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Comparison of the Pharmacokinetics of Nicotine Following Single and *Ad Libitum* Use of a Tobacco Heating System or Combustible Cigarettes

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Abstract

Introduction: We aimed to compare the pharmacokinetics of nicotine between the heat-not-burn Tobacco Heating System 2.1 (THS 2.1) and combustible cigarettes (CCs). We also examined whether the subjective urge to smoke was associated with the pharmacokinetics of nicotine.
Methods: This open-label, randomized, two-period, two-sequence crossover study conducted in 28 healthy smokers assessed the pharmacokinetics of nicotine after single and *ad libitum* use of the THS 2.1 or CCs. During the 7-day confinement period, blood samples were drawn for pharmacokinetic analysis. Subjective effects related to THS 2.1 or CC use were assessed using the Questionnaire of Smoking Urges (QSU-Brief).
Results: The nicotine delivery rate was similar with the THS 2.1 and CCs after single and *ad libitum* use. The time to the maximum nicotine concentration was 8 minutes after single use of the THS 2.1 and CCs. The time to the peak concentration following *ad libitum* use was similar between the THS 2.1 and CCs. The maximum plasma nicotine concentration after single use of the THS 2.1 was 8.4 ng/mL, 70.3% of that obtained with CCs. A transient reduction from baseline in the urge to smoke of 40% was observed 15 minutes after the single use of both the THS 2.1 and CCs. The mean QSU-Brief total scores following single and *ad libitum* use were similar for the THS 2.1 and CCs.
Conclusions: These results suggest that the THS 2.1 effectively delivers nicotine and achieves similar pharmacokinetic profiles to CCs. The THS 2.1 also reduced the urge to smoke similarly to CCs.
Implications: Reducing exposure to toxicants and safer delivery of nicotine are among the strategies that may reduce the harm of smoking-related diseases. In the present study, we investigated the pharmacokinetics of nicotine and their effects on the urge to smoke using the THS 2.1. It was developed to replicate the ritual of smoking as closely as possible by providing nicotine in a way that mimics CC smoking, but limits pyrolysis and combustion by heating tobacco at a much lower temperature than CCs (heat-not-burn).

Introduction

Reducing exposure to toxicants and safer delivery of nicotine are among the strategies that may reduce the harm of smoking-related diseases.[1] Several products aimed at reducing exposure to toxicants have been developed, including products with lower levels of toxicants such as smokeless tobacco, electronic cigarettes that vaporize nicotine-containing liquids, and products that heat instead of burn tobacco.[2–5] Decreased exposure to the toxic constituents of tobacco smoke is necessary but not sufficient for effective harm-reduction.[2,6,7] The alternative tobacco product should not only be

available but compete with combustible cigarette (CC) smoking to make consumers switch to the tobacco product with less exposure to harmful constituents. It is unlikely that products that do not satisfy smokers will make them switch to the new product.

Nicotine delivery and the rewarding subjective effects of tobacco products are critical components of product satisfaction and its actual use, and the lack of adoption of alternative nicotine delivery systems may be related to ineffective nicotine delivery and/or a low level of satisfaction.[2,4,8–12]

Previous heated tobacco products such as Eclipse, Accord, and Advance were reported to potentially reduce smokers' exposure to harmful and potentially harmful constituents, including nicotine-derived nitrosamines, polycyclic aromatic hydrocarbons, and carbon monoxide.[4,11] These products were also reported to be less satisfying, and relief from the urge to smoke was not consistent across studies.[2,4,10,11]

In the present study, we investigated the pharmacokinetics of nicotine and their effects on the urge to smoke using the Tobacco Heating System (THS 2.1). The THS 2.1 was developed with the objective of replicating the ritual of smoking as closely as possible by providing nicotine in a way that mimics CC smoking, but limits its pyrolysis and combustion by heating tobacco at a much lower temperature than CCs (heat-not-burn). In vivo and in vitro toxicity assessments revealed that earlier THS prototypes reduced exposure to harmful and potentially harmful constituents present in cigarette smoke.[13] A recent open-label, randomized, confinement clinical study showed that switching from CCs to THS 2.1 reduced selected biomarkers of exposure by 72.1% to 93.0% as compared with continuing to use CCs for 5 days.[14] These biomarkers of exposure measured exposure to harmful and potentially harmful constituents, and included carbon monoxide, benzene, 1,3-butadiene, and acrolein. The objectives of the present study were to compare the pharmacokinetics of nicotine uptake and the effects on urge to smoke in healthy smokers who switched from CCs to THS 2.1 compared with smokers who continued using CCs.

