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6.2.2 Product Usage Assessment among CC Smokers

6.2.2.1 Background

In accordance with the FDA MRTP draft guidance (FDA (Food and Drug Administration) 2012) the assessment of an MRTP should address the effect that an MRTP and its marketing might have on tobacco use behavior among current tobacco users ((FDA (Food and Drug Administration) 2012), lines 749-759), in particular:

- The likelihood that current tobacco product users will start using the MRTP
- The likelihood that tobacco users who adopt the MRTP will switch to or switch back to other tobacco products that present higher levels of individual health risk
- The likelihood that consumers will use the product in conjunction with other tobacco products
- The likelihood that users who may have otherwise quit using tobacco products will instead use the product
- The likelihood that consumer will use the product as intended or designed.

Product acceptance is one of the key factors for adult smokers to switch - and to stay switched to THS. In order to make the product acceptable to the user who would like to continue the use of tobacco products, several prerequisites should be met to ascertain continued use of the product:

(1) The product should deliver satisfactory levels of nicotine

(2) The product should provide a sufficiently satisfying experience to be an effective alternative for CC (satisfaction using the product, reduction of urge to smoke and withdrawal symptoms, sensorial experience, ease to use).

(3) The product should be easy to adapt to in a reasonably short amount of time to avoid relapsing to cigarette smoking

(4) Product consumption should not introduce new risks to the consumers (e.g., leading to a substantial increase in exposure to nicotine or impacting the potential exposure reduction to HPHCs)

(5) Product communication should be effective, accurate and easy to understand to generate intent to use among current adult smokers, in particular those who intend to continue using tobacco, the intended consumer group.

To assess product use and acceptance, the IOM, in its report on Scientific Standards for Studies on MRTPs (IOM (Institute of Medicine) 2012), recommends multiple complementary studies providing real-world relevance, with careful consideration on the degree of control imposed on experimental designs and balance of internal and external validity, not only within studies, but also across studies of the same product ((IOM (Institute of Medicine) 2012), page 10; see also page 247). Furthermore, the IOM emphasizes that clinical study methods need to reflect real-life use patterns within the context of a research study, including *ad libitum* use of an MRTP alone or in combination with CC, as well as inclusion of controls, such as nicotine replacement therapy (NRT) or forced switching conditions ((IOM (Institute of

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Medicine) 2012), page 56). Besides evidence on actual use of an MRTP, the MRTP Draft Guidance (FDA (Food and Drug Administration) 2012) recommends the applicant to provide data concerning: (i) consumer perception of the product, including its labeling, marketing and advertising (lines 746-747), (ii) the ability of consumer to understand and correctly comply with the instructions for use (lines 1024-1025), and (iii) the potential for product misuse (lines 744-745).

Table 1 summarizes the series of studies completed by PMI to address FDA's requirements on the effect of THS and its marketing on tobacco use behavior among current tobacco users. These included 4 clinical studies from the premarket clinical assessment program; 2 qualitative and 6 quantitative studies from the premarket consumer Perception and Behavior Assessment (PBA) program; as well as market research "Whole Offer Tests" (WOTs) conducted in 5 different countries, and submitted here as supportive evidence of THS product usage. All these studies focused on 3 major dimensions underlying product usage in order to assess whether THS meets the prerequisites to ascertain continued use of the product in adult current smokers:

- **Product use behavior** including (i) nicotine uptake, (ii) level of consumption, (iii) patterns of use (e.g., predominant use, combined use), (iv) human puffing topography (e.g., puff volume, puff duration, number of puffs), and (v) product acceptance **(**subjective reinforcing effects and sensorial experience)
- **Behavioral intention** including (i) intent to use THS (intention to try, intention to use) and (ii) change in intention to quit smoking based on exposure to THS communication materials
- **Product usability** including (i) ability to understand and correctly comply with the instruction of use THS and (ii) potential misuse

6.2.2.2 Overview of the Type of Studies

6.2.2.2.1 Clinical Confinement Studies

Clinical studies in confinement facilitate product compliance in an optimal clinical setting. The PMI clinical assessment program included 4 randomized, controlled, open-label, 3-arm parallel group reduced exposure (REX) studies. The confinement period in studies [ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP], [ZRHM-REXA-07-JP] and [ZRHM- REXA-08-US] primarily investigated the reduction of levels of Biomarkers of Exposure to HPHCs following a switch from CC to THS after 5 days of product use. In this setting, product use was directed and monitored by the study staff and participating smokers were controlled for product compliance. The smokers used THS without restriction (*ad libitum*) during an extended daily time window (06.30 AM to 11.00 PM). Dual use of CC, THS and any other nicotine-containing product was not permitted yet possible. Nicotine uptake over time was measured through quantification of nicotine and its metabolites in different matrices (plasma and urine) and product use behavior was investigated through recording of product consumption and assessment of human puffing topography. Subjective effects

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associated with smoking were assessed systematically during the study using questionnaires established in the field of tobacco research (Table 1).

6.2.2.2.2 Clinical Ambulatory Studies

Clinical ambulatory studies are more accurate representations of actual use behavior, as subjects are allowed to interact freely with the product in their home environment and have also practically the possibility of using other tobacco and nicotine-containing products. Complementary to the [ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP] studies conducted exclusively in confinement, the [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US] studies included a prolonged period in an ambulatory setting. The goal of these studies was to demonstrate that the exposure reduction seen under controlled conditions can be maintained in ambulatory, near to real-world conditions. Subjects were followed over 3 months to assess how product use behavior and acceptance evolved over a prolonged period of time, including nicotine uptake, level of consumption, use patterns, human puffing topography and product acceptance (Table 1).

6.2.2.2.3 Observational Studies on THS Actual Use

Pre-market observational studies were conducted to complement the clinical studies and to further substantiate THS acceptance among adult smokers. These studies aimed at providing insights on how adult smokers consume THS under near to real-world conditions. Data derived in a more natural setting are necessary to inform about (i) the likelihood that the product will be adopted (level of product consumption, sensory acceptance, easiness to use), (ii) the likelihood that smokers will use it with other tobacco products, in early stages of use and during continued use, and importantly from a public health perspective, (iii) the likelihood that a user may consume THS in a manner that may differ from the intended use. To closely mimic real-life situations, consumers are provided with the product for use at home and are asked to use it as they want (*ad-libitum*). This may potentially also include the combined use of the product with CC and other tobacco products. The Actual use study [THS-PBA-07-US] was conducted in a large sample of US adult daily smokers. Additional observational studies WOT pre-market studies were conducted in Europe (Germany, Italy and Switzerland) and Asia (Japan and South Korea). An overview of the findings are provided in this MRTPA as supportive evidence to evaluate the potential effect of THS on tobacco use behavior through comparing populations from different countries [7.3.3 Summary_WOT].

These studies captured self-reported data on stick-by-stick consumption of THS Tobacco Sticks and CC over a period of 4 or 6 weeks (Table 1). In [THS-PBA-07-US], sensorial experience and potential misuse of THS was also assessed.

6.2.2.2.4 Studies on the THS Communication Materials

<u>Labeling and advertising materials</u>

Effective communication of risk reduction potential of an MRTP is a critical element in switching adult smokers from cigarettes to MRTPs. Several studies have shown that, without a communication about the risk reduction benefit of the MRTP, there is

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significantly less incentive for adult smokers to switch - and to stay switched - and therefore much less chance that harm reduction to the population as a whole will be achieved (Borland 2012, Capella 2012, Rodu 2015). Six studies were completed, as part of the PBA program, to assess the extent to which THS communication generated intent to use within the intended section of the population, i.e., adult smokers who want to continue using tobacco. In addition, intention to quit smoking pre- and post-exposure to THS communication was also assessed. In these studies, subjects were not exposed to the product; rather, they were only exposed to THS labeling and advertising (e.g., potential messages and claims, mock-ups of label, labeling and marketing material). These studies included qualitative and quantitative studies conducted in the US of either of the 2 phases (Table 1):

(i) **Development phase**: 2 qualitative studies (THS-PBA-02-US and THS-PBA-04-US) and 1 quantitative study (THS-PBA-03-US) to guide the development of the most appropriate THS communication

(ii) **Assessment phase**: 3 quantitative studies (THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, and THS-PBA-05-REC-US) to assess the appropriateness of proposed THS label, labeling, and marketing material submitted in this application.

Instructions for Use

To determine whether the provided THS instructions for use communicate effectively how to use the THS product, the THS-PBA-06-US study, part of the PBA assessment program, was conducted with a user-centered interview design using a usability testing approach. In this study, subjects were asked to read the THS instructions for use, show their ability to correctly demonstrate some use tasks and answer open-ended questions about key communication messages of the instructions for use. Correct demonstration/correct comprehension was pre-defined and scored independently by 2 observers.

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Table 1 Overview of Studies Conducted on Product Usage

Study Code	Country	FSI-LSO	Design	Setting	Exposure Duration	Population	Sample size	Outcome Measure
ZRHR-REXC-03-EU	Poland	29-Jun 2013 to 26-Sep-2013	3-arm parallel	Confinement	5 days	S-NITQ	80 THS, 40 CC, 40 SA	Level of consumption, nicotine uptake, subjective effects, puffing topography
ZRHR-REXC-04-JP	Japan	23-Jul2013to 09-Dec 2013	3-arm parallel	Confinement	5 days	S-NITQ	80 THS, 40 CC, 40 SA	Level of consumption, nicotine uptake, subjective effects, puffing topography
ZRHM-REXA-07-JP	Japan	01-Aug-2013 to 03-Jul-2014	3-arm parallel	Confinement and ambulatory	3 months	S-NITQ	80 THS, 40 CC, 40 SA	Level of consumption, patterns of use, nicotine uptake, subjective effects, puffing topography
ZRHM-REXA-08-US	USA	17-Dec-2013 to 12-Oct-2014	3-arm parallel	Confinement and ambulatory	3 months	S-NITQ	80 THS, 40 CC, 40 SA	Level of consumption, patterns of use, nicotine uptake, subjective effects, puffing topography, intention to quit smoking
THS-PBA-07-US	USA	Sep 15 to Jan 16	1-arm actual use study	Observational	6 weeks	S-NITQ	1106	Patterns of use, level of consumption, sensorial experience, misuse
Whole Offer Test (WOT) Study	Italy, Germany, Switzerland, Japan, South Korea	IT: Sep to Oct 2013; DE: Sep to Oct 2014; CH: Oct to Dec 2014; JP: Jun to Aug 2013; KR: Apr to Jun 2015	1-arm	Observational	4 weeks	S-NITQ	2809	Patterns of use, level of consumption
THS-PBA-02-US	USA	Oct to Dec 2013	2-phase qualitative	FGD, IDIs	No product exposure	S-NITQ, S-ITQ, FS, NS	123in phase 1; 38 in phase 2	Intent to Use

(table continues)

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Study Code	Country	FSI-LSO	Design	Setting	Exposure Duration	Population	Sample size	Outcome Measure
THS-PBA-03-US	USA	Oct to Dec 2014	5-arm parallel quantitative	CASI in central location	No product exposure	S-NITQ, S-ITQ, FS, NS	1713	Intent to Use, Change in Intention to Quit Smoking
THS-PBA-04-US	USA	Dec 2014	Qualitative	IDIs	No product exposure	AS, FS, NS	28 IDIs	Intent to Use
THS-PBA-05-RRC-US	USA	Jul 2015	5-arm parallel quantitative	CASI in central location	No product exposure	S-NITQ, S-ITQ, FS, NS	2255	Intent to Use, Change in Intention to Quit Smoking and All Tobacco
THS-PBA-05-RRC2-US	USA	Sep 2015	5-arm parallel quantitative	CASI in central location	No product exposure	S-NITQ, S-ITQ, FS, NS	2247	Intent to Use, Change in Intention to Quit Smoking and All Tobacco
THS-PBA-05-REC-US	USA	Dec 2015	5-arm parallel quantitative	CASI in central location	No product exposure	S-NITQ, S-ITQ, FS, NS	2272	Intent to Use, Change in Intention to Quit Smoking and All Tobacco
THS-PBA-06-US	USA	May to Jun 2015	1-arm	IDIs	No product exposure	AS	258	Ability to understand and correctly comply with the instruction of use

FSI: first subject in; LSO: last subject out
FGD: Focus Group Discussion; IDIs: Individual Interviews; CASI: Computer-Assisted Self-Interview
AS: Adult Smokers; CC: Conventional cigarettes; S-NITQ: Adult Smoker with No Intention to Quit CC; S-ITQ: Adult Smoker with Intention to Quit CC; FS: Adult Former Smokers; NS: Adult Never Smokers, SA: Smoking abstinence; THS: Tobacco Heating System

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6.2.2.3 Methods

6.2.2.3.1 Product Use Behavior

6.2.2.3.1.1 Nicotine Uptake

Nicotine pharmacokinetics measuring extent and rate of nicotine absorption of THS in plasma was assessed in a single use setting in 4 PK/PD studies (Section 6.2.1). Nicotine uptake over time was further investigated in 4 REX studies in confined and ambulatory settings through the assessment of Nicotine Equivalents (NEQ) and Nicotine and Cotinine in plasma (Section 6.1.3.3 of this submission).

6.2.2.3.1.2 Level of Consumption

Product consumption was measured as the number of CC or THS Tobacco Sticks used per day by subjects during the conduct of the studies. Consumption was recorded by the study site staff when subjects were confined and was otherwise self-reported by subjects in a diary (paper or electronic) on a stick-by stick basis when in ambulatory or "home-use" setting.

6.2.2.3.1.3 Patterns of Product Use

To describe patterns of product use across the different studies, product use categories were defined based on the percentage of THS Tobacco Sticks used in a predefined period of time compared to the number of total tobacco products used.

THS use was defined as the proportion of THS Tobacco Stick use representing [70-100]% of the sum of the number of CC and THS Tobacco Sticks used, whereas Combined use of THS and CC or CC use was defined as the proportion of THS Tobacco Sticks used being in between]30-70[% and [0-30]% of the total number of tobacco products used, respectively (see Figure 1). Usage categories were further split into sub-categories in order to describe product use patterns with more granularity (exclusive use, predominant use, combined mostly, combined balanced, see Figure 1). Usage categories were defined identically in clinical and observational studies, with the exception that for controlled clinical studies, an additional sub-category was created to reflect the high compliance to THS that was expected, resulting in exclusive use of THS being restricted to 100% use of THS and Primarily use defined as]95%-100%] of THS.

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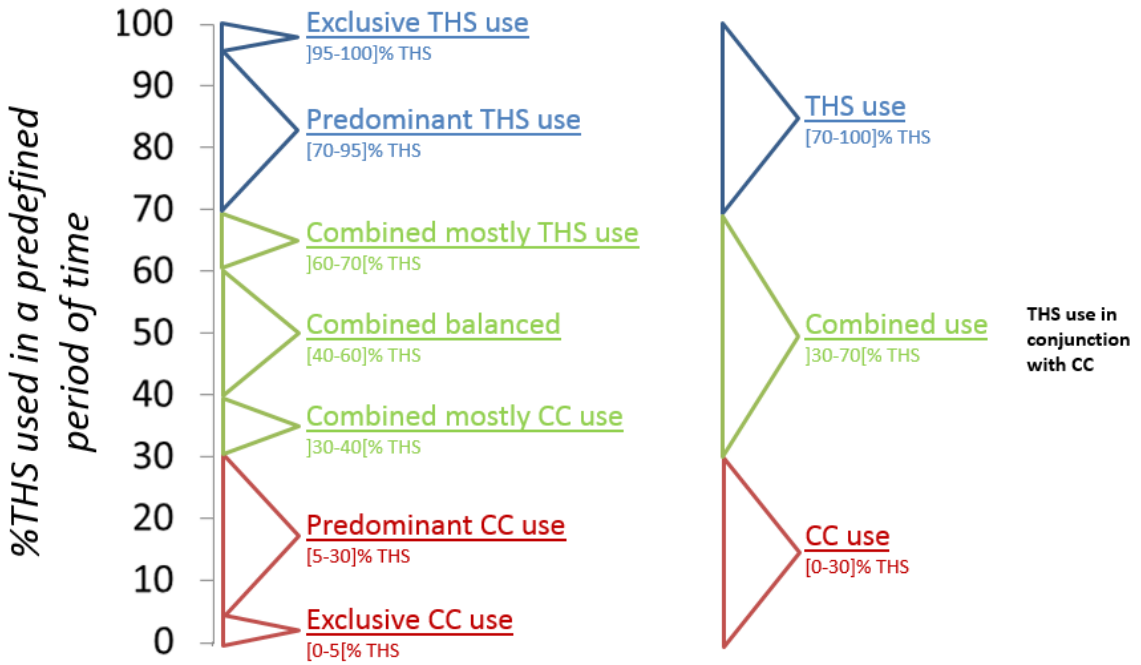


Figure 1 Product Use Categories

CC: Conventional cigarettes, THS. Tobacco heating system

6.2.2.3.1.4 Human Puffing Topography

Human puffing topography (HPT) assesses each user's unique way of using a product and constitutes an established research tool in smoking behavior research to assess individual product use patterns on a per single-use basis. Total puff volume, the sum of the volume of all puffs taken during the CC smoking or THS use experience, is a key measure quantifying mouth level exposure to cigarette smoke or in the case of THS, quantifying mouth level exposure to the THS aerosol. Considering additional parameters such as product use duration, puff volume and number of puffs, HPT allows to evaluate changes in product use behavior when switching from one product to another (e.g., subjects own brand of CC to THS) (Figure 2).

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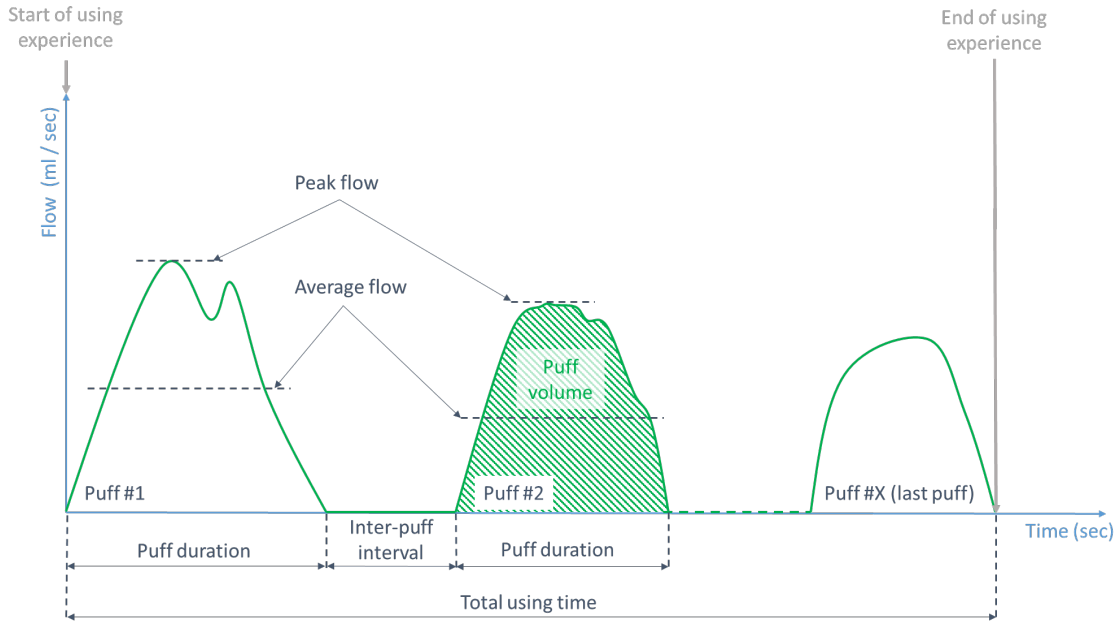


Figure 2 Human Puffing Topography Parameters

Human Puffing Topography was assessed in studies [ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP], [ZRHM-REXA-07-JP] and [ZRHM - REXA-08-US]. HPT was performed using the HPT SODIM® Device, model SPA/M (SODIM® Instrumentation, Fleury les Aubrais, France). Two types of Sample Holders (one to accommodate CC and one for THS) were used with the HPT SODIM® Device to capture HPT profiles (see Table 2 for the per puff and Table 3 for the per product use parameters). The Sample Holders for the HPT SODIM® Device were specifically designed for compatibility with CC and THS and the HPT SODIM® Device and Sample Holders were validated according to our internal Quality Management System to ensure that measurements performed with the HPT SODIM® Device and Sample Holder are accurate and repeatable. Furthermore HPT was only assessed in subjects who smoked CCs that were compatible with the HPT SODIM® Device (standard CC with a 8.04 mm filter diameter)

A total of 7 parameters, 3 at the puff level (average puff volume, average puff duration and average pressure drop) and 4 at the product use level (total puff volume, total number of puffs, total smoking duration and puff frequency) are described in section (Section 6.2.2.4.1.2.3). These 7 parameters were selected as they reflect how the user changed or adapted his/her puffing at an average puff level (i.e., by changing the length of the puffing duration and volume inhaled), but as well as during a full product use experience (i.e., at the product use level, by changing the puffing frequency). The other parameters were either correlated to the selected parameters (e.g., pressure drop is correlated to flow and resistance) or technical ones (e.g., work) describing the intrinsic properties of THS.

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Table 2 Human Puffing Topography - Per-puff parameters

Description	Variable	Unit
Average puff volume	Vi	ml
Average puff duration	Di	s
Average pressure drop	Pmi	mmWG

Table 3 Human Puffing Topography - Per product use

Description	Variable	Formula	Unit
Total number of puffs	NPC	Σ Ni	
Total puff volume	TVOL	Σ Vi	ml
Total smoking duration	TDFi	Σ DFi	s
Puff Frequency	PFeq	NPC/(TDFi/60)	

The full list of HPT parameters assessed is available in the individual clinical study reports of studies [ZRHR-REXC03-EU], [ZRHR-REXC04-JP], [ZRHM-REXA07-JP] and [ZRHM-REXA08-US], available in Section 7.3.1.

6.2.2.3.1.5 Product Acceptance

6.2.2.3.1.5.1 Subjective Effects

Subjective effect measures, in particular the assessment of reinforcing and aversive effects of smoking such as relieve from urge-to-smoke, craving and withdrawal symptoms as well as measures of product acceptance through self-report questionnaires are well established and widely used to serve as outcomes in the context of the assessment of pharmacodynamics effects and are important to measure to understand the potential of an MRTP to serve as an acceptable substitute for CC.

6.2.2.3.1.5.1.1 Modified Cigarette Evaluation Questionnaire

The modified Cigarette Evaluation Questionnaire (mCEQ) (Cappelleri 2007), assessing both the reinforcing and the aversive effects of smoking, was used as a measure of product acceptance in all clinical studies included in this dossier including 5 sub-scales, (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), and 2 single items, (iv) enjoyment of respiratory tract sensations (single-item assessment), and (v) craving reduction (single-item assessment) are included (Cappelleri 2007). A score is thus derived for each sub-scale.

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6.2.2.3.1.5.1.2 Urges-to-Smoke

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. In the context of MRTP assessment, the evaluation of urge-to-smoke has been recommended as a key outcome measure to prove that a MRTP can reduce the adverse effects of CC smoking "*through the ability of the MRTP to quell tobacco withdrawal (especially urges) and to reduce motivation to smoke conventional cigarettes due to preloading with the MRTP"* (IOM (Institute of Medicine) 2012).

The questionnaire of smoking urges (QSU) brief, which originates from the initial QSU 32-items questionnaire (Tiffany 1991) provides a multidimensional measure to assess the urge to smoke with 2 factor scores and a total score derived from the 10-item questionnaire:

- Factor 1: a positive reinforcement factor reflecting intention and desire to smoke and anticipation of pleasure from smoking
- Factor 2: a negative reinforcement factor reflecting the anticipation of relief from negative affect and nicotine withdrawal, and urgent and overwhelming desire to smoke.

6.2.2.3.1.5.1.3 Withdrawal Symptoms

Relief from withdrawal symptoms upon switching to THS and stopping or reducing CC use is another important aspect to evaluate if THS may serve as a substitute of CC among current tobacco users.

One of the most widely used measure of withdrawal symptoms from cigarette smoking (Hughes 1986) in tobacco research studies and indicated in the European Medicine Agency (EMA) guidelines for the development of medicinal products for the treatment of smoking is the Minnesota Nicotine Withdrawal Scale (MNWS). The MNWS has been shown to be of equal reliability and validity compared to other nicotine-withdrawal scales such as Mood and Physical Symptoms Scale, the Shiffman Scale, the Wisconsin Smoking Withdrawal Scale and the Cigarette Withdrawal Scale (West 2006). Many of the constituent items have demonstrated sensitivity to deprivation and to nicotine replacement therapy (Shiffman 2004b); (Hanson 2009).

A revised version (MNWS-R) which includes 15 symptoms that encompasses all the symptoms defining nicotine withdrawal, except depressed heart rate, mouth ulceration and malaise/weakness (DSM-IV; ICD-10) was recently proposed by the authors of the original scale (Hughes 2012) and was used in the reported studies.

6.2.2.3.1.5.2 Sensorial Experience

Sensorial experience plays a key role in product acceptance. The less pleasurable the sensorial experience, the less likely smokers will switch to a new product. In THS-PBA-07-US, sensorial experience was measured using ad-hoc questions on taste, smell and aftertaste using, for each of the 3 items, a 7-point Likert scales (from 1=I don't like it at all to 7=I like it very much).

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6.2.2.3.2 Behavioral Intention

6.2.2.3.2.1 Intent to Use

Effective communication of risk reduction potential is a critical element in switching adult smokers from cigarettes to MRTPs. Measure of Intent to use following exposure to product information is a well-accepted proxy to assess the extent to which consumers may adopt a tobacco product (Shiffman 2004a), (Parascandola 2008). However, no questionnaire has been identified as a standard and validated measure of Intent to Use in both current tobacco users and non-users. Acknowledging the lack of robust and validated measurement instruments, PMI has undertaken, as part of the PBA program, the development of new self-reported instruments based on best practices guidelines, including the current FDA guidance for patient-reported outcomes (PROs) in clinical trials (FDA (Food and Drug Administration) 2009). This project led to the development of the *Intent to Use Questionnaire* (ITUQ), comprised of two sets of single items assessing: (i) the intention to try (at least once) and (ii) intention to use (on a regular basis). The generation of items for ITUQ was based on the interpretation of the FDA draft guidance on MRTPs ((FDA 2012)) and the IOM report ((IOM 2012)) complemented with the input from consumer focus groups and expert opinions. A Research Summary Document describing key methodologies and outcomes underlying the development of the Intent to Use Questionnaire (ITUQ) is presented in Appendix [A732 PBA01Sum]. Two sets of items from the ITUQ were used in quantitative PBA studies (i.e., THS-PBA-03-US, THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US), yielding descriptive measures of: (i) Intention to Try (i.e., at least once) and (ii) Intention to Use (i.e., on a regular basis) (Table 4). In qualitative studies ([THS-PBA-02-US] and [THS-PBA-04-US], visual aids (in the form of lines anchored with 6 levels of intention to use) were used as the basis for discussion. These visual aids allowed participants to visually "rank" the potential messages or label, labeling and marketing material they were exposed to in terms of Intent to Try and Intent to Use.

Table 4 Measurement of Intention to Try and Intention to Use THS in Quantitative PBA Studies on the Effect of THS Communication

Items	Response Scale
Intention to Try items: How likely or unlikely are you… 1. to try THS 2. to try THS if one of your best friends were to offer THS to you **Intention to Use items**: 3. If you try THS and like it, how likely or unlikely are you to use THS regularly 4. If you try THS and like it, how soon would you being to use THS regularly	**For Items 1, 2 and 3:** 6-point Likert-like scale (1=definitely not, 2=very unlikely, 3= somewhat unlikely, 4=somewhat likely, 5=very likely, 6=definitely) **For item 4:** 6 ordinal timeframe response categories (1=within a week, 2=within a month, 3=within 3 months, 4=within 6 months, 5=more than 6 months, 6=never).

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6.2.2.3.2.2 Change in Intention to Quit

Communicating the modified risk of an MRTP may divert current smokers who intend stopping tobacco use from actually quitting. To assess the impact of THS communication on intention to quit among smokers, in quantitative PBA studies (i.e., THS-PBA-03-US, THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US), intention to quit was assessed pre and post exposure to THS labeling and marketing materials, using the Prochaska and DiClemente's Stages of Change model (DiClemente 1991), a widely used model to describe behavioral change associated to smoking (Etter 2002, Shiffman 2004a, Hughes 2005). Stage of Change was assessed for CC and for all tobacco products, pre and post exposure to labeling and marketing materials, using two closed-ended questions allowing smokers to be classified into contemplation stage (intention to quit within the next 6 months), and preparation stage (intention to quit in the next 30 days) (Table 5).

Table 5 Measurement of Change in Intention to Quit

Subcategory	Measurement method	Metric
Smoking	Change in responses (pre-post exposure) to closed-ended questions based on Prochaska and DiClemente's Stages of Change model.	Yes/no answers to the following questions: • *Are you seriously considering quitting smoking within the next 6 months?* • *Are you planning to quit smoking in the next 30 days?*
All tobacco	Change in responses (pre-post exposure) to closed-ended questions based on Prochaska and DiClemente's Stages of Change model.	Yes/no answers to the following questions: • *More generally, are you seriously considering quitting all tobacco products, (cigarettes, cigars, pipes, snuff, snus and chewing tobacco) within the next 6 months?* • *Are you planning to quit all tobacco products, (cigarettes, cigars, pipes, snuff, snus and chewing tobacco) in the next 30 days?*

6.2.2.3.3 Product Usability

6.2.2.3.3.1 Ability to Understand and Correctly Comply with Instruction for Use

On the basis of the content of the instruction for use THS, 9 usability tasks were defined and operationalized in 32 task steps (Table 6). In addition, 3 comprehension questions associated with the key communication messages of THS instructions for use were defined (Table 7). These measures constituted the main assessments of THS-PBA-06-US in which the correct demonstration of the THS use tasks and the correct comprehension of key messages of the THS instructions for use were assessed based on a usability assessment guide which defined what constitute a correct/acceptable demonstration/comprehension for each task step/key message.

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Table 6 Main Usability Tasks and Task Steps

Main Usability Task	Usability Task Steps
Task 1: How To Charge the THS 2.2 Holder and THS 2.2 Pocket Charger Simultaneously	Insert the THS 2.2 Holder into the Pocket Charger? With battery contacts facing down? With power button of THS 2.2 Holder aligned with notch in the Pocket Charger? Insert one end of the USB cable into the USB power adaptor and the other end into the THS 2.2 Pocket Charger? Close the hatch of the THS 2.2 Pocket Charger?
Task 2: How To Insert a THS 2.2 Tobacco Stick into the THS 2.2 Holder	Insert a THS 2.2 Tobacco Stick into the THS 2.2 Holder? Insert THS 2.2 Tobacco Stick into the THS 2.2 Holder without twisting it? Insert a THS 2.2 Tobacco Stick into the THS 2.2 Holder with the tobacco-side down? Align the line on the Tobacco Stick with the top of THS 2.2 Holder cap?
Task 3: How to Heat and Consume a THS 2.2 Tobacco Stick	Press the button on the side of the THS 2.2 Holder for 2 seconds until a flashing green light appeared? Return the THS 2.2 Holder to the interviewer, after the green light stopped flashing?
Task 4: How to Know When a THS 2.2 Tobacco Stick has Been Consumed and a Session is Over	Open-ended question “How will you know when the HeatStick has been consumed and the session is over?”
Task 5: How to Remove a THS 2.2 Tobacco Stick from the THS 2.2 Holder	Firstly, pull the cap away from the THS 2.2 Holder until the cap stops? Avoid twisting the THS 2.2 Tobacco Stick? Remove the THS 2.2 Tobacco Stick from the cap? Push the cap back into place? Align the cap with the power button?
Task 6: How to ‘heat clean’ the THS 2.2 Holder	Part A Open-ended question: “How will the Pocket Charger tell you it is time to heat clean your iQOS Holder?” Part B Insert the THS 2.2 Holder all the way into the THS 2.2 Pocket Charger? Close the hatch of the THS 2.2 Pocket Charger? Press and hold the power button to turn the THS 2.2 Pocket Charger on? Press and hold the Self-clean button for 3 seconds?

(table continues)

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Main Usability Task	Usability Task Steps
Task 7: How to Clean the THS 2.2 Holder with the THS 2.2 Cleaning Tool	Separate the cap of the THS 2.2 Holder from the body by pulling it apart? Pinch the center of the THS 2.2 Cleaner then pull the ends to release the two separate brushes? Insert the long THS 2.2 Holder body into the long brush? Clean the THS 2.2 Holder body using a twisting motion? Insert the THS 2.2 Holder cap into the short brush? Clean the THS 2.2 Holder cap with a twisting motion?
Task 8: How to remove a THS 2.2 Tobacco Stick that is stuck from the THS 2.2 Holder cap	Pull out the cleaning hook from the long brush? Push or pull the stuck THS 2.2 Tobacco Stick from the THS 2.2 Holder cap?
Task 9: How to Re-attach the THS 2.2 Holder Cap to the THS 2.2 Holder Body	Push the THS 2.2 Holder cap back into place on the THS 2.2 Holder body? Align the THS 2.2 Holder cap with the power button?

Table 7 Comprehension Assessments, Methods and Metrics

Communication Key Message	Measurement Method	Metric
1. Do not use the THS 2.2 Holder to smoke a conventional cigarette	Interviewer recorded subject's answers (using precoded response alternatives)	Percent of subjects with answers that were • Correct (the subject's answer fully captures the communication message of the instruction for use) • Acceptable (subject's answer varies from the strictly correct response but which reveals correct consumer intent that results in general understanding of THS 2.2 instructions) • Correct or Acceptable
2. Do not light a THS 2.2 Tobacco Stick with a lighter		
3. The THS 2.2 Holder must be fully charged to be heat cleaned		

6.2.2.3.3.2 Potential Misuse

In THS-PBA-07-US, ease of use and misuse were assessed. Ease of use was assessed using a 7-point Likert scale (from 1=not easy to use at all 7=very easy to use). Misuse was characterized by the 2 following situations reported by study participants: (1) "THS Tobacco Sticks consumed without THS Device" and (2) "THS Device used with a product other than THS Tobacco Sticks". For each situation, the kind of misuse was collected using 2 predefined response options:

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(1) "I lit up the HeatSticks (like a conventional cigarette)" or "others"

(2) "I used THS device with conventional cigarettes" or "others"

6.2.2.3.4 Statistical Methods

The general principles applied to evaluate and present Product use behavior data are provided below for clinical confinement/ambulatory studies and observational studies respectively.

6.2.2.3.4.1 Clinical Confinement/Ambulatory Studies

A detailed description of statistical methods applied to each of the individual studies is available in the individual study synopses (Section 6.1.3.4) and the statistical analysis plan of each study (Appendix 16.1.8 of the Study Report for studies [ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP], [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US]).

Analysis Sets:

For the analysis of product use behavior data 2 analysis sets were of importance:

The Full Analysis Set (FAS) and the Per-Protocol Set (PP).

The FAS consisted of all the randomized subjects who had at least 1 post-randomization product use experience (if randomized to THS or CC) and had at least 1 valid BoExp measurement (THS, CC, SA arms). In the context of product use behavior assessment, the FAS was selected as primary analysis set in the confined studies for product use behavior (nicotine exposure, product consumption and HPT) and product acceptance measures (QSU, MNWS and mCEQ) as, by definition, product adherence was enforced by controlled product distribution by the site staff.

The PP population for the studies was defined as:

- Subjects that were correctly randomized and assigned study product.
- Subjects with at least 1 post-randomization product use (for CC and THS).
- Subjects with at least 1 valid post-randomization BoExp measurement.
- Subjects that were adherent with their assigned study product.
- Subjects without major protocol deviations that impacted the validity of the evaluation of the study results.

The PP Population was selected as the primary analysis set for measures of product use behavior (HPT) and product acceptance (QSU, MNWS and mCEQ) in the 2 clinical studies in ambulatory conditions (i.e., Day 30 to Day 90 of studies [ZRHR-REXA-07-JP] and [ZRHM-REXA-08-US]), to assess the sole contribution of THS in subjects who were

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using THS ad-libitum and exclusively or predominantly, rather than the mixed effect of THS in combination with CC in the FAS representing a heterogeneous exposure (e.g., as mixed product use, or non-use of the assigned product). The analysis of product consumption and nicotine exposure was analyzed in both, the PP set and the FAS.

Dual Use:

In the studies [ZRHR-REXC-03-EU] and [ZRHR-REXC-04-JP] dual use was not possible as product adherence was enforced by controlled product distribution by the site staff. Although subjects were requested to use solely the product allocated to their respective study arm in studies [ZRHR-REXA-07-JP] and [ZRHM-REXA-08-US], it was considered that during the ambulatory period of these studies not all subjects randomized to the THS arm may exclusively use THS at all times during the study but may concomitantly use THS and CC. To assess the use of THS in combination with CC, product use / dual-use was calculated by study period (Period 1: Day 1 to Day 5 [confinement], Period 2: Day 6 to Day 30, Period 3: Day 30 to Day 60 and Period 4: Day 60 to Day 90) according to the product usage categories presented in Figure 1 and as described in section 6.2.2.3.1.3.

The more granular categorization scheme was used for the definition of the PP population and for the description of the product use patterns observed whereas the less granular scheme was used for the presentation of other study endpoints (e.g. safety endpoints) to better understand the impact of product.

6.2.2.3.4.2 Observational Studies on Actual Use

Statistical analyses from the actual use Study [THS-PBA-07-US] were conducted for 2 data sets, the FAS the PP set (also referred to as PPROT in study [THS-PBA-07-US]). The FAS consisted of all enrolled participants with at least: (i) 1 documented consumption of a CC in the electronic diary during the 1-week Baseline period and (ii) at least 1 documented consumption of a THS Tobacco Stick in the electronic diary during the 6-week observational period.

The PP consisted of all enrolled participants with:

- Documentation of CC consumption for at least 6 days of the 1-week Baseline period
- At least 1 documented consumption of a THS Tobacco Stick during the 6-week observational period
- Documentation of CC and / or THS Tobacco Sticks consumption for at least 39 days of the 6-week observational period.
- In addition, a participant was invalid for the PP if his / her cumulated THS Tobacco Stick consumption as self-reported in the e-diary exceeded the number of available THS Tobacco Sticks by more than 5 percent (Ratio documented THS Tobacco Sticks versus available THS Tobacco Sticks) and by more than 20 THS Tobacco Sticks in absolute numbers (Difference documented THS Tobacco Sticks minus available THS Tobacco Sticks).

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Due to the descriptive character of this Actual Use Study in a near to real-world conditions, the FAS was the primary analysis set for all analyses. Results of the PP were considered as supportive in the sense of a sensitivity analysis to evaluate the robustness of findings.

For the WOTs conducted abroad, the FAS consisted of all participants enrolled in the observational period with a documentation of CC and / or THS Tobacco Sticks consumption in the paper and pencil diary for at least 26 days of the 4-week observational period.

Detailed description of statistical methods applied to each of these observational studies, are presented in Appendix 16.1.8 of the Study Report for [THS-PBA-07-US] and in Section 10 of [WOT].

6.2.2.4 Study Results

6.2.2.4.1 Product Use Behavior

6.2.2.4.1.1 Summary of Individual Results of Confinement and Ambulatory Studies

6.2.2.4.1.1.1 Study Design: Reduced Exposure Studies

The reduced exposure studies consisted of 2 studies of 5 days in a confinement setting (REXC; [ZRHR-REXC-03-EU] and [ZRHR-REXC-04-JP]) conducted in Europe and Japan, respectively, and 2 studies with 5 days in confinement, followed by 85 days in an ambulatory setting (REXA; [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US]) conducted in Japan and in the US, respectively (see Table 1).

During confinement, product use was directed and monitored by the study staff and participating adult smokers were controlled for product compliance. Subjects used the THS without restriction (ad libitum) during an extended daily time window (16 hours). Dual use of CC and THS or any other nicotine-containing product was not permitted to allow the assessment of the maximal exposure reduction achievable when switching from CC to THS.

The ambulatory period of the REXA studies allowed to demonstrate that the exposure reduction seen under controlled conditions can be sustained in ambulatory, near to real-world conditions, where dual-use of THS and CC or other tobacco products can occur and how Subjective Effects and Product Use Behavior would evolve over a prolonged period of time in a setting where THS users are exposed to the possibility of using other tobacco and nicotine containing products.

The studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2008) (World Medical Association (WMA) 2008), International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and applicable national regulation. The Regular variant of THS and CC were used in studies [ZRHR-REXC-03-EU] and [ZRHR-REXC-04-JP] whereas the menthol variant was tested in studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US]. The studies were registered under ClinTrials.gov (NCT01959932, NCT01970982, NCT01970995 and

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NCT01989156) and a summary of the methodology and results for these studies is provided in Table 9, Table 10, Table 11 and Table 12, respectively.

Table 8 provides an overview on the schedule evens for the Product Consumption, Nicotine Exposure, HPT and Subjective Effects assessments in the Confined and Ambulatory Reduced Exposure Studies.

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Table 8 Schedule of Events for Product Consumption, Nicotine Exposure, HPT, Subjective Effects Assessments in the Confined and Ambulatory Reduced Exposure Studies

	Baseline Period			Confinement Period					Ambulatory Period			
	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day 30 Visit ± 3 days	Day 60 Visit ± 3 days	Day 90 Visit ± 3 days
Study Day	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**30/31**	**60/61**	**90/91**
Smoking History	●											
Product Consumption [a]		●	●	●	●	●	●	●		●	●	●
Nicotine/Cotinine [b]		●	●	●	●	●	●	●	●	●	●	●
QSU-brief questionnaire [c]		●	●	●	●	●	●	●		●	●	●
MNWS (revised version) [d]			●	●	●	●	●	●	●	●	●	●
mCEQ (modified version; THS and CC arms) [e]		●	●	●	●	●	●	●		●	●	●
HPT (THS and CC arms) [f]			●	●			●			●	●	●

a: Daily during ambulatory period only (from time of Discharge on Day 6 to time of discharge of Day 91). Use of any tobacco/nicotine containing products was captured in the e-diary.
b: Nicotine/cotinine; Day 0 to Day 4 (all study arms): 1 blood sample between 08:00 PM and 09:30 PM.
Day 5 and Day 6 (THS and CC arms): 1 sample within 15 minutes prior to the first product use; 8 blood samples after the start of product use (T0), each at 2 hour intervals. On Day 6, 2 blood samples was drawn. The first sample was 20 hours after T0 and the second blood sample was 24 hours after T0 (with T0 being the time of the first product use on Day 5).
Day 5 and Day 6 (SA arm): 1 blood sample in the evening between 08:00 PM and 09:30 PM on Day 5 and 1 blood sampling between 08:00 AM and 09:30 AM on Day 6.
Day 30 Visit (Day 30), Day 60 Visit (Day 60), Day 90 Visit (Day 90) (all study arms): 1 blood sample was drawn during the visit, irrespective of the time of product use.
c: QSU-brief: Daily, from Day -1 to Day 5 and at every visit during the ambulatory period, i.e. Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90) .
d: MNWS daily from Day 0 to Day 6 prior product use, but no later than 10:00 AM and at every visit during the ambulatory period, i.e. Day 30 Visit (Day 31), Day 60 Visit (Day 61) and Day 90 Visit (Day 91) no later than 10:00 AM irrespective of the time of product use
e: mCEQ: Day -1 to Day 5 on a daily basis, and on Day 30 Visit (Day 30), Day 60 Visit (Day 60) and Day 90 Visit (Day 90/91) in Day -1 and Day 0 on all subjects, from Day 1 in THS and CC arms.
f: On Day 0, HPT assessment was done in all subjects smoking CC compatible with the HPT SODIM® Device. On Day 1, Day 4, Day 30 Visit (Day 30), and Day 60 Visit (Day 60) and Day 90 Visit (Day 90), HPT was done in all subjects in the THS and CC arms. On Day 1 and Day 4, full day HPT recording was done. On Day 30 Visit (Day 30), Day 60 Visit (Day 60), and Day 90 Visit (Day 90), 4 hours of recording was done. Smoking topography with the HPT SODIM® Device was not done in subjects smoking CC that are incompatible with the HPT SODIM® Device (e.g. slim CC). No HPT assessments were done in subjects in the SA arm.

