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6.1.5 Human Safety

This section summarizes adverse events (AEs) and other related safety findings associated with the use of the tobacco heating system (THS) with the aim to identify new or increased health risks associated with THS use, as compared to cigarette smoking.

An adverse event is defined by the Food and Drug Adminstration (FDA) as stated in the Modified Risk Tobacco Product Applications Draft Guidance for Industry (USDHHS 2012a), i.e., any health-related event associated with the use of a tobacco product in humans that is adverse or unfavorable, whether or not it is considered tobacco product related. An AE can arise from any use of the product (including use in combination with other products and overdose). The same guidance document provides also the definition for a serious adverse event (SAE), which is an AE that results in any of the following: death, life-threatening condition or event, persistent or substantial disability or incapacitation, hospitalization or prolonged hospitalization, or congenital anomaly or birth defect. Important medical events, as per medical judgement, may also qualify as SAEs.

Intensity of adverse events were also categorized in clinical study protocols, as mild (AE easily tolerated without interference with daily activity), moderate (AE interfering with daily activities but subject is still able to function) and severe (AE is incapacitating and requires medical intervention).

In the context of this summary, the term *THS-emergent AEs* refers to AEs associated with THS use and means that a temporal (and biologically plausible) association between the onset of the AE (or the worsening of a pre-existing medical condition) has been observed regardless of whether it was related to the actual use of THS or to the exposure to THS.

There are four major sources of human safety data described in this summary, as follows:

1. Adverse events and other safety assessment observed during clinical studies (Section 6.1.5.1 to Section 6.1.5.5) in adult smokers switching to THS,
2. Adverse events spontaneously reported in other human studies by study participants (adult smokers using THS) upon passive safety surveillance in pre-marketing settings (Section 6.1.5.7),
3. Adverse events spontaneously reported by THS users and by others in countries where THS is already marketed outside the United States (post-marketing passive safety surveillance, (Section 6.1.5.8), and
4. Complemented by relevant safety literature.

During the life cycle of the development and assessment of THS, human safety information has been gathered from several THS variants (THS Regular, THS Menthol with various levels of menthol, see detailed list in Appendix A6.1.5.1).

For the sake of this human safety summary, the safety data lock point (DLP) is 31-Dec-2015. Critical late breaking safety information that occurred after the data lock point is also described (see Table 1).

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Table 1 Safety Data Lock Point

Stage	Date
Main safety data lock point	31-Dec-2015
Late breaking safety information until	30-Apr-2016

Findings described in this summary are of descriptive nature and results are interpreted according to global introspection and medical judgment. Unless otherwise specified, no statistical comparisons were carried out.

6.1.5.1 Exposure to THS in Clinical Studies

6.1.5.1.1 Clinical Study Narratives

A total of 8 open-labeled randomized controlled clinical studies were completed in adult smokers switching to THS (see Table 2).

Table 2 List of Completed Clinical Studies

Study Code	Country	FSI-LSO	Design	Exposure Duration	THS Use
THS Regular					
ZRHR-PK-01-EU	Poland	01-Nov-2013 to 21-Dec-2013	Cross-over	Single use	Puffing as desired
ZRHR-PK-02-JP	Japan	31-Jul-2013 to 15-Nov-2013	Cross-over	Single use	Puffing as desired
ZRHR-REXC-03-EU	Poland	29-Jun-2013 to 26-Sep-2013	3-arm parallel	5 days	*Ad libitum* exclusive use
ZRHR-REXC-04-JP	Japan	23-Jul-2013 to 09-Dec-2013	3-arm parallel	5 days	*Ad libitum* exclusive use
THS Menthol					
ZRHM-PK-05-JP	Japan	01-aug-2013 to 16-Nov-2013	Cross-over	Single use	Puffing as desired
ZRHM-PK-06-US	USA	02-Oct-2013 to 02-Dec-2013	Cross-over	Single use	Puffing as desired
ZRHM-REXA-07-JP	Japan	01-Aug-2013 to 03-Jul-2014	3-arm parallel	3 months	*Ad libitum* 5-day exclusive use followed by 85-day actual use
ZRHM-REXA-08-US	USA	17-Dec-2013 to 12-Oct-2014	3-arm parallel	3 months	*Ad libitum* 5-day exclusive use followed 85-day actual use

FSI: first subject in; LSO: last subject out
[Source: clinical study reports in Module 7.3.1]

In all these studies, AEs were monitored during the course of study, including a safety follow-up of 1 week (single use studies and 5-day studies) to 4 weeks (3-month studies). Laboratory safety parameters, physical examination, vital signs, electrocardiogram (ECG), spirometry, assessment of cough and device issues (malfunction, misuse) were

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part of safety-related assessments. Smoke-drug interaction (changes in cytochrome [CYP] CYP1A2 activity) has been evaluated in some of these studies.

One additional 6-month randomized clinical study (with THS Regular variant) and its 6-month extension with a similar safety assessment is ongoing at the time of this summary (see Table 3) and listed here for the occurrence of serious adverse events (SAE).

Table 3 List of Ongoing Clinical Studies

Study Code	Country	FSI-LSO	Design	Exposure Duration	Ref
ZRHR-ERS-09-US	USA	18-Mar-2015 to – ongoing	2-arm parallel	6 months	(a)
ZRHR-ERS-09-EXT-US	USA	30-Sep-2015 to – ongoing	2-arm parallel	6 months extension	(a)

FSI: first subject in; LSO: last subject out
[Source: ref (a) see THS safety update report 2016 in Module 7.3.1]

In the single use nicotine pharmacokinetic (PK) studies, the design was set as a 4-sequence 4-period incomplete block cross-over, each subject receiving 2 of the 3 products to be tested, namely THS and conventional cigarette (CC) or nicotine replacement therapy (NRT) product. The NRT product was the marketed nicotine nasal spray (NNS) for studies in Europe and USA and the marketed 2-mg nicotine gum for studies in Japan.

In the 5-day reduced exposure studies in confinement settings, subjects were randomized into 1 of the 3 arms, switching to THS exclusive use for 5 days, or to continuing smoking own preferred CC brand or to a 5-day smoking abstinence (SA) without smoking cessation pharmacotherapies. THS use and CC smoking was allowed *ad libitum* within the 6.30am to 11.00pm time window.

In the 3-month reduced exposure studies, the first week was conducted in confinement as described above for the 5-day exposure studies, including exclusive product use and regimen. The studies were continued for 85 days in ambulatory settings, and subjects were instructed to continue their assigned product/regimen, i.e., THS or own preferred CC or SA. During the ambulatory period, concurrent use of other tobacco products or nicotine-containing products, often referred as dual use, was not allowed in the THS arm, but was not a reason for exclusion from the study.

In the 6-month exposure-response study and its extension, subjects were randomized either in switching to THS or to continuing smoking their own preferred CC.

6.1.5.1.2 Overall Extent of Exposure (Completed Studies)

The overall safety population (all subjects who had at least one exposure to THS, i.e. as all subjects had a product trial prior to randomization) and randomized (per study arm) study population is presented per study (see Table 4) and per study type (see Table 5).

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Table 4 Overall Extent of Exposure in Completed Clinical Studies (per Study)

Study	Overall Safety Population (N)	Subjects in THS Arm (N)	Subjects in CC Arm (N)	Subjects in NRT Arm (N)	Subjects in Smoking Abstinence Arm (N)	Subjects Exposed to THS but Not randomized (N)
THS single use						
ZRHR-PK-01-EU	62	62	44	18	-	-
ZRHR-PK-02-JP	65	62	44	18	-	3
ZRHM-PK-05-JP	73	62	44	18	-	11
ZRHM-PK-06-US	64	62	44	18	-	2
THS 5-day use						
ZRHR-REXC-03-EU	169	80	41	-	39	9
ZRHR-REXC-04-JP	166	80	40	-	40	6
THS 3-month use						
ZRHM-REXA-07-JP	175	78	42	-	40	15
ZRHM-REXA-08-US	165	80	41	-	39	5

[Source: Clinical Study Reports ZRHR-PK-01-EU, Table 32; ZRHR-PK-02-JP, Table 31; ZRHM-PK-05-JP, Table 30; ZRHM-PK-06-US, Table 34; ZRHR-REXC-03-EU, Table 80; ZRHR-REXC-04-JP, Table 77; ZRHM-REXA-07-JP; Table 130. ZRHM-REXA-08-US, Table 130]

Among the 939 smokers enrolled (safety population) in the 8 completed clinical studies, a total of 566 smokers were exposed to THS (see Table 4 and Table 5). Fifty-one additional subjects tested the THS (up to 3 tobacco sticks) during pre-randomization procedures but were not randomized for various reasons, including for adverse events.

Table 5 Overall Extent of Exposure in Completed Clinical Studies (per Study Type)

Study	Overall Safety Population (N)	Subjects in THS Arm (N)	Subjects in CC Arm (N)	Subjects in NRT Arm (N)	Subjects in Smoking Abstinence Arm (N)	Subjects Exposed to THS but Not randomized (N)
Total in single-use studies	264	248	176	72	0	16
Total in 5-day studies	335	160	81	0	79	15
Total in 3-month studies	340	158	83	0	79	20
Overall Exposure	939	566	340	72	158	51

[Source: data derived from above Table 4]

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6.1.5.1.3 Overall Extent of Exposure (Ongoing Studies)

Up to 31-Dec-2015, a total of 430 additional subjects were randomized to the THS arm (426 in CC arm) in the ongoing 6-month ZRHR-ERS-09-US study, while 172 were continuing the THS use at the start of the 6-month extension as described in the latest THS Safety Update Report (Module 7.3.1, THS Safety Update Report 2016).

6.1.5.1.4 Demographics and Other Characteristics of Safety Population

In all completed clinical studies, the study safety population was composed of adult male and female smokers (at last 10 CC per day, and smoking for the last 3 years) not willing to quit smoking within the next 3 months and otherwise considered as healthy based on medical judgement and outcome of standard laboratory tests, including a post-bronchodilator spirometry. In study ZRHM-REXA-08-US, spirometry results indicating stage-1 chronic obstructive pulmonary disease (usually not requiring any pharmacotherapy) were not an exclusion criterion. A detailed summary of the study safety population characteristics is provided in Appendix A6.1.5.2. Of note, there are some differences in the inclusion criteria for the population in the 6-month study, mainly, smokers at least 30 years old, smoking at least for the 10 last years and not willing to quit smoking within the next 6 months.

6.1.5.2 Adverse Events in Clinical Studies

AEs were monitored from signature of the informed consent form (medical conditions diagnosed or uncovered at screening were considered as concomitant medical conditions / diseases and not as AEs) to the end of study, i.e., the end of the safety follow-up period. The MedDRA dictionary was used for AE coding.

Abnormal findings in the safety laboratory parameters (hematology, clinical biochemistry and urinalysis) were also considered for adverse events, based on Common Toxicity Criteria for Adverse Events (CTCAE) and principal investigators' judgment. CTCAE version 4.03 was used (USDHHS 2010b).

In this summary, AEs presented by clinical study are limited to AEs with incidence rate ≥ 5% in any study arm, in line with sample sizes of these studies, (around 60 in crossover studies, 40 to 80 per study arm in parallel-arm studies) and with the rule of three traditionally applied for safety (i.e., the rule of three states that if none of n subjects shows a given event, the approximated upper 95% confidence limit of this event is at most three in n; when n=60, 37n = 5%). The full lists of AEs per system-organ class (SOC) are tabulated per study in Appendix A6.1.5.4. AEs findings are presented as follows:

- Incidence of AEs in single use cross-over studies and the most commonly reported AEs are presented in Section 6.1.5.2.1.,
- Incidence of AEs in 5-day and 3-month studies and the most commonly reported AEs per study arms are presented for each study in Section 6.1.5.2.2. AEs reported during the confinement (exclusive use of the allocated product) and AEs reported during ambulatory settings (concurrent use of THS with other nicotine / tobacco products not prohibited) are summarized separately.

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6.1.5.2.1 Commonly Reported Adverse Events in Single Use Cross-over Studies

In the single-use cross-over studies, all subjects tried THS (1 to 3 sticks) prior to randomization, on Day-1, to allow them to understand how to use the product. Subsequent to this product trial, subjects were entering into the two consecutive periods, with wash-out on Day-0 and Day-2, and investigational tobacco product (THS) or reference/comparator product (CC or NRT) on Day-1 and Day-3. Due to the very short period of time and the cross-over design, the adverse events are presented in the respective clinical study reports per sequence rather than per product: the principal investigator was asked to assess the causality of AEs to the investigational tobacco product or to the NRT product, acknowledging the challenge for differentiating the causality of an AE to the investigational tobacco product from the background noise, including AEs which may be associated with the smoking lifestyle and the potential withdrawal symptoms.

Among the 264 subjects enrolled in the 4 single use cross-over studies, a total of 85 AEs were reported in 57 subjects (21.6%) with one out of four AEs being assessed by the principal investigators as investigational product (IP)-related (see Table 6). All but 2 AEs were mild or moderate severity. One subject from study ZRHM-PK-06-US reported 2 severe AEs (ocular hyperemia and eye pruritus) assessed by the investigator as not related to the investigational product. None of the AEs led to study discontinuation.

Table 6 Summary of Adverse Events in Single Use Cross-over Studies (Safety Population)

	ZRHR-PK-01-EU	ZRHR-PK-02-JP	ZRHM-PK-05-JP	ZRHM-PK-06-US	Overall
THS variant	Regular	Regular	Menthol	Menthol	
Safety population (N)	62	65	73	64	264
Number of:					
• AEs	39	14	4	28	85
• SAEs	0	0	0	0	0
• AEs leading to discontinuation	0	0	0	0	0
• AEs related to IP	14	3	0	5	22
Number (%) of subjects with:					
• AEs	23 (37.1%)	11 (16.9%)	4 (5.5%)	19 (29.7%)	57 (21.6%)
• AEs related to IP	12 (19.4%)	3 (4.6%)	0 (-)	4 (6.3%)	19 (7.2%)

[Source: clinical study reports ZRHR-PK-01-EU, Table 32: ZRHR-PK-02-JP, Table 31; ZRHM-PK-05-JP, Table 30; ZRHM-PK-06-US, Table 34]

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The AE incidence rates appear heterogeneous across these four studies. These apparent differences may be attributable to the between-investigators / countries variability rather than to product variant differences (see Section 6.1.5.5.1 for a discussion on intrinsic and extrinsic factors, and Section 6.1.5.2.8, AEs with other heated tobacco products from literature). Based on results shown in Table 6, safety data suggest that the menthol variant (study ZRHM-PK-05-JP and study ZRHM-PK-06-US, a total of 23 subjects with AEs out of a total sample of 137 subjects, 16.8%) was not a driver for increased occurrence of AEs vs. the regular variant (study ZRHR-PK-01-EU and study ZRHR-PK-02-JP, a total of 34 subjects with AEs out of a total sample of 127 subjects, 26.8%). Higher nicotine uptake, as observed in the 2 Japanese studies (described in more details in Module 6, Section 6.2.1 and 6.2.3), did not lead to higher incidence of AEs or to an increase in AE intensity. The summary tabulations of all AEs per study are presented in Appendix A6.1.5.4.

The number and incidence rate of the most commonly reported all-cause AEs, (i.e., with incidence rates ≥ 5% in any of the studies) from the overall safety population enrolled in single use studies are tabulated in Table 7.

