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Nicotine pharmacokinetic profiles of the Tobacco Heating System 2.2, cigarettes and nicotine gum in Japanese smokers

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ABSTRACT

Two open-label randomized cross-over studies in Japanese smokers investigated the single-use nicotine pharmacokinetic profile of the Tobacco Heating System (THS) 2.2, cigarettes (CC) and nicotine replacement therapy (Gum).

In each study, one on the regular and one on the menthol variants of the THS and CC, both using Gum as reference, 62 subjects were randomized to four sequences: Sequence 1: THS - CC (n = 22); Sequence 2: CC – THS (n = 22); Sequence 3: THS – Gum (n = 9); Sequence 4: Gum – THS (n = 9). Plasma nicotine concentrations were measured in 16 blood samples collected over 24 h after single use.

Maximal nicotine concentration (C_{max}) and area under the curve from start of product use to time of last quantifiable concentration ($AUC_{0\text{-last}}$) were similar between THS and CC in both studies, with ratios varying from 88 to 104% for C_{max} and from 96 to 98% for $AUC_{0\text{-last}}$. Urge-to-smoke total scores were comparable between THS and CC.

The THS nicotine pharmacokinetic profile was close to CC, with similar levels of urge-to-smoke. This suggests that THS can satisfy smokers and be a viable alternative to cigarettes for adult smokers who want to continue using tobacco.

1. Introduction

The delivery of nicotine without combustion aims at lowering the health risks of smoking cigarettes, as heating tobacco at lower temperatures reduces or eliminates the formation of many chemical substances (Borgerding and Klus, 2005; Forster et al., 2015; Schaller et al., 2016a, 2016b), resulting in reduced exposure to harmful and potentially harmful constituents (Haziza et al., 2016a, 2016b; Lüdicke et al., 2016; Lüdicke et al., 2017b; Roethig et al., 2008; Roethig et al., 2007). Clinical studies have consistently shown reductions in biomarkers of exposure and in clinical risk markers in smokers who switch from CC to different non-combustible products (Lüdicke et al., 2017a; Roethig et al., 2008; Roethig et al., 2010; Unverdorben et al., 2010).

Smokers are more likely to find such products acceptable if they provide nicotine in a way similar to what is achieved from smoking cigarettes. Thus it is expected that in order to satisfy smokers, heated tobacco products should have a nicotine pharmacokinetic (PK) profile close to that of CC, including comparable maximal concentration (C_{max}), time to maximal concentration (t_{max}), and overall nicotine exposure (area under the concentration-time curve, AUC). A study conducted with THS 2.1, the previous version of THS 2.2, indicated that nicotine absorption was comparable in speed and magnitude to CC (Picavet et al., 2016).

The objective of the two two-period crossover studies conducted in Japan was to evaluate the single use nicotine pharmacokinetic profiles of the two variants of THS 2.2, regular (rTHS) and menthol (mTHS), with CC and nicotine replacement therapy (Nicorette® gum) as a non-inhalative comparator. In addition, subjective effects (urge-to-smoke) were assessed.

2. Methods

The study on rTHS (registered at ClinicalTrials.gov as NCT01959607) was conducted in Tokyo from July to November 2013, the study on mTHS (NCT01967706) in Saitama from August to November 2013. Principles as defined in the International

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Conference on Harmonization Good Clinical Practice guideline and in the Declaration of Helsinki, as well as additional applicable national regulations were followed. The protocols were approved by two separate institutional review boards (Supplementary Material) and the subjects received complete information about the study and signed an informed consent form prior to any assessment. Subjects received a financial compensation for their participation in the studies.

2.1. Subjects

For both studies, subjects were recruited using the databases of the clinics. Eligible for participation were healthy adult Japanese smokers (aged from 23 to 65 years) with a smoking history of at least three years, a minimum consumption of 10 CCs per day with a maximum yield of 1 mg nicotine ISO during four weeks prior to admission, and urinary cotinine $\geq$ 200 ng/mL. Eligible subjects also had to have no plan to quit smoking within three months following admission, had to be ready to accept interruptions of smoking for up to four consecutive days, and had to be willing to use THS and Gum instead of smoking. Subjects with clinically relevant diseases or with a history of alcohol and/or drug abuse, as well as pregnant or breastfeeding women, were excluded from the study. Subjects had to be within the body mass index range of 18.5–32 kg/m^2.