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6.2.2.4.1.1.2 ZRHR-REXC-03-EU

In the context of product use assessment, product use behavior (nicotine exposure, product consumption and HPT) and product acceptance measures (QSU, MNWS and mCEQ) associated with smoking were systematically assessed during the study using validated methods (Section 6.2.2.3) and validated / published questionnaires. Such measures provide insight into product acceptance in terms of ritual, taste, sensory and nicotine delivery as well as adaptation mechanisms when switching to a new product such as THS, and are important to convert adult smokers to THS.

6.2.2.4.1.1.2.1 Methodology of the ZRHR-REXC-03-EU

A brief description of study design, endpoints and methodology related to *Product Use Behavior* assessment is given in Table 9.

Table 9 Methodology - Product Use Behavior Assessment in the ZRHR-REXC-03-EU Study

Reduced exposure study in smokers using the THS 2.2 for 5 days in a confinement setting
Title of the study: A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the THS 2.2 or smoking abstinence, compared to continuing to use CC, for 5 days in confinement
Study design: Randomized, controlled, open-label, 3-arm, parallel group, single-center study to compare the use of THS with continuing to smoke CC and smoking abstinence (SA). This was an ad libitum smoking study.
Subjects: Randomized: 160; Completed: 159; Number of subjects in the THS arm (completed): 80 (79). Number of subjects in the CC arm (completed): 41 (41); Number of subjects in the SA arm (completed): 39 (39).
Main criteria for inclusion: • Aged from 21 to 65 years (inclusive). • Subject was aged from 21 to 65 years (inclusive) • Subject was of Caucasian origin • Considered as healthy based in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening • Subject was a current smoker (based on self-reporting) who had smoked for the last 4 weeks at least 10 commercially available non-menthol CC per day (no brand restrictions). The subject had smoked for at least the last 3 consecutive years. Did not plan to quit smoking in the next 3 months. • Body mass index <18.5 or ≥32.0 kg/m^2
Test Product: THS Regular.
Reference Product: Commercially available CC with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) as labeled on the cigarette package.
Reference Point: Smoking abstinence. No Nicotine Replacement Therapy.
Duration of Use: Exposure period (5 days) defined as the period after randomization from Day 1, 06:30 AM until Day 5, 11:00 PM, in which the subject was allowed to use the assigned product (THS Regular or CC), or abstained from smoking.

(table continues)

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Analytical Method: All bioanalytical assays and laboratory assessments were carried out using validated methods. The methods used are summarized in [Section 6.1.3.3 Bioanalytical Methods] and in the [Appendix 16.1.9] of the [ZRHR-REXC03-EU] study report.

Selected Secondary Objectives (related to Product Use Behavior only)

Nicotine Exposure:

To determine levels of nicotine on Day 5 in smokers switching from CC to THS Regular as compared to smokers continuing to smoke CC and to describe their levels over the exposure period from Day 1 to Day 5.

Product Consumption:

To describe daily THS Tobacco Stick/CC consumption over the exposure period in smokers switching from CC to THS Regular as compared to smokers continuing to smoke CC.

Selected Exploratory Objectives (related to Product Use Behavior only):

Human Puffing Topography:

To describe puffing pattern through the assessment of human puffing topography (HPT) parameters over the course of the study in smokers switching from CC to THS Regular as compared to smokers continuing to smoke CC.

Urge-to-Smoke:

To describe total score, Factor 1 (relief) and Factor 2 (reward) from the QSU-brief in smokers switching from CC to THS Regular as compared to smokers continuing to smoke CC and smokers switching from CC to SA.

Craving and Withdrawal:

To describe total scores from the MNWS in smokers switching from CC to THS Regular as compared to smokers continuing to smoke CC and smokers switching from CC to SA.

Product Evaluation:

To describe product evaluation as measure with the mCEQ over the course of the study in smokers switching from CC to THS Regular as compared to smokers continuing to smoke CC.

6.2.2.4.1.1.2.2 Results of the ZRHR-REXC-03-EU

Nicotine Exposure:

The urinary concentrations of nicotine equivalents adjusted for creatinine (NEQ_{adjc}) were comparable at Baseline across study arms.

Geometric mean levels of NEQ_{adjc} increased from Baseline (9.01 mg/g creat) to Day 5 (10.60 mg/g creat) in the THS Regular arm, with the results from the CC arm (increase from 8.69 at Baseline to 9.76 mg/g creat at Day 5) comparable to those of the THS Regular arm. This corresponds to a change from Baseline of 23% and 15% for the THS Regular and CC arms, respectively. In the SA arm, NEQ_{adjc} values decreased from Baseline (9.53 mg/g creat) to Day 5 (0.14 mg/g creat), as expected, which corresponded to a -98% change from Baseline (Figure 3).

Nicotine and cotinine concentrations followed a similar pattern as NEQ_{adjc}.

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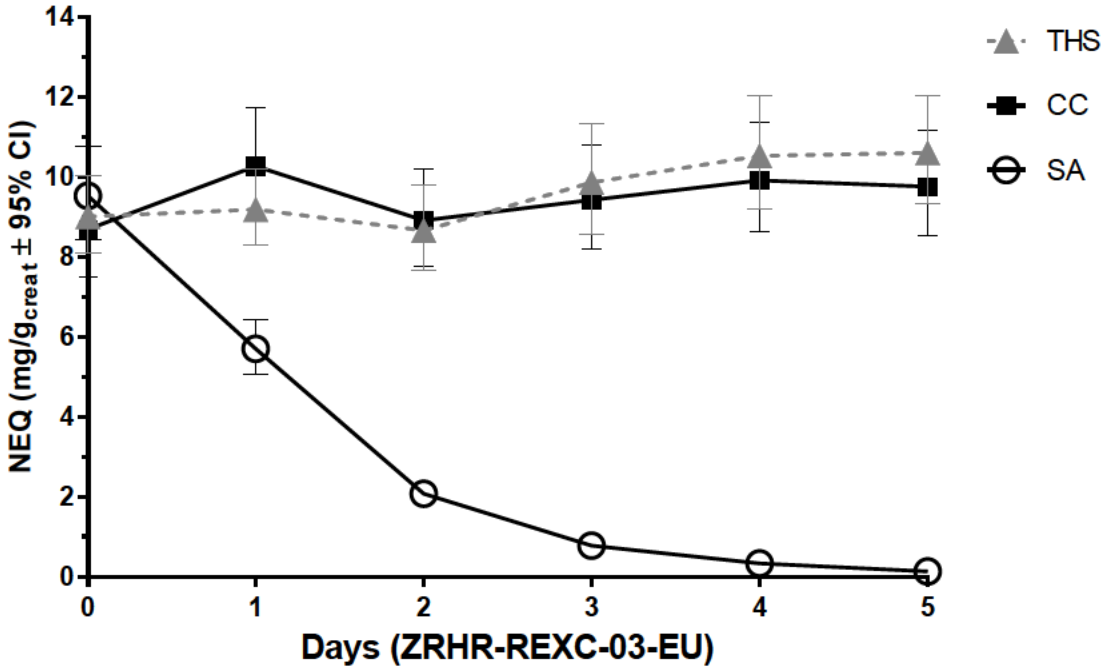


Figure 3 Geometric Mean NEQ Urinary Concentration Adjusted for Creatinine During the Course of the Study

Abbreviations: Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, nicotine equivalents adjusted to creatinine (NEQadjC), creatinine (creat), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI).
Note: Day 0 = Baseline.
Data Source: Clinical study report Appendix 15, Figure 15.1.2.34.

Product Consumption:

The mean number of THS Tobacco Sticks consumed increased from 16.0 CC/day at Baseline to 20.7 THS Tobacco sticks/day at Day 5. In the CC arm, the mean number of CC consumed daily remained stable (16.2 CC/day at Baseline and 16.6 CC/day at Day 5) (Figure 4).

In summary, the mean number of THS Tobacco Sticks increased from Baseline to Day 5 while the NEQ_{adjc} concentration remained constant.

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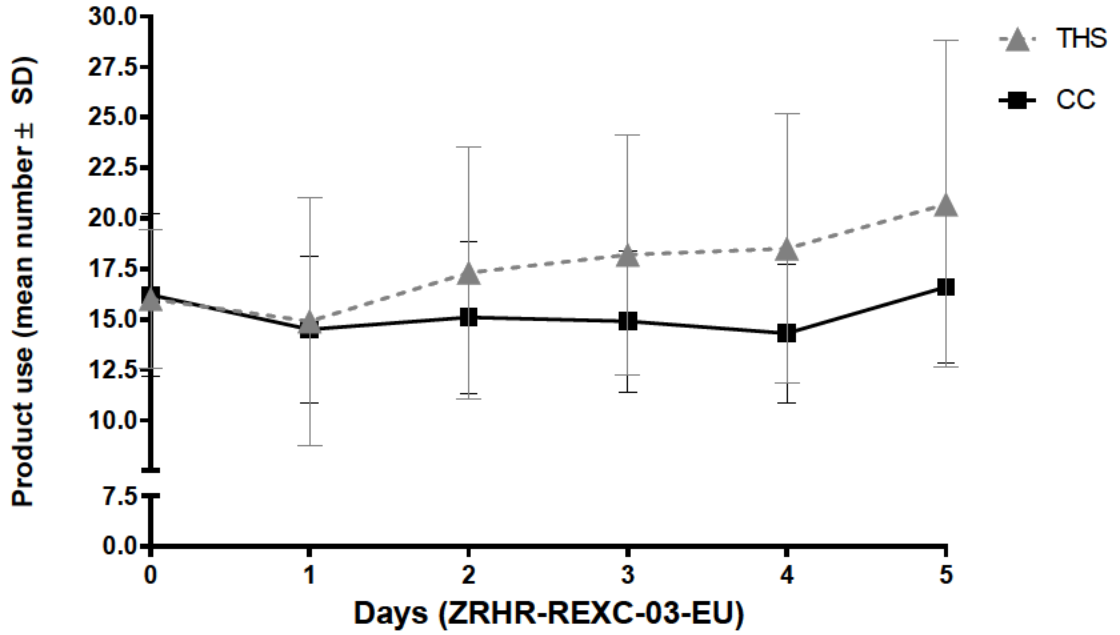


Figure 4 Product Consumption (Mean Number of Products Used) During the Course of the Study

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC); standard deviation (SD)
Note: Day 0 = Baseline
Data Source: Clinical study report Appendix 15, Table 15.2.2.1.

Human Puffing Topography:

Baseline values for most assessed HPT parameters were comparable between the THS Regular and the CC arms while subjects were using their usual brand of CC and remained stable between Baseline and Day 4 in the CC arm.

In the THS Regular arm, average puff duration, total puff duration, and puff frequency all increased from Baseline to Day 1 and remained increased for THS Regular use compared to CC use on both Day 1 and Day 4. Average inter puff interval and total smoking duration all decreased from Baseline to Day 1 and remained lower for THS Regular use compared to CC use on Day 4. In contrast, values for total number of puffs, total puff volume and average puff volume, were stable from Baseline (CC use) to Day 4 in the THS Regular arm.

On Day 4 the total puff volume showed little difference between THS Regular and CC (791.70 ml for THS Regular and 752.16 for CC; ratio: 105.26). For THS Regular, an increase of average puff duration (: 1.98s for THS and 1.49s for CC; ratio: 132.25) and puff frequency (5.25 puffs/min for THS and 4.00 puffs/min for CC; ratio: 132.33]) was observed.

The total smoking duration was approximately 3.25 min for THS and 4.18 min for the CC arms, respectively (ratio: 77.64).

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In summary, the HPT parameters indicated that THS Regular users were taking a similar number of puffs and puff volume, compared to CC, and adapted to the product by taking longer puffs, thus shortening the interpuff interval.

Subjective Effects:

The mean urge-to-smoke total scores were comparable across study arms at Baseline with mean urge-to-smoke total scores from 3.49 to 3.69. For the THS Regular and CC arms, the average urge-to-smoke total score remained stable and were comparable throughout the study (ranges of 2.93 to 3.30 and 3.20 to 3.46, respectively). In the SA arm, the urge-to-smoke total score increased from Baseline to Day 1 (score of 5.29, corresponding to an increase of 1.8 points). Total score values then decreased from 5.29 at Day 1 to 4.40 at Day 5 (Figure 5).

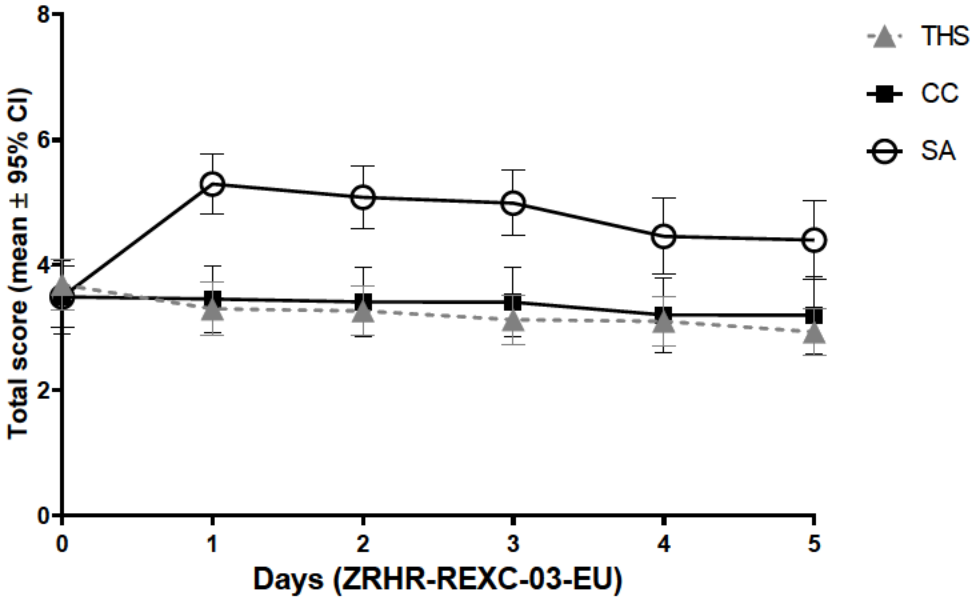


Figure 5 Total Score – Questionnaire of Smoking Urges During the Course of the Study

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI)
Note: Day 0 = Baseline
Data Source:Clinical Study Report Appendix 15, Table 15.2.4.43

Similar results were observed for withdrawal symptoms as assessed by the MNWS-R. MNWS-R total score 1 and 2 values were comparable at Baseline across study arms.

The average MNWS-R total score 1 values remained stable throughout the study for both, the THS Regular and CC arms. Similar results were observed for the average MNWS-R total score 2 in the CC arm, where values remained stable throughout the study. For the THS Regular arm, the average MNWS-R total score 2 increased from Baseline to Day 2

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before gradually decreasing over the course of the study reaching combarable scores as CC on Days 3 to 6.

In the SA arm, the MNWS-R total score 1 and 2 increased from Baseline to Day 2, decreased afterwards from Day 2 to Day 6, approaching the scores of the THS Regular and CC arms by Day 6.

The results for the mCEQ scale showed that on Day 5, craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction were all lower compared to Baseline for subjects who switched to THS Regular as compared to subjects who continued to smoke CC (Figure 6).

The LS mean differences on over all study days were of -1.12, -1.00, -0.72, and -1.26, respectively. Aversion slighty increased from Baseline in the THS Regular arm while there was a decrease from Baseline in the CC arm, with an overall LS mean difference of 0.25 over all time points (Figure 6).

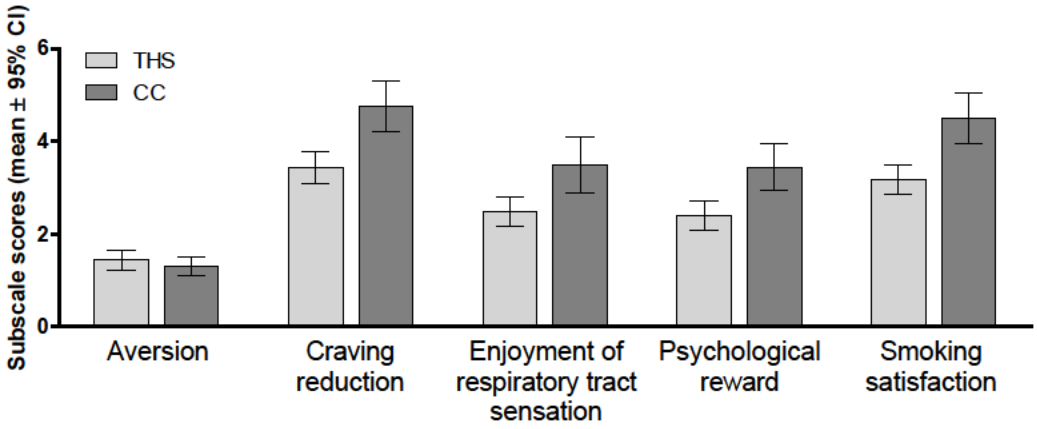


Figure 6 mCEQ Subscales on Day 5

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), confidence intervals (CI)
Data Source: Clinical Study Report Appendix 15, Table 15.2.4.47

The change in taste, sensorial experience, ritual, and differences in the ISO nicotine yield of THS Regular, are likely reasons for the observed differences in overall satisfaction. Nevertheless, overall subjective effects with THS Regular were close to CC.

In summary, this study showed that nicotine uptake was similar between the THS Regular and CC arms, and patterns of product use behavior (number of products used and HPT) indicated that users adapted quickly to the new product and achieved their desired nicotine levels with a satisfaction comparable to CC.

6.2.2.4.1.1.3 ZRHR-REXC-04-JP

The primary purpose of this study, similar in design to study [ZRHR-REXC03-EU], was to compare THS with CC in terms of exposure to selected HPHC after ad libitum use of THS for 5 days by adult healthy Japanese smokers as compared to smokers who continued smoking their own preferred brand of CC.

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6.2.2.4.1.1.3.1 Methodology of the ZRHR-REXC-04-JP

A brief description of study design, endpoints and methodology related to product use behavior assessment is given in Table 10.

Table 10 Methodology - Product Use Behavior Assessment in the ZRHR-REXC-04-JP Study

Reduced exposure study in smokers using the THS 2.2 for 5 days in a confinement setting
Title of the study: A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the THS 2.2 or SA, compared to continuing to use CC for 5 days in confinement
Study design: This was a randomized, controlled, open-label, 3-arm, parallel group, single-center study to compare the use of THS Regular with continuing to smoke CC and SA.
Subjects: Randomized: 160; Completed: 160; Number of subjects in the THS arm (completed): 80 (80). Number of subjects in the CC arm (completed): 40 (40); Number of subjects in the SA arm (completed): 38 (38).
Main criteria for inclusion: • Subject was aged from 23 to 65 years (inclusive) • Subject was of Japanese origin • Considered as healthy based in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening • Subject was a current smoker (based on self-reporting) who had smoked for the last 4 weeks at least 10 commercially available non-menthol CC per day (no brand restrictions). The subject had smoked for at least the last 3 consecutive years. Did not plan to quit smoking in the next 3 months. • Body mass index <18.5 or ≥32 kg/m^2.
Test Product: THS 2.2 Regular.
Reference Product: Commercially available CC with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) as labeled on the cigarette package.
Reference Point: Smoking abstinence. No Nicotine Replacement Therapy.
Duration of Use: The exposure period lasted 5 days and was defined as the period after randomization from Day 1, 06:30 AM until Day 5, 11:00 PM, in which the subject was allowed to use the assigned product (THS Regular or CC), or abstained from smoking.
Analytical Method: All bioanalytical assays and laboratory assessments were carried out using validated methods. The methods used are summarized in [Section 6.1.3.3 Bioanalytical Methods] and in the [Appendix 16.1.9] of the [ZRHR-REXC-04-JP] study report.
Secondary Objectives (related to Product Use Behavior only) Nicotine Exposure: To determine levels of nicotine on Day 5 in smokers switching from CC to THS Regular compared to smokers continuing to smoke CC and to describe their levels over the exposure period from Day 1 to Day 5. Product Consumption: To describe the daily THS Tobacco Stick/CC consumption over the exposure period in smokers switching from CC to THS Regular as compared to smokers continuing to smoke CC.

(table continues)

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Exploratory Objectives (related to Product Use Behavior only):

Human Puffing Topography:

To describe puffing pattern through the assessment of human puffing topography (HPT) parameters and the HPT questionnaire over the course of the study in smokers switching from CC to THS Regular as compared to smokers continuing to smoke CC.

Urge-to-Smoke:

To describe the total score, Factor 1 (relief) and Factor 2 (reward) from the QSU brief in smokers switching from CC to THS Regular as compared to smokers continuing to smoke CC and smokers switching from CC to SA.

Craving and Withdrawal:

To describe the total scores MNWS in smokers switching from CC to THS Regular as compared to smokers continuing to smoke CC and smokers switching from CC to SA.

Product Evaluation:

To describe product evaluation as measure with the mCEQ over the course of the study in smokers switching from CC to THS Regular as compared to smokers continuing to smoke CC.

6.2.2.4.1.1.3.2 Results of the ZRHR-REXC-04-JP

Nicotine Exposure:

The profiles from the THS Regular and CC arms were generally comparable throughout the entire confinement period. In both, the THS Regular and CC arm, geometric mean NEQ_{adjc} values increased slightly from Baseline (5.21 mg/g creat for THS Regular and 5.30 mg/g creat for CC) to Day 5 (5.44 mg/g creat for THS Regular and 5.52 mg/g creat for CC). These values correspond to percent changes from Baseline of 17% and 10% for the THS Regular and CC arms, respectively.

In the SA arm, NEQ_{adjc} values decreased from Baseline (5.00 mg/g creat) to Day 5 (0.15 mg/g creat), which corresponded to a -96% change from Baseline (Figure 7).

Plasma nicotine concentrations were different at Baseline with the highest levels observed in the CC arm and the lowest in the SA arm (CC: 18.28 ng/mL; THS: 15.14 ng/mL and SA: 14.43 ng/mL). Levels increased slightly from Day 0 to Day 5 but remained comparable between THS and CC on Day 5 with a LS mean difference of 2.44 ng/mL. In the SA arm, nicotine levels decreased from Baseline to Day 5 (SA: 0.10 ng/mL).

Cotinine concentration followed a comparable pattern as $NEQ_{adjc.}$

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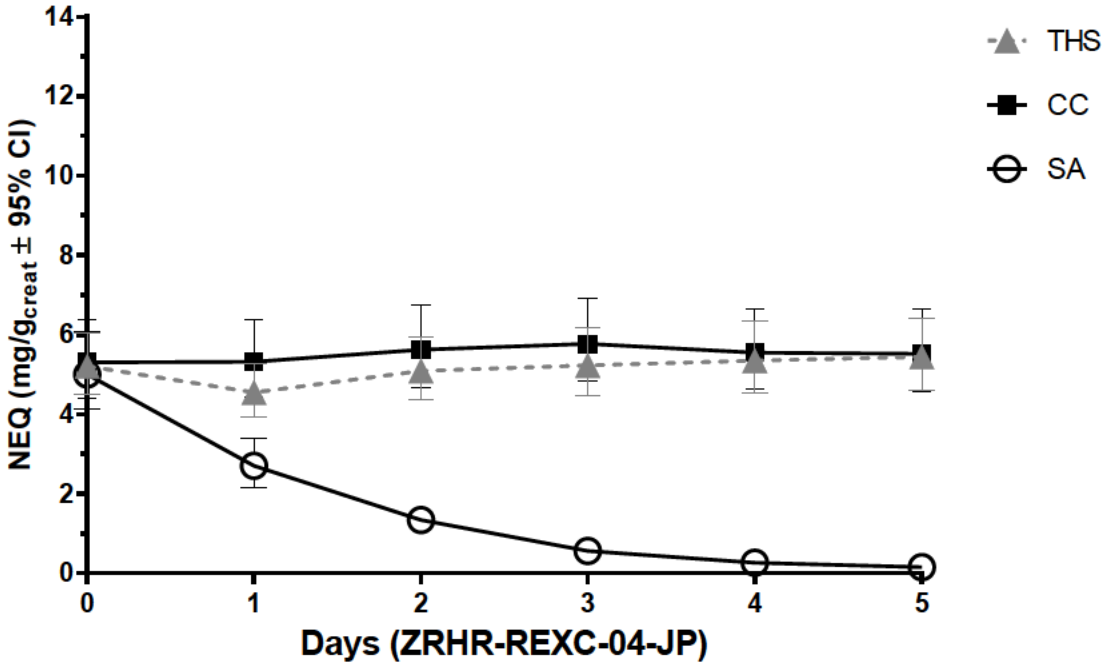


Figure 7 Geometric Mean NEQ Urinary Concentration Adjusted for Creatinine During the Course of the Study

Abbreviations: Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, nicotine equivalents adjusted to creatinine (NEQ_{adjC}), creatinine (creat), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI).
Note: Day 0 = Baseline.
Data Source: Clinical study report Appendix 15, Figure 15.1.2.34.

Product Consumption:

In the THS Regular arm, the mean number of THS Tobacco Sticks consumed decreased from Baseline to Day 1, with daily consumption from Day 2 onwards comparable to Baseline (Baseline: 10.3 cigarettes/day; Day 5: 9.9 THS Tobacco Sticks/day). In the CC arm, daily consumption increased from Baseline (10.5 cigarettes/day) to Day 5 (12.5 cigarettes/day). In addition, product consumption was consistently higher in CC compared to THS (Figure 8).

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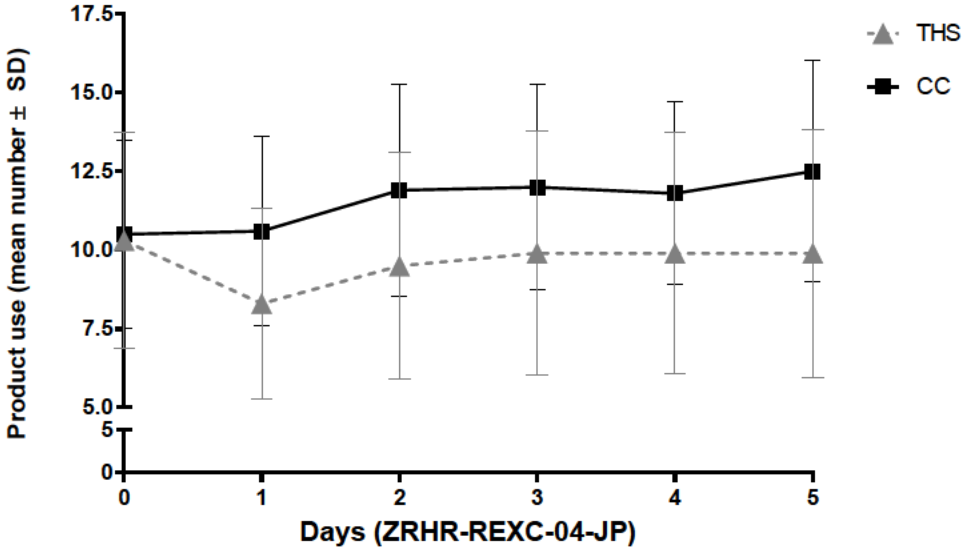


Figure 8 Product Consumption (Mean Number of Products Used) During the Course of the Study

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), standard deviation (SD)
Note: Day 0 = Baseline
Data Source: Clinical study report Appendix 15, Table 15.2.2.1.

Human Puffing Topography:

Baseline values for the assessed HPT parameter were generally comparable between the THS Regular and the CC arms and remained stable between Baseline and Day 4 in the CC arm compared to the THS Regular arm, with the exception of total number of puffs and total puff volume which decreased slightly in CC arm on Day 1, and the average inter puff interval which increased from Baseline to Day 4.

In the THS Regular arm, total puff volume, average puff volume and average inter puff interval decreased from Baseline to Day 1, whereas total number of puffs and puffing frequency increased at the same time resulting in a notable difference in the total number of puffs, puff frequency, average puff volume and average inter puff interval in THS compared to CC on Days 1 and 4. Total puff volume was also decreased on Day 1 in subjects who switched to THS Regular use compared to subjects who continued to smoke CC, but this difference disappeared between Day 1 and Day 4.

No notable differences were observed in average puff duration and total smoking duration on both Days 1 and 4 between THS and CC.

On Day 4 the total puff volume were similar between the THS Regular l and the CC arm (648.37 ml for THS and 653.36 ml for CC; THS:CC ratio: 99%) and the total number of puffs (17.22 puffs for THS and 14.52 puffs for CC; THS:CC ratio:119%) and puff frequency (4.39 puffs/min for THS and 3.47 puffs/min for CC; THS:CC ratio: 127) increased in the THS arm compared to the CC arm.

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The total smoking duration was approximately 4.03 min for THS and 4.35 min for the THS and CC arms, respectively (THS:CC ratio: 93).

In summary, the HPT parameters indicated that THS Regular users were taking a similar total puff volume, compared to CC, but adapted to the product by taking more and more frequent puffs, thus shortening the interpuff interval.

Subjective Effects:

The mean urge-to-smoke total scores were comparable across study arms at Baseline with mean urge-to-smoke total scores of 4.13 for the THS Regular arm, 4.13 for the CC arm and 3.98 for the SA arm. For the THS Regular and CC arms, the average urge-to-smoke total scores remained stable over the 5 days and were comparable throughout the study. In the SA arm, the urge-to-smoke total score increased from Baseline to Day 1 (score of 4.64, corresponding to an increase of 0.66 points). Total score values then decreased from 4.64 at Day 1 to 4.12 at Day 5 (Figure 9).

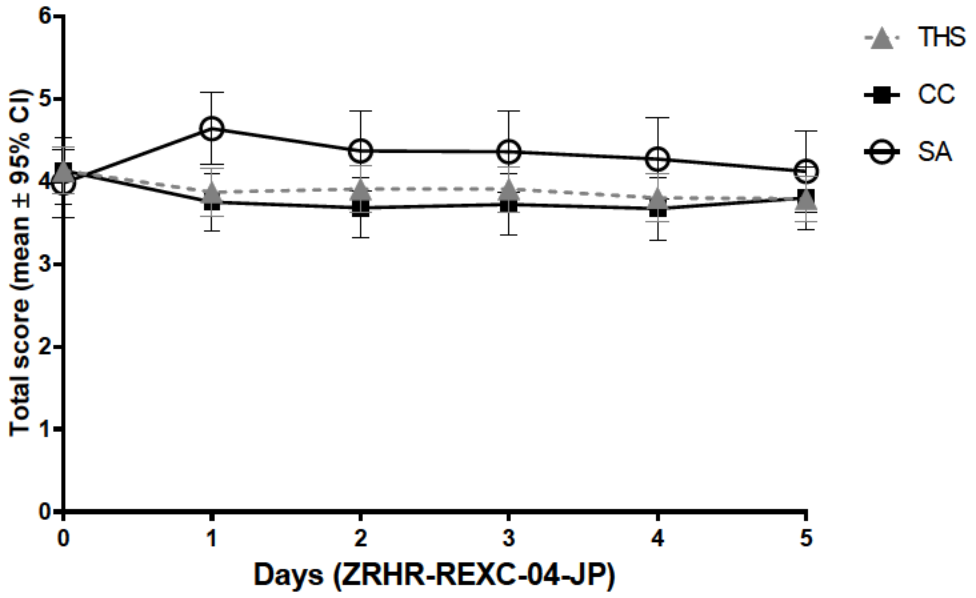


Figure 9 Total Score – Questionnaire of Smoking Urges During the Course of the Study

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI)
Note: Day 0 = Baseline
Data Source: Clinical Study Report, Appendix 15, Table 15.2.4.43..

Similar results were observed for withdrawal symptoms as assessed by the MNWS-R. MNWS-R total score 1 and 2 values. The average MNWS-R total score 1 and 2 values remained stable throughout the study for both, the THS Regular and CC arms.

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In the SA arm, the MNWS Total Score 1 and 2 increased from Baseline to Day 2, decreased moderately from Day 2 to Day 6, and was approaching Baseline and the scores of the THS Regular and CC arms by Day 6.

The mCEQ scale showed that on Day 5, psychological reward, and smoking satisfaction were slightly lower in THS compared to CC (differences of -0.18 and -0.69 respectively). Aversion, craving reduction, and enjoyment of respiratory tract sensation were comparable in the THS Regular and CC arms overall and on all individual study days, with the exception of craving reduction on Day 2 where it was decreased in THS Regular arm compared to the CC arm (Figure 10).

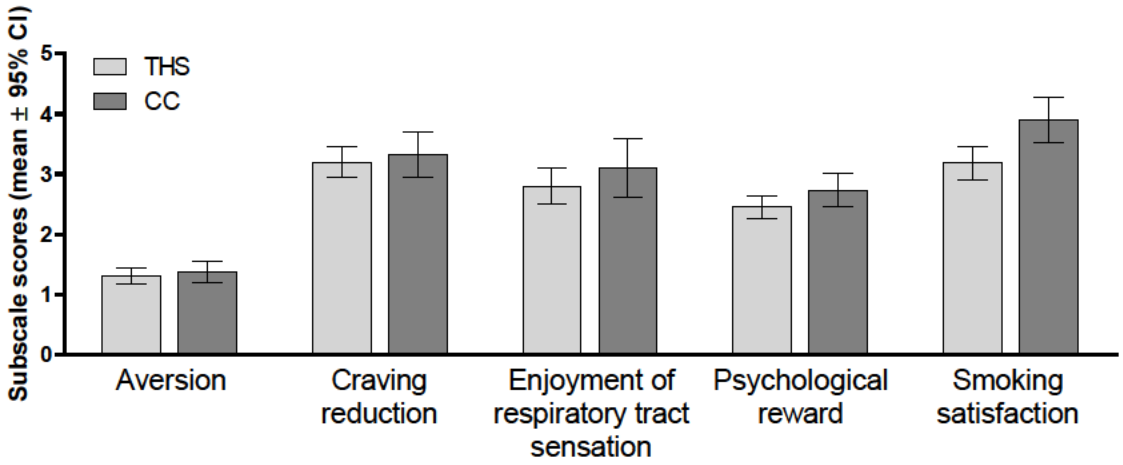


Figure 10 mCEQ Subscales on Day 5

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), confidence intervals (CI)
Data Source: Clinical Study Report, Appendix 15, Table 15.2.4.47.

The change in taste, sensorial experience, ritual, and differences in nicotine yield of THS Regular, are additional likely reasons for the observed differences in overall satisfaction. Subjective effects with THS Regular were close to CC.

In summary this study showed that the exposure to nicotine was similar between the THS Regular and CC arms indicating that users adapted gradually to the new product and achieved their desired nicotine levels. The combination of nicotine exposure and subjective effects measures indicated that THS Regular offered comparable satisfaction to CC.

6.2.2.4.1.1.4 ZRHM-REXA-07-JP

In addition to the data obtained in the studies in confinement ([ZRHR-REXC-3-EU] and [ZRHR-RE-04-JP]), the ambulatory setting of study [ZRHM-REXA-07-JP] allowed to assess product use behavior and product acceptance over a prolonged period of time in near to real-world conditions where dual-use of THS with other nicotine obtaining products could also occur.

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6.2.2.4.1.1.4.1 Methodology of the ZRHM-REXA-07-JP

A brief description of study design, endpoints and methodology related to product use Behavior Assessment is given in Table 11.

Table 11 Methodology - Product Use Behavior Assessment in the ZRHM-REXA-07-JP Study

Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting
Title of the study: A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the THS Menthol or observing SA, compared to continuing to use mCC, for 5 days in confinement and prolonged by 85 days in an ambulatory setting.
Study design: Randomized, controlled, open-label, 3-arm, parallel group, single-center study to compare the use of THS Menthol with continuing to smoke CC and SA. This was an ad libitum smoking study.
Subjects: Randomized: 216; Completed: 160; Number of subjects in the THS arm (completed): 78 (76). Number of subjects in the CC arm (completed): 42 (41); Number of subjects in the SA arm (completed): 40 (38).
Main criteria for inclusion: • Male and female Japanese aged 23 to 65 years • Considered as healthy based 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 for the last 4 weeks 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 or ≥32 kg/m^2.
Test Product: THS 2.2 Menthol
Reference Product: Commercially available mCC.
Reference Point: Smoking abstinence with support of Nicotine Replacement Therapy during the ambulatory period if considered necessary by the Principal Investigator or requested by the subject.
Duration of Use: Exposure period lasted 90 days, from Day 1, 06:30 AM until 11:00 PM on Day 90.The exposure period included both the exposure period in Confinement and the exposure periods in the ambulatory setting. Product use periods were subsets of the exposure period and were defined as confinement Period 1 (Day 1 to Day 6 [Confinement]), ambulatory Period 2 (Day 6 to Day 30 Visit), Period 3 (Day 30 Visit to Day 60 Visit), and Period 4 (Day 60 Visit to Day 90 Visit).
Analytical Method: All bioanalytical assays and laboratory assessments were carried out using validated methods. The methods used are summarized in [Section 6.1.3.3 Bioanalytical Methods] and in the [Appendix 16.1.9] of the [ZRHM-REXA-07-JP] study report.

(table continues)

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Selected Secondary Objectives (related to Product Use Behavior only)

Nicotine Exposure:

Levels of nicotine over the entire Exposure Period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire Exposure Period.

Product Consumption:

Daily THS Tobacco Stick/mCC consumption over the exposure period in smokers switching from mCC to THS Menthol as compared to smokers continuing to smoke mCC.

Selected Exploratory Objectives (related to Product Use Behavior only):

Human Puffing Topography (HPT):

Smoking pattern through the assessment of HPT parameters over the course of the study in smokers switching from mCC to Menthol as compared to smokers continuing to smoke mCC.

Urge-to-Smoke:

Total score, Factor 1 (relief) and Factor 2 (reward) from the QSU-brief in smokers switching from mCC to THS Menthol as compared to smokers continuing to smoke mCC and smokers switching from mCC to SA.

Craving and Withdrawal:

Total scores from MNWS in smokers switching from CC to THS Menthol as compared to smokers continuing to smoke CC and smokers switching from CC to SA.

Product Evaluation:

Product evaluation as measure with the mCEQ over the course of the study in smokers switching from mCC to THS Menthol as compared to smokers continuing to smoke mCC.

6.2.2.4.1.1.4.2 Results of the ZRHM-REXA-07-JP

Nicotine Exposure over time:

The NEQ_{adjc} urinary concentration adjusted for creatinine were comparable at Baseline across study arms and remained similar to Baseline throughout the Confinement Period (5.56 mg/g creat at Baseline and 5.22 mg/g creat on Day 5) in the mCC arm.

In contrast, NEQ_{adjc} values in the THS Menthol arm decreased from Baseline (5.71 mg/g creat) to Day 1 before increasing gradually for the remainder of the Confinement Period, reaching values above Baseline on Day 5 (6.16 mg/g creat). These values corresponded to percent changes from Baseline at Day 5 of +16% and -3%, for the THS Menthol and mCC, respectively and a 16% higher value of NEQadjc in the THS Menthol arm compared to the mCC arm. During the Ambulatory Period, the nicotine exposure profile in the THS Menthol arm was comparable to that of the mCC with NEQadjc values on Day 90 of 6.85 mg/g creat for THS Menthol and 6.33 mg/g creat for mCC. These values corresponded to percent changes from Baseline on Day 90 of 36% and 26% for the THS Menthol and mCC arms, respectively.

In the SA arm, NEQ_{adjc} values decreased steadily from Baseline (5.40 mg/g creat) to Day 5 (0.16 mg/g creat), corresponding to a -96% change from Baseline and remained lower than Baseline, with a -58% change from Baseline on Day 90 (0.37 mg/g creat) (Figure 11).

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On Day 90, no notable differences in LS (Least Square) means were observed for NEQ_{adjc} between the THS Menthol and mCC arms.

A similar trend as for NEQ_{adjc} was observed for nicotine and cotinine concentrations in plasma.

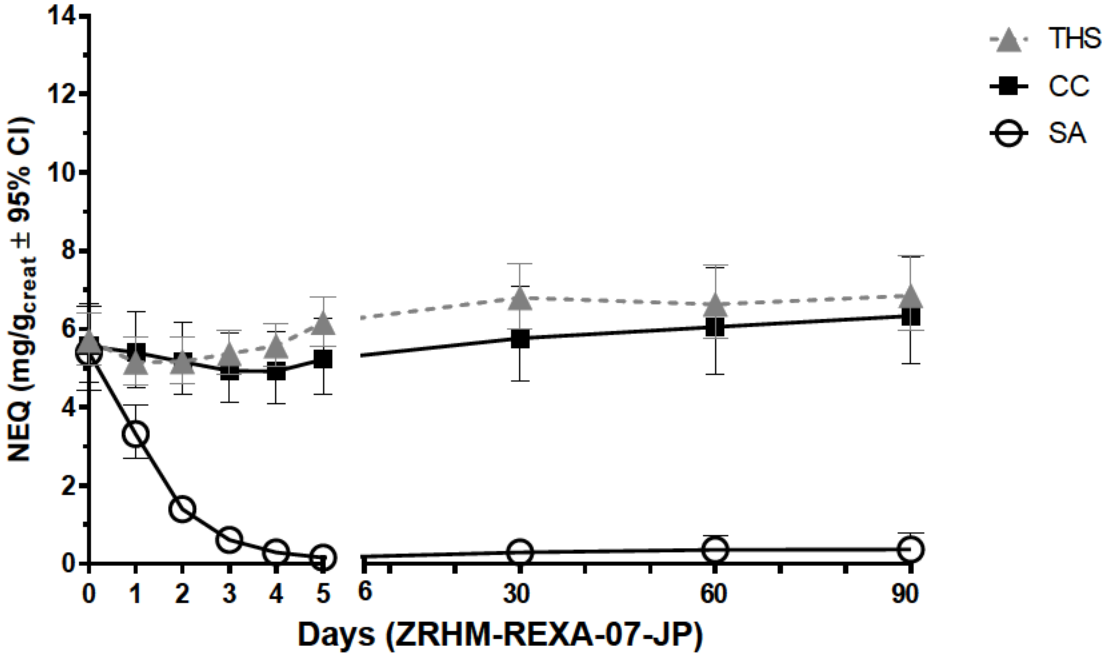


Figure 11 Geometric Mean NEQ Urinary Concentration Adjusted for Creatinine During the Course of the Study

Abbreviations: Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, nicotine equivalents adjusted to creatinine (NEQ_{adjC}), creatinine (creat), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI).
Note: Day 0 = Baseline.
Data Source NEQ: Clinical Study Report Appendix 15, Table 15.2.4.18.1

Product Consumption:

At Baseline, the mean number of mCC consumed daily in the THS Menthol and mCC arms was comparable (13.0 and 12.5 mCC/day, respectively).

The number of THS Menthol Tobacco Sticks consumed daily in the THS Menthol arm initially decreased during the Confinement Period (Period 1) from Baseline to Day 1 (11.4 THS Tobacco Sticks/day) and subsequently increased to Day 5 (13.9 THS Tobacco Sticks/day). Throughout the confinement period, a similar pattern was observed for mCC consumption (11.0 mCC/day on Day 1, 13.6 mCC/day on Day 5). During the Ambulatory Period, the mean number of THS Menthol Tobacco Sticks consumed daily in the THS Menthol arm returned to Baseline levels by the end of Period 3, and remained stable

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during Period 4 (12.7 THS Tobacco Sticks/day). In the mCC arm, mCC product use during the Ambulatory Period remained higher compared to Baseline, with 15.2 mCC/day reported during Period 4 (Figure 12).