Methods

Design

The study was designed as a randomized, controlled, two-period, two-sequence, open-label, single and *ad libitum* use cross-over study aimed at comparing the THS 2.1 with CCs. The study was conducted at Celerion GB Ltd, Northern Ireland, United Kingdom, between May 2012 and June 2012. The study was approved by an Independent Ethics Committee (Office for Research Ethics Committees, Customer Care & Performance Directorate, Northern Ireland, United Kingdom) in accordance with the International Conference on Harmonisation Good Clinical Practices principles and the Declaration of Helsinki (2008), and was registered at www.clinicaltrials.gov (NCT01780688). All participants provided written consent to participate in the study.

Subjects

Subjects were recruited via the clinical site's database and by advertisements. The sample size calculation was based on the maximum concentration (C_{max}) with an intra-subject geometric coefficient of variation of 25%.[15] A total of 28 smokers were needed to estimate the geometric mean C_{max} ratio between THS 2.1 and CC and ensure the 90% confidence interval did not exceed the 0.80 and 1.25 limits with 80% power. Male and female healthy Caucasian smokers aged 23–65 years were eligible to participate if they had smoked cigarettes for at least 3 consecutive years before screening. The subjects should have smoked at least 10 commercially available non-menthol CCs per day for the last 4 weeks prior to screening, with a maximum International Organization for Standardization (ISO) yield of 1 mg nicotine per CC, as labeled on the cigarette pack. Subjects were excluded if they had a body mass index of less than 18.5 or 30 kg/m^2 or more, a urinary cotinine level less than 200 ng/mL at screening, or smoked hand-rolled cigarettes, cigars, pipes, bidis, or other noneligible nicotine-containing products, including electronic cigarettes. Smokers unable to abstain from smoking for up to 2 consecutive days and subjects with clinically relevant diseases or a medical condition requiring smoking cessation were ineligible. The subjects were provided financial compensation for their time and the inconvenience of participating in the study, which was approved by the ethics committee.

Procedure

On the day of admission to the 7-day confined study period, the subjects were asked to try a maximum of three heatsticks on the THS 2.1 to familiarize themselves with the product. The confinement comprised two consecutive periods. Each period consisted of a 24-hour (at least) nicotine wash-out period, 1 day of single product use, and 1 day of *ad libitum* product use. On the second day of confinement, 28 subjects were randomized in a 1:1 ratio to one of two sequences, taking into account a marginal distribution of at least 40% of subjects of each sex and the nicotine level of the subject's preferred CC brand at admission (ISO nicotine levels ≤0.6 mg and >0.6 to 1 mg). Randomization was performed using an Interactive Web Response System. The subjects assigned to Sequence 1 used the THS 2.1 in Period 1 and CCs in Period 2. The subjects assigned to Sequence 2 used CCs in Period 1 and the THS 2.1 in Period 2.

The CCs were non-menthol, manufactured, commercially available cigarettes, with a maximum ISO yield of 1 mg nicotine per cigarette. The subjects were asked to purchase a sufficient quantity of a single, preferred CC brand before admission to provide sufficient cover for the study duration.

The THS 2.1, developed by Philip Morris International, has three components, the heatstick, the holder, and the charger. The heatstick has a tobacco plug containing processed tobacco cast leaf, which is covered by a paper wrap. Except for the much shorter length than CCs, the overall appearance of the heatstick is similar to that of a CC. The holder includes a battery, controlling electronics, and the heater element. The heatstick is inserted into the holder and heats the tobacco via an electronically controlled heating blade. The charger recharges the holder. The energy capacity of the holder is sufficient to maintain a product use session for up to 6 minutes.

Measures

Baseline Characteristics

The recorded baseline characteristics of subjects included age, sex, body mass index, and the ISO nicotine yield of the type of CCs smoked by the subject. Nicotine dependence was assessed using the revised Fagerström Test for Nicotine Dependence questionnaire.[16]

Pharmacokinetics

The pharmacokinetics of nicotine were measured on the days of single and *ad libitum* use in Periods 1 and 2. On single use days, 16 venous blood samples were collected for each subject. The first blood sample was collected within 15 minutes before a single use

of the allocated product in the morning, and then at 2, 4, 6, 8, 10, 15, 30, 45, and 60 minutes, and at 3, 4, 6, 9, 12 and 24 hours. T_0 was defined as the time of initiation of using either product (first puff of the THS 2.1 or lighting the CC) at 07:30 ± 1 hour on Days 1 and 4. On *ad libitum* use days, 13 venous blood samples were collected for each subject. The first blood sample was collected within 15 minutes before the first product use in the morning. The second and third blood samples were collected immediately after the first product use, and immediately before the next product use, respectively. Thereafter, three blood samples were collected during each of three time intervals (12:00 to 16:00 hours, 16:00 to 20:00 hours, and 20:00 to 23:00 hours), similarly to the first three blood samples. The final blood sample was collected after 24 hours on the wash-out days. During *ad libitum* use, T_0 was defined as the time of initiation of using either product (first puff of the THS 2.1 or lighting the CC) on the first day, and should occur at the same time or later as T_0 on the single use day. Plasma nicotine concentrations were determined by high performance liquid chromatography with mass spectrometric detection.[17] The pharmacokinetic parameters of nicotine were derived from its plasma concentrations using the noncompartmental model (WinNonlin Professional Network Edition, version 5.2; Pharsight Corp, Sunnyvale, CA).

