PMI RESEARCH & DEVELOPMENT

Safety Update Report

Electrically Heated Tobacco Product (EHTP) and Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS)

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Product Name:	Electrically Heated Tobacco Product (EHTP) and Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS)
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PURPOSE OF THE SUR

This Safety Update Report (SUR) provides a comprehensive and critical analysis of the safety profile of Electrically Heated Tobacco Product (EHTP) and Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS) (device versions 2.2 and 2.4 and all variants of THS tobacco sticks, herein referred to as THS products*)* in the period from 01-Jan-2017 to 31-Dec-2017 (Data Lock Point, DLP) and is compiled following the principles of the International Conference of Harmonisation (ICH) guideline E2C (R2).

EXECUTIVE SUMMARY

Philip Morris International (PMI) develops, assesses and commercializes a portfolio of Reduced-Risk Products (RRPs) that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continuing smoking.

This Safety Update Report (SUR) provides a comprehensive and critical analysis of the safety profile of Electrically Heated Tobacco Product (EHTP) and Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS) (device versions 2.2 and 2.4 and all variants of THS tobacco sticks*)* within the period from 01-Jan-2017 to 31-Dec-2017 (Data Lock Point, DLP), and is compiled according to the International Conference of Harmonisation (ICH) guideline E2C (R2). The EHTP is commercialized under the brand name Marlboro HeatSticks (Japan) and HEETS (rest of the world) and is to be used exclusively with the THD, commercialized under the brand name IQOS. Throughout the SUR the term THS products is used to refer to the THS 2.2 Regular and Menthol EHTPs used in PMI clinical studies and all EHTP variants marketed for both THS 2.2 and 2.4, Regular and Menthol products.

THS products use a "heat-not-burn" technology which generates an aerosol from heating tobacco to a lower temperature than combustible cigarettes. The concentrations of harmful and potentially harmful constituents (HPHCs) are significantly lower in THS aerosol than in smoke produced by combustible cigarettes.

The Development International Birth Date (DIBD) for THS products was 30-Apr-2013, which corresponds to the date of first approval for conducting a clinical study in any country in the world.

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

Since the IBD up to the DLP, THS products has been marketed in 35 markets worldwide. Cumulatively up to the DLP, 15’251´935.24 THDs and 28’595´868´950 EHTPs have been sold.

On 26-Sep-2017 a Corrective Action and Preventive Action (CAPA) entitled “*Warm aerosol understanding and mitigation*” was finalized to investigate two cases received on 20-Jul-2017 reporting two consumers who suffered from burnt lips while using THS products. Following the CAPA, agents in Customer Care Call Centers worldwide have been provided with consumer communication instructions to recommend not to expose the EHTP to high humidity but to keep it dry, especially during summer months.

The Investigator Brochure (IB) version 6.0 (dated 16-Aug-2016) for THS 2.2 Regular is considered as the Reference Safety Information (RSI) for all the clinical studies conducted with THS products as it contains the relevant safety information applicable to both THS

Regular and Menthol variants. For studies initiated in countries where THS products are marketed under the brand name IQOS, the Safety Product Information (SPI) IQOS with HeatSticks version 3.0 (dated 08-Nov-2017) replaced the IB covering all flavors of EHTP. None of them were updated during the reporting interval covered by this SUR.

The THS Safety Core Data Sheet (SCDS) for both THS Regular and Menthol variants (dated 18-Aug-2016) version 2.0 was used for Post-Marketing Safety Surveillance until 22-Nov-2017. From this date forward and until the DLP of this SUR the RSI used was the IQOS with HeatSticks SPI version 3.0 (dated 08-Nov-2017). The SCDS and the SPI were not updated during the reporting interval covered by this SUR.

During the reporting period, three PMI-sponsored open-label randomized controlled clinical trials were ongoing (ZRHR-ERS-09-US, ZRHR-ERS-09-US-EXT, and P1-OHS-01-JP).

New information received during the period covered by this SUR (01-Jan-2017 to 31-Dec-2017) and cumulatively from the IBD (04-Nov-2014) to the DLP of this SUR (31-Dec-2017) have been evaluated regarding: a) three important identified risks (namely, hypersensitivity, accidental exposure to product by child, and burning sensation (during hot and humid weather conditions); b) one important potential risk of thermal burn; c) as well as the exposure during pregnancy and lactation to THS products. A total of 293 Adverse Events (AEs) of hypersensitivity to THS products use (10 serious and 283 non-serious) have been received in 261 Individual Case Safety Reports (ICSRs); 1,132 ICSRs reporting 1,125 AEs of accidental exposure to product by child (1,106 non-serious and 19 serious) and 7 AEs of accidental exposure to product (all non-serious) have been received; 23 AEs of burning sensation (during hot and humid weather conditions) upon THS products use (all non-serious) have been received in 23 ICSRs; 703 AEs of thermal burn upon THS products use (all non-serious) have been received in 668 ICSRs. One non-serious AE of exposure during pregnancy was reported in one ICSR. The health-related events co-reported were dizziness and nausea both assessed as moderate and non-serious and resolved at the time of reporting.

