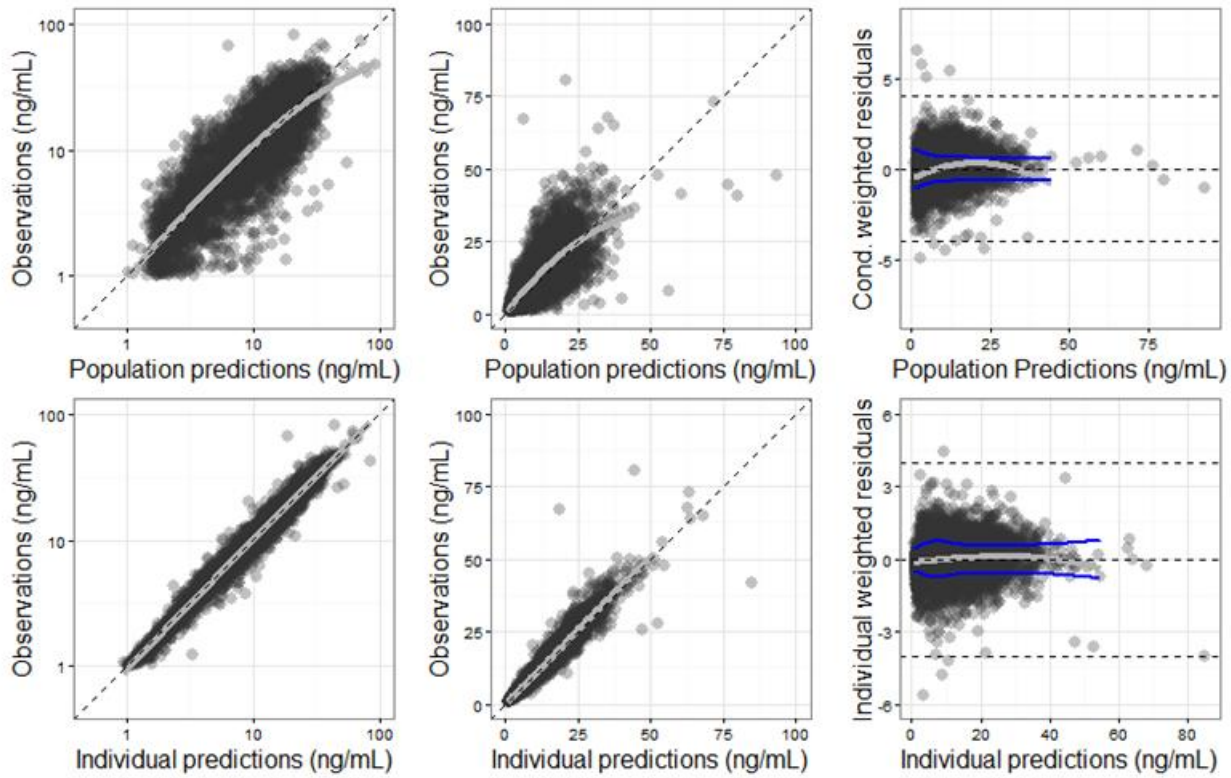


Figure 5 Goodness of fit Plots on the Final Model for Nicotine-Validation dataset

Blue curves: trend lines through positive and negative data points (obtained by LOESS: locally weighted scatterplot smoothing); Cond: Conditional; CWRES: conditional weighted residuals; Dashed line: either identity line or CWRES=0 line or CWRES=±4; Grey curve: trend line though all data points (LOESS); Ind.: Individual; Top panel is plotted on a semi-log scale
Source: Figure 13 Population PK Report