Urge to Smoke

The urge to smoke was assessed using the brief version of the Questionnaire of Smoking Urges (QSU-Brief) on single and *ad libitum* use days.[18] The QSU-Brief items are rated on a 7-point scale, ranging from 1 = of strongly disagree to 7 = strongly agree. Higher scores indicate greater urge to smoke. Two factors and a total score were derived. Factor 1 includes items representing the desire and intention to smoke with smoking perceived as rewarding. Factor 2 includes items representing an anticipation of relief from the negative effects of smoking with an urgent desire to smoke. On the single use days, the QSU-Brief was completed before using the allocated product in the morning, and then at 15, 30, and 45 minutes, at 1, 1.25, 1.5, 1.75, and 2 hours, and then hourly thereafter until 23:00 hours. On the *ad libitum* use days, the QSU-Brief was completed at approximately 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00, and 23:00 hours.

Modified Cigarette Evaluation Questionnaire

The Modified Cigarette Evaluation Questionnaire[19] was completed by all subjects on Days 1, 2, 4, and 5 after admission following single use and *ad libitum* use of CCs or the THS 2.1. The following domains were evaluated: smoking satisfaction (satisfying, tastes good, enjoys smoking); psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger); aversion (dizziness, nauseous); enjoyment of respiratory tract sensations (single-item assessment); and craving reduction (single-item assessment).

Cough Assessment

Subjects were asked if they experienced a regular need to cough (eg, coughing several times in the 24 hours before the assessment). If they responded "yes," they were asked to complete a questionnaire consisting of a visual analog scale, three Likert scales, and an open question relating to the subject's experience during the previous 24 hours. The visual analog scale assessed how bothersome the cough was to the subject ranging from "not bothering me at all" to "extremely bothersome." The subjects were also asked to assess the intensity and frequency of cough and the amount of sputum produced during the previous 24 hours on Likert scales. The intensity of cough was assessed on a 5-point Likert scale ranging from 1 to 5, where 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe. The frequency of cough was assessed on a 5-point Likert scale ranging from 1 to 5, where 1 = rarely, 2 = sometimes, 3 = fairly often, 4 = often, and 5 = almost always. The amount of sputum produced was assessed on a 4-point Likert scale ranging from 0 to 3, where 0 = no sputum, 1 = moderate amount of sputum, 2 = larger amount of sputum, and 3 = very large amount of sputum. The subjects were also asked whether they had any other important observations that they would like to share with the investigator about their coughing. Assessments were done every day during admission.

Safety

Safety outcomes included an assessment of adverse events (AEs), which included respiratory symptoms (cough assessment), and changes in vital signs, body mass index, and findings from spirometry, electrocardiography, clinical chemistry, hematology, urinalysis, and physical examinations.

Data Analyses

Data were analyzed for all randomized subjects who did not deviate from the protocol, who completed at least one of the single use or *ad libitum* days, and had at least one estimable pharmacokinetic parameter derived from the single or *ad libitum* days. Statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, NC).

The pharmacokinetic parameters determined from the nicotine concentrations, following single use, were maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration–time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-last}), and the terminal elimination half-life ($t_{½}$). Following *ad libitum* use, the maximum observed plasma concentration (C_{peak}), lowest observed plasma concentration during the same sampling interval in which C_{peak} was observed (C_{trough}), and time to C_{peak} (t_{peak}) were assessed. The pharmacokinetic parameters were calculated from t = 0 minutes (time of first puff of the THS 2.1 or lighting the CC) on the single use or *ad libitum* use days.

The pharmacokinetic profiles were compared between the two products using analysis of variance (ANOVA) with natural log-transformed values for single or *ad libitum* use, accounting for the study design by including terms for sequence, subjects within each sequence, period, and type of product as fixed effects. Adjusted geometric least square (LS) mean ratios (THS 2.1 vs. CCs) and 90% confidence intervals (CIs) were calculated. Hodges–Lehmann estimates with 90% CIs were calculated for the median differences between THS 2.1 and CCs for t_{max} and t_{peak}.[20]

The mean QSU-Brief total score and the sub-scores for craving (Factor 1) and anticipation of relief from the negative effects of not smoking (Factor 2) were calculated at each measurement time, following single and *ad libitum* use. The scores were compared between the two products using a mixed-effects model including all the different assessment time-points post exposure as repeated measurements, and the overall mean differences and 95% CIs were calculated.