Table 7 All-cause Adverse Events in ≥ 5% of Subjects in Single Use Cross-over Studies

Adverse Events (Preferred Terms)	ZRHR-PK-01-EU n (%)	ZRHR-PK-02-JP n (%)	ZRHM-PK-05-JP n (%)	ZRHM-PK-06-US n (%)
THS variant	Regular	Regular	Menthol	Menthol
Safety population (N)	62	65	73	64
Dizziness	7 (11.3%)	-	-	-
Headache	6 (9.7%)	-	-	7 (10.9%)
Presyncope	6 (9.7%)	-	-	-

[Source: clinical study reports ZRHR-PK-01-EU, Table 33: ZRHR-PK-02-JP, Table 31; ZRHM-PK-05-JP, Table 30; ZRHM-PK-06-US, Table 34]

The number and incidence rate of all IP-related AEs, i.e. from the overall safety population enrolled in single use studies are tabulated per study in Table 8..

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Table 8 IP-related Adverse Events Reported in Single Use Cross-over Studies

Adverse Events (Preferred Terms)	ZRHR-PK-01-EU n (%)	ZRHR-PK-02-JP n (%)	ZRHM-PK-05-JP n (%)	ZRHM-PK-06-US n (%)
THS variant	Regular	Regular	Menthol	Menthol
Safety population (N)	62	65	73	64
Number of subjects (%) with IP-related AEs	12 (19.4%)	3 (4.6%)	0 (-)	4 (6.3%)
Pre-syncope	6 (9.7%)	-	-	-
Dizziness	5 (8.1%)	-	-	-
Nausea	1 (1.6%)	-	-	2 (3.1%)
Vomiting	1 (1.6%)	-	-	2 (3.1%)
Pallor	1 (1.6%)	-	-	-
Dysphoria	-	2 (3.1%)	-	-
Hepatic function abnormal	-	1 (1.5%)	-	-
Headache	-	-	-	1 (1.6%)

[Source: clinical study reports ZRHR-PK-01-EU, Table 33: ZRHR-PK-02-JP, Table 34; ZRHM-PK-05-JP, Table 30; ZRHM-PK-06-US, Table 37]

The 22 IP-related AEs were nausea and vomiting (6), presyncope (6), dizziness (5), dysphoria (2), headache (1), pallor (1) and hepatic function abnormal (1) and they were all mild or moderate in severity

Apart from hepatic function abnormal (see Table 8), other THS-related AEs are symptoms which may be associated with mild nicotine overdose (See Table 33 for AEs associated with nicotine over-exposure). The abnormal hepatic function was observed in subject 0086 (study ZRHR-PK-02-JP) at the discharge visit with a marginal and transient increase above upper limit of normal range (ULN) of alanine aminotransferase (1.5x ULN), aspartate aminotransferase (2.1x ULN) and alkaline phosphatase (1.2x ULN) levels, not suggestive of a drug-induced liver injury. The nature and frequency of the IP-related AEs do not raise specific concerns in both menthol variant studies (ZRHM-PK-05-JP and ZRHM-PK-06-US) and regular variant studies (ZRHR-PK-01-EU and ZRHR-PK-02-JP).

6.1.5.2.2 Adverse Events in 5-day and 3-month Studies

Overall, and among the 655 subjects (safety population) enrolled in the two 5-day studies or randomized in the two 3-month studies, a total of 526 AEs were reported in 278 subjects (42.4 % of the subjects), with a total of 40 AEs (8% of all AEs) being assessed by the principal investigators as IP-related (see Table 9). As observed in single use studies, many fewer adverse events were reported in Japanese studies as compared to studies in the Western population (see Section 6.1.5.5.1 for the potential role of intrinsic and extrinsic factors).

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Table 9 Summary of Adverse Events in 5-day and 3-month Studies

	ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US	Overall
THS variant	Regular	Regular	Menthol	Menthol	
Safety population (N)	169	166	160	160	655
Number of:					
• AEs	227	11	93	195	526
• SAEs	0	0	0	0	0
• AEs leading to discontinuation	8	0	0	0	0
• AEs related to IP	26	0	6	8	40
Number (%) of subjects with:					
• AEs	112 (66.3%)	10 (6.0%)	60 (37.5%)	95 (59.4%)	278 (42.4%)
• AEs related to IP (a)	23 (13.6%)	0	1 (0.6%)	8 (5.0%)	32 (4.9%)

[Source: clinical study reports ZRHR-REXC-03-EU, Table 80; ZRHR-REXC-04-JP, Table 77, ZRHM-REXA-07-JP, Table 131; ZRHM-REXA-08-US, Table 131]
(a) in this table, IP refers to AEs related to the use of THS and CC.

Prior to randomization, and as done in the single use studies, all subjects had the opportunity of using a small number of THS tobacco sticks. For the 5-day studies, AEs which occurred during the pre-randomization period are accounted for in the overall safety population, while a separate analysis was done for the 3-month studies. In ZRHM-REXA-07-JP (see Module 7.3.1 clinical study report ZRHM-REXA-07-JP Table 130) and in ZRHM-REXA-08-US (see Module 7.3.1 clinical study report ZRHM-REXA-08-US Table 130), a total of 106 AEs were reported by 78 (22.9%) of the subjects among the 340 enrolled, while only one AE was assessed as IP-related.

The summary tabulations of all AEs per THS variant and per study are presented in Appendix A6.1.5.4.

6.1.5.2.2.1 Commonly Reported Adverse Events in 5-day Exclusive Use of THS

The number of adverse events reported during the 5 days of post-randomization confinement period from the two 5-day studies (THS Regular) and from the two 3-month studies (THS Menthol) are presented together, as product use was under control (exclusive THS use in THS arm, full abstinence in the SA arm, exclusive CC use in the CC arm). There was no apparent disproportion in the number of subjects reporting adverse events or reporting IP-related AEs and in the number of AEs per subjects between the 3 allocation arms. In the next four tables (Table 10 and Table 11 for THS Regular studies, Table 12 and Table 13 for THS Menthol studies), the most commonly reported all-cause AEs (incidence rate ≥ 5% in any of the study arms) during the 5-day exposure are presented per study.

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THS Regular – 5-day study ZRHR-REXC-03-EU

All-causality AEs reported in study ZRHR-REXC-03-EU are summarized in Table 10. AEs were reported by 62.5% of the subjects randomized to THS (70.7% in CC arm and 61.5% in SA arm), all cases with mild or moderate intensity (see definition for intensity categories in Section 6.1.5 introductory paragraph). There is no apparent disproportion in the number of subjects with AEs between the THS and the CC arms and between the THS and the SA arms, with the following exceptions:

- Subjects randomized in CC arm had the highest AEs incidence rate (70.7%),
- Syncope cases were only observed with THS (6 cases) and CC (4 cases) and not in the SA arm. One case (1.3%) was assessed as THS-related (see Table 17) and two cases (4.9%) as CC-related (See Appendix A6.1.5.4, Table 9). An investigational site effect should be considered as this study was conducted in the same investigational site as for ZRHR-PK-01-EU, reporting a total of 16 presyncope and syncope cases among a total of 268 AEs from this site, as compared to 1 case among 345 AEs from all other sites, across studies, ending with a disproportion reporting rate of 21.8.
- Abdominal distension, only observed in the SA, is a typical somatic symptom (gastro-intestinal discomfort) associated with tobacco / nicotine withdrawal (see Table 33), and
- Oropharyngeal pain, only reported with THS and CC, suggests local irritation associated with tobacco and nicotine use, also well known for NRT products (see Table 20).

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Table 10 All-cause Adverse Events in ZRHR-REXC-03-EU (≥ 5% in Any Study Arm)

Adverse Events (Preferred Terms)	THS n (%)	CC n (%)	SA n (%)
Safety population (N)	80	41	39
Number of subjects (%) with AEs	50 (62.5%)	29 (70.7%)	24 (61.5%)
Number of all AEs (n)	98	63	49
AEs with incidence rate ≥ 5%			
• Headache	24 (30.0%)	16 (39.0%)	13 (33.3%)
• Syncope	6 (7.5%)	4 (9.8%)	-
• Spirometry abnormal	4 (5.0%)	3 (7.3%)	2 (5.1%)
• Abdominal distension	-	-	2 (5.1%)
• Oropharyngeal pain	7 (8.8%)	3 (7.3%)	-
• Polyuria	6 (7.5%)	4 (9.8%)	2 (5.1%)
• Back pain	3 (3.8%)	2 (4.9%)	3 (7.7%)
• Hypertension	1 (1.3%)	1 (2.4%)	2 (5.1%)
• Influenza-like illness	-	1 (2.4%)	3 (7.7%)
• Vertigo	3 (3.8%)	-	2 (5.1%)

[Source: clinical study report ZRHR-REXC-03-EU, Table 81]

THS Regular – 5-day Study ZRHR-REXC-04-JP

All-causality AEs reported in study ZRHR-REXC-04-JP are summarized in Table 11. As observed for the other studies conducted in Japan, very few AEs were reported, in less than 8% of THS users, and limited to mild abnormal laboratory findings.

Table 11 All-cause Adverse Events in ZRHR-REXC-04-JP (≥ 5% in Any Study Arm)

Adverse Events (Preferred Terms)	THS n (%)	CC n (%)	SA n (%)
Safety population (N)	80	40	40
Number of subjects (%) with AEs	6 (7.5%)	3 (7.5%)	1 (2.5%)
Number of all AEs (n)	6	4	1
AEs with incidence rate ≥ 5%			
• Blood triglycerides increased	2 (2.5%)	2 (5.0%)	-

[Source: clinical study report ZRHR-REXC-04-JP, Table 78]

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THS Menthol - 5-day Confinement Period Study ZRHM-REXA-07-JP

All-causality AEs reported during the first five days in study ZRHM-REXA-07-JP are summarized in Table 12. As observed for the other studies conducted in Japan, very few (all of mild intensity) AEs were reported, in less 8% of THS users.

Table 12 All-cause Adverse Events in ZRHM-REXA-07-JP (≥ 5% in Any Study Arm - Confinement)

Adverse Events (Preferred Terms)	THS n (%)	CC n (%)	SA n (%)
Safety population (N)	78	42	40
Number of subjects (%) with AEs	6 (7.7%)	1 (2.4%)	8 (20.0%)
Number of all AEs (n)	9	2	10
AEs with incidence rate ≥ 5%			
• Vertigo	-	-	2 (5.0%)

[Source: clinical study report ZRHM-REXA-07-JP, Table 15.2.6.3.1]

THS Menthol - 5-day Confinement Period Study ZRHM-REXA-08-US

All-causality AEs reported during the first five days (confinement settings) in study ZRHM-REXA-08-JP are summarized in Table 13. Approximately 29% of THS users experienced AEs of mild or moderate intensity. There is no apparent disproportion in the number of subjects between the THS and the CC arms and between the THS and the SA arms, with the following exceptions:

- A decrease in hemoglobin was only reported in THS and SA arms. The potential mechanisms are discussed in Section 6.1.5.3.1.
- Headache and dizziness were only observed in THS and SA arms. These two symptoms may be associated with mild nicotine exposure or tobacco / nicotine withdrawal symptoms (see Table 33).

Table 13 All-cause Adverse Events in ZRHR-REXA-08-US (≥ 5% in Any Study Arm - Confinement)

Adverse Events (Preferred Terms)	THS n (%)	CC n (%)	SA n (%)
Safety population (N)	80	41	39
Number of subjects (%) with AEs	23 (28.8%)	11 (26.8%)	13 (33.3%)
Number of all AEs (n)	39	14	27
AEs with incidence rate ≥ 5%			
• Hemoglobin decreased	3 (3.8%)	-	2 (5.1%)
• Dizziness	1 (1.3%)	-	2 (5.1%)
• Headache	3 (3.8%)	-	2 (5.1%)

[Source: clinical study report ZRHM-REXA-08-US, Table 15.2.6.3]

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AEs During 5-day Exclusive Use of THS Menthol vs. THS Regular

Based on the number and nature of AEs reported during the confinement period, the menthol variant of THS (menthol level in aerosol 2.35mg per stick, Health Canada intense, see Appendix A6.1.5.1) does not raise safety questions vs. the regular THS variant. In particular, a similar AE incidence rate was observed between the 2 variants in the Japanese population, while there were less AEs reported with the menthol variant tested in the US as compared to the regular variant tested in Europe (see Table 14).

Table 14 Summary of Adverse Events in 5-day and 3-month Studies. Confinement Period in THS Users – Menthol vs. Regular

	ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
THS variant	Regular	Regular	Menthol	Menthol
THS Arm sample size	80	80	78	80
Number of AEs	98	6	9	39
Number of AEs related to IP	15	0	1	5
Number (%) of subjects with AEs:	50 (62.5%)	6 (7.5%)	6 (7.7%)	23 (28.8%)
Number (%) of subjects with AEs related to IP	14 (17.5%)	0	1 (1.3%)	5 (6.3%)

[Source: clinical study reports ZRHR-REXC-03-EU, Table 80; ZRHR-REXC-04-JP, Table 77, ZRHM-REXA-07-JP, Table 130 and Table 15.2.6.3.1; ZRHM-REXA-08-US, Table 130 and Table 15.2.6.3]

Menthol has been described in the literature as having smoothing and contra-irritant properties. When focusing on symptoms from the upper airways tract (cough) and mouth (nasal, pharyngeal, buccal irritation and pain, dry mouth and dry lips) observed in these four studies, close AE incidence rates were reported, with 6 cases (3.8%) found in THS Regular studies and 9 cases (5.7%) in the THS Menthol studies.

6.1.5.2.2.2 Commonly Reported Adverse Events in 3-month Ambulatory Use of THS

As described in Section 6.1.5.1.1, the ambulatory use of THS in the two clinical studies concerned only the THS Menthol variant. The setting of study became closer to real-world conditions in terms of product use, i.e. THS users were instructed to use only THS, but the concurrent use of other combustible tobacco products or other nicotine-containing products was not prohibited and subjects were instructed to report such use.

THS Menthol – Ambulatory Period Study ZRHM-REXA-07-JP

The most commonly reported all-cause AEs (incidence rate ≥ 5% in any of the study arms) AEs reported during the 3-month (85 days) ambulatory period in study ZRHM-REXA-07-JP are summarized in Table 15. Approximately 37% of THS users experienced

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AEs, all of mild intensity. There is no apparent disproportion in the number of subjects with any AEs between the THS and the CC arms and a trend toward a lower AE frequency in SA arm as compared to THS and CC. There are few exceptions:

- Decrease in hemoglobin levels was reported as AE in all 3 arms, with a twofold incidence rate in the THS arm vs. the two other arms. Potential mechanisms are discussed in Section 6.1.5.3.1,
- Decrease in neutrophils counts was reported as AE in all 3 arms, with a twofold incidence rate in THS and SA arms in contrast to CC arm. Potential mechanisms are discussed in Section 6.1.5.3.1.

Table 15 All-cause Adverse Events in ZRHM-REXA-07-JP (≥ 5% in Any Study Arm - Ambulatory)

Adverse Events (Preferred Terms)	THS n (%)	CC n (%)	SA n (%)
Safety population (N)	78	42	40
Number of subjects (%) with AEs	29 (37.2%)	14 (33.3%)	9 (22.5%)
Number of all AEs (n)	40	20	12
AEs with incidence rate ≥ 5%			
• Hemoglobin decreased	11 (14.1%)	3 (7.1%)	3 (7.5%)
• Neutrophils count decreased	4 (5.1%)	1 (2.4%)	2 (5.0%)
• Blood triglycerides increased	3 (3.8%)	1 (2.4%)	2 (5.0%)

[Source: clinical study report ZRHM-REXA-07-JP, Table 15.2.6.3]

THS Menthol – Ambulatory Period Study ZRHM-REXA-08-US

The most commonly reported all-cause AEs (incidence rate ≥ 5% in any of the study arms) reported during the 3-month (85 days) ambulatory period in study ZRHM-REXA-08-US are summarized in Table 16.