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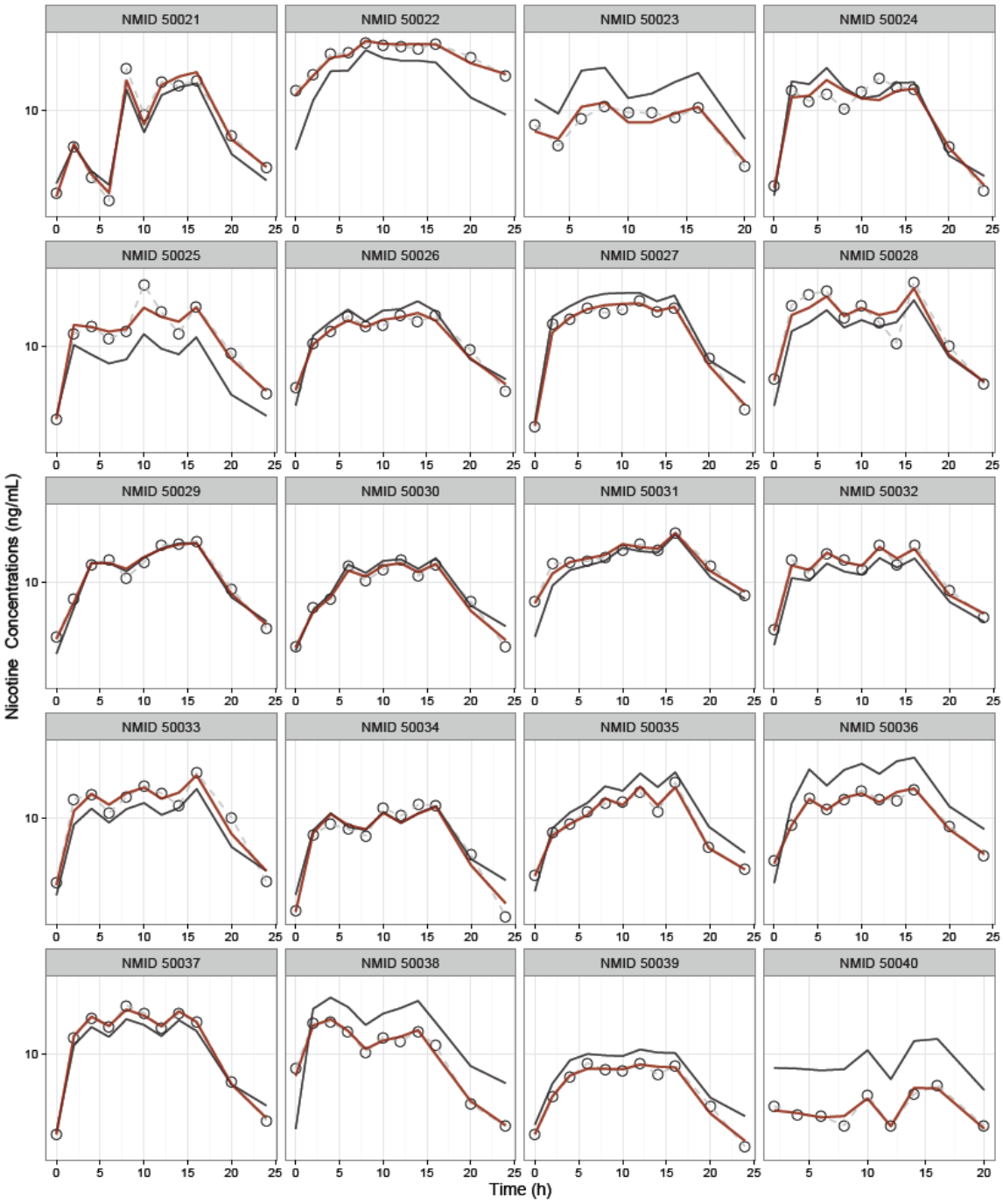


Figure 6 **Examples of individual observed concentrations (ng/mL) of nicotine and predictions derived from the final model-Validation dataset (REX studies)**

Source: Figure A 9-18 Population PK Report

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6.2.1.1.3.2.5. Exposure PK parameters

The exposure PK parameters derived from the final population PK model for the Learning dataset are provided in Table 20, with the differences of the PK parameters reflecting a difference in the populations and different ISO or nominal nicotine concentrations.