The evaluation of the new information received during the period covered by this SUR does not support an update of the characterization of the identified risks and missing information. Cumulatively, the information received on the identified risks and missing information does not show a different trend in the number of cases, or impact on the individual or public health throughout the period going from the IBD and the DLP of this SUR. PMI will continue regular monitoring activities on the identified risks and missing information to ensure the ongoing evaluation of new safety information.

In conclusion the data presented in this report do not lead to any safety-related action. The evaluation of information presented in this SUR, including data from Post-marketing Safety Surveillance (spontaneous reports) and from published literature, showed three new signals (acne, chest discomfort, rash) for which PMI will perform subsequent monitoring activities.

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LIST OF ABBREVIATIONS

AE	Adverse Event
BT	Blend Tests
CAPA	Corrective Action and Preventive Action
CC	Conventional Cigarettes
CO	Carbon Monoxide
COT	Commercial Offer Test
DIBD	Development International Birth Date
DLP	Data Lock Point
EHTP	Electrically Heated Tobacco Product
ENDS	Electronic Nicotine Delivery System
HPHCs	Harmful and Potentially Harmful Constituents
IB	Investigator Brochure
IBD	International Birth Date
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MedDRA	Medical Dictionary for Regulatory Activities
NAB	N-nitrosoanabasine
PAH	Polycyclic Aromatic Hydrocarbons
PBA	Perception and Behaviour Assessment

PMI	Philip Morris International
PMK	Philip Morris Korea
PT	Preferred Term
RRP	Reduced-Risk Products
RSI	Reference Safety Information
SAE	Serious Adverse Event
SCDS	Safety Core Data Sheet
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
THD	Tobacco Heating Device
US	United States
VOC	Volatile Organic Compounds
WOT	Whole Offer Tests

1 INTRODUCTION

Philip Morris International (PMI) develops, assesses and commercializes a portfolio of Reduced-Risk Products (RRPs) that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking[1]. These RRPs target to substantially reduce or eliminate the exposure to Harmful and Potentially Harmful Constituents (HPHCs) found in cigarette smoke, while providing nicotine delivery, taste, ritual, and a sensory experience similar to cigarettes in order to offer an acceptable substitute to cigarette smokers.

Among the RRPs portfolio, PMI developed the Electrically Heated Tobacco Product (EHTP) and Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS) which use a "heat-not-burn" technology generating an aerosol from tobacco heated to a lower temperature than combustible cigarettes. The EHTP is commercialized under the brand name Marlboro HeatSticks (Japan) and HEETS (rest of the world) and is to be used exclusively with the THD, commercialized under the brand name IQOS. Throughout the SUR THS products is used to refer to the THS 2.2 Regular and Menthol used in PMI clinical studies and all variants marketed for both THS 2.2 and 2.4, Regular and Menthol products.

The THS products have three distinct components that perform different functions[2]:

- EHTPs which are made up of a tobacco plug, a hollow acetate tube, a polymer-film filter, a mouth piece filter and mouth-end papers. The tobacco plug is made from tobacco, glycerin, water, guar gum, cellulose, propylene glycol, natural and artificial flavorings. The average amount of nicotine in the tobacco plug is 5–6 mg per EHTP. Table 1-1 below shows the ingredients contained in the tobacco plug of the EHTP per product variant.
- A THD into which the EHTPs are inserted and which heats the tobacco material by means of an electronically controlled heating blade. A light emitting diode indicates the end of the experience. Once this cycle is complete, the Holder must be recharged before a new EHTP can be used.
- A Charger that is used to recharge the THD. The Charger holds enough energy for approximately 20 uses of the THD and can be recharged from household power. The Charger stores the THD when not in use, and provides a secure environment for the cleaning process of the heater blade.

The THS products differ from a cigarette in significant ways[2]. First, the tobacco stick does not contain tobacco cut-filler (tobacco leaf cut in small pieces found in cigarettes). Instead, the tobacco is ground and reconstituted into sheets (termed cast-leaf) following the addition of water, glycerin, guar gum and cellulose fibers. Second, the tobacco stick contains smaller amounts of tobacco compared with a cigarette. The weight of the tobacco plug in the tobacco

stick is approximately 320mg compared with the 550-700mg cut-filler found in Conventional Cigarettes (CC). The reconstituted tobacco cast-leaf is fashioned into a small plug through a proprietary process known as 'crimping'. Third, unlike a cigarette, the tobacco stick contains two unique and independent filters: (i) a polymer-film filter to cool the aerosol and (ii) a low density cellulose acetate mouthpiece filter to mimic the sensory aspects of a cigarette. Furthermore, a hollow acetate tube separates the tobacco plug and the polymer-film filter.

