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Appendix

Appendix A6.2.3.1. PMI draft manuscript: Sanders E, Weitkunat R and Dempsey R. Menthol cigarettes, time to first cigarette, and smoking cessation

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6.2.3. Abuse Liability Summary

6.2.3.1. Background

In the draft guideline issued by Food and Drug Administration (FDA) in 1990, the term ‘‘abuse liability’’ refers to the likelihood that a drug with psychoactive or central nervous system effects will sustain patterns of non-medical self-administration that result in disruptive or undesirable consequences. In other words abuse liability is conceptualized through variations in either the likelihood/severity of self-administration or the likelihood/severity of undesirable consequences (FDA 1990). A more recent FDA draft guideline (USDHHS 2010) has restricted the definition of dependence potential (used interchangeably with abuse liability) and refers to a drug that is used in nonmedical situations, repeatedly or even sporadically, for the positive psychoactive effects it produces.

The Modified Risk Tobacco Product (MRTP) Application Draft Guidance for Industry defines abuse liability as the likelihood that individuals will develop physical and/or psychological dependence on the tobacco product (USDHHS 2012). Thus, the FDA Center for Tobacco Products’ (CTP) use of the term abuse liability is similar to assessing nicotine dependence using DSM-IV/DSM-V diagnostic (medical) criteria and defines it as dependence liability: nicotine use is characterized, both, as for a substance use disorder (dependence/abuse), and for a substance-induced disorder (withdrawal symptoms).

The public health perspective encompasses dependence potential assessment to address the pharmacologically determined risk of abuse and the risk of harm resulting from abuse (see Figure 1).



Figure 1. Abuse Liability – Public Health Insight

There is a continuum of reinforcement value (reinforcement is generally defined as the capacity of an agent to sustain self-administration), and in theory, a desirable MRTP should be more reinforcing than nicotine replacement therapy (NRT) products (IOM 2012). It should be sufficiently reinforcing so as to attract smokers away from conventional cigarettes but not enough to encourage the widespread dependent use of the product by individuals who were previously nonusers, or who would have quit smoking (IOM 2012).

It was part of PMI program to evaluate perceived risk perception, acceptance of the Tobacco Heating System (THS), and assess subjective effects already in pre-market and

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at the time of the MRTP application. Consumer behavior and use pattern will continue to be monitored post market (See Module 8). The evaluation of dependence potential alone is insufficient to assess the product impact on the individual health or the population as a whole. Assessment of abuse liability of THS should also consider the risks and/or harm resulting from dependence, and be comparative, e.g., to other tobacco/nicotine products.

PMI therefore considers a balanced view of abuse liability assessment (ALA) taking into account the potential of the product to cause dependence and the potential harm resulting from that dependence compared to other tobacco products. This is achieved for THS by evaluating various ALA domains (components) covering the majority of facets (as described in Carter 2009) involved in abuse liability (see Table 1). The likelihood that the self-administration of a product (or a drug) will result in persistent use or abuse is associated with its psychoactive or central nervous system effects, which can result in both positive and negative subjective effects, its reinforcing effects, and with tolerance, craving, and withdrawal that can result after repeated use of the product.

A greater likelihood of dependence is associated with faster speed of nicotine delivery and its rewarding effects. Conversely, adverse effects from a product can also influence abuse, e.g., the occurrence of undesirable adverse health effects such as nausea can lower the likelihood of repeated self-administration. The formulation and technical design of a product can also contribute to its abuse liability. For example, nicotine-containing products that are inhaled into the lungs are associated with faster rate of absorption (of nicotine) and tend to have greater abuse liability than products that are used orally.

Other elements such as the addition of flavorant agents, the overall look and feel of the product or its possibly disruptive mode of use (vs. the usual way of smoking) may have a positive or negative impact on the overall product attractiveness and accordingly its potential for abuse

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Table 1. ALA Domains Used for THS Abuse Liability Assessment

Cluster	Domains / Components	Measurements
Product features	1. Product design	Product description and content (nicotine, menthol)
	2. Aerosol chemistry	Delivery of nicotine, acetaldehyde and ammonia
Likelihood of use	3. Pharmacokinetic effects	Nicotine pharmacokinetics (absorption rate and extent) Nicotine uptake
	4. Pharmacodynamic effects	Subjective effects
	5. Reinforcing effects	Product use behavior in various studies Perception (heath risks, addiction risk), comprehension Intention to use by various populations
Consequence of use	6. Impaired functioning	Cognitive assessment Psychomotor performance Withdrawal symptoms
	7. Physical dependence	Withdrawal symptoms
	8. Adverse events	Aversive adverse events Nervous system disorders

Derived from Carter 2009

Several studies conducted by PMI on THS contribute to the assessment of THS abuse liability. These studies are listed in Table 2 together with relevant endpoints. None of these studies were specifically designed to test addiction potential, but they collectively cover the majority of ALA components.

Table 2. THS Studies Relevant for ALA

Study Types	Studies	Endpoints
Product analysis and nonclinical studies	Product characterization / chemistry • THS Regular • THS Menthol 1 (low menthol) • THS Menthol 2 (high menthol)	Nicotine yields Acetaldehyde yields Ammonia yields
	in vitro and i*n vivo* studies	None relevant for ALA

(table continues)

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Study Types	Studies	Endpoints
Randomized Clinical studies	Single use pharmacology studies with THS Regular • ZRHR-PK-01-EU • ZRHR-PK-02-JP Single use pharmacology studies with THS Menthol (high menthol) • ZRHM-PK-05-JP • ZRHM-PK-06-US	Nicotine pharmacokinetics (PK) (rate and extent of absorption) after 1-day nicotine washout Subjective effects Solicited adverse events
	5-day reduced exposure studies with THS Regular • ZRHR-REXC-03-EU • ZRHR-REXC-04-JP	Nicotine pharmacokinetics (repeated use) Nicotine uptake Subjective effects Product use in confinement Human puffing topography Withdrawal symptoms Solicited adverse events
	3-month reduced exposure studies with THS Menthol (high menthol) • ZRHM-REXA-07-JP • ZRHM-REXA-08-US	Nicotine uptake Subjective effects Product use in confinement and ambulatory Human puffing topography Withdrawal symptoms Solicited adverse events
Perception and behavior assessment studies and market research tests	Label, labeling and marketing material assessment studies • THS-PBA-05-RRC-US • THS-PBA-05-RRC2-US • THS-PBA-05-REC-US	Intent to use Comprehension Risks (health risks, addiction risk) perception
	Usability and Comprehension study • THS-PBA-06-US	Ability to understand and correctly comply with the instruction of use
	6-week actual use study with THS Regular and THS Menthol 1 • THS-PBA-07-US	Tobacco products use (THS, CC, others)
	4-week whole offer tests (WOT) with various THS variants • Analysis of WOT data	Product use from 5 market research studies outside the US
Surveillance	Passive safety surveillance	Unsolicited adverse events

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While most of the endpoints relevant for ALA were measured in adult smokers at different time points depending on the duration of product use, some, such as intent to use or risk perception, were also measured in non-smokers (including young adults) without being using THS during the study (see Table 3).

Table 3. ALA Endpoints and THS Use Duration in Humans

ALA Domain	Endpoints	No use	Single use	5 days	4 weeks	6 weeks	3 months	Post-market
Study type (number of studies)	*PK/PD (n=4)*		X					
	REXC (n=2)			X				
	REXA (n=2)			X			X	
	PBA05 (n=3)	X						
	PBA07 (n=1)					X		
	WOT (n=5)				X			
	Surveillance							X
Pharmaco-kinetics	Nicotine PK		X	X				
	Cotinine			X			X	
	NEQ			X			X	
Pharmaco-dynamics	QSU-brief		X	X			X	
	MCEQ		X	X			X	
	FTND						X	
Reinforcing effects	Product use		X	X	X	X	X	
	Intent to use	X				X		
	Risk perception	X				X		
	Comprehension	X						
Impaired functioning	MNWS			X			X	
	Solicited AEs		X	X			X	
	Unsolicited AEs				X	X		X
Physical dependence	MNWS			X	X		X	
	FTND						X	
Adverse events	Aversive AEs		X	X	X	X	X	X
	Nervous system		X	X	X	X	X	X

Abbreviations. AEs: adverse events; FTND: Fagerström test for nicotine dependence; MCEQ: modified cigarette evaluation questionnaire; MNWS: Minnesota nicotine withdrawal symptoms; NEQ: nicotine equivalents; QSU: Questionnaire on smoke urges

Type of studies. PBA: perception and behavior assessment; PK/PD: pharmacokinetics /pharmacodynamics (pharmacology) clinical study; REXA: reduced exposure ambulatory; REXC: reduced exposure in confinement; WOT: whole offer test.

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Close to 13'000 individuals participated in eight clinical studies, five whole offer test (WOT) market research studies and five perception and behavior assessment (PBA) studies, contributing to the ALA of THS. The smoking status of these study populations is shown in Table 4. The general characteristics of study population were as follows:

- Clinical studies: adult daily smokers in good health conditions with no intention to quit smoking within the next three months
- Label, labeling and marketing material assessment studies: adult smokers with no intention to quit smoking; adult smokers with intention to quit smoking, adult former smokers (having quit smoking more than 30 days ago) and adult never-smokers (had smoked fewer than 100 CC in their life), including young adult never-smokers age between legal age and 25 years of age
- Other studies: adult daily smokers.

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Table 4. Study Populations and Smoking Status at Enrolment

	Smokers with No Intention to Quit [(a)]	Smokers with Intention to Quit	Former Smokers	Never Smokers	Never Smokers LA - 25	Total
Clinical studies						939
• ZRHR-PK-01-EU	62					
• ZRHR-PK-02-JP	65					
• ZRHM-PK-05-JP	73					
• ZRHM-PK-06-US	64					
• ZRHR-REXC-03-EU	169					
• ZRHR-REXC-04-JP	166					
• ZRHM-REXA-07-JP	175					
• ZRHM-REXA-08-US	165					
Label, labeling & marketing material assessment studies						
• THS-PBA-05-RRC-US	472	472	471	477	478 [(b)]	2255
• THS-PBA-05-RRC2-US	471	475	469	468	471[(b)]	2247
• THS-PBA-05-REC-US	479	479	480	480	480 [(b)]	2272
Usability & comprehension study						
• THS-PBA-06-US	258					258
Observational studies						
• THS-PBA-07-US (FAS)	1106					1106
• Whole offer tests						3922
o Japan	868					
o Italy	800					
o Germany	605					
o Switzerland	581					
o South Korea	1068					
Grand Total	**7647**	**1426**	**1420**	**1425**	**1429**	**12'999**

FAS: full analysis set population: LA-25: age between adult legal age and 25 years
(a) includes also adult daily smokers with intention to quit not specified
(b) a subset of never smokers LA-25 are also in the never-smokers group
[Source: Respective study reports, Module 7, Section 7.3.1, Section 7.3.2 and Section 7.3.3]

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Across clinical studies, smokers of menthol CC were not evidently more dependent to nicotine (based on FTND scores at baseline) than smokers of non-menthol CC at baseline. Proportions of heavy smokers (reporting smoking more than 19 CC per day) were ranging from 36 to 48% and from 32 to 50% in menthol CC smokers and in non-menthol CC smokers, respectively. Proportions of smokers with severe nicotine dependence (FTND score between 7 and 10, as defined in study protocols) were ranging from 8 to 34% (highest proportion in US study ZRHM-REXA-08-US) and from 11 to 27% (highest proportion in Polish study ZRHR-REXC-03-EU) in menthol CC smokers and in non-menthol CC smokers, respectively.

African Americans represented a significant proportion of subjects/participants enrolled in the studies conducted in the US, ranging from approximately 13% to 55% across studies and study arms (27.5% in the actual use study THS-PBA-07-US).