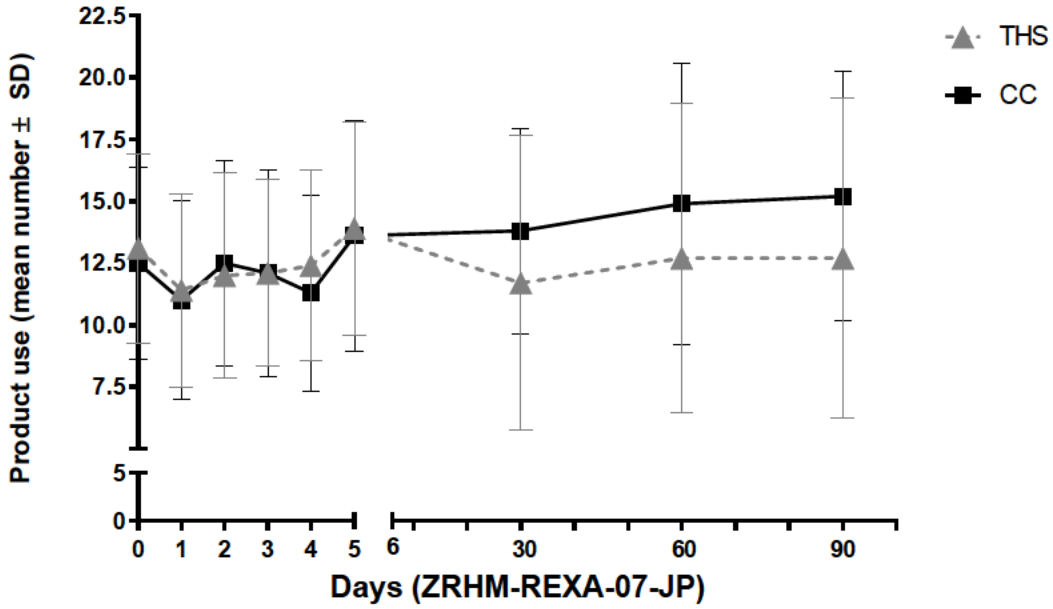


Figure 12 Product Consumption (Mean Number of Products Used) During the Course of the Study

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), standard deviation (SD)
Note: Day 0 = Baseline
Data Source: Clinical Study Report, Appendix 15, Table 15.2.2.1.2 and Table 15.2.2.3.2

Human Puffing Topography:

HPT parameters were comparable at Baseline for THS menthol and mCC.

On Day 1, total puff volume, average puff volume, average inter puff interval, and total smoking duration decreased from Baseline in the Menthol arm. Total puff volume and average puff volume increased to Day 4 and remained stable through the rest of the study until Day 90, although, total puff volume did fluctuate between Days 30 and 90. Average inter puff interval continued to decrease until Day 90 whereas total smoking duration continued to decrease from Day 1 to Day 30. It gradually increased afterwards from Day 30 to Day 90.

In contrast, total number of puffs, average puff duration, total puff duration, and puff frequency of the THS Menthol arm increased from Baseline to Day 1. Total number of puffs decreased to approximately Baseline levels by Day 4, and fluctuated over the remainder of the exposure period to reach levels above Baseline on Day 90. A similar profile was observed for average puff duration with levels at Day 90 comparable to what was observed on Day 1. Puff frequency continued to increase throughout the study to Day 90.

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In the mCC arm most HPT parameters remained at approximate Baseline levels through the Confinement Period, with the exception of a total puff volume decreasing slightly from Baseline.

On Day 90 the total puff volume showed little difference between subjects who switched to THS Menthol use and subjects who continued to smoke mCC (-23.5 mL). Total number of puffs (3.19 puffs difference) and puff frequency (+1.03 puffs/min) increased in the THS arm. Average puff duration was also 0.26 s longer in the THS menthol vs. mCC arm.

The total smoking duration was approximately 3.4 minutes for both arms (1.84 s difference).

In summary, the HPT parameters indicated that THS Menthol users were taking a similar total puff volume compared to mCC, but adapted to the product by increasing the number of puff, the puff frequency and duration.

Subjective Effects:

The mean urge-to-smoke total scores were comparable across study arms at Baseline (3.60, 3.22 and 3.65 for the for THS Menthol, mCC and SA arm, respectively).

For the THS Menthol and mCC arms, the mean urge-to-smoke total scores remained stable over the 5 days of the Confinement Period as well as during the Ambulatory Period, with Day 90 urge-to-smoke total scores of 3.25 and 2.83, respectively.

In the SA arm, the mean urge-to-smoke total score increased from Baseline to Day 1 (score: 5.01 corresponding to a percent changes from Baseline of 52 %). From Day 2 to 5, total score values continously decreased until Day 5 (score: 4.47) and further decreased until Day 90 (score: 2.19) (Figure 13).

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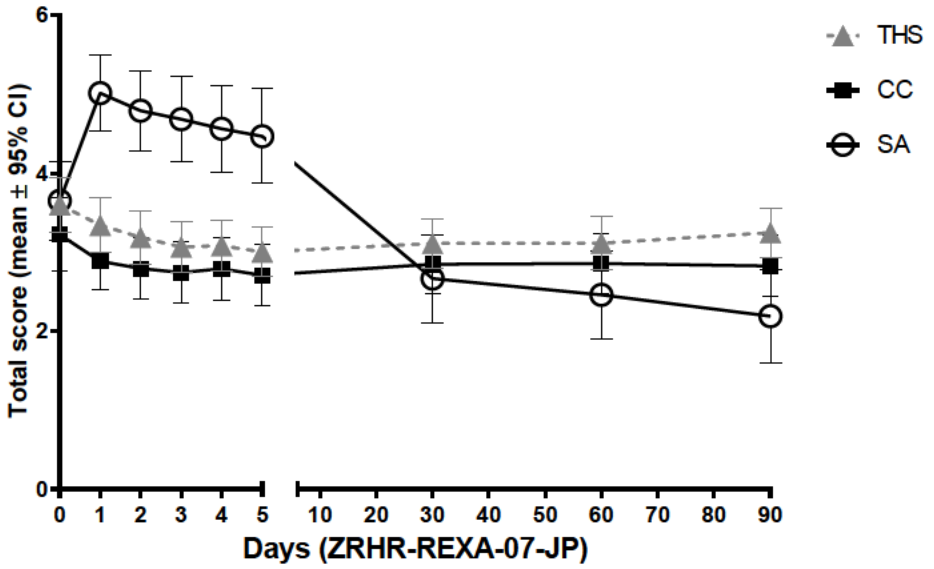


Figure 13 Total Score – Questionnaire of Smoking Urges During the Course of the Study

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI)
Note: Day 0 = Baseline
Data Source: Clinical Study Report, Appendix 15, Table 15.2.4.35.1.

Similar results were observed for withdrawal symptoms as assessed by the MNWS-R in the different study arms, with comparable MNWS-R total scores for THS menthol, mCC and SA arms at Baseline. For the Menthol and mCC arms, the MNWS-R withdrawal score values remained stable over the 5 days of the Confinement Period as well as during the Ambulatory Period with Day 90 values.

In the SA arm, the mean MNWS-R withdrawal score values increased markedly from Baseline on Day 1 (mean increase of 139%). Before returing towards Baseline on Day 5 and decreasing futher during the Ambulatory period, below Baseline values (change from Baseline of -39%).

The mCEQ showed that on Day 1, the scores for craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales were lower in subjects who switched to THS Menthol use compared to those observed in subjects who continued to smoke mCC. Between Day 1 and the end of the Exposure Period at Day 90 the differences between the THS Menthol and mCC arm became less pronounced for all subscales, with LS mean differences on Day 5 of -0.02, -0.13, -0.21, and -0.39 for the craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales, respectively, and were negligible on Day 90 with differences of -0.15, 0.30, 0.00, and 0.01, respectively (Figure 14).

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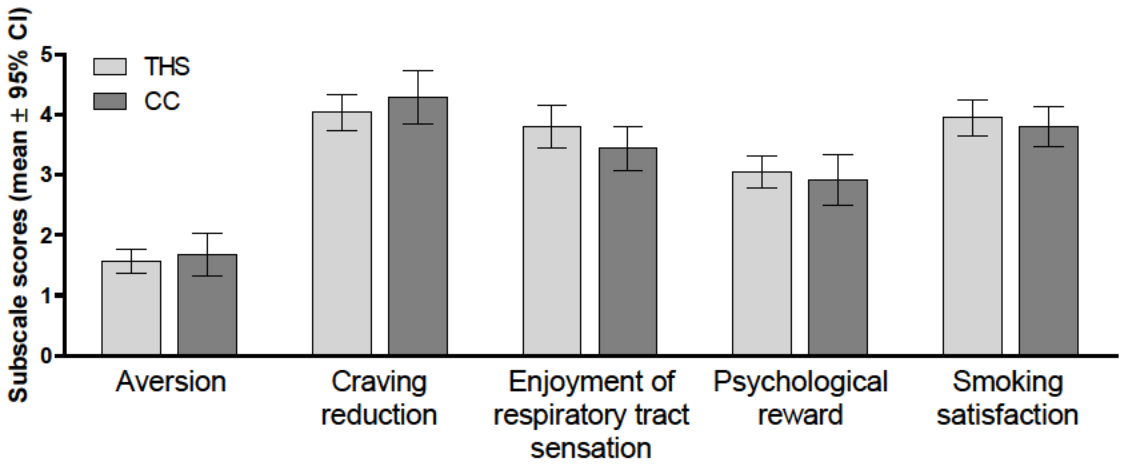


Figure 14 mCEQ Subscales on Day 90

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), confidence intervals (CI)
Data Source: Appendix 15, Table 15.2.4.38.1.

In summary, this study showed that nicotine uptake was similar between THS menthol and mCC, with a slightly lower product consumption of THS Menthol compared to mCC. THS Menthol achieve a comparable satisfaction to mCC and product use pattern indicated that users adapted quickly to the new product.

6.2.2.4.1.1.5 ZRHM-REXA-08-US

In addition to the data obtained in the studies in confinement ([ZRHR-REXC-3-EU] and [ZRHR-RE-04-JP]), the ambulatory setting of study [ZRHM-REXA-08-US] allowed to assess product use behavior and product acceptance over a prolonged period of time in real-world conditions where dual-use of THS with other nicotine obtaining products could also occur they were allocated to ad libitum during the day.

6.2.2.4.1.1.5.1 Methodology of the ZRHM-REXA-08-US

A brief description of study design, endpoints and methodology related to Product Use Behavior Assessment is given in Table 12.

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Table 12 Methodology - Product Use Behavior Assessment in the ZRHM-REXA-08-US Study

Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 86 days in an ambulatory setting

Title of the study: A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the THS 2.2 Menthol or observing smoking abstinence, compared to continuing to use mCC, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

Study design: Randomized, controlled, open-label, 3-arm, parallel group, single-center study to compare the use of THS Menthol with continuing to smoke mCC and SA. This was an ad libitum smoking study.

Subjects: Randomized: 160; Completed: 139; Number of subjects in the THS arm (completed): 80 (73). Number of subjects in the mCC arm (completed): 41 (35); Number of subjects in the SA arm (completed): 39 (31).

Main criteria for inclusion:

Main criteria for inclusion:

- Male and female smokers aged at a minimum 22 years
- Considered as healthy based 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 for at least the last 3 consecutive years. The smoking status was verified with a urinary cotinine test (cotinine ≥200 ng/mL).
- Did not plan to quit smoking in the following 3 months
- Body mass index between <18.5 or ≥35 kg/m2.

Test Product: THS 2.2 Menthol

Reference Product: Commercially available mCC.

Reference Point: Smoking abstinence with support of Nicotine Replacement Therapy during the ambulatory period if considered necessary by the Principal Investigator or requested by the subject.

Duration of Use: The exposure period lasted 91 days, from Day 1, 06:30 AM until 11:00 PM on Day 91.The exposure period included both the exposure period in Confinement and the exposure period in the ambulatory setting. Product use periods were subsets of the exposure period and were defined as confinement Period 1 (Day 1 to Day 6 [Confinement]), ambulatory Period 2 (Day 6 to Day 30 Visit), Period 3 (Day 30 Visit to Day 60 Visit), and Period 4 (Day 60 Visit to Day 90 Visit).

Analytical Method: All bioanalytical assays and laboratory assessments were carried out using validated methods. The methods used are summarized in [Section 6.1.3.3 Bioanalytical Methods] and in the [Appendix 16.1.9] of the [ZRHM-REXA-08-US] study report.

Selected Secondary Objectives (related to Product Use Behavior only)

Nicotine Exposure:

To determine the levels of nicotine over the entire Exposure Period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire Exposure Period.

Product Consumption:

To describe the daily THS Tobacco Stick/mCC consumption over the exposure period in smokers switching from mCC to THS Menthol as compared to smokers continuing to smoke mCC.

(table continues)

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Selected Exploratory Objectives (related to Product Use Behavior only):

Human Puffing Topography (HPT):

To describe puffing pattern through the assessment of HPT parameters and the HPT questionnaire over the course of the study in smokers switching from mCC to THS Menthol as compared to smokers continuing to smoke mCC.

Urge-to-Smoke:

To describe the total score, Factor 1 (relief) and Factor 2 (reward) from the Questionnaire of Smoking Urges in smokers switching from mCC to THS Menthol as compared to smokers continuing to smoke mCC and smokers switching from mCC to SA.

Craving and Withdrawal:

To describe the total scores from MNWS in smokers switching from mCC to THS Menthol as compared to smokers continuing to smoke mCC and smokers switching from mCC to SA.

Product Evaluation:

To describe product evaluation as measure with the mCEQ over the course of the study in smokers switching from mCC to THS Menthol as compared to smokers continuing to smoke mCC.

6.2.2.4.1.1.5.2 Results of the ZRHM-REXA-08-US

Nicotine Exposure:

The NEQ_{adjc} urinary concentrations adjusted for creatinine were comparable across studies arms at Baseline and remained similar to Baseline in the mCC arm throughout the Confinement Period. NEQ_{adjc} values in the THS Menthol arm decreased from Baseline (7.52 mg/g creat) to Day 2 before increasing gradually for the remainder of the Confinement Period for THS (Day 5: 6.74 mg/g creat), and mCC (Baseline: 8.30 mg/g creat and Day 5: 8.55 mg/g creat). These values corresponded to percent changes from Baseline of -2% and 6%, for the THS Menthol and mCC respectively.

During the Ambulatory Period, mean NEQ_{adjc} values reached levels comparable to Baseline at Day 30 for the THS Menthol and mCC arm with only moderate changes until Day 90 with a percent changes from Baseline at Day 90 of -4% for the THS Menthol and mCC arms.

In the SA arm, NEQ_{adjc} values decreased from Baseline (7.68 mg/g creat) to Day 5 (0.23 mg/g creat), corresponding to a 93% change from Baseline and remained low during the Ambulatory period (-63% change from Baseline at Day 90). The difference observed compared to the confinement period may reflect incomplete abstinence (Figure 15).

In comparison to mCC, NEQ_{adjc} was 13% lower in the THS Menthol arm on Day 5. This difference progressively reduced over time and on Day 90, where NEQ_{adjc} levels were comparable THS Menthol and mCC (THS:mCC LS Mean ratio: 96%).

A similar trend was observed for nicotine and cotinine concentrations in plasma.

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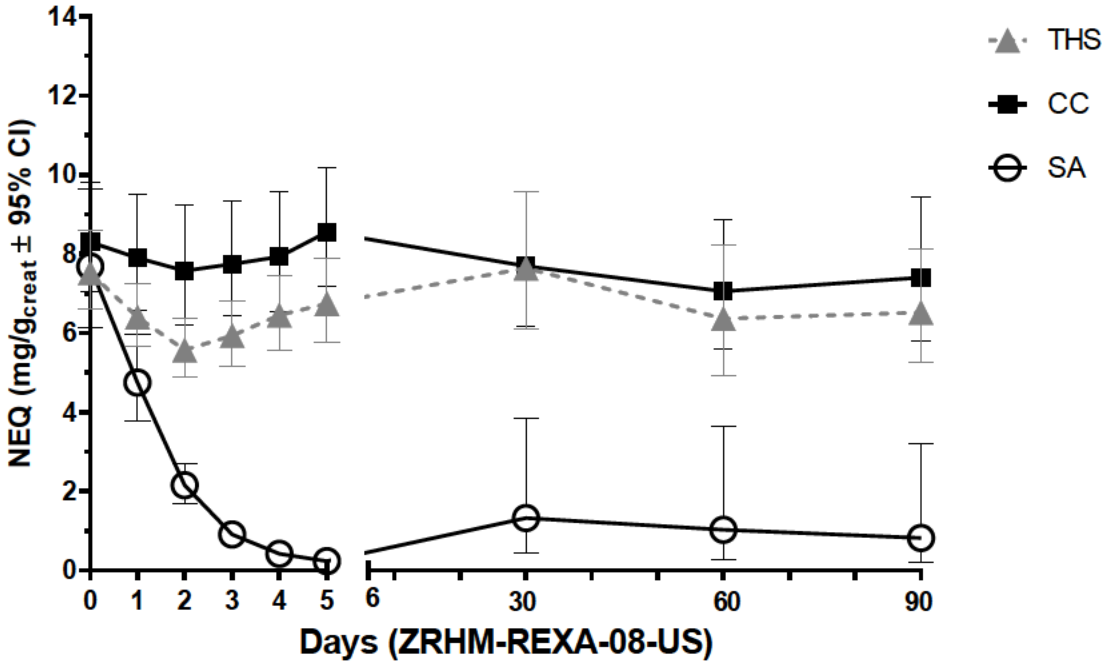


Figure 15 Geometric Mean NEQ Urinary Concentration Adjusted for Creatinine During the Course of the Study

Abbreviations: Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, nicotine equivalents adjusted to creatinine (NEQ_{adjC}), creatinine (creat), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI).
Note: Day 0 = Baseline.
Data Source: Clinical Study Report Appendix 15, Table 15.2.4.18.1.

Product Consumption:

THS Menthol and mCC arms consumption was comparable at Baseline (12.2 cigarettes/day). During the Confinement Period (Period 1), the mean number of THS Menthol Tobacco Sticks consumed daily increased from Day 1 to Day 5 (from 12.5 to 16.5 THS Tobacco Sticks/day). The mean number of mCC consumed daily also slightly increased throughout the Confinement Period from 11.3 to 13.7 mCC/day at Day 1 and Day 5, respectively.

During the Ambulatory Period the mean number of THS Menthol Tobacco Sticks consumed daily in the THS Menthol arm was lower than Day 5 but remained higher than the number of cigarettes consumed at Baseline, with a mean of 14.2 THS Tobacco Sticks/day reported during Period 4 (Day 60 to Day 90). In the mCC arm, daily consumption during the Ambulatory Period remained higher than at Baseline, with 15.5 mCC/day reported during Period 4. In consequence, THS Menthol Tobacco Sticks daily use was slightly lower than mCC at the end of the Ambulatory Period (Figure 16).

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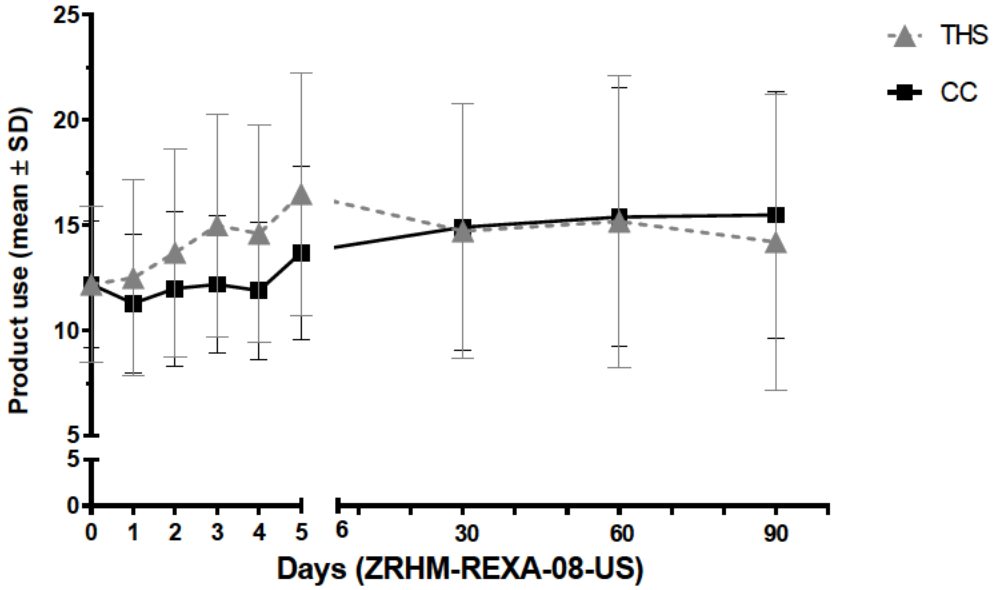


Figure 16 Product Consumption (Number of products used) During the Course of the Study

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), standard deviation (SD)
Note: Day 0 = Baseline
Data Source: Clinical Study Report Appendix 15, Table 15.2.2.3.2.

Human Puffing Topography:

Values were comparable at Baseline between the THS menthol and the mCC arms for each assessed parameter.

On Day 1, total puff volume, average puff volume, total number of puffs, average puff duration, and puff frequency increased from Baseline to Day 1 and continued to increase at Day 4 for THS. The total number of puffs and puff frequency remained comparable to the Day 4 value during the Ambulatory Period, whereas total puff volume, average puff volume, average puff duration, and total puff duration decreased from Day 4 to Day 30 and then stabilized for the remainder of the Ambulatory Period.

In contrast, average inter puff interval and total smoking duration decreased from Baseline to Day 4 in the THS Menthol arm continued to decrease through Day 4 and Day 30 before stabilizing for the remainder of the Ambulatory Period.

In the mCC arm, HPT parameters remained generally stable during the entire study period, with values similar to those of Baseline.

On Day 90 the total puff volume of THS Menthol versus mCC was 792.98 mL and 623.15 mL respectively. The total number of puffs (3.34 puffs difference) and puff frequency of 2.22 puffs/min increased with THS Menthol compared to mCC. Average puff volume and average puff duration remained comparable between THS Menthol and mCC, with a difference of 0.12 mL and 0.32 s, respectively.

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The total smoking duration was approximately 1.5 minutes shorter for THS Menthol compared to mCC (-88.62 s difference).

Subjective Effects:

The average urge-to-smoke total scores were comparable at Baseline across study arms (scores of 4.19, 4.17 and 3.99 for the the THS Menthol arm, the mCC arm SA arm, respectively). For the THS Menthol and mCC arms, the average urge-to-smoke total scores remained stable over the 5 days of the Confinement Period as well as during the Ambulatory Period, with Day 90 values of 3.84 and 3.93 for the THS Menthol and mCC arms, respectively.

In the SA arm, the urge-to-smoke total score increased from Baseline to Day 1 (score of 5.16, corresponding to a percent change increase of 53%). Total score value then slowly decreased and was comparable across the THS Menthol and mCC arms at Day 5 (score of 3.95) and to Baseline at Day 30 (-41%). It remained stable afterwards with a -40% decrease at Day 90 (Figure 17).

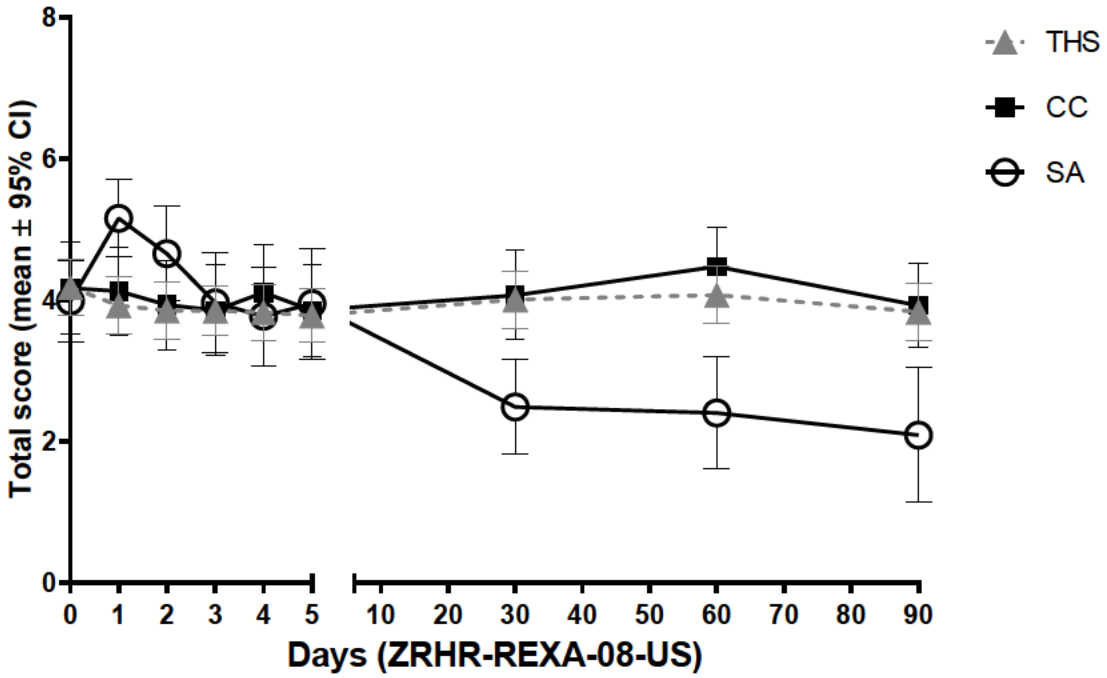


Figure 17 Total Score – Questionnaire of Smoking Urges During the Course of the Study

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI)
Note: Day 0 = Baseline
Data Source: Clinical Study Report Appendix 15, Table 15.2.4.52.1.

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The average MNWS-R withdrawal score values were comparable across study arms at Baseline.

For the THS Menthol and mCC arms, the MNWS-R withdrawal score values remained comparable to Baseline throughout the Confinement Period. During the Ambulatory Period, the mean MNWS-R withdrawal score values decreased modestly for the THS Menthol and mCC arms.

In the SA arm, the MNWS-R withdrawal score increased from Baseline to Day 2, then slowly decreased for the remainder of the Confinement Period. The MNWS-R withdrawal score further decreased from the end of the Confinement Period until Day 90 to reach appromately 50% of the Baseline value.

The mCEQ showed that craving reduction (THS Menthol – mCC difference: -1.1), enjoyment of respiratory tract sensation (difference: -0.6), psychological reward (difference: -0.40) and smoking satisfaction (difference: -1.0) were all lower on Day 5 for subjects who switched to THS Menthol use compared to mCC. Over the course of the study, these differences between the THS Menthol and mCC arms for the craving reduction, enjoyment of respiratory tract sensation, and smoking satisfaction subscales became subsequently less pronounced over time for THS Menthol compared to mCC with differences of 0.1, -0.2, -0.3 and -0.4 for aversion, enjoyment of respiratory tract sensation, psychological reward and smoking satisfaction mCEQ subscales. Craving reduction was still notably lower on Day 90 but less of a difference than on Day 5 (THS Menthol– mCC difference: -0.7) (Figure 18).

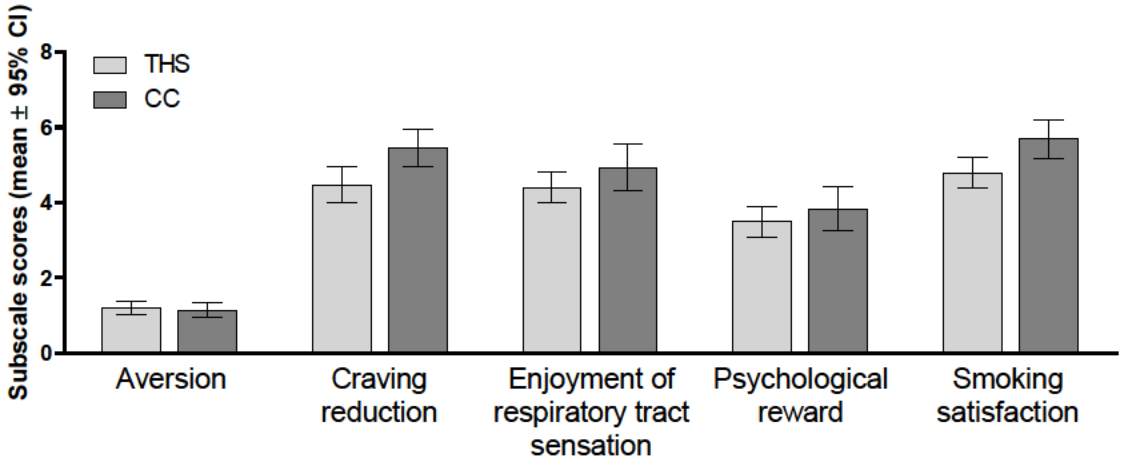


Figure 18 mCEQ Subscales on Day 90

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), confidence intervals (CI)
Data Source: Clinical Study Report Appendix 15, Table 15.2.4.54.1

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In summary, this study showed that exposure to nicotine was comparable between the THS Menthol and mCC arms, and patterns of product use behavior (number of products used and HPT) indicate, that users adapt to the new product over 90 days and achieve their desired nicotine levels. In combination of the results of subjective effects measures this indicates that THS Menthol product was satisfactory to users, relieved urge-to-smoke and withdrawal symptoms comparable to mCC.

6.2.2.4.1.2 Summary of Results Across Confinement and Ambulatory Studies

In this section, comparisons across studies is based on summary statistics of individual studies. The verbal qualifiers "comparable" and "similar" are used to qualitatively describe findings in a comprehensive rather than exclusively statistical manner; although CIs were considered for the assessment of findings, they mainly informed about the precision of parameter estimates, rather than on effects in an inferential manner.

6.2.2.4.1.2.1 Nicotine Exposure across Studies

THS is designed to provide to users a nicotine level comparable to that of CC. In such context, urinary nicotine equivalent levels (NEQ), together with nicotine and cotinine levels in plasma were measured to evaluate levels of nicotine exposure and to verify if smokers, switching from CC to THS, were able to maintain the desired levels of nicotine when using THS *ad libitum*.

6.2.2.4.1.2.1.1 Results on NEQ

Descriptive Analysis of NEQ Levels During the Confinement and Ambulatory Periods

The Baseline levels of urinary NEQ_{adjC} varied considerably across studies, with the lowest levels found in the 2 Japanese studies (5.00 mg/g_{creat} in [ZRHR-REXC-04-JP] and 5.40 mg/g_{creat} in [ZRHM-REXA-07-JP]) and the highest in the European [ZRHR-REXC-03-EU] and [ZRHM-REXA-08-US] studies (9.53 and 8.30 mg/g_{creat}, respectively) across arms.

The NEQ_{adjC} concentrations remained stable and were comparable between the THS and CC arms within studies and remained close to Baseline values, with the exception of a decrease in THS during the confinement period in [ZRHM-REXA-08-US] (Figure 19).

In consequence, the percent changes from Baseline on Day 5 were, overall comparable between THS and CC arms, ranging from -2% to +23% and from -15% to +9% in the THS and CC arms, respectively.

By contrast, NEQ_{adjC} levels were decreased by -93% to -98% in the SA arm. The maximum decrease of NEQ_{adjC} levels in the SA arms was reached within the first 3 days, plateauing thereafter in all 4 studies.

In the 2 REXA Ambulatory studies, levels of urinary NEQ at Day 90 were generally maintained and comparable in the THS and CC arms with percent changes from Baseline in study [ZRHM-REXA-08-US] of about +4% in both the THS and CC arms and +37% and +25% in the THS and CC arms in the study [ZRHM-REXA-07-JP], respectively.

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In contrast to the SA arm in the [ZRHM-REXA-07-JP] study, where NEQ_{adjC} during the Ambulatory period remained within the same range as observed during the Confinement period , the levels of NEQ_{adjC} slightly increased in the SA arm of the ZRHM-REXA-08-US study during the transition from the Confinement to the Ambulatory setting. However, at the end of the Ambulatory period at Day 90, levels were still largely decreased with percent change from Baseline ranging from -58% in [ZRHM-REXA-07-JP] to -63% in [ZRHM-REXA-08-US].

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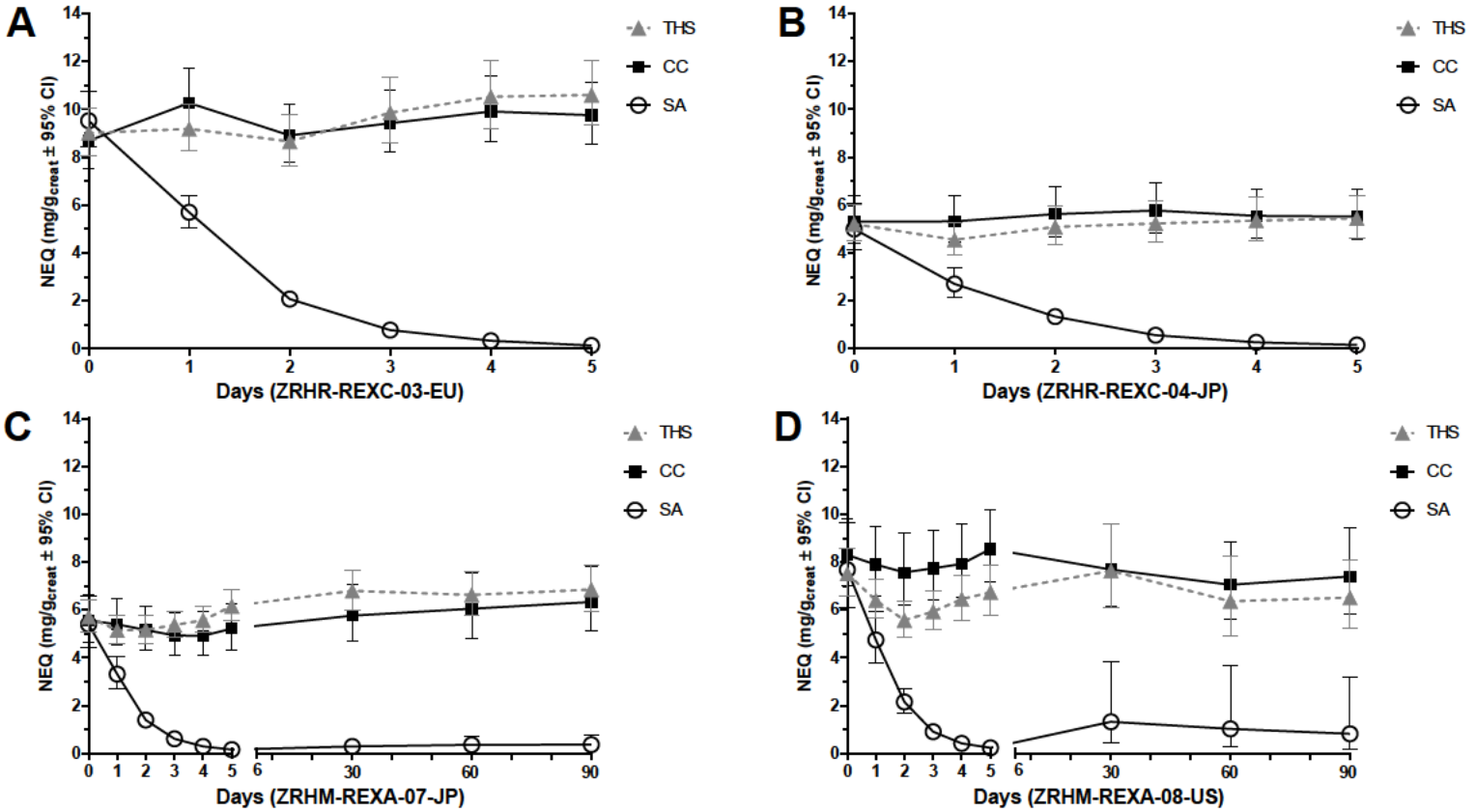


Figure 19 Geometric Mean and 95% CIs of Urinary NEQ Concentrations (mg/gcreat), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Note: Day 0 = Baseline.
Data Source: Clinical Study Reports Appendix 15; Table 15.2.4.34 [ZRHR-REXC-03-EU]; Table 15.2.4.34 [ZRHR-REXC-04-JP]; Table 15.2.4.18.1 [ZRHM-REXA-07-JP] and Table 15.2.4.18.1 [ZRHM-REXA-08-US]

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Analysis of Urinary NEQ Levels at Day 5 and Day 90

Levels of nicotine exposure were comparable between THS and CC in all studies. Switching to THS resulted in changes of NEQ_{adjC} levels ranging from -13% to +16% as compared to CC smoking (Table 13) at Day 5 across all studies, and at Day 90, from -4% to +4%, in both Ambulatory studies.

Table 13 Analysis of Urinary NEQadjC (mg/gcreat) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	Geometric LS Mean	104.89%	99.72%	116.00%	87.33%
		95% CI	92.03; 119.55	83.33; 119.33	98.91; 136.04	70.49; 108.18
	THS:SA Ratio	Geometric LS Mean	7737.73%	3486.74%	3797.93%	3137.39%
		95% CI	6773.9; 8838.7	2904.2; 4186.1	3225.8; 4471.5	2460.8; 4000.1
Day 90	THS:CC Ratio	Geometric LS Mean	NA	NA	104.30%	96.30%
		95% CI	NA	NA	66.65; 163.20	66.43; 139.59
	THS:SA Ratio	Geometric LS Mean	NA	NA	1695.18%	672.18%
		95% CI	NA	NA	1066.6; 2694.2	381.0; 1185.9

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System; CC = conventional cigarette
Data Source: Clinical Study Reports Appendix 15; Table 15.2.4.33 [ZRHR-REXC-03-EU]; Table 15.2.4.33 [ZRHR-REXC-04-JP]; Table 15.2.3.4 [ZRHM-REXA-07-JP] and Table 15.2.3.4 [ZRHM-REXA-08-US]

6.2.2.4.1.2.1.2 Results on Nicotine in Plasma

Descriptive Analysis of Nicotine Levels in Plasma During the Confinement and Ambulatory Periods

The Baseline levels of plasma nicotine concentrations differed between studies, with the lowest and highest concentrations reported in the Japanese studies (11.27 ng/mL in [ZRHM-REXA-07-JP] and 18.28 ng/mL in [ZRHR-REXC-04-JP]), across arms.

At Day 5, the levels of plasma nicotine were generally comparable between the THS and CC arms, with levels ranging from 14.91 to 19.13 and from 12.00 to 21.34 ng/ml; respectively. Concentrations were slightly lower in the THS than the CC arm of [ZRHM-REXA-08-US]. At Day 90, the levels of nicotine ranged from 8.82 to 12.69 and from 11.25 to 12.65 ng/ml in the THS and CC arms, respectively, and were still lower in the THS arm of [ZRHM-REXA-08-US] than the CC arm.

The maximum decrease of nicotine plasma concentrations in the SA arms was reached at Day 1, plateauing thereafter in all 4 studies. The concentrations of nicotine in the SA

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groups remained generally very low with levels at Day 5 of 0.10 and increased slightly during the ambulatory period, with concentrations from 0.57 to 0.74 ng/ml at Day 90 (Figure 20) in studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], respectively.

The levels of plasma nicotine in the THS and CC arms remained generally comparable and sustained throughout the 5 days of Confinement in the [ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP], and [ZRHM-REXA-07-JP] in both, the THS and CC arms, except for a transient decrease of nicotine plasma concentrations at Day 1 for both arms, with levels subsequently increasing up to Day 5, reaching Baseline values. This decrease was the most pronounced in the THS arm of [ZRHM-REXA-08-US], but levels of nicotine in the THS arms of [ZRHR-REXC-03-EU] and [ZRHR-REXC-04-JP] were also lower than those of the CC arms. In [ZRHM-REXA-07-JP], levels in the THS and CC arms fluctuated throughout the Confinement period. The profiles of nicotine in plasma were comparable to those observed for $NEQ_{adjC.}$

The levels of plasma nicotine were sustained and comparable during the Ambulatory period of [ZRHM-REXA-07-JP], both in THS and CC arms. A decrease of nicotine levels was observed during the Ambulatory period of [ZRHM-REXA-08-US], both in the CC and the THS arms, with levels being consistently lower in the THS than in the CC arm.

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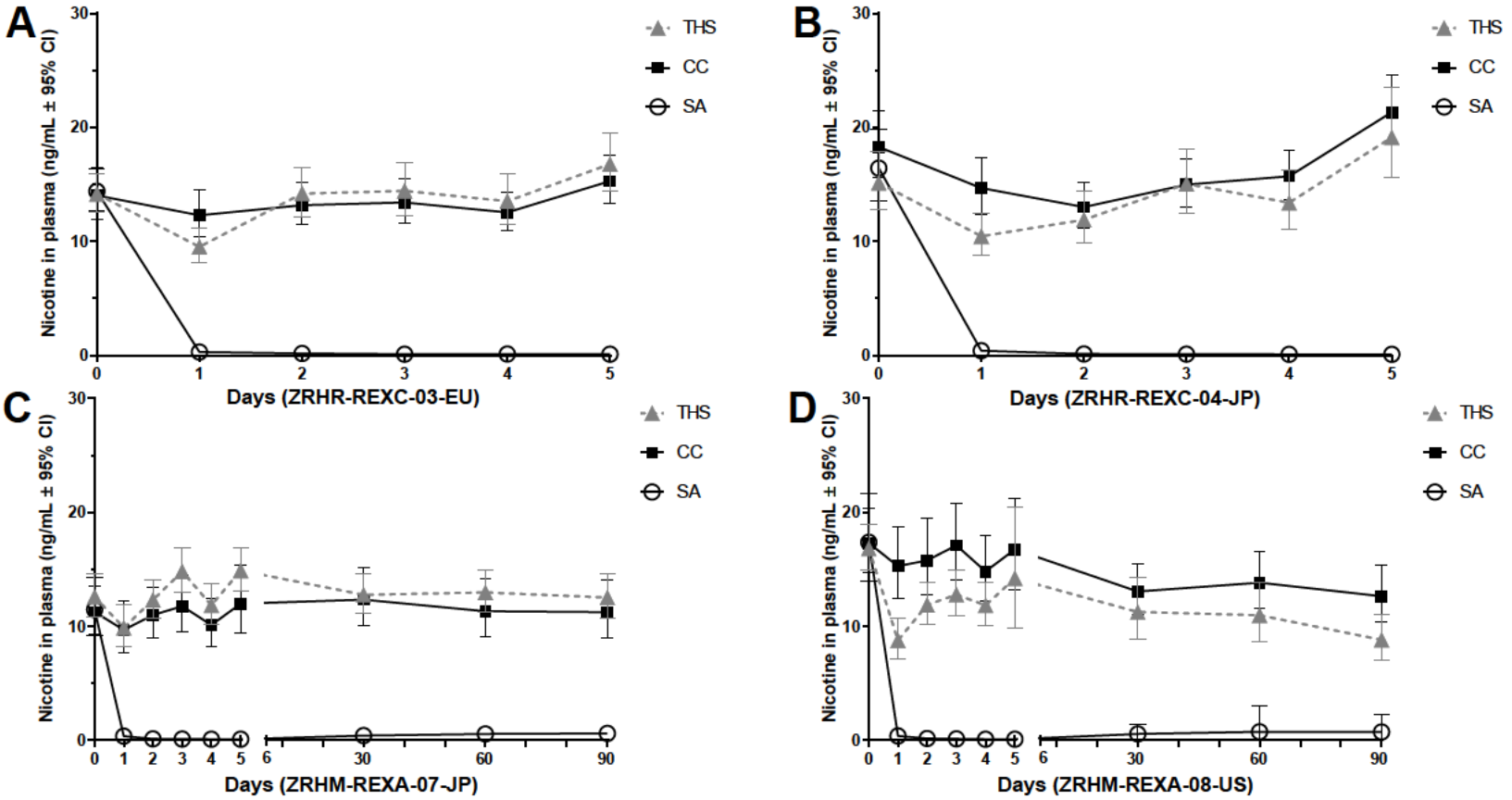


Figure 20 Geometric Mean and 95% CIs of Plasma Nicotine Concentrations (ng/mL), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Note: Day 0 = Baseline.
Data Source: Clinical Study Reports Appendix 15; Table 15.2.4.35 [ZRHR-REXC-03-EU]; Table 15.2.4.35 [ZRHR-REXC-04-JP,]; Table 15.2.4.19.1 [ZRHM-REXA-07-JP] and Table 15.2.4.19.1 [ZRHM-REXA-08-US]

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Analysis of Plasma Nicotine Levels at Day 5 and Day 90

In general, there was no meaningful differences in the levels of plasma nicotine at Day 5 between THS and CC for both [ZRHR-REXC-03-EU] and [ZRHR-REXC-04-JP] (THS – CC difference of 2.55 and 2.44 ng/mL), as well as for [ZRHM-REXA-07-JP] (THS:CC ratio of 111.64%) (Table 14). In [ZRHM-REXA-08-US], a marginal decrease of 20% was observed (THS:CC ratio of 80%). This tendency was maintained at Day 90, with no notable difference between THS and CC arms in [ZRHM-REXA-07-JP] (THS:CC ratio of 105%), while there was still a decrease of 28% in [ZRHM-REXA-08-US] (THS:CC ratio of 72%).

