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## PMI RESEARCH & DEVELOPMENT

# Safety Update Report

## Tobacco Heating System / iQOS

**Report Number:** PMI\_SURV\_2016\_SUR01

**International Birth Date:** 04 Nov 2014

**Interval Covered:** 01 May 2015 to 31 Dec 2015

**Products Covered:** Tobacco Heating System 2.2 and 2.4 / All variants

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## EXECUTIVE SUMMARY

This is the first Safety Update Report (SUR) combining Tobacco Heating System 2.2 and 2.4 (THS) Regular and Tobacco Heating System 2.2 and 2.4 Menthol (THS Menthol) all variants, herein referred to as THS products, summarizing relevant safety data received by Philip Morris International (PMI) within the period from 01 May 2015 to 31 Dec 2015 (THS Regular) and from 01 Jun 2015 to 31 Dec 2015 (THS Menthol). The safety data lock point (DLP) is 31 Dec 2015.

This SUR provides a comprehensive and critical analysis of the safety profile of THS products, which is compiled according to the [International Conference of Harmonisation \(ICH\) guideline E2C \(R2\)](#).

THS products were test marketed in Nagoya (Japan) as of 04 Nov 2014 and in Milan (Italy) as of 20 Nov 2014. National expansion in these two countries occurred in 2015 and THS products were also launched in 6 countries during the period covered by this SUR (Monaco, Portugal, Romania, Russia, Slovenia and Switzerland).

During the review period of this report, there were four ongoing clinical studies with THS products.

Cumulatively, based on the safety population concerning the ten clinical studies sponsored by PMI, approximately 1'924 subjects (safety population) have been exposed to THS products.

The estimated cumulative exposure to THS products in the market research studies (pre-marketing safety surveillance) from May 2014 until 31 December 2015 (DLP for the SUR) is 6'090 consumers. During the period of this report, the consumer exposure to THS products in the market research studies is 2'846 consumers and in the post-marketing safety surveillance 415'000 consumers.

During the review period, the Reference Safety Information (RSI) for THS 2.2 Regular was not updated. The current RSI ([Investigator's Brochure \[IB\] Edition 5.0, dated 27 Apr 2015](#)) adequately reflects the product's safety profile. Similarly, no changes to the RSI for THS 2.2 Menthol were made during the review period. The RSI for THS 2.2 Menthol at the beginning of the SUR review period was the [IB Edition 3.0, dated 27 April 2015](#).

Two safety concerns were discussed in this SUR: occupational exposure and hypersensitivity. The passive product safety surveillance at PMI ensures an appropriate safety concern assessment of the product and therefore effectiveness of routine safety concern minimisation measures is considered appropriate. Recommendations to minimize risks associated with occupational exposure will be integrated in the next update of THS IB. The IB will also be updated with respect to the potential risk for hypersensitivity reactions to THS ingredients in susceptible consumers.

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The data described in this report did not require any other actions for safety reasons which have been warranted based on the data collected. Case reports of hypersensitivity and occupational exposure will be monitored as part of routine safety surveillance and will be discussed in subsequent SURs if warranted.

The evaluation of information presented in this SUR, including data from clinical studies, published literature, pre-marketing studies with passive safety surveillance and spontaneous reports justify the conclusion that exposure to THS products did not raise any new safety concerns in the target population of THS products, i.e., in adult smokers.

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## LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event: 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 ( <a href="#">FDA 2012: MRTPA Draft Guidance</a> ).
AER	Adverse Event Report
CC	Conventional Cigarettes
CSR	Clinical Study Report
FDA	Food and Drug Administration
HCP	Health Care Professional
IB	Investigator Brochure
ICSR	Individual Case Safety Report
iQOS system	iQOS is the brand name of THS
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NRT	Nicotine Replacement Therapy
PBA	Perception and Behavior Assessment
PMI	Philip Morris International
PT	Preferred Term (MedDRA)
Randomized subject	Randomized subject refers to a subject who signed the Informed Consent Form, met all inclusion/exclusion criteria, and was randomized to one of the arm of a clinical study
RSI	Reference Safety Information
SA	Smoking Abstinence
SAE	Serious Adverse Event: A serious adverse event is an adverse event that results in any of the following: death; a life-threatening condition or event; persistent or substantial disability or incapacitation; hospitalization or prolonged hospitalization; or a congenital anomaly or birth defect ( <a href="#">FDA 2012: MRTPA Draft Guidance</a> ).
Safety Population	Subjects exposed to at least one single THS tobacco stick use
SOC	System Organ Class (MedDRA)
SSR	Safety Summary Report
THS	Tobacco Heating System
UK	United Kingdom
US	United States of America

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## 1 INTRODUCTION

This is the first Safety Update Report (SUR) combining Tobacco Heating System 2.2 and 2.4 (THS) Regular (THS Regular) and Menthol (THS Menthol) all variants, herein referred to as THS products, summarizing relevant safety data received by Philip Morris International (PMI, herein referred to as the Company) within the period from 01 May 2015 to 31 Dec 2015 (THS Regular) and from 01 Jun 2015 to 31 Dec 2015 (THS Menthol).

The reporting interval for this SUR is from 01 May 2015 to 31 Dec 2015, based on the earliest Data Lock Point (DLP) of previous safety update reports prepared for THS 2.2 products (see Section 13 Other Periodic Reports). The DLP is 31 Dec 2015.

The current SUR provides a comprehensive and critical analysis of the safety profile of THS products and takes into account new or emerging information, in the context of cumulative data, on risks and hazards. This SUR follows the spirit of the European Medicines Agency (EMA) and Heads of Medicines Agency ([Guideline on Good Pharmacovigilance Practices GVP Module VII](#)) and ICH format.

The first study approval was granted in the United Kingdom (UK) on 17 May 2013, by the local Ethic Committee (EC) for the first clinical study ZRHR-PK-01-EU testing the THS 2.2.

The first study approval was granted in the United States of America (USA) on 07 June 2013 by the local EC for the first clinical study ZRHM-PK-06-US testing the THS 2.2 Menthol.

The Development International Birth Date (DIBD) for THS products is 30 Apr 2013, based on the date of the first ethics committee approval for the first clinical study (17 May 2013).

The International Birth Date (IBD) for THS products is 04 Nov 2014, which corresponds to the date of the first market launch.

The THS 2.2 products were first market launched in Japan on 04 Nov 2014 (IBD) and in Europe on 20 Nov 2014.

As of the DLP of this SUR (31 Dec 2015), several THS product variants are marketed in Japan, Italy, Monaco, Portugal, Romania, Russia, Slovenia and Switzerland.

In line with the ICH guideline E2C (R2), which recommends that information on an active substance is to be included in a single safety report, the first single SUR combining THS 2.2 and 2.4 all variants is prepared, using harmonised DLPs based on the common IBD. Previous Safety Update Reports have been prepared separately for THS products (see Section 13 Other Periodic Reports). The DLP of 31 Dec 2015 has been set for practical reasons.

The THS is a new type of product which heats tobacco electronically. THS is a system composed by two main components:

- (1) A **Tobacco Stick** which is a novel, patent pending tobacco product with unique processed tobacco made from tobacco powder, and which is designed to function with the Holder, producing a THS aerosol.

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- (2) The **Tobacco Heating Device (THD)** which is composed by a Holder and a Charger. The Holder into which the Tobacco Stick is inserted, heats the tobacco material by means of an electronically controlled heater, and the Charger is used to recharge the Holder after each use. It stores sufficient energy for the use of approximately 20 Tobacco Sticks, and can be recharged from household power.

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## 2 WORLDWIDE MARKETING STATUS

THS products were first approved for the execution of clinical studies in the United Kingdom (UK) on 17 May 2013, and in the United States of America (US) on 07 June 2013. The Development International Birth Date (DIBD) for THS products is 30 Apr 2013, based on the date of the first ethics committee approval for the first clinical study (17 May 2013).

THS products were launched in Japan on 04 Nov 2014 (IBD) and in Italy on 20 Nov 2014.