2.2. Design

A total of 65 and 73 subjects were enrolled in the rTHS and mTHS studies, respectively. In each study, 62 subjects were randomized, the remaining subjects serving as back-up subjects, and 60 and 61 subjects completed the studies, respectively. Randomization was, stratified by sex and CC ISO nicotine yield ($\leq$0.6 mg vs 0.6–1 mg) but without consideration of smoking history, cigarette preference (menthol or nonmenthol), or number of cigarettes smoked per day, into one of four sequences:

Sequence 1: THS → CC (N = 22); Sequence 2: CC → THS (N = 22); Sequence 3: THS → Gum (N = 9); Sequence 4: Gum → THS (N = 9).

Quotas were used to ensure that each sex and nicotine yield group represented at least 40% of the study population. All enrolled subjects were exposed to THS and Gum during the product trial on the day prior to randomization (Day-1) and all were included in the safety population, safety being monitored throughout the study. The safety population included all subjects who were exposed to THS, regular or menthol, at any time during the study, including the product test at admission.

2.3. Investigational products

THS 2.2 is composed of the THS holder (the tobacco heating device), the THS tobacco stick, available in a regular and a menthol variant, and the charger unit (Smith et al., 2016). Additional details on THS 2.2 are provided in the Supplementary Material. The reference cigarettes, provided by the subjects, were their preferred brand of commercially available regular CC (rCC) in the rTHS study or menthol CC (mCC) in the mTHS study, with nicotine ISO yields $\leq$ 1 mg. The Gum used in both studies was the 2 mg version of Nicorette®, the only over-the-counter product available in Japan at that time. The average nicotine delivery from Nicorette® 2 mg gum was reported as 1.06 mg per chewed gum (53%) (Benowitz et al., 1987). For both studies, the selected 2 mg gum was the one without mint-flavor characteristics, aiming to keep a unique point of reference rather than trying to match subjects' preferences.

2.4. Procedures

On Day -1, subjects completed a product trial, first of up to three THS tobacco sticks and subsequently of Gum. Then, subjects were confined in the respective study sites for the study duration. In both studies, confinement periods 1 and 2 each consisted of at least 24 h of nicotine wash-out and 1 day of single product use. As the tobacco stick is not reduced in size during use it cannot be visually determined to what degree the product has been consumed. Subjects were instructed to completely use the THS for about 6 min (14 puffs), and subjects using Gum were asked to slowly chew it for 35 ± 5 min.

Compliance was ensured by strict distribution of individual products and collection of used Tobacco Sticks, CC butts and NRT gum, documented in logs. In addition, for subjects using NRT gum, compliance was chemically verified using exhaled CO breath tests, the cut-off point being 10 ppm. CO breath tests were also used as compliance measure during the wash-out days.

A total of 16 venous blood samples were taken to provide a 24-h nicotine PK profile after exposure to THS and CC (Day 1 and Day 3), with the first sample being drawn within 15 min prior to T_0, T_0 corresponding to the time of the first puff for THS use, the lightening of the cigarette for CC smoking, or the time of intake of the Gum. Subsequent samples were taken after 2, 4, 6, 8, 10, 15, 30, 45, 60 min, and after 2, 4, 6, 9, 12 and 24 h, all relative to T_0. For Gum, the first blood sample drawn to establish the 24-h PK profile was taken within 15 min prior to T_0, the other samples being taken 10, 20, 25, 30, 35, 40, 45, 60 min, and 2, 4, 6, 9, 12, and 24 h after T_0.

The determination of plasma nicotine concentrations was carried out using a validated LC-MS/MS method, over a calibration range spanning from the lower limit of quantification (LLOQ) of 0.2 ng/mL to 10.0 ng/mL.

Subjective effects of THS, CC and Gum were evaluated using the Questionnaire on Smoking Urges, brief version (QSU-brief) (Cox et al., 2001a), completed on Day 1 and Day 3 within 15 min (20 min for Gum) prior to T_0, 15, 30, 45, 60 min, and 2, 4, 6, 9, and 12 h after T_0.