Approximately 51% of THS users experienced AEs. There is no apparent disproportion in the number of subjects between the three study arms, but with a trend toward a higher AE frequency in the THS arm.

Regarding the most commonly reported AEs:

- Upper respiratory tract infection was reported with a twofold lower frequency in THS and SA arms, suggesting globally an improvement upon smoking cessation or switching to THS,
- Increase in lymphocyte counts was reported as AE in all 3 arms, with a more than twofold incidence rate in the THS arm vs. the two other arms. Of note, most events were due to reporting CTCAE Grade 2 systematically as AEs, despite being within the normal ranges of the medical laboratory providing hematology results. Changes in lymphocyte count is also discussed in Section 6.1.5.3.1.

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Table 16 All-cause Adverse Events in ZRHR-REXA-08-US (≥ 5% in Any Study Arm - Ambulatory)

Adverse Events (Preferred Terms)	THS n (%)	CC n (%)	SA n (%)
Safety population (N)	80	41	39
Number of subjects (%) with AEs	41 (51.3%)	14 (34.2%)	14 (35.9%)
Number of all AEs (n)	74	18	22
AEs with incidence rate ≥ 5%			
• Upper respiratory tract infection	3 (3.8%)	3 (7.3%)	1 (2.6%)
• Lymphocyte count increased	5 (6.3%)	1 (2.4%)	1 (2.6%)

[Source: clinical study report ZRHM-REXA-08-US, Table 15.2.6.3.1]

In the ambulatory period, 12 severe AEs were reported by 12 subjects; 8 in the THS arm, 2 in the CC arm, and 2 in the SA arm. All severe AEs (see definition for intensity categories in Section 6.1.5 introductory paragraph) were due to findings in clinical laboratory evaluations. Of the 12 severe AEs, 9 were due to decreased hemoglobin (5 in the THS arm and 2 in both the CC and SA arms). Severe AEs of increased GGT, hypertriglyceridemia, and glucosuria were also reported in the THS arm. None of these severe AEs were assessed as THS-related.

6.1.5.2.2.3 Adverse Events during Non-exclusive Use of THS

In study ZRHM-REXA-07-JP, at least 82% of subjects were exclusive THS users and 91% (N=71) predominantly THS users (THS use as 70-100% of all tobacco products used), while only 1 (2.5%) subject randomized in the SA arm was only partially abstinent. In study ZRHM-REXA-08-US, figures are significantly different. Among the 80 subjects randomized in the THS arm, 67 (84%) were predominant THS users, 10 (12%) were dual users (THS use 30 to 70% of all tobacco products) and 3 (4%) remained CC smokers, while only 6 (15%) of subjects randomized to the SA were fully abstinent.

In an attempt to explore the impact of concurrent use of THS with other tobacco products use (dual use) during the ambulatory period, the AE incidence rates were reviewed in various subpopulations (see Module 7.3.1, ZRHM-REXA-07-JP clinical study report Table 35 and Table 132 and ZRHM-REXA-08-US clinical study report Table 40 and Table 132). Predominant THS users had an AE incidence rate of 47.8% vs. 35.0% in CC smokers in ZRHM-REXA-08-US (30% were exclusive THS users) and 36.6% vs. 34.1% in ZRHM-REXA-07-JP (73.1% were exclusive THS users), while dual users tend to have higher AE incidence rates (60% in both studies) and full abstainers smaller AE incidence rates (16.7% and 22.7% in both studies). However, these figures remain to be confirmed as no firm conclusion can be made due to small or very small sample size in some of the subgroups.

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6.1.5.2.2.4 THS-related Adverse Events during 5-Day and 3-month Use

Among the 266 THS-emergent AEs reported in the 5-day and 3-month clinical studies, a total of 23 AEs (8.6 % of THS-emergent AEs) were reported as THS-related (as assessed by the principal investigators) in a total of 22 subjects (6.9% of subjects in THS arms). The full list of THS-related AEs (in preferred terms) is tabulated in Table 17. None of these AEs were severe in intensity.

Table 17 THS-related Adverse Events (Preferred Terms) Reported in 5-day and 3-month Clinical Studies

Adverse Events (Preferred Terms)	ZRHR-REXC-03-EU n (%)	ZRHR-REXC-04-JP n (%)	ZRHM-REXA-07-JP n (%)	ZRHM-REXA-08-US n (%)
THS variant	Regular	Regular	Menthol	Menthol
THS use duration	5 days	5 days	3 months	3 months
Safety Population, THS arm (N)	80	80	78	80
Number of subjects (%) with THS-related AEs	14 (17.5%)	0 (-)	1 (1.3%)	7 (8.8%)
Spirometry abnormal	4 (5.0%)	-	-	-
Cough	2 (2.5%)	-	-	1 (1.3%)
Vertigo	2 (2.5%)	-	-	-
Carbon monoxide diffusion capacity decreased	-	-	-	1 (1.3%)
Diarrhea	-	-	1 (1.3%)	-
Dry mouth	-	-	-	1 (1.3%)
Hyperhidrosis	1 (1.3%)	-	-	-
Hypertriglyceridemia	1 (1.3%)	-	-	-
Musculoskeletal chest pain	1 (1.3%)	-	-	-
Myocardial ischemia	1 (1.3%)	-	-	-
Non–cardiac chest pain	-	-	-	1 (1.3%)
Oral pain	1 (1.3%)	-	-	-
Oropharyngeal pain	1 (1.3%)	-	-	-
Salivary hypersecretion	-	-	-	1 (1.3%)
Sneezing	-	-	-	1 (1.3%)
Syncope	1 (1.3%)	-	-	-
Upper airway cough syndrome	-	-	-	1 (1.3%)

[Source: clinical study reports ZRHR-REXC-03-EU, Table 83: ZRHR-REXC-04-JP, Section 12.1.3.2.1 ZRHM-REXA-07-JP, Section 12.1.3.2.1 and Table 15.2.6.5.1; ZRHM-REXA-08-US, Table 135]

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6.1.5.2.3 Deaths

There were no deaths reported during the completed clinical studies.

Until 30-Apr-2016, one death (subject #04384, safety case PMI000452) was reported in the ongoing clinical study ZRHR-ERS-09-US: This was a 55-year old male randomized to THS. The subject used THS from 28-Sep-2015 to 10-Dec-2015 (reason for stopping THS use unknown). The subject was found on 16-Dec-2015 deceased in the bathtub at home. The autopsy report indicated that the death was caused by acute and chronic alcohol abuse (postmortem ethanol level 0.263 g/dL in blood). The post-mortem nicotine level in plasma was found to be 27ng/mL, i.e. within the expected ranges for a smoker. The principal investigator assessed the case as not related to the THS use.

The individual case safety report is available in Appendix A6.1.5.3.

6.1.5.2.4 Other Serious Adverse Events

Among the 8 completed clinical studies, there were two serious adverse events (hospitalization due to diabetic ketoacidosis and to acute sinusitis) in one THS-exposed not randomized subject (Subject 1119, safety case PMI000007, a 36-year-old woman who stopped metformin treatment before the use of one THS Tobacco Stick) in study ZRHM-REXA-08-US. This case was assessed as not related to the investigational product. The case report is available in Appendix A6.1.5.3.

The cumulative number of SAEs reported from completed and ongoing clinical studies at the 31-Dec-2015 safety data lock point is mentioned in the latest THS safety update report (See Module 7.3.1 THS Safety Update Report 2016). For completeness, SAEs reported beyond the safety data lock point are also considered. The other SAEs reported in THS study arm in ongoing clinical studies until 30-Apr-2016 are listed in Table 18. A total of 8 SAEs were reported in THS arm and none of them were assessed by the principal investigators or by PMP as being THS-related. All reported SAEs (all study arms) are listed in Appendix A6.1.5.3 and individual case safety reports are available in Module 7.3.1, THS Additional Safety Data Report.

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Table 18 Others THS-emergent SAEs in Ongoing Clinical Studies as of 30-Apr-2016

Study	Subject # Safety Case #	Type SAE	SAE Description	Related to THS
ZRHR-ERS-09-US	Subject 04260 PMI000350	Life-threat./ Hosp.	Severe Anemia, Metastatic Small Bowel Tumors	No
ZRHR-ERS-09-US	Subject 04384 PMI000452	Death	Death due to acute and chronic alcohol abuse	No
ZRHR-ERS-09-US	Subject 09236 PMI000463	Hosp.	Passed out and hit her head which caused a seizure and 5 day hospital stay	No
ZRHR-ERS-09-EXT-US*	Subject 04189 PMI000470	Hosp.	Left forearm laceration	No
ZRHR-ERS-09-EXT-US	Subject 04202 PMI000500	Hosp.	Costochondritis with shortness of breath	No
ZRHR-ERS-09-US	Subject 04267 PMI000511	Hosp.	Mycoplasma pneumonia	No
ZRHR-ERS-09-EXT-US	Subject 09134 PMI000518	Hosp.	Epiglottitis	No
ZRHR-ERS-09-EXT-US	Subject 01073 PMI000551	Hosp.	Influenza	No

Life-threat.: Life-threatening; Hosp.: hospitalization
* Case PMI000470 was reported on 14-Jan-2016 during ZRHR-ERS-09-EXT-US study but occurred on 01-Jan-2016 during ZRHR-ERS-09-US study

6.1.5.2.5 Other Significant Adverse Events

None of the subjects randomized in the 8 completed clinical studies were discontinued due to AEs.

Among the 51 subjects who were exposed to THS but not randomized, a total of 13 subjects (eight in study ZRHR-REXC-03-EU, Listing 15.3.6.1.1, two in study ZRHM-REXA-07-JP, Listing 15.3.6.1.3, and three in study ZRHM-REXA-08-US, Listing 15.3.6.3) experienced AEs leading to discontinuation, most of them assessed as not product related (hypertension, hypotension, elevated blood pressure, hyperkaliemia, hyperglycemia, common cold, syncope, worsening of spirometry results), while two cases of worsening of spirometry results were assessed by the principal investigator as related both to the investigational product and to the study procedures (study report ZRHR-REXC-03-EU, Listing 15.3.6.1.1).

Among the 8 completed clinical studies, two severe AEs (ocular hyperemia and eye pruritus were observed in one subject during single use of THS (study report ZRHM-PK-06-US, Listing 15.3.6.1.1) and 3 severe AEs in 2 exposed not randomized subjects (study report ZRHM-REXA-08-US, Listing 15.3.6.1), including the 2 SAE cases

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discussed above and one case of study procedure-related syncope. None of these severe AEs were assessed as related to the investigational product.

6.1.5.2.6 Analysis of Adverse Events per System Organ Classes in THS Users

Summary tables of reported AEs in the 8 completed clinical studies can be found in Appendix A6.1.5.4. AEs are tabulated per study and summary in AE preferred terms (PT) (MedDRA coded) and by system-organ classes (SOC).

The SOC *Investigations* came with a high incidence rate (or even alone in both single use studies in Japan, 13.6% with THS Regular and 5.5% with THS Menthol) in a number of studies, such as 8.8% in 5-day study in Europe up to 33.8% in the 3-month study in the US. This may be explained by the amount of laboratory tests executed in these studies and the approach taken of using the CTCAE grading system to systematically report all CTCAE grade 2 as an adverse event. Some of the observed changes could be seen as a favorable change when compared to the CC arm, as the incidence rate of some of these laboratory parameters (e.g., hemoglobin decreased, neutrophil count decreased) reported as AEs is often lower than the incidence rate seen in the CC arm, but no formal conclusion can be made; additional insights are provided below in Section 6.1.5.3. Among THS-emergent investigations AEs, only 7 cases were assessed as THS-related (hepatic function abnormal, spirometry abnormal, DLCO decreased, and hypertriglyceridemia, see Table 8 and Table 17).

Apart from SOC *Investigations*, and despite heterogeneity in adverse events, four SOCs are more frequently reported than others (within-study incidence rate from 5% up to approximately 35% and would have been expected based on the nature of the tested product.

Table 19 Most Common THS-emergent AEs (per SOC and PT) in Completed Clinical Studies

System-Organ Classes	All-cause AEs
Nervous system disorders	Headache, nervous system disorder, dizziness, presyncope and syncope, dysgeusia
Gastrointestinal disorders	Nausea, vomiting, constipation, dyspepsia, toothache, abdominal distention, abdominal pain, mouth ulceration, oral pain, dry mouth, lip dry,
Respiratory, thoracic and mediastinal disorders	Cough, oropharyngeal pain, sneezing, nasal congestion, sinus congestion
Infection and infestations	Nasopharyngitis, pharyngitis, urinary tract infection, hordeolum, upper respiratory tract infection

[Source: clinical study reports ZRHR-PK-01-EU, Table 33; ZRHR-PK-02-JP, Table 31; ZRHM-PK-05-JP, Table 30; ZRHM-PK-06-US, Table 34; ZRHM-REXA-07-JP, Table 15.2.6.3; ZRHM-REXA-08-US, Table 15.2.6.3.1]

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6.1.5.2.7 Adverse Events Associated with Device Malfunction and Misuse

A total of 325 device malfunction / defect events were reported by 163 subjects across all studies (8 events in 5 subjects in single use studies, 24 events in 15 subjects in the 5-day studies, 85 events in 53 subjects during the confinement period of the 3-month studies and 208 events in 90 subjects during the ambulatory period of the 3-month studies). There were no misuse events reported. Details on device malfunctions can be found in the respective clinical study reports.

Across the 8 completed studies, no adverse events were reported to be associated with device malfunction and/or device misuse.

In the ongoing clinical studies ZRHR-ERS-09-US and its extension ZRHR-ERS-09-EXT-US, there were so far no reports of SAEs associated with device malfunction/defect/misuse.

6.1.5.2.8 Analysis of Adverse Events vs. Other Heated Tobacco Products

Previous versions of THS (namely THS 1.0 and related variants, with a heating system operating approx. 200°C higher than current THS – see Module 3) have been tested in open-label, randomized, controlled clinical studies (e.g., see Table 9 in SUR R Appendix A, Module 7.3.1). THS 1.0 (also named as Electrically-Heated Cigarette Smoking System K6 [EHCSS-K6]) has been tested in 1-week confinement studies (with fixed product use regimen) in the UK (Tricker 2012a), in Japan (Tricker 2012b) and in a 1-month ambulatory study in Poland (Martin Leroy 2012). The menthol variant of THS 1.0 (EHCSS-K6M) was tested in a 1-week confinement study in Japan (Tricker 2012c). A lower nicotine version (EHCSS-K3) (0.2mg ISO for EHCSS-K6 vs. 0.3mg ISO for EHCSS-K3) was also tested in Korea (Tricker 2012d) and in Japan (Tricker 2012b). In the 1-week confinement study conducted in the UK, a total of 88 AEs (no SAEs) were reported by 53 subjects (33.1%), all assessed as not related to products. The most commonly reported AEs were nervous system disorders (headache, dizziness) and gastrointestinal disorders. In the three studies conducted in Japan and Korea, very few AEs were reported (3 to 7% of subjects), all being assessed as non-serious and unrelated to product. In the 1-month ambulatory study, 53% and 58% of subjects respectively in the EHCSS-K6 and CC arm reported AEs. The most commonly reported AEs that were considered as related to EHCSS-K6 were dry mouth, dry throat, cough and diarrhea, which occurred in 0.4 to 1.3% of subjects. Three SAEs were reported, one assessed as EHCSS-K6-related (deep vein thrombosis after end of study) and two as not related (post-traumatic splenic injury, and myocardial infarction, which occurred prior to randomization). The safety profile observed during the first three months usage of current THS in clinical studies looks similar to the nature and frequency of AEs observed with short-term (1-month) use THS 1.0 including the low AE incidence rates in Japan.