The current worldwide marketing status for THS products is provided in [Appendix 8](#).

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### **3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS**

No specific actions have been taken by the competent authorities, by the Company, by data monitoring committees or ethics committees that had an impact on the conduct of a specific clinical studies/on the overall clinical development programmes or on marketing activities for THS products during the period covered by this report.

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## 4 CHANGES TO REFERENCE SAFETY INFORMATION

The Reference Safety Information (RSI) for this SUR that was in effect at the end of the reporting interval (31 Dec 2015) is the Investigator Brochure (IB) edition 5.0 (dated 27 Apr 2015) for THS 2.2 Regular and the Investigator Brochure edition 3.0 (dated 27 Apr 2015) for THS 2.2 Menthol, respectively.

No changes were effected to the RSI for THS products during the reporting interval.

A copy of the RSI for each of the THS 2.2 products (Regular and Menthol) in effect at the start and at the end of the reporting interval as well as the package leaflet by country are presented in [Appendix 2](#)).

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## 5 ESTIMATED EXPOSURE AND USE PATTERNS

### 5.1 Cumulative subject exposure in Clinical Studies

#### 5.1.1 Methodology: Cumulative Subject Exposure in Clinical Studies

The estimated cumulative subject exposure in clinical studies from the DIBD up to DLP is based on (1) the safety population and on (2) the actual exposure of the subjects to the THS products, comparators or smoking abstinence in Company-sponsored completed studies (for which the final Clinical Safety Reports were available at the time of preparation of this SUR) and from ongoing studies (enrollment / randomization schemes).

#### Safety Population

The safety population consists of all subjects who had at least 1 exposure to THS products prior to the enrollment (tested at least one THS tobacco stick), regardless of whether or not they were enrolled in the clinical study. Since the DIBD (30 Apr 2013) until the DLP (31 Dec 2015), an estimated total of **1'920** subjects have been exposed to THS products in ten clinical studies sponsored by the Company. The inventory of all Company-sponsored clinical studies completed or ongoing at DLP including study description and estimated exposure is presented in [Appendix 3.1](#). The detailed information of the cumulative exposure in clinical studies by study arms is presented in [Appendix 3.2](#).

#### Actual exposure of the subjects to THS products

The actual exposure of the subjects to THS products corresponds to the number of subjects randomized to receive the THS products in the clinical study. Since the DIBD (30 Apr 2013), an estimated total of **1'012** subjects have been exposed to THS via clinical study participation. The cumulative actual exposure is estimated based on the number of subjects randomized to THS products study arms in completed clinical studies and on the planned number of subjects to be randomized to THS products for the ongoing clinical studies.

Duration of THS use in completed clinical studies varies from single use to 5 days while the exposure in ongoing studies is up to 6 months, while extended use is planned up to 12 months.

#### 5.1.2 Cumulative Subject Exposure in Clinical Studies

[Table 1](#) summarizes the estimated cumulative exposure to THS products, comparators and smoking abstinence in Company-sponsored clinical studies from DIBD to DLP. Both safety population and the estimated actual exposure of the subjects to THS products are used to estimate the cumulative exposure of the subjects to THS products in Company-sponsored clinical studies.

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**Table 1 Cumulative Subject Exposure to THS in Clinical Studies**

<b>Product</b>	<b>Safety Population exposed to THS</b>	<b>Actual exposure to THS from estimated randomized subjects</b>
THS	1'924	1'012
Comparators <sup>1</sup>	798	798
Smoking Abstinence	158	158

<sup>1</sup> Conventional Cigarette (CC), Nicotine Replacement Therapy (NRT gum, nasal spray)

### 5.1.3 Cumulative Subject Exposure in Clinical Studies by Demographics

The detailed listing of clinical studies by demographics is presented in [Appendix 3.3](#).

Cumulative exposure to THS products by demographics is estimated based on the safety population for all clinical studies except for study ZRHM-REXA-07-JP for which demographics figures were available for post randomization data at the time of this SUR report. This is the rationale for the difference between the number of subjects in [Table 2](#) and the cumulative number of subjects exposed (safety population) presented in [Table 1](#). This is due to the figures presented in [Table 1](#) being based on the safety population and exposure figures in [Table 2](#) being based on the the safety population or post randomization data (as presented in [Appendix 3.3](#)).

The typical demographic characteristics of the population of the clinical studies are: healthy male (56%) and female (44%) adult smokers, Caucasian, Black or African American, Japanese and Hispanic, aged 21 to 65 years old.

**Table 2 Cumulative Subject Exposure to THS in Clinical Studies by Gender**

<b>Gender</b>	<b>Number of subjects</b>	
Male	1'053	(56%)
Female	800	(44%)
<b>Total</b>	<b>1'853</b>	<b>(100%)</b>

### 5.1.4 Cumulative Subject Exposure in other populations from Clinical Studies

No studies have been performed so far by PMI in other populations such as pediatric, pregnancy/breastfeeding women or smokers with smoking-related diseases in the reporting interval and from DIBD.

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## 5.2 Cumulative and interval consumer exposure from Pre-Marketing experience

### 5.2.1 Methodology: Consumer Exposure from Pre-Marketing Experience

The estimated pre-marketing exposure to THS products is based on the exposed safety population (subjects who have been exposed to a single THS tobacco stick use).

### 5.2.2 Cumulative Consumer Exposure from Pre-Marketing Experience

Cumulatively, passive safety surveillance was implemented in six market research studies (blend tests [BT] and whole offer tests [WOT] and in one perception and behaviour assessment (PBA) study (pre-marketing safety surveillance) since the IBD until the DLP. The Details on the cumulative consumer exposure to THS products in these market research studies was about **6'090** consumers (market research respondents) (see details in [Table 3](#)).

**Table 3 Cumulative Exposure to THS in Pre-Market Safety Surveillance**

Product	BT1 Italy	WOT2 Italy	WOT1 Germany	WOT1 Switzerland	WOT1 Korea	BT1 Russia	PBA-07 <sup>1</sup> United States	Total
THS Regular	836	292	593	344	-	611	-	<b>2'676</b>
THS Menthol	211	310	-	236	-	-	-	<b>757</b>
THS Regular + Menthol	-	41 <sup>2</sup>	-	-	1'316	-	1'300 (estimated)	<b>2'657</b>
<b>Total</b>	<b>1'047</b>	<b>643<sup>2</sup></b>	<b>593</b>	<b>580</b>	<b>1'316</b>	<b>611</b>	<b>1'300 (estimated)</b>	<b>6'090</b>

WOT: Whole Offer Test; BT: Blend Test; PBA: Perception and Behaviour Assessment

<sup>1</sup> Exposure is based on estimated safety surveillance population exposed to THS products at the DLP

<sup>2</sup> Product allocation is not indicated in 41 consumers

The detailed cumulative exposure data in pre-marketing studies is presented in [Appendix 4](#).

### 5.2.3 Interval Consumer Exposure from Pre-Marketing Experience

During the period of this report (covering from 01 May 2015 to 31 Dec 2015), passive safety surveillance was implemented in three market research studies. The consumer exposure to

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THS products in these market research studies was about **2'846** consumers (market research respondents) (see details in [Table 4](#)).

**Table 4 Interval Exposure to THS in Pre-Market Safety Surveillance**

<b>Product</b>	<b>WOT1 Korea</b>	<b>BT01 Russia</b>	<b>PBA-07 United States</b>	<b>Total</b>
THS Regular	-	611	-	611
THS Menthol	935	-	-	935
THS Regular + Menthol	-	-	1'300 (estimated)	1'300 (estimated)
<b>Total</b>	<b>935</b>	<b>611</b>	<b>1'300 (estimated)</b>	<b>2'846</b>

### 5.3 Cumulative and interval consumer exposure from Post-Marketing experience

#### 5.3.1 Methodology: Consumer Exposure from Post-Marketing Experience

The estimated marketing exposure to THS products is based on the number of THS devices ( i.e., THS kit containing one THS device, accessories and tobacco sticks pack) sold during a reporting interval in the test market worldwide, based on the principle that one THS kit corresponds to one consumer.