Results

All 28 randomized subjects completed the study and no major protocol deviations were reported. The baseline characteristics of the subjects are summarized in Supplementary Table 1. On *ad libitum*

use days, the subjects used a mean ± standard deviation number of 16.7 ± 3.5 CCs/d and 10.9 ± 3.6 THS 2.1 heatsticks/d.

Pharmacokinetics

The mean nicotine concentration curves of the two products 24 hours following single use are shown in Figure 1. The overall shape of the concentration–time curves was similar for the THS 2.1 and CCs. The C_{max} for nicotine following single use and the C_{peak} after *ad libitum* use were 8.4 (95% CI: 6.8, 10.3) ng/mL and 14.9 (95% CI: 12.3, 18.1) ng/mL, respectively, for the THS 2.1, and were 11.9 (95% CI: 9.5, 14.9) ng/mL and 24.0 (95% CI: 21.7, 26.6) ng/mL, respectively, for CCs (Table 1). Thus, the C_{max} and C_{peak} of nicotine obtained using the THS 2.1 were about 70.3% and 62.0%, respectively, of those obtained with CCs (Table 1). The C_{trough} following *ad libitum* use was 4.1 (95% CI: 2.4, 7.0) ng/mL for the THS 2.1 and 12.3 (95% CI: 10.4, 14.6) ng/mL for CCs (Table 1). Therefore, the C_{trough} using the THS 2.1 was about 33.5% of the values obtained using CCs (Table 1). The coefficients of variation for C_{peak} and C_{trough} were two and five times higher, respectively, for the THS 2.1 compared with CCs (Table 1).

The geometric means of $AUC_{0–last}$ were 17.7 (95% CI: 15.0, 20.8) ng·h/mL and 22.8 (95% CI: 19.4, 26.8) ng·h/mL, respectively, for the THS 2.1 and CCs (Table 1). The $AUC_{0–last}$ value for the THS 2.1 was about 77.4% of the value obtained using CCs (Table 1). The mean $t_{½}$ of nicotine was similar for the two products, with values of 2.6 hours and 2.5 hours for the THS 2.1 and CCs, respectively (Table 1).

The t_{max} following single use was 8 minutes for both products (Table 1). Following *ad libitum* use, t_{peak} was not markedly different between the THS 2.1 (12.9 hours) and CCs (10.5 hours; Table 1).

Urge to Smoke

The mean QSU-Brief total scores following single use of the THS 2.1 and CCs followed the same pattern. At baseline (ie, after an overnight washout), the QSU-Brief total score was comparable between the two products (44.4 ± 15.6 for THS 2.1, and 43.6 ± 18.7 for CC). There was a transient reduction in the mean total score of 44% from baseline (−19.4 ± 22.4 for THS 2.1 and −19.5 ± 23.1 for CC), at 15 minutes, for both products. The mean total scores returned to the baseline values by 5–7 hours, representing an increase in the urge to smoke during this time. The mean QSU-Brief total score and the two sub-scores were comparable between the THS 2.1 and CCs, with overall mean differences of 1.2 (95% CI: −2.9, 5.3) for the total score, 0.8 (95% CI: −1.3, 2.9) for Factor 1, and 0.4 (95% CI: −1.7, 2.4) for Factor 2 (Table 2).

The mean QSU-Brief total scores following *ad libitum* use of the THS 2.1 and CCs were similar for both products. The total score and both sub-scores were not different between the two products, with overall mean differences of 1.4 (95% CI: −1.0, 3.7) for the total score, 0.5 (95% CI: −0.8, 1.9) for Factor 1, and 0.8 (95% CI: −0.3, 1.9) for Factor 2 (Table 2).

Cough Assessment

There were no apparent differences in the Likert scores for cough frequency, cough intensity, or sputum production between the study groups (Supplementary Table 2).

Modified Cigarette Evaluation Questionnaire

Following single use of each product, mean differences between THS 2.1 and CC (ie, THS 2.1 – CC) were observed for aversion (−0.8; 95% CI: −1.4, −0.2) and enjoyment of the respiratory tract sensations (−0.7; 95% CI: −1.4, 0.0; Table 3). The differences between the two products were greater following *ad libitum* use for smoking satisfaction (−2.0; 95% CI: −2.7, −1.4), psychological reward (−0.8; 95% CI: −1.2, -0.4), craving reduction (−1.6; 95% CI: −2.1, −1.0), and enjoyment of the respiratory tract sensations (−2.0; 95% CI: −2.7, −1.4).