6.2.3.2. ALA Domain 1 - Product Design

The product design of THS is described in detail in Module 3, Section 3.1. In summary, THS is a system composed by three main components (see Figure 2):

- A Tobacco Stick, which is designed to function with the Holder.
- A Holder, which is a slim electrical heating unit that heats the tobacco stick in a controlled manner and stores enough energy for a single experience. The power supply for the Holder is the Charger.
- A Charger, which holds enough energy for approximately 20 experiences and can be recharged from household power. The Charger stores the Holder when not in use, and provides a safe, secure environment for the cleaning process of the heater blade. These two units, together with essential accessories, are collectively known as the Tobacco Heating Device (THD).



Figure 2. Picture of Tobacco Heating System

The Holder and the Tobacco Stick deliver puffs over a period of about 6 minutes or 14 puffs (whichever comes first), with the LED indicating the end of the inhalation experience. Once this cycle is complete, the Holder must be recharged before a new Tobacco Stick can be used.

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There are three tobacco stick variants expected to be introduced in the US market, THS Regular and THS Menthol with two menthol levels (Menthol 1 and Menthol 2, also referred as low menthol and high menthol, respectively – see Module 3). During the course of the assessment of THS in humans, several variants (tobacco blends / flavor systems) were used (see additional details in Module 6, Section 6.1.5, Appendix 1).

The THS product design has an advanced technology and sophisticated look, which may be attractive for some consumers while it could be seen as cumbersome and/or disruptive for others. Due to its technology, THS requires more handling than a traditional cigarette, such as charging the holder after the use of each tobacco stick, charging time for the holder (approximately six minutes), and holder cleaning. Other potential disruptive limitations include (b) (4) , and the absence of burning (the length of the tobacco stick remains unchanged after use and there is no production of ash, i.e. no flicking ritual). Similarly, due to the absence of burning of the tobacco stick, the lack of combustion byproducts with "flavoring" / organoleptic characteristics may be seen as attractive for some consumers and bystanders (e.g., less smell) and less satisfying for others. Product satisfaction (see Section 6.2.3.5) and actual product use (see Section 6.2.3.6) are proxy measures on product acceptance influenced by product design features.

6.2.3.2.1. Nicotine in Tobacco Stick

The relative content nicotine in the tobacco filler (see Table 5) for both THS Regular and THS Menthol tobacco sticks (around 18mg/g tobacco, 1.8%) is toward the lower range of nicotine content in CC marketed in the US (1.84% – 2.41%) (Bodnar 2012) and approximately 20% below the 2.25% level found in the reference cigarette 3R4F (Eldridge 2015). Due to the two to three-fold lower weight of the THS tobacco plug (vs. CC), the average nominal nicotine content is substantially lower (around 4.4 to 4.8mg/stick) than in a CC. However, it is more relevant to discuss abuse liability based on nicotine deliveries, i.e., nicotine yields in aerosol from THS tobacco stick (see Section 6.2.3.3.1).

Table 5. Nicotine Content in THS Tobacco Filler (3 Batches)

	THS Regular variant	THS Menthol 1 (low menthol)	THS Menthol 2 (high menthol)
Nicotine per gram tobacco (µg/g, average per batch)	17809 – 17827 – 17942	18246 –18564 – 18791	17591 – 17759 – 18000

[Source: Module 3, Section 3.3]

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6.2.3.2.2. Menthol in Tobacco Stick

The menthol yields in the two THS Menthol tobacco stick variants expressed as menthol in aerosol (MIA) are 0.7mg ISO (1.5mg Health Canada Intense regime) per unit for Menthol 1 (low menthol) and 1.2mg ISO (2.26mg Health Canada Intense) for Menthol 2 (high menthol) (see Module 3, Section 3.1, Tobacco Stick Ingredients, for menthol quantity in tobacco). Another high menthol variant (MIA 1.2mg ISO) was assessed in some clinical studies (see Table 2). The menthol level in both menthol variants (Menthol 1 and Menthol 2) are within the range of menthol cigarettes currently marketed in the US. In a report prepared by Altria Client Services (ALCS) for the Tobacco Products Scientific Advisory Committee (TPSAC) meeting held in 2011 on mentholated cigarettes (ALCS 2010), levels of menthol in whole cigarette (tobacco filler and filter) and menthol in smoke were measured in 64 US cigarettes (period 2008 – 2009), representing 80% of US market share of menthol CC segment. The levels of menthol in smoke ranged from 0.35 to 1.29mg/cig (approximately 80% within the range 0.47 to 0.82mg/cig) and levels in whole cigarette from 2.6 to 9.8mg/cig. A recent work published by the FDA CTP (Ai 2015) found the menthol levels in whole cigarettes (from 22 most popular US CC) ranging from 2.9 to 19.6mg/cig. Excluding the three products exceeding 10mg/cig, the menthol levels were ranging from 2.9 to 7.2mg/cig, confirming results from ALCS study.

The FDA's opinion (USDHHS 2013) based on the thorough review of available scientific information relevant to the impact of menthol tobacco products on public health, is summarized as follows: "*While there is little evidence to suggest that menthol cigarettes are more or less toxic or contribute to more disease risk to the user than nonmenthol cigarettes, adequate data suggest that menthol use is likely associated with increased smoking initiation by youth and young adults. Furthermore, the data indicates that menthol in cigarettes is likely associated with greater addiction. Menthol smokers show greater signs of nicotine dependence and are less likely to successfully quit smoking. These findings, combined with the evidence indicating that menthol's cooling and anesthetic properties can reduce the harshness of cigarette smoke and the evidence indicating that menthol cigarettes are marketed as a smoother alternative to non-menthol cigarettes, make it likely that menthol cigarettes pose a public health risk above that seen with non-menthol cigarettes*.".

PMI conducted recently a literature review on menthol in cigarettes (See draft manuscript in Appendix A.6.2.3.1). The conclusion of PMI's review provides an additional insight which differs from FDA's opinion. The goal was to determine if menthol and non-menthol cigarette smokers differ with respect to time to first cigarette (TTFC) and successful smoking cessation via a meta-analysis of published results. For 13 independent estimates, menthol smokers displayed a small but statistically significant shorter TTFC<5 min (random-effects odds ratio (OR) = 1.12; 95% confidence interval (CI), 1.04-1.21), while 17 independent estimates provided a non-significant difference for TTFC<30 min (random-effects OR = 1.06; 95% CI, 0.96-1.16). For cessation studies, meta-analysis of 30 published estimates indicated a decreased likelihood for menthol cigarette smokers to quit (random-effects OR = 0.87; 95%CI, 0.80-0.96). There was no difference between cessation rates for Caucasian menthol and non-menthol cigarette smokers, but the results support that African American menthol cigarette smokers find it

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more difficult to quit. Adjustment of cessation for socioeconomic status eliminated any statistically significant advantage for smoking cessation in non-menthol smokers. In conclusion, these results suggest that the observed differences in cessation rates between menthol and non-menthol cigarette smokers can consistently be explained by differences in socioeconomic status and that menthol cigarettes do not differ from their non-mentholated counterpart for cigarette addiction.

6.2.3.3. ALA Domain 2 - Addictive HPHCs in THS Aerosol

The FDA (USDHHS 2012a) has issued the full list of harmful and potentially harmful constituents (HPHC), including four HPHCs classified as addictive (nicotine, nornicotine, anabasine and acetaldehyde). In the FDA draft guideline on abbreviated list of HPHCs (USDHHS 2012b), the list of addictive HPHCs is restricted to nicotine and acetaldehyde.

The THS aerosol chemistry methodology and results for THS variants are summarized in Module 6, Section 6.1.1. Aerosol chemistry data were generated under Health Canada Intense smoke regime laboratory conditions as these conditions are more representative of the human smoking topography patterns). HPHC yields from THS aerosol were compared to the Kentucky reference cigarette 3R4F.

The HPHC yields with addiction potential (USDHHS 2012b), i.e., nicotine and acetaldehyde, are presented in Table 6. Two additional compounds, menthol and ammonia, not listed as HPHCs with addictive potential, are also considered here. Menthol, as an ingredient in the mentholated Tobacco Stick variants and ammonia yields in THS aerosol are reviewed as these two constituents are subject to many discussions on their potential direct or indirect role on addiction as mentioned in recent reports issued by the FDA (USDHHS 2013), by the Surgeon General (USDHHS 2014) and by the European Commission (SCENIHR 2016). Menthol is discussed above in Section 6.2.3.2.2.

Table 6. Comparative Aerosol Chemistry THS (Nicotine, Acetaldehyde and Ammonia) vs. 3R4F

Aerosol Constituents (Health Canada Intense Regime)	THS Regular	THS Menthol 1 (low menthol)	THS Menthol 2 (high menthol)
Nicotine (mg/stick) – mean (SD)	1.29 (0.047)	1.19 (0.05)	1.17 (0.03)
Acetaldehyde			
• Nominal yield (µg per stick) – mean (SD)	192 (11.6)	206 (6)	192 (9)
• Relative yield per mg nicotine vs. 3R4F	16.2%	19.9%	19.1%
Ammonia			
• Nominal yield (µg per stick) – mean (SD)	12.2 (0.973)	11.1 (1.1)	10.7 (0.943)
• Relative yield per mg nicotine vs. 3R4F	49.8%	53.6%	66.0%

SD: standard deviation
[Source: Module 6, Section 6.1.1]

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6.2.3.3.1. Nicotine in THS Aerosol

The average nicotine delivery in aerosol from the three THS variants, Regular, Menthol 1 and Menthol 2, under Health Canada intense regime are 1.29mg/stick, 1.19mg/stick, and 1.17mg/stick respectively (see Table 6). This is within the lower-end range (1.32 to 4.92mg nicotine per cigarette) from a representative sample of cigarettes sold on the US market in 2009 (Bodnar 2012). Nicotine yields from THS are approx. 25%, 35% and 40% lower vs. the Kentucky reference cigarette 3R4F for THS Regular THS Menthol 1 and THS Menthol 2, respectively as well below (approx. 36%, 41% and 42%, respectively) the 2mg median nicotine yields from 31 US CC brands as detailed in Module 6, Section 6.1.1.

6.2.3.3.2. Minor Tobacco Alkaloids and Acetaldehyde in THS Aerosol

There are no available data for THS on minor tobacco alkaloids (i.e., nornicotine and anabasine). Information from published literature is provided. Nicotine represents usually more than 95% of all alkaloids found in tobacco (Lisko 2013). Other minor tobacco alkaloids (including nornicotine and anabasine) have been measured in 50 popular US cigarettes and their yields in tobacco were found to be at one order of magnitude lower that nicotine and at similar levels to those measured in the Kentucky reference cigarette 3R4F (Lisko 2013).

As compared to 3R4F on a per mg nicotine basis, the amount of acetaldehyde delivered in the THS aerosol under Health Canada intense regime is approx. 84%, 80% and 88% lower for the THS Regular, THS Menthol 1 and THS Menthol 2 variant, respectively (see Table 6). It is unclear what this reduction means in term of THS abuse liability in humans as the currently knowledge is limited to *in vivo* experimental data suggesting a potential role of acetaldehyde in ethanol addiction (Hoffman 2013).

In a recent review published by the FDA CTP, the authors concluded that further research is needed to determine the abuse potential of non-nicotine tobacco smoke constituents (Hoffman 2013).

6.2.3.3.3. Ammonia in THS Aerosol

Ammonia yields in aerosol from THS variants (11.1, 12.2 and 10.7µg/stick, Health Canada intense regime and approximately half of the yield measured in 3R4F, see Table 6) can be qualified as low when compared to published literature (see McKinney 2011), where the ammonia yield is 10.1 µg/cigarette (Federal Trade Commission regime) for the low level ammonia cigarette. The average ammonia yields in THS aerosol is also 69.3% lower than the median yields from 31 US CC brands, as detailed in Module 6, Section 6.1.1.