Adverse events, including abnormal clinical examination and laboratory findings, were collected throughout the study.

2.5. Analysis

The rate and amount of nicotine uptake was assessed by C_{max} and AUC from start of product use to time of last quantifiable concentration ($AUC_{0\text{-last}}$). Other PK parameters were AUC to infinity ($AUC_{0\text{-}\infty}$), t_{max} and apparent half-live ($t_{1/2}$), derived from plasma concentrations by non-compartmental analysis (Phoenix WinNonlin version 5.2, Pharsight Corp).

A total of 44 subjects were determined to be necessary to estimate the C_{max} and $AUC_{0\text{-last}}$ ratio between THS and CC with a 90% power of obtaining a margin of error of ±20% at an alpha level of 5%, assuming THS and CC having similar nicotine C_{max} and $AUC_{0\text{-last}}$. The underlying coefficient of variation (CV) estimates for nicotine C_{max} (36%) and $AUC_{0\text{-last}}$ (21%) were based on data collected in a previous clinical study (Picavet et al., 2016).

Eighteen subjects were determined to be necessary to estimate the geometric mean C_{max} ratio between THS and Gum (assumed to be 2.0, based on (Dautzenberg et al., 2007)), with a precision allowing for the lower bound of the 95% CI to exceed unity with 90% power and for a 10% drop-out rate.

The PK parameters were statistically assessed in all randomized subjects for whom at least one PK parameter could be derived. Analysis of variance (ANOVA) was conducted on logarithmically transformed $AUC_{0\text{-last}}$, C_{max}, $AUC_{0\text{-}\infty}$, and $t_{1/2}$ values. The model included terms for sequence, subject within sequence, period, and

exposure group, and served for calculating adjusted geometric least square (LS) means and 95% confidence intervals (CIs) for the THS:CC and THS:Gum ratios. Hodges-Lehmann estimates of the 95% CIs of the median t_{max} group differences THS − CC and THS − Gum were calculated.

Urge to smoke was assessed using the QSU-brief (Cox et al., 2001b) which is a self-reported questionnaire with 10 items (Supplementary Table 3) to be rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores indicate a higher urge to smoke. Total QSU-brief scores were calculated by averaging the 10 urge-to-smoke questionnaire scores, as long as more than 50% of the responses were available within a questionnaire. They were analyzed with a repeated mixed-effects ANOVA, with subject nested within sequence used as random effects factor and sequence, period, product, and product × time point as fixed effect factors, time point being treated as a repeated measurement factor.

3. Results

3.1. Baseline characteristics

110 and 147 subjects were screened at the Koganeibashi Sakura Clinic (Tokyo) and at the Ageo Medical Clinic (Saitama), respectively. Of these, 65 and 73 were enrolled in the rTHS (Tokyo) and mTHS (Saitama) studies, respectively. In both studies, the THS:CC population (sequences 1 and 2) consisted of 44 and the THS:Gum population (sequences 3 and 4) of 18 subjects. The overall population (sequences 1 to 4) consisted of 60 and 61 subjects in the rTHS and mTHS studies, respectively, 3 subjects (2 in the rTHS study, one each in sequence 1 and sequence 2, and 1 in sequence 1 of the mTHS study) having withdrawn their consent on Day 1.

Both study populations were comparable, with 52.5–55.0% male subjects, the mean age (±standard deviation [SD]) being 34.0 ± 9.18 years and 32.6 ± 9.44 years in the rTHS and mTHS studies, respectively. The majority of subjects smoked less than 20 cigarettes per day (56.7% and 59%, respectively) and cigarettes with nicotine ISO levels ≤ 0.6 mg (53.3% and 57.4%, respectively).

3.2. Pharmacokinetics

3.2.1. Cigarette

The plasma nicotine concentration curves presenting geometric means over 1 and 24 h following single use of CC (Fig. 1) and the derived PK parameters were similar for both studies, with geometric least square means C_{max} of 13.82 ng/mL for rCC and 12.09 ng/mL for mCC and $AUC_{0\text{-last}}$ of 24.66 ng × h/mL for rCC and 24.45 ng × h/mL for mCC.

Similarly, $AUC_{0\text{-}\infty}$, $t_{1/2}$, and tmax were almost identical for rCC and mCC (Table 1).