#### 5.3.2 Cumulative Consumer Exposure from Post-Marketing Experience

Since November 2014 (date of 1<sup>st</sup> launch) to DLP, an estimated total of 455'000 consumers have been exposed to THS products from marketing experience, based on number of THS devices sold from November 2014 to 31 Dec 2015 in the test market worldwide.

#### 5.3.3 Interval Consumer Exposure from Post-Marketing Experience

In the reporting interval 01 May 2015 to 31 Dec 2015, an estimated total of 415'000 consumers have been exposed to THS products from marketing experience.

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### 5.3.4 Pattern of Use of THS products

#### **Clinical Studies**

The population enrolled in the Company-sponsored clinical studies are adult smokers in good health conditions.

#### **Pre-marketing studies (passive safety surveillance studies)**

In market research and Perception and Behaviour Assessment studies, the enrolled subjects are adult smokers irrespective on underlying medical condition(s) except for pregnant and breast feeding subjects.

The Company investigated the combined use conventional cigarettes (CC) and THS products by conducting a market research study conducted for THS products in a number of countries. The results show that between 39.90% and 60.68% of study participants used both CC and THS products by the end of the 4-week observational period.

From Sep 2015 to Feb 2016, the Company has conducted a passive surveillance study THS-PBA-07-US (Perception and Behaviour Assessment) Actual Use Study in United States (US) which focused on how US adults which were daily smokers of conventional / combustible cigarettes (CC) use the iQOS system under near to real world conditions. In particular, the study assessed the quantities of CC and of tobacco sticks consumed by individual participants over time. The results of this study were not available yet at the time of the current SUR preparation and therefore will be presented in the next SUR.

#### **Post-Marketing experience**

iQOS is the brand name under which the Company has chosen to commercialize the THS products. The target population for THS products is adult smokers.

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## 6 DATA IN SUMMARY TABULATIONS

The safety data presented in this section is divided into two summary tabulations. The first tabulation includes cumulative serious adverse events from Company-sponsored clinical studies. The second tabulation presents both cumulative and interval data that includes serious and non-serious adverse reactions from pre and post-marketing sources.

The company safety databases includes all AEs reported from pre-and post-marketing safety surveillance as well as SAEs reported from clinical studies. The summary tabulations which were used as sources of information in this safety update report were generated from the Company Safety databases. For the generation of summary tabulations which were used as sources of information, Argus Pharmacovigilance databases were searched for individual case safety reports (ICSRs; also called “cases”) reported from clinical studies, pre-market studies and post-market safety surveillance to the Company or any affiliate. The line listings which served to the generation of summary tabulations are available on request.

### 6.1 Reference Information

The current version of Medical Dictionary for Regulatory Activities (MedDRA) has been used for the coding of AEs; as of May 2015, the version in use was 18.0 and as of November 2015 the version in use was 18.1. The line listings and the summary tabulations are sorted alphabetically by primary System Organ Class (SOC) and Preferred Term (PT) level. The Summary Tabulations presented in the [Appendices 3 and 4](#) of the SUR were generated from the safety database and was prepared using MedDRA version 18.1.

“Expectedness” for THS is based on the IB that was available at the assessment date of the case (see [Section 4](#) and [Appendix 2](#)).

### 6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

The cumulative summary tabulations of serious adverse events (SAEs) received from Company-sponsored clinical studies, from the DIBD (30 Apr 2013) until the DLP (31 Dec 2015, inclusive) is provided in [Appendix 5](#).

The summary tabulations are presented by MedDRA System Organ Class (SOC), for THS products, comparator arm (Conventional Cigarettes [CC]) and smoking abstinence.

#### 6.2.1 Methodology: Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

The Serious Adverse Events (SAEs) recorded in the Company safety database are presented as a summary tabulation of all Company-sponsored clinical studies which were ongoing or complete in the period since the DIBD to the SUR DLP.

The summary tabulation have the following columns per SOC:

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- Preferred Term (PT)
- Unique event count
- THS product
- Comparator product (CC)

An AE qualifies for inclusion in the summary tabulation if the following conditions are met:

- Adverse Event Report (AER) originates from a Company-sponsored clinical study
- Event is serious
- Event has THS products / comparators as suspect product

### 6.2.2 Summary of Cumulative Serious Adverse Events from Clinical Studies

The summary tabulations of serious adverse events received since the DIBD from Company-sponsored clinical studies ([Appendix 5](#)) identified a total of 7 Individual Case Safety Reports (ICSRs) including 14 SAEs from which 6 SAEs concerned the THS products and 6 SAEs concerned the comparators (CC). Two SAEs were reported in the context of case PMI000304 in which the subject was enrolled but not randomized.

The seven serious ICSR are presented in [Table 5](#) below.

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**Table 5 Cumulative Serious Adverse Events received from Clinical Studies up to DLP**

Study ID	Case ID	Subject ID	Study Arm	SAE Criteria	SAE Description [PT]	Related to THS
<b>SAE reported before SUR interval</b>						
ZRHR-REXA-08-US	PMI000304	1119	Enrolled but not randomised	H	Diabetic ketoacidosis, Sinusitis	Not Related
<b>SAE reported during SUR interval</b>						
ZRHR-ERS-09-US	PMI000350	04260	THS	LT, H	Metastases to small intestine, Anaemia	Not Related
ZRHR-ERS-09-US	PMI000360	01094	CC	H	Urosepsis, Pyelonephritis acute, Nephrolithiasis	Not Related (subject randomized to CC arm)
ZRHR-ERS-09-US	PMI000369	12097	CC	H, IME	Papillary thyroid cancer	Not Related (subject randomized to CC arm)
ZRHR-ERS-09-US	PMI000385	14046	CC	H	Vertebral osteophyte, Cervical myelopathy	Not Related
ZRHR-ERS-09-US	PMI000452	04384	THS	F	Death due to acute and chronic alcohol abuse	Not Related
ZRHR-ERS-09-US	PMI000463	09236	THS	H	Loss of consciousness, Head injury, Seizure	Not Related

F = Fatal; LT = Life-Threatening; H = Hospitalisation; IME = Important Medical Event

A cumulative summary tabulation of the total number of SAEs from clinical studies is presented in [Table 6](#).

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**Table 6 Cumulative Summary Table of Serious Adverse Events from Clinical Studies**

<b>Number of unique events</b>	<b>THS products</b>	<b>Comparator CC</b>	<b>Smoking abstinence</b>	<b>Enrolled but not randomised</b>
14	6 ( 43%)	6 (43%)	0	2 (14%)

CC = Conventional Cigarettes

The incidence and frequency of SAEs were comparable in THS (6 SAEs in 3/7 subjects) [43%] and in CC arm (6 SAEs in 3/7 subjects) [43%].

All the SAEs reported from subjects enrolled in the THS arm were not related to the use of THS products. One subject died for reasons not related to the THS product use. The cause of death was reported as Death due to acute and chronic alcohol abuse.

### **6.3 Cumulative and Interval Summary Tabulations from Post-Marketing Sources**

#### **6.3.1 Methodology: Cumulative and Interval Summary Tabulations from Post-Marketing Sources**

These adverse events are derived from spontaneous ICSRs, including worldwide reports from healthcare professionals, consumers, scientific literature, and from pre-marketing passive safety surveillance. Serious and non-serious adverse events from spontaneous sources, as well as serious adverse events from non-interventional solicited sources (pre-marketing passive safety surveillance) are presented in a single table, with interval and cumulative data presented side-by-side. The table is organized by MedDRA SOC in the internationally agreed order.

The seriousness of the adverse reactions corresponds to the seriousness assigned to events included in the ICSRs using the criteria established in ICH-E2A (Clinical safety data management: Definitions and standards for expedited reporting). When serious and non-serious reactions are included in the same ICSR, the individual seriousness per reaction is reflected in the summary tabulations.

Adverse events in cases which are foreseen for deactivation and databased cases which do not meet the criteria for an ICSR are excluded from the summary tabulations.