Table 20 Mean (CV%) of Population PK Predicted Nicotine Exposure Metrics by Product-Learning dataset

Metric (unit)	THS (N=240)	CC (N=170)	GUM (N=36)	NNS (N=36)
Cmax (ng/mL)	7.49 (85.8)	9.72 (70.4)	5.7 (44.4)	2.72 (73)
AUC_{inf} (ng.min/mL)	1655.81 (82.3)	2010.74 (70.1)	1618.29 (70.1)	1020.86 (67.9)
AUC_{0-24h} (ng.min/mL)	1240.3 (68.4)	1575.48 (59.1)	1278.6 (59.2)	592.41 (38.9)
Tmax (min)	5.52 (34.5)	5.56 (36.3)	46.17 (24)	5.44 (34.9)
t1/2(beta) (h)	15.18 (142.3)	14.61 (135.7)	11.97 (156.8)	23.98 (130.2)
t1/2(alpha) (h)	0.92 (113.3)	0.94 (108.1)	0.8 (181.4)	1.04 (76.1)

CC: Conventional cigarette; Cmax; Maximum concentration; AUC0-24h: Area under a concentration-time curve from time 0 to 24 hours; AUCinf: Area under a concentration-time curve from time 0 to infinity; CV%=percent coefficient of variation; N: Number of subjects; NNS: Nicotine nasal spray; THS: Tobacco Heating System; Tmax: Time to maximum concentration; t1/2(beta): Terminal half-life; t1/2(alpha): Initial half-life.
Source: Table 4 Population PK Report

6.2.1.1.3.2.6. Conclusion

- The population PK model allowed to estimate nicotine plasma exposure based on total and background-adjusted concentrations obtained, from a wide range of nicotine-containing products such as CC or THS, but as well as different nicotine replacement therapies (nicotine gum and NNS) with different routes of administration (inhalation, oral and nasal) in different populations (Americans, Japanese and Europeans).
- The nicotine PK was well described by a two-compartment linear disposition model, with a zero-order absorption process and a mono-exponential decrease for the background concentration.
- The final population PK model did not include effect of age, ALT, AST, body height, body mass index, creatinine clearance, daily use of CC, region (i.e., Japanese versus non-Japanese), total bilirubin, total FTND score, or score of the first item from the FTND questionnaire as they were not significant during the covariate analysis. The model validity was assessed in a variety of ways.
- Nicotine ISO yield, body weight and product were statistically significant covariates on relative bioavailability (Frel), CYP2A6 activity and sex on apparent clearance (Cl/F), menthol on volume (V/F), menthol and product (nicotine gum) on duration of the zero-absorption process (T_{dur}), black and CYP2A6 activity on the background concentration (CO).

The effects of the covariates CYP2A6, body weight and nicotine ISO levels on the model PK parameters were moderate to high, with any doubling of the value resulting in

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changes of the associated PK parameters estimates of -39% to +25%, an effect of 26% of being female on Cl/F and an effect of 50% of being black on CO.

Effects of menthol were lower and marginal (5% on T_{dur} and 9.5% on V/F), and possibly confounded with some covariates as nicotine gum (which contains menthol) was only assessed in Japanese subjects, and the two US studies ([ZRHM-PK-06-US] and [ZRHM-REXA-08-US]) were conducted only with the Menthol variant of THS in a mixed population (e.g., African and White American). Menthol had no effect on parameters Frel and Cl/F, which are the determinants of plasma exposure (AUC) at a given nicotine ISO yield.

The T_{dur} for nicotine gum was markedly different from the other products, consistent with the exposure parameters calculated in section 6.2.1.1.2, showing as a consequence of study design a longer t_{max} with nicotine gum vs THS. The product effects on the relative bioavailability (Frel) between THS and CC are negligible (2% higher for CC compared to THS), while the values were markedly lower for nicotine gum (39% lower) and NNS (76% lower). This is consistent with the observations presented in section 6.2.1.1.2, including the rationale for higher PK exposure parameters for CC compared to THS, when a subject uses a CC with the higher nicotine ISO level compared to THS, assuming the same product use pattern. The absence of product effects on other PK model parameters indicates that the nicotine disposition (distribution in the tissues and elimination) of THS is not altered in comparison with the other nicotine-containing products tested (e.g., no difference in terminal half-life). This also suggests that the difference in t_{max} in the US studies ([ZRHM-PK-06-US] and [ZRHM-REXA-08-US]) or between THS and NNS, are not product related (at the population level), but at the individual level (e.g., longer product duration in some subjects).