Table 14 Analysis of Plasma Nicotine Concentrations (ng/mL or percent) in All Studies, at Day 5

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	**THS - CC**	**LS Mean**	2.55	2.44	NC	NC
		95% CI	-0.19; 5.29	-0.89; 5.76	NC	NC
	THS:CC Ratio	**Geometric LS Mean**	NC	NC	111.64%	79.69%
		95% CI	NC	NC	99.95, 124.68	65.75, 96.57
Day 90	**THS:CC Ratio**	**Geometric LS Mean**	NA	NA	105.48%	71.98%
		95% CI	NA	NA	89.24, 124.66	51.13; 101.33

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; NC = not calculated; SA = smoking abstinence; THS = Tobacco Heating System
ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors. For ZRHR-REXC-03-EU and ZRHR-REXC-04-JP, values correspond to 8:00 pm values.
Data Source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU and ZRHR-REXC-04-JP, Tables 15.2.4.41; ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Tables 15.2.4.20.1

Descriptive Analysis of Cotinine Levels in Plasma During the Confinement and Ambulatory Periods

The Baseline plasma cotinine concentrations differed between studies, from 140.37 ng/mL in [ZRHR-REXC-04-JP] to 262.31 ng/mL in [ZRHR-REXC-03-EU] across arms. The lowest levels were observed in the 2 Japanese studies, i.e., [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP], while levels in the US and European populations were comparable.

At Day 5, the levels of plasma cotinine still differed between studies, but were overall comparable between THS and CC arms, with levels ranging from 161.00 to 224.82 and from 153.51 to 231.652 ng/mL; respectively Levels were slightly lower in the THS than

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the CC arm of [ZRHM-REXA-08-US]. At Day 90, the levels of cotinine reached comparable levels in both arms across studies, with levels ranging from 175.22 to 183.16 and from 172.69 to 193.39 ng/mL in the THS and CC arms, respectively. The levels of cotinine in the SA groups remained generally very low with levels ranging at Day 5 from 2.05 to 4.90 and from 27.93 to 28.49 ng/mL at Day 90 between studies.

The maximum decrease of cotinine levels in the SA arms was reached after 3 days, plateauing thereafter (Figure 21) for all 4 studies. The concentrations of cotinine in the SA groups remained generally very low at Day 5 ranging from 2.05 to 4.90 and 8.49 ng/ml in [ZRHM-REXA-07-JP] and in 27.93 [ZRHM-REXA-08-US] at Day 90 (Figure 20).

The profiles of plasma cotinine levels were overall comparable between studies and the levels of plasma cotinine in the THS and CC arms remained generally stable throughout the 5 days of Confinement, except for a decrease observed in the THS arm of [ZRHM-REXA-08-US] during the first 2 days. From Day 3 onwards levels increased steadily until Day 5. A decrease of cotinine levels was observed during the Ambulatory period of [ZRHM-REXA-08-US], both in the THS and the CC arms, from Day 30 onwards. Overall, the profiles of cotinine levels in the THS arms were comparable to those observed in the CC arms, even though slightly lower in [ZRHM-REXA-08-US], particularly during the Confinement period, while they were slightly higher in [ZRHM-REXA-07-JP] throughout the whole study.

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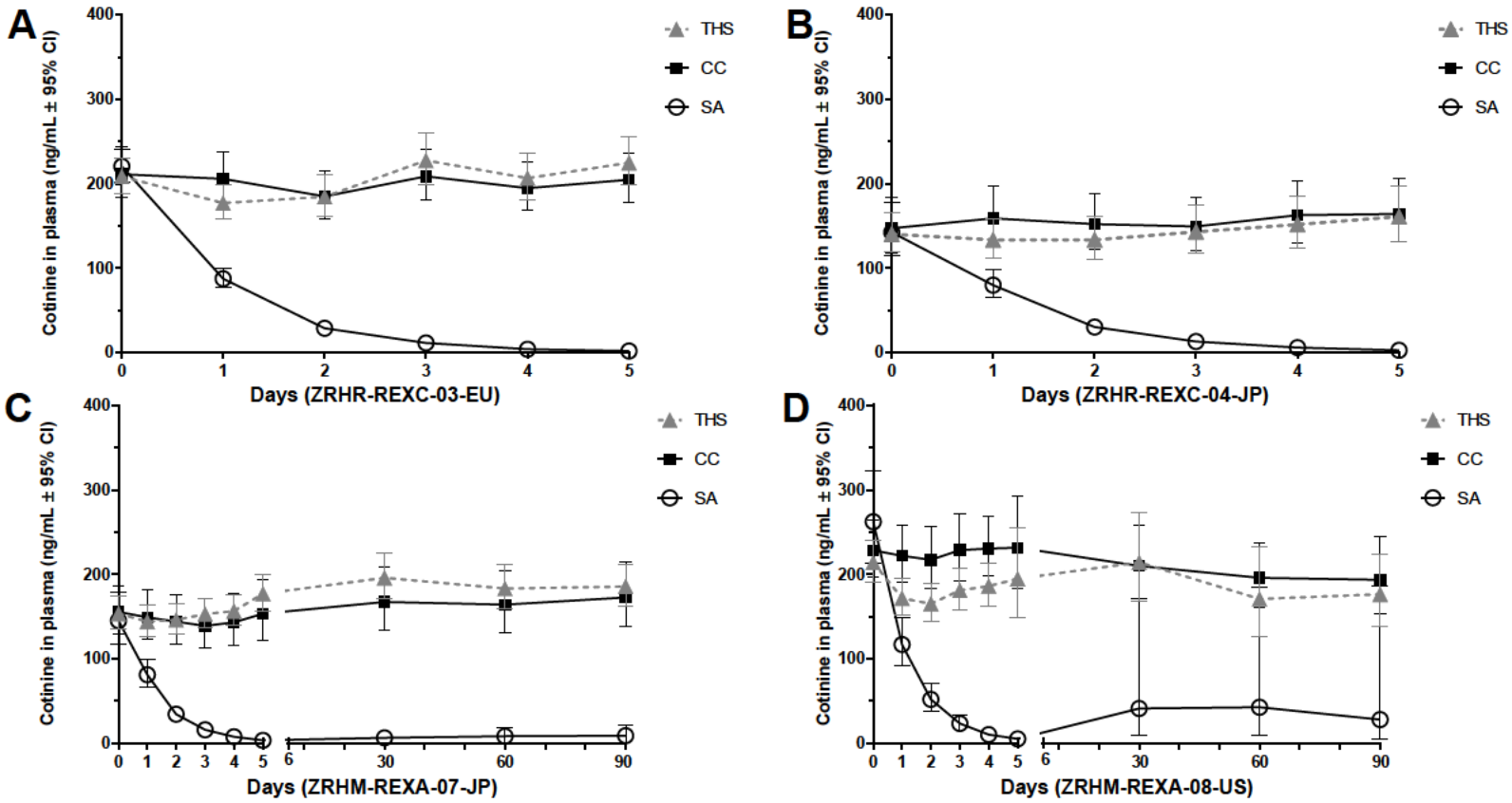


Figure 21 Geometric Mean and 95% CIs of Plasma Cotinine Concentrations (ng/mL), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Note: Day 0 = Baseline.
Data Source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU and ZRHR-REXC-04-JP, Tables 15.2.4.36; ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Tables 15.2.4.19.1

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Analysis of Plasma Cotinine Levels at Day 5 and Day 90

In general, the levels of plasma cotinine levels at Day 5 were comparable or slightly higher in subjects who switched to THS use than in subjects who continued to smoke CC for both [ZRHR-REXC-03-EU] and [ZRHR-REXC-04-JP] (THS – CC difference of 30.91 and 11.66 ng/mL, respectively), as well as for [ZRHM-REXA-07-JP] (THS:CC ratio of 111.63%) (Table 15). In [ZRHM-REXA-08-US], a marginal decrease of 16% was observed (THS:CC ratio of 84.10%). At Day 90, no notable difference of plasma cotinine levels between THS and CC arms was observed, either in [ZRHM-REXA-07-JP] or in [ZRHM-REXA-08-US] (THS:CC ratio of 105.94% and 102.65%, respectively).

Table 15 Analysis of Plasma Cotinine Concentrations (ng/mL or percent) in All Studies, at Day 5

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS - CC	LS Mean	30.91	11.66	NC	NC
		95% CI	6.36, 55.45	-10.98, 34.30	NC	NC
	THS:CC Ratio	Geometric LS Mean	NC	NC	111.63%	84.10%
		95% CI	NC	NC	99.87, 124.77	72.01, 98.22
Day 90	THS:CC Ratio	Geometric LS Mean	NC	NC	105.94%	102.65%
		95% CI	NC	NC	89.89, 124.84	65.82, 160.08

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; NC = not calculated; SA = smoking abstinence; THS = Tobacco Heating System
ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors. For ZRHR-REXC-03-EU and ZRHR-REXC-04-JP, values correspond to 8:00 pm values.
Data Source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU and ZRHR-REXC-04-JP, Tables 15.2.4.41; ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Tables 15.2.4.20.1

6.2.2.4.1.2.1.3 Conclusion

Approximately 85% of the total nicotine uptake and excretion in smokers can be accounted for by the molar sum of nicotine, cotinine and trans-3'-hydroxycotinine amounts, as well as their respective glucuronide conjugates, expressed as nicotine equivalents (NEQ) (Benowitz 1994). In combination with the assessment of cigarette consumption per day (CPD) and human puffing topography (HPT) (see Section 6.2.2.4.1.2.2 and Section 6.2.2.4.1.2.3, respectively), NEQ is expected to provide valuable insight on the effects of potential adaptation processes in product use patterns over time, as well as metabolic activity. NEQ was thus used as the main marker to evaluate nicotine exposure following ad libitum product use in PMI's reduced exposure studies. Nicotine and its metabolite cotinine were furthermore measured in plasma, as an

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additional assessment for the exposure of the subjects to nicotine after product use or smoking abstinence.

At Baseline, urinary NEQ levels varied considerably between studies, with the highest levels of NEQ_{adjC} and CYP2A6 activity were observed in the Polish study [ZRHR-REXC-03-EU]. Cotinine concentrations in plasma were in line with profiles observed for NEQ. Conversely, the highest nicotine concentrations were found in the Japanese study [ZRHR-REXC-04-JP], with the lowest NEQ_{adjC} and cotinine concentrations.

The Polish population has been shown to have a high prevalence of heavy smokers (Jassem 2014), which could explain why levels of nicotine and its metabolites at Baseline were in the highest range in the European study. This hypothesis is reinforced by the results observed for daily product consumption with levels higher in Poland (mean: approximately 16 CC per day) as compared to Japan (between 10 to 12 CC per day) at Baseline (Section 6.2.2.4.1.2.2.1). NEQ and cotinine exposure was lowest in the studies in Japan ([ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP]), with the lowest concentrations of urinary NEQ_{adjC}, nicotine and cotinine in plasma found across all studies in the study [ZRHM-REXA-07-JP]. In contrast to the low levels of NEQ and cotinine, plasma nicotine levels were the highest in study [ZRHR-REXC-04-JP]. CYP2A6 activity was low in [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP]), compared to the levels observed in the study in Poland [ZRHR-REXC-03-EU]. Therefore a differences in phenotypes of CYP2A6 activity is not likely to explain the high levels of nicotine in plasma in study [ZRHR-REXC-04-JP]. Factors such as diet, or physical activity known to affect nicotine metabolism could potentially have played a role prior to study start (Benowitz 2009).

In the SA arms across studies, the maximum decrease of NEQ and cotinine was reached after 3 days, with NEQ_{adjC} levels at Day 5 reduced by more than 93%, consistent with published data (Frost-Pineda 2008, Roethig 2007, Theophilus 2015, Tricker 2012a, Tricker 2012b, Tricker 2012c). The reduced difference in change from Baseline for NEQ_{adjC} at Day 90 (-58% to -63% in studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], respectively) is likely due to situational use of CC or second hand exposure. Plasma nicotine levels reached their lowest levels already after 1 day.

In summary, nicotine exposure varied across studies, but the profiles of urinary NEQ, plasma nicotine and cotinine throughout the 4 studies were comparable between the THS and CC arms, indicating that THS delivers nicotine to the users at comparable levels than those delivered by CC.

CYP2A6 was variable between studies. CC smoking and THS use did not affect CYP2A6 activity, while smoking abstinence increased CYP2A6 activity during the confinement period and to lesser extend during the ambulatory period.

6.2.2.4.1.2.2 Level of Consumption and Use patterns

6.2.2.4.1.2.2.1 Product Consumption

The FDA Draft Guidance on Modified Risk Tobacco Product Applications Draft (FDA (Food and Drug Administration) 2012) requires to provide data on the use of the candidate MRTP alone and in conjunction with other tobacco products. These data are

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important to determine the extent to which adult smokers find a novel tobacco product acceptable as a cigarette substitute. Daily product consumption in combination with patterns of use (e.g., dual or combined use with other tobacco or nicotine-containing products) as assessed in PMI clinical and actual use studies provide first insight on how a THS 2.2 might be used after introduction in the market.

Graphical presentation of daily product use is presented in Figure 22. The summary of product use by product use category during the Ambulatory Period ([ZRHM-REXA0-7-JP] and [ZRHM-REXA-08-US] only) is provided in Appendix A.6.2.2.1.

At Baseline, product consumption in the THS arm, when subjects used their own preferred brand of CC, ranged from 10.3 cigarettes/day in study [ZRHR-REXC-04-JP] to 16.0 cigarettes/day in study [ZRHR-REXC-03-EU]. Comparable levels of product consumption were reported in the CC arms across all studies (from 10.5 to 16.2 cigarettes/day).

During the confinement period, an initial decrease in product consumption in the THS arms from Baseline to Day 1 was observed in all studies, except study [ZRHM-REXA-08-US] where product consumption increased from Day 1 onwards. The highest decrease in consumption of THS Tobacco Sticks (10.3 and 8.3 THS Tobacco Sticks) on Day 1 compared to Baseline (13.1 and 11.4 CC/Day) was observed in the 2 studies conducted in Japan in [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP], respectively. From Day 2 onwards THS Tobacco Sticks consumption increased in the 2 Japanese studies reaching levels comparable to Baseline between Day 3 and Day 5. In studies [ZRHR-REXC-03-EU] and [ZRHM-REXA-08-US] THS Tobacco Stick use was higher from Day 2 and Day 3 onwards compared to Baseline with an about 30% and 35% increase of product consumption observed at Day 5 (20.7 THS Tobacco Sticks/day and 16.5 THS Tobacco Sticks/day in [ZRHR-REXC-03-EU] and [ZRHM-REXA-08-US], respectively). In the CC arm a similar decrease of product consumption from Baseline to Day 1 was observed in most of the studies, except [ZRHR-REXC-04-JP] where product consumption remained at levels comparable to Baseline. CC consumption increased afterwards in all studies exceeding Baseline levels, except of [ZRHR-REXC-03-EU] where CC use was comparable to Baseline (Figure 22).

During the Ambulatory Period, THS Tobacco Stick consumption decreased in both studies between Day 5 (13.9 THS Tobacco Sticks/day for [ZRHM-REXA-07-JP] and 16.9 THS Tobacco Sticks/day for [ZRHM-REXA-08-US]) and Day 30 (11.7 THS Tobacco Sticks/day for [ZRHM-REXA-07-JP] and 14.7 THS Tobacco Sticks/day for [ZRHM-REXA-08-US]). THS Tobacco Stick consumption returned to levels comparable to Baseline in study [ZRHM-REXA-07-JP] from Day 60 onwards (Day 60: 12.7 THS Tobacco stick consumption/day) with no changes afterwards. In study [ZRHM-REXA-08-US] levels remained only slightly above Baseline on Day 90 (14.2 THS Tobacco Stick/day or 16% difference compared to Baseline).

Consumption of CC in the mCC arms during the Ambulatory Period further increased in both studies during the ambulatory period, remained higher as compared to Baseline, and higher than the number of THS Menthol Tobacco Sticks consumed at Day 30, Day 60 and Day 90 (Figure 22 and Table 16).

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6.2.2.4.1.2.2.2 Patterns of Product Use:

Product use was strictly controlled during the Confinement Period in studies [ZRHM-REXA-07-JP], [ZRHM-REXA-08-US], [ZRHR-REXC-04-JP] and [ZRHR-REXC-03-EU] ensuring that all subjects in each study arm (i.e., THS, CC, and SA) were compliant with their assigned product. During the ambulatory period, subjects were instructed to exclusively use their allocated product but due to the ambulatory setting, they had the possibility to use other nicotine-containing products. Compliance to the assigned product was assessed based on self-reported product consumption.

Patterns of product use were comparable between the Confinement and Ambulatory periods with high compliance to product allocation in study [ZRHM-REXA-07-JP] during the Ambulatory Period in the THS study arm (at least 82.1% of subjects in each period exclusively using the assigned THS product [100%]). More than 85.9% of subjects were classified as primarily THS users (>95% of THS arm) during the Ambulatory Period overall. Dual-use of THS and CC or switching back from THS use to mainly CC use occurred in under 2.6% and 3.8% of the subjects, respectively.

In [ZRHM-REXA08-US], product use patterns were different, with a higher level of dual-use (up to 15% of subjects) and mainly CC use (up to 7.5% of subjects) in the THS arm and a lower compliance to product allocation with at least 42.5% of subjects in each period exclusively using THS, reaching 55% during period 4 (Day 61 to Day 90). More than 58.8% of subjects in each period were classified as primarily THS users (>95% of THS arm).

With the exception of 1 subject in study [ZRHM-REXA08-US], subjects in the mCC arm of both studies who completed the study, used the assigned product exclusively in each period (Table 16).

6.2.2.4.1.2.2.3 Conclusion

Changing patterns of product consumption, during the first days of exposure to a new product with different characteristics compared to subjects own brand of CC are expected and part of the adaptation process to a new product such as THS. These variations in product consumption observed early on after switching to THS tended to disappear over time.

Patterns of product consumption were different between the study population in Japan and in the US In Japan, higher rates of adherence to use the allocated product than in the US and almost no dual-use with CC or other nicotine-containing products was observed.

Product consumption is not to be considered in isolation but needs to be put in the context of other product use behaviour measurements, such as HPT, nicotine uptake and subjective effects as switching to a new product with different characteristics in terms of nicotine yield, taste, sensory and ritual compared to the subjects own brand of CC (Section 6.2.4). More importantly, the variations in product consumption observed with THS between different users did not affect the observed reduction in exposure to HPHCs as reported in Section 6.1.3.

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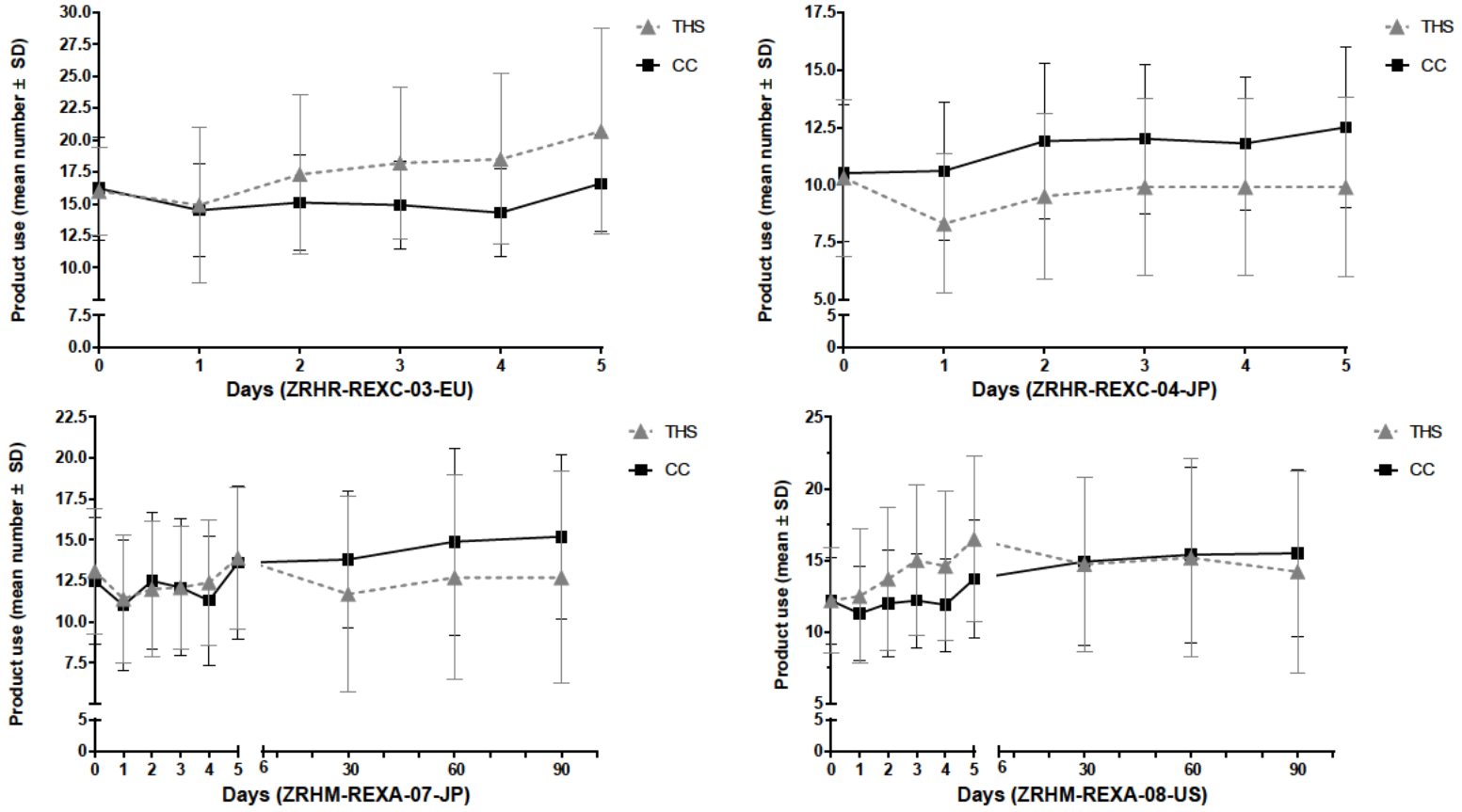


Figure 22 Product Consumption (Number of products used) between Baseline and at Day 5 (ZRHR-REXC03-EU and ZRHR-REXC04-JP) and Baseline and Day 90 (ZRHM-REXA07-JP and ZRHM-REXA08-US)

Abbreviations: THS = Tobacco Heating System, CC= Conventional cigarette, SD = standard deviation
Note: Day 0 = Baseline.
Data Source: Clinical Study Report [ZRHR-REXC03-EU] Appendix 15, Table 15.2.2.1., [ZRHR-REXC04-JP] Appendix 15, Table 15.2.2.1., [ZRHM-REXA07-JP] Appendix 15, Table 15.2.2.1.2 and Table 15.2.2.3.2 and [ZRHM-REXA08-US] Appendix 15, Table 15.2.2.3.2.

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Table 16 Average Number of THS Tobacco Sticks and Conventional Cigarettes Consumed Daily across Studies During the Ambulatory Periods – PP and FAS Sets (Arithmetic mean [SD])

		ZRHM-REXA-07-JP		ZRHM-REXA-08-US	
Study Arm	Visit	Number of Subjects	Arithmetic Mean (SD)	Number of Subjects	Arithmetic Mean (SD)
THS – PP Set	Period 2	74	11.7 (5.95)	39	14.7 (6.07)
	Period 3	71	12.7 (6.25)	39	15.2 (6.95)
	Period 4	70	12.7 (6.48)	47	14.2 (7.03)
THS – FAS Set	Period 2	76	11.6 (6.11)	78	11.68 (7.10)
	Period 3	76	12.2 (6.42)	77	12.90 (9.09)
	Period 4	76	12.3 (6.65)	74	12.02 (7.20)
CC – PP Set	Period 2	41	13.8 (4.16)	34	14.91 (5.85)
	Period 3	41	14.9 (5.70)	32	15.36 (6.12)
	Period 4	41	15.2 (5.04)	31	15.50 (5.84)
CC – FAS Set	Period 2	41	13.8 (4.16)	40	14.96 (5.51)
	Period 3	41	14.9 (5.70)	36	15.51 (5.80)
	Period 4	41	15.2 (5.04)	35	15.79 (5.56)

Note: CC = conventional cigarettes; NA = Not applicable; SD_= standard deviation; THS = Tobacco Heating System
Note: Ambulatory periods defined as Period 2 ([Day 6 ambulatory - Day 30 Visit]), Period 3 (]Day 30 Visit - Day 60 Visit]) and Period 4 (]Day 60 Visit - Day 90 Visit]).
Note: FAS: Full Analysis Set and PP: Per-Protocol Set
Note: Product use categories are calculated using imputation rules.
Data Source: Clinical Study Report [ZRHM-REXA07-JP] Table 34 and Clinical Study Report [ZRHM-REXA08-US] Table 39.

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6.2.2.4.1.2.3 Human Puffing Topography

6.2.2.4.1.2.3.1 At the Puff Level

Average Puff Volume

How subjects switching to THS changed their puffing topography was different across studies, particularly for the HPT parameter Average Puff Volume.

Graphical presentation of the geometric values are displayed in Figure 23.

On Day 1 and Day 4 of the confinement period, Average Puff Volumes measured in the THS arm of the Japanese studies ([ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP]) were lower (34 to 39 mL) than Baseline (46 to 48 mL). Average Puff Volumes were and stable for CC in these 2 studies (46 to 49 mL from Baseline to Day 4). The THS:CC ratios were 85% in [ZRHR-REXC-04-JP] and 91% in ZRHM-REXA-07-JP at Day 4, respectively.

In the [ZRHR-REXC-03-EU] study, Average Puff Volume was stable and comparable for THS and CC (46 to 52 mL for THS and CC between Baseline and Day 4with a THS:CC ratio was 106% at Day 4.

In the [ZRHM-REXA-08-US] study, Average Puff Volume was higher for THS (51 mL at Day 1 and 56 mL at Day 4) compared to Baseline (47 mL) and to CC (from 45 mL to 48 mL between Baseline and Day 4). The THS:CC ratio was 113% at Day 4.

During the ambulatory period of the [ZRHM-REXA-07-JP] study, Average Puff Volume for THS (38 to 40 mL) remained comparable to that observed during the confinement period and remained lower than CC (45 to 49 mL) with a THS:CC ratio of 81% at Day 90.

During the same period, Average Puff Volume for THS (from 47 to 52 mL) in [ZRHM-REXA-08-US] decreased in comparison to the confinement period while it remained stable for CC (from 50 to 54 mL) with a THS:CC ratio of 98% at Day 90.

In conclusion, Average Puff Volume for THS varied between the different populations, with comparable values to Baseline and CC in Europe in the Polish study [ZRHR-REXC-03-EU], and a decreased volume from Baseline for THS in Japan. In the US, values for THS were higher than Baseline and CC during most of the study, with values returning close to Baseline at the end of the ambulatory period (Day 90). This suggests different pattern of adaptations to THS across populations, with a reduction in average puff volumes in Japan and stable puff volumes in the non-Japanese regions. In the Japanese study [ZRHM-REXA-07-JP], the adaptation to THS seemed faster than in the US.

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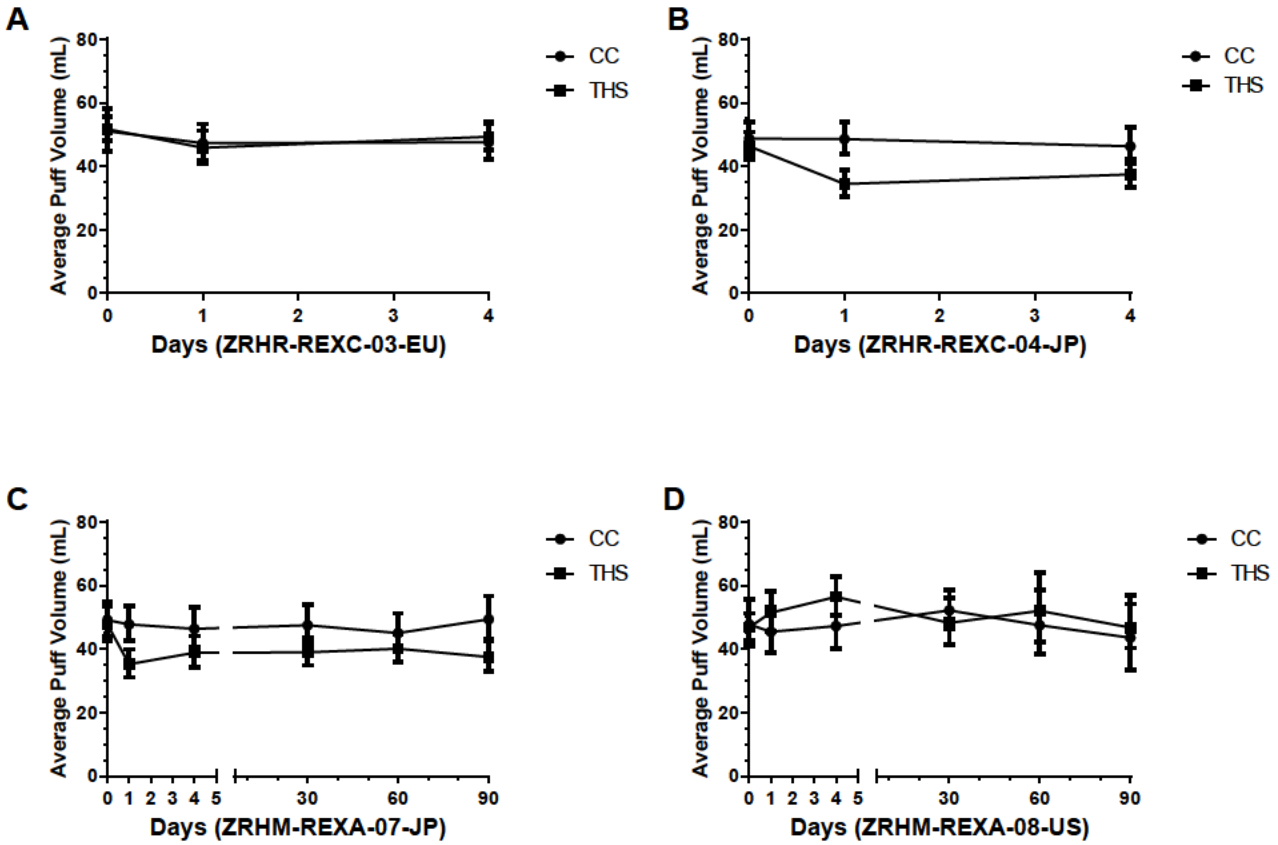


Figure 23 Geometric Mean of Average Puff Volume (mL) with 95% CI by Study Arm in A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US Studies, at Baseline, Day 1, Day 4, Day 30, Da y 60 and Day 90

Note: Day 0 = Baseline.
CC= conventional cigarettes, THS = Tobacco Heating System
Data Source: Clinical Study Report; Appendix 15.3.7.1 [ZRHR-REXC-03-EU]; Appendix 15.3.7.1 [ZRHR-REXC-04-JP]; Appendix 15.3.7.1 [ZRHM-REXA-07-JP]; Appendix 15.3.7.1 [ZRHM-REXA-08-US]

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Average Puff Duration

When using a novel tobacco products, it is expected that users might change their puffing behavior to adapt to the intrinsic properties of the new product, such as altering their normal puffing duration.

Graphical presentation of the arithmetic values are displayed in Figure 24.

During the confinement period of all studies (Day 1 and Day 4), Average Puff Duration was longer for THS on Day 1 and Day 4 compared to Baseline and CC. This was particularly marked for studies [ZRHR-REXC-03-EU] (THS, Day 1 to Day 4: 1.89s to 1.96s, Baseline 1.57s) and [ZRHM-REXA-08-US] (THS, Day 1 to Day 4: 1.89s to 2.1s, Baseline: 1.55s). In contrast values obtained for CC were stable between Baseline and Day 4, and ranged between from 1.49 to 1.51s for the [ZRHR-REXC-03-EU] study and from 1.55 to 1.6 s for the [ZRHM-REXA-08-US] study. The THS:CC ratios on Day 4 were respectively 132 and 117%.

In the [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP] studies, Average Puff Duration was only slightly longer for THS compared to Baseline and to CC. In study [ZRHR-REXC-04-JP], the Average Puff Duration for THS and CC were stable and close to Baseline (1.87 to 1.89 for THS and 1.67 to 1.74 for CC between Baseline and Day 4) during the confinement period. In [ZRHM-REXA-07-JP], values for THS on Day 1 and Day 4 were also slightly higher (1.65 to 1.67s) compared to Baseline (1.55s) and CC (from 1.60 to 1.65s at Day 1 to Day 4, Baseline: 1.61s). The THS:CC ratios on Day 4 were 102% for [ZRHR-REXC-04-JP] and 117% for [ZRHM-REXA-07-JP].

During the ambulatory period (Day 30 to Day 90) of the [ZRHM-REXA-07-JP], the trend observed during confinement was confirmed. Average Puff Duration was longer for THS (1.59 to 1.74s) compared to CC (1.53 to 1.61s), with a THS:CC ratio of 114% at Day 90.

In the [ZRHM-REXA-08-US] study, the values obtained for THS were stable between Day 30 and Day 90 (1.78 to 1.93 s), and lower than at the end of the confinement period (Day 4: 2.10 s). Values observed for CC were generally lower than THS, with values continuously decreasing from Day 30 to Day 90 (from 1.78 s to 1.37s). The THS:CC ratio indicated values 16% higher at Day 90 for THS compared to CC.

In conclusion, the Average Puffing Duration with THS in the Japanese studies [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP] was comparable to Baseline and CC, while the puffing duration increased in the Polish study [ZRHR-REXC-03-EU] compared to Baseline and CC. In the US study, puffing duration was variable, although values with THS remained higher than CC.

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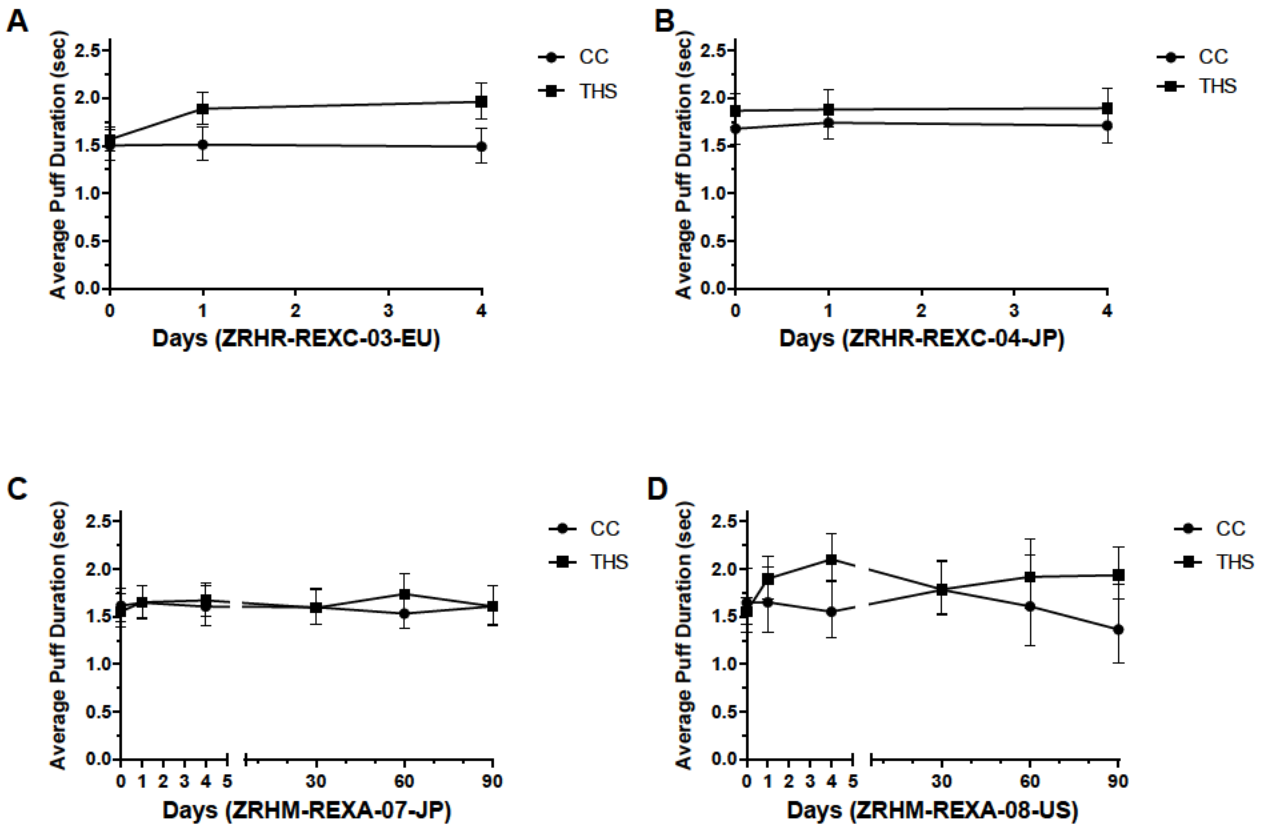


Figure 24 Geometric Mean Average Puff Duration (sec) with 95% CI by Study Arm in A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US Studies, at Baseline, Day 1, Day 4, Day 30, Day 60 and Day 90

Note: Day 0 = Baseline.
CC= conventional cigarettes, THS = Tobacco Heating System
Data Source: Clinical Study Report; Appendix 15.3.7.1 [ZRHR-REXC-03-EU]; Appendix 15.3.7.1 [ZRHR ZRHR-REXC-04-JP]; Appendix 15.3.7.1 [ZRHM-REXA-07-JP]; Appendix 15.3.7.1 [ZRHM-REXA-08-US]

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Average Pressure Drop

A change in pressure drop, an indicator of the resistance to draw (how easy or difficult is to draw a puff), is generally linked to the level of ventilation into the cigarette filter, which influences smoke yield and changes puffing behavior. An increase in pressure drop reflects the increased work needed by the user to draw a puff from a product. Pressure drop is also related to the flow rate of aerosol through the mouthpiece of the HPT SODIM® Device.

Graphical presentation of the arithmetic values are displayed in Figure 25.

Throughout the confinement periods, the Average Pressure Drop was stable from Baseline to Day 4 for THS in all studies, with the exception of a decrease from Baseline on Day 1 and Day 4 (221 and 219 mmWg, respectively, Baseline: 266 mmWg) in [ZRHM-REXA-08-US].

Between studies, Baseline levels varied from 174 to 266 mmWg with lowest value reported in [ZRHR-REXA-04-JP] and the highest in [ZRHM REXA-08-US]. For CC, an increase from Baseline (233 mmWg) was observed in [ZRHM-REXA-08-US] at Day 4 (252 mmWg), while it remained stable in the other studies (from 201 to 218 mmWg) during the same time period.

At Day 4, the THS:CC ratios varied from 88 to 94% in studies [ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP], while it was higher in [ZRHM-REXA-08-US] (THS:CC ratio: 112%).

In the ambulatory periods of the [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US] studies, Average Pressure Drop for subjects who used THS was markedly higher than during the confinement period and increased from visit to visit. The increase was substantial from Day 4 to Day 30 for both studies, with values increasing from 229 to 283 mmWg for ZRHM-REXA-07-JP and from 219 to 252 mmWg for ZRHM-REXA-08-US, respectively. The increase was then slight, but continuous, between Day 30 and Day 90, from 283 to 312 mmWg in study [ZRHM-REXA-07-JP] and from 252 to 275 mmWg in [ZRHM-REXA-08-US], respectively.

The Average Pressure Drop remained stable for CC in the study [ZRHM-REXA-07-JP] during the ambulatory period (from 209 to 217 mmWg). It was more variable in the [ZRHM-REXA-08-US] study (from 219 to 257 mmWg).

The THS:CC ratio was 146% at Day 90 in study [ZRHM-REXA-07-JP], while it was 98% in [ZRHM-REXA-08-US] as a result of an increase in CC at Day 90.

In conclusion, the Average Pressure Drop was stable and comparable during the confinement period for THS and CC within studies, with the exception of a relative decrease of THS compared to CC in [ZRHM-REXA-08-US]. Between studies, Baseline values were markedly different.

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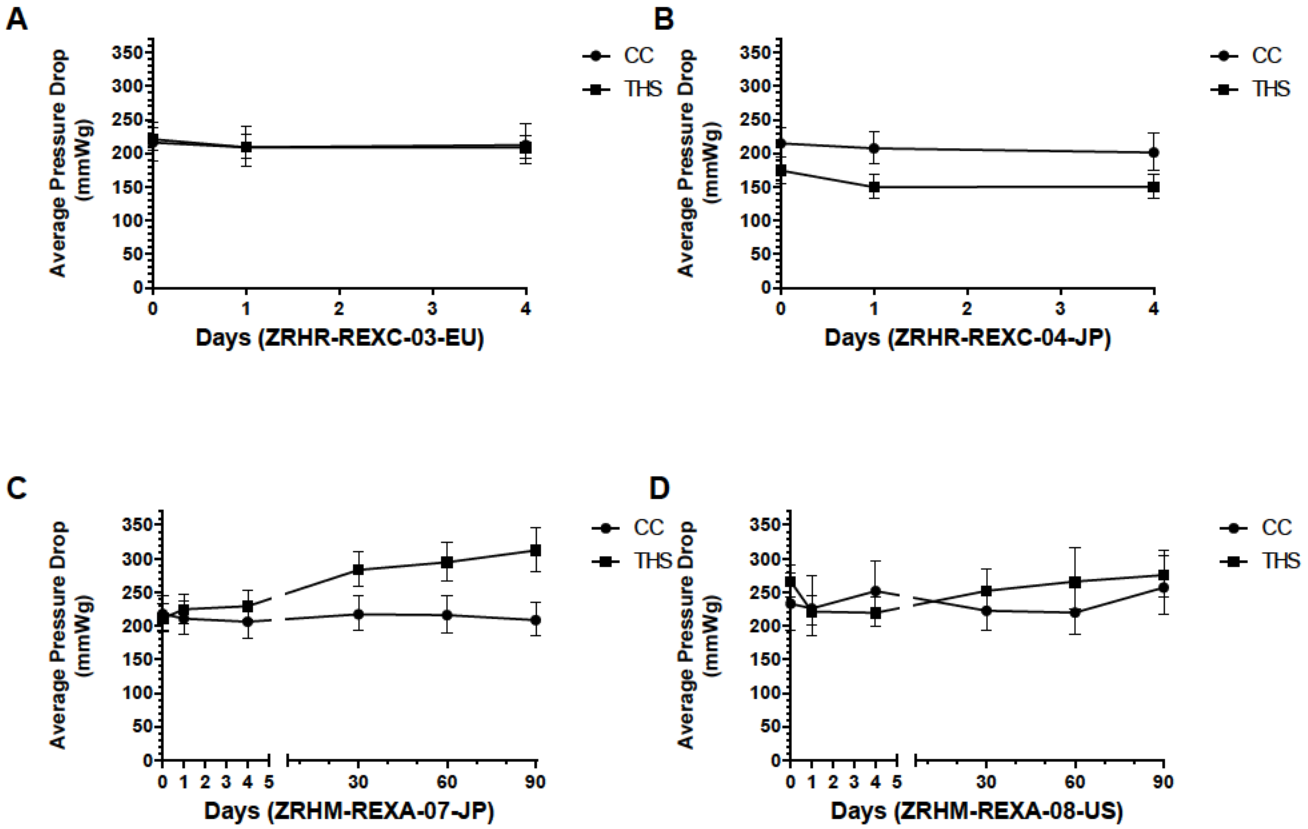


Figure 25 Geometric Mean Average Pressure Drop (mmWg) with 95% CI by Study Arm in A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US Studies, at Baseline, Day 1, Day 4, Day 30, Day 60 and Day 90

Note: Day 0 = Baseline.
CC= conventional cigarettes, THS = Tobacco Heating System
Data Source: Clinical Study Report; Appendix 15.3.7.1 [ZRHR-REXC-03-EU]; Appendix 15.3.7.1 [ZRHR-REXC-04-JP]; Appendix 15.3.7.1 [ZRHM-REXA-07-JP]; Appendix 15.3.7.1 [ZRHM-REXA-08-US]

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6.2.2.4.1.2.3.2 At the Product Use Level

Total Puff Volume

The HPT parameter Total Puff Volume, expressed in mL, is a measure to estimate the subjects' exposure to a product (CC and THS) at their mouth level.