#### **6.3.2 Summary of Serious and Non-Serious Adverse Events from Post-Marketing Sources**

Cumulative (since IBD 04 Nov 2014 to the DLP 31 Dec 2015), a total of 91 case reports were spontaneously reported by consumers.

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Cumulative (since IBD 04 Nov 2014 to the DLP 31 Dec 2015) and interval (from 01 May 2015 to 31 Dec 2015) summary tabulations of AEs from post-marketing sources are provided in [Appendix 6](#).

The assessment of the reported events showed that the largest group was Gastrointestinal disorders SOC group with a total number of 47 AEs cumulatively (all spontaneous) with 32 AEs reported in the reporting interval. There were no SAEs reported in this group. The most frequently reported event was nausea (15 AEs cumulatively and 12 AEs during the reporting interval) which was assessed as expected event according to the RSI. The events of General SOC group (36 events reported cumulatively and 29 AEs in the interval) included 2 SAEs from pre-marketing studies cumulatively (2 SAEs in the reporting interval). Of these 2 SAEs, one SAE was reported as 'adverse event' assessed as serious (due to hospitalization), with very limited information regarding to the patient's unspecified health problem. One SAE was injury associated with device (see [Section 8](#) for more details on these is case report). The most frequently reported non-serious events were malaise (12 AEs cumulatively and 12 AEs during the reporting interval, all non-serious). Malaise is assessed as unexpected event as per the RSI.

Within the Respiratory SOC, cumulatively there were 43 AEs reported, with 29 AEs reported during the SUR interval. Of these 43 AEs, only one (tonsillar cyst) was assessed as SAE (from pre-market study) and unlisted as per the RSI. The most frequently reported non-serious events were cough and productive cough (15 AEs cumulatively and 8 AEs during the reporting interval), oropharyngeal pain (clinically equivalent to Throat irritation) and throat irritation (14 AEs cumulatively and 10 AEs in the interval). Cough, oropharyngeal pain and throat irritation were expected events according to the RSI.

The events of Nervous system disorder group (28 AEs cumulatively and 24 AEs in the interval) included 2 spontaneously reported SAEs in the interval. Of the 2 spontaneous SAEs reports, one was loss of consciousness and the second one was syncope. The information provided in both of SAEs was very limited, particularly regarding the relevant medical history, concomitant medications, treatment administered or temporal sequence (for syncope). Loss of consciousness and syncope were assessed as unexpected as per the RSI. The most frequently reported non-serious event was headache (15 AEs cumulatively and 14 AEs during the reporting interval). Headache is expected event as per the RSI.

A summary tabulation of the total number of SAEs and non-serious AEs from post-marketing sources is presented in [Table 7](#) below.

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**Table 7 Cumulative Serious and Non-Serious Adverse Events from Post-Marketing Sources**

Spontaneous source					Pre-market studies		
Serious		Non-serious		Total	Serious		
Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative	
Total	2	2	125	172	174	23	23

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## 7 SUMMARIES OF SIGNIFICANT SAFETY FINDINGS FROM CLINICAL STUDIES DURING THE REPORTING PERIOD

The cumulative list of all Company-sponsored clinical studies completed or ongoing at DLP is presented in [Appendix 3.1](#).

[Table 8](#) presents the list of the Company-sponsored clinical studies conducted with THS products that were ongoing (n = 4) or completed (n = 3) in the reporting interval of this SUR (01 May 2015 to 31 Dec 2015).

**Table 8 Ongoing and Completed Clinical Studies in the reporting interval**

<b>Ongoing Clinical Studies (n = 4)</b>	<b>Completed Clinical Studies (n = 3)</b>
ZRHM-REXA-07-JP <sup>1</sup>	ZRHR-REXC-04-JP
ZRHM-REXA-08-US <sup>1</sup>	ZRHM-PK-05-JP
ZRHR-ERS-09-US	ZRHM-PK-06-US
ZRHR-ERS-09-US-EXT	

<sup>1</sup>The Clinical Study Report was not available at the time of this SUR report

The clinical findings for the ongoing and completed Company-sponsored clinical studies are presented in [Section 7.1](#) and [Section 7.2](#), respectively.

### 7.1 Ongoing clinical studies

#### 7.1.1 Pregnancy and Lactation

Cumulatively, there were four medically confirmed exposure during pregnancy cases reported by the DLP, all for the reporting interval of this SUR. All reports originated from clinical study ZRHR-ERS-09-US (three subjects enrolled in the THS arm and one subject in CC arm). The subjects using THS discontinued the product and all the subjects were withdrawn from the study.

The reported event in all pregnancy cases was exposure during pregnancy. No adverse events were reported in association with exposure during pregnancy in these pregnancy reports.

There was no lactation cases reported cumulatively for THS products.

As part of due diligence safety activities, all the pregnancy reports are followed-up until an outcome is reached. This information was not available at the time of preparation of this SUR.

The information received on the use of THS products in pregnancy/lactation during the review period of this SUR does not alter the safety profile of THS products.

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### 7.1.2 Occupational exposure

In the context of the clinical study ZRHR-ERS-09-US, four cases of adverse events were spontaneously reported by four Clinical Research Associates (CRAs) who experienced various AEs while executing investigational product (IP) accountability of the THS 2.2 Regular at the investigation site. See Section 9.1 and Section 15.3.1 for detailed information on these case reports.

## 7.2 Completed clinical studies

During the reporting period covered by this SUR the following three clinical studies have been completed (i.e. clinical study report was finalized):

- **ZRHR-REXC-04-JP:** A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching from conventional cigarettes to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to smokers continuing to use conventional cigarettes (CC) for 5 days in confinement.

**Safety results:** There were no SAEs reported in this study and no randomized subjects discontinued from the study due to an AE. Overall, there were 11 AEs reported by 10 of the 166 subjects (6.0%) in the safety population, all of which were mild in intensity. The incidence and frequency of AEs were comparable in the THS 2.2 (6 AEs in 6/80 subjects [7.5%]), the CC (4 AEs in 3/40 subjects [7.5%]), and the SA arms (1 AE in 1/40 subjects [2.5%]). The most frequent AEs after THS 2.2 or CC exposure were blood triglycerides increased, neutrophil count decreased, blood potassium decreased, protein urine present, and white blood cell count decreased. The only AE reported after SA was hemoglobin decreased. The incidence of blood triglycerides increased and neutrophil count decreased were comparable between the THS 2.2 and CC arms (maximum of 2 AEs reported in each arm). Blood potassium decreased and protein urine present were only reported by subjects in the THS 2.2 arm (1 of each AE reported) and white blood cell count decreased was only reported by 1 subject in the CC arm. None of AEs reported were assessed as being related to THS 2.2 or CC use. During THS 2.2 use, 4 subjects experienced a total of 5 major device events or malfunctions, which led to the replacement of the THS Tobacco Stick Holder or Charger. None of these events led to an AE.

- **ZRHM-PK-05-JP:** A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine gum.

**Safety results:** There were no SAEs or severe AEs reported in this study and no subjects discontinued from the study due to an AE. Overall, there were only 4 AEs (lymphocyte count increased, bilirubin conjugated increased, blood bilirubin

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increased, and hemoglobin decreased) reported by 4 of the 73 subjects (5.5%) in the safety population (which included 11 subjects who were enrolled but not randomized). All 4 AEs were mild in severity. None of the subjects who were exposed but not randomized reported an AE. No AEs were assessed as being related to investigational product (THS 2.2 Menthol or mCC), NRT gum, or study procedures. None of the subjects experienced a device event or malfunction.

- **ZRHM-PK-06-US:** A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine nasal spray.