As overall conclusion, the PK model supports the PK results analyzed by non-compartmental analysis provided in section 6.2.1.1.2 with a comparable PK profile between THS and CC at the same nicotine yield (ISO).

6.2.1.1.3.3. Pharmacodynamics Results across Studies

In the PK studies, pharmacodynamics were evaluated by the means of two self-reported questionnaires, the Questionnaire on Smoking Urges (QSU brief) (assessed at the following timepoints: prior to T_0, at 15, 30, 45 minutes, 1, 2, 4, 6, 9 and 12 hours), and modified Cigarette Evaluation Questionnaire (mCEQ) to assess reinforcing and aversive effects after product administration. mCEQ was only assessed in group 1 (THS-CC and once on Day 1 and Day 3 after product use).

The subjective effects were compared using a mixed-effects model including terms for product, sequence, period, and subject nested within sequence as a random effect. This method is consistent with the recommendation for the assessment of tobacco craving and withdrawal (Shiffman 2004). The use of a mixed model allowed to estimate the effect of THS adjusting for study design factors by including fixed effects for controlled factors (sex and nicotine level) and accounting for the correlation of observations taken within the same subject (i.e., repeated assessments) over time and across periods (random

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effects). Differently from a traditional ANOVA (or t-test) this approach also does not require complete data for all subjects assuming the data are missing at random.

6.2.1.1.3.3.1. QSU brief

The urge-to-smoke is a subjective motivational state which is, among other aversive effects, made responsible for maintenance of or relapse to CC use. It provides a multidimensional measure to assess the urge to smoke. The QSU in its brief version, the QSU-Brief, is accepted as a quick, valid and reliable measure of urge-to-smoke, including multi-dimensional aspects of smoking urge (Hanson 2009, Rosenberg 2009). It has produced consistent findings across many studies and the psychometric properties were acceptable and consistent across samples and settings.

The QSU-brief is a self-reported questionnaire with 10 items to be rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores in this questionnaire indicate a higher urge-to-smoke. Factor 1 reflects the desire and intention to smoke with smoking perceived as rewarding and Factor 2 reflects anticipation of relief from negative effects of not smoking. The total score is the average of Factor 1 and Factor 2.

6.2.1.1.3.3.2. Results

The urge-to-smoke total score -time profiles were similar across studies for THS and CC (Figure 7). A maximum reduction in urge-to-smoke from baseline was observed at the first assessment after single product use (T_0+15min) for both products and all studies (total score of 2.7 to 3.8 at T_0+15min with baseline values from 4.2 to 5.3 for THS, total score of 2.7 to 3.5 at T_0+15min with baseline values from 3.9-5.2 for CC , apart from the CC arm in [ZRHM-PK-05-JP] where the minimum score was observed at the second assessment after single product use (T_0+20min). Using the T_0 + 15min time point as a reference, the difference between THS and CC for the total score ranged between -0.4 up to 0.8 (i.e., higher than on overall), with absolute values of the total score for urge-to-smoke approximately 1-point lower in the two Japanese [ZRHR-PK-02-JP] and [ZRHM-PK-05-JP] studies compared to the EU [ZRHR-PK-01-EU] and US [ZRHM-PK-06-US] studies (Table 21).

The urge-to-smoke was consistently higher during the first 2-4 hours post-product use for the NRT (NNS and NRT gum) compared to THS for all studies apart from [ZRHR-PK-01-EU] where values were comparable for THS and NNS.

There was no notable difference in QSU-brief total score for THS compared to NNS over the whole assessment period (T_0 + 15min to T_0 + 12h) in [ZRHR-PK-01-EU], while THS reduced the urge-to-smoke more than NNS in study [ZRHM-PK-06-US], with a THS-NRT difference of -0.5 points at T_0 + 15min (Table 22).

Consistent results were reported in the two Japanese studies, with a stronger reduction from baseline QSU-brief total score for THS compared to NRT gum. In particular, at T_0+20 min, with a maximal mean reduction between THS and NRT Gum of -0.7 and -0.8 in [ZRHR-PK-02-JP] and [ZRHM-PK-05-JP], respectively (Table 22).

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In conclusion, the effect on urge-to-smoke between THS and CC is comparable, while THS reduced it at least, as efficiently as or better than NNS or NRT gum.