There are few scientific publications with other heated tobacco products. In a study conducted by PMI on a carbon-heated tobacco product, headache was the most common AE, occurring in 23% and 29% in the heated tobacco product arm and CC arm respectively (Lüdicke 2016). This figure looks very similar to the incidence rate of headache as reported in study ZRHR-REXC-03-EU (see Table 10), having similar design

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than the one in Lüdicke et al, article. Very few AEs were reported in 3 Japanese studies investigating heated tobacco products developed by Japan Tobacco Inc., with very limited product-emergent AEs details, apart from diarrhea, pharynx strange sensation, increased white blood cells in urine, increased triglycerides in plasma (1 case each) (Miura 2013, Miura 2015, Sakaguchi 2014), concurring with the nature and with the very low AEs incidence rate observed in PMI studies conducted in Japan.

6.1.5.2.9 Analysis of Adverse Events vs. FDA-approved Smoking Cessation Products

The safety profile of smoking cessation pharmacotherapies (namely, NRT products, varenicline and bupropion) approved by US Food and Drug Administration (FDA) have been reviewed and summarized (see Appendix A6.1.5.5) based on labels and summary of product characteristics of these products.

In an attempt to compare the safety profile of THS vs. NRT products, a side-by-side table (see Table 20) presents the most commonly reported IP-emergent AEs from NRT (using Nicotine inhaler US Summary of Product characteristics (see Appendix A6.1.5.5) and from the 3-month study ZRHM-REXA-08-US. Data are represented the same way as done for the nicotine inhaler labeling, indicating AEs with an incidence rate threshold of 3%. The results are only indicative, as the sample size is tenfold lower in THS vs. nicotine inhaler studies. The THS-emergent AEs observed until present do not raise safety concerns in their nature or frequency when put in perspective vs. NRT products.

In a systematic review and meta-analysis of 120 NRT clinical trials involving 177,390 individuals (Mills 2010), a number of side effects were significantly associated (95% odds ratio confidence intervals excluding 1) with NRT use as compared to control: heart palpitation, nausea/vomiting, indigestion, mouth/throat soreness (oral NRT), skin irritation (NRT patches), hiccups (oral NRT), mouth ulcers, coughing and insomnia. The odds ratios for other frequently reported adverse events in these clinical trials (headache, dizziness, arthralgia, urticaria, sweating, anxiety, and depression) vs. control were not significantly different from 1.

The THS-emergent AEs observed in PMI clinical studies were very similar in nature and frequency as adverse drug reactions reported in NRT clinical trials and do not raise new safety concerns.

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Table 20 THS-emergent AEs vs. NRT-emergent AEs from Clinical Studies

Adverse Event Group	Nicotine Inhaler Clinical Trials	THS 3-month Clinical Study ZRHM-REXA-08-US
Sample size	1439 (730 on NRT)	160 (80 on THS)
Common smoker's complaints (smoking related)	chest discomfort, bronchitis, and hypertension	Upper respiratory tract infection (3.8% in THS group, 9.8% in CC and 2.6% in SA)
Tobacco withdrawal symptoms	common in both active and placebo groups dizziness, anxiety, sleep disorder, depression, withdrawal syndrome, drug dependence, fatigue and myalgia	Psychiatric disorders (abnormal dreams/nightmares, anxiety, depressed mood, insomnia, restlessness and tension primarily reported in SA group (7.7%, vs, THS group 1.3%). Dizziness in 1.3% in THS vs. 5.1% in SA groups
Effect of the device	In both active and placebo groups: Local irritation in mouth and throat (40% active vs. 18% placebo) Coughing (32% active vs. 12% placebo) Rhinitis (23% active vs. 16% placebo) Others: taste comments, pain in jaw and neck, tooth disorders and sinusitis	Mouth and throat irritation / pain reported by in less than 3% Cough (3.8% in THS group, 2.4% in CC and none in SA).
Nicotine-related adverse events	The most common nicotine-related AE was dyspepsia (18% active vs. 9% placebo) Others nicotine-related events nausea, diarrhea, and hiccup	Most common AEs were nausea (3.8%) and constipation (3.8%)
Other adverse events	Headache (26% active vs. 15% placebo), influenza-like symptoms, pain, back-pain, allergy, paresthesia, flatulence and fever	Headache the most common AE in THS group (5.0%) vs. CC (2.4%) and vs. SA (7.7%)

[Source: Nicotine inhaler: Appendix A6.1.5.5, Section 2.1.2.4.2, THS study: clinical study report ZRHM-REXA-08-US, Table 15.2.6.3]

The safety profile of other first line smoking cessation pharmacotherapies (varenicline and bupropion) is also summarized in Appendix A6.1.5.5 for reference purposes. Side-by-side comparisons of THS and varenicline or bupropion safety profile were considered unecessary, as THS is not developed as a smoking cessation aid, and as varenicline and bupropion are prescription products (not other-the-counter) and have additional safety warnings as compared to NRT products.

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6.1.5.3 Clinical Laboratory Evaluations

For safety purposes, clinical laboratory evaluations (hematology, clinical biochemistry and urinalysis) were done at baseline and at end of study in all 8 clinical studies. Additional checks were done monthly in the two 3-month studies.

A brief overview of major changes, central tendencies and relevant shifts (in at least 2 subjects in any study arm) from normal range values at baseline to above the upper limit of the normal range (normal-to-high shift) and from normal range at baseline to below the lower limit of the normal range (normal-to-low shift) is provided in this section.

Individual clinically relevant changes / important abnormalities in safety laboratory parameters (i.e. all shifts towards CTCAE grade 2 or higher, shifts from normal to CTCAE grade 1, if assessed as clinically significant by principal investigators, or any shift towards below or above normal range and assessed as clinically significant by the principal investigator in case CTCAE grading is not available) were reported as adverse events (See Section 6.1.5.2). Details on individual clinically important abnormalities are also described in the respective clinical study reports (See Module 7.3.1) in their safety section.

6.1.5.3.1 Hematology

Short-term Studies

In the single-use PK studies and in the 5-day studies, mean changes from baseline in hematology parameters were small and showed no notable differences between sequences or study arms.

Relevant shifts from baseline in the 5-day and PK studies were essentially towards lower values (with high variability) and concerned mainly erythrocytes, hemoglobin and hematocrit. In the 5-day studies, there was no apparent trend in the distribution of subjects who had these parameters which shifted from normal to low between the THS, CC and SA arms, except in study ZRHR-REXC-04-JP, where hemoglobin shifted (non-clinically significant) only in the THS arm in 2 subjects (who had both no medical history and no concomitant medication reported). The amount of blood withdrawal in the course of a week or so (blood volume of 260 ml was taken from the subjects in ZRHR-PK-01-EU and 190 ml in the other studies) could have contributed to some extent to the observed shifts.

3-month Studies – Central Tendencies

In the 3-month studies (ZRHM-REXA-08-US and ZRHM-REXA-07-JP), mean changes from baseline in erythrocytes, hemoglobin, hematocrit and mean corpuscular hemoglobin concentration were small and showed no notable differences between study arms, outside a slightly more pronounced decrease in hemoglobin in the smoking abstinence and THS arms of both studies.

This decrease in erythrocyte counts and in hemoglobin level may suggest a trend towards normalization of oxygen supply in the SA and THS arms, associated with substantial decrease of carboxyhemoglobin levels (see Section 6.1.3). The observed changes in humans are supported by *in vivo* studies in rats and mice where a much higher carbon

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monoxide exposure in 3R4F arm was leading to much higher COHb levels and increase in hematology parameters, but not observed in animals in THS arm (see Module 6, Section 6.1.2). Cessation of exposure to 3R4F and switching to THS normalized these values in Apo-$e^{-/-}$ knockout mice study (see Module 6, Section 6.1.4).

Mean changes from baseline in leucocyte counts where small and showed in the Japanese study a slight increase in the CC arm and a slight decrease in the SA and THS arms (which may suggest a decreased chronic inflammation in the SA and THS arms), mainly driven by neutrophil counts. A slight decrease in leukocyte counts was observed in all arms in the US study, mainly driven by neutrophil and lymphocyte counts.

Mean changes from baseline in platelet counts were small and showed no notable differences between study arms in each study, but decreased slightly in the US study (in all arms), while increasing slightly in the Japanese study (in all arms).

3-month Studies – Shifts

Normal-to-low shifts for erythrocytes, hemoglobin, erythrocyte mean corpuscular hemoglobin concentration, neutrophils, hematocrit, platelets, leukocytes, and monocytes were seen across all study arms in both ZRHM-REXA-08-US and ZRHM-REXA-07-JP studies.

Normal-to-high shifts for neutrophil counts and erythrocyte mean corpuscular volume were observed in all 3 arms of both ZRHM-REXA-08-US and ZRHM-REXA-07-JP studies. Normal-to-high shifts for hematocrit, platelet counts, lymphocytes, monocytes, eosinophils, and leukocytes were seen across all study arms instudy ZRHM-REXA-08-US.

Considering the findings described above, it appears that no particular safety signal seems to emerge from the interpretation of the hematology results in these studies.

6.1.5.3.2 Clinical Chemistry

Short-term Studies

In the 5-day studies (ZRHR-REXC-03-EU and ZRHR-REXC-04-JP) and in the PK studies, no specific trends were observed in mean values of clinical chemistry parameters.

Normal-to-high shifts (with high variability) were observed for:

- alanine-aminotransferase (ALT), cholesterol, glucose, triglycerides were observed in all arms in both 5-day studies,
- total bilirubin and direct bilirubin in the THS arm of study ZRHR-REXC-03-EU and in the conventional cigarette and THS arms of study ZRHR-REXC-04-JP (see discussion below in the normal-to-high shifts observed in the 3-month studies),
- albumin in the smoking abstinence and THS arms of study ZRHR-REXC-03-EU and in the THS arm of study ZRHR-REXC-04-JP.

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3-month Studies – Central Tendencies

In the two 3-month studies, mean changes from baseline in liver tests (ALT, aspartame-aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, direct bilirubin and gamma-glutamyl transferase [GGT]), albumin, protein, creatinine, glucose, sodium and potassium levels were small and showed no notable differences between study arms. However, some changes were noticed as follows:

- a very slight increase in direct bilirubin in the THS and SA arms (more pronounced in the THS arm) in study ZRHM-REXA-08-US,
- a very slight decrease in blood glucose in both the CC and THS arms in study ZRHM-REXA-08-US,
- a slight increase (but with a high variability) in blood glucose in all arms in study ZRHM-REXA-07-JP, more pronounced in the CC arm, and
- a slight increase in potassium in the SA arm of study ZRHM-REXA-08-US.

Changes from baseline in triglycerides were small and showed no notable differences between study arms in both 3-month studies. Changes in cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were as follows:

- an [expected, see Section 6.1.4] increase in HDL-cholesterol in both the SA and THS arms in study ZRHM-REXA-07-JP in the THS arm only in study ZRHM-REXA-08-US (only 15% of subjects in SA arm were abstinent at 3 months)
- a slight decrease in total cholesterol and LDL-cholesterol both the CC and THS arms in study ZRHM-REXA-07-JP (where the average body weight increased by 2.5 kg in the SA arm)
- a slight decrease in LDL-cholesterol in all arms in study ZRHM-REXA-08-US.

3-month Studies – Normal-to-low Shifts

Normal-to-low shifts included potassium, total cholesterol, triglycerides, and protein in study ZRHM-REXA-08-US and total cholesterol, LDL cholesterol, protein and glucose in study ZRHM-REXA-07-JP.

There was no apparent trend in the distribution of subjects who had normal-to-low shifts between study arms, except for potassium only observed in 2 subjects (no concomitant medication and no relevant medical history reported) in the THS arm of study ZRHM-REXA-08-US.

3-month Studies – Normal-to-high Shifts

Normal-to-high shifts included

- total cholesterol, triglycerides, AST, ALT, GGT, total bilirubin and glucose in both studies ZRHM-REXA-08-US and ZRHM-REXA-07-JP,
- creatinine and potassium in study ZRHM-REXA-08-US, and
- LDL-cholesterol, HDL-cholesterol and albumin in study ZRHM-REXA-07-JP.

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There was no apparent trend in the normal-to-high shifts distribution between study arms, with the following exceptions in study ZRHM-REXA-07-JP where the shifts were observed for :

- albumin in the CC and SA arms
- HDL-cholesterol in the THS ans SA arms, and
- total bilirubin (in 3 subjects who had no relevant medical history and no concomitant medication reported) in the THS ans SA arms. It has been reported in the literature that smoking cessation, even after short-term abstinence, seems to be associated with an increase in bilirubin concentration, which may be explained by UGT activity de-induction, as suggested by O'Malley (O'Malley 2014). UGT catalyzes the conjugation of bilirubin, the major metabolic pathway responsible for its disposition. Polycyclic aromatic hydrocarbons (PAH) are known to induce some isoforms of the uridine diphosphate glucuronosyltransferase (UGT) family (Zevin 1999). Suppression of exposure to PAH upon exclusive THS use or upon smoking abstinence may provide some explanations on the bilirubin increase

Considering the findings described above, it appears that no particular safety signal seems to emerge from the interpretation of the clinical chemistry results in the studies of concern.

6.1.5.3.3 Urinalysis

In all studies, mean changes from baseline in pH and specific gravity were small and urinalysis results showed no notable differences between sequences or study arms.

Main clinically relevant urinalysis results observed were positive occult blood in female subjects (suggesting contamination of the urine by menstrual blood).

Bilirubin was found (non-clinically significant levels) in 48 % of all subjects in study ZRHM-PK-06-US (where urinary dipsticks were provided by the site), but 25 % of all subjects had bilirubin in urine at baseline. Review of liver tests results from study ZRHM-PK-06-suggests that the bilirubin in urine was not correlated with liver disorders: less than 4% of subjects had high values of ALT, AST or GGT at baseline and at discharge; none had biological cholestasis (4.7 % had high values of total bilirubin at baseline and 6.3 % at discharge but no subjects had high values of direct bilirubin or ALP). In addition, in all other studies and at any visit (including baseline), subjects had no bilirubin in urine, except 1 subject at baseline in study ZRHR-PK-01-EU.

Considering the findings described above, it appears that no particular safety signal seems to emerge from the interpretation of the urinalysis results in the studies of concern.

6.1.5.4 Vital Signs, Physical Findings and Other Observations Related to Safety

In addition to the monitoring of adverse events and to clinical laboratory findings, the safety evaluations of THS also included the evaluations of additional clinical signs and symptoms (vital signs, physical examinations, changes in bodyweight and a specific

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assessment of cough) and other laboratory evaluations (12-lead electrocardiograms, spirometry and CYP1A2 enzymatic activity).