Table 1-1 Ingredients contained in the tobacco plug of the EHTP

Ingredient Name	Regular Variant	Menthol Variant
Glycerol	X	X
Water	X	X
Guar Gum	X	X
Cellulose	X	X
Menthol		X
Propylene Glycol	X	X
Peppermint Oil		X
Natural and artificial Flavorings	X	X

To operate the THS products, the user inserts an EHTP into the holder and turns on the device by means of a switch. This initiates the heating of the tobacco via the heating blade inserted into the tobacco plug. The tobacco neither ignites nor burns. The electronically controlled heating, in combination with the uniquely processed tobacco, prevents combustion from occurring. Heat is supplied to the tobacco stick for a fixed period of approximately six minutes and allows up to 14 puffs to be taken during that time. The temperature of the heating blade is carefully controlled and the energy supply to the blade is cut if its operating temperature exceeds 350 °C. The operating temperature of the THS products is substantially lower than that required to cause ignition and combustion of tobacco (from 600 to 900 °C) and the temperature measured in the tobacco does not exceed 300 °C. When a puff is taken from the tobacco stick the tobacco temperature drops as ambient air is drawn through the tobacco stick. This absence of combustion, because of controlled heating, is designed to reduce by more than 90% the formation of HPHCs by the THS products compared with

cigarettes[3-5] except for carbonyls, ammonia, and N-nitrosoanabasine (NAB), which are about 50–80% lower[5].

This Safety Update Report (SUR) provides a comprehensive and critical analysis of the safety profile of THS products within the period from 01-Jan-2017 to 31-Dec-2017 (Data Lock Point, DLP), and it is compiled according to the International Conference of Harmonisation (ICH) guideline E2C (R2).

The Development International Birth Date (DIBD) for THS products was 30-Apr-2013, which corresponds to the date of first approval for conducting a clinical study in any country in the world.

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

2 WORLDWIDE MARKETING STATUS

The DIBD for THS products is based on the date of the first ethics committee approval for the first clinical study worldwide which was on 30-Apr-2013 in the United Kingdom.

The IBD for THS products is based on the date of first market launch worldwide which was on 04-Nov-2014 in Japan.

Up to the DLP of this SUR (31-Dec-2017), THS products were marketed in 35 markets worldwide (Bulgaria, Canada, Colombia, Croatia, Curaçao, Czech Republic, Denmark, Duty-free, France, Germany, Greece, Greek Cyprus, Guatemala, Israel, Italy, Japan, Kazakhstan, Lithuania, Netherlands, New Zealand, Palestine, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Slovenia, South Africa, South Korea, Spain, Switzerland, Turkish Cyprus, Ukraine, and United Kingdom).

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

On 26-Sep-2017 a Corrective Action and Preventive Action (CAPA) entitled "*Warm aerosol understanding and mitigation*" was finalized to investigate two cases received on 20-Jul-2017 reporting two consumers who suffered burning lips while using THS products. A root cause investigation revealed that the high level of ambient climatic humidity could have been the main contributor to a sensation of hot lips reported by consumers, which was also supported by experimental laboratory tests simulating humid climatic conditions (30°C/75%RH). Nevertheless, under these conditions the maximum temperature measured was far below the threshold for which lesions may appear. Measures to prevent the hot aerosol sensation under high humidity conditions were implemented:

- ✓ Customer Care agents have been provided with a consumer communication reminding consumers to not expose THS products to high humidity but to keep the products dry especially during summer months.
- ✓ A warning recommending the storage of THS products in a dry environment to avoid exposing the products to high humidity was incorporated in the THS products SPI version 3 (dated 08-Nov-2017).

Further actions will be taken to reflect the safety findings in a communication to consumers in the THD product packages.

4 CHANGES TO REFERENCE SAFETY INFORMATION

4.1 Reference Safety Information for Clinical Studies

The Investigator Brochure (IB) version 6.0 (dated 16-Aug-2016) for *THS 2.2 Regular* (Appendix 1a) is considered the Reference Safety Information (RSI) for all the clinical studies conducted with THS products as it contains the relevant safety information applicable to both *THS Regular* and *Menthol* variants. For studies initiated in countries where THS products are marketed under the brand name *IQOS*, the Safety Product Information (SPI) *IQOS with HeatSticks* version 3.0 (dated 08-Nov-2017) (Appendix 1c) replaced the IB covering all flavors. None of the available RSIs were updated during the reporting interval covered by this SUR.

4.2 Reference Safety Information for Post-Marketing Safety Surveillance

The THS Safety Core Data Sheet (SCDS) for both *THS Regular* and *Menthol* variants (dated 18-Aug-2016) version 2.0 (Appendix 1d) was used for Post-Marketing Safety Surveillance until 22-Nov-2017. From this date forward and until the DLP of this SUR (31-Dec-2017) the RSI used was the *IQOS with HeatSticks* SPI version 3.0 dated 08-Nov-2017 (Appendix 1c). The THS SCDS and IQOS *with HeatSticks* SPI were not updated during the reporting interval covered by this SUR.