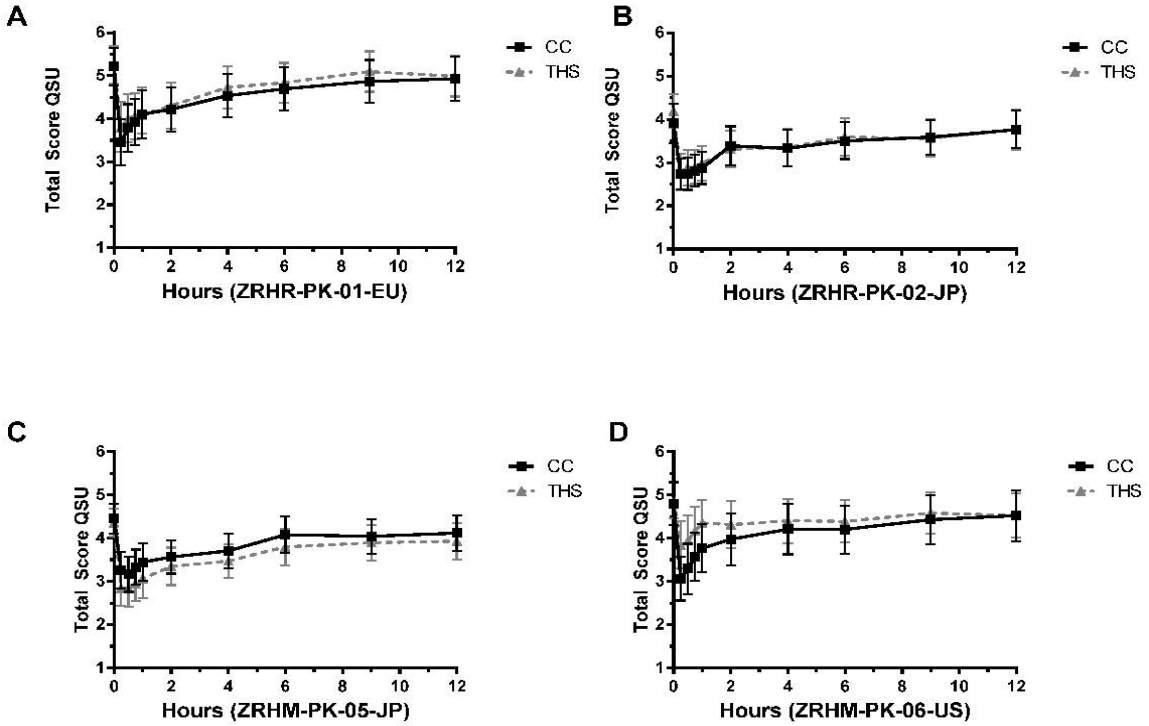


Figure 7 Total score of the QSU brief–Group 1 (arithmetic mean and 95% confidence intervals)

CC: conventional cigarettes, THS: Tobacco Heating System
Source: Appendix 15.2.4.14 ZRHR-PK-01-EU, Appendix 15.2.4.14 ZRHR-PK-02-JP, Appendix 15.2.4.14 ZRHM-PK-05-JP, Appendix 15.2.4.14 ZRHM-PK-06-US.

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Table 21 Analysis of Urge to Smoke after Single Use by Study – THS vs CC

QSU-b Total Score	ZRHR-PK-01-EU (N=42)	ZRHR-PK-02-JP (N=42)	ZRHM-PK-05-JP (N=43)	ZRHM-PK-06-US (N=41)
Overall				
THS	4.47 [3.37, 5.57]	3.24 [2.49, 3.98]	3.36 [2.74, 3.97]	4.28 [3.69, 4.87]
CC	4.30 [3.20, 5.40]	3.19 [2.45, 3.94]	3.64 [3.02, 4.26]	3.91 [3.32, 4.50]
THS-CC	0.17 [-0.93, 1.26]	0.04 [-0.70, 0.79]	-0.28 [-0.79, 0.22]	0.37 [-0.02, 0.77]
T_0 + 15min/20min				
THS	3.82 [2.55, 5.09]	2.78 [2.10, 3.46]	2.85 [2.13, 3.57]	3.84 [3.12, 4.56]
CC	3.46 [2.19, 4.74]	2.73 [2.05, 3.41]	3.26 [2.54, 3.98]	3.08 [2.36, 3.80]
THS-CC	0.35 [-1.06, 1.77]	0.05 [-0.55, 0.65]	-0.41 [-1.14, 0.31]	0.77 [0.06, 1.47]