6.1.5.4.1 Vital Signs

In all 8 completed clinical studies, changes in vital signs vs. baseline were assessed daily during the corresponding confinement periods. Additional assessments at Days 30, 60 and 91 were performed in the 3-month studies.

The changes from baseline in systolic blood pressure were small and in both directions across the pharmacokinetic studies. In contrast, a slight decrease was consistently observed at Days 6 and 91 in all groups of the 5-day and 3-month studies, with the exception of a very slight increase (and a large associated standard deviation) in the SA arm of the ZRHM-REXA-08-US study at Day 91.

Concerning diastolic blood pressure, the observations were mixed, with changes in both directions, in the pharmacokinetic studies, in the 5-day studies, and also at Day 6 in the 3-month studies:

- the direction of the changes was the same across sequences and groups in the pharmacokinetic studies and at Day 6 of the 3-month studies, respectively,
- on the other hand, slight increases or decreases were observed in both the CC and THS arms of the ZRHR-REXC-03-EU and ZRHR-REXC-04-JP, respectively, whereas the parameter remained essentially stable in the SA arm of both studies.
- at Day 91 of both 3-month studies, a slight decrease was observed in the CC and THS arms. Concerning the SA arm, a slight decrease was noted in the ZRHM-REXA-07-JP study and remained stable in the ZRHM-REXA-08-US study, in the same timeframes.

In most of the studies, a slight decrease in pulse rate was noted in all the groups or sequences at Days 6 and 91 (where applicable). Notably regarding that parameter, in study ZRHR-PK-02-JP, a slight decrease in the THS – NRT sequence, and a slight increase in the NRT – THS sequence were observed. In apparent contrast with that finding, in study ZRHM-PK-06-US, a slight increase in the THS-NNS sequence and a slight decrease in the NNS – THS sequence were noted.

Overall, considering the findings described above, in particular regarding the direction, the intensity, and the distribution of the changes across sequences and groups, it appears that no particular safety signal seems to emerge from the interpretation of the vital signs results in the studies of concern.

6.1.5.4.2 Physical Examinations

In all 8 completed clinical studies, changes in physical examination vs. baseline were assessed at the day of discharge. Additional monthly examinations were done in the 3-month studies. Bodyweight changes are presented in Section 6.1.5.4.3.

There were no abnormal clinically significant changes in physical examinations observed in the completed clinical studies except in the ZRHM-REXA-07-JP study. In the Japanese study, a total of 6 findings were observed in 5 subjects. All cases were also

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reported as not IP- or study procedure-related and were all non-serious and mild in intensity. Three subjects were in THS arm (rectal prolapse caused by constipation, signs consistent with common cold and tooth fracture observed twice) and two subjects in the SA arm (parotiditis and finger fracture).

6.1.5.4.3 Body Weight

Smoking cessation is associated with weight gain of about 1 kg per month for the first three months of smoking cessation, leading to an estimated weight increase of about 4-5 kg at one year of cessation (Aubin 2012). Some researchers have suggested that weight gain observed upon smoking cessation could increase the short-term risk for diabetes (Yeh 2010). Change in bodyweight was assessed in the 3-month studies. At baseline, the average bodyweight was 15 kg lower in the Japanese study (62 kg) than in the US study (77 kg). In the Japanese study (ZHRM-REXA-07-JP, safety population, Table 15.2.4.33.2), an average bodyweight increase of 2.5 kg (95% confidence interval 1.57 – 3.46) was observed at 3 months in the smoking abstinence arm, while it remained unchanged in both THS and CC arms. In the US study (ZRHM-REXA-08-US, safety population, Table 15.2.6.24), the bodyweight remained unchanged in all 3 arms, including in the smoking abstinence arm, where only 15% of subjects remained abstinent at 3 months.

6.1.5.4.4 Cough Assessment

A specific assessment of cough was done daily during confinement in the 8 clinical studies. In addition, cough was also assessed monthly during the ambulatory period in the 3-month studies. Subjects were asked if they had experienced a regular need to cough during the previous 24 hours. If yes, additional assessment included a visual analogue scale (VAS) on how bothersome their cough was, and 3 Likert scales (intensity of cough, frequency of cough, and amount of sputum production).

Single-use Studies

In the single use cross-over studies, the percentage of subjects who reported coughing at baseline (at Day-1) was between 17% and 57%. The Japanese subjects reported twice more times coughing (57% and 41% in ZRHR-PK-02-JP and in ZRHM-PK-05-JP study respectively) than Western subjects (22% and 17% in ZRHR-PK-01-EU and ZRHM-PK-06-US study, respectively) with a less bothersome cough (mean VAS of 14.2mm to 17.5mm vs. 26.3mm to 27.2mm in Japanese subjects and in Western subjects, respectively). Across the four studies, intensity of coughing was very mild to moderate, its frequency was from rarely to fairly often (and from sometimes to often in the ZRHM-PK-06-US study) and the amount of sputum production from no sputum to moderate. Despite some apparent variability, there were no remarkable changes in the incidence of coughing, its intensity, frequency and sputum production following the single use of THS.

A similar pattern of coughing was observed at baseline in the 5-day studies and 3-month studies.

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First Five Days of *ad libitum* and Exclusive THS Use

When looking at the first week in these four studies, despite some apparent variability within and between studies, there were no remarkable changes in the incidence of coughing in the 3 arms. In addition, the menthol flavor, usually shown to be reducing the irritation and harshness of smoking, as concluded by FDA in the executive summary of the report on menthol cigarettes (USDHHS 2013) seems not to have an impact on coughing in THS users (see Table 21); 32% (51/158) and 30% (48/160) of subjects reported coughing over the last 24 hours on Day 5 with THS Menthol and THS Regular respectively.

Table 21 Cough Assessment at Day 5. THS Regular vs. THS Menthol

	Regular Variant		Menthol Variant	
	ZRHR-REXC-03-EU	**ZRHR-REXC-04-JP**	**ZRHM-REXA-07-JP**	**ZRHM-REXA-08-US**
Number (%) subjects who had cough during last 24 hours	28/80 (35%)	20/80 (25%)	33/78 (42%)	18/80 (22.5%)
VAS (mm) How bothersome was the cough. mean (SD)	33.4 (31.0)	21.3 (16.7)	20.9 (20.5)	23.6 (24.6)

[Source: clinical study report ZRHR-REXC-03-EU, Table 15.2.6.20.1; ZRHR-REXC-04-JP, Table 15.2.6.20.1; ZRHM-REXA-07-JP, Table 15.2.6.25.1, ZRHM-REXA-08-US, Table 15.2.6.25.1]

A transient increase in respiratory symptoms (increased cough and sputum production) has been described (and challenged) in the literature (Etter 2010, Gratziou 2009, Hughes 2007) during the first days of smoking cessation with a proposed mechanism of prompt re-sensitization of cough reflex receptors upon smoking cessation (Stikausteine 2010). Increased cough is also listed as part of criteria forming the WHO International Classification of Diseases (ICD-10) F17.3 diagnosis for tobacco withdrawal syndrome. As for cough incidence, high variability within and between studies was observed in subjects in the SA arm experiencing cough over the last 24 hours for VAS, cough intensity, cough frequency and sputum production. Highest proportions for cough incidence, cough intensity (subjects with moderate, severe or very severe intensity), cough frequency (subjects with fairly often, often or almost always) and sputum production (all amounts) were most often observed between 2 and 4 days of smoking abstinence.

In subjects switching to exclusive THS use, similar variability as for smoking abstinence was observed between and within studies. Here again, highest proportions for cough intensity, cough frequency and sputum production were observed at Day 1 to 3, with a trend toward a decrease at day 5. Few subjects experienced more intense (severe cough) or more frequent (almost always) during the first days of use.

Changes in Respiratory Symptoms Over 3 Months

Pulmonary benefits at 3 months of smoking cessation include the reduced presence and severity of respiratory symptoms (Gratziou 2009). An internet survey has reported a

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significant and rapid (even after 1 week) decrease in self-reported respiratory symptoms upon smoking cessation (Etter 2010).

The time course of the incidence of cough (proportion of subjects who experienced cough during the last 24 hours) in the two 3-month studies is shown in Figure 1. Day-1 to Day 6 represents the daily evaluation during the confinement period of study and Day 30 to Day 90 the evaluation of the previous 24 hours at monthly visits during the ambulatory period of the studies. The cough incidence rates were about twice as high in the Japanese study as compared to the US study at baseline and at all time-points. The Japanese rates are in line with rates observed in Caucasian data as reported from a Swiss survey in smokers and quitters (Etter 2010). The reasons for the US study population exhibiting low cough incidence rates are unclear, and not explained by subject's characteristics as age, sex, cigarette consumption per day as they were very similar in both studies; additionally, subjects from the US study had much higher average bodyweight (77.8 kg vs. 62.2 kg), more often concomitant diseases, including respiratory diseases and abnormal spirometry results at baseline, than subjects from the Japanese study. Other confounding factors may explain these Japanese / US differences, such as ethnicity, cultural differences or exposure to environmental pollution, as suggested by highest carboxyhemoglobin (COHb) results in the SA arm during confinement being observed in the Japanese studies (at Day 5, median COHb levels 2.4% and 2.5% in the ZRHR-REXC-04-JP and ZRHM-REXA-07-JP study respectively vs. 1.0% and 2.2% in the ZRHR-REXC-03-EU and ZRHM-REXA-08-US study, respectively).

In the CC arm (i.e, smoking conditions remaining similar along the study), a higher cough incidence rate was observed during confinement as compared to the ambulatory period. This could be explained by a sensitization effect under confined conditions, leading to higher rates than in real-world settings. As a consequence, cough results from the ambulatory period should not be compared to results obtained during the confinement period, as study conditions are obviously different.

In the CC arm, the cough incidence remained stable over time (31 to 36% in Japanese subjects and 9 to 12% in US subjects).

In the SA arm, the cough incidence was much lower after 1 month as compared to the CC arm (2.6% vs. 9.8% and 20% vs. 29.5% in the US study and in the Japanese study, respectively). The cough incidence rates trended to continue to decline over time, despite that only 23% of quitters remained abstinent (non-abstinent quitters were smoking on average less than 3 CC per day during the last month of the study) at day 90 (Module 7.3.1, ZRHM-REXA-08-US, Table 15.2.4). Other cough parameters improved as well.

In THS arm, the cough incidence rates at 1 month were similar to cough rates from the CC arm in both studies. In the Japanese study, the cough incidence rates continued to decline towards rates similar to those observed upon smoking abstinence, while more than 80% of subjects were exclusive THS users within each month and 73% of subjects were exclusive THS users throughout the full ambulatory period (ZRHM-REXA-07-JP, Table 35). In the US study, a similar trend in cough incidence rate was observed at 2 months (75% of switchers were predominantly THS users and 47.5% were exclusive

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users). At the 3-month visit, the cough incidence rate was back to the incidence rate reported at the 1-month visit, while dual use was increasing over time. Subjects who were not predominately THS users were smoking an average of 4 to 5 CC per day.

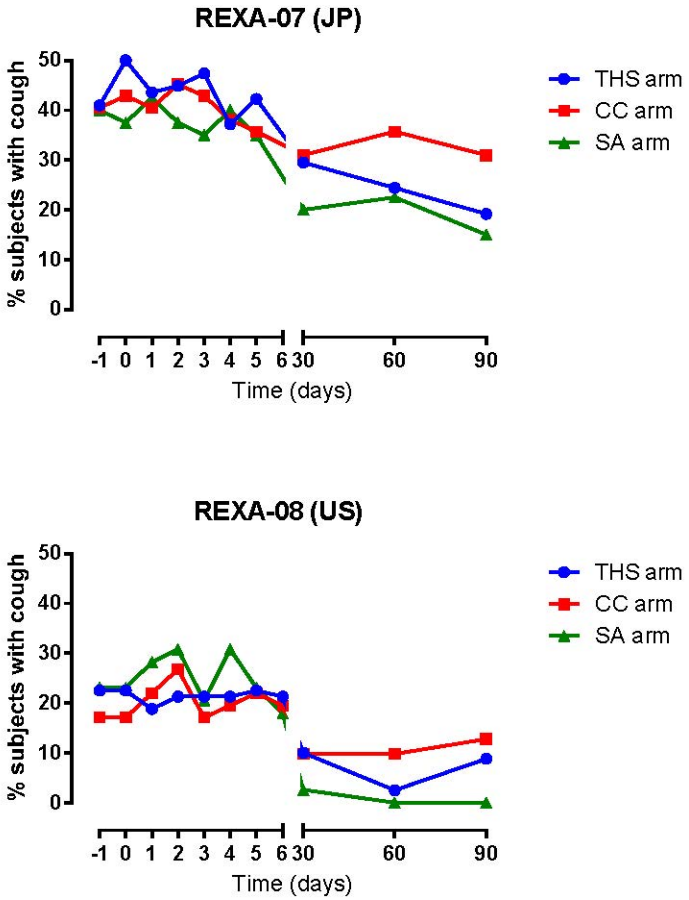


Figure 1 Time Course of Cough in the 3-month Studies (Safety Population)

[Source: clinical study reports: ZRHM-REXA-07-JP, Table 15.2.6.25.1; ZRHM-REXA-08-US, Table 15.2.6.25.1]

The analysis of cough burden, intensity, frequency and sputum production is limited by the small number of coughers, especially in the Japanese study and remains therefore only descriptive.

The burden of coughing measured by the VAS in THS switchers who experienced coughing was low and rather stable over time. Highest values were observed at 2 months with mean (standard deviation [SD]) VAS of 23 (22.2) mm and 29.0 (41.0) mm in the Japanese study and in the US study, respectively. At the same time point, VAS was 45.8 (49.9) mm in the CC arm of the US study and 40.3 (26.4) mm in the SA arm of the Japanese study.

In both studies, the general tendency for THS switchers who experienced cough is to have a higher intensity at 2 months, a lower frequency at 2 and 3 months and higher sputum production.

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To conclude, current results suggest a transient increase of the presence and/or intensity of respiratory symptoms occurring during the first days of THS use, followed by a decrease of presence and intensity of cough associated with an increased sputum production, i.e., a similar pattern as observed with smoking cessation, but with a 1-month lag time as compared to smoking cessation. These results remain to be confirmed with on the ongoing clinical studies and with postmarket data.

6.1.5.4.5 Tobacco / Nicotine Withdrawal Symptoms

As observed at baseline in both ZRHM-REXA-07-JP and ZRHM-REXA-08-US, more than 75% of smokers had one or several withdrawal symptoms, usually at a low score, when completing the Minnesota Nicotine Withdrawal Symptoms (MNWS) questionnaire. MNWS results are summarized in Section 6.2.2 and also discussed in Section 6.2.3.

In most of the completed clinical studies, some of the withdrawal symptoms were reported as adverse events by few subjects, with a trend toward a similar or higher incidence rate as compared to CC but lower than the rate observed in the smoking abstinence arms.

Established tobacco / nicotine withdrawal symptoms are listed in Section 6.1.5.9 and in Table 33.

6.1.5.4.6 Electrocardiogram

Standard 12-lead ECG measurements were done in all 8 clinical studies. Results include individual changes from baseline and shifts from baseline in overall ECG interpretation.

Across all 8 studies, one abnormal ECG result in one subject in THS arm was reported as an adverse event in ZRHR-RECX-03-EU study. On Day 6 (discharge) interpretation of ECG data for this 38-year subject (20-year smoking history and actual CC smoking >19 CC per day) indicated myocardial ischemia of the anterior wall, which was not present at Screening. The AE was considered related to IP and was mild in severity; no concomitant treatment or intervention was required and the ECG was otherwise normal. The subject was not discontinued from the study.