3.2.2. Tobacco Heating System vs Cigarette

As shown in Fig. 1, the plasma nicotine concentration-time curves for THS followed a similar profile as for CC, with the THS curve almost superimposed over CC, indicating that nicotine absorption as well as rate of absorption were similar between THS and

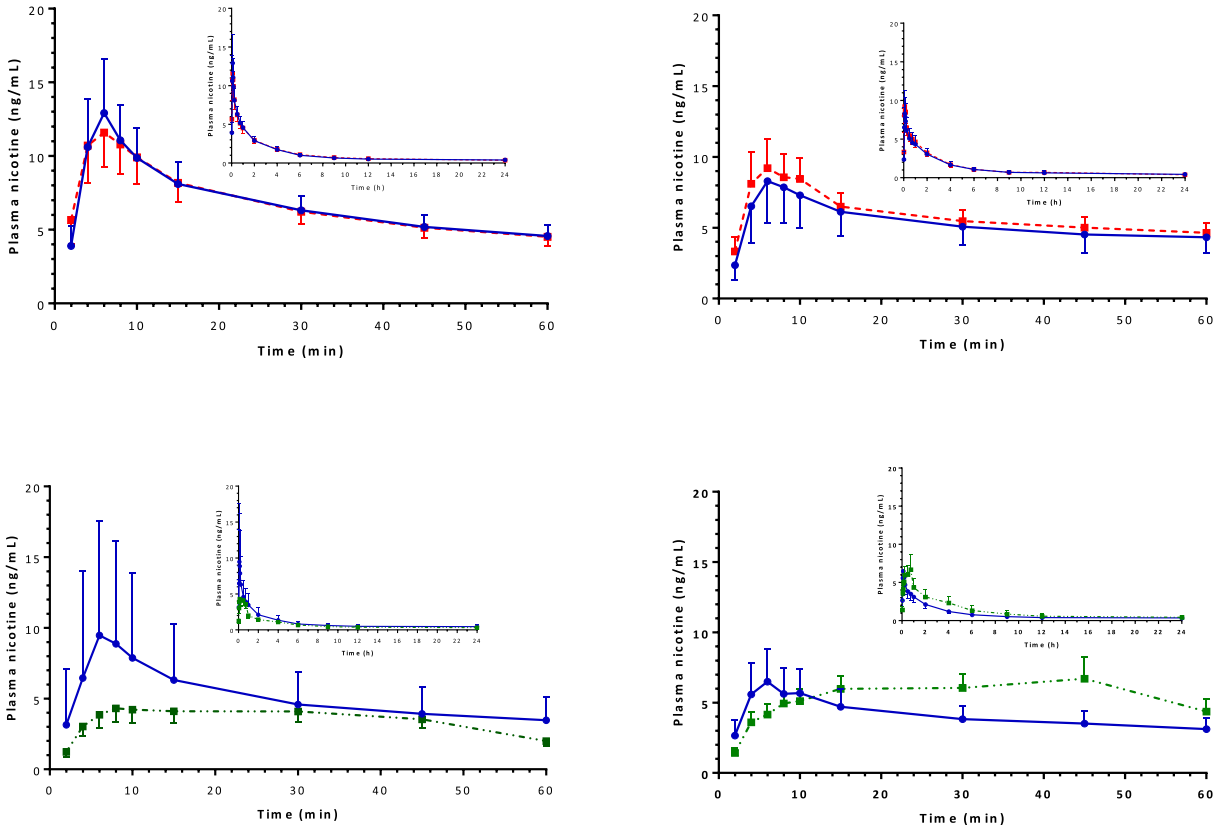

Fig. 1. Nicotine plasma concentration (ng/mL, geometric mean ± 95% CI) over 60 min (large graphs) and over 24 h (small graphs). The two graphs in the upper row depict the results for sequences 1 and 2 (THS and CC), the two graphs in the lower row depict the results for sequences 3 and 4 (THS and Gum). The left column shows the results from the rTHS study and the right column, the results from the mTHS study. THS profiles are shown in blue (continuous lines), CC profiles in red (dashed lines) and Gum profiles in green (dotted-dashed lines).