Safety

During the study 14 subjects experienced AEs after THS 2.1 exposure and 10 subjects experienced AEs after CC exposure. Most AEs were mild in severity. No AEs were reported by the investigator based on coughing symptoms. No notable changes in spirometry parameters were observed from baseline to the end of the study in either exposure group. The most frequently reported AEs (number of subjects in the THS 2.1 and CC groups) were: nausea (4 and 5), headache (5 and 2); dizziness (4 and 2); presyncope (1 and 4); and abdominal pain (0 and 2).

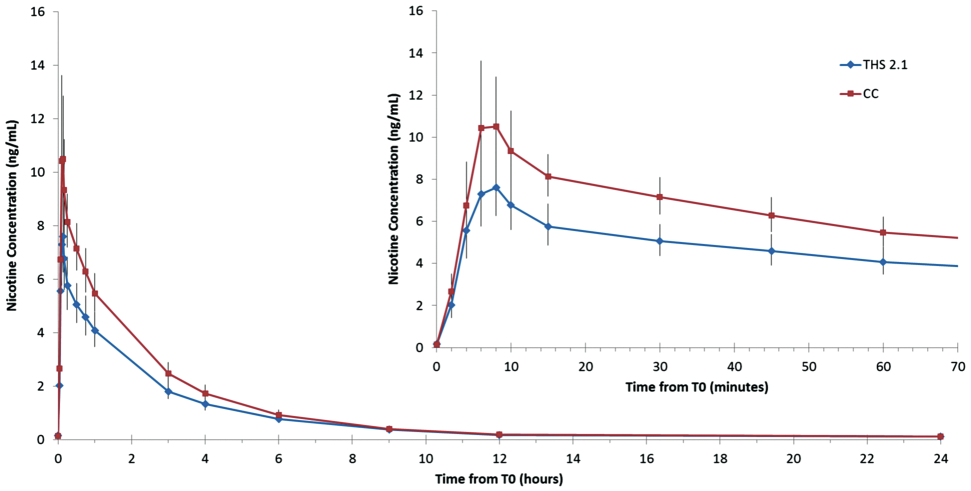

Figure 1. Geometric means and 95% confidence intervals of nicotine concentrations during single use of the Tobacco Heating System 2.1 (THS 2.1) or combustible cigarettes (CCs) over 24 hours. The inset shows an expanded view of the nicotine concentrations from T_0 to 70 minutes. T_0, start of product use.

Table 1. Pharmacokinetics of Nicotine Following Single and *Ad Libitum* Use of the Tobacco Heating System 2.1 (THS 2.1) or Combustible Cigarettes (CCs)

Parameter	THS 2.1 (n = 28)	CC (n = 28)	THS/CC ratio (90% CI)
Single use			
AUC_{0-last} (ng·h/mL)			
Geometric mean (95% CI)	17.7 (15.0, 20.8)	22.8 (19.4, 26.8)	77.4% (70.5%, 85.0%)
Range	5.4–32.3	8.3–55.0	
CV (%)	44.1	43.0	
C_{max} (ng/mL)			
Geometric mean (95% CI)	8.4 (6.8, 10.3)	11.9 (9.5, 14.9)	70.3% (60.0%, 82.2%)
Range	2.7–31.8	5.0–38.1	
CV (%)	58.8	62.2	
t_{max} (min)			
Median	8	8	<0.1 (–1.0, 2.0)[b]
Range	4–61	2–17	
$t_{½}$ (h)[a]			
Geometric mean (95% CI)	2.6 (2.3, 3.0)	2.5 (2.2, 2.8)	110.9% (101.7%, 120.9%)
Range	1.7–6.5	1.6–6.6	
CV (%)	28.7	28.8	
Ad libitum use			
C_{peak} (ng/mL)			
Geometric mean (95% CI)	14.9 (12.3, 18.1)	24.0 (21.7, 26.6)	62.0% (53.6%, 71.8%)
Range	4.8–31.3	14.5–39.3	
CV (%)	53.3	26.7	
C_{trough} (ng/mL)			
Geometric mean (95% CI)	4.1 (2.4, 7.0)	12.3 (10.4, 14.6)	33.5% (21.9%, 51.2%)
Range	0.3–23.9	4.9–25.4	
CV (%)	231.7	45.0	
t_{peak} (h)			
Median	12.9	10.5	1.6 (0.0, 2.4)[b]
Range	5.7–14.1	0.1–14.1	

AUC_{0-last} = area under the plasma concentration–time curve from time 0 to the last quantifiable concentration; C_{max} = maximum observed plasma concentration; C_{peak} = maximum observed plasma concentration; C_{trough} = lowest observed plasma concentration during the same sampling interval in which C_{peak} was observed; CI = confidence interval; CV = geometric coefficient of variation; $t_{½}$ = terminal elimination half-life; t_{max} = time to C_{max}; t_{peak} = time to the maximum observed concentration.