5 ESTIMATED EXPOSURE

5.1 Cumulative Subject Exposure in Clinical Studies

Up to the DLP of this SUR, a total of eight PMI-sponsored open-label randomized controlled Clinical Studies were completed and three studies were ongoing.

The estimated cumulative subject exposure in Clinical Studies from the DIBD (30-Apr-2013) up to DLP (31-Dec-2017) is based on the safety population and on the number of subjects randomized to THS products, comparators or Smoking Abstinence (SA) in PMI-sponsored completed studies and from ongoing studies (enrolment/randomization schemes). The inventory of all PMI-sponsored Clinical Studies at DLP including the Study Title, Study Status at DLP, Exposure Duration as well as the estimated Safety Population and the number of subjects exposed to *THS Reg*ular or *Menthol* variants (THS), Conventional Cigarettes (CC), Nicotine Replacement Therapy (NRT), and Smoking Abstinence (SA) including the subjects exposed to THS products but not randomized (NR) and are presented in Table 5-1 below.

Table 5-1 Cumulative Subject Exposure in Clinical Studies

Study Title	Study Status	Exposure Duration	Safety Population[1]	THS	CC	NRT	SA	NR
ZRHR-PK-01-EU	Closed	Single use	62	62	44	18	-	-
ZRHR-PK-02-JP	Closed	Single use	65	62	44	18	-	3
ZRHM-PK-05-JP	Closed	Single use	73	62	44	18	-	11
ZRHM-PK-06-US	Closed	Single use	64	62	44	18	-	2
ZRHR-REXC-03-EU	Closed	5 Days	169	80	41	-	39	9
ZRHR-REXC-04-JP	Closed	5 Days	166	80	40	-	40	6
ZRHM-REXA-07-JP	Closed	3 Months	175	78	42	-	40	15
ZRHM-REXA-08-US	Closed	3 Months	165	80	41	-	39	5
ZRHR-ERS-09-US[2]	Ongoing	6 Months	1039	488	496	-	-	55
P1-OHS-01-JP[3]	Ongoing	6 Months	33	18	15	-	-	-
ZRHR-ERS-09-US-EXT[2]	Ongoing	Up to 1-year	672	309	363	-	-	-
Total Exposure	**NA**	**NA**	**2683**	**1381**	**1214**	**72**	**158**	**106**

[1]The overall safety population does not sum up the total of subjects in studies arms due to PK/PD crossover studies.
[2]Preliminary figures, all the subjects have been enrolled. The study is considered ongoing because the Study Report was under preparation at the DLP.
[3]Actual number of subjects enrolled at the DLP.

The estimated cumulative exposure to THS products presented by demography is shown in Table 5-2 below.

Table 5-2 Cumulative Subject Demographics in Clinical Studies

Demographics		**Total**
Sex	Male	1131
	Female	847
	Total	**1978**[1]
Race	Caucasian (White)	1177
	Asian (Japanese)[2]	522
	Black or African American	275
	Native Hawaiian or Other Pacific Islander	14
	American Indian or Alaska Native	7
	Other	16
	Total	**2011**

[1]The total does not include study P1-OHS-01-JP.
[2]It includes the actual number of subjects enrolled in study P1-OHS-01-JP at the DLP (31-Dec-2017).

No studies have been performed so far by PMI in other populations such as paediatric, pregnancy/breastfeeding women or smokers with smoking-related diseases in the reporting interval and from DIBD (30-Apr-2013).

5.2 Cumulative Participants Exposure from Passive Surveillance Pre-Market Studies.

Since May 2014 up to the DLP (31-Dec-2017) PMI has implemented a Passive Safety Surveillance carrying out eight market research studies: seven market research studies including Blend Tests (BT), Whole Offer Tests (WOT), Commercial Offer Test (COT) and one Perception and Behaviour Assessment (PBA) study. All the eight studies were completed at the DLP of this SUR.

The estimated pre-marketing exposure to THS products is based on the exposed safety population and on the number of study participants who tested at least one *THS product* (Regular and Menthol variants).

The inventory of all PMI-sponsored Passive Surveillance Pre-Market studies at DLP of this SUR (31-Dec-2017) including the Study Title, Study Status at DLP, Country, as well as the estimated Safety Population and the number of subjects exposed to *THS Variants* (*THS Regular*, *Menthol*, both *Regular* and *Menthol*) is presented in Table 5-3 below.