Unprotonated nicotine ("freebase") and its role to reinforce nicotine delivery through presence of ammonia in tobacco has been raised as possible concern but could not be substantiated. Comparing arterial blood nicotine pharmacokinetics of high diammonium phosphate and low diammonium phosphate containing cigarettes, no differences were detected between CC with high or low ammonia yields (McKinney 2011).

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More recently, the European Commission's opinion on additives in tobacco products, despite some studies indicating that ammonium compounds increases the pH of the smoke which would consequently increase the amount of unprotonated/free nicotine, is that it cannot be concluded that it may result in faster and increased absorption of nicotine (SCENIHR 2016).

Based on the above considerations, it is reasonable to conclude that the ammonia yields in THS aerosol would not affect the nicotine pharmacokinetics and therefore do not raise an abuse liability concern for THS.

6.2.3.3.4. Conclusion on Aerosol Chemistry

Based on available aerosol chemistry data and considerations from the literature, the abuse liability resides primarily with nicotine delivery (yield in aerosol) which is within the range (toward the lower range) of nicotine delivered by CC, supporting a similar abuse liability THS vs. CC.

6.2.3.4. ALA Domain 3 - Nicotine Exposure in Humans

For a long time, health scientists viewed smoking as primarily psychological and social, rather than under a pharmacological or biological point of view. The 1988 report of the Surgeon General, reviewing new available scientific evidence on smoking and addiction, concluded that: "Cigarettes and other forms of tobacco are addicting" and "Nicotine is the drug in tobacco that causes addiction" (USDHHS 2014, p30). Addiction to nicotine arises from a combination of genetic, environmental and pharmacological factors, but the characteristics of the nicotine delivery system are also crucially important (RCP 2007). This section will not discuss the mechanisms involved in nicotine addiction but will focus on specific nicotine pharmacokinetic characteristics known to be influential in nicotine addiction, such as the rate and extent of nicotine absorption, nicotine exposure and how these characteristics from THS compare with those from CC.

Four clinical studies have been conducted with THS Regular and four with THS (high) Menthol (see Table 2 and Table 7). The yield of menthol in aerosol from THS Menthol was 1.20mg/stick ISO for these four studies. The THS use instructions were described in the study protocols and summarized in Table 7. Apart from the ambulatory period of the two 3-month studies, during which the use of tobacco and nicotine products was self-reported in a diary, the product use was controlled and closely monitored by study staff. Smokers of nonmenthol CC were enrolled in clinical studies with the THS Regular variant, while smokers of menthol CC were enrolled in the THS Menthol variant studies.

Nicotine exposure was measured in all 8 clinical studies as follows:

- Nicotine pharmacokinetics after single use of THS and CC, and after THS and NRT product use in the four crossover studies
- Nicotine and cotinine pharmacokinetics after five days of repeated use of THS and CC *(ad libitum* exclusive use within a large but fixed use time window), and
- Nicotine exposure over 3 months of actual use of THS and CC, based on plasma cotinine and urinary excretion of nicotine and its five major metabolites, referred as nicotine equivalents (NEQ) (*ad libitum* actual use).

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Table 7. Product Use Instruction in Clinical Studies

Study Code	Country	Study Design	Exposure Duration	THS Use Instructions
THS Regular				
ZRHR-PK-01-EU	Poland	Cross-over	1-stick use	Puffing as desired
ZRHR-PK-02-JP	Japan	Cross-over	1-stick use	Puffing as desired
ZRHR-REXC-03-EU	Poland	3-arm parallel	5 days	*Ad libitum* exclusive use
ZRHR-REXC-04-JP	Japan	3-arm parallel	5 days	*Ad libitum* exclusive use
THS Menthol				
ZRHM-PK-05-JP	Japan	Cross-over	1-stick use	Puffing as desired
ZRHM-PK-06-US	USA	Cross-over	1-stick use	Puffing as desired
ZRHM-REXA-07-JP	Japan	3-arm parallel	3 months	*Ad libitum* exclusive 5 days in clinic and then 85 days ambulatory
ZRHM-REXA-08-US	USA	3-arm parallel	3 months	*Ad libitum* exclusive 5 days in clinic and then 85 days ambulatory

[Source: clinical study reports in Module 7.3.1]

6.2.3.4.1. Nicotine Pharmacokinetics after Single Use

The four single use clinical pharmacology studies were conducted in confinement settings, following the same crossover design. After at least 24 hours of smoking abstinence/nicotine washout, and following the single use of THS (puffing and inhaling as desired by subjects) and comparators (CC or NRT), serial blood samples were collected during 24 hours for the determination of nicotine plasma concentrations. Standard non-compartmental pharmacokinetics (PK) parameters were derived to compare the rate and extent of nicotine absorption in THS vs. CC and THS vs. NRT products (nicotine 2mg gum in Japan, and nicotine nasal spray in US and Europe). The maximum concentration (C_{max}) of nicotine in plasma and the time to C_{max} (t_{max}) were the two PK parameters used as a proxy for the rate (speed) of nicotine absorption while the area under the curve (plasma concentration vs. time) until last quantifiable nicotine plasma concentration ($AUC_{(0\text{-last})}$) represents the amount of nicotine absorbed in the body. Geometric least square means of ratio THS/CC and THS/NRT were carried out to compare C_{max} and AUC results. The full description and detailed results are provided in Module 6, Section 6.2.1.

Across the four single use clinical pharmacology studies, the time course of nicotine plasma concentrations after THS use was broadly similar to the time course after CC use, with a rapid peak within approximately six minutes (see Figure 3 and Figure 4). Of particular interest in the Japanese studies (ZRHR-PK-02-JP with THS Regular, and ZRHM-PK-05-JP with THS Menthol), mean ratios and median t_{max} were similar,

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suggesting that menthol does not have a deleterious impact on nicotine exposure after single use.

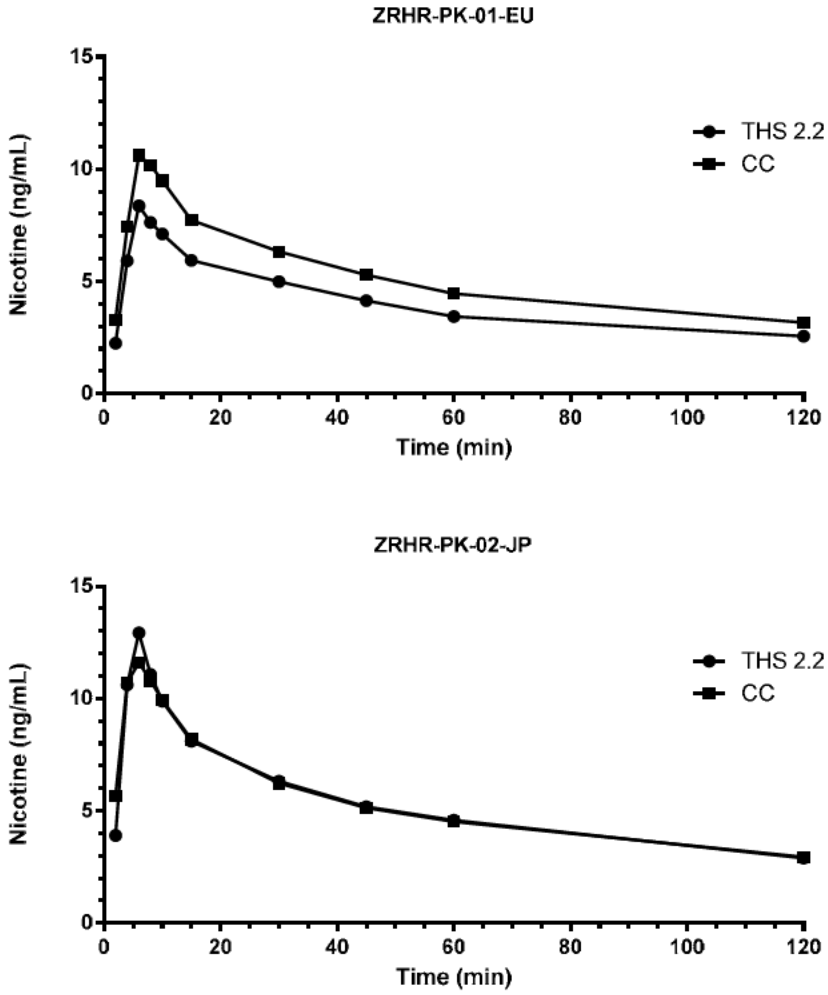


Figure 3. Plasma Nicotine after Single Use of THS Regular and CC

[Source: Appendix 15, Figure 15.1.2.1.1 ZRHR-PK-01-EU ; Appendix 15, Figure 15.1.2.1.1 ZRHR-PK-02-JP]

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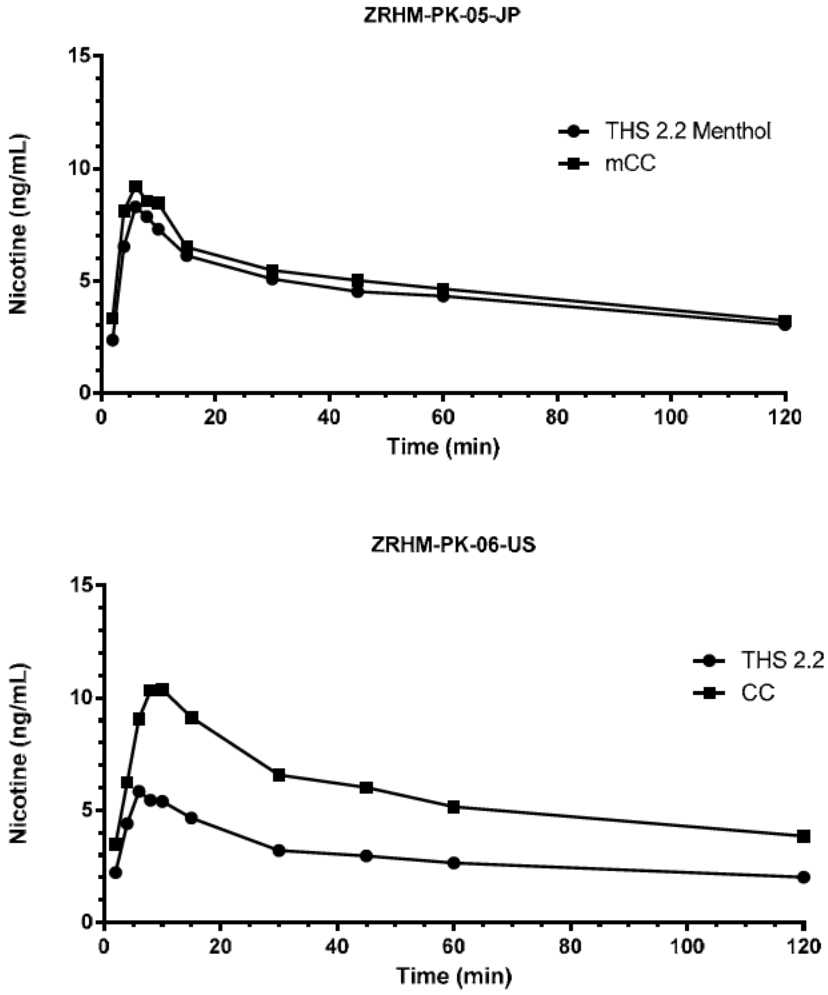


Figure 4. Plasma Nicotine after Single Use of THS Menthol and CC

[Source: Appendix 15, Figure 15.1.2.1.1 ZRHM-PK-05-JP; Appendix 15, Figure 15.1.2.1.1 ZRHM-PK-06-US]
mCC: menthol conventional cigarette

The rate and amount of nicotine absorption after single use of THS was higher than after NRT, with time to peak shorter than after NRT gum (see Figure 6) and with time to peak similar to nicotine nasal spray (see Figure 5).