[a]n = 24 following single use of the THS 2.1 and n = 27 following single use of CC because $t_{½}$ could not be estimated for five subjects. All of the other parameters were analyzed in all 28 subjects.

[b]Median difference (90% CI) for THS 2.1 – CC.

Table 2. Mixed-Effects Model Results of Brief Questionnaire of Smoking Urges (QSU) Following Single and *Ad Libitum* Use of the Tobacco Heating System 2.1 (THS 2.1) or Combustible Cigarettes (CCs)

	THS 2.1, LS mean ± *SE*	CC, LS mean ± *SE*	THS 2.1 – CC, LS mean (95% CI)
Single use			
Factor 1 score	23.9 ± 1.4	23.1 ± 1.4	0.8 (–1.3, 2.9)
Factor 2 score	18.1 ± 1.4	17.7 ± 1.4	0.4 (–1.7, 2.4)
Total score	42.0 ± 2.6	40.8 ± 2.6	1.2 (–2.9, 5.3)
Ad libitum use			
Factor 1 score	17.2 ± 1.1	16.7 ± 1.1	0.5 (–0.8, 1.9)
Factor 2 score	13.3 ± 1.0	12.4 ± 1.0	0.8 (–0.3, 1.9)
Total score	30.5 ± 2.0	29.1 ± 2.0	1.4 (–1.0, 3.7)

CI = confidence interval; *SE* = standard error.

Values are presented as the least square mean ± SE or least square mean (95% CI), as determined using a mixed-effects model applied to the absolute QSU-Brief questionnaire scores.

Discussion

Smokers can modulate their nicotine intake by controlling their smoking profile, including the number of heatsticks/CCs used, duration and volume of puffs, or the depth/intensity of inhalation.[21] We did not apply a fixed puffing regimen, but instead the subjects controlled their own puffing behavior, which allows for a realistic evaluation of a tobacco consumer product. In the *ad libitum* phase, the products were used between 6:30 to 23:00, and blood samples were scheduled depending on the subject's specific use of the products. An advantage of this adaptive approach is that the C_{peak} and C_{trough} are estimated more reliably than with a fixed time sampling schedule. In fact, the peak exposure is likely to occur immediately after the product use, and the lowest nicotine concentration associated with the peak may occur either just before the product use or before the next product use.

The pharmacokinetics of nicotine following smoking a single CC, including t_{max}, $t_{½}$, AUC_{last}, and C_{max}, are consistent with the previously reported values.[22–24] We found that the t_{max} and t_{peak} following single and *ad libitum* use of the THS 2.1 were not *markedly* different from those obtained using CCs, which suggests that the THS 2.1 delivers nicotine via inhalation and absorption similar to CCs. However, the THS 2.1 provided lower exposure to nicotine of about 30% compared with CCs, based on AUC_{last} and C_{max}. This difference could be explained by incomplete adaptation to the THS 2.1, and that each THS 2.1 heatstick delivered 0.3 mg nicotine (per ISO smoking machine) compared with up to 1 mg for each CC in this study. Following *ad libitum* product use, incomplete adaptation

Table 3. Modified Cigarette Evaluation Questionnaire Subscale Scores Following Single and *Ad Libitum* Use of the Tobacco Heating System 2.1 (THS 2.1) or Combustible Cigarettes (CCs)

	THS 2.1, mean ± *SD*	CC, mean ± *SD*	THS 2.1 – CC LS mean (95% CI)
Single use			
Smoking satisfaction	4.1 ± 1.50	4.6 ± 1.92	−0.49 (−1.26, 0.28)
Psychological reward	3.9 ± 1.22	3.7 ± 1.38	0.13 (−0.50, 0.76)
Aversion	2.2 ± 1.45	3.0 ± 1.80	−0.80 (−1.42, −0.19)
Enjoyment of respiratory tract sensations	3.6 ± 1.38	4.3 ± 1.77	−0.71 (−1.42, 0.00)
Craving reduction	4.7 ± 1.63	4.6 ± 1.65	0.11 (−0.58, 0.79)
Ad libitum use			
Smoking satisfaction	3.3 ± 1.40	5.2 ± 1.24	−1.95 (−2.46, −1.44)
Psychological reward	3.3 ± 1.45	4.1 ± 1.25	−0.79 (−1.24, −0.35)
Aversion	1.8 ± 1.07	1.7 ± 1.07	0.07 (−0.41, 0.55)
Enjoyment of respiratory tract sensations	2.6 ± 1.45	4.6 ± 1.62	−2.04 (−2.66, −1.41)
Craving reduction	3.9 ± 1.87	5.4 ± 1.29	−1.57 (−2.10, −1.04)