**Safety results:** There were no SAEs reported during the study and no subjects discontinued from the study due to an AE. Overall, there were 28 AEs reported in 19 of the 64 subjects (30%) in the safety population, the majority of which were mild or moderate in severity. Two severe AEs were reported by 1 subject. The incidence of AEs was comparable in the THS 2.2 Menthol – mCC sequence (10 AEs in 7 out of 22 subjects [31.8%]), the mCC – THS 2.2 Menthol sequence (9 AEs in 7 out of 22 subjects [31.8%]), and the THS 2.2 Menthol – NNS sequence (7 AEs reported in 3 out of 9 subjects [33.3%]). Only 2 subjects reported 2 AEs from the 9 subjects in the NNS – THS 2.2 Menthol sequence (22.2%). The most frequent AEs were headache (7 AEs), vomiting (3 AEs), nasal congestion (3 AEs), and spirometry abnormal (2 AEs). All other AEs were reported by 2 or fewer subjects only and a maximum of 1 subject per sequence. During the study, 4 subjects experienced 5 AEs that were considered to be related to the investigational product (IP). Vomiting and nausea were each reported by 2 subjects, and headache was reported by 1 subject. An AE of sneezing was also considered to be related to NNS use. During THS 2.2 Menthol use, 3 subjects experienced 6 device events or malfunctions which led to the replacement of both the Tobacco Stick Holder and the Charger. None of these events led to an AE.

Overall, 33 subjects (10%) out of 303 subjects in the safety population reported 43 AEs (all non-serious), the majority of which were mild or moderate in severity. There were no SAEs reported during the studies and no subjects discontinued from the study due to an AE. There were no significant findings from the completed clinical studies during the review period of this SUR.

### 7.3 Long-term Follow-up

None of the study protocols concerning THS products presented in this SUR have protocol-mandated periods of long-term safety follow-up. The safety follow-up period in repeated use studies was 28 days after the last product use.

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## **7.4 Conclusion**

No relevant safety-related information was identified from ongoing or completed clinical studies during the period of this SUR.

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## 8 FINDINGS FROM PRE-MARKET SAFETY SURVEILLANCE

The detailed description of Company-sponsored ongoing and completed of Company-sponsored market research and PBA studies with pre-marketing passive safety surveillance conducted with THS products during the reporting interval is presented in [Appendix 7](#).

The ongoing (n = 1) and completed studies (n = 2) in the reporting interval of this SUR (01 May 2015 to 31 Dec 2015) are summarised in [Table 9](#).

**Table 9 Ongoing and Completed Pre-Market Studies in the reporting interval**

Ongoing Studies (n = 1)	Completed Studies (n = 2)
THS-PBA-07-US	P1_BT1_RU P1_WOT1_KO

The safety findings for the ongoing and completed Company-sponsored pre-marketing studies are presented in [Section 8.1](#) and [Section 8.2](#), respectively.

### 8.1 Ongoing pre-marketing studies

During the review period of this SUR, one market research study for passive safety surveillance was considered as not completed (safety summary reports was not finalized).

**THS-PBA-07-US** conducted in United States, started in September 2015 and was completed in February 2016 (closure of the hotline), while the last THS use was in December 2015. The safety surveillance population was estimated at 1'300 consumers (respondents), all have being enrolled up to DLP (31 Dec 2015). The program was conducted to study consumer perception and behavior in relation to THS 2.2, known as the *Perception and Behavior Assessment* (PBA) program. Two product variants were used:

- THS 2.2 regular (Dorado II / Ron) (i.e. Tobacco Stick regular)
- THS 2.2 menthol (Dorado I / Vinny Low menthol) (i.e. Tobacco Stick menthol)

### 8.2 Completed pre-marketing studies

During the review period of this SUR, two passive safety surveillance for market research studies were completed and safety summary reports finalized.

- **Study P1\_BT1\_RU** conducted in Russia, started on 25 August 2015 and was completed—on 10 September 2015. This was a blend test to identify the Tobacco Heating System (THS) 2.4 products with the most broadly accepted sensorial profile among two product variants, in a blinded manner:
  - THS 2.4 Regular (Scion 1 Walt)
  - THS 2.4 Regular (Scion 1 Fitz)

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**Safety results:** Overall, a total of nine non-serious AEs were spontaneously reported by seven of the 611 study participants all of which were considered non-serious (6 reported from respondents using the THS 2.4 Regular Scion 1 Fitz and 3 from respondents using the THS 2.4 Regular (Scion 1 Walt). Headache (n=2), Dizziness (n=2) and Nausea (n=2) were the most frequently reported AEs overall across both tested product variants, with the exception of Dizziness which was reported in THS 2.4 regular (Scion 1 Fitz) users only. The reported events were considered related by the company and relatedness to the tested products was not commented on by the reporter in all cases<sup>1</sup>. According to the RSI, the following events were expected: Headache, Nausea, Cough, Dizziness, and Oropharyngeal pain (clinically equivalent to Throat irritation). Dysgeusia was not mentioned in the RSI as an expected AE for THS 2.4. However, in this study, respondents were given a new product to use, which they were likely not familiar with, as they were used to conventional cigarettes (CC). As they were comparing the taste of the new product with the one of the CC they were used to, and upon finding a difference, they were more prone to report such an AE. The occurrence of Dysgeusia does not affect the safety profile of THS 2.4.

- **Study P1\_WOT1\_KO conducted in Korea started on 10 April 2015 and was completed on 5 June 2015** (closure of the hotline). The P1 Whole Offer Test South Korea (P1\_WOT1\_KO) was a large scale quantitative survey with a four week home usage of three product variants with the same tipping paper and all to be used with the Tobacco Heating System 2.2, to assess adult smoker interest in Platform 1 (P1), based on all elements of the product offer: design, communication, and the overall sensorial experience / acceptance (product taste and the perceived gap compared to manufactured cigarettes). Three product variants were used:
  - THS 2.2 regular (Dorado II / Fitz)
  - THS 2.2 regular (Ginebra / Fitz)
  - THS 2.2 menthol (Dorado I / Vinny low menthol)

**Safety results:** Overall, a total of 141 non-serious AEs and 5 SAEs were spontaneously reported in 83 cases among the 1'316 study participants. The overall reporting rate was 6.3%. The vast majority of AEs (81.5%; 119/146) was reported under the three following System Organ Classes (SOC): Respiratory, thoracic and mediastinal disorders (n=59) with the leading event of Oropharyngeal pain (n=18), General disorders and administration site conditions (n=35) with the leading event of Feeling hot (n=10), and Gastrointestinal disorders (n=25) with the leading event of Nausea (n=8). According to

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<sup>1</sup> 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.

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the RSI, the following events were expected: Oropharyngeal pain (clinically equivalent to Throat irritation), Cough, Nausea, Headache, and Dizziness. The reporting frequency of these AEs does not affect the safety profile of the three tested THS 2.2 product variants. The two cases considered as serious and the events considered as severe are described as follows:

- Vertigo and nausea were reported in a 55-year-old male respondent (PMI000135) with a medical history of hypertension and concomitant use of antihypertensive and digestant drugs. The respondent regularly smoked on average 23 cigarettes per day. He experienced vertigo and nausea seven days after he started using the THS 2.2 Regular (Ginebra / Fitz) product. The product was used for three days since starting. On the day the events occurred, he had used five sticks and smoked 13 conventional cigarettes. The reported events did not improve after he stopped using the product and the events returned when he restarted using the sticks. At the time of reporting, the events were not resolved.
- A 44-year old male respondent (PMI000109) reported a fall (from the first floor), spinal disorder and spinal pain. A medical history of (slight) mental illness was reported, and a drug for psychiatric disorders (not specified) was reported as concomitant medication. The respondent was a daily smoker (on average 10 cigarettes per day). He was hospitalized five days after he started using the THS 2.2 Regular (Ginebra / Fitz) for hurting vertebra. On the day of the event, the respondent used six tobacco sticks and smoked seven conventional cigarettes. The respondent used the product every day. It was reported that the usage of the product was not interrupted following the event.
- Injury associated with device, thermal burn, and device battery issue were reported in a 40-year old male respondent (PMI000128) with no medical history or concomitant medications. No information on smoking habits was provided. The respondent used both THS 2.2 Regular (Ginebra / Fitz) and THS 2.2 Menthol (Dorado I / Vinny low menthol) products. Nine days after starting to use the THS 2.2 products, the charger caught fire and the respondent was injured. The respondent mentioned that “he was hurt by debris of something”. Regarding the charger, it was reported that the charger caught fire, and possibly exploded. It was also mentioned that “he dropped charger” (the holder on was it) on the floor during they were charging. He also stated that the holder was too hot because “he dropped holder on the floor”. It was not clearly explained if the charger was dropped before or after the injury occurred. The device was collected back from this consumer and a technical investigation was performed by the Company. It appeared that the device pieces were physically damaged due to external causes, including dismantling of the charger and of the battery. The Injury associated with device and Thermal burn were assessed as serious (medically significant). The device battery issue was assessed as non-serious. Injury associated with device and Thermal burn are unlisted for THS 2.2 Regular or THS 2.2 Menthol, according to the RSI. There is limited information in this case. However, considering the temporal relationship, the Company assessed the reported adverse events as related to the use of THS 2.2 Regular and THS 2.2 Menthol.