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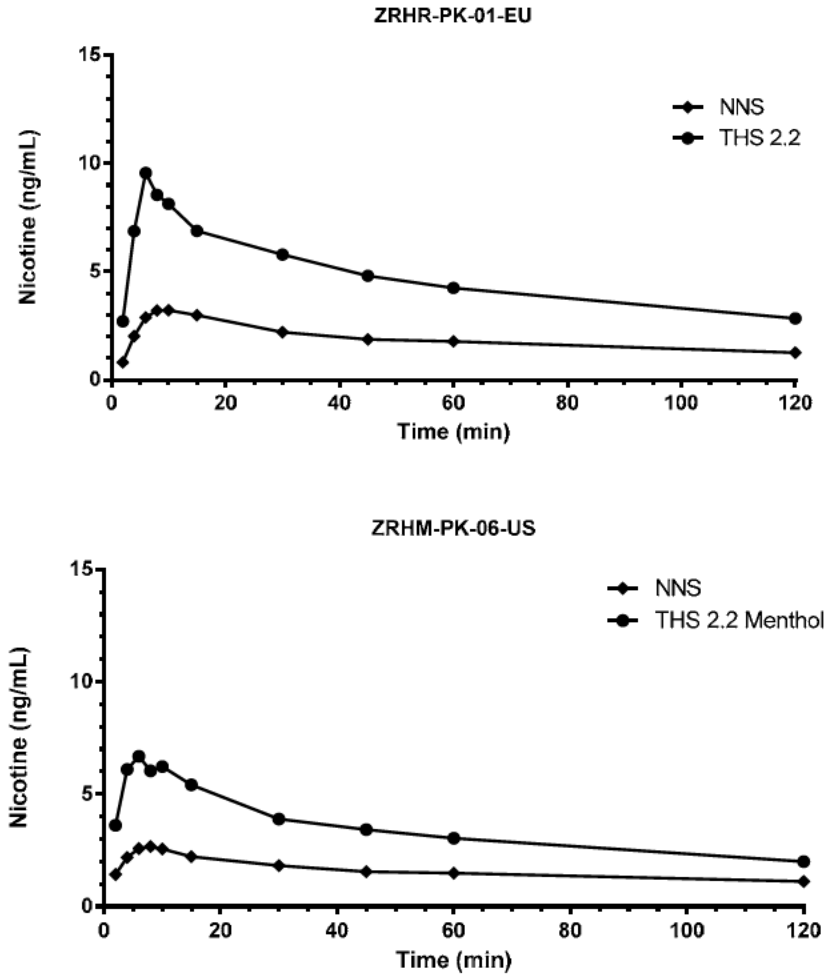


Figure 5. Plasma Nicotine after Single Use of THS and Nicotine Nasal Spray

[Source: Appendix 15, Figure 15.1.2.1.2. ZRHR-PK-01-EU ; Appendix 15, Figure 15.1.2.1.2 ZRHM-PK-06-US]
NNS : nicotine nasal spray

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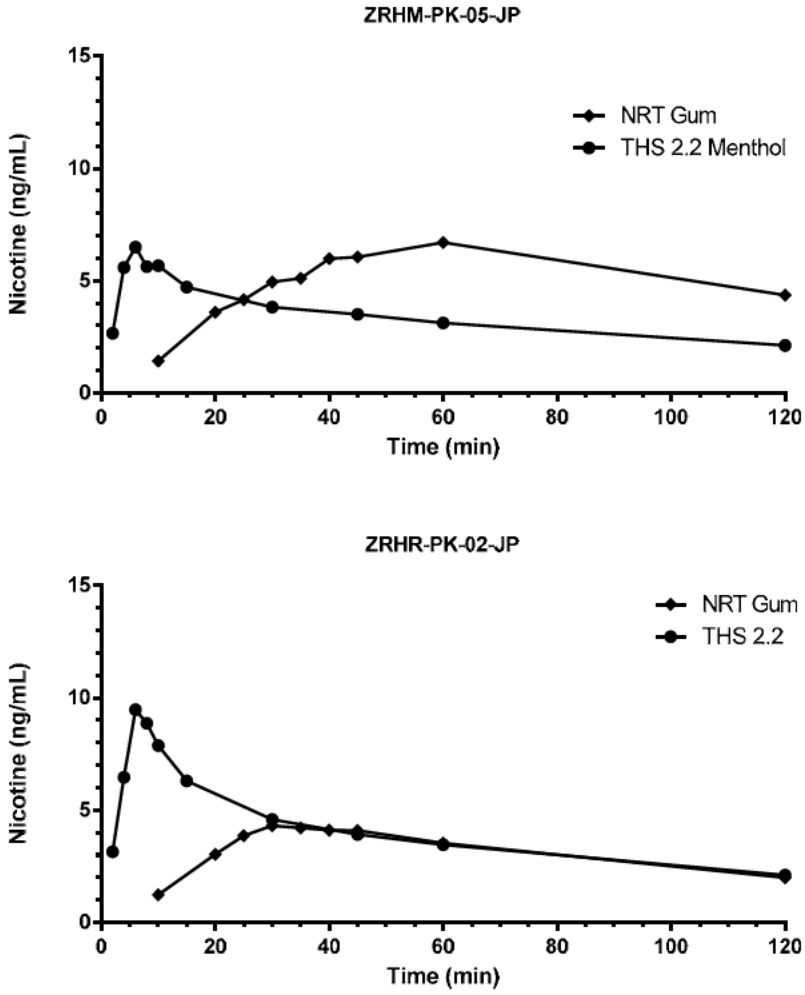


Figure 6. Plasma Nicotine after Single Use of THS and Nicotine 2mg Gum

[Source: Appendix 15, Figure 15.1.2.1.2 ZRHR-PK-02-JP; Appendix 15, Figure 15.1.2.1.2 ZRHM-PK-05-JP]

These study results suggest that the THS Regular and THS Menthol abuse liability, with respect to nicotine pharmacokinetics after single use in non-experienced users, is higher than for NRT products and is not higher than for CC.

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6.2.3.4.2. Nicotine Pharmacokinetics after Repeated Use

The two 5-day reduced exposure clinical studies were conducted in confinement settings, following the same three-arm parallel (THS, CC, and smoking abstinence (SA)) design. Study details and results are described in Module 6, Section 6.2.2. THS and CC use was closely monitored by study staff to ensure exclusive use of allocated product. Nicotine and cotinine plasma concentrations were measured twice a day (morning and evening) from baseline to Day 5 and once in the morning on Day 6 in all three study arms. In addition, serial blood samples were collected during the last day of repeated product use for the determination of nicotine and cotinine plasma concentrations. Standard non-compartmental pharmacokinetics parameters were derived for comparison of the rate (observed peak plasma concentration C_{peak}) and extent of nicotine absorption (weighted average plasma concentration C_{avg}) in THS vs. CC. The extent of nicotine exposure (nicotine uptake) was also evaluated daily by measuring the urinary excretion of nicotine and five major nicotine metabolites (namely cotinine, *trans*-3'-hydroxycotinine and their respective glucuronides) referred to as nicotine equivalents (NEQ) in all three arms. NEQ represents approximately 85 to 90% of the systemic nicotine dose/nicotine uptake (Benowitz 1999).

The results of systemic nicotine uptake, plasma cotinine and nicotine repeated dose PK after THS use were broadly similar to the results after smoking CC, but they were fairly heterogenic across the four studies and inconsistent with product use, suggesting that the adaptation to product is not yet achieved after five days of THS use. These results support the trend toward similar abuse liability (in its pharmacokinetics component) THS vs. CC observed after THS single use.

6.2.3.4.3. Three-month Nicotine Exposure and Nicotine Metabolism

Following a first week in confinement (see above Section 6.2.3.4.2), the two 3-month reduced exposure clinical studies were conducted during three months (85 days) in ambulatory settings. The studies had the same 3-arm parallel (THS, CC, and SA) design. As mentioned in Table 7, subjects allocated to THS were instructed to use THS exclusively, but the concomitant use of other tobacco products was not exclusionary. Cotinine plasma concentrations and urinary NEQ measurements were repeated at Day 30, Day 60, and Day 90. CYP2A6 activity (molar ratio of plasma *trans*-3'-hydroxycotinine and cotinine) was used to explore potential changes in nicotine metabolism upon switching to THS. Study details and results are described in more derails in Module 6, Section 6.2.2.

Urinary excretion of NEQ is a valuable parameter, directly reflecting the average nicotine exposure of the last 3 to 4 days, accounting for all the self-titration methods adopted by THS users to obtain the satisfying nicotine levels. The elimination half-life of nicotine in urine is 11 hours (Benowitz 1999), which represents a more stable nicotine exposure biomonitoring measurement compared to plasma nicotine.

As the terminal half-life of cotinine in plasma is much longer (16 hours) than for plasma nicotine (2 hours) (Benowitz 1999) concentrations of cotinine in plasma are also used as a proxy for nicotine exposure. Plasma cotinine is therefore used as an indirect

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measurement for the nicotine exposure covering nicotine/tobacco use for the last 3 – 4 days.

In both Japanese and US studies, per-protocol populations, the time courses of urinary NEQ (geometric mean) were broadly similar in THS (subjects characterized as predominantly THS users) vs. CC smokers (see Figure 7 and Figure 8). Similar outcomes were observed for plasma cotinine. Results from the full analysis set (i.e. including subjects using THS in combination with other tobacco products to various degrees, i.e. dual use) remain similar. For example, in ZRHM-REXA-08-US, the full analysis set population, the mean ratio THS/CC plasma cotinine and ratio THS/CC NEQ were 107.24% (vs. 104.30% in the per-protocol population) and 99.69% (vs. 96.30% in the per-protocol population), respectively, indicating that combined use of THS with other nicotine/tobacco products did not lead, on average, to nicotine overexposure.

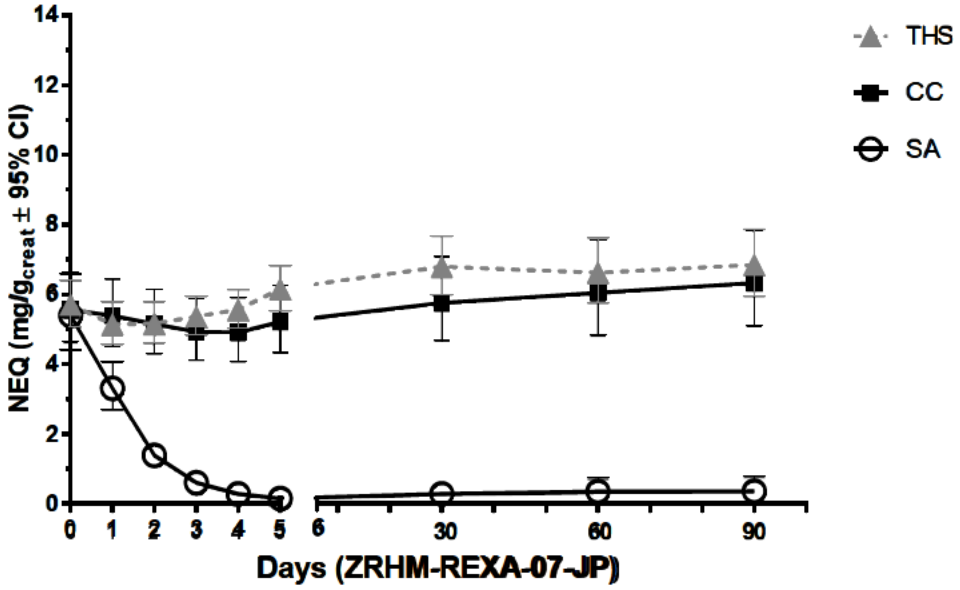


Figure 7. Nicotine (NEQ) in Urine during Study ZRHM-REXA-07-JP

NEQ is expressed in mg excreted in urine per g of creatinine
Abbreviations: creatinine (creat), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI).
[Source: Clinical Study Report ZRHM-REXA-07-JP: section 11.2.4.1, Appendix 15, Table 15.2.4.18.1 and Table 15.2.4.18.2, Table 90 and 91 and Appendix 15, Table 15.2.4.44]