Means [95% CI] are the adjusted least squares means and 95% confidence intervals from an ANOVA model. Overall corresponds to the least squares mean difference over all time points.
CC: conventional cigarettes, THS: Tobacco Heating System
Source: Appendix 15.4.4.12 and 15.3.6.11 ZRHR-PK-01-EU, Appendix 15.4.4.12 and 15.3.6.11 ZRHR-PK-02-JP, 15.4.4.12 and 15.3.6.11 ZRHM-PK-05-JP, 15.4.4.12 and 15.3.6.11 ZRHM-PK-06-US.

Table 22 Analysis of Urge to Smoke after Single Use by Study –THS vs NRT

QSU-b Total Score	ZRHR-PK-01-EU (N=18)	ZRHR-PK-02-JP (N=18)	ZRHM-PK-05-JP (N=18)	ZRHM-PK-06-US (N=17)
Overall				
THS	3.92 [2.55, 5.28]	3.00 [2.13, 3.87]	3.33 [2.35, 4.31]	3.34 [2.64, 4.05]
NRT	4.07 [2.70, 5.44]	3.20 [2.33, 4.07]	3.66 [2.69, 4.64]	3.70 [2.99, 4.40]
THS-NRT	-0.15 [-1.35, 1.05]	-0.20[-0.87, 0.48]	-0.34 [-0.87, 0.19]	-0.35 [-0.79, 0.09]
T_0 + 15/20min				
THS	3.41 [2.14, 4.67]	2.58 [1.61, 3.54]	2.94 [1.85, 4.04]	2.97 [2.11, 3.82]
NRT	3.69 [2.43, 4.96]	3.28 [2.32, 4.25]	3.71 [2.61, 4.80]	3.51 [2.64, 4.38]
THS-NRT	-0.29 [-1.23, 0.65]	-0.71 [-1.61, 0.20]	-0.76 [-1.65, 0.12]	-0.54 [-1.38, 0.29]

Means [95% CI] are the adjusted least squares means and 95% confidence intervals from an ANCOVA model. Overall corresponds to the least squares mean difference over all time points.
CC: conventional cigarettes, THS: Tobacco Heating System
Source: Appendix 15.4.4.12 and 15.3.6.11 ZRHR-PK-01-EU, Appendix 15.4.4.12 and 15.3.6.11 ZRHR-PK-02-JP, 15.4.4.12 and 15.3.6.11 ZRHM-PK-05-JP, 15.4.4.12 and 15.3.6.11 ZRHM-PK-06-US.

6.2.1.1.3.3.2.1. MCEQ

The modified Cigarette Evaluation Questionnaire (mCEQ) is the most widely used assessment tool to assess reinforcing and aversive effects of smoking (Cappelleri 2007). The 12-item mCEQ measures: (i) smoking satisfaction (satisfying, tastes good and enjoys smoking), (ii) psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger), (iii) aversion (dizziness, nauseous), (iv) enjoyment of respiratory tract sensations (single-item assessment), and (v) craving reduction (single-

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item assessment). Each item is rated on a 7-point scale, with 1= not at all and 7=extremely.

The mCEQ has been commonly applied in clinical studies to evaluate if pharmacological treatments may decrease the reinforcing effects of smoking (Cappelleri 2007). In the context of the assessment of THS, the mCEQ is used to evaluate how close THS may come to the profile of reinforcing and aversive effects observed for CC and therefore may allow an estimate on adoption and future use of the new product. In our studies, mCEQ was assessed between 8.00-11.00 PM on the day of product use.

6.2.1.1.3.3.2.2. Results

The results for product evaluation using the mCEQ subscale scores following single product use showed differences in all the domains (Figure 8 and Table 23, only smoking satisfaction shown), with the exception of Aversion where the effect of THS compared to CC was similar (range between -0.1 and 0.4 for THS and CC).