Graphical presentation of the arithmetic values are displayed in Figure 26.

In the study [ZRHR-REXC-03-EU], Total Puff Volume values were stable from Baseline to Day 4 for subjects who switched to the THS (757 to 762mL). In the CC arm, the volume decreased from Baseline (854 mL) to Day 1 (786 mL) and returned towards Baseline levels by Day 4 (816 mL).

In the Japanese studies, an initial decrease from Baseline of Total Puff Volume was observed in the THS arm at Day 1, followed by a slight increase at Day 4, with values still lower compared to Baseline ([ZRHR-REXC-04-JP], Baseline: 680 mL, Day 1: 538 mL and Day 4: 632 mL; [ZRHM-REXA-07-JP], Baseline: 821 mL, Day 1: 626 mL and Day 4: 667 mL). In the CC arms, values were comparable for each time point, ranging from 688 mL to 754 mL for [ZRHR-REXC-04-JP] and from 716 mL to 779 mL for [ZRHM-REXA-07-JP].

By contrast, in [ZRHM-REXA-08-US] study, a marked and continuous increase was observed for THS compared to Baseline (601 mL), with 728 mL at Day 1 and 833 mL at Day 4, while values were stable for CC from Baseline (609 mL) to Day 4 (627 mL).

At Day 4, in studies [ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP] studies, Total Puff Volume was comparable between THS and CC with THS:CC ratios ranging from 95% to 105%. Values for THS were 30% higher than CC in study [ZRHM-REXA-08-US].

In the ambulatory period of study [ZRHM-REXA-07-JP] (Day 30 to Day 90), Total Puff Volumes for THS fluctuated at all time points (from 624 mL to 695 mL), but remained lower than Baseline (821 mL) and CC, with the exception of Day 60 (THS: 696 mL; CC: 595 mL). For CC, values were also lower between Day 30 and Day 90 (595 to 707 mL) compared to Baseline (779mL).

In the US study [ZRHM-REXA-08-US] Total Puff Volumes for THS fluctuated beween Day 30 and Day 90 (685 to 788 mL), like in the Japanese studies, and were higher than at Baseline (601 mL). For CC a decrease was observed at Day 90, with a value of 517 mL, compared to Day 30 and Day 60 (640 mL and 645 mL respectively), which was also lower than the 627 mL observed at Baseline.

Total Puff Volume was comparable between THS and CC during the ambulatory period of [ZRHM-REXA-07-JP], with THS:CC ratios from 90 to 112%. By contrast, they were always higher in THS compared to CC in [ZRHM-REXA-08-US] study, with THS:CC ratios ranging between 116% and 132% for all visits during the ambulatory period.

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In conclusion, Total Puff Volume for THS decreased in the Japan studies from the beginning of the confinement period but increased afterwards and reached levels comparable to CC, but remained generally lower than Baseline through out the study. In contrast, Total Puff Volume remained stable in the study in Europe ([ZRHR-REXC03-EU]) and increased in the US study [ZRHM-REXA08-US] from Day 1 onwards, remaining consistently at higher levels compared to Baseline and CC.

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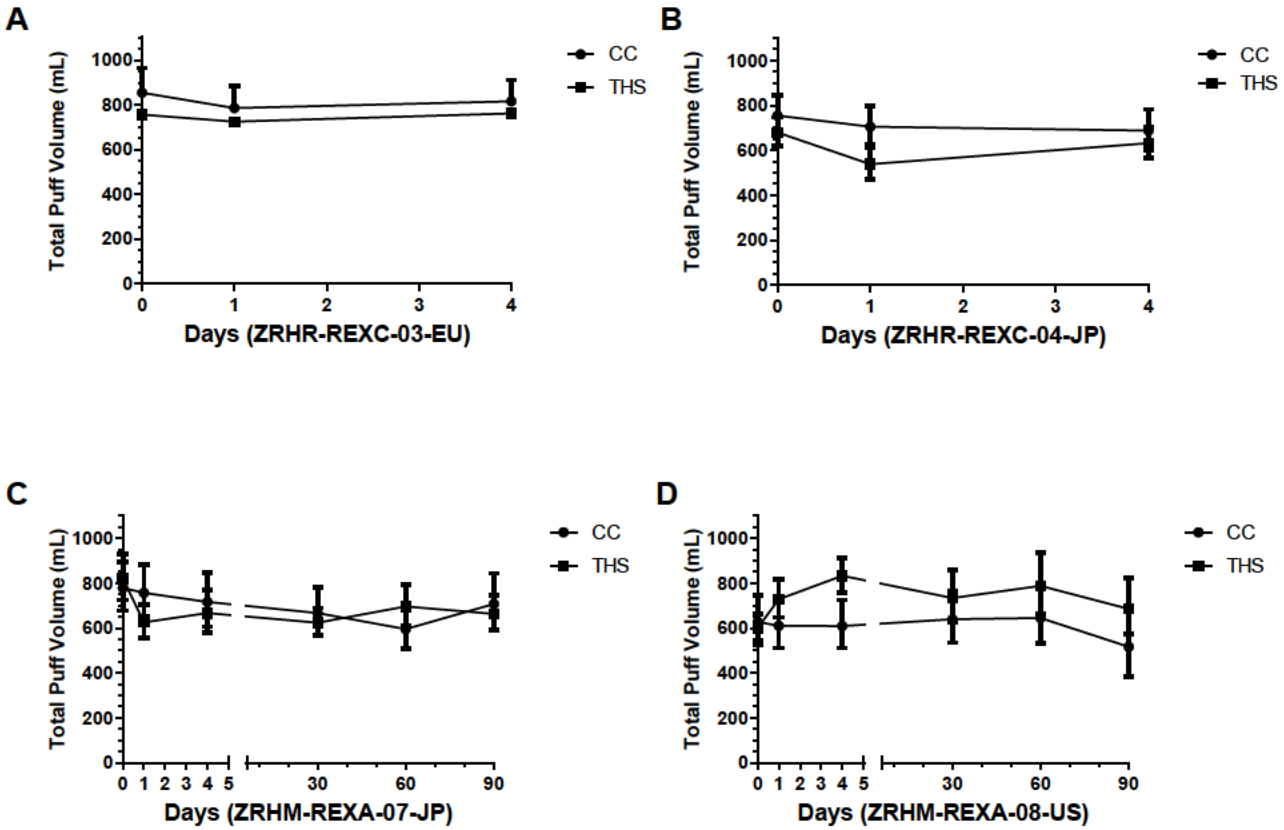


Figure 26 Geometric Mean Total Puff Volume (mL) with 95% CI by Study Arm in A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US Studies, at Baseline, Day 1, Day 4, Day 30, Day 60 and Day 90

Note: Day 0 = Baseline.
CC= conventional cigarettes, THS = Tobacco Heating System
Data Source: Clincial Study Report; Appendix 15.3.7.1 [ZRHR-REXC-03-EU]; Appendix 15.3.7.1 [ZRHR ZRHR-REXC-04-JP]; Appendix 15.3.7.1 [ZRHM-REXA-07-JP]; Appendix 15.3.7.1 [ZRHM-REXA-08-US]

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Total Number of Puffs

The HPT parameter Total Number of Puffs, is a key parameter in a subject's individual puffing profile and one of the parameters most often affected when smokers adjust their puffing behavior after switching to a new product. For THS, the system limits the product use experience to a maximum of 6 minutes or 14 puffs, whichever comes first. The HPT HPT SODIM® Device used to perform HPT assessment in PMI studies (see Section 6.2.2.3.1.4) however is more sensitive in puff detection than the THS puff sensor and therefore able to detect "multi-puffs" (i.e., continuous puffing with various intensity, such intense puffing followed by a continuous shallow puff and intense puffing again). Therefore, the number of puff can exceed the THS Device limitation of 14 non-contiguous puffs.

Graphical presentation of the arithmetic values are presented in Figure 27.

During the confinement periods, Total Number of Puffs drawn by subjects who switched to THS increased from Baseline at Day 1 and Day 4 in the [ZRHR-REXC-04-JP], [ZRHR-REXC-03-EU] and [ZRHM-REXA-08-US] studies, while Total Number of Puffs remained stable in [ZRHM-REXA-07-JP] study. In [ZRHR-REXC-03-EU], the Total Number of Puffs increased from 14.7 puffs at Baseline to 15.4 puffs at Day 4 and was lower than CC (16.6 to 17.2 puffs) at all timepoints. For [ZRHR-REXC-04-JP] and [ZRHM-REXA-08-US], Total Number of Puffs was higher at Day 4 in THS (17.0 puffs and 14.8 puffs, respectively) compared to Baseline (14.7 and 12.8 puffs, respectively), and CC (14.9 and 12.9 puffs, respectively) at Day 4. In study [ZRHM-REXA-07-JP], the Total Number of Puffs remained stable from Baseline to Day 4 (17.3 puffs on both visits) in THS and was higher than CC (15.5 to 16.0 puffs between Baseline and Day 4).

At Day 4, the THS:CC ratios were all below 100%, with higher ratios in the Japanese studies (93% and 91% for [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP], respectively) compared to the Polish (78% for [ZRHR-REXC-03-EU]) and the US studies (80% for [ZRHM-REXA-08-US]).

During the ambulatory periods, Total Number of Puffs in THS was stable from Day 30 to Day 90 (from 14.7 to 15.2 puffs) in [ZRHM-REXA-08-US], while it continuously increased in [ZRHM-REXA-07-JP] (from 16.1 at Day 30 to 17.7 puffs at Day 90). These values in THS users were comparable to those obtained at the end of the confinement and higher than CC. In the CC arms, Total Number of Puffs varied from 13.2 to 14.3 puffs in [ZRHM-REXA-07-JP] and from 11.8 to 13.6 puffs in [ZRHM-REXA-08-US] studies. The THS:CC ratio for Total Number of Puffs was 123% and 121% in Japan and US, respectively.

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In conclusion, the Total Number of Puffs drawn increased when the smokers switched to THS. With the exception of [ZRHR-REXC-03-EU], values for THS were higher than in the CC arms. As the geometric means values were exceeding the intrinsic limitation of the system of 14 puffs, this suggest that users were adapting their puffing behavior by using a multipuff technique (i.e., not stopping completely the inhalation between all puffs). This is supported by the evaluation of individual profiles showing the presence of multiple peaks in some individual puffs. Furthermore, the number of puffs in the THS Holder is calculated by differences in temperature on the surface of the blade of the THS Holder, while the number of puffs is determined in the HPT SODIM® Device by differences in air flow rate (i.e., by a different method).

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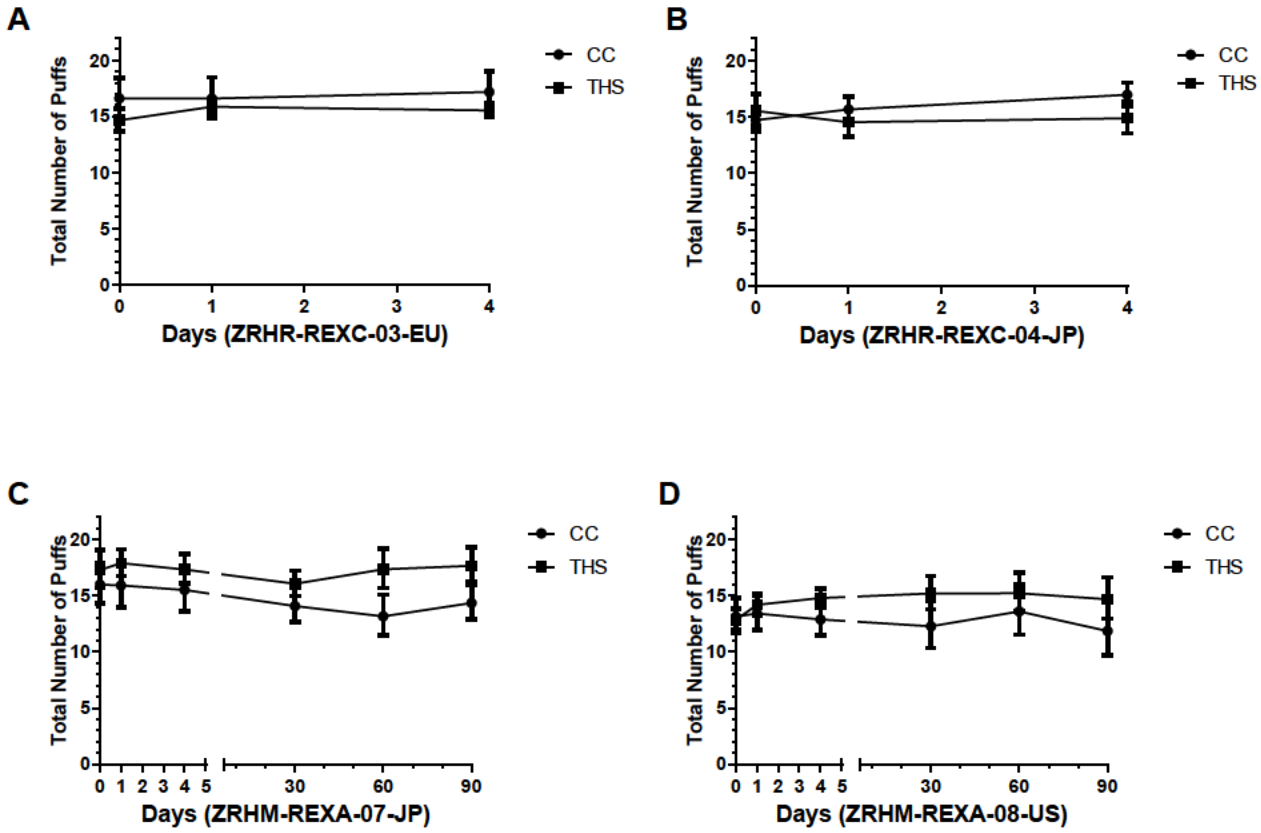


Figure 27 **Geometric Mean Total Number of Puffs with 95% CI by Study Arm in A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US Studies, at Baseline, Day 1, Day 4, Day 30, Day 60 and Day 90**

Note: Day 0 = Baseline.
CC= conventional cigarettes, THS = Tobacco Heating System
Data Source: Clinical Study Report; Appendix 15.3.7.1 [ZRHR-REXC-03-EU]; Appendix 15.3.7.1 [ZRHR ZRHR-REXC-04-JP]; Appendix 15.3.7.1 [ZRHM-REXA-07-JP]; Appendix 15.3.7.1 [ZRHM-REXA-08-US]

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Total Smoking Duration

The HPT parameter Total Smoking Duration, expressed in seconds, is a measure to estimate the subjects' duration of a product use experience, from the time of the first to the time of the last puff. For THS, the system limits the product use experience to a maximum of 6 minutes or 14 puffs, whichever comes first.

Graphical presentation of the arithmetic values are presented in Figure 28.

There was a general decrease in Total Smoking Duration observed in all studies for subjects who switched to THS use, compared to values recorded at Baseline and in the CC arm. The decrease was less marked in the studies conducted in Japan ([ZRHR-REXA-04-JP] and [ZRHM-REXA-07-JP]) that in the US ([ZRHM-REXA-08-US]) and Polish ([ZRHR-REXC-03-EU]) studies.

During the confinement periods of [ZRHR-REXC-03-EU] and [ZRHM-REXA-08-US] studies, the Total Smoking Duration decreased markedly in the THS arms from the first day of use (Day 1) in comparison with Baseline when subjects were smoking their own brand of CC. In study [ZRHR-REXC-03-EU], the subjects shortened their product use experience from 264 s at Baseline to 204 s at Day 1 and 194 s at Day 4. In [ZRHM-REXA-08-US] study, it decreased from 342 s at Baseline to 267 s at Day 1 and 256 s at Day 4. In the CC arms, Total Smoking Duration remained stable from Baseline to Day 4 and ranged from 242 to 247 s in [ZRHR-REXC-03-EU] and from 310 to 322 s in [ZRHM-REXA-08-US], respectively. Total Smoking Duration was shorter with THS compared to CC, with THS:CC ratios of 78% and 80%, respectively.

For the Japanese population, the decrease of Total Smoking Duration with THS was slight between Baseline and Day 4, with product use experiences reduced from 249 s at Baseline to 239 s at Day 4 in the study [ZRHR-REXC-04-JP] and from 226 s at Baseline to 206 s at Day 4 in the [ZRHM-REXA-07-JP] study. In the CC arms the values remained stable during the whole confinement period from 243 to 258 s for [ZRHR-REXC-04-JP] and from 224 to 228 s for [ZRHM-REXA-07-JP]. At Day 4, the THS:CC ratio were respectively 93 and 91%.

During the ambulatory periods of [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], Total Smoking Duration with THS decreased further at Day 30 compared to end of the confinement period (Day 4) and remained stable afterwards until Day 90. In study [ZRHM-REXA-07-JP], Total Smoking Duration ranged from 180 to 188 s in the ambulatory period (Day 30 to Day 90) with THS (compared to 206s at Day 4) and from 231 to 243 s in [ZRHM-REXA-08-US] (compared to 256 s at Day 4). The change in CC smokers in Japan ([ZRHR-REXA-07-JP]) was comparable to THS users with a decrease of the Total Smoking Duration during the ambulatory period (195 to 197 s) compared to Day 4 (223 s) while the Total Smoking Durations varied from 313 to 376 s for the US smokers ([ZRHM-REXA-08-US]), compared to Day 4 (322 s). Finally the duration of the product use experience in Japanese users of THS ([ZRHR-REXA-07-JP]) was comparable to CC smokers (THS:CC ratio: 98%) and lower for THS compared to CC in the US study population ([ZRHM-REXA-08-US]) at Day 90 (THS:CC ratio: 68%).

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In conclusion, Total Smoking Duration was shorter with THS compared to CC, with a more pronounced reduction in the non-Japanese studies ([ZRHM-REXA-08-US] and [ZRHR-REXC-03-EU]). This reduction with THS might due to the intrinsic limitation of the THS system (a maximum of 14 puffs or 6 minutes product use, whichever comes first). Total smoking duration at Baseline was markedly higher in study [ZRHM-REXA-08-US] than in the other studies and remained higher compared to all other studies at all time points and across all study arms.

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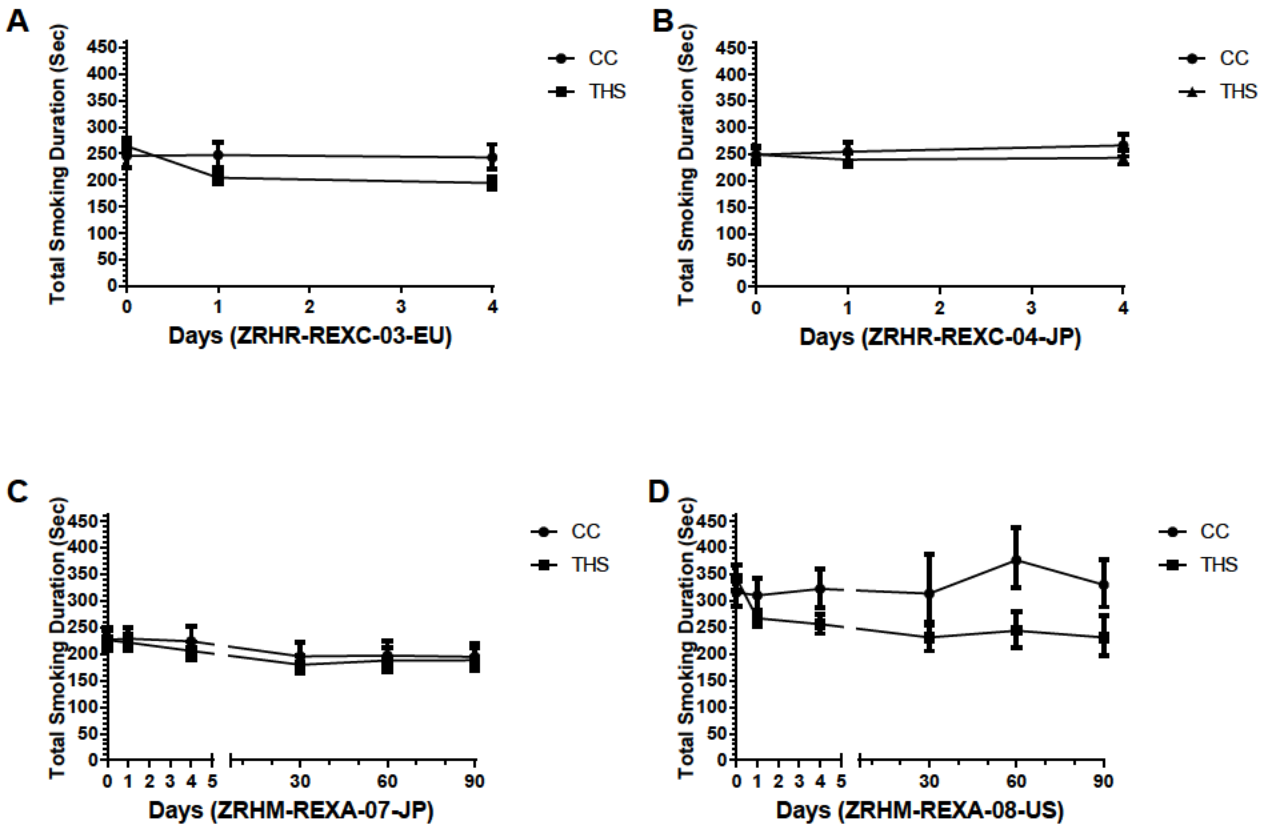


Figure 28 Geometric Mean Total Smoking Duration (seconds) with 95% CI by Study Arm in A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US Studies, at Baseline, Day 1, Day 4, Day 30, Day 60 and Day 90

Note: Day 0 = Baseline.
CC= conventional cigarettes, THS = Tobacco Heating System
Data Source: Clinical Study Report; Appendix 15.3.7.1 [ZRHR-REXC-03-EU]; Appendix 15.3.7.1 [ZRHR ZRHR-REXC-04-JP]; Appendix 15.3.7.1 [ZRHM-REXA-07-JP]; Appendix 15.3.7.1 [ZRHM-REXA-08-US]

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Puff Frequency

The Puff Frequency is defined as the Total Number of Puffs divided by the Total Smoking Duration and allows to estimate how often, on average, a subject is taking a puff from a tobacco product during a defined period of time (puffs/min).

Graphical presentation of the arithmetic values are presented in Figure 29.

Subjects who switched to THS increased their Puff Frequency already at Day 1, when they began to use THS and stabilized at Day 4 in all studies. Puff Frequency was higher for THS users than for CC smokers, for which Puff Frequency was stable during confinement. A high variability in Baseline Puff Frequency was observed, with 2.4 puffs/min in THS in [ZRHM-REXA-08-US] and 4.7 puff/min for THS in [ZRHM-REXA-07-JP].

For the THS users in the study [ZRHR-REXC-03-EU], an increase in Puff Frequency from 3.4 puffs/min at Baseline to 5.0 puffs/min at Day 4 was observed, while values remained stable in the CC arm during the confinement period (from 4.2 puffs/min at Baseline to 4.5 puffs/min at Day 4). Comparable values were reached for THS at Day 4 (5.2 puffs/min) in study [ZRHM-REXA-07-JP], although the increase from Baseline (4.7 puffs/min) was more modest. Values were stable for CC in this study (4.3 to 4.4 puffs/min). The ratios THS:CC were 107% at Day 4 for this study and 132% for [ZRHR-REXC-03-EU].

In the [ZRHM-REXA-08-US] study, Puff Frequency increased in the THS arm from 2.4 puffs/min at Baseline to 3.6 puffs/min at Day 4, while values in the CC arm remained stable (from 2.5 and 2.7 puffs/min). The THS:CC ratio at Day 4 was 139%. The Puff frequency increase was more modest for THS for [ZRHR-REXC-04-JP] (from 3.6 puffs/min at Baseline to 4.3 puffs/min at Day 4), and remained stable for CC (3.6 puffs/min at Day 4 compared to 3.9 puffs/min at Baseline) leading to a THS:CC ratio at Day 4 of 127%.

During the ambulatory period of [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], Puff Frequency increased from end of the confinement period (5.2 puffs/min and 3.6 puffs/min, respectively) to Day 30 for THS, before stabilizing from Day 30 onwards (from 5.5 to 5.7 puffs/min and from 3.8 to 4.0 puffs/min in [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US] between Day 30 and Day 90). Values for CC smokers remained stable during the ambulatory period (4.2 to 4.6 puffs/min for [ZRHM-REXA-07-US] and from 2.2 to 2.4 puffs/min for [ZRHM-REXA-08-US]). The difference between THS and CC was also higher during the ambulatory periods with ratios THS:CC reaching 122% for the [ZRHM-REXA-07-JP] study and 174% for the [ZRHM-REXA-08-US] study at Day 90.

In conclusion, the Puff Frequency increased in all studies from Day 1 until Day 30 when subjects switched to THS, before reaching stabilization through Day 90.

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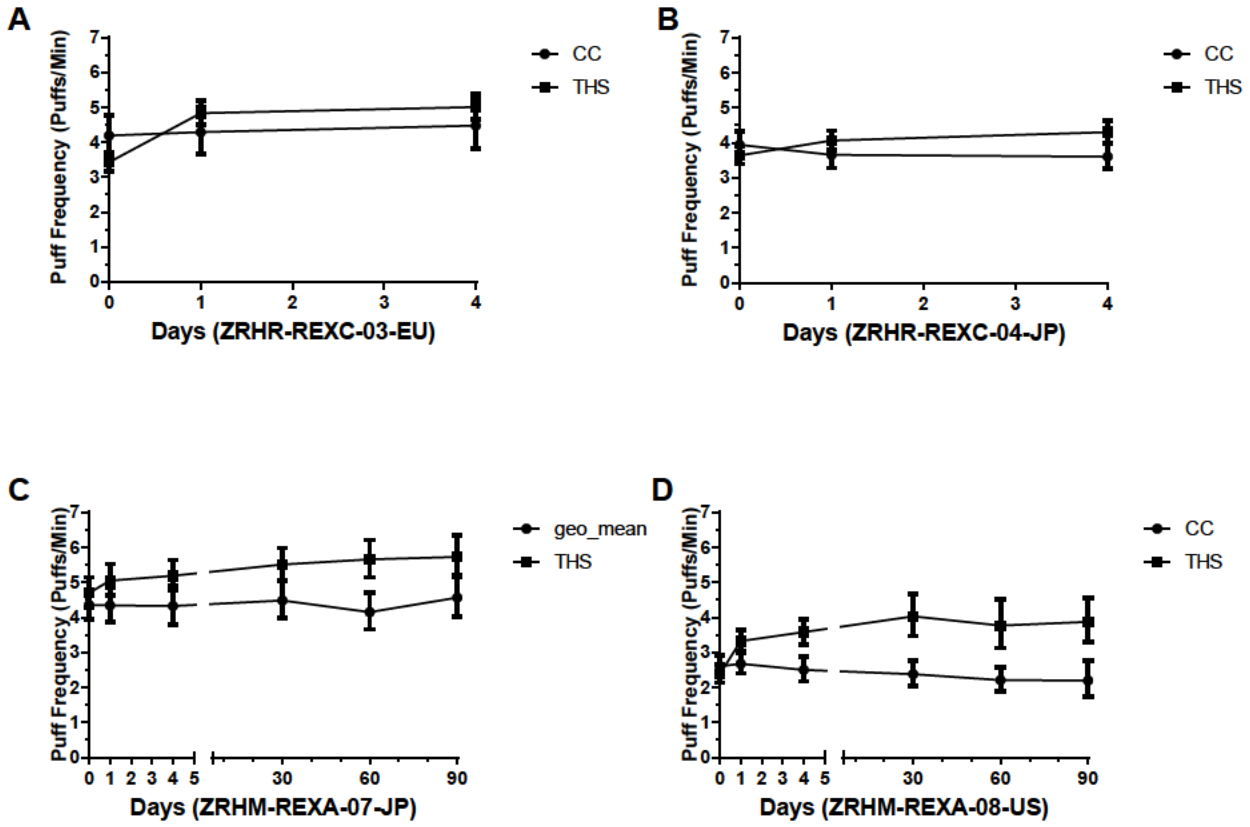


Figure 29 Geometric Mean Puff Frequency (puffs/min) with 95% CI by Study Arm in A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US Studies, at Baseline, Day 1, Day 4, Day 30, Day 60 and Day 90

Note: Day 0 = Baseline.
CC= conventional cigarettes, THS = Tobacco Heating System
Data Source: Clinical Study Report; Appendix 15.3.7.1 [ZRHR-REXC-03-EU]; Appendix 15.3.7.1 [ZRHR ZRHR-REXC-04-JP]; Appendix 15.3.7.1 [ZRHM-REXA-07-JP]; Appendix 15.3.7.1 [ZRHM-REXA-08-US]

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6.2.2.4.1.2.3.3 Conclusion

At the puff level, Average Puff Volume decreased from Baseline onwards for THS in the studies in Japan, whereas comparable values to Baseline and CC were observed in Europe in the Polish study and higher values for THS compared to Baseline and CC during most of the study in the US. Similarly, Average Puffing Duration varied between the different populations with a comparable Average Puffing Duration to Baseline and CC in the Japanese studies [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP], while the puffing duration increased in the Polish study [ZRHR-REXC-03-EU] and was variable in the US study with THS values remaining higher than CC. Average Pressure Drop was stable and comparable during the confinement period for THS and CC within studies, with the exception of a relative decrease of THS compared to CC in [ZRHM-REXA-08-US] whereas Average Pressure Drop continuously and markedly increased during the ambulatory period in both studies ([ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US]) for THS compared to Baseline and CC.

In the CC arms, values were stable over time, with the exception of [ZRHM-REXA-08-US] where the HPT parameters at the Puff Level (Average Puff Volume, Average Puffing Duration and Average Pressure Drop) varied over time.

Overall, these results suggest a different pattern of adaptation when switching from CC to THS across populations at the puff level, with a reduction in average puff volumes in Japan and stable puff volumes in the non-Japanese countries. Average Puffing duration was stable in Japan compared to an increase observed in the European ([ZRHR-REXC03-EU]) and US ([ZRHM-REXA-08-US]) studies.

At the product use level, Total Puff Volume for THS decreased in the Japanese studies ([ZRHR-REXC04-JP] and [ZRHM-REXA-07-JP]) from the beginning of the confinement period but increased afterwards and reached levels comparable to CC, remaining however generally lower than Baseline levels throughout the studies. In contrast, Total Puff Volume remained stable in the study in Europe ([ZRHR-REXC03-EU]) and increased in the US [ZRHM-REXA08-US] from Day 1 onwards, remaining consistently at higher levels compared to Baseline and CC. No regional differences were observed for the Total Number of Puffs drawn, which increased in all studies when the smokers switched from CC to THS. Users seemed to adapt their puffing behavior by using a multipuff technique (i.e. one puff with multiple peaks caused by a modulating inhalation). This is supported by the evaluation of individual profiles showing the presence of multiple peaks in some individual puffs. Similarly, Puff Frequency increased in all studies from Day 1 until Day 30 when subjects switched to THS, before reaching stabilization in all studies. Total Smoking Duration was shorter with THS compared to CC in all studies, with the most pronounced reduction from Baseline in the non-Japanese studies ([ZRHM-REXA-08-US] and [ZRHR-REXC-03-EU]). This reduction with THS might due to the intrinsic limitation of the THS system (a maximum of 14 puffs or 6 minutes product use, whichever comes first). To note, Total smoking duration at Baseline was markedly higher in study [ZRHM-REXA-08-US] than in the other studies and remained higher compared to all other studies at all time points and across all study arms.

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In summary THS users took more puffs from THS compared to CC, at a higher frequency and for shorter total duration of use. Total puff volume was variable, with an increase observed in the US, a stable volume in the EU and an initial decrease in the Japanese studies. No relevant changes were observed in subjects who continued to use their CC.

Taken together, the results from the "at the puff level" and "at the product use experience level" indicate that smokers switching from CC to THS adapted their puffing behaviors. Changes in Average and Total Puff Volume were different between the studies, as well as the effect on the other parameters, but a general trend for longer and more frequent puffs with a shorter Total Puff Duration was observed for THS compared to CC in all studies.

It is likely that differences in product satisfaction, ritual, sensory and taste are the cause of the observed adaptations. The limit to 14 puffs or to a maximum of 6 minutes of product use may also have played a role.

6.2.2.4.1.2.4 Product Acceptance

Subjective effect measures, in particular the assessment of reinforcing and aversive effects of smoking such as relieve from urge-to-smoke, craving and withdrawal symptoms as well as measures of product acceptance through validated questionnaires are well established and widely used to serve as outcomes in the context of the assessment of pharmacodynamic effects and are important to measure to understand the potential of an MRTP to serve as an acceptable alternative for CC.

Reinforcement refers to the observation that behaviors increase or decrease according to whether a person associates a particular behavior (e.g., smoking) with a positive or negative experience. In the context of CC smoking, an example of positive reinforcement would be the strengthening of a certain product use behavior due to the rewarding effects of the product such as pleasurable sensory cues, euphoria, etc… Withdrawal symptoms which are perceived as a negative stimulus and lead to smoking in order to alleviate this aversive state are in contrast an example for a negative reinforcement. Aversive stimuli such as craving and withdrawal have therefore been characterized as motivating negative reinforcing effects of tobacco products.

6.2.2.4.1.2.4.1 QSU brief

The QSU is accepted as a quick, valid and reliable measure of urge-to-smoke including multi-dimensional aspects of smoking urge (Hanson 2009, Rosenberg 2009), has produced consistent findings across many studies and the psychometric properties were acceptable and consistent across samples and settings. More details are provided in Section 6.2.1, and includes the results from single product use in the PK studies ([ZRHR-PK-01-EU], [ZRHR-PK-02-JP], [ZRHM-PK-05-JP] and US [ZRHM-PK-06-US]). In the context of the confinement studies, results across studies are presented for the total score, as the 2 subfactors, the Factor 1 and Factor 2, were generally consistent with the total score. The results from the 2 factors can be found in their respective clinical study reports ([ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP], [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US]).

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Graphical presentation of the arithmetic values are presented in Figure 30.

During the confinement period, the total score of urge-to-smoke for THS was stable and comparable to CC (THS:CC difference -0.4 to 0.0 on Day 5) across studies and remained stable during the ambulatory period of study [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], with slightly higher values for THS compared to CC (THS:CC differences of 0.32 and 0.4, respectively).

The scores for SA were higher during the confinement period in [ZRHR-REXC-03-EU] and [ZRHM-REXA-07-JP] (difference: -1.6 and -1.4, respectively), but values closer to THS in [ZRHR-REXC-04-JP] and [ZRHM-REXA-08-US] (-0.5 and -0.3, respectively). Values in the SA arms continuously decreased from the end of the confinement (Day 5) until the last day of the ambulatory period (THS-SA differences at Day 90 of 1.1 and 1.3).

In conclusion, effects on urge-to-smoke were stable and comparable between THS and CC. Values were higher for SA compared to THS during the confinement period before decreasing continuously during the ambulatory period, and reaching values lower than THS and CC.

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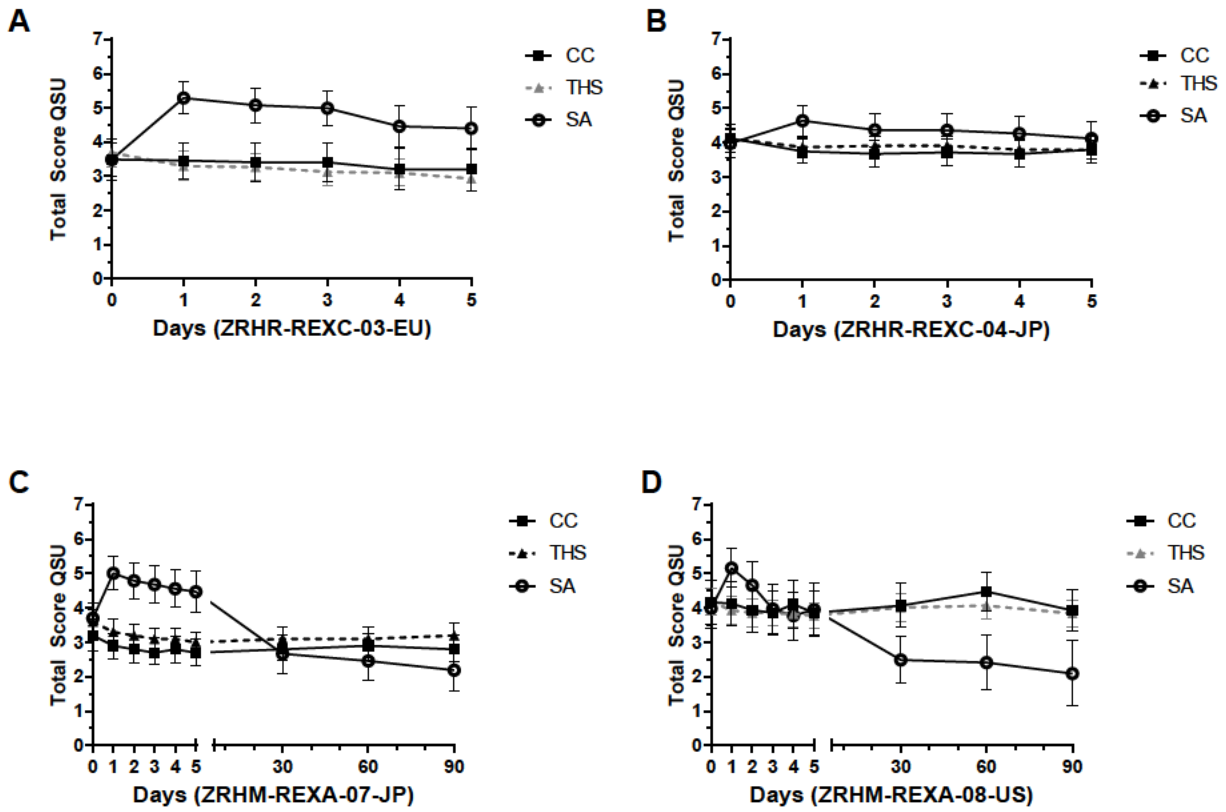


Figure 30 Arithmetic Mean of the Total Score for QSU with 95% CI by Study Arm in A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US Studies, at Baseline, Day 1 to Day 5, Day 30, Day 60 and Day 90

Note: Day 0 = Baseline.
CC= conventional cigarettes, THS = Tobacco Heating System, SA: Smoking Abstinence
Data Source: Clinical Study Report; Appendix 15, Figure 15.1.2.33 [ZRHR-REXC-03-EU]; Appendix 15, Figure 15.1.2.33 [ZRHR-REXC-04-JP]; Appendix 15, Figure 15.1.2.4.1 [ZRHM-REXA-07-JP]; Appendix 15, Figure 15.1.2.4.1.[ZRHM-REXA-08-US]

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6.2.2.4.1.2.4.2 mCEQ

The modified Cigarette Evaluation Questionnaire (mCEQ) is the most widely used assessment tool to assess reinforcing and aversive effects of smoking (Cappelleri 2007). It was 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.

Graphical presentation of the THS and CC values at Baseline and Day 5 are presented in Figure 31.

During the confinement, a general trend for reduction in the subscales was observed for THS on Day 1 before stabilizing from Day 2 to Day 5. Aversion was comparable between the studies, with score slightly higher for THS compared to CC (Day 5 THS-CC differences from 0.0 to 0.2). For the other parameters, the highest differences were systematically reported in [ZRHR-REXC-03-EU] and the lowest in the 2 Japanese studies ([ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP]). In the Japanese studies, craving reduction, enjoyment of respiratory tract sensation, psychological rewards and smoking satisfaction with THS were lower but close to CC, with differences lower than -0.7. Scores for these subscales in [ZRHM-REXA-08-US] were close to [ZRHR-REXC-03-EU]. Differences (THS-CC) of 1 point or more were observed for craving reduction in these 2 studies, and for enjoyment of respiratory tract sensation and smoking satisfaction in [ZRHR-REXC-03-EU].

During the ambulatory period, scores for all subscales in [ZRHM-REXA-07-JP] were comparable between THS and CC (THS-CC differences at Day 90 from -0.2 to 0.3). In [ZRHM-REXA-08-US], aversion remained comparable to the confinement period (THS-CC difference of 0.0 at Day 90), while differences between THS and CC attenuated over time, with differences lower than 1 point for all other subscales (from -0.7 to -0.3).

In conclusion, no differences in aversions were observed between THS and CC across the studies. For the other subscales, regional differences were observed, with scores comparable between THS and CC in the Japanese studies ([ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP].

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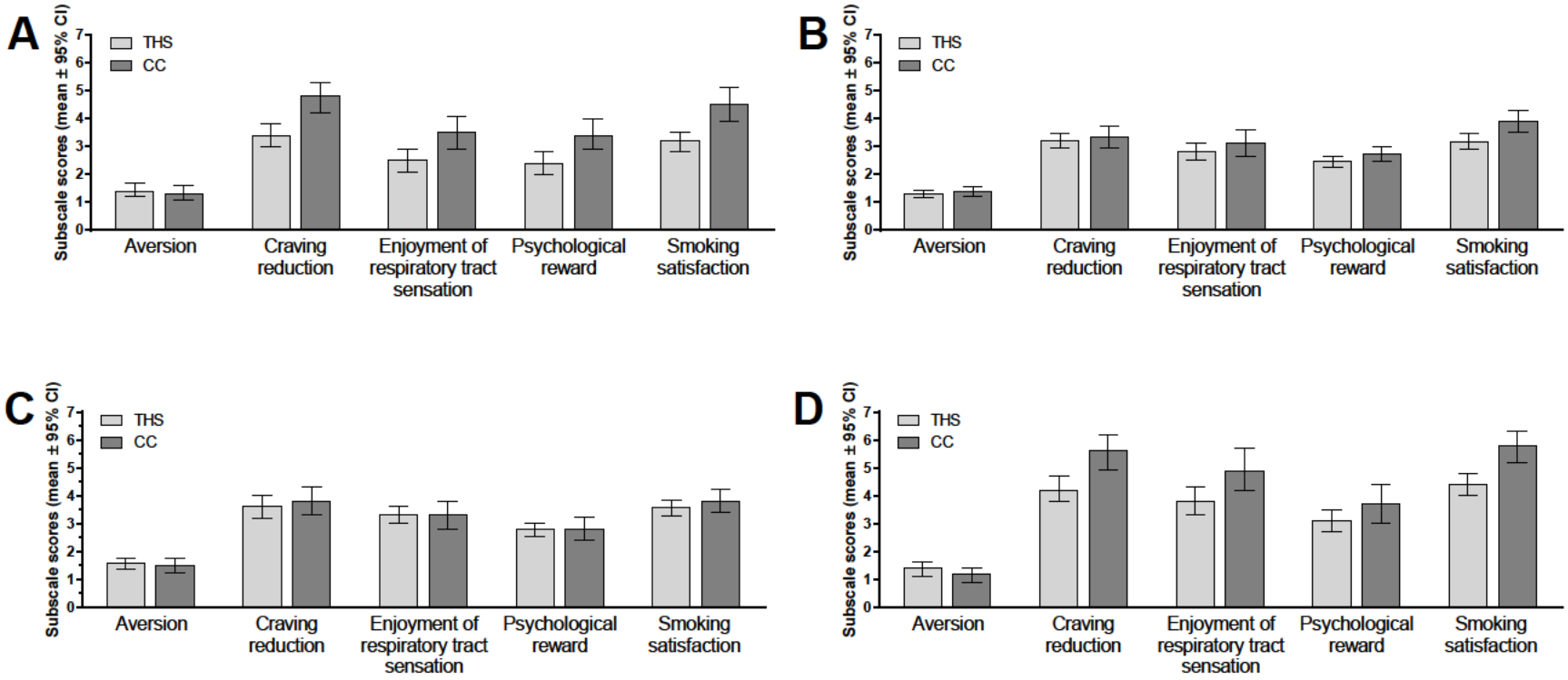


Figure 31 mCEQ Subscales in A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US Studies, at Day 5

CC= conventional cigarettes, THS = Tobacco Heating System.
Data Source: Clinical Study Report; Appendix 15, Table 15.2.4.47 [ZRHR-REXC-03-EU]; Appendix 15, Table 15.2.4.47 [ZRHR-REXC-04-JP]; Appendix 15, Table 15.2.4.37.1 [ZRHM-REXA-07-JP]; Appendix 15, Table 15.2.4.54.1 [ZRHM ZRHM-REXA-08-US]

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6.2.2.4.1.2.4.3 MNWS-R

MNWS revised version (MNWS-R) is a valid and reliable scale of withdrawal. Subjects were asked to rate items for the previous 24 hours on a scale ranging the total score was calculated by summing the results of the first 9 responses on the MNWS questionnaire.