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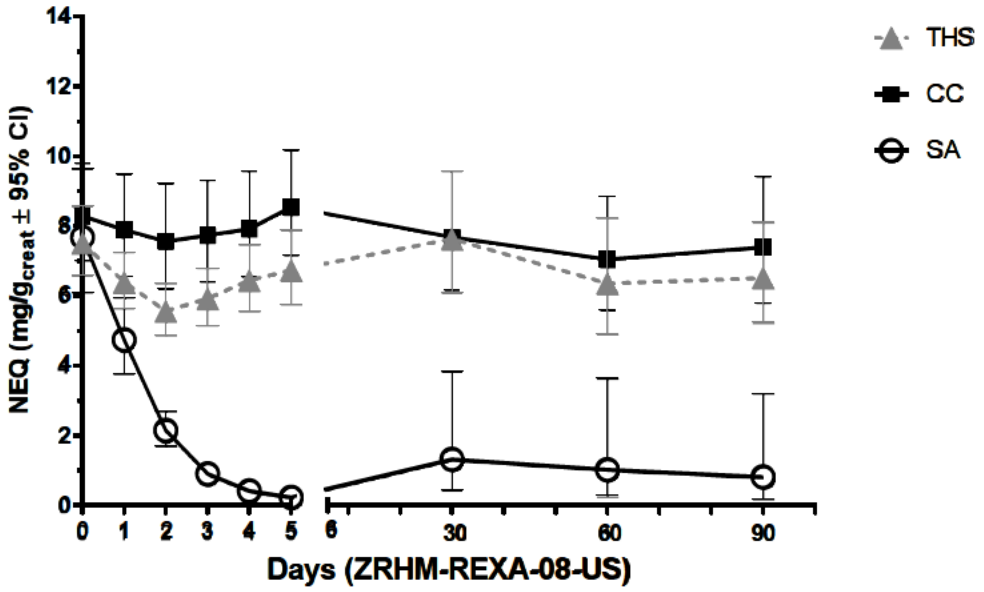


Figure 8. Nicotine (NEQ) in Urine during Study ZRHM-REXA-08-US

NEQ is expressed in mg excreted in urine per g of creatinine
Abbreviations: creatinine (creat), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI).
[Source: Clinical Study Report ZRHM-REXA-08-US: section 11.2.4.1, Table 98 and 99 and Appendix 15, Table 15.2.4.18.1 and Table 15.2.4.18.2]

CYP2A6 enzymatic activity (driving the metabolism of nicotine into cotinine) – also called CYP2A6 phenotype - can be used as an indirect measure of nicotine metabolism. The baseline levels of CYP2A6 activity were markedly different between studies, with levels ranging from 26.05% to 44.31% across all arms and studies. Across studies, the profiles of CYP2A6 activity over time were comparable in the THS arms to those observed in the CC arms. By contrast, CYP2A6 activities of subjects abstinent from smoking increased during the confinement periods of all studies, but then decreased during the ambulatory periods of the 3-month studies, remaining higher than in THS users and CC smokers. These results (data not shown, see detailed results in Module 6, Section 6.2.2) suggest that the nicotine metabolism remains unchanged upon switching from CC to THS, and therefore would not explain changes in cotinine levels, if any, after switching from CC to THS.

The nicotine exposure measured by plasma cotinine and by NEQ is an outcome of nicotine yield in the aerosol, the intrinsic nicotine pharmacokinetic properties followed by product use adaptation and nicotine self-titration. Product use adaptation is discussed in Section 6.2.3.6.1. The results suggest that 1) exposure to nicotine upon THS use (including dual use) tend to be similar with nicotine exposure with CC, and 2) self-titration / product use adaptation requires one month or more to reach a level close to CC. The data do not suggest that switching partially or completely to THS Menthol increases the exposure to nicotine. It can be reasonably assumed, extrapolating the 5-day

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data, that the nicotine exposure with THS Regular would not behave differently upon actual use.

The results suggest that after three months of product use, the THS abuse liability, with respect to nicotine exposure upon three months of THS use, is at par with CC.

6.2.3.4.4. Conclusion on Nicotine Pharmacokinetics and Exposure

The speed (rate) and amount of nicotine absorption, the levels of exposure to nicotine, measured by systemic nicotine levels (nicotine in plasma, cotinine in plasma, nicotine and metabolites excreted in urine), the absence of apparent changes in nicotine metabolism (based on CYP2A6 activity) upon various conditions and duration of use in the context of randomized clinical studies, do not indicate a higher risk of abuse liability with THS both variants, for smokers switching to THS, when compared to CC. The THS abuse liability is higher than for NRT products. With respect to nicotine pharmacokinetics, the abuse liability of THS could be considered as follows: NRT < THS ≤ CC.

6.2.3.5. ALA Domain 4 - Pharmacodynamic Effects

Several questionnaires were administered in the eight clinical studies, measuring subjective effects when smokers switch to THS, thus, contributing to gauge the pharmacodynamics effects of the product. These questionnaires assess various dimensions of abuse liability such as craving (urges to smoke), the impact of the product on smoking satisfaction, enjoyment of respiratory tract sensation, psychological reward, aversion, craving reduction and nicotine dependence. Evaluation of subjective withdrawal symptoms is discussed in Section 6.2.3.8. Description of these study endpoints and related results are provided in more details in Module 6, Section 6.2.1 (single use pharmacological clinical studies) and in Module 6, Section 6.2.2 (reduced exposure clinical studies).

6.2.3.5.1. Urges-to-Smoke

In the four single use pharmacological clinical studies, craving (urges-to-smoke) and craving relief was assessed by the serial self-administration of the brief questionnaire for smoking urges (QSU-brief) prior to product use and during 12 hours post product use. QSU-brief was also administered daily during the confinement period of the four reduced exposure clinical studies and at each of the visits during the ambulatory period of the two 3-month studies. QSU-brief is the most widely used smoking craving questionnaire (Carter 2009).

Across all eight clinical studies, THS consistently provided a similar relief to smoking urges (cigarette craving) for THS and for CC users when assessed with the QSU-brief, based on the evaluation of the 95% confidence interval of mean differences THS-CC for the three QSU-brief score (total score, subscale score 1 - positive experience and subscale score 2 - alleviation of negative experience). This was observed in serial measurements after single use, in daily measurements in 5-day studies and at monthly visits in the per-protocol subjects from the 3-month studies.

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6.2.3.5.2. Product Evaluation - Satisfaction

THS and CC were evaluated in terms of smoking satisfaction, enjoyment of respiratory tract sensation, psychological reward, aversion and craving reduction, using the modified cigarette evaluation questionnaire (MCEQ). MCEQ is widely used for assessing reinforcing and aversive effects of smoking. The MCEQ was self-administered once in the morning of THS use and of CC use, daily in confinement settings and monthly in ambulatory settings.

The results of MCEQ were interpreted based on the review of 95% confidence interval of THS-CC differences for the five subscales across the eight clinical studies (See Table 8). Apart from ZRHM-REXA-07-JP, in which all subscales were rated as not different, in all other studies, there were one or several subscales rated as lower, meaning that THS provided less satisfaction to users than CC. The aversion subscale was generally rated as not different with one exception: THS was more aversive than CC in ZRHR-REXC-03-EU study, mimicking the high difference in adverse events incidence rates between the two 5-day studies, see Module 6, Section 6.1.5. In the repeated use studies for both menthol and regular THS variants, the general observed trend was toward an even less satisfying experience during the first one or two days of use (data not shown here; details available in respective clinical study reports).

Table 8. Overview of Differences THS – CC for MCEQ Subscales

Study	Smoking Satisfaction	Enjoyment Respiratory Tract Sensations	Psychological Reward	Aversion	Craving Reduction
ZRHR-PK-01-EU	Lower	Lower	Not different	Not different	Lower
ZRHR-PK-02-JP	Lower	Lower	Lower	Not different	Not different
ZRHM-PK-05-JP	Lower	Lower	Not different	Not different	Not different
ZRHM-PK-06-US	Lower	Lower	Lower	Not different	Lower
ZRHR-REXC-03-EU					
• Day 5	Lower	Lower	Lower	Higher	Lower
ZRHR-REXC-04-JP					
• Day 5	Lower	Not different	Lower	Not different	Not different
ZRHM-REXA-07-JP					
• Day 5	Not different	Not different	Not different	Not different	Not different
• Day 90	Not different	Not different	Not different	Not different	Not different
ZRHM-REXA-08-US					
• Day 5	Lower	Not different	Not different	Not different	Lower
• Day 90	Not different	Not different	Not different	Not different	Not different

Not different when 0 is included in 95% confidence interval THS-CC
Lower when entire 95% confidence interval < 0
Higher when entire 95% confidence interval > 0;
[Source: Clinical study reports ZRHR-PK-01-EU, Table 15.2.4.15, ZRHR-PK-02-JP Table 15.2.4.15; ZRHM-PK05-JP Table 15.2.4.15; ZRHM-PK-06-US Table 15.2.4.15, ZRHR-REXC-03-EU Table 15.2.4.48; ZRHR-REXC-04-JP Table 15.2.4.48; ZHRM-REXA-07-JP Table 15.2.4.38.1; and ZRHM-REXA-08-US Table 15.2.4.55.1]

Five-day study results suggest that the THS Menthol variant seems to play a role by providing a better satisfaction than with the THS non-menthol variant, for some (but not

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all) of the components (e.g., enjoyment of the respiratory tract sensations, psychological reward, aversion) with variations across studies. Potential impact of menthol (in contrast to the non-menthol, "Regular" THS variant) on satisfaction may be linked to menthol pharmacological properties (cooling and anesthetic properties, nicotine harshness reduction and smoother alternative for smokers).

6.2.3.5.3. Nicotine Dependence

The Fagerström test for nicotine dependence (FTND) is the most widely used questionnaire to characterize the "severity" of the dependence to nicotine in smokers (e.g. as part of therapeutic strategies). For exploratory purposes, the FTND questionnaire was completed by subjects at baseline and at day 90 in the two 3-month studies. At baseline, Japanese subjects were scored as less dependent to nicotine than American subjects (See Table 9); as mentioned above in Section 6.2.3.1, 34.4% of subjects enrolled in the US study ZRHM-REXA-08-US were rated as having severe nicotine dependence (FTND score between 7 and 10 as defined in respective study protocols) at baseline as compared to the 14.0% in the Japanese study ZRHM-REXA-07-JP. The validity of the FTND is questionable when used to assess heated tobacco product as it was only validated for CC (Fagerström 2012). In our two studies, it is unclear if subjects answered the questionnaire considering the behavior with THS, with CC or both. An overview of FTND scores at baseline and at Day 90 is shown in Table 9. While results suggest a decrease in nicotine dependence upon smoking cessation (in subjects reported as successfully abstinent), a differential evolution was not observed in subjects allocated in THS or in CC arms.