Table 1
PK parameters in the THS:CC population.

PK Parameter	Product Variant	Product Exposure	Number of Subjects	Geometric LS Mean	Ratio[a] (THS:CC) (%)	CV (%)	95% CI
C_{max} (ng/mL)	Regular	rTHS	42	14.30	103.50	47.14	84.94, 126.11
		rCC	42	13.82			
	Menthol	mTHS	43	10.70	88.47	63.54	68.64, 114.03
		mCC	43	12.09			
$AUC_{0\text{-last}}$ (ng*h/mL)	Regular	rTHS	42	23.75	96.34	28.68	85.10, 109.07
		rCC	42	24.66			
	Menthol	mTHS	43	23.99	98.13	47.55	80.61, 119.46
		mCC	43	24.45			
$AUC_{0\text{-}\infty}$ (ng*h/mL)	Regular	rTHS	39	26.20	97.88	26.52	86.81, 110.36
		rCC	39	26.76			
	Menthol	mTHS	34	26.33	94.97	42.31	77.69, 116.09
		mCC	34	27.73			
$t_{1/2}$ (h)	Regular	rTHS	39	3.81	93.07	20.99	84.58, 102.40
		rCC	39	4.10			
	Menthol	mTHS	34	4.11	102.30	37.94	85.31, 122.66
		mCC	34	4.02			
				Median	**Median Difference**		
t_{max} (min)	Regular	rTHS	42	6.00	0.04		−1.00, 1.05
		rCC	42	6.00			
	Menthol	mTHS	43	6.00	1.00		0.00, 2.50
		mCC	43	6.00			

mTHS: mentholated tobacco heating system; rTHS: regular tobacco heating system version 2.2; mCC: mentholated cigarette; rCC: regular cigarette; $AUC_{0\text{-last}}$: area under plasma concentration-time curve from start of product use extrapolated to the last measurable concentration; $AUC_{0\text{-}\infty}$: area under plasma concentration-time curve from start of product use extrapolated to infinity; CI: confidence interval; CV: coefficient of variation; LS: least square; $t_{1/2}$: terminal half-life; t_{max}: time to maximum plasma concentration.
[a] Geometric least square mean ratio.

CC. For C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, and $t_{1/2}$, the THS:CC ratios varied between 88 and 104% (Table 1) and the 95% CIs covered 100%.

PK parameters were similar between rTHS and mTHS, although the geometric least square mean C_{max} for mTHS (10.70 ng/mL) was lower than for rTHS (14.30 ng/mL).

In sequences 1 and 2, 27 subjects (64.3%) and 31 subjects (72.1%) had relatively low plasma concentrations above LLOQ prior to T_0 in the rTHS (highest concentration 1.61 ng/mL) and the mTHS (highest concentration 2.15 ng/mL) studies, respectively.

3.2.3. Gum

Median t_{max} was reached slightly earlier in the rTHS (35 min) than in the mTHS (45 min) study, and the other parameters were slightly lower in the rTHS study (e.g., geometric least square means C_{max} of 4.80 ng/mL and $AUC_{0\text{-last}}$ of 14.88 ng × h/mL in the rTHS study vs. 7.52 ng/mL and 27.94 ng × h/mL, respectively, in the mTHS study; Table 2).

3.2.4. Tobacco Heating System vs Gum

The THS and Gum nicotine profile and PK parameter comparisons differed between studies (Fig. 1 and Table 2). C_{max} was higher in rTHS compared to Gum (THS:Gum ratio: 240%) but similar between mTHS and Gum (ratio 102%). $AUC_{0\text{-last}}$ was comparable between rTHS and Gum (ratio 127%) but lower for mTHS compared to Gum (ratio 56%). $AUC_{0\text{-}\infty}$ was higher for rTHS and lower for mTHS compared to Gum (ratios 174% and 51%, respectively). The t_{max} for Gum were markedly longer than for THS, with median differences of 29 and 38 min in the rTHS and the mTHS studies, respectively.

In sequences 3 and 4, 11 subjects (61.1%) and 13 subjects (72.2%) had relatively low plasma concentrations above LLOQ prior to T_0 in the rTHS (highest concentration 1.25 ng/mL) and the mTHS (highest concentration 0.92 ng/mL) studies, respectively.