Table 5-3 Cumulative Exposure Pre-Marketing Studies

Study Title	Country	Safety Population	TSH Variant			Study Status
			Regular	Menthol	Regular and Menthol	
P1-BT1-IT	Italy	1047	836	211	0	Completed
P1-WOT2-IT	Italy	643	292	310	41	Completed
P1-WOT1-CH	Switzerland	580	344	236	0	Completed
P1-WOT1-DE	Germany	593	593	0	0	Completed
P1-WOT1-KO	South Korea	1316	724	354	238	Completed
P1-BT1-RU	Russia	611	611	0	0	Completed
THS-PBA-07-US	US	1158	441	512	205	Completed
P1_COT_DK	Denmark	350[1]	350	350	350	Completed
Total Exposure	**NA**	**6298**	**4191**	**1973**	**834**	**NA**

[1] All the 350 participants accepted to test THS products at home. Each participant received 1 bundles of each THS variant (Regular and Menthol).

5.3 Cumulative and Interval Consumer Exposure from Post-Marketing Experience

Given the nature of the product it is not possible to estimate a proper "Defined Daily Dose" to which consumers are exposed. Thus, the consumer exposure to THS products from Post-Marketing experience is based on "In Market Sales" which represent the number of THDs and EHTPs that were sold to retailers.

Interval and cumulative exposure by EHTP variant is presented in Table 5-4 below.

Table 5-4 Interval and Cumulative Consumer Exposure

	Interval			**Cumulative**		
	Regular	**Menthol**	**Total**	**Regular**	**Menthol**	**Total**
THD	*NA*	*NA*	11'689504,24	*NA*	*NA*	15'251´935.24
EHTP	8'505´226´700	14'383´670´000	22'888´896´640	10'448´990´920	18'146´878´030	28'595´868´950

6 DATA IN SUMMARY TABULATIONS

6.1 Reference Information

The summary tabulations presented in the Appendices 2a-2b-2c of this SUR were generated from the PMI Global Safety Database, using MedDRA (Medical Dictionary for Regulatory Activities) versions effective at the time of receipt of the Individual Case Safety Reports (ICSRs) (the last MedDRA version used was 20.1).

The seriousness of the Adverse Events (AEs) 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[6]). When serious and non-serious events are included in the same ICSR, the individual seriousness per event is reflected in the summary tabulations.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

Cumulative summary tabulations of Serious Adverse Events (SAEs) received from all PMI-sponsored Clinical Studies, from the DIBD (30-Apr-2013) until the DLP of this SUR (31-Dec-2017) are presented in Appendix 2a. The summary tabulations are presented by MedDRA System Organ Class (SOC), for THS products as well as for the comparator arm CC.

Cumulative summary tabulations present 44 SAEs reported in 32 ICSRs, from which 20 SAEs were reported in the THS arm and 24 SAEs in the CC arm.

A total of 20 SAEs were reported cumulatively from the DIBD in the THS study arm. The most represented SOCs were: Injury, poisoning and procedural complications (20%, n=4), Infections and infestations (15%, n=3), and Neoplasms benign, malignant and unspecified (incl cysts and polyps) (15%, n=3). None of the SAEs was assessed by principal investigators or by PMI as causally related to THS.

6.3 Cumulative Summary Tabulations of Serious Adverse Events from Passive Surveillance Pre-Market Studies

Cumulative summary tabulations of SAEs received from all PMI-sponsored Passive Safety Surveillance Pre-Market Studies until the DLP of this SUR (31-Dec-2017) are presented in Appendix 2b. The summary tabulations are presented by MedDRA System Organ Class (SOC) for THS products.

Cumulative summary tabulations present 25 SAEs reported in 11 ICSRs. None of the SAEs was assessed by principal investigators or by PMI as causally related to THS. The most represented SOCs were Injury, poisoning and procedural complications (48%, n=12) and Infections and infestations (28%, n=7).

6.4 Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Events from Post-Marketing Experience

Cumulative and Interval Summary Tabulations of AEs generated from the PMI Global Safety Database, using MedDRA version 20.1 are presented in Appendix 2c. SAEs and non-serious AEs received from unsolicited sources (spontaneous Post-Marketing Safety Reports and literature review) collected within the period covered by this SUR and cumulatively from the IBD (04-Nov-2014) are presented in the summary tabulations organized by MedDRA System Organ Class (SOC).

The definition of "spontaneous report" is derived from ICH E2C (R2) Guidance [7], and refers to an unsolicited communication by a healthcare professional, or consumer to a competent authority, marketing authorisation holder or other organisation (e.g. Regional Pharmacovigilance Centre, Poison Control Centre) that describes one or more suspected adverse reactions in an individual (e.g., consumer) who was using or exposed to THS products and that does not derive from a study or any organised data collection systems where adverse events reporting is actively sought.