Craving reduction with THS was close to CC in the two Japanese studies [ZRHR-PK-02-JP] and [ZRHM-PK-05-JP], while effects were lower in THS compared to CC in the non-Japanese studies, in particular for the [ZRHM-PK-06 US] study where the difference between THS and CC was higher than 1 point (THS-CC= 1.2 points).

For the enjoyment of respiratory tract sensation and psychological reward domain scores remained slightly higher for CC compared to THS, with the highest differences in the two non-Japanese studies [ZRHR-PK-01-EU] and [ZRHM-PK-06-US], but with differences between THS and CC of less than 1-point, ranging from 0.6 to 0.9 points for the respiratory tract score and from 0.2 to 0.6 points for psychological reward score.

Smoking satisfaction was higher following single use of CC compared to THS, with THS-CC differences ranging between 1.0 and 1.3 points (Table 23).

In conclusion, reinforcing and aversive effects after the use of THS were less reduced than after smoking a CC, with the exception of a comparable effect on aversion. Differences in craving reduction between THS and CC were lower in the Japanese versus non-Japanese studies. No relevant differences were observed for the other parameters between studies.

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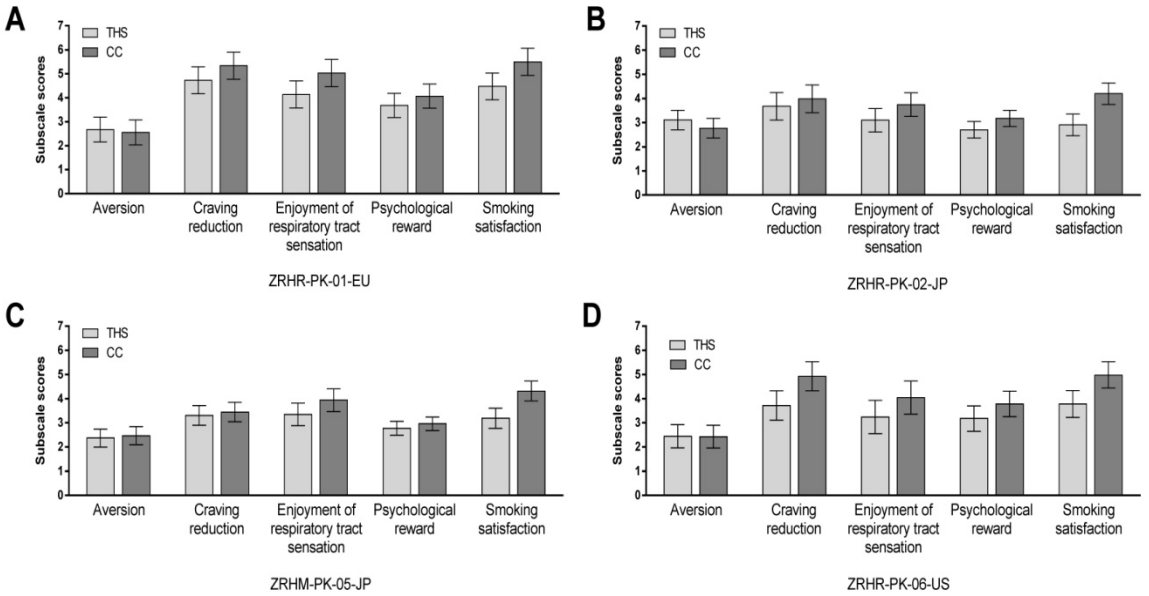


Figure 8 mCEQ subscales brief–Group 1 (arithmetic mean and 95% confidence intervals)

CC: conventional cigarettes, THS: Tobacco Heating System
Source: Appendix 15.4.4.15 and 15.3.6.12 ZRHR-PK-01-EU, 15.4.4.15 and 15.3.6.12 ZRHR-PK-02-JP, Appendix 15.4.4.15 and 15.3.6.12 ZRHM-PK-05-JP, 15.4.4.15 and 15.3.6.12ZRHM-PK-06-US,