3.3. Urge-to-smoke

Urge-to-smoke total scores were comparable throughout the assessment period following THS and CC (least square mean of 3.24 for rTHS, 3.36 for mTHS, 3.19 for rCC and 3.64 for mCC). The least square mean difference (95% confidence interval) over all time-points was 0.04 (−0.70; 0.79) between rTHS and rCC and −0.28 (−0.79; 0.22) between mTHS and mCC. The least square mean difference was −0.20 (−0.87; 0.48) for rTHS-Gum and −0.34 (−0.87; 0.19) for mTHS-Gum (Fig. 2). The urge-to-smoke time profiles were different for Gum (maximum suppression 45–60 min after start of product use) compared to both THS and CC (maximum suppression 15–30 min after first puff; Fig. 2). Also, maximum urge-to-smoke suppression was lower for Gum than for THS and CC by 0.6 and 0.4 QSU-brief total score units, respectively.

3.4. Safety

No serious or severe adverse event was reported in subjects who had any product exposure. Fourteen adverse events (3 in sequence 1, 5 each in sequence 2 and 3, and 1 in sequence 4) were reported in 11 of the 65 subjects of the rTHS study against four (1 each in sequence 1 and 4, and 2 in sequence 2) in 4 of the 73 subjects of the mTHS study, mostly mild in severity and mostly related to investigations, none of which led to discontinuation. Adverse events per system organ class and preferred term are listed per sequence for each study in the Supplementary Material (Supplementary Table 2).

4. Discussion

To provide adult smokers with a suitable alternative to smoking and eventually substitute cigarettes, THS should have a nicotine uptake profile similar to cigarettes. In addition, for THS to provide a viable alternative to cigarettes, suppression of urge-to-smoke must be achieved. In 2016, Picavet et al. have reported similar pharmacokinetic profiles in CC smokers and THS users (Picavet et al., 2016), but the study was only conducted on the regular variant of THS. In a study published in 2004, Benowitz et al. reported similar nicotine levels in smokers of menthol and non-menthol cigarettes (Benowitz et al., 2004), but as the literature on nicotine absorption

Table 2
PK parameters of the THS:Gum population.

PK Parameter	Product Variant	Product Exposure	Number of Subjects	Geometric LS Mean	Ratio[a] (THS:Gum) (%)	CV (%)	95% CI
C_{max} (ng/mL)	Regular	rTHS	18	11.53	240.23	105.08	130.60, 441.90
		Gum	18	4.80			
	Menthol	mTHS	18	7.64	101.63	78.75	62.21, 166.04
		Gum	18	7.52			
$AUC_{0\text{-last}}$ (ng*h/mL)	Regular	rTHS	18	18.92	127.15	80.22	77.26, 209.24
		Gum	18	14.88			
	Menthol	mTHS	18	15.61	55.87	57.19	38.36, 81.36
		Gum	18	27.94			
$AUC_{0\text{-}\infty}$ (ng*h/mL)	Regular	rTHS	12	28.94	174.05	52.46	110.44, 274.28
		Gum	12	16.63			
	Menthol	mTHS	15	15.77	50.72	51.05	34.66, 74.21
		Gum	15	31.09			
$t_{1/2}$ (h)	Regular	rTHS	12	4.16	87.32	31.80	65.58, 116.27
		Gum	12	4.76			
	Menthol	mTHS	15	3.20	92.06	28.97	73.55, 115.22
		Gum	15	3.47			
				Median	**Median Difference**		
t_{max} (min)	Regular	rTHS	18	6.00	−29.00		−35.50, −23.75
		Gum	18	35.38			
	Menthol	mTHS	18	8.00	−37.50		−45.00, −31.50
		Gum	18	45.00			

mTHS: mentholated tobacco heating system 2.2; rTHS: regular tobacco heating system 2.2; Gum: nicotine gum; $AUC_{0\text{-}t}$: area under plasma concentration-time curve from start of product use to the last measurable concentration; $AUC_{0\text{-}\infty}$: area under plasma concentration-time curve from start of product use to infinity; CI: confidence interval; CV: coefficient of variation; LS: least square; $t_{1/2}$: terminal half-life; t_{max}: time to maximum plasma concentration.
[a] Geometric least square mean ratio.