Interval summary tabulations present 10928 AEs: 164 serious (1,5%) and 10764 (98.5%) non serious from 5385 ICSRs. The most represented SOCs (>5%) were: Respiratory, thoracic and mediastinal disorders (19.78%, n=2162, 2122 non-serious AEs and 40 SAEs), Injury, poisoning and procedural complications (18.36%, n=2006, 1982 non-serious AEs and 24 SAEs), Gastrointestinal disorders (18.05%, n=1972, 1952 non-serious AEs and 20 SAEs), General disorders and administration site conditions (17.12%, n=1871, 1858 non-serious AEs and 13 SAEs?), Product issues (9.38%, n=1025 all non-serious AEs), and Nervous system disorders (9.09%, n=993, 982 non-serious AEs and 11 SAEs). Out of the total 164 SAEs, the most frequently reported (>5%) were: Accidental exposure to product by child (11.59%, n=19), Choking (9.76%, n=16), Asphyxia (6.10%, n= 10) and Vomiting (6.10%, n=10). Out of the total 10764 non-serious AEs the most frequently reported (>5%) were: Accidental exposure to product by child (10.30%, n=1109, Device physical property issue (6.06%, n=652), Cough (5.85%, n=630, and Thermal burn (5.17%, n=557).

Cumulative summary tabulations report 13667 AEs: 208 serious (1,5%) and 13459 (98,5%) non-serious from 6602 ICSRs. The most represented SOCs (>5%) were: Respiratory, thoracic and mediastinal disorders (19.01%, n=2598, 2555 non-serious AEs and 43 SAEs), Injury, poisoning and procedural complications (19.00%, n=2597, 2562 non-serious AEs and 35 SAEs), Gastrointestinal disorders (18.32%, n=2504, 2479 non-serious AEs and 25 SAEs),

General disorders and administration site conditions (17.28%, n=2362, 2345 non-serious AEs and 17 SAEs), Product issues (9.80%, n=1340 all non-serious AEs), and Nervous system disorders (8.45%, n=1155, 1140 non-serious AEs and 15 SAEs). Out of the total 208 SAEs, the most frequently reported (>5%) were: Accidental exposure to product by child (14.42%, n=30), Choking (7.69%, n=16), Vomiting (7.21%, n=15), and Asphyxia (5.29%, n=11). Out of the total 13459 the most frequently reported non-serious AEs (>5%) were: Accidental exposure to product by child (10.60%, n=1427, Cough (5.47%, n=736), and Thermal burn (5.35%, n=720).

7 SUMMARY OF SIGNIFICANT SAFETY FINDINGS FROM CLINICAL STUDIES DURING THE REPORTING INTERVAL

7.1 Completed Clinical Studies

No PMI-sponsored Clinical Studies have been completed for THS products during the period covered by this SUR.

7.2 Ongoing Clinical Studies

Three PMI-sponsored Clinical Studies were ongoing for THS products during the period covered by this SUR.

Study ZRHR-ERS-09-US is a randomized, controlled, 2-arm parallel group, multi-center study, to evaluate biological and functional changes in healthy smokers switching to *THS 2.2* compared to continuing smoking CC for 26 weeks in an ambulatory setting.

Study ZRHR-ERS-09-US-EXT is a 26 week extension study to ZRHR-ERS-09-US, a 26 weeks, randomized, controlled, 2-arm parallel group, multi-center study, to determine biological and functional changes in healthy smokers who had either switched from CC to THS 2.2 or who had continued to smoke CC.

Study P1-OHS-01-JP is a 6-month randomized, controlled, open-label, 2-arm parallel group, multicenter study to evaluate the effect on oral health status of switching from cigarette smoking to THS products in smokers with generalized chronic periodontitis on the response to mechanical periodontal treatment.

7.3 Long-term Follow-up

No PMI-sponsored Long-Term Follow-up studies including medical oversight have been conducted for THS products during the period covered by this SUR.

8 SUMMARY OF SIGNIFICANT SAFETY FINDINGS FROM PASSIVE SURVEILLANCE PRE-MARKET STUDIES DURING THE REPORTING INTERVAL

8.1 Completed Passive Surveillance Pre-Market Studies

One PMI-sponsored Passive Surveillance Pre-Market Studies has been completed for THS products during the period covered by this SUR.

Study P1_COT_DK conducted in Denmark was a wide scale study with 350 participants placed for four weeks ad libitum home usage of the *THS 2.4 Regular* and *Mentho*l, aiming to understand the perception and adoption of the new products offer.

During the study 42 AEs were spontaneously reported in 30 ICSRs. The AEs fell under the MedDRA SOCs: Respiratory, thoracic and mediastinal disorders (n=15), Infections and infestations (n=9), Gastrointestinal disorders (n=6), Nervous system disorders (n=6), General disorders and administration site conditions (n=5), and Ear and labyrinth disorders (n=1).