Table 9. Nicotine Dependence in 3-month Studies

FTND Score	Baseline Median (min-max)	Day 90 Median (min-max)	Comment
ZRHM-REXA-07-JP			
• THS arm	4 (1-8)	4 (0-9)	Unchanged in THS and CC arms
• CC arm	4 (1-8)	4 (0-7)	
• SA arm	5 (0-9)	3 (0-8)	2-point decrease in SA arm
ZRHM-REXA-08-US			
• THS arm	6 (1-10)	5 (1-9)	1-point decrease in THS and CC arms
• CC arm	6 (1-9)	5 (2-9)	
• SA arm	6 (2-8)	1.5 (0-3)	Unreliable results for SA arm as only 9 subjects were abstinent and only 4 completed day 90 questionnaire

[Source: clinical study report ZHRM-REXA-07-JP Table 15.2.4.34.1; and ZRHM-REXA-08-US Table 15.2.4.51.1]

6.2.3.5.4. Conclusion on Pharmacodynamics Effects

Pharmacodynamics effects upon switching to THS do not fully correlate to nicotine exposure, especially in the short-term. This was outlined in study ZRHR-REXC-03-EU,

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where no differences in THS vs. CC were observed for QSU-brief, in contrast to a lower craving reduction from MCEQ with THS vs. CC (less effective than CC), while average nicotine systemic exposure was 12% higher vs. CC. Despite its central role in tobacco use, nicotine is increasingly recognized as a secondary rather than a primary (or at least not the unique) reinforcer, as other pharmacological (including flavorant agents) and non-pharmacological factors may play a role in product use satisfaction and sustained self-administration (Fagerström 2012).

In the short-term (the first days of use), the general observed trend was toward a less rewarding/satisfying product, which may be explained by 1) the time needed to adapt and self-titrate the nicotine systemic exposure, and 2) the disruptive behavior due to the product design and differences in the organoleptic components of the THS aerosol. The results suggest that the menthol variant may provide an extra-benefit in term of reward and enjoyment but does not cover the craving relief as good as with CC.

In a longer term (after one month of use of THS Menthol), there are no longer differences in pharmacodynamic effects in THS vs. CC, with the exception of craving reduction which was not as good as with CC in the US study; as noted, subjects enrolled in the US study had, on average, a nicotine dependence level higher than subjects from the Japanese study and nicotine yields in US CC are on average higher than Japanese CC.

With respect to pharmacodynamics effects, the abuse liability of THS could be considered as follows: THS (THS Regular < THS high menthol) < CC during the first days of use and then THS (THS Regular < THS high menthol) ≤ CC.

6.2.3.6. ALA Domain 5 - Reinforcing Effects

Complementary to positive and negative reinforcing effects associated with pharmacological effects, reinforcing effects are also viewed from a product use behavior lens, i.e. how the product is perceived by smokers, and nonsmokers (never-smokers and former smokers), what is their intention to try and use THS vs. other tobacco products and actually how smokers use the product both in controlled settings and in near-to-real world situations.

6.2.3.6.1. Product Use Behavior in Clinical Studies

The design of the clinical studies, in terms of instructions to product use, should be considered as supportive to understand product self-administration, as puffing was allowed as desired in single stick use studies (no imposed regime, the only limitation being the limitations set in the product design with pre-determined cap in number of puffs and use duration – see Section 6.2.3.2) and product use was *ad libitum* in repeated use studies, with concomitant or intermittent use of other tobacco products (dual use) being possible but not encouraged (see Section 6.2.3.4.3) in ambulatory period of the 3-month reduced exposure studies.

Puffing behavior (from human puffing topography) results from the clinical studies (see detailed results and interpretation in Module 6, Section 6.2.2) have shown that

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smokers switching from CC to THS have adapted their puffing methods at both puff and product use experience level.

Variations in product use (see study details and results in Module 6, section 6.2.2), in particular during the first days of exposure to a new product with different characteristics compared to subjects own brand(s) of CC are expected and part of the adaptation process to a new product such as THS. These variations in product use observed early after switching to THS disappeared to the most extent when followed up for a period of more than 30 days to levels comparable of what was observed at baseline and to the levels of use reported for CC at the end of the ambulatory period. The time course of product use in the US study ZRMH-REXA-08-US is presented as an example in Figure 9. Patterns of product use were different between the study population in Japan and in the U.S., with for Japan, higher rates of adherence to use the allocated product and almost no dual-use with CC or other nicotine-containing products (at 3 months, 84.6% of exclusive THS users among subjects randomized to THS) compared to the study in the U.S. (55.0% exclusive THS users at 3 months).

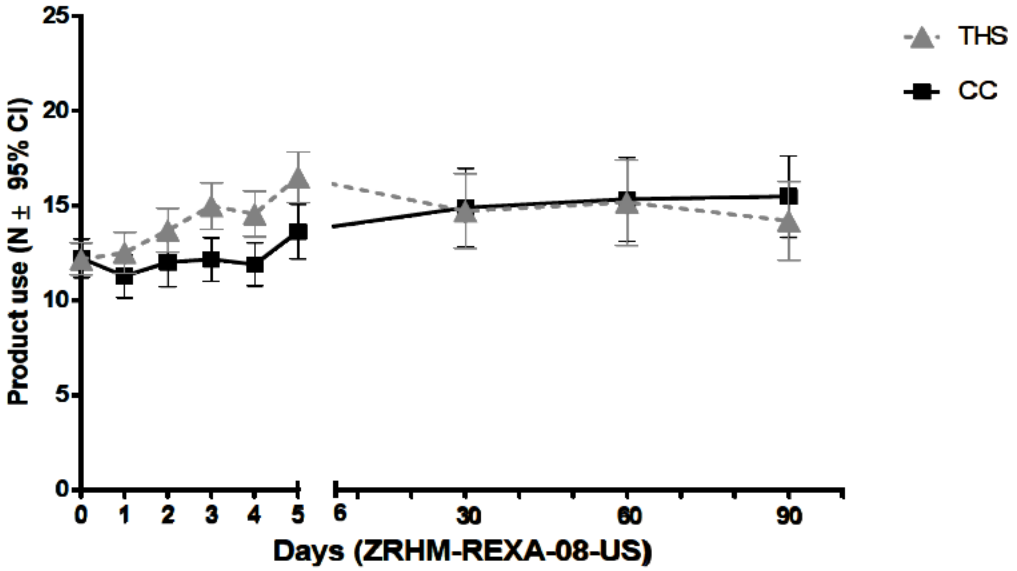


Figure 9. Product use - ZRHM-REXA-08-US Full Analysis Set

Overall, when taken together with nicotine exposure results (see Section 6.2.3.4), the transient variations in THS use and the subsequent puffing behavior adaptations show that subjects switching to THS (fully or partially) self-titrate their nicotine intake, i.e. seeking nicotine levels similar they are used to with CC. Thus, the product use behaviors observed in clinical settings do not raise an abuse liability concern higher than for CC.

6.2.3.6.2. Product Use in Near-to-Real-World Conditions

Two type of observational (non-interventional) studies evaluated how smokers actually use THS over a period of four weeks (five WOT market research studies conducted

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outside the US) and over a period of six weeks (THS-PBA-07-US conducted in the US) (see Table 2 and Table 4).

Market Research Studies in Europe and Asia

The five WOT market research studies (Europe and Asia) were conducted in adult smokers from two or more large cities and representative of the local market adult smokers population based on quotas (see countries in Table 2). The studies started with a first phase assessing the responses to THS (regular and/or menthol variants) based on one THS Tobacco Stick trial and to hypothetical marketing material, followed by a second phase (only smokers having indicated a non-negative purchase interest, with a score of at least 3 on the 5-point intention to purchase scale [1 = definitely not, 5 = definitely]), assessing the THS actual use (start of use, switch to THS, combined use of CC and THS, switch back to CC) characterizing the overall consumption of tobacco products. Details on study design and results are presented in Module 6, Section 6.2.2. These WOT studies provide an initial insight on product use.

Across the five studies, it is noteworthy there was approx. 11% to 28% attrition between phase 1 and phase 2, suggesting that THS has a limited appeal to a portion of adult smokers after the first exposure to it.

Across the five studies, approx. 36% to 76% started to use THS (use of ≥100 THS tobacco sticks) within the 4 weeks of observation (highest proportions in Asian populations) with peak at week 2 and week 3, suggesting that smokers need a rather limited time to adopt the THS product. Across studies, 10% to 37% of adult smokers switched to THS (>70% of tobacco products use is THS use). Most of the THS switchers switched during the first week (approx. 18% to 47% among starters) and very few (<4%) switched back to CC during the last week of study. These results suggest that the adoption of THS is either rapid or non-existent. Consistent across the 5 WOT studies, and even with a behavior of combined use of THS and CC reported in approx. 40% to 60% of participants, the overall tobacco products use (THS + CC) remained stable during the 4 weeks of observation, suggesting that THS is not promoting increase of tobacco product use.

Actual Use Study in the US

The six-week actual use study, THS-PBA-07-US, used the same principles as for the WOT. The THS-PBA-07-US study was conducted in 8 limited geographic areas of the US. Special attention was given to the sampling of participants aiming at approximating the adult smoker distribution contained in the Centers for Disease Control and Prevention report (CDC 2012) in terms of sex (male/female), age (young adults from legal age (LA) to 25yr, adults 25-44yr and adults 45+yr), race (minorities (including African Americans) and Whites) and income (below 45'000 USD / ≥ 45'000 USD). Similar to the WOT studies, only adult daily smokers who expressed a positive intention to use (score of at least 4 on the 6-point intention to use scale [1 = definitely not, 6 = definitely]) THS after being exposed to the THS marketing material were eligible to participate in the observational study period. THS Regular and THS Menthol were available to study participants for free. Stick-by-stick consumption of CC and THS was recorded by study participants in an electronic diary. Study participants were interviewed at baseline and at

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the end of the study via a computer-assisted web interview (CAWI). Interim computer-assisted telephone interviews (CATI) were executed twice. Study details and results are available in Module 6, Section 6.2.2, and in study report THS-PBA-07-US, in Module 7.3.2.

From an abuse liability point of view, the actual use study THS-PBA-07-US could be used as a proxy for the evaluation of choice procedures (participants were given the possibility to choose to use the THS variant(s) they wish to use) and the evaluation of self-administration (participants were fully free to use the THS as much as they wanted), with the caveat of getting the product for free over 6 weeks and of having a cap for tobacco sticks supply to individuals based on their self-reported daily CC use (using an inflation factor of 3). The full analysis set population (N=1106) is considered relevant to evaluate product use for the ALA.

During the analysis of safety data from THS-PBA-07-US (safety population with the 1158 participants who used at least one THS tobacco stick, see Module 7.3.1, THS-PBA-07-US safety summary report), 44.2%, 38.1% and 17.7% of participants used THS Menthol only, THS Regular only, both variants, respectively. The majority of participants who used THS Menthol only were White (54.3%) followed by African Americans (41.6%). Majority (66.5%) of African Americans have used THS Menthol only, approx. twofold higher proportion than for White (35.0%).

Three main product usage categories were defined: THS sticks use (THS use represents ≥70% of THS + CC use), combined use (THS use between 30% and 70% of THS + CC use) and CC use (THS use ≤30% of THS + CC use). The average daily use of CC and THS (units per day) as reported in electronic diary is shown in Table 10. The overall number of tobacco products consumed on average per day (CC + THS) remain stable in the three main product usage categories, suggesting that THS is not an incentive to increase tobacco use all together, concurring with findings from WOT studies.