LS = least squares; CI = confidence interval.

may also cause greater variability of the C_{peak} and C_{trough} values observed for the THS 2.1 compared with CCs. Similar to single use exposure, nicotine exposure in terms of C_{peak} and C_{trough} following *ad libitum* use was lower with the THS 2.1 compared with CCs; this could explain the greater number of CCs used per day (16.7 CCs/d) compared with THS 2.1 heatsticks (10.9 heatsticks/d) during *ad libitum* use.

The QSU-Brief measures the desire to smoke and was considered to be a pharmacodynamic measure of this subjective effect to inform about the craving control of THS 2.1 compared with CCs.[2,18,25–27] Our results show that the magnitude and the time course of the reduction in the urge to smoke following single and *ad libitum* use were comparable for both products. Overall, the rapid delivery of nicotine and the reduction in the urge to smoke suggest that the THS 2.1 can satisfy smokers, and this system could offer a viable replacement for CCs.

Limitations of the study are that it involved a relatively small sample (28 subjects) and that the study duration was short (1 week). Furthermore, subjects could use the THS 2.1 on just 2 days, which is too short to allow the subjects to fully adapt their smoking behaviors to a new product.[21,28] In order to assess whether the THS has the potential to induce switching behavior at a sufficient level, other studies are required that take into account the complexity involved in smoking behaviors under real-world conditions. Such longer-term studies are underway to assess the acceptance and possible role of the THS-heated tobacco platform to switch adult smokers to reduced risk tobacco-containing products. Despite the limitations of this study, the results suggest that the THS 2.1 effectively delivers nicotine and reduces the urge to smoke, similarly to CCs, and warrants further development work.

Supplementary Material

Supplementary Tables 1 and 2 can be found online at http://www.ntr.oxfordjournals.org

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Declaration of Interests

All authors are employees of Philip Morris Products S.A.

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References

1. Stratton K, Shetty P, Wallace R, Bondurant S. Clearing the smoke: assessing the science base for tobacco harm reduction. *Tob Control*. 2001;10(2):189–195. doi:10.1136/tc.10.2.189.
2. Breland AB, Buchhalter AR, Evans SE, Eissenberg T. Evaluating acute effects of potential reduced-exposure products for smokers: clinical laboratory methodology. *Nicotine Tob Res*. 2002;4(suppl 2):S131–140. doi:10.1080/1462220021000032780.
3. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control*. 2010;19(2):98–103. doi:10.1136/tc.2009.031567.
4. Breland AB, Kleykamp BA, Eissenberg T. Clinical laboratory evaluation of potential reduced exposure products for smokers. *Nicotine Tob Res*. 2006;8(6):727–738.
5. Orr MS. Electronic cigarettes in the USA: a summary of available toxicology data and suggestions for the future. *Tob Control*. 2014;23(suppl 2):ii18–22. doi:10.1136/tobaccocontrol-2013-051474.
6. Hatsukami DK, Biener L, Leischow SJ, Zeller MR. Tobacco and nicotine product testing. *Nicotine Tob Res*. 2012;14(1):7–17. doi:10.1093/ntr/ntr027.
7. Le Houezec J, McNeill A, Britton J. Tobacco, nicotine and harm reduction. *Drug Alcohol Rev*. 2011;30(2):119–123. doi:10.1111/j.1465-3362.2010.00264.x.
8. Slade J, Connolly GN, Lymperis D. Eclipse: does it live up to its health claims? *Tob Control*. 2002;11(suppl 2):ii64–70. doi:10.1136/tc.11.suppl_2.ii64.
9. Wonnacott S, Russell MAH, Stolerman IP. *Nicotine Psychopharmacology: Molecular, Cellular, and Behavioural Aspects*. Oxford, United Kingdom: Oxford University Press; 1990.
10. Lee EM, Malson JL, Moolchan ET, Pickworth WB. Quantitative comparisons between a nicotine delivery device (Eclipse) and conventional cigarette smoking. *Nicotine Tob Res*. 2004;6(1):95–102. doi:10.1080/14622200310001656911.
11. Breland AB, Acosta MC, Eissenberg T. Tobacco specific nitrosamines and potential reduced exposure products for smokers: a preliminary evaluation of Advance. *Tob Control*. 2003;12(3):317–321. doi:10.1136/tc.12.3.317.

12. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tob Control*. 2010;19(1):87–88. doi:10.1136/tc.2009.033498.
13. Zenzen V, Diekmann J, Gerstenberg B, Weber S, Wittke S, Schorp MK. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 2: smoke chemistry and in vitro toxicological evaluation using smoking regimens reflecting human puffing behavior. *Regul Toxicol Pharmacol*. 2012;64(2) (suppl):S11–S34. doi:10.1016/j.yrtph.2012.08.004.
14. Picavet P, Haziza C, De La Bourdonnaye G, et al. Reduced exposure to harmful and potentially harmful smoke constituents after five days of use of a candidate modified risk tobacco product: the Tobacco Heating System 2.1. Presentation at the 20th Annual Meeting of the Society for Research on Nicotine and Tobacco; February 5–8, 2014; Seattle, WA. Abstract PA-10-2. www.srnt.org/conferences/2014/pdf/SRNT_2014_Abstracts_F.pdf. Accessed December 12, 2014.
15. Gourlay SG, Benowitz NL. Arteriovenous differences in plasma concentration of nicotine and catecholamines and related cardiovascular effects after smoking, nicotine nasal spray, and intravenous nicotine. *Clin Pharmacol Ther*. 1997;62(4):453–463. doi:10.1016/S0009-9236(97)90124-7.
16. Fagerstrom K, Russ C, Yu CR, Yunis C, Foulds J. The Fagerstrom Test for Nicotine Dependence as a predictor of smoking abstinence: a pooled analysis of varenicline clinical trial data. *Nicotine Tob Res*. 2012;14(12):1467–1473. doi:10.1093/ntr/nts018.
17. Jacob P III, Yu L, Duan M, Ramos L, Yturralde O, Benowitz NL. Determination of the nicotine metabolites cotinine and trans-3'-hydroxycotinine in biologic fluids of smokers and non-smokers using liquid chromatography-tandem mass spectrometry: biomarkers for tobacco smoke exposure and for phenotyping cytochrome P450 2A6 activity. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2011;879(3–4):267–276. doi:10.1016/j.jchromb.2010.12.012.
18. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-Brief) in laboratory and clinical settings. *Nicotine Tob Res*. 2001;3(1):7–16. doi:10.1080/14622200124218.
19. 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(5):912–923.
20. Lingling H. Calculating the point estimate and confidence interval of Hodges-Lehmann's median using SAS® software. Presentation at the Annual Meeting of the SouthEast SAS® Users Group; October 19–22, 2008; Birmingham, AL. Paper (ST-154). http://analytics.ncsu.edu/sesug/2008/ST-154.pdf. Accessed July 10, 2014.
21. Scherer G. Smoking behaviour and compensation: a review of the literature. *Psychopharmacology (Berl)*. 1999;145(1):1–20. doi:10.1007/s002130051027.
22. Benowitz NL, Hukkanen J, Jacob P III. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handb Exp Pharmacol*. 2009;(192):29–60. doi:10.1007/978-3-540-69248-5_2.
23. Digard H, Proctor C, Kulasekaran A, Malmqvist U, Richter A. Determination of nicotine absorption from multiple tobacco products and nicotine gum. *Nicotine Tob Res*. 2013;15(1):255–261. doi:10.1093/ntr/nts123.
24. Yuki D, Kikuchi A, Miura N, Kakehi A, Onozawa M. Good relationship between saliva cotinine kinetics and plasma cotinine kinetics after smoking one cigarette. *Regul Toxicol Pharmacol*. 2013;67(2):240–245. doi:10.1016/j.yrtph.2013.08.002.
25. Teneggi V, Squassante L, Iavarone L, Milleri S, Bye A, Gomeni R. Correlation and predictive performances of saliva and plasma nicotine concentration on tobacco withdrawal-induced craving. *Br J Clin Pharmacol*. 2002;54(4):407–414. doi:10.1046/j.0306-5251.2002.01650.x.
26. Cobb CO, Weaver MF, Eissenberg T. Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. *Tob Control*. 2010;19(5):367–373. doi:10.1136/tc.2008.028993.
27. Hanson K, O'Connor R, Hatsukami D. Measures for assessing subjective effects of potential reduced-exposure products. *Cancer Epidemiol Biomarkers Prev*. 2009;18(12):3209–3224. doi:10.1158/1055-9965.EPI-09-0971.
28. Trtchounian A, Williams M, Talbot P. Conventional and electronic cigarettes (e-cigarettes) have different smoking characteristics. *Nicotine Tob Res*. 2010;12(9):905–912. doi:10.1093/ntr/ntq114.