Cough (n=7), Influenza (n=5), Headache (n=4), Nausea, Dyspnoea, and Oropharyngeal pain, each (n=3), and Nasopharyngitis (n=2) were the most reported Preferred Terms (PTs) ($n \geq 2$) representing 64.3% (21/42) of all AEs reported during the study. The remaining AEs were reported once each (Abdominal discomfort, Chest discomfort, Dizziness, Dry mouth, Fatigue, Malaise, Motion sickness, Oral mucosal blistering, Paranasal sinus discomfort, Pharyngitis, Pneumonia, Pyrexia, Somnolence, Thirst and Throat tightness) not presenting any significant clinical clusters.

One SAE of Pneumonia was reported and considered related to the THS 2.4 use (implied causality).

No new safety concerns emerged during the P1_COT_DK Study and safety data were considered in line with the safety profile of *THS 2.4 Regular* and *Menthol*.

8.2 Ongoing Passive Surveillance Pre-Market Studies

No PMI-sponsored Passive Surveillance Pre-Market Study was ongoing for THS products during the period covered by this SUR.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

No other Clinical Trials were conducted for THS products during the period covered by this SUR.

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 PMI-sponsored studies.

The current THS 2.2 Regular IB version 6.0 (dated 17-Aug-2016) contains a concise summary of non-clinical data relevant to THS products.

11 LITERATURE

The PubMed and Embase databases were screened for publications containing new safety information associated with THS products published during the reporting period from 01-Jan-2017 to 31-Dec-2017 included. The literature research was performed on 23-Jan-2018 using the search strings:

- ✓ PubMed: “iqos[All Fields] OR (Morris, Philip[Full Author Name] AND "electronic"[All Fields] AND ("nicotine"[MeSH Terms] OR "nicotine"[All Fields]) AND "delivery"[All Fields] AND (system[All Fields] OR "device"[All Fields]) OR "heat-not-burn"[All Fields] OR "heated"[All Fields] AND ("tobacco"[MeSH Terms] OR "tobacco"[All Fields] OR "tobacco products"[MeSH Terms] OR ("tobacco"[All Fields] AND "products"[All Fields]) OR "tobacco products"[All Fields]))”
- ✓ Embase: “iqos “OR” Morris, Philip” OR “tobacco products” OR “cigarette” OR “heat-not-burn” OR “ENDS” OR NEXT/2 (nicotine*OR delivery* OR system*)

A total of 39 publications were retrieved and analysed. None of them reported new safety information regarding THS products.

12 OTHER PERIODIC REPORTS

No other Periodic Reports have been prepared for THS products by PMI during the period covered by this SUR.

13 LATE-BREAKING INFORMATION

On 08-Feb-2018 a CAPA entitled "*Battery electrolyte leakage*" was finalized to investigate a number of complaints received regarding the THD's battery leakage. A root cause analysis showed that an external short circuit of the THD's battery caused a gas pressure build up that in turn caused the rupture of the safety cap of the battery which led to the leakage of small amounts of electrolytes to the surface of the THD. The external short circuit was most likely due to the detachment of soldering material and the leakage of condensed aerosol from the THD's upper compartment into the battery compartment. A risk assessment was performed in parallel showing no risk of harm for users upon exposure to toxic substances found in the battery fluid (lithum iron phosphate, lithium hexafluorophosphate, and ethylene carbonate) and generated by the leakage (hydrogen fluoride) as the respective levels of those substances were under the threshold above which dermal or inhalation toxicity may occur. External factors such as humidity may have contributed to the root causes of the device issue.

Measures to prevent the battery electrolyte leakage were implemented:

- ✓ PMI is continuing the investigations and has implemented additional quality testing during the manufacturing process to mitigate soldering issues.
- ✓ To avoid the slurry leakage the tightness of the THD between the two compartments, upper and lower, containing the EHTP and the battery has been improved.
- ✓ Customers were advised by Customer Care Call Center Agents to discontinue the use of devices presenting this issue and a notice was added on the local Philip Morris website to inform consumers.

14 OVERVIEW OF SIGNALS: NEW, ONGOING OR CLOSED

PMI conducts periodic and ad-hoc safety signal detection activities of current safety data within the clinical and global safety databases. The sources of safety data within the global safety database include spontaneous reports, published literature, clinical and other studies with medical oversight (SAEs).

The three key steps in PMI's signal detection process are:

1. Signal detection: consists of activities that result in the identification of a new signal from the assessment of studies sponsored by PMI (PMI-sponsored Clinical and Passive Surveillance Pre-Market Studies) as well as from other sources of information such as: literature monitoring and Post-Marketing unsolicited sources (Call center, Poison center, PMI-sponsored social media platforms/local and global websites, AEs spontaneously reported by a PMI employee).
2. Signal validation: verifies the existence of a new potentially causal association or a new aspect of a known association, and justify further analysis.
3. Signal assessment: involves an investigation of the validated signal, including the preparation of a Signal Evaluation Report.