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Table 10. THS and CC Use per Day in THS-PBA-07-US (FAS Population)

Mean (SD)	FAS overall (n=1106)	THS use at Week 6 (n=141)	Combined use at Week 6 (n=217)	CC use at Week 6 (n=607)
During baseline period				
• Number of CC	10.2 (7.22)	9.0 (5.89)	9.3 (6.34)	10.9 (7.69)
During observational period				
• Number of THS sticks and CC	9.3 (6.56)	8.1 (5.37)	8.9 (6.21)	9.9 (6.75)
• Number of CC	6.3 (5.78)	1.4 (1.57)	4.8 (3.72)	8.3 (6.32)
• Number of THS sticks	3.0 (3.57)	6.7 (4.82)	4.1 (3.06)	1.7 (1.99)

FAS: full analysis set
[Source: Study report THS-PBA-07-US, Table 18, Table 15.2.3.11, Table 15.2.4.1, Table 15.2.4.2, and Table 15.2.4.3]

Trajectories of use patterns are presented in details in Module 6, Section 6.2.2. More than 33% of the FAS population started to use THS (≥100 THS tobacco sticks over the 6 weeks) with the two most frequent trajectories being THS use as of first week (14.4%) and combined use along the 6 weeks (10.7%) among starters. Approximately 15% of the FAS population adopted THS (i.e. THS use category). The use of THS in combination with CC (i.e. combined use) was reported by 22.4% of the FAS population at Week 6. The proportion of exclusive THS use was stable, between 7% and 8% of the FAS population, on a weekly basis. The proportion of participants who switched back to CC (CC use category) after having switched (THS use category) during the 6 weeks observational period was 15.5%. At the end of the study, the majority of participants (FAS population) would probably (21.3%) or definitely (39.5%) not buy the product, while approx. half of the adopters (THS use category at Week 6) would probably (31.2%) or definitely (15.9%) buy it (5-point rating scale ranging from "1=definitely would buy it" to "5=definitely would not buy it"). This intention to buy should be put in perspective to sensorial findings, as the median score for taste, smell and aftertaste was 3.0 (min-max 1-7 Likert scales ranging from a 1 - don't like at all - to 7 – like it very much – scale). About half of the FAS population did not like the taste (53.5%), the smell (53.7%) and aftertaste (58.2%).

The results of this study are consistent with results from WOT studies conducted abroad. Results suggest that, for adult smokers, THS is not as appealing as CC (i.e. lower abuse potential), as only a portion of smokers offered to use THS transitioned to THS use, without promoting an increase in tobacco product use all together.

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6.2.3.6.3. Intent to Use and Risk Perceptions by Adult Smokers

Three label, labeling and marketing material assessment studies (THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US, see Table 4) sharing the same study design, but testing different marketing material, were conducted in the US. Study participants were only exposed to one instance of label, labeling and marketing material and there was no THS use. The measurements included intent to use (intention to try at least once, intention to use regularly), change in the intention to quit smoking and all tobacco products (in smokers with the intention to quit), comprehension of messages (label, labeling and marketing material) and risk (Perceived Health Risks, Perceived Addiction Risk and perceived Harm to Others) perception for THS and for the comparators (CC, e-cigarettes, NRT products, and smoking cessation). Data was acquired by using a Computer-Assisted Self Interviewing methodology. The study population included adult smokers with no intention to quit CC (have smoked at least 100 CC and no intention to quit within the next 6 months), adult smokers with intention to quit CC (have smoked at least 100 CC and intention to quit within the next 6 months), adult former smokers (had smoked more than 100 CC in their life and quit smoking CC more than 30 days ago) and adult never smokers (had smoked less than 100 CC in their life and never been a daily smoker). A fifth group was composed of adult never smokers between legal smoking age and 25 years of age (LA-25 adult never smokers), in order to oversample young adults who never smoked. These five groups were randomly allocated to five arms (i.e., THS Brochure with Surgeon General's warnings, THS brochure with PMI Important Warning, THS Tobacco Sticks Pack with Surgeon General's warnings, THS Tobacco Sticks Pack with PMI Warning and THS Direct Mail with PMI Warning). Study details and results are described in Module 6, Section 6.2.2 (product use) and in Module 6, Section 6.4.1 (consumer understanding and perception).

The PMI Important Warnings tested in the three PBA-05 studies are presented in Table 11.

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Table 11. Reduced Risk and Reduced Exposure Claims Assessment

Study	Assessed PMI Important Warnings
THS-PBA-05-RRC-US	Reduced risk claim 1 – PMI Important Warning with 3 statements: • "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."
THS-PBA-05-RRC2-US	Reduced risk claim 2 – PMI Important Warning with 2 statements • "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."
THS-PBA-05-REC-US	Reduced exposure claim – PMI Important Warning with 3 statements • "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."

The Surgeon General's warnings (currently mandated for CC) tested in the three PBA-05 studies are as follows:

- "Smoking causes lung cancer, heart disease, emphysema, and may complicate pregnancy."
- "Quitting smoking now greatly reduces serious risks to your health.";
- "Smoking by pregnant women may result in fetal injury, premature birth, and low birth weight.";
- "Cigarette smoke contains carbon monoxide."

The effect of the label, labeling and marketing material in current smokers is presented below. The effects in former smokers and in never smokers is presented in the next section (see Section 6.2.3.6.5).

Overall, THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, THS-PBA-05-REC-US studies showed consistent results among adult smokers with or without intention to quit smoking over the three THS claims proposed (see Table 11), the different materials tested, and between the PMI and Surgeon General's warnings.

The proportion of participants who expressed the intention to try THS (ranging from 30.2% to 51.6%) was generally 10% higher than the intention to use in both smokers with or without intention to quit smoking.

Substantial levels of intention to use THS were reported within the intended segment of the population i.e. adult smokers with no intention to quit CC: positive intention to use

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THS[1] was between 28.4% and 38.9%, between 20.2% and 37.9%, and between 20.8% and 36.8% across all arms, in THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, THS-PBA-05-REC study, respectively.

Similar substantial levels of intention to use THS were observed within adult smokers with the intention to quit CC (positive Intention to Use THS was between 21.3% and 35.1% across all arms, across the 3 studies). At the same time, the levels of change in intention to quit smoking CC in smokers with change in intention to quit were between 4.3% and 11.6%, between 1.1% and 11.8% and between 4.2% and 9.4% across all arms, in THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, THS-PBA-05-REC, respectively. Some of these smokers viewed THS as a mean to help them on their path to stop smoking but understood it is not a substitute to cessation.

Across the 3 PBA-05 assessment studies, PMI Important Warning and Surgeon General's warnings were associated with similar comprehension levels (proportion of correct answers ranging from 46.8% to 78.4% for global comprehension) across the different materials tested (i.e., THS Brochure, Tobacco Sticks Pack, and THS Direct Mail). At the same time, for the 2 studies that tested communication with reduced risk claims (THS-PBA-05-RRC-US and THS-PBA-05-RRC2-US), higher levels of correct comprehension of disease risk were found for the THS Brochure when associated with the PMI Important Warning, than when associated with Surgeon General's warnings. This was found despite of the fact that the information on disease risk for THS was contained within the main body of the THS Brochure, which was identical between Arm 1 and Arm 2, and not referred to in either type of warning. Likewise, in the study testing THS communications with a reduced exposure claim (THS-PBA-05-REC-US), disease risk information was consistently better comprehended when presented in materials with PMI Important Warning compared to materials with Surgeon General's warnings. An explanation could be that the combination of the claim with the PMI Important Warning reflects a coherent set of product-specific information concerning reduced risk.

A marginal proportion of subjects (<6% across all arms in THS-PBA-05-RRC-US study, <4% in THS-PBA-05-RRC2-US study and <4% in THS-PBA-05-REC-US study) indicated that THS is risk-free.

Consistent across studies, study arms and study population groups (smokers with or without intention to quit), the perceived health risk and the perceived addiction risk for THS was below that of CC, higher than NRT products and/or cessation, and similar to e-cigarettes. The perceived addiction risk is discussed in more details in Section 6.2.3.6.6.

Overall, the exposure to the proposed THS communications does not suggested a greater risk of abuse, based on intent to use (intention to try at least once, intention to use regularly), comprehension of messages (label, labeling and marketing material) and risk (Perceived Health Risks, and Perceived Harm to Others) and perception for THS and for

[1] 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.

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the comparators (CC, e-cigarettes, NRT products, and smoking cessation). Two aspects may need to be explored postmarket on their potential effect on product use behavior as i) a small proportion (usually less than one out of ten) adult smokers with intention to quit smoking and all tobacco products had expressed to change their intention to quit (at least transiently) after being exposed to THS communication material, and ii) as the THS addiction risk (Perceived Addiction Risk) is perceived as lower than for CC (even with the Surgeon's General mandated warnings).

6.2.3.6.4. Comprehension of THS Instructions to Use by Adult Smokers

THS-PBA-06-US was a single-arm usability and comprehension study conducted in four US cities to evaluate whether adult daily smokers can and are likely to comply with any instruction of product use and to verify consumer understanding about key communication messages of the product instruction for use. The study was conducted via one-to-one interviews in 258 adult smokers. Special attention was given in regards to sampling with quotas of at least 30% of males, 30% of females, 30% aged 18-40yr, 30% aged 40yr+ and 30% of high school education or less. Study details are presented in Module 6, Section 6.2.2.

The majority of use tasks (charging the holder, how to consume the stick, end of stick use, how to remove a stuck stick from the holder) were executed correctly by more than two-third of the participants. A few tasks (how to insert the stick into the holder, how to remove the stick with the pull-pull technique, how to heat clean the holder, how to use cleaning tool) were less well executed. Key messages such as not using the 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 half of these (23 of 47, 48.9%) reported one occasion of misuse, 14 participants (29.8%) reported 2 to 4 occasions, 7 participants (14.9%) reported 5 to 9 occasions and 3 participants (6.4%) reported 10 times or more occasions of misuse. This misuse was more likely due to negligence (the habit of smoking) rather than toward any intentional way to use THS Tobacco Stick like a CC.

The level of comprehension of THS instructions to use and the anecdotal misuse cases at hand do not pose an abuse liability concern.

6.2.3.6.5. Intent to Use by Former Smokers and Never Smokers

Overall, THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, THS-PBA-05-REC-US studies (see additional information in above Section 6.2.3.6.4, in full details in Module 6, Section 6.3.1) showed consistent results on intent to use among non-users of CC over the three claims proposed, the different materials tested, and between the PMI and Surgeon General's warnings. There was only a small intention to try/use THS among all three examined non-smoker groups. Intent to use THS was slightly higher for adult former smokers (in the range of 1 to 10%), while adult never smokers had no more than 2.1 % of positive intention to try/use across the different materials throughout all three studies. Similarly, positive responses throughout all tested materials were no more than 3.0% of positive intention to try/use for LA-25 adult never smokers.

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Consistent across studies and study arms, the perceived health risk for THS by former smokers was below that of CC, higher than NRT products and/or cessation, and similar to e-cigarettes. The perceived addiction risk is discussed in Section 6.2.3.6.6.

Importantly for public health protection, the results provide evidence that the low levels of intention to try or use in adult non-smokers were in the same range than for CC and e-cigarettes. We conclude that the existent low levels of Intent to Use THS among non-smokers exposed to THS communication materials were not specific to THS, but rather represent either a general interest in tobacco or nicotine-containing products and/or unsystematic variance within the data. The results for young adult never smokers (LA-25 adult never smokers) are consistent with those observed in adult never smokers. Thus our current results provide no evidence that exposure to THS communication generated intent to initiate tobacco with THS among young adult never smokers. THS is neither targeted towards, nor attractive to young non-smokers and is likely to have a non-differentiated effect compared to other commercialized tobacco products already on the market when it comes to initiation of tobacco use among young adults.

From an abuse liability point of view, the study results suggest that the proposed communication on reduced risk claim or on reduced exposure claim would not encourage adult former smokers and adult never smokers to initiate tobacco use. Similarly, the PBA-05 studies results also indicated that very few (almost no) adult never smoker young adults (LA-25 - best approximation of the larger group of legal age and below) were interested in using THS after viewing THS communication materials.

6.2.3.6.6. Perceived Addiction Risk

Consistent across THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US, and across study arms and study population groups within these three studies, the level of perceived addiction risk for THS was below that of CC, higher than NRT products and/or cessation, and similar to e-cigarettes, regardless of the type of claim or marketing material. Details are presented in Module 6, Section 6.4.1. The perceived addition risk for THS by young adult never smokers (legal age to 25 years old) remains at a similar level than with adult never-smokers, rating THS less addictive than CC and at par with e-cigarettes.