In the single use cross-over studies, ECG was done at baseline and after product use at Days 1 and 3. Slight and inconsistent changes in both directions were observed in heart rate (HR) in all the sequences, with no predominance or pattern being evidenced. A very mild decrease in the corrected QT interval (QTc) was observed in all the sequences in 3 out of 4 studies, whereas in the fourth study (ZRHR-PK-02-JP) changes were very slight and in both directions in all the sequences.

In the 5-day studies, ECG was done at baseline and at Day 6. A small decrease in HR was found in all the arms, slightly deeper in the SA one, but insufficient to determine a clear difference from the other groups. QTc was decreased in all the groups, but the corresponding standard deviations of the shifts were large.

In the 3-month studies ECG was done at baseline and at Days 6, 30, 60 and 91. At Day 6, HR increased slightly in the THS and CC arms in both studies, whereas it changed slightly in both directions in the SA group. At Day 91, changes in HR were small and in both directions across arms and studies. Concerning QTc, small changes in both

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directions were observed across studies in all groups at Day 6, with large standard deviations. At Day 91, mild decreases with large standard deviations were found in all groups in both studies.

Overall, it appears that observations were consistent across studies and timeframes. No particular patterns were evidenced and no safety signal emerged in the studies addressed concerning the ECG.

6.1.5.4.7 Spirometry and Lung Function

Lung function using spirometry measurements was assessed at baseline (all studies), at end of confinement period (all studies) and end of ambulatory period (3-month studies). Main lung function parameters included forced expiratory volume in 1 second (FEV1), the percent FEV1 predicted (FEV1%), the forced vital capacity (FVC) and the FEV1/FVC ratio. In the ZRHM-REXA-08-US study, mid expiratory flow 25-75 and diffusion capacity for lung carbon monoxide (DLCO) (also more often called transfer factor in Europe [TLCO]) were also measured.

In the 4 single use cross-over studies, no clinically relevant differences in spirometry parameters or in changes from baseline were observed between sequences. For all sequences, no clinically significant values or changes from baseline in spirometry parameters were observed. In the ZRHR-PK-01-EU only, a total of seven abnormal results which were not clinically significant were recorded for 4 subjects (6.5%; 2 subjects each in the THS − CC, and CC − THS sequences [9.1%]). These abnormal results were reported as adverse events.

In the two 5-day studies, for all sequences, no notable changes from baseline in spirometry parameters were observed at Day of Discharge. No clinically relevant differences in spirometry parameters or in changes from baseline were observed between study arms. In the ZRHR-REXC-03-EU study only, 10 subjects (5.9%) had at least 1 clinically significant abnormal spirometry interpretation (3 subjects in the THS arm [3.8%], 3 subjects in the CC arm [7.3%], 1 subject in the SA arm [2.6%], and 3 enrolled not randomized subjects [33.3%]). These events were recorded as mild AEs.

In the ZRHM-REXA-07-JP study, and for all study arms, no clinically significant spirometry results were observed at baseline, on Day 5 and on Day 90. Few subjects had non-clinically significant spirometry anomalies at baseline (2 [2.6%], 1 [2.4%] and 3 [7.5%] in THS, CC and SA arms, respectively) and even less anomalies observed on Day 90 (none in THS arm, and 1 subject in both CC and SA arms).

In study ZRHM-REXA-08-US, full lung function and DLCO, was evaluated at baseline (Day 0), end of confinement period (Day 6) and end of ambulatory period (Day 91), in addition to standard spirometry. A significant proportion (54.2%) of subjects in the 3-month US study had abnormal spirometry (52.9% non clinically significant and 1.3% clinical significant anomalies) findings at baseline. Non-consistent changes Day 91 vs. baseline were observed for some parameters but without obvious difference between study arms. A total of 7 abnormal spirometry parameters results were reported after randomization as adverse events in 5 subjects (2 subjects in the THS arm [2.5%], with FEV1 decrease and vital capacity decrease; DLCO decrease in 1 subject in THS arm

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[1.3%)], in 1 subject in CC arm [2.4%] and in SA arm [2.6%]. There was no apparent change in gas transfer parameters (DLCO and Krogh permeability factor KCO) or lung volume (functional residual capacity [FRC], vital capacity [VC], total lung capacity [TLC], and inspiratory capacity [IC]). There was no apparent change in spirometry parameters (FEV_1, FVC, and FEV_1/FVC), with the exception of middle expiratory flow MEF_{25-75}, as changes from baseline tended to be small or comparable between study arms. MEF_{25-75} increased in the THS and CC arms between baseline and Day 91/Discharge Ambulatory while MEF_{25-75} remained stable in the SA arm.

Overall, it appears that observations were consistent across studies and timeframes. No particular patterns were evidenced and no safety signal emerged in the studies addressed concerning lung function assessment.

6.1.5.4.8 CYP1A2 Activity

In our clinical program, a special attention was given to CYP1A2 activity changes. The time response of CYP1A2 activity upon smoking cessation has been previously published (Faber 2004). Then using caffeine as the CYP1A2 substrate, the initial caffeine clearance, estimated from paraxanthine/caffeine plasma ratios (also called caffeine metabolic ratio (CMR) decreased approximatively by 36% upon smoking with an apparent half-life of CYP1A2 activity decrease of 38 hours (Faber 2004). Changes in CMR vs. baseline were assessed in the 5-day (Day 5 vs. baseline) and in the 3-month (Day 5 and day 90 vs. baseline) studies.

At baseline, the average CMR was lower in the Japanese study as compared to the US study (geometric mean about 70-74% and 114-121% respectively). This difference between races is in line with published data (Myrand 2008).

After 5 days of exclusive THS use, CMR levels significantly decreased to a similar extent as upon smoking abstinence in all clinical studies (see Table 22 and Table 23) with difference THS vs. CC between 21.7% and 37%. The CMR levels remained decreased in THS users at 3 months in the Japanese study while the effect was partially diluted in the US study with a less sustained decrease in THS arm vs. CC (ratio 63.0% at day 5 and then 77.1% at day 90) (see Table 23), which may be explained by the concomitant use of CC in addition to THS during the ambulatory period.

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Table 22 Changes in CYP1A2 Activity in 5-day Studies (Full Analysis Set Population)

Study	Relative change vs. baseline (%) Mean (SD) [1]			Change vs. reference (%) LS mean [95% CI] [1]	
	THS	CC	SA	THS-CC	THS-SA
ZRHR-REXC-03-EU (Day 5)	-16.5 (18.0)	12.7 (15.7)	-14.9 (15.8)	-33.6 [-40.6;-26.6]	-2.0 [-9.1;5.1]
ZRHR-REXC-04-JP (Day 5)	-27.4 (14.1)	-1.0 (15.6)	-30.5 (14.8)	-21.7 [-25.5;-17.8]	2.3 [-1.6;6.2]

CI: confidence interval; SD: standard deviation
(1) numbers were rounded at 1 decimal
[Source: Clinical Study Report ZRHR-REXC-03-EU, Table 66 and Table 67. ZRHR-REXC-04-JP, Table 63 and Table 64]

Table 23 Changes in CYP1A2 Activity in 3-month Studies (Full Analysis Set Population)

Study	Relative change vs. baseline (%) Mean (SD) [1]			Ratio of change vs. reference (%) LS mean [95% CI] [1]	
	THS	CC	SA	THS:CC	THS:SA
ZRHM-REXA-07-JP (Day 5)	-21.6 (15.3)	9.7 (23.2)	-23.2 (16.9)	72.1 [67.3;77.3]	101.8 [94.9;109.3]
ZRHM-REXA-07-JP (Day 90)	-19.0 (26.7)	15.4 (39.3)	-15.9 (21.5)	70.4 [63.0;78.7]	93.4 [83.4;104.6]
ZRHM-REXA-08-US (Day 5)	-33.3 (17.0)	3.2 (13.0)	-29.1 (15.6)	63.0 [58.2;68.3]	98.4 [90.4;107.1]
ZRHM-REXA-08-US (Day 90)	-31.7 (27.3)	-13.5 (19.6)	-19.2 (23.7)	77.1 [66.0;90.0]	84.2 [71.8:98.9]

CI: confidence interval; SD: standard deviation
(1) numbers were rounded at 1 decimal
[Source: Clinical Study Report ZRHM-REXA-07-JP, Table 15.2.4.24.2 and Table 15.2.4.23.2. ZRHM-REXA-08-US, Table 15.2.4.23.2 and Table 15.2.4.24.2]

The observed decrease in CMR, the proxy for CYP1A2 enzymatic activity, is not a THS-drug interaction but a pattern similar to the pattern observed upon smoking cessation where a de-induction of CYP1A2 is resulting from the absence of inducers such as polycyclic aromatic hydrocarbons in the THS aerosol.

These results are convergent with in vitro experiments conducted by PMI on bronchial culture exposed to 3R4F cigarette smoke and to THS aerosol (more details are available in Module 7.5). In this experiment, the levels of CYP1A1/1B1 activity following 3R4F smoke were greater than the air control despite high variability. The activity levels of the THS aerosol-exposed bronchial culture were comparable to the air control. CYP1A1, CYP1B1 (both being expressed in a wide range of extrahepatic tissues, particularly in the

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lung tissue) and CYP1A2 (expressed mainly in the liver, and measurable in blood) activities are inducible by polycyclic aromatic hydrocarbons (USDHHS 2010a).

6.1.5.5 Safety in Special Groups and Situations

The analysis of safety in special groups and situations is currently limited as 1) the study population enrolled in the 8 completed clinical studies was primarily of adult smokers in general good health conditions (see Section 6.1.5.1.1) and, 2) the underlying medical conditions of adult smokers enrolled in other premarket human studies with passive safety surveillance (see Section 6.1.5.7) were not reported or usually not available.

6.1.5.5.1 Effects of Intrinsic and Extrinsic Factors

There is an obvious difference in the incidence rate of AEs between the studies executed in Japan vs. studies in Europe and US. The paucity of AEs in the Japanese population in the single use and in the 5-day studies may be explained by cultural differences in reporting AEs. The cultural factors leading to AEs underreporting in the Japanese studies was suggested in a review (Ferner 2005). In PMI studies investigating early prototypes of THS, low AEs incidence rates (3 to 7%) were observed in studies conducted in Japan and in Korea in contrast to high incidence rates (33 to 85%) in studies conducted in US and in Europe (See THS 2.2 Investigator Brochure in Appendix 1 of the THS Safety Update Report 2016, Module 7.3.1).

There is a known genetic polymorphism in CYP2A6 activity leading to a decreased nicotine clearance in Japanese (Benowitz 2006, Nakajima 2006). This was also observed in our studies (see details in the pharmacokinetic summary, Section 6.2.1) but was not a factor for AEs as the AEs incidence rate in our Japanese nicotine pharmacokinetic studies (ZRHR-PK-02-JP and ZRHM-PK-05-JP) was twice as low vs. non-Japanese studies.

In the 3-month studies, the AEs incidence rate was lower in the Japanese study (37.4%) as compared to the US study (59.4%). Here as well, the cultural differences may explain part of the situation as the number of AEs per subject with AEs was 1.6 (Japanese study) and 2.1 (US study). However, in contrast to the Japanese population, the US study population, despite being considered as in general good health, had relevant baseline differences which may also explain the difference in AEs incidence rate with a 15 kg higher average bodyweight, presence of concomitant diseases in 62% of the subjects (13% in the Japanese), concomitant medications in 18% of subjects (<1% in Japanese) and presence of non-clinically and clinically relevant spirometry abnormalities at baseline in the US study population.

6.1.5.5.2 Smoke-Drug Interactions

Tobacco smoke has been associated with modulation of several physiological processes involved in drug disposition and various pharmacokinetic and pharmacodynamic mechanisms have been identified (Kroon 2007, Petros 2012, Zevin 1999). Polycyclic aromatic hydrocarbons are considered as potent inducers of the cytochrome P-450 (CYP), in particular their CYP1A1 (in bronchial epithelium tissue), 1A2 (in liver), and possible 2E1 isoenzymes. Tobacco smoke also inhibits CYP2A6 isoenzyme, involved in nicotine disposition. Nicotine itself does not affect CYP2A6 activity (Benowitz 2009, Hukkanen 2009). These interactions may have clinically relevant consequences on drug

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disposition, especially for medications primarily metabolized by the induced or inhibited cytochrome. The most relevant interactions are for caffeine, clozapine, olanzapine, fluvoxamine, tacrine, ropinirole and theophylline, most of them with narrow therapeutic index. These drugs, all metabolized by CYP1A2 enzyme, exhibit an increased metabolism in smokers, explained by an induction of CYP1A2 activity. Upon smoking cessation, the de-induction of CYP1A2 activity may lead to medication overdose and higher risk of adverse events. There are conflicting results on smoke-drug interaction with uridine 5'-diphosphate-glucuronosyltransferase isoenzymes family and clinical consequences (Petros 2012). Smoke-drug pharmacodynamic interactions have been less investigated and their clinical / therapeutic consequences upon smoking cessation are not well understood (Kroon 2007, Schaffer 2009)

Physiological changes resulting from the absence of some cigarette smoke toxicants in the THS aerosol may alter the pharmacokinetics or pharmacodynamics of certain drugs, such as drugs primarily metabolized by CYP1A2 and having a narrow therapeutic index (e.g., theophylline, olanzapine, clozapine, ropinirole) for which dosage adjustment may be necessary.

6.1.5.5.3 Use in Pregnancy and Lactation

Pregnancy and lactation were exclusion criteria and reason for immediate withdrawal in all completed and ongoing clinical studies. As a consequence, THS use was not tested in these 2 conditions. Women of childbearing potential (WOCBP) were instructed to use adequate contraceptive methods during the course of the study and urine pregnancy test (UPT) was checked at enrolment and at end of study. Additional monthly UPT checks were done for studies longer than 1 month. No cases of pregnancy or lactation were reported in the 8 completed clinical studies.

Pregnancy and lactation were exclusion criteria and reason for immediate withdrawal in the behavioral study THS-PBA-07-US and based on self-reporting at screening and during the study. One pregnancy case with THS exposure was spontaneously reported in THS-PBA-07-US study (see THS-PBA-07-US Safety Summary Report in Module 7.3.1)

As of 31-Dec-2015 (DLP) a total of three pregnant women were reported to be exposed to THS in the ongoing ZRHR-ERS-09-US study. Beyond this DLP and as of 30-Apr-2016, one additional pregnant woman was exposed to THS in study THS-PBA-07-US (study mentioned in Section 6.1.5.7) (see THS Safety Update Report 2016, Module 7.3.1).

No other pregnancy cases associated with THS use / exposure were reported in earlier reviews or from postmarket safety surveillance (see Module 7.3.1: THS 2.2 Safety Update report 2015, THS 2.2 menthol Safety Update Report 2015, THS Safety Update Report 2016).

A summary of reported pregnancy cases with exposure to THS is presented in Table 24. The four women were exposed to THS during their first month of pregnancy and they were discontinued from the study.