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**Conclusion**

From the both completed market research studies, overall, 155 AEs (the majority of which were mild or moderate in severity) were reported by 90 consumers out of corresponding 1'927 respondents, with an overall reporting rate of 4.6 case reports per 100 market research respondents.

The majority of the reported AEs during the reporting period of this SUR study were considered expected as per the current RSI. No safety issues/concerns emerged based on the information received during the completed pre-marketing studies.

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## 9 INFORMATION FROM POST-MARKETING SAFETY SURVEILLANCE

During the reporting period, a total of 165 events (163 non-serious AEs and 2 SAEs) were spontaneously reported by 74 consumers, with an estimated reporting rate of 1.6 cases per 10'000 consumers.

### 9.1 Occupational Exposure

Four clinical research associates have experienced headache and respiratory symptoms (see [Table 10](#) below), while executing accountability of unused Tobacco Heating System (THS) tobacco stick and packs for up to several hours in the context of the monitoring of the ZRHR-ERS-09-US clinical study. These reports were spontaneously reported to the Company.

**Table 10 List of Adverse Events concerning Occupational Exposure**

PMI Case	Subject	Day 0	Onset Date	AE PT	Comments
<b>PMI000308</b>	Female, 40y Nonsmoker	20-Jul- 2015	03-Jun- 2015 15-Jul-2015	Head discomfort	Positive dechallenge
				Sneezing	Positive rechallenge
				Throat irritation	Ongoing upper
				Hemoptysis Cough	respiratory infection
<b>PMI000313</b>	Female, 27y Nonsmoker	25-Aug- 2015	20-Aug- 2015	Headache (mild) Product odour abnormal	Positive dechallenge Chronic sinusitis
<b>PMI000315</b>	Female, 40y Nonsmoker	01-Sep- 2015	19-Aug- 2015	Headache	Positive rechallenge
<b>PMI000316</b>	Female, 29y Nonsmoker	02-Sep- 2015	12-Aug- 2015	Headache	

The suspected product was the THS 2.2., tobacco sticks Regular, with the blend and flavor system Dorado II / Ron (referred to as THS).

The 4 cases were entered in the PMI safety database for case processing and coded as occupational exposure cases. The 4 cases were rated as non-serious and possibly related to the THS due to the temporal association of the events and the exposure to the product.

Similar adverse events have been reported by THS consumers and have also been found in the literature and reported by nonusers exposed to e-cigarette vapor. Nicotine, glycerol and odorant chemicals (including some of the ingredients present in the THS Ron flavor system) are reported to possibly trigger headache and other symptoms such as those associated with airways irritation.

In the current situation, other causes may also explain, at least partially, the reported events, such as high sensitivity to odor/smell, the presence of underlying medical conditions

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affecting the upper respiratory tract and the stressful nature of the activity, requiring close and sustained attention.

## **Conclusion**

During the review period of this SUR, no other safety issues/concerns emerged from the adverse event reports received from the post-market safety surveillance.

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## 10 NON-CLINICAL DATA

No safety findings concerning the non-clinical usage of THS products became available during the reporting interval of this SUR from Company-sponsored studies.

The current THS Investigator's Brochure ([IB edition 5.0 dated 27 Apr 2015 for THS 2.2 Regular](#) and [IB edition 3.0 dated 27 Apr 2015 for THS 2.2 Menthol](#)) contain a concise summary of non-clinical data relevant to THS products.

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## 11 OTHER CLINICAL STUDIES AND SOURCES

Not applicable.

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## 12 LITERATURE

The Company continually monitors standard, recognized medical and scientific literature for safety information on THS products. A thorough search of the medical literature was performed for the reporting interval of this SUR from 01 May 2015 to 31 Dec 2015, using the Embase and PubMed databases.

There were no new and significant safety findings either published in the peer-review scientific literature or made available as unpublished manuscripts, when relevant to THS products that the Company became aware during the reporting interval.

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## 13 OTHER PERIODIC REPORTS

No other periodic reports were prepared by the Company for THS products in the reporting interval.

### Periodic Reports prepared prior to current SUR

Prior to the review interval of current SUR, separate Safety Update Reports were prepared for THS 2.2 Regular and THS 2.2 Menthol, respectively. An overview of the previous SURs prepared for THS products is presented in [Table 11](#).

**Table 11 Previous SURs prepared for THS products**

Product	SUR	Review Interval
THS 2.2 Regular	DSUR 1	01 May 2013 – 30 Apr 2014
	SUR 01 <sup>1</sup>	01 May 2014 – 30 Apr 2015
THS 2.2 Menthol	DSUR 1	01 Jun 2013 – 31 May 2014
	SUR 01 <sup>1</sup>	01 Jun 2014 – 31 May 2015

<sup>1</sup> Prepared in the ICH-E2F format.

Based on the available data from the clinical studies, pre-market studies and post-marketing safety surveillance, the previous SURs prepared concluded that the exposure to THS products did not raise any new safety concerns in adult smokers.

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## 14 LATE-BREAKING INFORMATION

Two ICSRs (PMI000492 and PMI000483) which were received after the DLP of this SUR (31 Dec 2015) were considered safety relevant to be included in this section.

Of note, these cases are presented below in more details as there are not part of the line-listings with all cases received for THS products during the reporting period (from 01 May 2015 to 31 Dec 2015).

**Case PMI000492** was initially received on 10 Feb 2016. This case concerns a 9-month-old baby subject who was accidentally exposed to an unspecified iQOS product. The baby's mother reported that the baby ate the tobacco of the tobacco stick. The baby was given a gastro-protective medicine and kept under observation in the emergency room for 5 hours. No other events were reported and the baby was discharged on the same day without problems.

- **Company comment:** *Accidental exposure to product by child* (reportedly, a baby ate the tobacco of the tobacco stick) is assessed as serious (due to the required emergency room care). Listedness and causality assessments are not applicable for Accidental exposure to product by child. However, the listedness has been recorded as unlisted, by default, in the safety database. Of note, although the infant was kept under observation for several hours in the emergency room, where she has also reportedly received a gastro-protective medicine, there was no adverse event reported in association with this accidental iQOS product intake by the infant.

**Case PMI000483** was initially received on 03 Feb 2016. This report concerns a 30-year-old female subject who took part in the PBA Study THS-PBA-07-US: Comprehensive program to study consumer perception and behaviour in relation to THS 2.2. The respondent reported she stopped using the THS products on an unspecified date in Dec 2015 and on 10 Jan 2016 pregnancy has been medically confirmed. No other adverse events were reported in this case.

- **Company comment:** *Maternal exposure timing unspecified* was assessed as non-serious event. Expectedness and causality assessment are not applicable for *Maternal exposure timing unspecified*. However, expectedness for this event has been captured as unlisted, by default, in the safety database.

Since DLP, no new other important information has been received which would have a significant impact on the conclusions of the overall safety evaluation for THS products in the period from the Data Lock Point until the date of preparation of this report.

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## 15 SIGNAL EVALUATION

### 15.1 PMI Signal Management Process

The Company employs comprehensive processes to ensure signal detection, validation, prioritization, and assessment.