Table 23 Product Evaluation after Single Use by Study – THS vs CC

mCEQ Scores	ZRHR PK-01-EU (N=42)	ZRHR PK-02-JP (N=42)	ZRHM PK-05-JP (N=43)	ZRHM PK-06-US (N=40)
Smoking Satisfaction				
THS	4.47 [3.91, 5.03]	2.91 [2.46, 3.35]	3.19 [2.77, 3.60]	3.78 [3.22, 4.33]
CC	5.49 [4.93, 6.06]	4.20 [3.75, 4.64]	4.31 [3.90, 4.73]	4.97 [4.43, 5.52]
THS-CC	-1.03 [-1.55, -0.50]	-1.29 [-1.71, -0.87]	-1.12 [-1.53, -0.72]	-1.20 [-1.79, -0.60]

CC: conventional cigarettes, THS: Tobacco Heating System
Source: Appendix 15.4.4.15 and 15.3.6.12 ZRHR-PK-01-EU, 15.4.4.15 and 15.3.6.12 ZRHR-PK-02-JP, Appendix 15.4.4.15 and 15.3.6.12 ZRHM-PK-05-JP, 15.4.4.15 and 15.3.6.12ZRHM-PK-06-US,

Urge-to-smoke, reinforcing and aversive effects were assessed for THS in the studies [ZRHR-PK-01-EU], [ZRHR-PK-02-JP], [ZRHM-PK-05-JP] and [ZRHM-PK-06-US] (N=41-43) and compared to CC. In addition, the urge to smoke was assessed between THS and NRT (NNS in studies [ZRHR-PK-01-EU] and [ZRHM-PK-06-US] and NRT gum in studies [ZRHR-PK-02-JP], [ZRHM-PK-05-JP]).

THS was able to reduce the effects on smoking urges as effectively as CC, and at least as well, if not better, than NRT (NNS or NRT Gum). Variability was high, but the effects at the numerous time points assessed (10 per product exposure) were consistent with the general effects and for both factors (Factor 1 and Factor 2).

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As mCEQ is a questionnaire that can be used only once every 24-hours, the number of assessments per subject was low (n=2). However, product evaluation was conducted in a large number of subjects (n=167). Aversion was comparable between CC and THS, and all other scores of THS were lower than CC (i.e., lower effects on urge-to-smoke and on reinforcing effects with THS compared to CC). Craving reduction was close to CC with THS in the [ZRHR-PK-02-JP] and [ZRHM- PK-05-JP] studies.

6.2.1.1.4 References

Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol. 2009; 49(1):57-71.

Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addict Behav. 2007; 32:912–23.

European Medicines Agency (EMA). Guideline on Reporting the Results of Population Pharmacokinetic Analyses, Doc. Ref. CHMP/EWP/185990/06. 2007.

FDA (Food and Drug Administration). Guidance for industry - Statistical approaches to establishing bioequivalence. 2001.

Hanson K, O'Connor R, Hatsukami D. Measures for assessing subjective effects of potential reduced-exposure products. Cancer Epidemiol Biomarkers Prev. 2009; 18(12):3209-24.

Hukkanen J, Jacob P, 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacol Rev. 2005; 57(1):79-115.

Karlsson MO, Savic RM. Diagnosing model diagnostics. Clinical pharmacology and therapeutics. 2007; 82(1):17-20.

Lunell E, Curvall M. Nicotine delivery and subjective effects of Swedish portion snus compared with 4 mg nicotine polacrilex chewing gum. Nicotine Tob Res. 2011; 13(7):573-8.

Lunell E, Lunell M. Steady-state nicotine plasma levels following use of four different types of Swedish snus compared with 2-mg Nicorette chewing gum: a crossover study. Nicotine Tob Res. 2005; 7(3):397-403.

Rosenberg H. Clinical and laboratory assessment of the subjective experience of drug craving. Clin Psychol Rev. 2009; 29:519–34.

Shiffman S, West RJ, Gilbert DG. Recommendation for the assessment of tobacco craving and withdrawal in smoking cessation trials. Nicotine & Tobacco Research. 2004; 6(4):599–614.

Wahlby U, Jonsson EN, Karlsson MO. Comparison of stepwise covariate model building strategies in population pharmacokinetic-pharmacodynamic analysis. AAPS pharmSci. 2002; 4(4):E27.

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