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Table 24 Reported Pregnancy Cases with THS Exposure

Safety Case #	Study	Subject #	Age (yr)	THS Exposure Gestational Weeks	Pregnancy Outcome
PMI000311	ZRHR-ERS-09-US	20170	35	1 to 4	Normal pregnancy ongoing
PMI000312	ZRHR-ERS-09-US	20104	35	1 to 6	Caesarian section week 39 No maternal pregnancy /delivery-associated AE Normal baby with biophysical score 8/8
PMI000406	ZRHR-ERS-09-US	20245	32	1 to 4	Normal pregnancy ongoing
PMI000483	THS-PBA-07-US	751296	30	1 to 2	Normal pregnancy ongoing

[Source: THS safety update report 2016]

Maternal prenatal smoking has been associated with ectopic pregnancy, spontaneous abortion, early pregnancy, intrauterine growth restriction and low birth weight, and birth defects (such as orofacial clefts, clubfoot, gastroschisis, and atrial septal heart defects) and neurobehavioral disorders in children (disruptive behavioral disorders, and attention deficit hyperactivity disorder) as described in the latest Surgeon General report (USDHHS 2014). Pre- and peri-conception smoking was reported to be associated with higher risk of congenital heart diseases (Lassi 2014).

Nicotine is classified by the US FDA as a pregnancy category D compound (*There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks*) and is reflected as such in NRT products labeling (See Appendix A6.1.5.5). The evidence is sufficient to infer that nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse outcomes such as preterm delivery and stillbirth (USDHHS 2014). There is also sufficient evidence to infer that nicotine exposure during fetal development, a critical window for brain development, has lasting adverse consequences on brain development (USDHHS 2014). Nicotine (and other factors) may play an important role in sudden infant death syndrome (USDHHS 2014).

A number of smoke constituents have been listed in the US Federal Register as reproductive or developmental toxicants (USDHHS 2012a). Nicotine exposure from THS remains at levels similar to that of CC (see Section 6.2.1); exposure levels to carbon monoxide, 1,3-butadiene and benzene upon exclusive THS use are similar to levels during smoking abstinence as shown in our human studies (see Section 6.1.3); in addition to nicotine,THS aerosol contains reproductive or developmental toxicants (according to FDA list, USDHHS 2012) which are not fully eliminated (See Section 6.1.1).

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Due to the presence in THS aerosol of nicotine and other listed reproductive or developmental toxicants, even at concentrations much lower than in cigarette smoke, the use of THS during pregnancy or breast feeding is expected to be at a higher risk than with NRT products but not at the same level than for cigarette smoking. Use of any tobacco product, including THS should be avoided during pregnancy and breast feeding.

6.1.5.5.4 Nicotine Over-exposure

In a review of 28 nicotine replacement therapy randomized controlled trials (a total of 7120 subjects exposed to NRT), 10.5% of the subjects had an increase in cotinine levels of 50% or more vs. baseline. Typical nicotine over-exposure symptoms (nausea, vomiting, palpitations, dizziness and headache, all of mild or moderate intensity) were uncommonly reported (99% upper confidence interval incidence rate between 0.1 and 0.7%) (Tonstad 2014). All these symptoms are non-specific to nicotine overdose and some of them are also reported as nicotine withdrawal symptoms (See Table 33).

Potential signs and symptoms associated with nicotine over-exposure (nicotine intoxication) are listed in Section 6.1.5.9 and in Table 33.

6.1.5.6 Abuse Liability

The abuse liability assessment for THS is described separately in Section 6.2.3.

6.1.5.7 Pre-market Safety Surveillance

Since May 2014, PMI has implemented a study-specific passive safety surveillance mechanism in some field market research studies (blend test [BT] and whole offer test [WOT]) and in human studies part of the Perception and Behavior Assessment program, when THS was used. These studies are listed in Table 25. Adverse events spontaneously reported by study participants were collected using a structured AE questionnaire. The AE questionnaires were then transferred to a pharmacovigilance provider for triage, case processing, and medical assessment. In study THS-PBA-07-US, an additional mechanism was implemented to collect and follow up self-reported pregnancies occurring during the course of the study that were exposed to THS.

All spontaneously reported AEs are suspected to be tobacco product related ("implied causality") unless impossible from a temporal point of view, as people who spontaneously report an AE judge that this AE has been caused by use of the investigational product. None of these AEs were reported by healthcare professionals.

The THS Menthol and THS Regular variants used on these studies are listed in Appendix A6.1.5.1.

A total of 5948 study respondents/participants participated in the seven human studies having a passive safety surveillance implemented. A total of 340 participants (AE reporting rate 5.7 %) reported a total of 653 AEs (see Table 25). The THS-emergent AEs are summarized as AE preferred terms per SOC in Module 7.3.1, THS Additional Safety Data Report. A total of 4079 and 1861 participants used the THS Regular variant and the THS Menthol variant, respectively (see Appendix A6.1.5.6).

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Table 25 Passive Safety Surveillance in Premarket Human Studies with THS Use

Study	Country	Safety Population N	Subjects with AEs N (%)	Total number of AEs N	SAEs N	Ref
P1-BT1-IT	Italy	1047	76 (7.2%)	159	0	(a) (b) (c)
P1-WOT2-IT	Italy	643	21 (3.2%)	36	0	(a) (b) (c)
P1-WOT1-CH	Switzerland	580	84 (14.5%)	145	0	(a) (b) (c)
P1-WOT1-DE	Germany	593	21 (3.5%)	42	0	(a) (c)
P1-WOT1-KO	South Korea	1316	83 (6.3%)	141	5	(a) (b) (c)
P1-BT1-RU	Russia	611	7 (1.1%)	9	0	(a) (b) (c)
THS-PBA-07-US	USA	1158	48 (4.14%)	121	19	(d)
Grand Total		5948	340 (5.7%)	653	24	

[Source: Ref (a) THS2.2 safety update report 2015, Ref (b) THS2,2 menthol safety update report 2015, Ref (c) THS safety update report 2016, Ref (d) THS-PBA-07 safety summary report , see Module 7.3.1)

As the THS-PBA-07-US was the only study with passive safety surveillance conducted in the US, safety findings are presented separately for this study in Table 26. The eight SAEs reported in study THS-PBA-07-US are shown in Table 28. One pregnancy case was reported in study THS-PBA-07-US. More details are provided in Section 6.1.5.5.3. Approximatively, 38%, 44% and 18% of study participants used the THS Regular variant, the THS Menthol variant or both variants, respectively. There are no obvious reporting rate disproportion between the different user groups (Table 26) and the overall 4.14% reporting rate is within the reporting rates observed in other studies conducted outside the USA (Table 25).

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Table 26 Most Commonly Reported AEs in THS-PBA-07-US

Adverse Event Preferred Term	THS Regular Only	THS Menthol Only	THS Regular and THS Menthol	Overall
Number of exposed participants	441	512	205	1158
Number of AEs (cases)	46 (16)	61 (23)	14 (9)	121 (48)
AE reporting rate (%)	3.63%	4.49%	4.39%	4.14%
Most commonly reported AEs (n, % of all reported AE)				
Headache	6 (13.04%)	6 (9.84%)	1 (7.14%)	13 (10.74%)
Malaise	3 (6.52%)	2 (3.28%)	2 (9.76%)	7 (5.78%)
Nausea	4 (8.70%)	2 (3.28%)	0	6 (5.00%)
Dizziness	2 (4.35%)	2 (3.28%)	0	4 (3.30%)
Abdominal discomfort	1 (2.17%)	1 (1.64%)	1 (7.14%)	3 (2.48%)
Oral discomfort	1 (2.17%)	2 (3.28%)	0	3 (2.48%)
Chest pain	1 (2.17%)	1 (1.64%)	1 (7.14%)	3 (2.48%)
Cough	0	2 (3.28%)	1 (7.14%)	3 (2.48%)
Throat irritation	1 (2.17%)	2 (3.28%)	0	3 (2.48%)
TOTAL	19 (41.30%)	20 (32.79%)	6 (42.86%)	45 (37.19%)

[Source: THS-PBA-07-US-PSS safety summary report, Table 6 and Table 7]

The summary tables and corresponding line listings of THS-emergent AEs from premarket passive safety surveillance are presented in Module 7.3.1, THS Additional Safety Data Report. Four SOCs predominate the reported AEs, covering approximatively 90% of all AEs: general disorders and administration site conditions (approx. 25-30%), respiratory, thoracic and mediastinal disorders (approx. 20-30%) gastrointestinal disorders (approx. 15-20%) and nervous system disorders (approx. 15-20%), without obvious difference between the different THS variants. The most commonly (≥ 5% and ≥ 1% of all reported AEs in any of the two flavor variants) reported AEs during passive surveillance in these premarket studies are listed in Table 27 per THS variant.

The nature and frequency of AEs reported in the US study look similar to the nature and AEs reported globally during premarket passive safety surveillance.

It appears that nausea and dysgeusia are reported approx. at a twofold lower rate with THS Menthol variant vs. THS Regular variant. This may be linked to the fact that study participants reported much more often abnormal product taste with THS Regular variant (Table 27). Menthol is also known to have smoothing properties, but other administration site conditions (e.g., throat irritation, local discomfort) reported are not in favor of these smoothing properties, even if oropharyngeal pain was only reported in by participants exposed to THS Regular.

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Table 27 Most Commonly Reported AEs during Premarket Passive Safety Surveillance

Adverse Event Preferred Term	THS Regular Variants		THS Menthol Variants	
	N	%	N	%
Number of all AEs (cases)	503 (254)		190 (89)	
5% or more of all reported AEs	*263*	*52.3%*	*72*	*37.9%*
Headache	54	10.7%	14	7.4%
Nausea	51	10.1%	11	5.8%
Product taste abnormal	50	9.9%	11	5.8%
Cough / productive cough	49	9.7%	21	11.1%
Throat irritation	32	6.4%	10	5.3%
Dysgeusia	27	5.4%	5	2.6%
1% to < 5% of all reported AEs	*128*	*25.4%*	*54*	*28.4%*
Oropharyngeal pain	20	4.0%		0.0%
Product quality issues	14	2.8%	5	2.6%
Chest discomfort	14	2.8%	2	1.1%
Malaise	13	2.6%	8	4.2%
Dizziness	13	2.6%	9	4.7%
Dry throat	10	2.0%	3	1.6%
Feeling hot	9	1.8%	3	1.6%
Oral discomfort	7	1.4%	2	1.1%
Abdominal discomfort / abdominal pain upper	7	1.4%	4	2.1%
Feeling abnormal	5	1.0%	-	-
Chest pain	5	1.0%	2	1.1%
Dry mouth	1	0.2%	2	1.1%
Device difficult to use	2	0.4%	5	2.6%
Product odor abnormal	4	0.8%	5	2.6%
Nasopharyngitis	1	0.2%	2	1.1%
Laryngeal discomfort	3	0.6%	2	1.1%

[Source: Appendix A6.1.5.6, derived from Summary Tables]

Among the 340 AE cases (a total of 653 AEs) spontaneously reported during premarket safety surveillance, a total of 10 cases (2.9 % of all AEs cases) were assessed by PMI as serious (a total of 24 SAEs) because the subject was hospitalized or because the case was seen as an important medical event, based on appropriate medical judgment (see Table 28).

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Table 28 Cumulative SAEs from Passive Safety Surveillance in Premarket Human Studies as of 30-Apr-2016

Study Code	Case ID	Subject	THS variant	SAE Criteria	SAE Description	Causality[1]
P1-WOT1-KO	PMI000109	1181271	Regular	H	Fall, Spinal disorder, Spinal pain	Related
	PMI000128	1410947	Regular and Menthol	IME	Injury associated with device, Thermal burn	Related
THS-PBA-07-US	PMI000347	200851	Regular	H	Road traffic accident, Concussion, Joint injury, Muscle strain, Skin abrasion	Related
	PMI000365	209653	Menthol	H	Hospitalisation[2]	Not Related
	PMI000367	654390	Regular and Menthol	H	Accident, Limb Injury, Skeletal injury, Osteomyelitis, Nerve injury	Related
	PMI000381	821416	Menthol	H	Head injury	Related
	PMI000394	652030	Regular	H	Sepsis, Cholecystitis infective, Pneumonia	Related
	PMI000404	656993	Menthol	H, IME	Bronchitis, Ear infection	Possibly Related
	PMI000409	184377	Menthol	IME	Tonsillar cyst	Related
	PMI000410	759991	Menthol	H	Adverse Event[3]	Possibly Related

H = Hospitalization; IME = Important Medical Event
[1] All spontaneously reported AEs are suspected to be tobacco product related ("implied causality") unless impossible from a temporal point of view, as people who spontaneously report an AE judge that this AE has been caused by use of the investigational product.
[2] (Unspecified) Health related problem requiring hospitalization.
[3] Respondent was hospitalized for (unspecified) health problem.

6.1.5.8 Post-marketing Safety Surveillance

THS is currently marketed outside the US since November 2014. At safety data lock point (31-Dec-2015) the list of countries and respective marketing date is presented in Table 29. Details on THS variants are available in Appendix A6.1.5.1. Country-specific brand names for THS variants can be found in Module 7.3.1, THS Safety Update Report 2016.

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Table 29 THS Marketing Status (31-Dec-2015)

Countries	First Launch
Japan	Nov-2014
Italy	Nov-2014
Switzerland	May-2015
Monaco	Nov-2015
Portugal	Nov-2015
Romania	Nov-2015
Russia	Nov-2015
Slovenia	Nov-2015

[Source: THS Safety Update Report 2016]

In these countries, a passive safety surveillance mechanism has been put in place. Users and concerned people can call a dedicated local or regional call center to ask questions about THS use or to report problems with product use including adverse events they think are associated with THS use. The country-specific call center phone number is printed on THS packs. Calls are entered into a PMI global consumer response system database. In case of adverse events, and if allowed by local regulations, trained call center operators invite callers to provide additional health information using a structured AE questionnaire. Collected adverse events information is then transferred to a safety vendor for triage, data entry into a validated safety database (Argus©), case processing and medical assessment.

As these AEs are spontaneously reported, an implicit causality to THS use is made and all AEs reported through this mechanism are considered as suspected adverse events, unless the role of THS can be ruled out (e.g., AE onset or medical condition worsening is prior to THS use).

The number of exposed consumers is estimated as the number of THS kits sold, with the assumption that 1 kit sold represents 1 consumer, irrespective of the amount and duration of tobacco sticks consumed. This method of THS exposure estimation may evolve, once more comprehensive information on THS pattern of use becomes available postmarket.

During the period from November 2014 to May 2015, 17 AEs were reported by 5 THS Menthol users, with an AE case reporting rate of 2.2 cases per 10’000 consumers (THS 2.2 menthol Safety Update Report 2015, Module 7.3.1).

During the period from November 2014 to April 2015, 8 AEs were reported by 4 THS Regular users, with an AE case reporting rate of 2.4 cases per 10’000 consumers (THS 2.2 Safety Update Report 2015, Module 7.3.1).

During the period from May 2015 to December 2015, 165 AEs (including 2 SAEs) were reported by 74 THS Regular and THS Menthol consumers, with an AE case reporting rate of 1.6 cases per 10’000 consumers (THS Safety Update Report 2016, Module 7.3.1).

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Since first THS marketing in November 2014 and up to the safety data lock point as of 31-Dec-2015, a total of 174 AEs (including 2 SAEs) were spontaneously reported by 91 THS consumers (THS Safety Update Report 2016, Module 7.3.1). There are no medically-confirmed AEs, as none of the AEs were reported by healthcare professionals. Two AE cases were assessed as serious (important medical event as per appropriate medical judgement. The first case (PMI000323) concerns a 33-old-female consumer who experienced loss of consciousness and dizziness after taking one or two puffs of THS Menthol which occurred after two months of daily product usage. The second case (PMI000465) concerns a male consumer who started using the THS Regular and experienced loss of consciousness (syncope) on the same day while coughing (suggesting a cough syncope) after having used (for the first time) 2 or 3 tobacco sticks.