Graphical presentation of the arithmetic values are presented in Figure 32.

In the REXC studies, the MNWS-R Total score was not calculated. Results were instead assessed by the means of MNWS total score 1 and 2. In study [ZRHR-REXC-03-EU], the total score 1 was higher for THS (score: 6.2) compared to CC (score: 5.5) at Baseline and remained stable throughout the confinement period (from 4.8 to 6.0 for THS and 4.7 to 5.7 for CC). In the SA arm, the total score 1 increase markedly from Baseline (score: 6.5) to Day 2 (score: 11.1) and then progressively returned towards Baseline (score of 7.4 at Day 6). The profile for the MNWS-R Total score 2 was comparable to the MNWS-R Total score 1 for the 3 study arms.

Effects for [ZRHR-REXC-04-JP] were consistent with [ZRHR-REXC-03-EU], with comparable values between THS and CC. Values for total score 1 ranged from 5.7 to 6.3 for THS (Baseline: 6.4) and from 5.7 to 6.0 for CC (Baseline: 6.9). The increase for the SA at Day 2 was more moderate than in [ZRHR-REXC-03-EU], with total score 1 increasing from 7.3 at Baseline to 9.8, before continuously decreasing towards Baseline values. The profile for the MNWS-R Total score 2 was comparable the one for MNWS-R Total score 1 for the 3 study arms.

During the confinement period of studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], the values for the MNWS-R Total scores at Baseline were higher for THS compared to CC in the 2 studies. Values remained stable between Day 1 and Day 5 in [ZRHM-REXA-07-JP] for both products, with a THS-CC difference of 0.1 at Day 5. In study [ZRHM-REXA-08-US] the MNWS-R Total score declined from Baseline (score of 0.9) to Day 1 in the THS arm and then remained stable until Day 5 (score of 0.7), Values were overall comparable or only slightly lower than observed for the CC arm (from 0.7 to 0.8 from Day 1 to Day 5) resulting in a THS-CC difference of -0.15 at Day 5.

During the ambulatory period, from Day 30 to Day 90, the profiles were comparable between THS and CC in [ZRHM-REXA-07-JP], with higher values for THS (from 0.7 to 0.8) compared to CC (from 0.5 to 0.6), and with the same THS-CC difference as observed on Day 5 (difference: 0.11). In [ZRHM-REXA-08-US], scores for THS and CC were stable but lower compared to the confinement period. Scores for CC remained however generally higher than those for THS. At Day 90, the THS-CC difference was -0.08.

In the SA arms, the values increased markedly between Baseline (score of 0.9 for both studies) and Day 1 (score of 1.6 in [ZRHM-REXA-07-JP] and 1.3 in [ZRHM-REXA-08-US]) before declining, with values returning to Baseline by Day 4 in [ZRHM-REXA-08-US] or close to Baseline at Day 5 (score of 1.3) in [ZRHM-REXA-07-JP]. During the ambulatory period, the score continuously decreased in the SA arms of both studies, with a score lower than THS and CC at Day 90 (0.5 and 0.4 in [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], respectively).

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In conclusion, effects on withdrawal were comparable between THS and CC, while withdrawal scores increased markedly between Baseline and Day 1 in the smoking abstinence arm, before progressively decreasing throughout the study and to reach scores lower than Baseline by Day 90.

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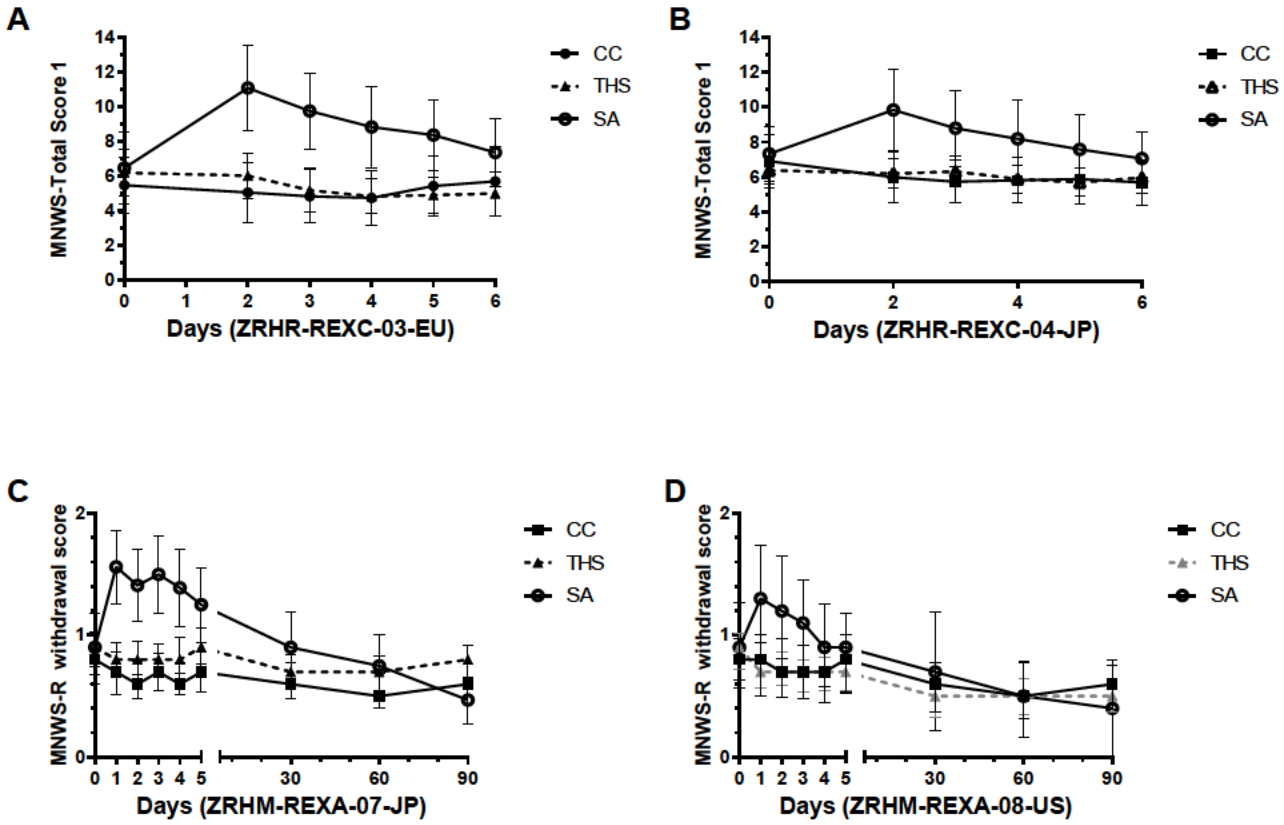


Figure 32 Arithmetic Mean of the MNWS- Total Score 1 (REXC) and MNWS-R Withdrawal Score (REXA) with 95% CI by Study Arm in A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP and B) ZRHM-REXA-08-US Studies, at Baseline, Day 2 to Day 6, Day 30, Day 60 and Day 90

Note: Day 0 = Baseline.
CC= conventional cigarettes, THS = Tobacco Heating System, SA: Smoking Abstinence.
Data Source: Clinical Study Report; Appendix 15, Figure 15.1.2.35 [ZRHR-REXC-03-EU]; Appendix 15, Figure 15.1.2.35 [ZRHR-REXC-04-JP]; Appendix 15, Figure 15.1.2.8.1 [ZRHM-REXA-07-JP]; Appendix 15, Figure 15.1.2.8.1 [ZRHM-REXA-08-US]

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6.2.2.4.1.3 Summary of Results of the Observational Studies

Pre-market observational studies aimed at providing insights on how adult smokers consume THS under near to real-world conditions. Data derived in a more natural setting are necessary to inform about (i) the likelihood that the product will be adopted (level of product consumption, sensory acceptance, easiness to use), (ii) the likelihood that smokers will use it predominantly, with other tobacco products, or switch back to CC, and (iii) the likelihood that users may consume THS in a manner that may differ from the intended use. In this section, we first present a summary of THS-PBA-07-US Actual use Study of THS conducted in a large sample of US adult daily smokers. We then present an overview of similar data coming from WOT pre-market studies as an element of supportive evidence that will be then used in Section 6.2.2.4.1.2.3 to evaluate the potential effect of THS on tobacco use behavior in adult daily smoker populations from different countries.

6.2.2.4.1.3.1 THS-PBA-07-US Study

The main purpose of the THS-PBA-07-US Study was to investigate how US adult current daily CC smokers use the THS system under near to real-world conditions. More details can be found in the summary [PBA07Sum] and full report of the study [THS-PBA-07-US].

6.2.2.4.1.3.1.1 Methodology of THS-PBA-07-US

A description of the study methods is presented in Table 17.

Table 17 Methodology of THS-PBA-07-US

Study Title: Actual Use Study of THS 2.2 – THS-PBA-07-US
Study design: Single group, mid-term prospective observational study from 8 limited geographic areas of the United States, implying an assessment of subject-reported stick-by-stick consumption of THS Tobacco Sticks and of CC with participants receiving THS Tobacco Sticks free of charge.
Subjects: Enrolled: 1336; Full Analysis Set (FAS): 1106; Per Protocol (PPROT): 465.
Main criteria for inclusion: • Aged 18 and above, or above state legal smoking age if above 18 years • Current daily smokers of regular and/or menthol CC, having smoked at least 100 CC in lifetime, currently smoking at least 1 CC/day, and having no intention of quitting within the next 30 days. • Positive intention to use the THS system as assessed during screening (scoring at least 4 on the intention to use item from 1 to 6 [1 = definitely not, 6 = definitely]) following presentation of the THS brochure containing the reduced risk claim that "Scientific studies have shown that switching completely from conventional cigarettes to the iQOS system can reduce the risks of tobacco-related diseases" (THS-PBA-07-US Report Appendix 16.1.1)
Test Product: Tobacco Heating System 2.2 (THS 2.2) regular and menthol variants. *Ad-libitum* use

(table continues)

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Duration of Use: Observational period of 6 weeks

Methods: 8 weeks duration study: 1-week Baseline period + 6-week observational period + 1-week close out period. Participants received THS Tobacco Sticks free of charge and were able to consume THS Tobacco Sticks of both regular and menthol variants. CC and other products containing nicotine could be consumed *ad libitum* at the expense of the participants. Subjects were requested to make an entry into an electronic diary (e-diary) every time they consumed a CC during the 1-week Baseline and a THS Tobacco Stick or CC during the 6-week observational period. Additional information related to "product assessment" (ease of use, sensorial experience, occasion of use, and potential misuse) was collected during follow-up interviews, every 2 week during the observational period. All participants were able to call a toll-free hotline to order THS tobacco Sticks, raise queries related to the study, resolve issues related to the e-diary and report product quality complaints, including adverse health events associated with the use of the iQOS system.

Analyses:

Use patterns

Product use described per week according to 3 product usage categories:

- *THS Tobacco Sticks use* (≥ 70% of tobacco products used are THS Tobacco Sticks)
- *Combined use* (>30% and <70% of tobacco products used are THS Tobacco Sticks)
- *CC use* (≤ 30% of tobacco products used are THS Tobacco Sticks)

Analysis of usage categories over different time points via transition tables, created for each week to any other posterior week in the observational period starting with week 0 (i.e. Baseline period).

Levels of Consumption

Average daily consumption of THS and CC during the observational period in comparison to Baseline consumption of CC as reported by the study participant in the e-diary.

Product Assessment

- Ease of use the THS system (7-point rating scale; 1=not easy to use at all, 7=very easy to use)
- Sensorial experience comprised of taste, smell and after-taste of THS Tobacco Sticks (7-point rating scale; 1=I don't like it at all to 7=I like it very much)
- Occasions of use of the THS system based on pre-determined categories characterized by location, situation, and time of day

Potential misuse

Use of the THS Device with product other than THS Tobacco Sticks (n, frequency)
Use THS Tobacco Sticks without the THS Device (n, frequency)

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6.2.2.4.1.3.1.2 Results of THS-PBA-07-US

The FAS population consisted of 1106 participants, all had recorded consumption of at least 1 CC in the electronic diary during the 1-week Baseline period and at least 1 consumption of a THS Tobacco Stick during the 6-week observational period. The PPROT population consisted of 465 FAS subjects (34.0%) who recorded their CC consumption for at least 6 days of the 1-week Baseline period and their CC and / or THS Tobacco Sticks consumption for at least 39 days of the 6-week observational period. The details on the disposition of subjects are reported in Section 10 of the study report [THS-PBA-07-US].

Due to the descriptive character of this Actual Use Study under near real-world conditions, the FAS was the primary analysis set for all analyses. All analyses on the PPROT can be found in the study report [THS-PBA-07-US].

Demographics and Baseline characteristics

Demographics and smoking habits are summarized in Table 18 for the FAS and the PPROT populations. Demographic characteristics were closely in line with the distribution of the US adult smoker population for sex and age (U.S Department of Health and Human Services 2012). Demographics and Baseline characteristics were fairly comparable between the FAS and PPROT participants.

Table 18 Demographic and Baseline Characteristics – THS-PBA-07-US

	FAS (N=1106)	PPROT (N=465)	FAS Participants with *THS Tobacco Stick use* at Week 6 (N=141)
Sex			
Male	559 (50.5%)	208 (44.7%)	81 (57.4%)
Female	547 (49.5%)	257 (55.3%)	60 (42.6%)
Age			
Mean (SD)	38.3 (14.04)	42.7 (13.68)	39.5 (13.53)
Min - Max	18 - 83	18 - 83	18-71
Age (categories)			
18 to 24 years	294 (26.6%)	65 (14.0%)	24 (17.0%)
25 to 44 years	400 (36.2%)	173 (37.2%)	59 (41.8%)
Above 44 years	412 (37.3%)	227 (48.8%)	58 (41.1%)
Race[1]			
White	760 (68.9%)	338 (72.7%)	88 (62.4%)
Black or African American	303 (27.5%)	118 (25.4%)	52 (36.9%)
Other	40 (3.6%)	9 (1.9%)	1 (0.7%)

(table continues)

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	FAS (N=1106)	PPROT (N=465)	FAS Participants with *THS Tobacco Stick use* at Week 6 (N=141)
Ethnicity[2]			
Hispanic or Latino	131 (11.9%)	53 (11.4%)	27 (19.1%)
Not Hispanic or Latino	974 (88.1%)	412 (88.6%)	114 (80.9%)
Prefer not to answer	0	0	0
Education level			
Less than High School	22 (2.0%)	12 (2.6%)	3 (2.1%)
Some High School or General Education Development (GED)	125 (11.3%)	38 (8.2%)	14 (9.9%)
High School Graduate	375 (33.9%)	159 (34.2%)	55 (39.0%)
Some College	398 (36.0%)	167 (35.9%)	44 (31.2%)
College Graduate	164 (14.8%)	72 (15.5%)	23 (16.3%)
Advanced Degree	21 (1.9%)	16 (3.4%)	2 (1.4%)
Prefer not to answer	1 (<0.1%)	1 (0.2%)	0
Occupational status			
Working now	681 (61.6%)	257 (55.3%)	87 (61.7%)
Only temporarily laid off, sick leave or maternity leave	27 (2.4%)	13 (2.8%)	3 (2.1%)
Looking for work, unemployed	155 (14.0%)	66 (14.2%)	22 (15.6%)
Retired	55 (5.0%)	33 (7.1%)	6 (4.3%)
Disabled, permanently or temporarily	89 (8.0%)	49 (10.5%)	11 (7.8%)
Homemaker, keep housing	64 (5.8%)	37 (8.0%)	7 (5.0%)
Student	28 (2.5%)	5 (1.1%)	4 (2.8%)
Other	6 (0.5%)	4 (0.9%)	1 (0.7%)
Prefer not to answer	1 (<0.1%)	1 (0.2%)	0
Income			
Less than $10,000	138 (12.5%)	60 (12.9%)	22 (15.6%)
$10,000 to $29,999	236 (21.3%)	109 (23.4%)	32 (22.7%)
$30,000 through $44,999	207 (18.7%)	92 (19.8%)	29 (20.6%)
$45,000 through $59,999	279 (25.2%)	98 (21.1%)	33 (23.4%)
$60,000 through $74,999	94 (8.5%)	44 (9.5%)	8 (5.7%)
$75,000 through $99,999	62 (5.6%)	30 (6.5%)	5 (3.5%)
$100,000 through $149,999	33 (3.0%)	19 (4.1%)	4 (2.8%)
$150,000 and over	10 (0.9%)	0	2 (1.4%)
I do not know	9 (0.8%)	1 (0.2%)	2 (1.4%)
Prefer not to answer	38 (3.4%)	12 (2.6%)	4 (2.8%)
Socioeconomic status[3]			
Low	15 (1.4%)	9 (2.0%)	3 (2.2%)
Moderate	365 (34.5%)	162 (35.9%)	51 (37.8%)
High	678 (64.1%)	280 (62.1%)	81 (60.0%)
Average number of cigarettes per day at rescreening			
Mean (SD)	15.1 (8.83)	15.2 (8.85)	12.9 (8.27)
Min - Max	1 - 60	1 - 60	1-40

(table continues)

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	FAS (N=1106)	PPROT (N=465)	FAS Participants with *THS Tobacco Stick use* at Week 6 (N=141)
Average number of cigarettes per day at rescreening (categories)			
1-4 cigarettes	106 (9.6%)	43 (9.2%)	20 (14.2%)
5-10 cigarettes	350 (31.6%)	145 (31.2%)	52 (36.9%)
11-20 cigarettes	511 (46.2%)	220 (47.3%)	58 (41.1%)
21-30 cigarettes	101 (9.1%)	41 (8.8%)	8 (5.7%)
≥ 31 cigarettes	38 (3.4%)	16 (3.4%)	3 (2.1%)
Favorite brand of cigarettes			
Menthol	599 (54.2%)	235 (50.5%)	87 (61.7%)
Regular	507 (45.8%)	230 (49.5%)	54 (38.3%)
Current usage of any nicotine replacement therapy products as stated at rescreening			
Yes	1 (<0.1%)	0	1 (0.7%)
No	1105 (99.9%)	465 (100%)	140 (99.3%)
Current usage of e-cigarettes as stated at rescreening			
Yes	59 (5.3%)	20 (4.3%)	12 (8.5%)
No	1047 (94.7%)	445 (95.7%)	129 (91.5%)
Attempt to quit smoking within the next six months			
Yes	43 (3.9%)	17 (3.7%)	7 (5.0%)
No	1036 (93.7%)	440 (94.6%)	130 (92.2%)
Don't know	27 (2.4%)	8 (1.7%)	4 (2.8%)
Last attempt to quit smoking			
Less than 6 months ago	29 (2.6%)	11 (2.4%)	2 (1.4%)
More than 6 months ago	409 (37.0%)	208 (44.7%)	41 (29.1%)
Never	668 (60.4%)	246 (52.9%)	98 (69.5%)

N= sample size, FAS= Full Analysis Set, PPROT= Per Protocol Set.
Note: Percentages are calculated based on available responses.
[1] For 3 subject information on race was missing in the FAS.
[2] For 1 subject information on ethnicity was missing in the FAS.
[3] Information on socioeconomic status was missing for 48 participants in the FAS and for 14 participants in the PPROT. Socioeconomic status is a composite measure of annual household income and level of educational attainment ((King 2011)). Annual household income was categorized as low ($44,999 or less), moderate/high ($45,000 or more). Educational attainment was categorized as low (less than high school diploma), moderate (high school diploma) and high (some university training or a university degree). Socioeconomic status could not be computed for 6 participants included in those with a THS Tobacco Use pattern at Week 6 and were thus counted as missing data.
Source Data: Section 15.2; FAS, Table 15.2.2.1, Table 15.2.2.2, Table 15.2.2.4, Table 15.2.2.9, Table 15.2.2.11, Table 15.2.2.12, Table 15.2.2.14, Table 15.2.2.16, Table 15.2.2.18, Table 15.2.3.1, Table 15.2.3.2, Table 15.2.3.3, Table 15.2.3.4, Table 15.2.3.5, Table 15.2.3.6, Table 15.2.3.7. Section 15.2; PPROT, Table 15.2.2.1, Table 15.2.2.2, Table 15.2.2.4, Table 15.2.2.9, Table 15.2.2.11, Table 15.2.2.12, Table 15.2.2.14, Table 15.2.2.16, Table 15.2.2.18, Table 15.2.3.1, Table 15.2.3.2, Table 15.2.3.3, Table 15.2.3.4, Table 15.2.3.5, Table 15.2.3.6, Table 15.2.3.7. FAS_ByUsageW6, Table 15.2.2.1, Table 15.2.2.2, Table 15.2.2.4, Table 15.2.2.9, Table 15.2.2.11, Table 15.2.2.12, Table 15.2.2.14, Table 15.2.2.16, Table 15.2.2.18, Table 15.2.3.1, Table 15.2.3.2, Table 15.2.3.3, Table 15.2.3.4, Table 15.2.3.5, Table 15.2.3.6, Table 15.2.3.7.

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Use Patterns During the 6 Weeks Observational Period

A summary of product use by product usage categories (as defined in Section 6.2.2.3.1.3 and summarized in Table 17) is tabulated in Table 19 for each of the 6 weeks during the observational period, considering the number of participants still in the study in each week

In Week 1, 19.4% of the FAS participants reported *THS Tobacco Stick use*, 41.5% *Combined use* and 39.0% reported *CC use*. In Week 6, 14.6% reported *THS Tobacco Stick use*, 22.4% reported *Combined use* and 62.7% *CC use* (Table 19). A similar pattern of results was found in the PPROT population as contained in the study report [THS-PBA-07-US].

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Table 19 Product Use by Usage Category and by Week for the FAS Population in THS-PBA-07-US

n (% column) ***95% CI (%,%)***	Week 1 (n=1106)	Week 2 (n=1061)	Week 3 (n=1038)	Week 4 (n=1009)	Week 5 (n=997)	Week 6 (n=968)
THS Tobacco Sticks use	215 (19.4) (17.1 , 21.9)	181 (17.1) (14.8 , 19.5)	170 (16.4) (14.1 , 18.8)	162 (16.1) (13.8 , 18.5)	156 (15.6) (13.4 , 18.1)	141 (14.6) (12.4 , 17.0)
Exclusive THS Tobacco Sticks use	81 (7.3) (5.8 , 9.1)	83 (7.8) (6.2 , 9.7)	88 (8.5) (6.8 , 10.4)	85 (8.4) (6.7 , 10.4)	71 (7.1) (5.6 , 8.9)	73 (7.5) (5.9 , 9.4)
Predominant THS Tobacco Sticks use	134 (12.1) (10.2 , 14.2)	98 (9.2) (7.5 , 11.2)	82 (7.9) (6.3 , 9.8)	77 (7.6) (6.0 , 9.5)	85 (8.5) (6.8 , 10.5)	68 (7.0) (5.4 , 8.9)
Combined use	459 (41.5) (38.5 , 44.5)	360 (33.9) (31.0 , 36.9)	326 (31.4) (28.5 , 34.4)	267 (26.5) (23.7 , 29.3)	243 (24.4) (21.7 , 27.2)	217 (22.4) (19.8 , 25.2)
CC use	431 (39.0) (36.0 , 42.0)	518 (48.8) (45.7 , 51.9)	542 (52.2) (49.1 , 55.3)	576 (57.1) (53.9 , 60.2)	596 (59.8) (56.6 , 62.9)	607 (62.7) (59.5 , 65.8)
Exclusive CC use	71 (6.4) (5.0 , 8.1)	192 (18.1) (15.8 , 20.6)	245 (23.6) (21.0 , 26.4)	272 (27.0) (24.2 , 29.9)	303 (30.4) (27.5 , 33.4)	334 (34.5) (31.5 , 37.6)
Predominant CC use	360 (32.5) (29.7 , 35.5)	326 (30.7) (27.9 , 33.6)	297 (28.6) (25.8 , 31.5)	304 (30.1) (27.3 , 33.1)	293 (29.4) (26.5 , 32.4)	273 (28.2) (25.3 , 31.2)
No CC or THS Tobacco Sticks use	1 (<0.1) (<0.1 , 0.6)	2 (0.2) (<0.1 , 0.7)	0 (0 , 0.4)	4 (0.4) (0.1 , 1.1)	2 (0.2) (<0.1 , 0.8)	3 (0.3) (<0.1 , 1.0)

n= number of values reported, CC= conventional cigarette; CI= Confidence Interval. FAS = Full Analysis Set.
Data Source: Appendix 15.2; FAS, Table 15.2.6.1.2

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Analysis of the quantity of THS Tobacco Sticks used during the total observational period provided additional insights on the level of product adoption. About a third of the participants in the FAS (374 out of 1106) met the definition of established user according to WHO (IARC (International Agency for Research on Cancer) 2008), i.e., they consumed ≥ 100 THS Tobacco Sticks during the observational period, suggesting that they were no longer experimenting with THS Tobacco Sticks, but rather using the product on a continuous basis. The proportion of participants passing the threshold of 100 THS Tobacco Sticks peaked at Week 3, and decreased over time after that. Importantly, the large majority of participants who reported *THS Tobacco Stick use* at Week 6 actually reached the 100 THS Tobacco Sticks threshold (116 out of 141 participants).

Based on the analysis of transition tables over the 6-week observational period (Study Report THS-PBA-07-US, Table 15.2.5.14 and Table 15.2.6.3), additional information was extracted on how participants transitioned to *THS Tobacco Stick use*, *CC use* and *Combined use*. Of the 141 participants who reported *THS Tobacco Stick use* at Week 6, 89 (63.1%) reported this use pattern as early as Week 1 (n=63), Week 2 (n=15) or Week 3 (n=11) and remained with *THS Tobacco Stick use* until Week 6. Of the 215 participants who reported *THS Tobacco Stick use* at Week 1, 84 (39.1%) remained with *THS Tobacco Stick use* at Week 6, 39 (18.1%) transitoned to *Combined use* and 55 (25.6%) went back to *CC use*. Of the 459 participants who reported *Combined use* at Week 1, 133 (29.0%) remained with *Combined use* at Week 6, while 50 (10.9%) transitioned to *THS Tobacco Stick use*, and 223 (48.6%) went back to *CC Use.* Of the 431 participants who reported *CC use* at Week 1, 329 (76.3%) remained with *CC use* at Week 6, while very few participants (2%) transitioned to *THS Tobacco Stick use*, and 45 (10.4%) transitioned to *Combined Use.*

Profile of Participants with THS Tobacco Stick use at Week 6

A summary of the demographic characteristics for participants with *THS Tobacco Stick use* at Week 6 compared to the total FAS is given in Table 18. Compared to the total FAS, higher proportions of participants with *THS Tobacco Stick use* at Week 6 were observed for the following characteristics: male (57.4% with *THS Tobacco Stick use* at Week 6 vs. 50.5% in the FAS), high school graduates (39.0% vs. 33.9%), older age groups (25 to 44 years: 41.8% vs 36.2%; above 44 years: 41.1% vs. 37.3%), Black or African Americans (36.9% vs. 27.5%), or Hispanic or Latinos (19.1% vs. 11.9%).

Levels of Tobacco Consumption at Baseline and During the Observational Period

A summary of tobacco consumption during the Baseline period and the observational period is provided in Table 20. The results are for the overall FAS as well as stratified by the 3 usage category at Week 6. Overall, the total tobacco consumption (CC and THS Tobacco Sticks) during the 6 weeks observational period was slightly lower than the average daily consumption of CC during Baseline. This was true for the overall FAS and the stratified groups by usage category at Week 6 (Table 20).

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Table 20 THS Tobacco Sticks and/or CC Consumed Daily (Mean±SD) at Baseline and During the Observational Period (Average across the 6 Weeks) in THS-PBA-07-US –Overall (FAS) and Stratified by Usage Category at Week 6

	Baseline (1 week)	Observational Period (6 weeks)		
	CC	All tobacco (THS+CC)	CC	THS Tobacco Sticks
Stratified by Usage Category at Week 6				
Participants with *THS Tobacco Sticks use* at Week 6 (n=141)	**9.0 ±5.89**	**8.1±5.37**	1.4±1.57	6.7±4.82
Participants with *Combined use* at Week 6 (n=217)	**9.3 ±6.34**	**8.9±6.21**	4.8±3.72	4.1±3.06
Participants with *CC use* at Week 6 (n=607)	**10.9 ±7.69**	**9.9±6.75**	8.3±6.32	1.7±1.99
Overall (FAS) (n=1106)	10.2 ±7.22	9.3±6.56	6.3±5.78	3.0±3.57

n= number of values reported, CC= conventional cigarette; SD= Standard Deviation, FAS= Full Analysis Set.
Data Source: Appendix 15.2; FAS, Table 15.2.3.11, Table 15.2.4.1, 15.2.4.2; Appendix 15.2; FAS By usage Week 6, Table 15.2.3.11, Table 15.2.4.1, 15.2.4.2

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Product Assessment

Assessment of ease to use THS and sensorial experience are summarized in Table 21 for the overall FAS and for participants who reported *THS Tobacco Stick use* at Week 6.

For the overall FAS, slightly less than a third of the participants liked the taste (30.2%), smell (31.5%) and aftertaste (26.4%) and about half of the participants (53.1%) rated THS as easy to use (53.1%).

For participants with *THS Tobacco Stick use* at Week 6, about two thirds (taste: 60.9%) and slightly less than half (smell: 47.8% and aftertaste: 46.4%) liked the product. The vast majority of the participants (81.9%) rated THS as easy to use.

Table 21 Summary of Product Assessment - Follow-up Interview #4 in THS-PBA-07-US

			Sensorial Experience		
		Ease of Use	Taste	Smell	Aftertaste
All (FAS)					
Rating					
	n	985	985	985	985
1-4		462 (46.9%)	687 (69.7%)	672 (68.2%)	723 (73.4%)
5-7		523 (53.1%)	297 (30.2%)	310 (31.5%)	260 (26.4%)
Don't know		0	1 (0.1%)	3 (0.3%)	2 (0.2%)
Participants with THS Tobacco Stick use pattern at Week 6					
Rating					
	n	138	138	138	138
1-4		25 (18.1%)	54 (39.1%)	72 (52.2%)	74 (53.6%)
5-7		113 (81.9%)	84 (60.9%)	66 (47.8%)	64 (46.4%)
Don't know		0	0	0	0

N=number of values reported
Note: Ease of use was rated on a 7-point scale ranging from 1=Not easy to use at all; 7=Very easy to use. Rating is summarized as % responses 1 to 4 and % responses 5 to 7 (positive rating)
Note: Sensorial experience, including Taste, Smell and aftertaste were rated on a 7-point scale ranging from 1=I don't like it at all; 7=I like it very much. Rating is summarized as % responses 1 to 4 and % responses 5 to 7 (positive rating).
Note: Follow Up interview #4 was conducted at Week 6.
Data Source: THS-PBA-07-US Appendix 15.2, FAS Table 15.2.6.37, Table 15.2.6.12, Table 15.2.6.14, Table 15.2.6.16; FAS_ByUsageW6 Table 15.2.6.37, Table 15.2.6.12, Table 15.2.6.14, Table 15.2.6.16

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Participants reported that they were using the product in a variety of places (e.g., home, work, bar/restaurant/nightclubs), primarily when alone (68.4%), and more often outside of public places, even though 27.2% of participants often or sometimes used inside a bar/restaurant/nightclub and 15.4% often/sometimes used it inside at work.

Reported Misuse

A total of 47 FAS participants reported using THS Tobacco Sticks without the THS Device. Of those, 23 reported 1 occasion of misuse, 14 reported 2 to 4 occasions, 7 reported 5 to 9 occasions, and 3 reported misuse 10 times or more. Of the 47 participants, 46 lit the THS Tobacco Sticks like a CC and 1 participant chewed it.

Two participants used the THS Device with a product other than THS Tobacco Sticks. One participant used it on 1 occasion with marijuana, the second used it on 10 or more occasions using CC instead of using THS Tobacco Sticks.

Conclusions

In summary, this study showed that 15% of adult daily smokers were able to adopt THS (i.e., *THS Tobacco Stick use*) at the end of a 6-week usage period, after being exposed only once to the product communication including a reduced risk claim at screening. The proportion was relatively constant during the observational period of the study. This was further confirmed by the fact that 63% of participants who adopted THS at the end of the observational period, had already done it in the first 3 weeks of the observational period. THS was somewhat more attractive for adult smokers who were: male, aged above 25 years, Black or African American, Hispanic or Latino, with moderate education level, reporting smoking fewer cigarettes per day when entering in the study, and favoring menthol cigarettes.

A certain proportion of participants reported *Combined use* over the course of the observational period, however this proportion decreased over time and, on average, CC consumption was reduced by half for participants with *Combined use* at Week 6 compared to their baseline CC consumption. For those who reported *THS Tobacco Stick use* as early as Week 1, the likelihood of moving back to predominant CC use was low.

Findings on overall tobacco consumption indicated that the availability of THS did not lead to any increase in daily average total tobacco product consumption (CC+THS Tobacco Sticks). Finally, THS was overall used as intended.

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6.2.2.4.1.3.2 Whole Offer Tests (WOTs)

The main purpose of WOT market research studies was to evaluate in 5 countries adult smokers' response to different elements of the THS offer (e.g., pack design and other branded materials) and the likelihood of switching from CC to THS. More details can be found in the summary report [WOTSTUDYREPORT].

6.2.2.4.1.3.2.1 Methodology of the Whole Offer Test

A description of study methods is presented in Table 22.

Table 22 Methodology of The Whole Offer Test

Study Title: Analysis of Whole Offer Test Data Japan, Italy, Germany, Switzerland, and South Korea
Study design: A single group, observational study of THS in 5 countries (Japan, Italy, Germany, Switzerland and South Korea), involving an assessment of participants' self-reported stick-by-stick consumption of THS Tobacco Sticks and CC during a 4-week observational period where participants took THS home and were able to consume THS Tobacco Sticks, and CC *ad libitum*.
Subjects: Full Analysis Set (FAS) Japan: 638; FAS Italy: 535; FAS Germany: 377; FAS Switzerland: 416; FAS South Korea[1]: 843.
Main criteria for inclusion: • Aged 1 year above the country legal smoking age. Upper age limit was 64 years • Residing in the country for at least 1 year • Smokers having smoked at least 100 CC since reaching legal smoking age, currently smoking at least 3 CC per day for at least 6 months, and having smoked the last 7 days. • Non-negative purchase interest (scoring at least 3 on a purchase intention scale from 1 to 5 [1 = definitely not, 5 = definitely]) after trying a single THS Tobacco Stick
Test Product: Tobacco Heating System 2.2 (THS 2.2) regular and menthol variants. *Ad-libitum* use
Duration of Use: Observational period of 4 weeks
Methods: Participants received THS Tobacco Sticks free of charge and were able to consume THS Tobacco Sticks of both regular and menthol variants. Depending on the country, respondents were given Regular THS Tobacco Sticks or either Regular THS Tobacco Sticks or Menthol Tobacco Sticks (Regular THS Tobacco Sticks only in Italy and Germany; either Regular THS Tobacco Sticks or Menthol THS Tobacco Sticks in Japan, Switzerland and Korea). CC and other nicotine-containing products could be consumed *ad libitum* at the expense of the participants. Subjects were requested to make an entry into a paper and pencil diary every time they consumed a THS Tobacco Stick or CC during the 4-week observational period.

(table continues)

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Criteria of evaluation:

Use patterns

THS use patterns described per week according to 3 usage categories:

- "THS Tobacco Sticks use" (≥ 70% of tobacco products used are THS Tobacco Sticks)
- "Combined use" (>30% and <70% of tobacco products used are THS Tobacco Sticks)
- "CC use" (≤ 30% of tobacco products used are THS Tobacco Sticks)

Analysis of usage categories over different time points via transition tables, created for each week to any other posterior week in the observational period starting with week 0 (i.e. Baseline period).

Levels of Consumption

Average daily consumption of THS and CC during the observational period in comparison to Baseline consumption of CC as reported by the study participant in their paper and pencil diary.

[1] In South Korea, the sample consisted of male participants only.

6.2.2.4.1.3.2.2 Results of the Whole Offer Test

Use Patterns during the 4 weeks observational period

A summary of product use patterns according to product usage categories (as defined in Section 6.2.2.3.1.3 and summarized in Table 22) is tabulated in Table 23 for each of the 5 countries during the 4 weeks observational period. At Week 4, between 9.9% (Switzerland) and 37.1% (South Korea) of the study participants reported *THS Tobacco Sticks use*. The number of participants with *Combined use* was reduced by Week 4 in all countries compared to Week 1 (ranging from 27.3% and 39.4% across the 5 countries in Week 4), whereas the proportion of participants with *CC use* ranged between 25.9% (South Korea) and 51.2% (Italy) at Week 4.

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Table 23 Product Use by Usage Category and by Week in 5 WOTs

n (% column) *95% CI (%,%)*	Week 1	Week 2	Week 3	Week 4
Japan (n=638)				
THS Tobacco Stick use	130 (20.4)	161 (25.2)	185 (29.0)	190 (29.8)
	(17.3, 23.7)	(21.9, 28.8)	(25.5, 32.7)	(26.6, 33.5)
Exclusive THS Tobacco Stick use	20 (3.1)	58 (9.1)	74 (11.6)	87 (13.6)
	(1.9, 4.8)	(6.98, 11.6)	(9.22, 14.3)	(11.07, 16.6)
Predominant THS Tobacco Stick use	110 (17.2)	103 (16.1)	111 (17.4)	103 (16.1)
	(14.4, 20.4)	(13.4, 19.2)	(14.5, 20.6)	(13.4, 19.2)
Combined use	277 (43.4)	229 (35.9)	209 (32.8)	206 (32.3)
	(39.5, 47.4)	(32.8, 39.8)	(29.1, 36.6)	(28.7, 36.1)
CC use	231 (36.2)	248 (38.9)	244 (38.2)	241 (37.8)
	(32.5, 40.1)	(35.1, 42.8)	(34.5, 42.1)	(34.0, 41.7)
Exclusive CC use	18 (2.8)	51 (8.0)	64 (10.0)	64 (10.0)
	(1.7, 4.4)	(6.0, 10.4)	(7.8, 12.6)	(7.8, 12.6)
Predominant CC use	213 (33.4)	197 (30.9)	180 (28.2)	177 (27.7)
	(29.7, 37.2)	(27.3, 34.6)	(24.8, 31.9)	(24.3, 31.4)
No CC or THS Tobacco Stick use	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
	(0.0, 0.6)	(0.0, 0.6)	(0.0, 0.6)	(0.0, 0.9)
Italy (n=535)				
THS Tobacco Stick use	66 (12.3)	76 (14.2)	65 (12.2)	65 (12.2)
	(9.7, 15.4)	(11.4, 17.5)	(9.5, 15.2)	(9.5, 15.2)
Exclusive THS Tobacco Stick use	11 (2.1)	19 (3.6)	23 (4.3)	28 (5.2)
	(1.0, 3.7)	(2.2, 5.5)	(2.7, 6.4)	(3.5, 7.5)
Predominant THS Tobacco Stick use	55 (10.3)	57 (10.7)	42 (7.9)	37 (6.9)
	(7.8, 13.2)	(8.2, 13.6)	(5.7, 10.5)	(4.9, 9.4)
Combined use	256 (47.9)	229 (42.8)	204 (38.1)	203 (37.9)
	(43.6, 52.2)	(38.6, 47.1)	(34.0, 42.4)	(33.8, 42.2)
CC use	213 (39.8)	230 (43.0)	266 (49.7)	267 (49.9)
	(35.6, 44.1)	(38.8, 47.3)	(45.4, 54.0)	(45.6, 54.2)
Exclusive CC use	14 (2.6)	34 (6.4)	37 (6.9)	57 (10.7)
	(1.4, 4.4)	(4.4, 8.8)	(4.9, 9.4)	(8.2, 13.6)
Predominant CC use	199 (37.2)	196 (36.6)	229 (42.8)	210 (39.3)
	(33.1, 41.5)	(32.5, 40.9)	(38.6, 47.1)	(35.1, 43.5)
No CC or THS Tobacco Stick use	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	(0.0, 0.7)	(0.0, 0.7)	(0.0, 0.7)	(0.0, 0.7)

(table continues)

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n (% column) *95% CI (%,%)*	Week 1	Week 2	Week 3	Week 4
Germany (n=377)				
THS Tobacco Stick use	71 (18.8)	70 (18.6)	73 (19.4)	75 (19.9)
	(15.0, 23.2)	(14.8, 22.9)	(15.5, 23.7)	(16.0, 24.3)
Exclusive THS Tobacco Stick use	14 (3.7)	20 (5.3)	28 (7.4)	32 (8.5)
	(2.0, 6.2)	(3.3, 8.1)	(5.0, 10.6)	(5.9, 11.8)
Predominant THS Tobacco Stick use	57 (15.1)	50 (13.3)	45 (11.9)	43 (11.4)
	(11.7, 19.1)	(10.0, 17.1)	(8.8, 15.6)	(8.4, 15.1)
Combined use	176 (46.7)	141 (37.4)	131 (34.8)	103 (27.3)
	(41.6, 51.9)	(32.5, 42.5)	(30.0, 39.8)	(22.9, 32.1)
CC use	130 (34.5)	164 (43.5)	170 (45.1)	193 (51.2)
	(29.7, 39.5)	(38.4, 48.7)	(40.0, 50.3)	(46.0, 56.4)
Exclusive CC use	17 (4.5)	58 (15.4)	80 (21.2)	100 (26.5)
	(2.7, 7.1)	(11.9, 19.4)	(17.2, 25.7)	(22.2, 31.3)
Predominant CC use	113 (30.0)	106 (28.1)	90 (23.8)	93 (24.7)
	(25.4, 34.9)	(23.6, 33.0)	(19.7, 28.5)	(20.4, 29.4)
No CC or THS Tobacco Stick use	0 (0.0)	2 (0.5)	3 (0.8)	6 (1.6)
	(0.0, 1.0)	(0.1, 1.9)	(0.2, 2.3)	(0.6, 3.4)
Switzerland (n=416)				
THS Tobacco Stick use	49 (11.8)	49 (11.8)	50 (12.0)	41 (9.9)
	(8.8, 15.3)	(8.8, 15.3)	(9.1, 15.5)	(7.2, 13.1)
Exclusive THS Tobacco Stick use	10 (2.4)	14 (3.4)	22 (5.3)	18 (4.3)
	(1.2, 4.4)	(1.9, 5.6)	(3.4, 7.9)	(2.6, 6.8)
Predominant THS Tobacco Stick use	39 (9.4)	35 (8.4)	28 (6.7)	23 (5.5)
	(6.8, 12.6)	(5.9, 11.5)	(4.5, 9.6)	(3.5, 8.2)
Combined use	200 (48.1)	179 (43.0)	165 (39.7)	164 (39.4)
	(43.2, 53.0)	(38.2, 47.9)	(34.9, 44.5)	(34.7, 44.3)
CC use	167 (40.1)	186 (44.7)	199 (47.8)	210 (50.5)
	(35.4, 45.0)	(39.8, 49.6)	(43.0, 52.8)	(45.6, 55.4)
Exclusive THS Tobacco Stick use	16 (3.9)	42 (10.1)	66 (15.9)	83 (20.1)
	(2.2, 6.2)	(7.4, 13.4)	(12.5, 19.7)	(16.2, 24.1)
Predominant THS Tobacco Stick use	151 (36.3)	144 (34.6)	133 (32.0)	127 (30.5)
	(31.7, 41.1)	(30.1, 39.4)	(27.5, 36.7)	(26.1, 35.2)
No CC or THS Tobacco Stick use	0 (0.0)	2 (0.5)	2 (0.5)	1 (0.2)
	(0.0, 0.9)	(0.1, 1.7)	(0.1, 1.7)	(0.0, 1.3)

(table continues)

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n (% column) *95% CI (%,%)*	Week 1	Week 2	Week 3	Week 4
South Korea (n=843)				
THS Tobacco Stick use	294 (34.9)	333 (39.5)	334 (39.6)	313 (37.1)
	(31.7, 38.2)	(36.2, 42.9)	(36.3, 43.0)	(33.7, 40.5)
Exclusive THS Tobacco Stick use	219 (26.0)	211 (25.0)	187 (22.2)	181 (21.5)
	(23.1, 29.1)	(22.1, 28.1)	(19.4, 25.1)	(18.7, 24.4)
Predominant THS Tobacco Stick use	75 (8.9)	122 (14.5)	147 (17.5)	132 (15.7)
	(7.1, 11.0)	(12.2, 17.0)	(14.9, 20.2)	(13.3, 18.3)
Combined use	408 (48.4)	336 (39.9)	318 (37.7)	306 (36.3)
	(45.0, 51.8)	(36.5, 43.3)	(34.4, 41.1)	(33.1, 39.7)
CC use	140 (16.6)	173 (20.5)	186 (22.1)	218 (25.9)
	(14.2, 19.3)	(17.8, 23.4)	(19.3, 25.0)	(22.9, 29.0)
Exclusive CC use	8 (1.0)	34 (4.0)	49 (5.8)	72 (8.5)
	(0.4, 1.9)	(2.8, 5.6)	(4.3, 7.6)	(6.7, 10.6)
Predominant CC use	132 (15.7)	139 (16.5)	137 (16.3)	146 (17.3)
	(13.3, 18.3)	(14.1, 19.2)	(13.8, 18.9)	(14.8, 20.1)
No CC or THS Tobacco Stick use	1 (0.1)	1 (0.1)	5 (0.6)	6 (0.7)
	(0.0, 0.7)	(0.0, 0.7)	(0.2, 1.4)	(0.3, 1.5)

n= number of values reported, CC= conventional cigarette; CI= Confidence Interval.
Data Source: WOTSTUDYREPORT, Table 11-6, Table 11-7, Table 11-14, Table 11-15, Table 11-22, Table 11-23, Table 11-30, Table 11-31, Table 11-38, Table 11-39.