Study findings are in line with two recently published scientific articles (surveys conducted in the US) on e-cigarettes where e-cigarette users perceive e-cigarettes as less addictive than conventional cigarettes (Berg 2015, Harrell 2015), concurring with Fagerström's commentary (Fagerström 2012). Fagestrom commented that, besides the central role of nicotine, other pharmacological and non-pharmacological determinants in CC may play a role in the development of tobacco abuse.

6.2.3.6.7. Conclusions on Reinforcing effects

From a product use behavior lens from various situations and populations, it appears that the abuse liability of THS is not worse than CC in smokers with no intention to quit. A small proportion (less than 10%) of smokers having the intention to quit smoking may delay their quit attempt and may perceive THS as an alternative to CC. The proportion of never-smokers who intent to try or use THS was not exceeding 3%. The risk of addiction

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with THS was perceived as lower than for CC, higher than for NRT products and similar to e-cigarette.

6.2.3.7. ALA Domain 6 - Impaired Functioning

Psychomotor performance and cognitive evaluation are proposed by some experts for the assessment of impaired functioning (Carter 2009). These endpoints were not measured in our assessment program Despite some controversies on the solely role of nicotine on addiction (see Section 6.2.3.5.4), it is assumed that, based on the accepted concept of associating most of tobacco addiction to pharmacokinetic and pharmacodynamic properties of nicotine, psychomotor and cognitive functioning would remain unchanged (or marginally affected) as no or limited differences were observed between THS and CC, with respect to nicotine pharmacokinetic (see Section 6.2.3.4.4) and product pharmacodynamic (see Section 6.2.3.5.4) properties.

No notable differences were observed for nicotine withdrawal symptoms in THS vs. CC (see more details in Section 6.2.3.8.)

There were no signals from adverse events associated with or related to THS suggesting impaired functioning different from CC (More details in Section 6.2.3.9.2).

In terms of impaired functioning and based on limited data at hand, it is assumed that THS abuse liability is not different from CC.

6.2.3.8. ALA Domain 7 - Physical Dependence

The FTND questionnaire is discussed in Section 6.2.3.5.3 as it accounts also for psychosocial determinants of tobacco dependence.

The Minnesota nicotine withdrawal scale (MNWS) questionnaire is considered for the assessment of physical dependence and was administered in the four reduced exposure clinical studies. MNWS Score 1 is based on nine validated questions and Score 2 on six additional questions thought to be associated with nicotine withdrawal. The 24-hour recall questionnaire was completed by the subjects. MNWS was administered daily in the 5-day clinical studies with MNWS total score, score 1 and score 2. MNWS score 1 only was used in the 3-month clinical studies, daily during the confinement period and then at each monthly visit. More details can be found in Module 6, Section 6.2.2.

Consistently across the 4 studies, the MNWS scores increased sharply upon smoking cessation, with a peak after 1 to 2 days of smoking abstinence, and usually returning to baseline values with 1 week (1 month in ZRHM-REXA-04-JP).

In the 5-day studies (THS Regular vs. CC, exclusive use), the daily time course of MNWS scores was similar for THS and CC arms. There were no statistically significant differences between the two arms, based on the analysis of 95% confidence intervals.

In the 3-month studies (THS Menthol vs. menthol CC), the time course of MNWS scores was similar for THS and CC arms, in the per-protocol population (i.e., predominantly THS users in the THS arm). There were no statistically significant differences between the two arms, based on the analysis of 95% confidence intervals.

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In conclusion, there were no notable differences in MNWS scores between subjects who switched to THS use (both menthol and regular variants) and subjects who continued to smoke CC, i.e., no changes in physical dependence were observed, thus suggesting an abuse liability for THS similar to CC with respect to physical dependence.

6.2.3.9. ALA Domain 8 - Adverse Events

Adverse events (AEs) were monitored during the course of all clinical studies. Apart from cough assessment, there were no specific AEs of special interest to be reported and monitored. Adverse events spontaneously reported by respondents in market research tests with THS use, by study participants enrolled in the THS-PBA-07-US study and by THS consumers in postmarket settings were collected and assessed. AEs and other safety evaluations are described in details in Module 6, Section 6.1.5.

Reported adverse events are considered from two point of views. On one hand, there are aversive adverse events which may refrain smokers to switch to THS, or non-smokers to initiate use, such as events which may be seen as cumbersome or annoying (e.g., nausea, vomiting, dizziness, coughing, and throat irritation). However, such events are also likely to occur when never-smokers initiate CC smoking. When initiating smoking, tolerance to aversive adverse events develops and/or certain events become part of the smokers "normal life" (see as an example cough as described in Module 6, section 6.1.5). On the other hand, there are events, mainly belonging to the central nervous system or to the psychiatric system, which are signals for substance abuse or which are seen as desirable by some smokers (e.g., looking for a "high" or for improved cognitive / psychomotor performance). Similarly, there is a tenuous threshold between pleasure and pain, the enjoyable respiratory tract sensations vs. throat irritation being a typical example.

6.2.3.9.1. Aversive Adverse Events

Nausea and dizziness are two symptoms which are articulated in the MCEQ questionnaire (See Section 6.2.3.5.2). The aversion MCEQ subscale for THS was reported in clinical studies as not different to CC, except in study ZRHR-REXC-03-EU (higher), which may put in perspective with higher (+12%) nicotine exposure. Such correspondence between aversion and nicotine exposure was not observed at five days with THS Menthol flavor, suggesting some interactions with menthol and its pharmacological properties (see FDA's opinion, in Section 6.2.3.2.2).

Nausea, vomiting and dizziness were reported in some of the clinical studies (often as related to THS use) for both THS regular and menthol variants, with within-study incidence rates from 1.3% to 11.3%. Surprisingly, in study ZRHR-REXC-03-EU reporting a higher score in aversion subscale in THS vs. CC, dizziness was not reported as an AE, and nausea/vomiting was only reported in the smoking abstinence arm.

Nausea and dizziness were among the most often reported AEs in passive surveillance (in WOT studies, except the WOT study conducted in Japan where safety data were not collected, and in THS-PBA-07-US, see details in Section 6.1.5.7). Nausea represents 10.1% and 5.8% of all AEs spontaneously reported by THS Regular users and THS Menthol users, respectively, while dizziness was 2.6% and 4.7% of all reported AEs, respectively. No definite conclusion could be made on the potential role of the menthol

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flavor on reducing the incidence of aversive adverse events as, for the AE showing the greatest apparent difference, i.e. nausea, the proportional reporting rate THS Regular / THS Menthol is 1.8 when using premarket safety surveillance data and 2.8 when using safety data limited to THS-PBA-07-US, i.e., below the threshold of 3 to 5, from spontaneously reported AEs, usually accepted for the determination of a safety signal associated with a product (Evans 2001).

Other AEs and health complaints, such as cough, throat irritation and dry throat may also be part of aversive adverse events, which may overall contribute to the lower satisfaction observed during the initial use of THS, as reported in clinical studies. They could also have played a negative role on the THS use rate in THS-PBA-07-US.

6.2.3.9.2. Nervous System Disorders and Psychiatric Disorders

Very few AEs suggesting reinforcing substance abuse were reported in clinical studies, with two cases of dysphoria in ZRHR-PK-02-JP, one case of abnormal dreams during the first week of use in study ZRHM-REXA-07-JP. Psychiatric disorders and nervous system disorders usually associated with tobacco withdrawal were more likely reported upon smoking abstinence (as no pharmacotherapy options were proposed in the studies). From passive surveillance, no psychiatric disorders AEs were reported and all reported nervous system disorders AEs should be considered as aversive AEs. More details are available in Module 6, Section 6.1.5, Human Safety Summary).

Nicotine/tobacco withdrawal symptoms are described in more details in Section 6.2.3.8.

The analysis and interpretation of adverse events does not suggest differences in abuse liability THS vs. CC.

6.2.3.10. Overview on Abuse Liability Assessment

THS abuse liability was assessed in contrast to conventional cigarettes, based on the review of available information from various sources, including product design and content, chemistry, human clinical and behavioral data. THS tobacco sticks contain nicotine, a (highly) addictive substance with nicotine delivery broadly similar to CC. The nicotine exposure in humans under various use conditions, confirms the similarity of nicotine uptake THS vs. CC, indicating a similar abuse liability for THS vs. CC. The other product features (design, handling and usage limitations, and delivery of toxicants with addiction potential other than nicotine) do not seem to add an additional risk on the abuse liability on top of the nicotine (see Table 12). The consequences of THS use, in term of components associated with abuse, are not worse than with CC.

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Table 12. Abuse Liability Domains Overview

Domain	Measurements	Interpretation of ALA Outcome
1. Product design	Nicotine content	THS = CC
	Menthol content	THS Menthol = CC menthol
2. Aerosol chemistry	Delivery of nicotine	THS = CC (3R4F)
	Delivery of acetaldehyde	THS < CC (3R4F)
	Delivery of ammonia	THS < CC (3R4F)
3. Pharmacokinetic effects	Nicotine pharmacokinetics single use	NRT < THS ≤ CC
	Nicotine pharmacokinetics repeated use	THS = CC
	Nicotine exposure at 3 months	THS = CC
4. Pharmacodynamic effects	Subjective effects early use	THS < CC THS regular < THS high menthol
	Subjective effects up to 3-month use	THS ≤ CC THS regular < THS high menthol
5. Reinforcing effects	Product use in clinical studies	THS ≤ CC
	Product use in near-to-real world	THS < CC
	Perception (health risks, addiction risk) and comprehension	THS = CC (smokers) THS ≥ CC (smokers with intention to quit) THS = CC (never- and former smokers)
	Intention to use by never and former smokers	THS = CC
6. Impaired functioning	Cognitive assessment	THS = CC
	Psychomotor performance	THS = CC
	Withdrawal symptoms	THS = CC
7. Physical dependence	Withdrawal symptoms short term	THS = CC
	Withdrawal symptoms up to 3 months	THS = CC
8. Adverse events	Aversive adverse events	THS = CC THS regular ≤ THS high menthol
	Nervous system disorders	THS = CC

The collected evidence indicates that CC smokers switching to THS keep their physical and/or psychological dependence to the tobacco product to a level not higher to the level associated with CC use. The tolerance to tobacco product use and/or the onset of withdrawal symptoms upon stopping the use of the tobacco product is maintained (not increased). Psychological dependence characterized by persistent tobacco-seeking and tobacco-use behaviors, impairment in behavioral control, craving, and inability to abstain

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consistently) is likely unchanged. On the other side, switching to THS requires several weeks of efforts due to the intended disruptive behavior and the necessary adaptation to the product use.

The available information suggests that THS meets the IOM recommendation (see Section 6.2.3.1), for a desirable MRTP that should be more reinforcing than nicotine replacement therapies. It should be sufficiently reinforcing so as to attract smokers away from conventional cigarettes but not enough to encourage the widespread dependent use of the product by individuals who were previously nonusers, or who have quit smoking. There are two points which may require verification in the postmarket setting, as 1) smokers willing to quit smoking may want to switch to THS (at least transiently), and 2) the addiction risk is perceived as lower than CC by smokers, former smokers and never-smokers, currently not supported by the pharmacological (mainly related to nicotine) evidence collected so far.

6.2.3.11. Abuse Liability Conclusion

Based on the totality of available evidence covering abuse liability domains from THS product features, likelihood of use and consequence of use, THS shares a similar abuse liability than conventional cigarettes, and there is no significant evidence of THS attractiveness to nonusers of tobacco. The actual usage patterns and use/smoking trajectories in smokers, never-smokers, former smokers and smokers with intention to quit remain to be verified in postmarketing conditions. The abuse potential of THS should be balanced against the observed trends in biological and functional health improvements (see Section 6.1.6) as well as against the subsequent projected harm reduction to the population (see Section 6.5.6).

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