The summary tables and corresponding line listings of THS-emergent AEs from postmarket passive safety surveillance are presented in Module 7.3.1, THS Additional Safety Data Report. Among the 174 AEs, 87% affect 4 system-organ classes (gastro-intestinal disorders 27%, respiratory, thoracic and mediastinal disorders 25%, general disorders and administration site conditions 19% and nervous system disorders 16%). The ten most commonly reported AEs (representing more than 50% of all AEs) during post market passive surveillance are listed in Table 30.

Table 30 Ten Most Commonly Reported AEs from THS Postmarket Passive Safety Surveillance

Adverse Event Preferred Term	Number of cases	Percentage AEs vs. All Reported AEs
Headache	15	8.6%
Nausea	15	8.6%
Cough	12	6.9%
Malaise	12	6.9%
Oropharyngeal pain	9	5.2%
Dizziness	6	3.4%
Vomiting	6	3.4%
Dry throat	5	2.9%
Thermal burns	5	2.9%
Throat irritation	5	2.9%

[Source: THS Safety Update Report 2016]

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6.1.5.9 Expected Adverse Events and Foreseeable risks

6.1.5.9.1 Expected Adverse Events

Based on the current safety knowledge accumulated so far with THS use, a relatively low proportion of THS users reported THS-related AE cases (as assessed by investigators), consistent across randomized clinical study types:

- 7.2% of the subjects in single use PK studies (see Table 6)
- 6.9% of the subjects in 5-day and 3-month studies (See Section 6.1.5.2.2.4)

Similar low proportions of THS users spontaneously reported AEs (by default categorized as suspected to be THS-related) during passive safety surveillance implemented in studies,

- 4.1% of study participants enrolled in study THS-PBA-07-US (see Table 26)
- 5.7% of study participants enrolled in all studies with passive safety surveillance (see Table 25).

Table 31 provides the list of reported adverse events which were assessed to be related to THS use during clinical studies and ordered per frequency. Table 32 lists the adverse events reported during passive safety surveillance and suspected to be related to THS use or exposure. The frequency classes mentioned in Table 31 are those used for medicinal products labeling in Europe. Frequencies below 1% are set as not known, as the overall THS-exposed population (N=318 in repeated use studies and N= 566 overall, see Table 4) does not allow an accurate estimation of frequencies below 1%, based on the rule of thumb in usage in pharmacovigilance (300 subjects needed to estimate frequency of 1%). As only a small subset of THS-emergent AEs were assessed as related to THS, none of these THS-related AEs reached an incidence rate > 1%. As an example, headache, which was reported up to 30% in one study, was reported in 42 occurrences (7.4% of THS-exposed subjects) and only 1 case was assessed as THS-related.

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Table 31 THS Expected AEs: THS-related Adverse Events from Clinical Studies

Frequency Class	THS-related Adverse Events (Preferred Terms) per System-Organ Class
Very common (≥1/10)	None
Common (≥1/100 to <1/10)	None
Not known (cannot be estimated from the available data, due to exposed population)	• Nervous system disorders: headache, dizziness, presyncope and syncope • Gastrointestinal disorders: nausea, vomiting, oral pain, diarrhea, dry mouth, salivary hypersecretion • Respiratory, thoracic and mediastinal disorders: cough, upper airway cough syndrome, oropharyngeal pain, sneezing • Cardiac disorders: myocardial ischemia • Ear and labyrinth disorders: vertigo • General disorders and administration site conditions: non-cardiac chest pain • Hepatobiliary disorders: hepatic function abnormal • Investigations: carbon monoxide diffusion capacity decreased, spirometry abnormal • Metabolism and nutrition disorders: hypertriglyceridemia • Musculoskeletal and connective tissue disorders: pallor, musculoskeletal chest pain • Psychiatric disorders: dysphoria • Skin and subcutaneous tissue disorders: hyperhidrosis

[Source: above Table 8 and Table 17]

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All AEs spontaneously reported during passive surveillance activities that are associated with THS use / THS exposure are listed in Table 32, and presented by SOC and preferred terms. As expected, almost all SOCs are subject to AEs associated with THS use.

Table 32 Adverse Events Associated with THS Use from Passive Surveillance (All Variants)

System-Organ Class	Adverse Events (Preferred Terms)
Cardiac disorders	Tachycardia
Ear and labyrinth disorders	Vertigo
Eye disorders	Chromatopsia, eye irritation, eyelid disorder
Gastrointestinal disorders	Abdominal discomfort, Abdominal distension, Abdominal pain upper, Dry mouth, Diarrhea, Dyspepsia, Dysphagia, , Esophageal pain, Eructation, Frequent bowel movements, Gastric disorder, Gingival disorder, Gingival pain, Glossitis, Glossodynia, Hypoesthesia oral Lip blister, Lip swelling, Mouth ulcer, Nausea, Odynophagia, Oral discomfort, Oral mucosa discoloration, Oral pain, Paresthesia oral, Retching, Salivary hypersecretion, Stomatitis, Tongue pruritus, Tongue coated, Tongue discoloration, Tongue swollen, Vomiting,
General disorders and administration site conditions	Adverse event, Asthenia, Chest discomfort, Chest pain, Condition aggravated, Device battery issue, Device damage, Device defective, Device difficult to use, Device issue, Device use error, Device malfunction, Discomfort, Energy increased, Fatigue, Feeling abnormal, Feeling hot, Hunger, Injury associated with device, Malaise, Mucosal induration, Pain, Preexisting condition improved, Product odor abnormal, Product quality issue, Product taste abnormal, Pyrexia, Sensation of foreign body, Sense of oppression, Sluggishness, Unevaluable event,
Immune system disorders	Hypersensitivity
Infections and infestations	Abscess oral, Bronchitis, Cholecystitis infective, Ear infection, Influenza, Laryngitis, Naso-pharyngitis, Osteomyelitis, Pharyngitis streptococcal, Pneumonia, Respiratory tract infection, Sepsis, Sinusitis, Tonsillitis, Tracheitis,
Injury, poisoning and procedural complications	Accident, Burn, Burn oral cavity, Concussion, Fall, Head injury, Joint injury, Limb injury, Maternal exposure, Muscle strain, Nerve injury, Respiratory fume inhalation disorder, Road traffic accident, Skeletal injury, Skin abrasion, Thermal burn Tobacco poisoning, Wrong technique in product use,
Investigations	Blood pressure increased, Heat rate increased,
Musculoskeletal and connective tissue disorders	Muscular weakness, Spinal disorder, Spinal pain,
Nervous system disorders	Aphonia, Dizziness, Dysgeusia, Head discomfort, Headache, Loss of consciousness, Movement disorder, Neuralgia, Somnolence, Syncope, Tremor,
Psychiatric disorders	Agitation, Anxiety, Aversion, Mental status changes, Nervousness, Panic reaction,
Respiratory, thoracic and mediastinal disorders	Bronchial irritation, Bronchial secretion retention / sputum retention, Choking sensation, Chronic obstructive pulmonary disease, Cough, Cough decreased, Cough productive, Dry throat, Dysphonia, Dyspnea, Hemoptysis, Hiccups, Laryngeal discomfort, Nasal discomfort, Oropharyngeal discomfort, Oropharyngeal pain, Pharyngeal disorder, Pharyngeal edema, Respiratory tract irritation, Sputum discolored, Suffocation feeling, Tracheal irritation, Throat irritation, Tonsillar cyst
Skin and subcutaneous tissue disorders	Blister, Cold sweat, Decubitus ulcer, Pruritus, Urticaria,
Vascular disorders	Hypotension

[source: compiled from summary tables from Module 7.3.1, THS Additional Safety Data Report]

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6.1.5.9.2 Other Foreseeable Risks with THS Use

Table 33 provides a list of events which can be foreseen based on the nature of the product and its composition, its pattern of use, the over- or under-exposure to nicotine and from the carry-over of smoking history.

Signs and symptoms suggesting mild nicotine intoxication, such as those described under ICD-10, F17.0 (WHO 2016), are due to the stimulation of the autonomic nervous system by nicotine and can be observed with too intense use by THS consumers, accidental poisoning (e.g. child poisoning) or intentional poisoning. More intense symptoms are associated with higher levels of nicotine and are due to secondary depression of the autonomic nervous system (Nicotine:Martindale 2016, Goodman & Gilman 2011). Severe nicotine intoxication is not expected under normal use conditions; it can occur upon intentional or accidental poisoning. One THS tobacco stick contains approximatively 5 to 6 mg nicotine, as described in the current THS Investigator's Brochures (see THS Safety Update Report 2016, Module 7.3.1). The acute lethal oral dose in adult humans is traditionally set at 60mg (ca 0.8mg/kg bodyweight) but this is currently challenged, as nonfatal nicotine intoxications cases reported do not support a lethal dose of 60mg in adult. The current data indicates that the nicotine oral acute lethal dose would be more than 500mg (6 to 7mg/kg) (Mayer 2014).

Tobacco and nicotine withdrawal symptoms are common in smokers and even exacerbated in quitters; they were also reported by THS users, as described above in Section 6.1.5.4.5. These symptoms usually emerge after a few hours after nicotine abstinence and reflect the imbalance in brain neurochemistry (Paolini 2011). These symptoms can be clustered in affective, somatic and cognitive symptoms (see Table 33) (McLaughlin 2015). Seven of these symptoms are primary symptoms (*in italic in* Table 33) for the DSM-5 diagnosis of nicotine withdrawal symptoms (American Psychiatric Association 2016). The Minnesota Nicotine Withdrawal Symptoms questionnaire (administered in our clinical studies) incorporates most of the signs and symptoms (Hughes 2008, West 2006). Soreness of throat and aphthous mouth ulcers are also listed as possible withdrawal symptoms (McRobbie 2004).

Few cases (<1%) of skin disorders (pruritus, rashes, erythema, urticaria) have been reported in the 8 completed clinical studies (0.7% in THS users, 0.3% in CC users), all assessed as not related to THS. Two cases of urticaria and generalized rash associated with THS use have been reported postmarket (THS Safety Update Report 2016, Module 7.3.1). In a metanalysis of AEs associated with NRT for smoking cessation (a total of 177,390 individuals in 120 studies), urticaria cases were reported in 3 studies with an odds ratio (NRT vs. control) of 1.13 (95% confidence interval 0.77 – 1.65) (Mills 2010). Similar skin disorders and hypersensitivity reactions have been reported in studies with NRT products (e.g., nasal spray, inhaler), varenicline and bupropion, usually with an incidence rate <1% in both active and placebo (See Appendix A6.1.5.5). Skin disorders through local irritation or through hypersensitivity reactions in susceptible subjects have been reported with nicotine and ingredients such as menthol, propylene glycol and glycerol (Nicotine:Martindale 2016, Menthol:Martdindale 2016, Martin Leroy 2012, Propylene Glycol: Martindale 2016, Glycerol:Martindale 2016).

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The suppression of smoke-drug interactions in CC smokers switching fully to THS and potential impact in some patients is described in Section 6.1.5.4.8.

The identification of safety signals related to THS use is challenging, as smoking-attributable morbidity and mortality reversibility upon smoking cessation is not immediate and takes years if not decade(s) to return to the natural course of diseases in absence of use of combustible tobacco products (Dresler 2006). As a consequence, the occurrence of these smoking-attributable diseases and their signs and symptoms is expected as 1) smoking is one among other risk factors having a very long half-life for effects, and 2) the concurrent use of THS with conventional cigarettes and/or with other combustible tobacco products is a not an uncommon pattern of THS use, at least during the first month of use, as observed in quasi real-life (see Section 6.2.2.).

Table 33 Other Foreseeable Risks with THS Use and Exposure

Risks Associated with:	Potential Adverse Events
Over-exposure to nicotine / nicotine intoxication / poisoning	Mild intoxication: Nausea, hyper-salivation, abdominal pain, vomiting, diarrhea, cold sweat, headache, dizziness, hearing and visual disturbances, mental confusion, tremor, weakness, weak analgesia, increase of respiratory reflex and coughing, increase bronchial secretions, increase in heart rate and blood pressure Severe intoxication: [unexpected under normal conditions of use] faintness, prostration, dyspnea, seizure, hypotension, weak, irregular, rapid pulse rate / transient cardiac standstill or paroxysmal atrial fibrillation. Death with terminal convulsions and respiratory failure due to paralysis of respiratory muscles
Under-exposure to nicotine / tobacco and nicotine withdrawal symptoms	Affective symptoms: *Irritability/anger/frustration*, *anxiety*/anxious/nervous, *depressed mood* /depression/ sad/ anhedonia, *insomnia*/sleep problems, dysphoria, hyperalgesia, impatient, *restlessness*, nightmares/ dreaming Somatic symptoms: tremors, bradycardia, gastrointestinal discomfort, nausea, constipation, *increased appetite*, hungry, weight gain, coughing, dizziness, sore throat, mouth ulcer Cognitive symptoms: *difficulty concentrating*, impaired memory
Hypersensitivity reactions	Susceptible consumers may experience hypersensitivity reactions such as skin disorders (e.g., localized or generalized rash, pruritus), urticaria and/or angioedema
Suppression of smoke-drug interaction and changes in CYP1A2 activity	Physiological changes resulting from the absence of some cigarette smoke toxicants in the THS aerosol may alter the pharmacokinetics or pharmacodynamics of certain drugs, such as drugs primarily metabolized by CYP1A2 and having a narrow therapeutic index (e.g., theophylline, olanzapine, clozapine, ropinirole) for which dosage adjustment may be necessary
Smoking history and dual use THS with combustible tobacco products	Smoking-attributable morbidity (and corresponding signs and symptoms) and mortality may occur

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6.1.5.10 Human Safety Conclusion

The review of THS human safety data at hand indicates that there are no safety signals suggesting new or increased risks in smokers switching to THS, as compared to smokers continuing smoking CC. From a medical judgement point of view, the so far observed adverse events associated with or related to THS seem to be close to the safety profile of smoking cessation pharmacotherapies such as NRT.

Fewer adverse events were reported upon 3 months of smoking abstinence, as compared to continuing CC smoking or THS exclusive use. Results suggest that concurrent use of THS with other tobacco products may lead to more adverse events than exclusive THS use.

Depending on the history of cigarette smoking (duration and intensity of smoking) and the age of switching from CC to THS, even with full switch, it is expected that smoking-attributable diseases are likely to occur during several months or even years post-switch, due to the heterogeneity of smoking-related diseases reversibility and other individual risk factors.

As for all tobacco and nicotine conaining products, maternal use of THS should be avoided during pregnancy and breastfeeding.

Safety of THS in patients (e.g., suffering from cardiovascular diseases, respiratory diseases, neuro-psychiatric diseases, diabetes mellitus, or under pharmacotherapies) remains to be established.

Drug dosage adjustment may be necessary in patients treated by certain drugs, such as drugs primarily metabolized by CYP1A2 and having a narrow therapeutic index (e.g., theophylline, olanzapine, clozapine, ropinirole).

Susceptible consumers may experience hypersensitivity reactions such as skin disorders, urticaria and/or angioedema.

Overall safety conclusion concurs with the general thoughts that heated tobacco products individual risk is greater than smoking cessation, close but above NRT product risks and not higher (most likely lower) than combustible tobacco products.

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