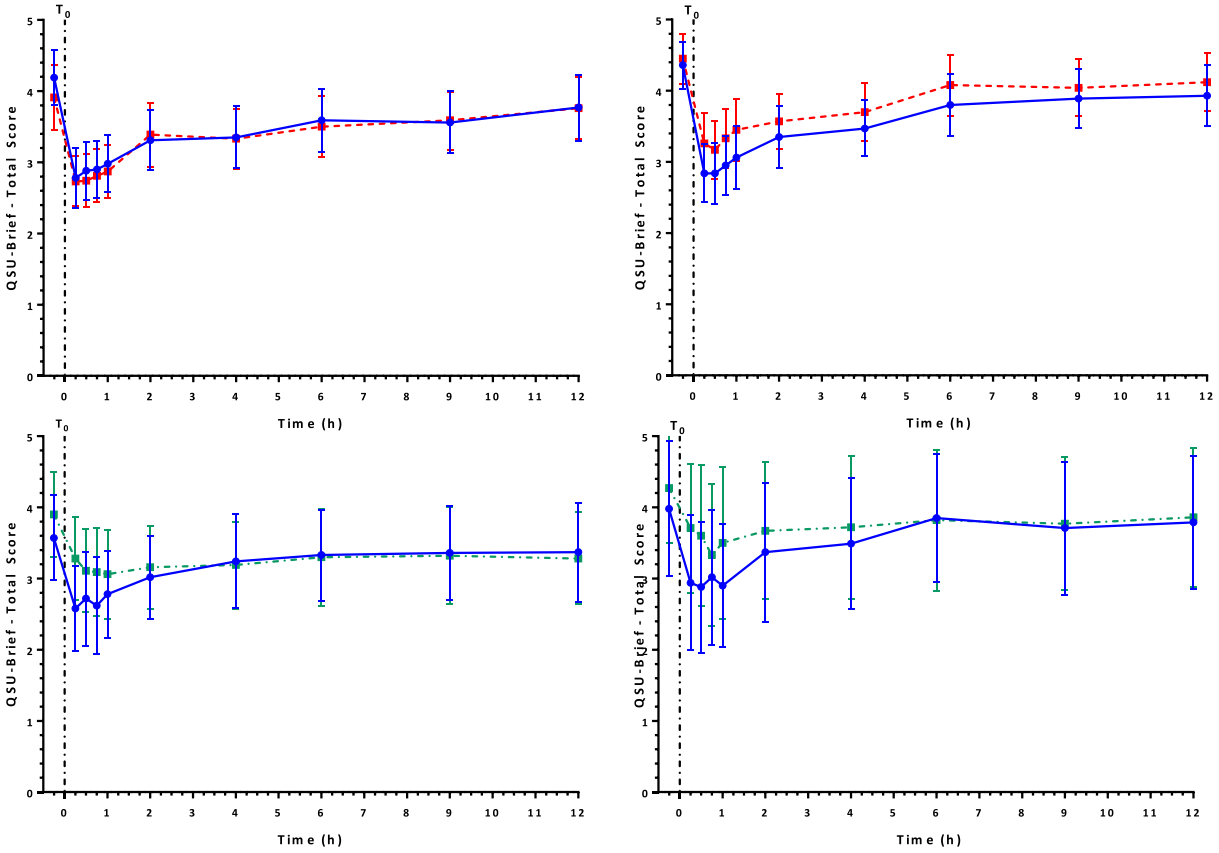

Fig. 2. QSU-Brief total scores (arithmetic mean ± 95% CI) over 12 h after time of first product use (T_0). The two graphs in the upper row depict the results for sequences 1 and 2 (THS and CC), the two graphs in the lower row depict the results for sequences 3 and 4 (THS and Gum). The left column shows the results from the rTHS study and the right column, the results from the mTHS study. THS profiles are shown in blue (continuous lines), CC profiles in red (dashed lines) and Gum profiles in green (dotted-dashed lines).

from menthol versus non-menthol cigarettes is sparse, investigating both variants of a heat-not-burn product such as THS expands this knowledge. The present pharmacokinetic studies assessed nicotine PK parameters and urge-to-smoke following

single use of THS 2.2 (menthol and regular), CC (menthol and regular) and nicotine gum (Nicorette® 2 mg). They were both of identical two-period crossover design, which allows for efficient and unbiased within-subject effect estimation. By subjects being randomly assigned to one sequence of product exposure and thus serving as their own controls, between-subjects variability is removed from the analysis. The prerequisite is a wash-out period being sufficiently long to avoid residual nicotine levels from the first exposure period influencing the measurements of the second exposure period.