Analysis of the quantity of THS Tobacco Sticks used during the total observational period provided additional information on product adoption in the different countries. The proportion of study participants who met the definition of established user according to WHO (IARC (International Agency for Research on Cancer) 2008), i.e., they consumed ≥ 100 THS Tobacco Sticks during the observational period, ranged from 36.1% to 76.3% across the five countries (Japan: 61.3%; Italy 36.1%; Germany: 50.1%; Switzerland: 49.5%; South Korea: 76.3%). Across the 5 countries, the proportion of participants passing the threshold of 100 THS Tobacco Sticks peaked in study Weeks 2 or 3, and declined in study Week 4.

Transition tables of the 3 usage categories from Week 1 to Week 4 are provided in Appendix A.6.2.2.2 for all 5 countries. From these tables, additional information was extracted on how participants transitioned to *THS Tobacco Stick use, CC use and Combined use*. Of the participants who reported *THS Tobacco Stick use* at Week 4, between 53.7% (Japan) and 68.1% (South Korea) reported *THS Tobacco Stick use* already at Week 1. Of the participants who reported *THS Tobacco Stick use* at Week 1, between 0.8% (Japan) and 12.2% (Switzerland) went back *CC use* at Week 4. Of the participants who reported *Combined use* at Week 1, between 46.0% (Germany) and

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58.5% (Switzerland) remained with *Combined use* at Week 4, between 9.4% (Italy) and 27.4% (Japan) transitioned to *THS Tobacco Stick use* and between 22.7% (Japan) and 39.8% (Germany) went back to *CC use*.

Levels of Tobacco Consumption at Baseline and during the Observational Period

A summary of tobacco consumption during the observational period is provided in Table 24. The average number of tobacco products (CC and THS Tobacco Sticks) consumed per day during the observational period ranged from 10.1 (Italy) to 14.6 (Japan). The daily average total tobacco consumption was approximately 2 sticks lower than the self-reported consumption of CCs prior to the observational period. This was consistent across all countries and study weeks.

In summary, the results of WOTs show that between 10% and 37% of adult daily smokers, depending of the country, were able to adopt THS as a substitute to their CC. For those who reported *THS Tobacco Stick use* as early as Week 1, the likelihood of moving back to *CC use* was low. Findings indicate that a certain proportion of adult daily smokers used CC and THS combined. However, data also indicates that this proportion decreased over time, with smokers returning to *CC use* in Week 4 or, to a less extent, transitioning towards *THS Tobacco Stick use*. Findings on overall tobacco consumption indicate that the availability of THS did not lead to an increase in daily average total tobacco product consumption (CC+THS Tobacco Sticks) during the 4 weeks period. Some variation of the level of THS adoption between European countries on one hand and Asian countries on the other hand was observed.

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Table 24 Average Daily Consumption of THS Tobacco Sticks and CC in Week 4 and Difference to Daily Average CC Consumption at Screening for WOTs

		JP	IT	DE	CH	KR
		Study Week 4	Study Week 4	Study Week 4	Study Week 4	Study Week 4
	n	638	535	377	416	843
Daily average Tobacco Consumption (THS Tobacco Sticks+CC)	Mean ±SD	14.57±7.76	10.13±5.56	12.64±7.35	14.31±7.77	14.00±6.98
	95% CI	[13.97, 15.17]	[9.66, 10.60]	[11.89, 13.38]	[13.56, 15.05]	[13.53, 14.48]
Difference: (THS Tobacco Sticks+CC) in Week 4 – (self-reported CC daily consumption prior starting the observational period)	Mean ±SD	-1.95±4.42	-2.57±5.42	-4.72±6.84	-2.95±6.54	-1.17±6.02
	95% CI	[-2.30, -1.61]	[-3.03, -2.11]	[-5.41, -4.03]	[-3.58, -2.32]	[-1.57, -0.76]

Abbreviations: CH = Switzerland; DE = Germany; IT = Italy; JP = Japan; KR = South Korea; SD = Standard Deviation; CI = Confidence Interval.
Note: In each cell, the mean is the average number of the sum of THS Tobacco Sticks and CC consumed per day in Week 4.
Note: Difference with a negative value indicates that daily average combined THS Tobacco Sticks+CC consumption in Week 4 is lower than self-reported CC daily consumption prior starting the observational period.
Data Source: WOTSTUDYREPORT, Table 11-8, Table 11-16, Table 11-24, Table 11-32, Table 11-40.

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6.2.2.4.1.3.3 Conclusions across Observational Studies

Observational Actual Use studies represent the most appropriate study design to approximate real-world conditions in a premarket environment, in which the product is not yet commercially available to the public. To address the requirements from the FDA Draft Guidance on the effect of THS on tobacco use behavior among tobacco users, The THS-PBA-07-US Actual Use Study was designed as a single group, prospective observational study, in which subjects reported stick-by-stick consumption of THS Tobacco Sticks and of CC. Data derived from this study provided pre-market insights on (i) the likelihood that the product will be adopted by US daily smokers (level of product consumption, sensory acceptance, easiness to use), (ii) the likelihood that US daily smokers will switch to THS, use it with other tobacco products, or switch back to CC, and (iii) the likelihood that users may consume THS in a manner that may differ from the intended use.

The **strength** of THS-PBA-07-US is the fact that US adult daily smokers of CC used THS Tobacco Sticks, CC and other products containing nicotine in a near to real-world conditions, without any specific restrictions. **Additional strengths** of this study were:

- The study was conducted in 8 metropolitan sites geographically diverse and spread out across the US.
- The sampling method aimed at approximating the adult smoker distribution contained in the report published by the CDC in 2012.
- The length of the study allowed enough time for the participant to try, experiment and use the investigational product over a long period of time.
- The study participants were able to receive and/or order THS Tobacco Sticks through multiple channels (i.e., by going to the mall facilities, by calling the hotline), making the product easily available throughout the entire observational period.
- The study participants had access to both regular THS Tobacco Sticks and menthol THS Tobacco Sticks depending on their personal choice, closely reflecting the situation of both variants being available in the market.

However, the THS-PBA-07-US study has certain **limitations** mainly inherent to the fact that the study was conducted in a premarket environment. In particular:

- Study participants did not pay for the THS tobacco Sticks, while they continued to pay for their CC or any other nicotine containing products.
- Information regarding THS could not be actively disseminated, e.g., through product communication or exchange information, opinions and perceptions with other CC smokers, with a potential impact on how some participants may have used the product.
- Study participants were reimbursed for their study participation. However, participants received their compensation after their completion of the study, limiting the impact of the compensation on their tobacco consumption/behavior during the observational period.

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Supportive evidence was presented with similar data collected pre-market in 3 European countries (Italy, Germany, Switzerland) and 2 Asian countries (Japan and Korea). The overall findings provide consistent evidence across the different studies that THS has the potential to be adopted by adult daily smokers (about 10% to 37% of participants across the US and all 5 countries where WOTs were conducted used THS tobacco sticks predominantly or exclusively at the end of the obsevervational period). Results also indicate that the smokers who adapted rapidly to THS were more likely to adopt a continued use of THS and thus less likely to switch back to CC.

The proportion of participants with *CC use* at the end of the usage period varied between 26% and 63% across the different studies. This proportion tended to increase over the course of the usage period, suggesting that smokers who could not adapt rapidly to THS went back to smoking CC. This result may reflect the relative resistance of daily smokers to adopt a new tobacco product which differs from their usual smoking ritual. The overall results also provide insights on cultural taste preferences and ability to adapt to new tobacco products.

Although a certain proportion of participants still reported *Combined use* of THS and CC at the end of the usage period (between 22% and 39% of participants depending of the country), none of the findings from all 6 countries pointed towards the availability of THS leading to an increase in daily average total tobacco product consumption (CC+THS Tobacco Sticks). This suggests that, even if THS was used in conjunction with CC, consumption of CC decreased during the observational period.

6.2.2.4.2 Behavioral Intention

6.2.2.4.2.1 THS-PBA-02-US Study

The main purpose of the THS-PBA-02-US study was to contribute to the development of THS potential product messages by exploring how each element of different messages contributes to the comprehension of the modified risk information, intent to use THS, and risk perception of THS compared to other tobacco and nicotine-containing products, and compared to quitting tobacco use. More details can be found in the summary and full report of the study [Section 7.3.2].

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6.2.2.4.2.1.1 Methodology of the THS-PBA-02-US

A brief description of study methods is provided in Table 25.

Table 25 Methodology of THS-PBA-02-US

Study Title: Qualitative Study to Develop THS 2.2 Hypothetical Product Messages
Study Design: 4-cities, 2-phase, sequential, qualitative study. Phase 1 'Product Message Development' consisted of 1 pilot focus group discussion (FGD) and 20 FGDs, where participants shared their opinions and reactions to a variety of discussion topics in an interactive group setting to contribute to the development and refinement of the THS product messages. Phase 2 'Product Message Understanding' consisted of 1 pilot individual interview (IDI) and 37 IDIs conducted to collect detailed perceptions, opinions, beliefs, and attitudes of participants as well as of evaluating the clarity of the revised product messages resulting from Phase 1.
Subjects: Enrolled: 123 in FGDs and 38 in IDIs; Full analysis population (FAP): 117 in FGDs and 37 in IDIs; Number of adult smokers in the FAP: 93 in FGDs and 25 in IDIs; Number of adult former smokers in the FAP: 24 in FGDs and 6 IDIs; Number of adult never smokers in the FAP: 6 (IDIs).
Main Criteria for Inclusion: • Aged 21 or older • Adult Smokers with no Intention to Quit CC: currently smoking at least 1 CC/day, started more than 30 days ago with no intention to quit within 6 months; Adult Smokers with Intention to Quit CC: currently smoking at least 1 CC/day, started more than 30 days ago with the intention to quit within 6 months ; Adult Former Smokers: quit smoking CC more than 30 days ago; Adult Never Smokers (Phase 2 only): never smoked or never smoked daily and less than 100 CC
Criteria of Evaluation: Verbal data, transcribed from the FGDs and IDIs, were examined for each potential product message in general, and by smoking status in particular, to identify the extent of endorsement.

Nine product messages were assessed in Phase 1 and 7 in Phase 2 as a result of refinement and revisions to the product messages tested in Phase 1.

The structure of the messages was identical across all messages and composed of information concerning THS features, risks, claims and intended users. The elements in the left panel included the "**Information**" and the "**Intended Users"** sections, which were constant across all the potential product messages tested. The elements in the right panel included the "**Evidence to Date"** and "**Important Warning"** sections and varied depending on the type of modified risk claim. An example is given in Figure 33.

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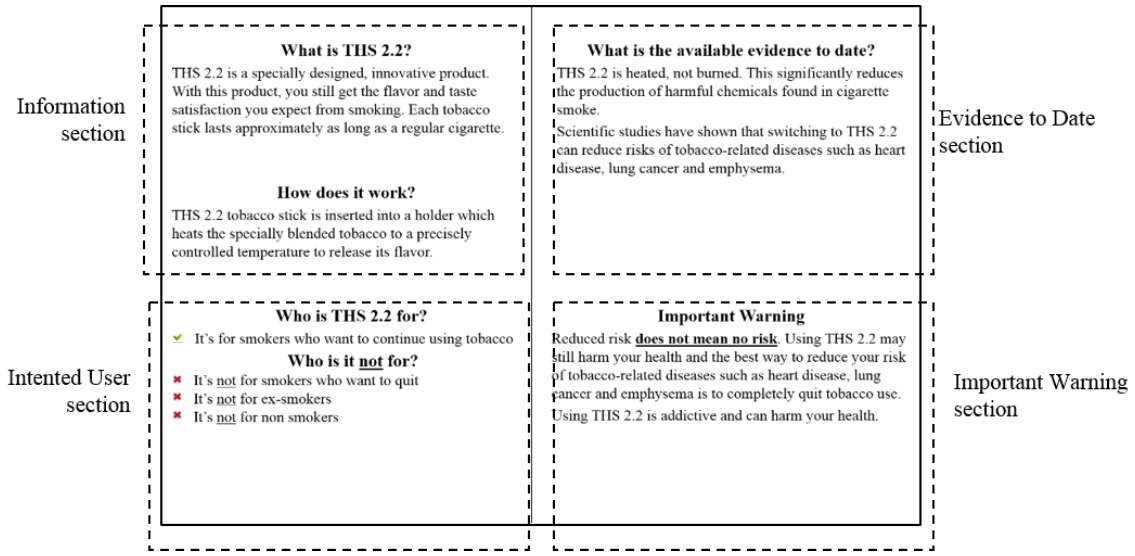


Figure 33 Example of a THS Potential Product Message

A summary of the modified risk claims assessed in THS-PBA-02-US are shown in Table 26 for Phase 1 and Phase 2.

Table 26 THS Potential Product Messages tested in THS-PBA-02-US

	Phase 1	
	Specific Potential Claims	**General Potential Claims**
Reduced Exposure	**A**. With THS 2.2, the production of carbon monoxide is reduced by more than 95%	**C**. Switching to THS 2.2 significantly reduces your body's exposure to many harmful chemicals found in cigarette smoke which are identified as likely causes of smoking-related diseases
	B. THS 2.2 produces at least 90% less second-hand smoke than CCs	**D**. THS 2.2 significantly reduces the production of harmful chemicals found in cigarette smoke
Reduced Risk	**E**. Switching to THS 2.2 can lower your cardiovascular disease risks	**H**. Switching to THS 2.2 can lower several risk factors that could lead to smoking-related diseases
	F. Switching to THS 2.2 improves several biomarkers, which are seen as early indicators of emphysema	**J**. Switching to THS 2.2 can reduce risks of smoking-related diseases
	G. Switching to THS 2.2 can improve the level of good cholesterol and can reduce the risk of clogging of arteries due to smoking	

(table continues)

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Phase 2

	Specific Potential Claims	General Potential Claims
Reduced Exposure	**B**. THS 2.2 produces at least 90% less second-hand smoke than CCs	**C**. Switching to THS 2.2 significantly reduces your body's exposure to many harmful chemicals found in cigarette smoke which are identified as likely causes of tobacco-related diseases
	L. THS 2.2 significantly reduces the production of harmful chemicals, such as carbon monoxide which is reduced by 95%, found in cigarette smoke	
Reduced Risk	**E**. Switching to THS 2.2 can lower your cardiovascular disease risks	**H**. Switching to THS 2.2 can lower several risk factors that could lead to tobacco-related diseases
	K. Switching to THS 2.2 can improve lung function	**J**. Switching to THS 2.2 can reduce risks of tobacco-related diseases

Data Source: THS-PBA-02-US Study Report Appendix c

6.2.2.4.2.1.2 Results of THS-PBA-02-US

In general, participants' comments indicated that the THS product messages generated an intent to use in adult smokers. Among adult smokers with no intention to quit, intent to use was driven by the fact that THS has the flavor and taste satisfaction of a CC yet because it is heated, not burned, there is a significant reduction of the production of harmful chemicals found in CC smoke. Some of the adult smokers with the intention to quit viewed THS as a potentially lower risk alternative that could be used as a 'step down' product, as a means to help them on their way to quitting smoking. For them, THS was understood not to be a substitute to cessation.

Below verbatims are shown for illustrative purposes:

> *"I would be willing to pay more upfront if you could still get all the benefits ... well there is no benefit to smoking, but if you could get all the things that you enjoy about smoking without the harmful chemicals and components."* (Adult smoker, male, 21-35, Charlotte)

> *"Well just another alternative I guess for people who want to quit whether they want to try the Nicoderm stuff or ultra-light [tasting cigarettes] or e-cigarette or the patch. Just another alternative it sounds like to me."* (Adult smoker motivated to quit, male, 51+, Phoenix)

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THS product messages that resonated most strongly among the intended audience (i.e. adult smokers with no intention to quit) included a relevant benefit. Along with relevancy, product messages that resonated most strongly were perceived as honest and straight-forward, and using wording that is easily understood.

Product Message J (reduced risk, general claim), Product Message C (reduced exposure, general claim) and Product Messages L and B (reduced exposure, specific claim) resonated with adult smokers with no intention to quit. The common elements of these 4 product messages were that they are broadly relevant, easy to understand and come across as honest, straight-forward and credible. It is these factors that are most important when formulating product messaging for THS. In addition, including references to flavor and taste satisfaction help position THS for adult smokers with no intention to quit and allay sensory concerns this intended audience might have about the usage experience.

Below verbatims are shown for illustrative purposes:

> *"Because of the reduction in the risk…if their message is designed to give you the satisfaction, flavor and taste of a cigarette, and they're reducing the risk of harmful chemicals, and the probability of reducing diseases, it's a positive message for a smoker. (A positive message for) somebody who's concerned about their health. That's a great idea to heat instead of burn if it has all these benefits, I think it's great."* (Adult smoker, male, 51+, Charlotte)
>
> *"Not burned, that's very intriguing. Reduce the production of harmful materials in cigarette smoke. Scientific studies. Human nature when you see scientific studies you sort of like give it the more positive than negative."* (Adult smoker, male, 51+, Boston)
>
> *"I think the Important Warning was just way more blunt and to the point. It just lays it out. No sugar-coating it. It just gives you the facts. Although it reduces risk it's still there."* (Adult smoker, female, 21-35, Phoenix)

In brief, the qualitative findings obtained in THS-PBA-02-US allowed to make a short selection of potential claims out of the initial pool of messages tested. Three core messages were selected and carried over in THS-PBA-03-US and THS-PBA-04-US studies.

6.2.2.4.2.2 THS-PBA-03-US Study

The overall aim of the THS-PBA-03-US study was to further inform the selection of appropriate THS communication using quantitative assessment of 5 potential "plain text" THS messages in terms of Intent to Use THS, Comprehension of different communication objectives, Risk Perception of THS and the comparators CC, Nicotine Replacement Therapies (NRTs), E-cigarettes, and Cessation. Change in Intention to Quit Smoking within adult smokers was also assessed as part of the Study. More details can be found in the summary and full report of the study (Section 7.3.2).

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6.2.2.4.2.2.1 Methodology of THS-PBA-03-US

A brief description of study methods is provided in Table 27.

Table 27 Methodology of THS-PBA-03-US

Study Title: Study to Quantitatively Assess THS 2.2 Potential Messages

Study design: 4-cities, 5-arm parallel-group experiment. The 5 arms corresponded to the 5 different THS messages, each of them being tested by approximately equal numbers of subjects from different smoking status groups.

Subjects: *Full Sample* for analysis: 1713; Number of Adult Smokers with no Intention to Quit CC included in the *Main Sample*: 359; Number of Adult Smokers with Intention to Quit CC included in the *Main Sample*: 355; Number of Adult Former Smokers included in the *Main Sample*: 358; Number of Adult Never Smokers included in the *Main Sample*: 362; Number of Adult Never Smokers from the legal age of smoking to 25 years of age (*LA-25 Adult Never Smokers*) included in the *Full Sample*: 358 (including 79 from the main sample).

Main criteria for inclusion:

- Aged 18 and above, or above state legal smoking age if above 18 years
- Adult Smokers with no Intention to Quit CC: currently smoking at least 1 CC/day, started more than 30 days ago with no intention to quit within 6 months; Adult Smokers with Intention to Quit CC: currently smoking at least 1 CC/day, started more than 30 days ago with the intention to quit within 6 months; Adult Former Smokers: quit smoking CC more than 30 days ago; Adult Never Smokers: never smoked or never smoked daily and less than 100 CC

Methods:

Intent to Use

2 sets of items from the Intent to Use Questionnaire (ITUQ) yielded descriptive measures of:

- Intention to Try (i.e., to sample at least once; 2 items)
- Intention to Use (i.e., for continued usage; 2 items)

Change in Intention to Quit Smoking (Only for Adult Smokers)

Closed-ended questions based on Prochaska and DiClemente's Stages of Change model (Prochaska 1983) measured before and after exposure to THS message to determine change in Intention to Quit Smoking

Criteria for Evaluation:

Intent to Use:

Positive Intention to Try THS (operationalized as the sum of % Very Likely and % Definitely responses for each item of Intention to Try) and Positive Intention to Use THS (operationalized as the sum of % Very Likely and % Definitely responses for the first item of Intention to Use), by study arm and smoking status group.

Change in Intention to Quit Smoking:

Change in Intention to Quit Smoking and All Tobacco, respectively, compared pre- and post-exposure to the THS material, by study arm.

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Five messages were tested through combinations of 3 claims (selected based on THS-PBA-02-US findings) and different warnings. A summary of the different combinations of modified risk claims and warnings assessed in THS-PBA-03-US are shown in Table 28.

Table 28 Different Combinations of Evidence Statements and Warnings Tested in THS-PBA-03-US

	Claim	Warning
Message 1 **Reduced Exposure**	With the exception of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals	• **It <u>has not been demonstrated</u>** that switching to THS 2.2 reduces the risk of developing tobacco-related diseases compared to smoking cigarettes. • THS 2.2 tobacco sticks contain nicotine which is addictive. • Using THS 2.2 can harm your health.
Message 2 **Reduced Exposure**	With the exception of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals	• A significant reduction in the production of harmful chemicals, compared to cigarettes, **<u>does not mean a reduction in the risk of developing tobacco-related diseases</u>.** • THS 2.2 tobacco sticks contain nicotine which is addictive. • Using THS 2.2 can harm your health.
Message 3 **Reduced Exposure**	Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals.	• **It <u>has not been demonstrated</u>** that switching to THS 2.2 reduces the risk of developing tobacco-related diseases compared to smoking cigarettes. • THS 2.2 tobacco sticks contain nicotine which is addictive. • Using THS 2.2 can harm your health.
Message 4 **Reduced Exposure**	Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals.	• A significant reduction in your body's exposure to harmful chemicals, compared to cigarettes, **<u>does not mean a reduction in the risk of developing tobacco-related diseases</u>.** • THS 2.2 tobacco sticks contain nicotine which is addictive. • Using THS 2.2 can harm your health.
Message 5 **Reduced Risk**	Scientific studies have shown that switching completely from cigarettes to THS 2.2 can reduce the risks of tobacco-related diseases.	• Reduced risk **<u>does not mean no risk</u>.** The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. • THS 2.2 tobacco sticks contain nicotine which is addictive. • Using THS 2.2 can harm your health.

Data Source: THS-PBA-03-US Study Report Appendix 16.1.1

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6.2.2.4.2.2.2 Results of THS-PBA-03-US

Intention to Try or Use THS in Adult Smokers with No Intention to Quit

Table 29 summarizes the numbers of Adult Smokers with No Intention to Quit who were willing to try THS and willing to use THS regularly. Within this group, positive intention to try THS ranged from 38.4% for Message 3 to 56.9% for Message 2. A majority of subjects across all message groups, from 51.4% of subjects in Message 2 to 65.3% of subjects in Message 4, stated they were willing to use THS regularly (Table 29).

Table 29 Proportion of Subjects with Positive Intention to Try and Intention to Use THS 2.2- Adult Smokers with No Intention to Quit in THS-PBA-03-US

		Message				
	Statistics	**1 (N=72)**	**2 (N=72)**	**3 (N=73)**	**4 (N=72)**	**5 (N=70)**
Positive Intention to Try THS 2.2						
	n (%)	36 (50.0)	41 (56.9)	28 (38.4)	37 (51.4)	34 (48.6)
	95% CI	(38.0, 62.0)	(44.7, 68.6)	(27.2, 50.5)	(39.3, 63.3)	(36.4, 60.8)
Positive Intention to Use THS 2.2 regularly						
	n (%)	40 (55.6)	37 (51.4)	39 (53.4)	47 (65.3)	44 (62.9)
	95% CI	(43.4, 67.3)	(39.3, 63.3)	(41.4, 65.2)	(53.1, 76.1)	(50.5, 74.1)

N=total sample size; n=number of values reported.
Abbreviations: CI, confidence interval; THS 2.2, Tobacco Heating System 2.2.
Note: the 95% confidence intervals are calculated using the exact Clopper-Pearson method.
Data Source Study report THS-PBA-03-US: Appendix 15, Table 15.2.2.1.

Intention to Try or Use THS in Adult Smokers with the Intention to Quit CC

Table 30 summarizes the numbers of Adult Smokers with the Intention to Quit CC who were willing to try or use THS regularly. Within this group, positive intention to try THS ranged from 35.7% for Message 3 to 53.6% for Message 4. The number of subjects who expressed a positive intention to use THS regularly ranged from 44.4% for Message 2 to 61.1% in Message 1 (Table 30).

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Table 30 Proportion of Subjects with Positive Intention to Try and Intention to Use THS 2.2- Adult Smokers With the intention to Quit CC in THS-PBA-03-US

		Message				
	Statistics	1 (N=75)	2 (N=72)	3 (N=71)	4 (N=69)	5 (N=68)
Positive Intention to Try THS 2.2						
	n (%)	34 (45.3)	29 (40.3)	25 (35.7)	37 (53.6)	31 (45.6)
	95% CI	(33.8, 57.3)	(28.9, 52.5)	(24.6, 48.1)	(41.2, 65.7)	(33.5, 58.1)
Positive Intention to Use THS 2.2 regularly						
	n (%)	46 (61.3)	32 (44.4)	33 (47.1)	37 (53.6)	38 (55.9)
	95% CI	(49.4, 72.4)	(32.7, 56.6)	(35.1, 59.4)	(41.2, 65.7)	(43.3, 67.9)

N=total sample size; n=number of values reported.
Abbreviations: CI = confidence interval; THS 2.2 = Tobacco Heating System 2.2.
Note: the 95% confidence intervals are calculated using the exact Clopper-Pearson method.
Data Source Study Report THS-PBA-03-US: Appendix 15, Table 15.2.2.1.

Intention to Quit in Adult Smokers with the Intention to Quit CC

Within Adult Smokers with the initial Intention to Quit CC (prior to exposure to the THS Messages), between 83% (Message 1 and 4) and 97% (Messages 3 and 5) of subjects across the different THS Messages still had the Intention to Quit CC after exposure to the THS Messages.

6.2.2.4.2.3 THS-PBA-04-US Study

Building upon the insights gained in THS-PBA-02-US and THS-PBA-03-US, the purpose of this qualitative study was to contribute to the development of THS potential label, labeling and marketing material. To this end, the study examined how each element of the materials contributes to the Comprehension of the modified risk information, Intent to Use THS, and Risk Perception of THS, compared to other tobacco and nicotine-containing products as well as to quitting tobacco use. More details can be found in the summary and full report of the study (Section 7.3.2).

6.2.2.4.2.3.1 Methodology of THS-PBA-04-US

A description of the study methods is provided in Table 31.

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Table 31 Methodology of THS-PBA-04-US

Study Title: Qualitative Study to Develop THS 2.2 Potential Label, Labeling and Marketing Material
Study design: 2-cities qualitative study, which consisted of 30 IDIs (including 2 pilot IDIs), designed to capture participants' comments and responses when exposed to specific label, labeling and marketing material.
Subjects: Enrolled: 30; Full analysis population (FAP): 28; Number of adult smokers in the FAP: 20; Number of adult former smokers in the FAP: 4; Number of adult never smokers in the FAP: 4.
Main Criteria for Inclusion: • Aged 18 or older • Adult Smokers: currently smoking at least 1 CC/day, started more than 30 days ago; Adult Former Smokers: quit smoking CC more than 30 days ago; Adult Never Smokers Phase 2 only: never smoked or never smoked daily and less than 100 CC
Methods: Moderators (5+ years of experience) were utilized to conduct the IDIs. A discussion guide was employed in each IDI in order to elicit participant feedback in a consistent manner across the various IDIs.
Criteria for Evaluation: Verbal data, transcribed from the FGDs and IDIs, were examined for each potential product message in general, and by smoking status in particular, to identify the extent of endorsement.

Five potential communication materials were assessed: (i) brochure, (ii) direct mail, (iii) advertising concept, (iv) point of sales advertisement, and (v) (b) (4) In the brochure and direct mail, 3 potential claims, selected on the basis of THS-PBA-02-US and THS-PBA-03-US findings, were included Table 32.

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Table 32 Modified Risk Claims Assessed in THS-PBA-04-US

Reduced Exposure A	Reduced Exposure B	Reduced Risk
• With the exception of nicotine, with the iQOS system there is a significant reduction in the production of harmful or potentially harmful chemicals.	• Scientific studies have shown that switching completely from cigarettes to the iQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.	• Scientific studies have shown that switching completely from cigarettes to the iQOS system can reduce the risks of tobacco-related diseases.
Important Warning A	**Important Warning B**	**Important Warning C**
• It **has not been demonstrated** that switching to the iQOS system reduces the risk of developing tobacco-related diseases compared to smoking cigarettes. • Heatsticks™ contain nicotine which is addictive. • Using the iQOS system can harm your health.	• A significant reduction in your body's exposure to harmful chemicals, compared to cigarettes, **does not mean a reduction in the risk of developing tobacco-related diseases**. • Heatsticks™ contain nicotine which is addictive. • Using the iQOS system can harm your health.	• Reduced risk **does not mean no risk**. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco-use. • Heatsticks™ contain nicotine which is addictive. • Using the iQOS system can harm your health.

Data Source: THS-PBA-04-US Study Report Appendix b
iQOS is the commercial name and registered trademark for THS. *Heatsticks* is the commercial name and registered trademark for THS Tobacco Sticks.

6.2.2.4.2.3.2 Results of THS-PBA-04-US

Results of the THS-PBA-04-US study showed that, by using the words real tobacco and/or tobacco heating system in communication materials, participants viewed the THS system as a tobacco product and understand that there is health risk associated with using it. The research demonstrated that the THS system was viewed as an innovative tobacco product because it heats, rather than burns, tobacco using electronic technology. The THS system was therefore described as able to combine the tobacco taste satisfaction of CC's with hygiene benefits (less odor, no ash, less mess) and the potential to present less risk of harm than to continue smoking CC. Understanding was found to be generally consistent across communication materials and subject groups. This resulted in (i) clarity that the THS system is for adult current smokers who want to continue using tobacco and not for former smokers or never smokers, (ii) favorable responses among adult current smokers to communication materials leading to some intention to use the THS system on an ongoing, regular basis, and (iii) the understanding that there is risk to health associated with the use of THS system.

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Below verbatims are shown for illustrative purposes:

> *"It's for smokers who want to continue to use tobacco. Who is it not for – for smokers who want to quit, it's not for ex-smokers…it is not for smokers who want to quit – I disagree with that because I want to quit. In the meantime I'd like to reduce…I'd like to maybe get into something a little bit different. This would help me; this would help me to quit."* (Adult smoker, male, 36-50, Chicago)
>
> *"I like that it shows all the things that you're getting – the charger, the cigarettes and then the actual heater. I like that it shows you everything that it is. I like the 'Real Tobacco No Fire' slogan. I would definitely be interested if I saw this. It would definitely grab my attention if I was just standing in line."* (Adult smoker, female, 18-25, Chicago)
>
> *"I feel like it was very clear…they're putting the print right in front of you – read it but this is the truth…they're saying that just because it reduces the risk does not mean it takes all risk out."* (Adult smoker, male, 18-25, Phoenix)

6.2.2.4.2.4 THS-PBA-05 Studies

Based on the insights generated during the development phase, 3 types of communication were crafted for the assessment phase:

(1) A communication including Claim #1 "Reduced risks of tobacco-related disease" based on Message 5 from study THS-PBA-03-US (Figure 34)

(2) A communication including Claim #2 – "Reduced risk of harm" (Figure 35).

(3) A communication including Claim #3 – "Reduced body's exposure to harmful and potentially harmful chemicals" based on Message 3 from study THS-PBA-3-US (Figure 36).

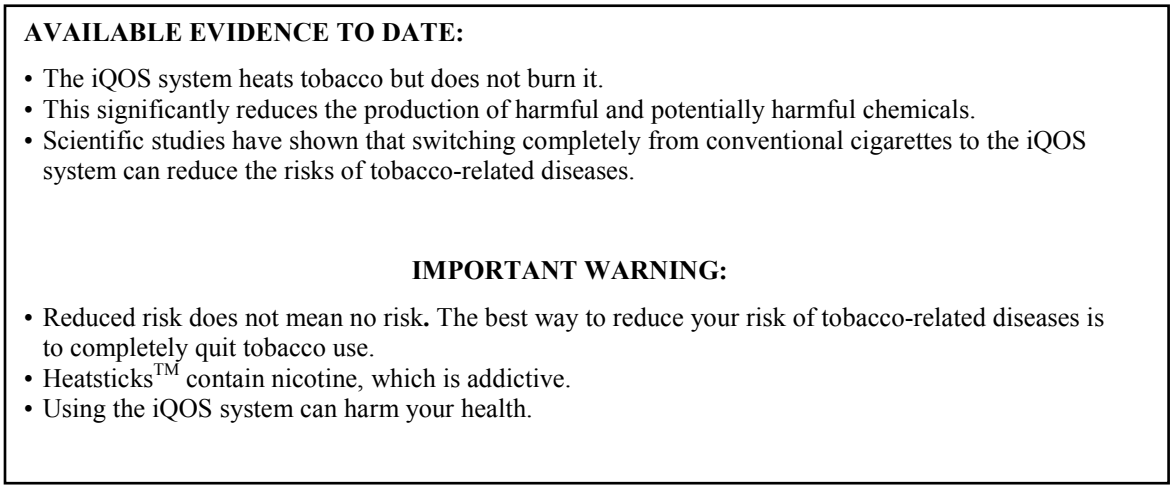


Figure 34 Reduced Risk Claim (RRC) and Associated Warning

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AVAILABLE EVIDENCE TO DATE:

- Switching completely to iQOS presents less risk of harm than continuing to smoke cigarettes.

IMPORTANT WARNING:

- Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.
- Heatsticks™ contain nicotine, which is addictive.

Figure 35 Reduced Risk Claim 2 (RRC2) and Associated Warning

AVAILABLE EVIDENCE TO DATE:

- The iQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
  - Scientific studies have shown that switching completely from conventional cigarettes to the iQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

IMPORTANT WARNING:

- It has not been demonstrated that switching to the iQOS system reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes.
- Heatsticks™ contain nicotine, which is addictive.
- Using the iQOS system can harm your health.

Figure 36 Reduced Exposure Claim (REC) and Associated Warning

The objective of the assessment phase was to describe responses to different instances of label, labeling and marketing material in the following populations: 1) adult Smokers with no Intention to Quit CC, Adult Smokers with the Intention to Quit CC, Adult Former Smokers, and Adult Never Smokers (including LA-25 Never Smokers). The assessment phase included 3 studies, THS-PBA-05-RRC-US (Claim #1 RRC), THS-PBA-05-RRC2-US (Claim #2 RRC2), THS-PBA-05-REC-US (Claim #3 REC), all using a similar methodology and a randomized parallel 5-arm design, with subjects in each arm being presented with a single instance of THS communication material (Table 33).

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Table 33 THS Communication Materials, Warning Type and Study Arms in THS-PBA-05 Studies

		Type of Material		
		THS Brochure	**THS Tobacco Sticks Pack**	**THS Direct Mail**
Warning Type	**Surgeon General**[a]	Arm 1	Arm 3	NA
	PMI[b]	Arm 2	Arm 4	Arm 5

Abbreviations: NA = not assessed.
[a] The Surgeon General (SG) warnings currently mandated for CC include: 1) "Smoking causes lung cancer, heart disease, emphysema, and may complicate pregnancy."; 2) "Quitting smoking now greatly reduces serious risks to your health." ; 3) "Smoking by pregnant women may result in fetal injury, premature birth, and low birth weight."; 4) "Cigarette smoke contains carbon monoxide." Note: Subjects randomized to the Surgeon General warning were assigned 1 of the 4 warnings.
[b] The PMI Important Warning statements were adapted for each study to present a coherent set of information between the claim and the warning concerning the modified risk risk (see Figure 34, Figure 35, and Figure 36, for RRC, RRC2 and REC respectively).

Two warning types were used in the study to assess how Comprehension, Risk Perception, and Intent to Use were related to both the currently mandated Surgeon General's warnings for CC and the Important Warning developed by PMI.

6.2.2.4.2.4.1 Methodology of THS-PBA-05-RRC-US

A description of the study methods is provided in Table 34.

Table 34 Methodology of THS-PBA-05-RRC-US

Study Title: Quantitative Assessment of THS 2.2 Label, Labeling, and Marketing Material with Reduced Risk Claims
Study Design: 4 cities, 5-arm parallel-group experiment. The 5 arms corresponded to 5 different combinations of communication materials and warning type, each of the materials being tested by approximately equal numbers of subjects from different smoking status groups.
Subjects: *Full Sample* (N=2255) stratified into Adult Smokers with no Intention to Quit CC (N=472), Adult Smokers with the Intention to Quit CC (N=472), Adult Former Smokers (N=471) and Adult Never Smokers (N=477). An additional oversampling of 478 Adult Never Smokers from the legal age of smoking to 25 years of age (*LA-25 Adult Never Smokers*) which includes 115 Adult Never Smokers from the *Main Sample*.

(table continues)

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Main Criteria for Inclusion:

- Aged 18 and above, or above state legal smoking age if above 18 years
- Adult Smokers with no Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with no intention to quit within 6 months; Adult Smokers with Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with the intention to quit within 6 months; Adult Former Smokers: quit smoking CCs more than 30 days ago; Adult Never Smokers: never smoked or never smoked daily and less than 100 CC

Methods:

Intent to Use

2 sets of items from the Intent to Use Questionnaire (ITUQ) yielded descriptive measures of:

- Intention to Try (i.e., to sample at least once; 2 items)
- Intention to Use (i.e., for continued usage; 2 items)

Change in Intention to Quit Smoking and All Tobacco (only for Adult Smokers with Intention to Quit CC)

Closed-ended questions based on Prochaska and DiClemente's Stages of Change model (Prochaska 1983) measured before and after exposure to THS message to determine change in Intention to Quit Smoking and All Tobacco

Criteria for Evaluation:

Intent to Use:

Positive Intention to Try (operationalized as the sum of % Very Likely and % Definitely responses for each item of Intention to Try) and Positive Intention to Use (operationalized as the sum of % Very Likely and % Definitely responses for the first item of Intention to Use), by study arm and smoking status group.

Change in Intention to Quit Smoking and All Tobacco:

Change in Intention to Quit Smoking and All Tobacco, respectively, compared pre- and post-exposure to the THS material, by study arm.

[a] Include Regular Smokers (smoke at least 1 CC a day) and Intermittent Smokers (between 4 and 27 days per month, with no restrictions on total number of CC smoked over that period, between 10% and 40%).

Mockup versions of branded THS Brochure, THS Tobacco Sticks Pack and Direct Mail (*iQOS* for THS and *Marlboro* for the THS Tobacco Sticks) were presented to the subjects with a hypothetical price for the THS Device (b) (4)) and for a pack of 20 THS Tobacco Sticks (price of a *Marlboro* pack of CC in the specific city of the research). All materials included at least the following 2 elements:

(1) Information on THS, including the modified risk claim that "Scientific studies have shown that switching completely from conventional cigarettes to the iQOS system can reduce the risks of tobacco-related diseases".

(2) Warning Section (Surgeon General's warnings or PMI Important Warning)

The mockups are presented in THS-PBA-05-RRC-US study report Appendix 16.1.1.

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6.2.2.4.2.4.2 Results of the THS-PBA-05-RRC-US Study

Positive Intention to Try and positive Intention to Use THS were substantial among Adult Smokers with No Intention to Quit CC for all materials tested and with both SG warnings and PMI Warning (positive Intention to Try ranged from 34.4% to 47.4% and positive Intention to Use from 28.4% to 38.9% across study Arms, Table 35). Positive Intention to Try and Positive Intention to Use was also substantial among Adult Smokers with Intention to Quit CC, regardless of the warning type or types of materials (positive Intention to Try ranged from 33.0% to 50.0% and positive Intention to Use between 23.2% to 34.0%, across study Arms Table 35).

Table 35 Proportion of Subjects with Positive Intention to Try[1] and Intention to Use[2] THS in THS-PBA-05-RRC-US

		THS Brochure		THS Tobacco Sticks Pack		THS Direct Mail
	Statistics	**SG warnings**	**PMI Warning**	**SG warnings**	**PMI Warning**	**PMI Warning**
Positive *Intention to Try*[1]						
S-NIQ	N	93	95	93	95	95
	n (%)	42 (45.2)	44 (46.3)	32 (34.4)	33 (34.7)	45 (47.4)
	(95% CI)	(34.8, 55.8)	(36.0, 56.8)	(24.9, 45.0)	(25.3, 45.2)	(37.0, 57.9)
S-IQ	N	94	95	93	96	94
	n (%)	47 (50.0)	39 (41.1)	33 (35.5)	37 (38.5)	31 (33.0)
	(95% CI)	(39.5, 60.5)	(31.1, 51.6)	(25.8, 46.1)	(28.8, 49.0)	(23.6, 43.4)
Positive *Intention to Use*[2]						
S-NIQ	N	93	95	93	95	95
	n (%)	32 (34.4)	37 (38.9)	30 (32.3)	27 (28.4)	28 (29.5)
	(95% CI)	(24.9, 45.0)	(29.1, 49.5)	(22.9, 42.7)	(19.6, 38.6)	(20.6, 39.7)
S-IQ	N	94	95	93	96	94
	n (%)	32 (34.0)	22 (23.2)	23 (24.7)	32 (33.3)	24 (25.5)
	(95% CI)	(24.6, 44.5)	(15.1, 32.9)	(16.4, 34.8)	(24.0, 43.7)	(17.1, 35.6)

N=total sample size; n=number of values reported.
Abbreviations: CI = confidence interval; SG = Surgeon General; S-IQ, Adult Smokers with the Intention to Quit CC; S-NIQ, Adult Smokers with No Intention to Quit CC; THS = Tobacco Heating System. Note: the 95% confidence intervals are calculated using the exact Clopper-Pearson method.
[1] Positive *Intention to Try* refers to the proportion of subjects whose response to the single item assessing intention to try THS 2.2 was either *Very Likely* or *Definitely*.
[2] Positive *Intention to Use* refers to the proportion of subjects whose response to the single item assessing intention to use THS 2.2 was either *Very Likely* or *Definitely*.
Data Source: Study Report THS-PBA-05-RRC-US, Table 15.2.2.1.1, Table 15.2.2.1.3, and Table 15.2.2.1.4

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Among Adult Smokers with the Intention to Quit CC, downward shift in Intention to Quit following exposure to the communication materials ranged between 4.3% and 11.6% for Intention to Quit Smoking, and between 1.1% and 11.6% for Intention to Quit All Tobacco (Table 36).