The key steps in the Company's signal detection process are presented below:

- **Signal detection** consists in activities that result in the identification of a new signal from all assessment studies sponsored by the Company as well as other sources of information as ICSRs, SURs, literature monitoring, safety web portals, and media.
- **Signal validation** verifies the existence of a new potentially causal association or a new aspect of a known association, and justify further analysis.
- **Signal assessment** involves an investigation of the validated signal, including the preparation of a Signal Evaluation Report.

### 15.2 PMI Routine Product Assessment Activities

The Company proactively identifies and evaluate potential safety issues from reported AEs and other available safety data and assess the potential impact of these data on the risk profile of Company's products.

The following strategies are employed to systematically review safety data:

- Standardized periodic listings
- Literature:systematic, regular searches of internationally recognized biomedical databases are reviewed for publications reporting potential signals.

### 15.3 Summary of safety concerns

At the start date of this SUR (01 May 2015), there were no safety concerns. During the review interval of this SUR, two important potential risks (Occupational exposure and Hypersensitivity reactions) were identified and presented in Sections [15.3.1](#) and [15.3.2](#) respectively.

#### 15.3.1 Occupational exposure

Four clinical research associates have experienced headache and respiratory symptoms (see Section [9.1](#)), while executing accountability of unused THS tobacco sticks and packs for up to several hours in the context of the on-site monitoring of the ZRHR-ERS-09-US clinical study. These reports were spontaneously reported to the Company. As these were the first cases associated with exposure of THS and reported by non-users in an occupational context, a safety investigation was conducted to:

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- Understand the environmental conditions of the events
- Explore other possible explanations, such as underlying (medical) conditions
- Verify the plausibility of these events
- Develop a safety recommendation if deemed necessary

## Recommendations

Based on the current knowledge, the recommendations for personnel handling a significantly high number of open THS packs, such as it is needed for product accountability, include:

- Working in large room with relatively cool temperature, ideally with ventilation
- Limiting the duration of accountability time by organizing the work with breaks at least once an hour
- Wearing standard protective mask and gloves during open packs handling, especially when the activity includes also tobacco sticks handling in addition to visual inspection of open packs
- Recommending pregnant women not to execute such activity, due to the potential exposure to nicotine even from unused tobacco sticks, due to the volatile nature of nicotine.

These recommendations were provided to study staff and will be integrated in the next update of the Investigator's Brochure.

The total number of PTs concerning occupational exposure in the SUR interval and cumulatively are presented in [Table 12](#) below.

**Table 12 Number of PTs concerning Occupational Exposure**

MedDRA PT	Number of PTs	
	Interval	Cumulative
Headache	25	77
Head discomfort	1	2
Occupational exposure	4	4
Product odour abnormal	3	12
Sneezing	1	1
Throat irritation	10	46
Hemoptysis	1	2
Cough	19	75
<b>Total PTs</b>	<b>63</b>	<b>219</b>

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### 15.3.2 Hypersensitivity reactions

Triggered by few spontaneously reported case suggesting hypersensitivity reactions, a cumulative search was performed in Company's database with a cut-off date of 31 Dec 2015. The electronic search for hypersensitivity included all serious and non-serious events and was carried out under the MedDRA version 19.0 SMQs "Hypersensitivity" and "Angioedema" (narrow). The following PTs were identified and are presented in [Table 13](#) below.

**Table 13 Number of PTs concerning Hypersensitivity reactions**

MedDRA PT	Number of PTs	
	Interval	Cumulative
Hypersensitivity	0	1
Pharyngeal oedema	4	4
Pruritus	0	1
Swollen tongue	0	1
Urticaria	0	1
<b>Total</b>	<b>4</b>	<b>8</b>

## 15.4 Signal evaluation

The qualitative signal detection is based on the assessment of the likelihood of association between the suspect product and the reported adverse event(s). This is determined by the type, source and the completeness of the data originating from individual case safety reports (ICSRs) (post-marketing sources and studies performed), data aggregated from scientific literature or other data sources available to PMI PSSD during the reporting period.

During the reporting period, two ongoing safety signals (occupational exposure and hypersensitivity reactions) have been detected based on cumulative review of cases from post-marketing sources.

## 15.5 Characterisation of potential risks

The characterization of potential risks at the DLP of this SUR are presented below in [Section 15.5.1](#) and [Section 15.5.2](#), respectively.

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### 15.5.1 Summary of Occupational exposure

The potential risk Occupational exposure is summarized in [Table 14](#).

**Table 14 Summary of Occupational exposure**

Seriousness/outcomes	<ul style="list-style-type: none"> <li>All reported AEs from 4 occupational exposure cases (and similar events) have also been reported by THS consumers: Headache and cough are expected adverse events</li> <li>Head discomfort, throat irritation, hemoptysis and sneezing are not expected</li> <li>Occupational exposure is not listed</li> </ul> <p>The 4 cases were rated as non-serious and possibly related to the THS due the temporal association of the events and the exposure to the product.</p>
Severity and nature of risk	<p>Flavors, as other odorant chemicals, are known to trigger headache and migraine (Silva-Neto et al 2014) or may pose an inhalation hazard in some conditions (FEMA 2012). The National Health System from the UK provides also hints to individuals susceptible to perfume odors (NHS 2015).</p> <p>Handling of open packs, i.e., opening and closing packs to visually count remaining tobacco sticks (without manipulation of tobacco sticks) could virtually expose workers to chemicals which can be transferred in the ambient air at room temperature. This is theoretically possible for glycerol (melting point 18°C, NOAEL 165 mg/m<sup>3</sup>, respiratory track irritation at 662 mg/m<sup>3</sup>, occupational exposure limits 10 mg/m<sup>3</sup> for 8 hours, (OECD 2002)), for nicotine and for flavors.</p> <p>After THS use, indoor air contains nicotine and acetaldehyde in quantities above background noise, but at least 16 times lower than observed after smoking combustible cigarettes. Flavors and glycerol were not measured as they were not expected to be quantifiable under study conditions.</p>
Background incidence/prevalence	Similar symptoms were also reported by nonusers exposed to e-cigarettes vapors (Durmowicz 2015).
Risk groups or risk factors	<p>The 2 main root causes of headache at work place (in the industrial / manufacturing setting) are:</p> <ol style="list-style-type: none"> <li>Exposure to solvents and stressful conditions at work, which can also aggravate or be a signal for stressful personal conditions.</li> <li>Respiratory symptoms are more often observed in susceptible workers, i.e. those who already have underlying respiratory diseases.</li> </ol>

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	Working in non-ventilated small rooms contributes to the AEs observed due to a likely higher concentration of chemicals in an unventilated environment.
Potential mechanisms	Nicotine, glycerol and odorant chemicals (including some of the ingredients present in the THS Ron flavor system) are reported to possibly trigger headache and other symptoms such as those associated with airways irritation.
Preventability	<p>Based on the current knowledge, the recommendations for personnel handling a significantly high number of open THS packs, such as needed for product accountability in clinical studies, include:</p> <ul style="list-style-type: none"> <li>• Indoor air quality under standard conditions should be evaluated prior to starting the work with unused THS tobacco stick or THS open packs in the dedicated room</li> <li>• Working in large room with relatively cool temperature, ideally with ventilation</li> <li>• Limiting the duration of accountability time by organizing the work with breaks at least once an hour</li> <li>• Wearing standard protective mask and gloves during open packs handling, especially when the activity includes also tobacco stick handling in addition to visual inspection of open packs</li> </ul> <p>Recommending pregnant women not to execute such activity, due to the potential exposure to nicotine even from unused tobaccos, due to the volatile nature of nicotine.</p>
Impact on individual patient	<p>Four cases of adverse events were spontaneously reported by 4 clinical research associates (CRAs) who experienced various adverse events (AEs) (see <a href="#">Table 10</a>) while executing investigational product (IP) accountability of the Tobacco Heating System (THS) 2.2 Regular at the investigation site. Consumers are associating headache with the smell /odor of the THS aerosol.</p> <p>The reported hemoptysis may be a symptom of airways irritation (cough, sneezing). For this specific case, there was an ongoing upper respiratory infection which could explain at least partially the event.</p> <p>Re-occurrence of the AEs were observed in two cases (2 times over 2 visits for case PMI000308, 3 times over 5 visits for case PMI000316) and only once in the 2 other cases (1 over 6 visits for case PMI000315 and for case PMI000316). Three of the 4 cases were reported when the duration of accountability was greater than</p>

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	1 hour while there was no apparent trend linked to the number of packs / sticks.
Potential public health impact of safety concern	NA
Evidence Source	Safety Surveillance Report – Investigation for Occupational Exposure Adverse Events. Issued: 30 Sep 2015

### 15.5.2 Signal evaluation of Hypersensitivity reactions

The potential risk Hypersensitivity reactions is summarized in [Table 15](#).