Both studies were conducted in the same target population of healthy adult Japanese smokers, resulting in comparable sex, age, and smoking behavior distributions. Also, in both studies single product use was assessed, as the focus was on assessing product-specific pharmacokinetic parameters rather than a combination of product use- and product-related nicotine uptake. To allow for a realistic evaluation, including with respect to Gum, no fixed puffing regimen was imposed and subjects controlled their own puffing behavior. This is reflected in the inter-study variability of the geometric least-square mean nicotine pharmacokinetic parameter estimates between the identical Gum exposure conditions.

The pharmacokinetic results were markedly different for Gum versus THS. C_{max} for Gum was comparable to mTHS, but less than half of that of rTHS. $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ were almost twice as high for Gum than for mTHS and 27% and 74%, higher for rTHS than for Gum. As expected, t_{max} was markedly longer for Gum than for rTHS (median difference: 29 min) and for mTHS (median difference: 38 min). The observed differences can be explained by the route of administration and the chew rate. The apparent nicotine half-life, being similar for all products with values ranging from 3.20 h (mCC) to 4.76 h (Gum), is consistent with the literature on Japanese smokers (Miura et al., 2013; Sobue et al., 2006). For Gum, considerable variability of nicotine PK parameters as well as the slow nicotine absorption were previously noted as well (Benowitz et al., 2009; Hukkanen et al., 2005; Lunell and Curvall, 2011; Lunell and Lunell, 2005).

The pharmacokinetic parameter estimates were generally similar in both THS variants, the lower geometric least square mean C_{max} estimate for the menthol variant being consistent with the magnitude of inter-study variability observed between the Gum exposure conditions of the two studies.

Nicotine absorption was comparable between THS and CC (THS:CC ratios being above 88%), with CC parameters similar to published Japanese population data (Miura et al., 2013). The $t_{1/2}$ values were comparable between THS and CC at approximately 4 h, which appears longer than what has been previously reported in the literature for a Caucasian population (2–2.5 h (Hukkanen et al., 2005);). However, a study conducted by Gries et al. in 1996 estimated a $t_{1/2}$ of 11 h, calculated using urinary excretion of nicotine, which is more sensitive in detecting lower levels than plasma measurements (Gries et al., 1996). One possible reason of this longer half-life might have been that Japanese more often exhibit cytochrome P450 2A6 (CYP2A6) polymorphism resulting in a lower metabolic rate of nicotine; in this case the 24-h wash-out period prior to single product use was not sufficient to completely eliminate nicotine (Nakajima et al., 2006; Nakajima and Yokoi, 2005). Also, with the analytical method used in this study, the LLOQ was 0.2 ng/mL, whereas LLOQ values typically reported in the literature are approximately 0.5–1 ng/mL (Gries et al., 1996; Lerman et al., 2015). The combination of genetic predisposition of the study population, the low LLOQ for nicotine, and the extended sampling period of 24 h might have contributed to longer than expected plasma nicotine half-life. This finding of the plasma nicotine half-life being longer than previously reported in the literature is in line with a recent estimate of the terminal half-life actually being 17 h (Marchand et al., 2017). This indicates that in future studies the wash-out period of 24 h should be extended to eliminate all carry-over from the first to the second exposure period.

Overall, the results demonstrate similar PK profiles for both THS and CC, and for both THS variants (menthol and non-menthol). Also, the reduction in urge-to-smoke was comparable for THS and cigarettes. THS can satisfy smokers and thus, in contrast to Gum, provide a viable alternative to cigarettes for smokers unwilling to quit.

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Declaration of interest

P.B. is a former and all other authors are current employees of Philip Morris Products S.A.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.yrtph.2017.07.032.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2017.07.032.

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