Table 36 Proportion of Subjects with Change in Intention to Quit Smoking or All Tobacco following Exposure to the THS Material in THS-PBA-05-RRC-US

		THS Brochure		THS Tobacco Sticks Pack		THS Direct Mail
		SG warnings	PMI Warning	SG warnings	PMI Warning	PMI Warning
		(N=94)	(N=95)	(N=93)	(N=96)	(N=94)
Pre Exposure– Post Exposure *						
Quitting Smoking						
Yes#	%	5.3	11.6	4.3	8.3	5.3
Yes, next 30 days	%	6.4	4.2	-1.1	2.1	3.2
Yes, next 6 months	%	-1.1	7.4	5.4	6.3	2.1
Quitting All Tobacco						
Yes#	%	7.4	11.6	1.1	2.1	3.2
Yes, next 30 days	%	6.4	9.5	2.2	2.1	5.3
Yes, next 6 months	%	1.1	2.1	-1.1	0.0	-2.1

N=total sample size; n=number of values reported.
Abbreviations: # Includes intention to quit in the next 30 days or 6 months.
Calculated as the percentage with the intention to quit pre-exposure minus the percentage with the intention to quit post-exposure.
Data Source Study Report THS-PBA-05-RRC-US: Appendix 15, Table 15.2.2.4.3. and Table 15.2.2.4.4

6.2.2.4.2.4.3 Methodology of the THS-PBA-05-RRC2-US study

A brief description of study methods is provided in Table 37.

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Table 37 Methodology of THS-PBA-05-RRC2-US

Study Title: Second Quantitative Assessment of THS 2.2 Label, Labeling and Marketing Material with Reduced Risk Claims

Study Design: 4 cities, 5-arm parallel-group experiment. The 5 arms corresponded to 5 different combinations of communication materials and warning type, each of the materials being tested by approximately equal numbers of subjects from different smoking status groups.

Subjects: *Full Sample* (N=2247) stratified into Adult Smokers with no Intention to Quit CC (N=471), Adult Smokers with the Intention to Quit CC (N=468), Adult Former Smokers (N=469) and Adult Never Smokers (N=480). An additional oversampling of 471 Adult Never Smokers from the legal age of smoking to 25 years of age (*LA-25 Adult Never Smokers*) which includes 107 Adult Never Smokers from the *Main Sample*.

Main Criteria for Inclusion:

- Aged 18 and above, or above state legal smoking age if above 18 years
- Adult Smokers with no Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with no intention to quit within 6 months; Adult Smokers with Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with the intention to quit within 6 months; Adult Former Smokers: quit smoking CCs more than 30 days ago; Adult Never Smokers: never smoked or never smoked daily and less than 100 CC

Methods:

Intent to Use

2 sets of items from the Intent to Use Questionnaire (ITUQ) yielded descriptive measures of:

- Intention to Try (i.e., to sample at least once; 2 items)
- Intention to Use (i.e., for continued usage; 2 items)

Change in Intention to Quit Smoking and All Tobacco (only for Adult Smokers with Intention to Quit CC)

Closed-ended questions based on Prochaska and DiClemente's Stages of Change model (Prochaska 1983) measured before and after exposure to THS message to determine change in Intention to Quit Smoking and All Tobacco

Criteria for Evaluation:

Intent to Use:

Positive Intention to Try (operationalized as the sum of % Very Likely and % Definitely responses to the item Intention to Try) and Positive Intention to Use (operationalized as the sum of % Very Likely and % Definitely responses to the item Intention to Use Regularly), by study arm and smoking status group.

Change in Intention to Quit Smoking and All Tobacco:

Change in Intention to Quit Smoking and All Tobacco, respectively, compared pre- and post-exposure to the THS material, by study arm.

[a] Include Regular Smokers (smoke at least 1 CC a day) and Intermittent Smokers (between 4 and 27 days per month, with no restrictions on total number of CC smoked over that period, between 10% and 40%).

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Mockup versions of branded THS Brochure, THS Tobacco Sticks Pack and Direct Mail (*iQOS* for THS and *Marlboro* for the THS Tobacco Sticks) were presented to the subjects with a hypothetical price for the THS Device (b) (4) and for a pack of 20 THS Tobacco Sticks (price of a *Marlboro* pack of CC in the specific city of the research). All materials included at least the following 2 elements:

(1) Information on THS, including the modified risk claim that "Switching completely to iQOS presents less risk of harm than continuing to smoke cigarettes".

(2) Warning Section (Surgeon General's warnings or PMI Important Warning)

The mockups are presented in THS-PBA-05-RRC2-US study report Appendix 16.1.1.

6.2.2.4.2.4.4 Results of the THS-PBA-05-RRC2-US Study

Positive Intention to Try and positive Intention to Use THS were substantial among Adult Smokers with No Intention to Quit CC for all materials tested and with both SG warnings and PMI Warning (positive Intention to Try ranged from 30.9% to 54.3% and positive Intention to Use from 20.2% to 37.9% across study Arms, Table 38). Positive Intention to Try and positive Intention to Use was also substantial among Adult Smokers with Intention to Quit CC, regardless of the warning types and the types of materials (Positive Intention to Try ranged from 40.9% to 51.6% and positive Intention to Use ranged from 21.3% to 35.1% across study Arms, Table 38).

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Table 38 Proportion of Subjects with Positive Intention to Try[1] and Intention to Use[2] THS in THS-PBA-05-RRC2-US

		THS Brochure		THS Tobacco Sticks Pack		THS Direct Mail
	Statistics	**SG warnings**	**PMI Warning**	**SG warnings**	**PMI Warning**	**PMI Warning**
Positive *Intention to Try*[1]						
S-NIQ	N	95	96	94	96	94
	n (%)	50 (52.6)	47 (49.0)	29 (30.9)	34 (35.4)	51 (54.3)
	(95% CI)	(42.1, 63.0)	(38.6, 59.4)	(21.7, 41.2)	(25.9, 45.8)	(43.7, 64.6)
S-IQ	N	93	93	96	94	94
	n (%)	38 (40.9)	48 (51.6)	47 (49.0)	39 (41.5)	47 (50.0)
	(95% CI)	(30.8, 51.5)	(41.0, 62.1)	(38.6, 59.4)	(31.4, 52.1)	(39.5, 60.5)
Positive *Intention to Use*[2]						
S-NIQ	N	95	96	94	96	94
	n (%)	36 (37.9)	33 (34.4)	19 (20.2)	27 (28.1)	30 (31.9)
	(95% CI)	(28.1, 48.4)	(25.0, 44.8)	(12.6, 29.8)	(19.4, 38.2)	(22.7, 42.3)
S-IQ	N	93	93	96	94	94
	n (%)	29 (31.2)	32 (34.4)	31 (32.3)	20 (21.3)	33 (35.1)
	(95% CI)	(22.0, 41.6)	(24.9, 45.0)	(23.1, 42.6)	(13.5, 30.9)	(25.5, 45.6)

N=total sample size; n=number of values reported.
Abbreviations: CI = confidence interval; SG = Surgeon General; S-IQ, Adult Smokers with the Intention to Quit CC; S-NIQ, Adult Smokers with No Intention to Quit CC; THS = Tobacco Heating System. Note: the 95% confidence intervals are calculated using the exact Clopper-Pearson method.
[1] Positive *Intention to Try* refers to the proportion of subjects whose response to the single item assessing intention to try THS 2.2 was either *Very Likely* or *Definitely*.
[2] Positive *Intention to Use* refers to the proportion of subjects whose response to the single item assessing intention to use THS 2.2 was either *Very Likely* or *Definitely*.
Data Source Study Report THS-PBA-05-RRC2-US: Appendix 15, Table 15.2.2.1.1, Table 15.2.2.1.3, and Table 15.2.2.1.4

Among Adult Smokers with the Intention to Quit CC, downward shift in Intention to Quit following exposure to the communication materials ranged between 1.1% and 11.8% for Intention to Quit Smoking, and reached up to 9.7% for Intention to Quit All Tobacco Table 39).

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Table 39 Proportion of Subjects with Change in Intention to Quit Smoking or All Tobacco following Exposure to the THS Materials in THS-PBA-05-RRC2-US

		THS Brochure		THS Tobacco Sticks Pack		THS Direct Mail
		SG warnings	PMI Warning	SG warnings	PMI Warning	PMI Warning
		(N=94)	(N=95)	(N=93)	(N=96)	(N=94)
Pre Exposure– Post Exposure*						
Quitting Smoking						
Yes#	%	5.4	11.8	5.2	1.1	5.4
Yes, next 30 days	%	4.3	5.4	0.0	0.0	4.3
Yes, next 6 months	%	1.1	6.5	5.2	1.1	1.1
Quitting All Tobacco						
Yes#	%	4.3	9.7	2.1	-3.2[1]	4.3
Yes, next 30 days	%	1.1	10.8	1.0	0.0	1.1
Yes, next 6 months	%	3.2	-1.1[1]	1.0	-3.2[1]	3.2

N=total sample size; n=number of values reported.
Abbreviations: # Includes intention to quit in the next 30 days or 6 months.
* Calculated as the percentage with the intention to quit pre-exposure minus the percentage with the intention to quit post-exposure.
[1] This change in Intention to Quit is negative indicating an increase from Baseline, whereas most changes were decreases from Baseline.
Data Source Study Report THS-PBA-05-RRC2-US: Appendix 15, Table 15.2.2.4.3. and Table 15.2.2.4.4

6.2.2.4.2.4.5 Methodology of the THS-PBA-05-REC-US study

A brief description of study methods is provided in Table 40.

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Table 40 Methodology of THS-PBA-05-REC-US

Study Title: Quantitative Assessment of THS 2.2 Label, Labeling and Marketing Material with Reduced Exposure Claims

Study design: 4 cities, 5-arm parallel-group experiment. The 5 arms corresponded to 5 different combinations of communication materials and warning type, each of the materials being tested by approximately equal numbers of subjects from different smoking status groups.

Subjects: *Full Sample* (N=2272) stratified into Adult Smokers with no Intention to Quit CC (N=479), Adult Smokers with the Intention to Quit CC (N=479), Adult Former Smokers (N=480) and Adult Never Smokers (N=480). An additional oversampling of 480 Adult Never Smokers from the legal age of smoking to 25 years of age (*LA-25 Adult Never Smokers*) which includes 126 Adult Never Smokers from the *Main Sample*.

Main criteria for inclusion:

- Aged 18 and above, or above state legal smoking age if above 18 years
- Adult Smokers with no Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with no intention to quit within 6 months; Adult Smokers with Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with the intention to quit within 6 months; Adult Former Smokers: quit smoking CCs more than 30 days ago; Adult Never Smokers: never smoked or never smoked daily and less than 100 CC

Methods:

Intent to Use

2 sets of items from the Intent to Use Questionnaire (ITUQ) yielded descriptive measures of:

- Intention to Try (i.e., to sample at least once; 2 items)
- Intention to Use (i.e., for continued usage; 2 items)

Change in Intention to Quit Smoking and All Tobacco (only for Adult Smokers with Intention to Quit CC)

Closed-ended questions based on Prochaska and DiClemente's Stages of Change model (Prochaska 1983) measured before and after exposure to THS message to determine change in Intention to Quit Smoking and All Tobacco

Criteria for Evaluation:

Intent to Use:

Positive Intention to Try (operationalized as the sum of % Very Likely and % Definitely responses to the item on Intention to Try) and positive Intention to Use (operationalized as the sum of % Very Likely and % Definitely responses to the item on Intention to Use Regularly).

Change in Intention to Quit Smoking and All Tobacco:

Change in Intention to Quit Smoking and All Tobacco, respectively, compared pre- and post-exposure to the THS material, by study arm.

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Mockup versions of branded THS Brochure, THS Tobacco Sticks Pack and Direct Mail (*iQOS* for THS and *Marlboro* for the THS Tobacco Sticks) were presented to the subjects with a hypothetical price for the THS Device ((b) (4)) and for a pack of 20 THS Tobacco Sticks (price of a *Marlboro* pack of CC in the specific city of the research). All materials included at least the following 2 elements:

(1) Information on THS, including the modified risk claim that "Switching completely from conventional cigarettes to the iQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals".

(2) Warning Section (Surgeon General's warnings or PMI Important Warning)

The mockups are presented in THS-PBA-05-REC-US study report Appendix 16.1.1.

6.2.2.4.2.4.6 Results of the THS-PBA-05-REC-US Study

Positive Intention to Try and positive Intention to Use THS were substantial among Adult Smokers with No Intention to Quit CC for all materials tested and with both SG warnings and PMI Warning (positive Intention to Try between 30.2% to 49.5% and positive Intention to Use between 20.8% to 36.8% across study Arms, Table 41). Positive Intention to Try and positive Intention to Use was also substantial among Adult Smokers with Intention to Quit CC, regardless of the warning types or types of materials (positive Intention to Try between 32.6% to 39.6% and positive Intention to Use between 22.3% to 29.2% across study Arms, Table 41).

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Table 41 Proportion of Subjects with Positive Intention to Try[1] and Intention to Use[2] THS in THS-PBA-05-REC-US

		THS Brochure		THS Tobacco Sticks Pack		THS Direct Mail
	Statistics	**SG warning**	**PMI Warning**	**SG warning**	**PMI Warning**	**PMI Warning**
Positive *Intention to Try*[1]						
S-NIQ	N	95	95	95	96	96
	n (%)	44 (46.3)	47 (49.5)	31 (32.6)	42 (43.8)	29 (30.2)
	(95% CI)	(36.0, 56.8)	(39.1, 59.9)	(23.4, 43.0)	(33.6, 54.3)	(21.3, 40.4)
S-IQ	N	96	94	96	95	96
	n (%)	36 (37.5)	36 (38.3)	38 (39.6)	31 (32.6)	34 (35.4)
	(95% CI)	(27.8, 48.0)	(28.5, 48.9)	(29.7, 50.1)	(23.4, 43.0)	(25.9, 45.8)
Positive *Intention to Use*[2]						
S-NIQ	N	95	95	95	96	96
	n (%)	35 (36.8)	32 (33.7)	24 (25.3)	26 (27.1)	20 (20.8)
	(95% CI)	(27.2, 47.4)	(24.3, 44.1)	(16.9, 35.2)	(18.5, 37.1)	(13.2, 30.3)
S-IQ	N	96	94	96	95	96
	n (%)	22 (22.9)	21 (22.3)	28 (29.2)	24 (25.3)	22 (22.9)
	(95% CI)	(15.0, 32.6)	(14.4, 32.1)	(20.3, 39.3)	(16.9, 35.2)	(15.0, 32.6)

N=total sample size; n=number of values reported.
Abbreviations: CI = confidence interval; SG = Surgeon General; S-IQ, Adult Smokers with the Intention to Quit CC; S-NIQ, Adult Smokers with No Intention to Quit CC; THS = Tobacco Heating System. Note: the 95% confidence intervals are calculated using the exact Clopper-Pearson method.
[1] Positive *Intention to Try* refers to the proportion of subjects whose response to the single item assessing intention to try THS 2.2 was either *Very Likely* or *Definitely*.
[2] Positive *Intention to Use* refers to the proportion of subjects whose response to the single item assessing intention to use THS 2.2 was either *Very Likely* or *Definitely*.
Data Source Study Report THS-PBA-05-REC-US: Appendix 15, Table 15.2.2.1.1, Table 15.2.2.1.3, and Table 15.2.2.1.4

Among Adult Smokers with the Intention to Quit CC, downward shift in Intention to Quit following exposure to the communication materials ranged between 4.2% and 9.6% for Intention to Quit Smoking, and between 1.0% and 5.2% for Intention to Quit All Tobacco, Table 42).

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Table 42 Proportion of Subjects with Change in Intention to Quit Smoking or All Tobacco following Exposure to the THS Materials in THS-PBA-05-REC-US

		THS Brochure		THS Tobacco Sticks Pack		THS Direct Mail
		SG Warnings	PMI Warning	SG Warnings	PMI Warning	PMI Warning
		(N=94)	(N=95)	(N=93)	(N=96)	(N=94)
Pre Label – Post Label*						
Quitting Smoking						
Yes#	%	9.4	9.6	6.3	4.2	6.3
Yes, next 30 days	%	7.3	7.4	3.1	0.0	1.0
Yes, next 6 months	%	2.1	2.1	3.1	4.2	5.2
Quitting All Tobacco						
Yes#	%	5.2	1.1	3.1	1.1	1.0
Yes, next 30 days	%	7.3	5.3	-1.0[1]	8.4	4.2
Yes, next 6 months	%	-2.1[1]	-4.3[1]	4.2	-7.4[1]	-3.1[1]

Abbreviations: # Includes intention to quit in the next 30 days or 6 months.
* Calculated as the percentage with the intention to quit pre label minus the percentage with the intention to quit post label.
[1] This change in Intention to Quit is negative indicating an increase from Baseline, whereas most changes were decreases from Baseline.
Data Source Study Report THS-PBA-05-REC-US: Appendix 15, Table 15.2.2.4.3. and Table 15.2.2.4.4

6.2.2.4.2.5 Conclusions across studies

In addition to evidence on actual use, findings on Intent to Use provide complementary evidence on how adult current CC smokers are likely to accept and use THS. In all 6 studies conducted on the effect of THS labeling and advertising materials (THS-PBA-02-US, THS-PBA-03-US, THS-PBA-04-US, THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US), exposure to THS Communications generated a substantial level of Intent to Use THS among the intended section of the population, i.e., adult smokers with no intention to quit CC. Of importance, the overall pattern of results for Intent to Use THS was broadly consistent across the 3 PBA-05 studies (between 28.4% and 38.9% for THS-PBA-05-RRC-US; between 20.2% and 37.9% for THS-PBA-05-RRC2-US; and between 20.8% and 36.8% for THS-PBA-05-REC-US, respectively, reported that they would very likely or definitively use THS regularly after being exposed

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to any of the 3 claims and associated communication materials subject to this application).

These levels of Intent to Use THS are in line with similar data that have been reported on e-cigarettes (Wackowski 2016, Zhu 2013). These results are, therefore, consistent with PMI's goal to develop and commercialize products that reduce risk and are an acceptable alternative to continued cigarette smoking. Key communication messages that helped position THS as an attractive alternative to CC for adult smokers are (i) the references to the presence of tobacco, and (ii) flavor and taste satisfaction which address concerns about usage experience (qualitative findings from studies THS-PBA-02-US and THS-PBA-04-US).

Overall, Intent to Use THS was broadly similar between CC smokers with and with no intention to quit smoking, in that there was also substantial level of Intent to Use THS within Adult Smokers with the Intention to Quit CC (between 23.2% and 35.1% reported that they would very likely or definitively use THS after being exposed to any of the 3 claims and associated communication materials subject to this application). However Adult Smokers with Intention to Quit CC did not change their intention to quit smoking and all tobacco after being exposed to THS communication materials (ranged between 1.0% and 11.8% across all THS-PBA-05 Studies). Overall, these results suggest that the communication materials did not significantly alter their intention to quit smoking and all tobacco.

Our findings did not provide evidence that the type of communication material (i.e. THS Brochure, THS Tobacco Sticks Pack, and THS Direct Mail) used to market THS would have a notable influence on Intent to Use among the Adult Smoker Population. Of importance, our results indicate that the materials are successful to target current smokers while not attracting consumer groups for whom THS is not intended, such as former and never smokers (see Section 6.3.1 for more details). However, it does seem to be appealing to adult smokers with an intent to quit, however without altering such intent. No evidence was found on the association between the type of claims and Intent to Use THS. Altogether, results support the conclusion that all 3 claims are suitable to be used to market THS in the US.

6.2.2.4.3 Product Usability

This section describes results on product usability for adult current users of CCs.

6.2.2.4.3.1 THS-PBA-06-US Study

The main purpose of the THS-PBA-06-US study was to describe the ability of prospective consumers (adult smokers) to correctly comply with the THS instructions for use and understand those instructions. More details can be found in the summary and full report of the individual study (Section 7.3.2).

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6.2.2.4.3.1.1 Methodology of THS-PBA-06-US

A brief description of THS-PBA-06-US study methods is given in Table 43.

Table 43 Methodology of THS-PBA-06-US

Study Title: Usability and Comprehension Study of THS 2.2 Instructions for Use Within Adult Smokers
Study design: 4 cities, single-arm study with adult smokers, consisting of individual interviews to assess usability and comprehension of the Instructions for Use of THS
Subjects: Enrolled: 274; Full analysis population (FAP): 258
Main criteria for inclusion: • Aged 18 and above, or above state legal smoking age if above 18 years • Current adult smoker: having smoked at least 100 CC and currently smoking at least 1 CC per day (no brand restrictions, disregarding religious fasting)
Methods: Individual personal interviews where subjects were asked to read the THS instructions for use and show their ability to correctly demonstrate 9 specific use tasks (Usability assessment). Each of these use tasks was broken down into discrete steps, corresponding to the information in the instructions for use for a particular use task. For the comprehension assessment, subjects were asked to answer 3 open-ended questions about key messages of the instructions for use.
Criteria for evaluation: Correct demonstration of the steps of the THS 2.2 use tasks Combined score for both correct and acceptable answers as rated by 2 raters using pre-specified definitions of correct performance. Comprehension of key messages of THS 2.2 instructions for use Combined score for both correct and acceptable answers as rated by 2 raters using pre-specified definitions of correct understanding.

6.2.2.4.3.1.2 Results of THS-PBA-06-US

Results on the correct demonstration of the use tasks are summarized in Table 44. Five out of the 9 use tasks were correctly demonstrated by a large majority of subjects (all the necessary steps within each task were well performed): to charge the THS Holder and THS Pocket Charger simultaneously; to insert a THS Tobacco Stick into the THS Holder; how to heat and consume a THS Tobacco Stick; how to know when a THS Tobacco Stick has been consumed and a session is over, how to remove a stuck THS Tobacco Stick, and how to re-attach the THS Holder cap. However, the subjects found some tasks more complicated: to remove a THS Tobacco Stick from the THS Holder using the 'pull-pull' technique, to heat clean the THS Holder, how to clean the THS Holder with the THS Cleaning Tool (more specifically cleaning the THS Holder cap). In all of the tasks (both those that were correctly demonstrated by a large majority of subjects and those tasks that were more difficult for subjects) there were some steps that performed well and others that did not (Table 44).

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Table 44 Appropriate Demonstration of Specific Usability Tasks for THS 2.2 (Correct and Acceptable Responses) in THS-PBA-06-US

N=258	n (%)	95% CI (%)
I said before, imagine you recently purchased the iQOS system from a local convenience store and you are using it for the first time to consume a HeatStick.		
Task 1: ***Based on the directions in the instructions for use, please show me how you would charge the iQOS Holder and Pocket Charger simultaneously.***		
Subjects insert the THS 2.2 Holder into the Pocket Charger	244 (94.6)	91.1, 97.0
Subjects insert the THS 2.2 Holder with battery contacts facing down?	240 (93.0)	89.2, 95.8
Subjects align the power button of THS 2.2 Holder with the notch in the Pocket Charger?	189 (73.3)	67.4, 78.6
Subjects insert one end of the USB cable into the USB power adaptor and the other end into the THS 2.2 Pocket Charger?	246 (95.3)	92.0, 97.6
Subjects close the hatch of the THS 2.2 Pocket Charger?	176 (68.2)	62.2, 73.9
Task 2: ***Now, please show me how you would insert a HeatStick into the iQOS Holder before consuming it.***		
Subjects insert a THS 2.2 Tobacco Stick into the THS 2.2 Holder?	249 (96.5)	94.0, 98.6
Subjects insert THS 2.2 Tobacco Stick into the THS 2.2 Holder without twisting it?	243 (94.2)	91.0, 97.0
Subjects insert a THS 2.2 Tobacco Stick into the THS 2.2 Holder with the tobacco-side down?	233 (90.3)	86.4, 93.9
Subjects align the line on the Tobacco Stick with the top of THS 2.2 Holder cap?	137 (53.1)	46.8, 59.3
Task 3: ***Now that the HeatStick is in the Holder, please show me how you would consume a HeatStick using the iQOS system. When the HeatStick is ready to be consumed, hand the Holder and the HeatStick back to me.***		
Subjects press the button on the side of the THS 2.2 Holder for 2 seconds until a flashing green light appeared?	211 (81.8)	76.5, 86.3
Subjects return the THS 2.2 Holder to the interviewer, after the green light stopped flashing?	177 (68.6)	62.6, 74.2
Task 4: ***How will you know when the HeatStick has been consumed and the session is over?***		
Subjects respond: "A green light will turn into a constant orange light" and "The Holder will turn off" OR "A green light will turn into a constant orange light?"	208 (80.6)	75.3, 85.3

(table continues)

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N=258	n (%)	95% CI (%)
Task 5: ***Please show me how you would remove the HeatStick from the Holder after consuming a HeatStick using the 'pull-pull technique', as described in the instructions for use.***		
Subjects pull the cap away from the THS 2.2 Holder until the cap stops?	144 (55.8)	49.5, 62.0
Subjects avoid twisting the THS 2.2 Tobacco Stick?	250 (96.9)	94.0, 98.7
Subjects remove the THS 2.2 Tobacco Stick from the cap?	250 (96.9)	94.0, 98.7
Subjects push the cap back into place?	106 (41.1)	35.0, 47.4
Subjects align the cap with the power button?	107 (41.5)	35.4, 47.7
Task 6: ***How will the Pocket Charger tell you it is time to heat clean your iQOS Holder?***		
Part A Subjects respond: An orange/red symbol will light up on the THS 2.2 Pocket Charger?	228 (88.4)	83.8, 92.0
Task 6: ***Please show how you would heat clean or self-clean the iQOS Holder.***		
Part B Subjects insert the THS 2.2 Holder all the way into the THS 2.2 Pocket Charger?	124 (48.1)	41.8, 54.3
Subjects close the hatch of the THS 2.2 Pocket Charger?	142 (55.0)	48.7, 61.2
Subjects press and hold the power button to turn the THS 2.2 Pocket Charger on?	125 (48.4)	42.2, 54.7
Subjects press and hold the Self-clean button for 3 seconds?	164 (63.6)	57.4, 69.4
Task 7: ***Please show me how you would clean the Holder with the cleaning tool.***		
Subjects separate the cap of the THS 2.2 Holder from the body by pulling it apart?	170 (65.9)	59.8, 71.7
Subjects pinch the center of the THS 2.2 Cleaner then pull the ends to release the two separate brushes?	251 (97.3)	94.5, 98.9
Subjects insert the long THS 2.2 Holder body into the long brush?	196 (76.0)	70.3, 81.1
Subjects clean the THS 2.2 Holder body using a twisting motion?	196 (76.0)	70.3, 81.1
Subjects insert the THS 2.2 Holder cap into the short brush?	127 (49.2)	43.0, 55.5
Subjects clean the THS 2.2 Holder cap with a twisting motion?	128 (49.6)	43.4, 55.9

(table continues)

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N=258	n (%)	95% CI (%)
Task 8+9: ***Please show me how you would remove the stuck HeatStick from this Holder cap and then re-attach the cap to the Holder body.***		
Pull out the cleaning hook from the long brush?	192 (74.4)	68.6, 79.6
Push or pull the stuck THS 2.2 Tobacco Stick from the THS 2.2 Holder cap?	202 (78.3)	72.8, 83.2
Push the THS 2.2 Holder cap back into place on the THS 2.2 Holder body?	205 (79.5)	74.0, 84.2
Align the THS 2.2 Holder cap with the power button?	189 (73.3)	67.4, 78.6

N=total sample size; n=number of values reported.
Abbreviations: CI = confidence interval.
Note: 95% CI based on Clopper-Pearson method. The CI is based on the proportion of subjects who gave a correct or acceptable response out of all subjects demonstrating this task. *iQOS* is the commercial name for Tobacco Heating System 2.2 (THS 2.2). *HeatStick* is the commercial name for THS Tobacco Stick.

Correct comprehension of key messages associated with use of THS are summarized in Table 45. In the THS instructions for use there were 2 key messages that, if misunderstood, would completely diminish the potential health benefits of THS use: (i) the instruction to not use the THS Holder with a conventional cigarette; this was well comprehended, with 85% of subjects correctly understanding this message and (ii) the direction to not attempt to smoke a THS Tobacco Stick like a CC (i.e., light it with a match or lighter); this was also well comprehended, with 95% of subjects correctly understanding this message. The third and last comprehension key message assessed the extent to which subjects understood that the THS Holder must be fully charged to be heat cleaned. For this message, 67% of subjects provided a correct or acceptable answer, indicating that there was some confusion surrounding the heat clean process, including what it meant to heat clean and what was actually being cleaned.

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Table 45 Correct/Acceptable Comprehension of Key Messages for THS 2.2 Use in THS-PBA-06-US

N=258	n (%)	95% CI (%)
John left his HeatSticks at home and would like to use his iQOS Holder to smoke a conventional cigarette. What, if anything, do the instructions for use say John should do?		
Do not smoke the conventional cigarette using the *iQOS* Holder (*Correct*) OR Never use conventional cigarettes with the *iQOS* Holder (*Acceptable*)	220 (85.3)	80.3, 89.4
Sam's iQOS Holder is out of batteries and he is thinking about lighting a HeatStick with a lighter to smoke it. What, if anything, do the instructions for use say about this?		
Do not light *HeatStick* with a match/lighter (*Correct*) OR Not OK (*Acceptable*)	244 (94.6)	91.1, 97.0
Zach needs to heat clean his iQOS Holder, but notices that his iQOS Holder isn't fully charged. What, if anything do the instructions for use say about this?		
iQOS Holder must be fully charged to heat clean (*Correct*) OR Not OK (*Acceptable*)	172 (66.7%)	60.6, 72.4

N=total sample size; n=number of values reported.
Abbreviations: CI = confidence interval.
Note: 95% CI based on Clopper-Pearson method. The CI is based on the proportion of subjects who gave a correct or acceptable response out of all subjects demonstrating this task. *iQOS* is the commercial name for Tobacco Heating System 2.2 (THS 2.2). *HeatStick* is the commercial name for THS Tobacco Stick.

6.2.2.4.3.1.3 Conclusions on Product Usability

THS-PBA-06-US study evaluated the usability and the comprehension of THS instructions in 258 adults CC smokers in the US. The majority of use tasks (charging the THS Holder, how to consume the THS Tobacco Stick, end of THS Tobacco Stick use, how to remove a stuck THS Tobacco Stick from the THS Holder) were executed correctly by more than two-third of the participants. A few tasks (how to insert the THS Tobacco Stick into the THS Holder, how to remove the THS Tobacco Stick, how to heat clean the THS Holder, how to use the THS Cleaning Tool) were less well executed. Key messages such as not using the THS Device with a CC or not to smoke the THS Tobacco Stick as a CC were well comprehended by 85% and 95% of users, respectively. The second message should be put in perspective with misuse observations from study THS-PBA-07-US where 4.8% of participants reported to have smoked at least once the THS Tobacco Stick as a CC, by lighting it. About 80% of the reported misuse cases occurred 1

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to 4 times, more likely due to negligence or curiosity rather than being a another way to use THS Tobacco Stick.

In general, the results of the THS-PBA-06-US study indicate that the THS instructions for use seem to be adequate in explaining the various tasks required to normally operate THS. However, subjects' understanding and demonstration of certain parts of the instructions for use were more difficult (understood by less than two third of the subjects) and needed to be improved, either through revisions to the description of specific tasks or the way tasks are to be executed in an improved version of the THS Device. The instructions for use tested in the THS-PBA-06-US study were related to the THD version 2.2 (A3.4.3 PBA06User Guide). Based on the study results, the instructions for use and, to some extent, the device, have been significantly improved (A3.4.1 Userguide):

- Format of the instructions for use: instead of a folded leaflet, the THD version 2.4 User Guide comes in the form of a small booklet, therefore presenting the information in an easier to handle, sequential and more logical fashion.
- How to remove a Tobacco Stick from the THS 2.2 Holder using the pull-pull technique (Task 5) is presented with only 2 steps, with clearer figures and no reference to a "special pull-pull technique".
- "How to 'heat clean' the THS 2.2 Holder" (Task 6) in the THD version 2.4 device has been simplified with an automatic heater cleaning process (see Section 3.1.3.3.2.). This eliminates the need for users to manually perform this task every 20 *HeatSticks*.
- "How to clean the THS 2.2 Holder using the THS 2.2 Cleaning Tool" (Task 7, and more specifically the Holder cap) is presented in two clearly separate steps of cleaning the *iQOS* Holder and the *iQOS* Holder body. Therefore, it is more apparent that there is the need to clean both parts of the *iQOS* Holder, each with the appropriate brush of the cleaning tool.
- "insert a THS 2.2 Tobacco Stick into the THS 2.2 Holder" (Task 2): the THS Tobacco Sticks that are planned to be commercialized will have a clearly visible line at the beginning of the filter portion of the THS Tobacco Stick. Therefore, it will be more obvious to the user how to insert the THS Tobacco Stick into the THS Holder correctly and push the THS Tobacco Stick further to the indicated point.

The Section 3.5.1.2 presents a detailled description of the modifications and improvements of the THS instructions for use that resulted from the THS-PBA-06-US Study findings.

In addition to the improvement of the instruction for use, it is also worth noting that subjects were assessed in how they performed at their very first and single attempt at these tasks, and while being observed (a factor that could introduce a certain level of evaluation pressure, possibly affecting performance (Aiello 2001). It is reasonable to assume that the proper use of the system would become clear after repeated attempts to

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use it. Thus, it is conceivable that these findings may capture lower levels of performance than may be found under real-world conditions.

Overall, based on totality of available evidence on product usability, our results suggest that THS is likely to be used as designed and intended by adult smokers.

6.2.2.5 Conclusions on Product Usage

The results summarized in this section covered various parameters of product usage, from product use behavior, behavioral intention and product usability. In brief, the different results pertaining to each of these parameters consistently point toward THS having a high potential to be accepted by current adult smokers as an alternative to CC.

Sensorial experience, taste, ritual and nicotine delivery are among the attributes that contribute to the acceptance of a new product by a current adult smoker and therefore significantly influence product use behavior. The 4 Reduced Exposure studies (ZRHR-REXC-03-EU, ZRHR-REXC-04-JP, ZRHM-REXA-07-JP and ZRHM-REXA-08-US) demonstrated that participants using THS *ad libitum,* were able to reach nicotine levels similar to CC smoking. In the same lines, measures on subjective effects e.g., urge-to smoke, withdrawal symptoms, product evaluation, illustrated that THS offered a close experience to what was observed in smokers when smoking CC. In other words, product satisfaction for THS, as measured by nicotine uptake and subjective effects, is comparable to a CC, which is critical to adult smoker acceptance of THS as a suitable alternative to CC.

Results on product consumption and use patterns, both in controlled as well as in near to real-world conditions, provide consistent evidence that THS has the potential to be adopted by current CC smokers, and thus encouraging them to switch from CC to THS. Indeed, results from observation studies indicate that the proportion of subjects who switched to THS in the THS-PBA-07-US study was comparable to 3 other European countries such as Italy, Germany and Switzerland, providing support for the acceptance of THS by current CC smokers. At the same time, an adaptation process is expected and was indeed observed within the first month of product use in most of the PMI studies assessing product use behavior (e.g., variation in product consumption, puffing behavior, or use patterns). Over a prolonged product exposure, the level of THS consumption tended to stabilize to reach levels comparable to what was reported at Baseline for CC in most of the studies. Patterns of product consumption and product satisfaction differed across study populations with differences between Japan and the US populations consistently observed, regardless of the type of studies. Product satisfaction was initially higher and adoption of THS was faster in Japan compared to the US, with eventually marginal differences only towards the end of the 3-month exposure studies. Cultural differences in taste preferences, difference in the products used prior to switching to THS, or more generally in the propensity to try new tobacco products may likely explain the differences observed on THS product use behavior across the different PMI studies. These cultural differences may also explain why complete switch was higher in some countries while combined/dual use of THS and CC was the predominant pattern in other countries in observational studies.

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Product use data were further supported by PBA data generated on the effect of THS communication, which consistently showed that, the way potential risks and benefits of THS are communicated to the consumers, generated substantial intent to use THS among adult smokers, while not encouraging non-smokers to try/use THS (see Section 6.3.1 for more details). This interest in using THS was true for adult smokers with no intention to quit smoking, the intended consumer group, but also for smokers who expressed an intention to quit smoking at the time of the study. However, for smokers who expressed an intention to quit smoking, the communication materials did not significantly alter their intention to quit smoking and all tobacco.

Finally, data on product usability suggested that the instruction for use seem adequate in explaining the majority of the tasks required to normally operate THS, with the exception of the pull-pull technique to remove the sticks and the cleaning process of the THS holder, which were improved in the version of the instruction for use and the THS device part of this MRTPA submission.. These results, put in perspective with the very low level of misuses observed in near to real-world conditions such as THS-PBA-07-US, suggest that THS is likely to be used as designed and intended by adult smokers.

In conclusion, based on totality of available evidence on product usage, THS offers an experience sufficiently close to CC to provide an overall satisfying experience. In combination with the appropriate communication on THS potential risks and benefits, THS could make smokers switch quickly, as this was shown to be a crucial point to ensure a continued use of the product and reduce likelihood of switching back to CC.

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6.2.2.6 References

Aiello JR, Douthitt EA. Social facilitation from Triplett to electronic performance monitoring. Group Dynamics: Theory, Research, and Practice. 2001; 5(3):163-80.

Benowitz NL, Hukkanen J, Jacob P, 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol. 2009; (192):29-60.

Benowitz NL, Jacob P, 3rd. Metabolism of nicotine to cotinine studied by a dual stable isotope method. Clin Pharmacol Ther. 1994; 56(5):483-93.

Borland R, Li L, Cummings KM, O'Connor R, Mortimer K, Wikmans T, Ramstrom L, King B, McNeill A. Effects of a Fact Sheet on beliefs about the harmfulness of alternative nicotine delivery systems compared with cigarettes. Harm Reduct J. 2012; 9:19.

Capella ML, Taylor CR, Kees J. Tobacco harm reduction advertising in the presence of a government-mandated warning. Journal of Consumer Affairs. 2012; 46(2):235-59.

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.

DiClemente CC, Prochaska JO, Fairhurst SK, Velicer WF, Velasquez MM, Rossi JS. The process of smoking cessation: an analysis of precontemplation, contemplation, and preparation stages of change. J Consult Clin Psychol. 1991; 59(2):295-304.

Etter JF, Sutton S. Assessing 'stage of change' in current and former smokers. Addiction. 2002; 97(9):1171-82.

FDA. Guidance for Industry – Modified Risk Tobacco Product Applications (Draft Guidance) http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf2012.

FDA (Food and Drug Administration). Guidance for industry - Modified risk tobacco product applications - Draft Guidance. 2012.

FDA (Food and Drug Administration). Guidance for industry - Patient-reported outcome measures: use in medical product development to support labeling claims. 2009.

Frost-Pineda K, Zedler BK, Oliveri D, Feng S, Liang Q, Roethig HJ. Short-term clinical exposure evaluation of a third-generation Electrically Heated Cigarette Smoking System (EHCSS) in adult smokers. Regul Toxicol Pharmacol. 2008; 52:104-10.

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.

Hughes JR, Hatsukami D. Background on the Minnesota Withdrawal Scale-Revised (MNWS-R). 2012; Available from: http://www.uvm.edu/medicine/behaviorandhealth/documents/Background_8_2012.pdf (Accessed on 11 July 2016).

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Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry. 1986; 43(3):289-94.

Hughes JR, Keely JP, Fagerstrom KO, Callas PW. Intentions to quit smoking change over short periods of time. Addict Behav. 2005; 30(4):653-62.

IARC (International Agency for Research on Cancer). IARC handbook of cancer prevention: methods for evaluating tobacco control policies. Chpater 3.1. ed.: 2008. Measuring tobacco use behaviours. p. 75-105.

IARC (International Agency for Research on Cancer). Measuring tobacco use behaviours. IARC handbook of cancer prevention: methods for evaluating tobacco control policies. 122008. p. 75-105

IOM. Scientific standards for studies on modified risk tobacco products Washington DC: The National Academies Press; 2012.

IOM (Institute of Medicine). Scientific standards for studies on modified risk tobacco products. Washington, DC: The National Academies Press. 2012.

Jassem J, Przewozniak K, Zatonski W. Tobacco control in Poland-successes and challenges. Transl Lung Cancer Res. 2014; 3(5):280-5.

King BA, Hyland AJ, Borland R, McNeill A, Cummings KM. Socioeconomic variation in the prevalence, introduction, retention, and removal of smoke-free policies among smokers: findings from the International Tobacco Control (ITC) Four Country Survey. 2011.

Parascandola M, Hurd AL, Augustson E. Consumer awareness and attitudes related to new potential reduced-exposure tobacco products. Am J Health Behav. 2008; 32(4):431-7.

Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. J Consult Clin Psychol. 1983; 51(3):390-5.

Rodu B, Plurphanswat N, Hughes JR, Fagerstrom K. Associations of proposed relative-risk warning labels for snus with perceptions and behavioral intentions among tobacco users and nonusers. Nicotine Tob Res. 2015.

Roethig HJ, Zedler BK, Kinser RD, Feng S, Nelson BL, Liang Q. Short-term clinical exposure evaluation of a second-generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol. 2007; 47:518.

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

Shiffman S, Pillitteri JL, Burton SL, Di Marino ME. Smoker and ex-smoker reactions to cigarettes claiming reduced risk. Tob Control. 2004a; 13(1):78-84.

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

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Theophilus EH, Coggins CRE, Chen P, Schmidt ER, Borgerding MF. Magnitudes of biomarker reductions in response to controlled reductions in cigarettes smoked per day: a one-week clinical confinement study. Regul Toxicol Pharmacol. 2015; 71(2):225-34.

Tiffany ST, Drobes DJ. The development and initial validation of a questionnaire on smoking urges. Br J Addict. 1991; 86:1467-76.

Tricker AR, Jang IJ, Martin Leroy C, Lindner D, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 4: eight-day randomized clinical trial in Korea. Regul Toxicol Pharmacol. 2012a; 64(2 Suppl):S45-53.

Tricker AR, Kanada S, Takada K, Martin Leroy C, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 6: 6-day randomized clinical trial of a menthol cigarette in Japan. Regul Toxicol Pharmacol. 2012b; 64:S64-S73.

Tricker AR, Stewart AJ, Leroy CM, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 3: eight-day randomized clinical trial in the UK. Regul Toxicol Pharmacol. 2012c; 64:S35-S44.

U.S Department of Health and Human Services. Preventing tobacco use among youth and young adults - a report of the Surgeon General. 2012; Available from: http://www.surgeongeneral.gov/library/reports/preventing-youth-tobacco-use/full-report.pdf (Accessed on 07 July 2016).

Wackowski OA, Bover Manderski MT, Delnevo CD, Giovenco DP, Lewis MJ. Smokers' early E-cigarette experiences, reasons for use, and use intentions. Tob Regul Sci. 2016; 2(2):133-45.

West R, Ussher M, Evans M, Rashid M. Assessing DSM-IV nicotine withdrawal symptoms: a comparison and evaluation of five different scales. Psychopharmacology (Berl). 2006; 184:619-27.

World Medical Association (WMA). Ethical principles for medical research involving human subjects (Declaration of Helsinki). 2008.

Zhu SH, Gamst A, Lee M, Cummins S, Yin L, Zoref L. The use and perception of electronic cigarettes and snus among the U.S. population. PLoS ONE. 2013; 8(10):e79332.

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