**Table 15 Summary of Hypersensitivity reactions**

Seriousness/outcomes	Clinical studies, Post marketing data
Severity and nature of risk	See above
Background incidence / prevalence	Overall, 12% to 22% of the general population will suffer from at least one subtype of urticaria at some time in their lives with a prevalence of 0.11% to 0.6%. Of all patients with urticaria, only a low proportion of 7.6% to 16% have acute urticaria. The variation may be related to the population studied and the interests of the department or doctor to whom patients are referred. However, it may be recurrent and can progress to chronic disease.
Risk groups or risk factors	Acute urticaria is common allergic complaint that can occur as an isolated incident or as a recurring problem, and presents in all age groups. The age group studied may be particularly important, because acute urticaria seems to be more common than chronic disease in very young children.
Potential mechanisms	Attacks of acute urticaria are thought to be idiopathic in 30% to 50% of cases. It is most often idiopathic but can be triggered by infection, drugs, and less frequently by foodstuffs, with estimates of causality ranging from 0% to 18% of cases. Although acute urticaria can occur as part of a type I hypersensitivity reaction, and sometimes as part of anaphylaxis, the mechanism leading to mast cell release is often unknown. If an allergen is suspected as the cause of the reaction, the patient should be referred to an allergist-immunologist for further evaluation. When possible, triggers should be identified to ensure avoidance and prevent future reactions.
Preventability	A significant portion of cases are idiopathic and subsequently unpredictable.
Impact on individual patient	Its transient and usually benign nature means that it may not come to the attention of doctors. Thus, the incidence may be underestimated, typical disease severity may be overestimated, the proportion with causative factors is difficult to ascertain, and the response to treatment is difficult to quantify. The diagnosis is usually straightforward because of the transient nature of the urticarial weals, but it can be

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	confused with several other conditions, especially in the first 24 hours. Investigations may be unnecessary. Management is aimed at removing or treating any cause, and symptom control, usually with H1 antihistamines.
<b>Potential public health impact of safety concern</b>	NA
<b>Evidence Source</b>	<a href="#">Sabroe RA. Acute Urticaria. Immunology and Allergy Clinics; 2014; 34: 11-21.</a> <a href="#">Williams KW, Sharma HP. Anaphylaxis and Urticaria. Immunology and Allergy Clinics; 2015; 35: 199-219.</a>

A literature review was performed for the retrieval of hypersensitivity reactions associated with cigarette smoking, nicotine / nicotine replacement therapy and electronic cigarette ([Safety Report – Allergic skin reactions, 25 Mar 2016](#)). Apart from contact dermatitis associated with nicotine transdermal systems, only few isolated cases of allergic reactions have been found and confirmed by positive allergic tests to nicotine and to other ingredients such as propylene glycol, glycerol, menthol and other flavors. In addition, skin reactions are known adverse reactions of nicotine-containing medicinal products; i.e. erythema, urticaria and susceptibility to angioedema are listed as uncommon adverse reactions in the Summary of Product Characteristics of Nicorette® Gum and Nicorette® Inhalator (McNeil Products Ltd). Rash is an adverse event reported with a frequency of <1% among active spray users in the Nicotrol® Nasal Spray label (Pfizer). Whether these reactions are linked to nicotine itself or to the excipients present in these products is not known. In the context of THS clinical studies, a total of 4 similar cases (0.7%) was reported in THS-exposed subjects in completed studies, all cases being assessed as not related to THS products.

## 15.6 Summary of potential risks

Summary of safety concerns at the end of the reporting interval for this SUR is presented in [Table 16](#) below.

**Table 16 Summary of ongoing safety concerns at Data Lock Point**

<b>Risk</b>	<b>Safety Concern</b>
Potential risks	Occupational exposure Hypersensitivity

The information received from clinical studies, from pre-market studies and post-market safety surveillance during the reporting period does not suggest any safety concerns or new emerged health related risk associated with the exposure to the THS products as compared to conventional cigarettes.

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## 16 CONCLUSIONS AND ACTIONS

This SUR covers all relevant safety data received for THS products during the period from 01 May 2015 to 31 Dec 2015.

From the safety perspective, based on data reviewed and analysed originating from post-marketing sources and studies performed, the following signals were recognized and placed under further monitoring via routine surveillance: occupational exposure and hypersensitivity reactions. These signals were revealed using the regular signal detection in PMI. Recommendations to minimize risks associated with occupational exposure will be integrated in the next update of THS Investigator's Brochure (IB). The IB will also be updated with respect to the potential risk for hypersensitivity reactions to THS ingredients in susceptible consumers.

The passive product safety surveillance at PMI ensures an appropriate safety concern assessment of the product, and therefore effectiveness of routine safety concern minimisation measures is considered appropriate.

Based on the information received during the review period and the cumulative safety data there is no change in the safety concern assessment. The sections concerning safety in the current relevant documentation is considered adequate and no changes are proposed. The data described in this report did not require any other actions for safety reasons which have been warranted based on the data collected. Case reports of occupational exposure and hypersensitivity will be monitored as part of routine safety surveillance, but will only be discussed in subsequent SURs if warranted.

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## **17 REFERENCES**

### **17.1 PMI Internal references**

Investigator Brochure (IB) THS 2.2, Edition 5.0, 27 Apr 2015

Investigator's Brochure (IB) THS 2.2 Menthol Edition 3.0, 27 Apr 2015

Safety Report – Allergic skin reactions. Issued 25 Mar 2016.

Safety Surveillance Report – Investigation for Occupational Exposure Adverse Events.  
Issued: 30 Sep 2015

### **17.2 External published references**

Guideline on Good Pharmacovigilance Practices (GVP) Module VII – Periodic Safety Update Report [EMA/816292/2011].

ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER). Step 5 (EMA/CHMP, January 2013).

Sabroe RA. Acute Urticaria. Immunology and Allergy Clinics; 2014; 34: 11-21.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products. Modified Risk Tobacco Product Applications: Draft Guidance. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products; 2012.

Williams KW, Sharma HP. Anaphylaxis and Urticaria. Immunology and Allergy Clinics; 2015; 35: 199-219.

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## **18 APPENDICES TO THE SUR**

[Appendix 1: Signatures](#)

[Appendix 2: Reference Safety Information](#)

[Appendix 2.1: Investigator's Brochure THS 2.2](#)

[Appendix 2.2: Investigator's Brochure THS 2.2 Menthol](#)

[Appendix 2.3: Package Leaflets](#)

[Appendix 3: Description of clinical studies and estimated exposure to THS products](#)

[Appendix 3.1: Description of Completed and Ongoing Clinical Studies](#)

[Appendix 3.2: Estimated cumulative subject exposure for completed and ongoing Clinical Studies since DIBD](#)

[Appendix 3.3: Estimated cumulative subject exposure by Demographics for completed and ongoing Clinical Studies](#)

[Appendix 4: Estimated cumulative consumer exposure from pre-marketing studies since IBD](#)

[Appendix 5: Cumulative Summary Tabulation of Serious Adverse Events from Clinical Studies](#)

[Appendix 6: Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Reactions from Post-Marketing data sources](#)

[Appendix 7: Description of Ongoing and Completed Pre-Marketing Studies for THS products in reporting interval](#)

[Appendix 8: Worldwide Marketing Status of THS products at DLP](#)

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