Based on the cumulative assessment of safety data received up to the DLP, three new safety signals have been identified for THS products: Acne, Rash, and Chest discomfort. For Rash and Chest discomfort an increased reporting rate (Number of AEs/Million units EHTP sold) has been observed comparing cumulative data up to 31-Dec-2016 to those up to 31-Dec-2017 (Rash increased by 3 folds and Chest discomfort by 1.5 folds). The AE Acne appeared for the first time upon analysing cumulative data up to 31-Dec-2017. The three new signals were open for investigation in Dec-2017.

15 SIGNAL AND RISK EVALUATION

15.1 Summary of Safety Concerns

A summary of the safety concerns at the beginning of the reporting interval of this SUR is presented in Table 15-1 below. New information received during the period covered by this SUR have been evaluated regarding: a) three important identified risks of hypersensitivity, accidental exposure to product by child, and burning sensation (during hot and humid weather condition); b) one important potential risk of thermal burn; c) as well as about the exposure during pregnancy and lactation to THS products.

Table 15-1 Summary of Safety Concerns-New information during the reporting interval

	Risk	Search criteria for Risk Assessment	Interval Retrieved AEs within Safety Database
Important Identified Risks	Hypersensitivity	MedDRA SMQ Hypersensitivity (Narrow)	293 AEs Retrieved: Most reported AEs (>1%): - Hypersensitivity, n=76, 25.94% - Lip swelling, n=47, 16.04% - Pharyngeal oedema, n=39, 13.31% - Rash, n=39, 13.31% - Rash generalised, n=15, 5.12% - Swollen tongue, n=14, 4.78% - Gingival swelling, n=10, 3.41% - Urticaria, n=10, 3.41% - Eye swelling, n=8, 2.73% - Allergic cough, n=4, 1.37% - Rash erythematous, n=4, 1.37% - Angioedema, n=3, 1.02% - Rash pruritic, n=3, 1.02% - Swelling face, n=3, 1.02%
	Accidental exposure to product by child	Age: <18 years old Age groups: - Adolescent - Child - Infant - Neonate Selected PTs:	1132 AEs Retrieved: - Accidental exposure to product, n=7 - Accidental exposure to product by child, n=1125 Co-reported AEs representing at least 1% of the total: - Vomiting, n=131, 11.57%

		- Accidental exposure to product by child; - Accidental exposure to product; - Accidental exposure to product packaging by child;	- Pallor, n=20, 1.77% - Nausea, n=14, 1.24%
	Burning sensation (during hot and humid weather conditions)	Customised search of MedDRA PTs: - Burning sensation - Burning sensation mucosal - Skin burning sensation	23 AEs Retrieved: - Burning sensation, n=22 - Burning sensation mucosal, n=1
Important Potential Risks	Thermal burn	Customised search of MedDRA PTs: - Airway burns - Burn oesophageal - Burn of internal organs - Burn oral cavity - Burns first degree - Burns fourth degree - Burns second degree - Burns third degree - Eye burns - Thermal burn	703 AEs Retrieved: - Thermal burn, n=557 - Burn oral cavity, n=131 - Burn oesophageal, n=10 - Airway burns, n=2 - Burns second degree, n=2 - Burns first degree, n=1
Missing Information	Pregnancy and lactation	MedDRA SOC Pregnancy, puerperium and perinatal conditions and MedDRA SMQs Neonatal exposures via breast milk	1 AE Retrieved: Exposure during pregnancy, n=1 Co-reported AEs: – Dizziness, n=1 – Nausea, n=1 – Occupational exposure to product, n=1

15.2 Signal Evaluation

No safety signals have been closed during the reporting interval covered by this SUR.

15.3 Evaluation of Risks and New Information

15.3.1 New information on Important Identified Risks

15.3.1.1 Hypersensitivity

A search covering the period from 01-Jan-2017 to the DLP of this SUR (31-Dec-2017) was performed in the global safety database to retrieve all the Hypersensitivity events upon THS products use. The electronic search for Hypersensitivity included SAEs and non-serious AEs from all sources for all THS products and was carried out under the MedDRA version 20.1 SMQ Hypersensitivity (narrow).

During the review period of this SUR, a total of 293 AEs of Hypersensitivity to THS products use (10 serious and 283 non-serious) have been received in 261 ICSRs. The SAEs were: Hypersensitivity (n=4), Angioedema (n=3), Rash, Rash Generalized, and Laryngeal oedema (n=1 each). Three SAEs required hospitalization (Hypersensitivity n=2 and Rash Generalized n=1), all the others were assessed as medically serious. Six out of ten SAEs resolved at the time of reporting (Hypersensitivity, n=2; Angioedema, n=3; Laryngeal oedema n=1), one was not resolved (Rash generalized), the outcome of the remaining SAEs was unknown. As per the current RSI all the SAEs but Laryngeal oedema were listed. The consumer experiencing Laryngeal oedema (case PMI006034) was a 34-year-old female ex-smoker who stopped smoking cigarettes one month prior to reporting. Nine days after initiation of THS 2.4 Parliament Blue the consumer lost her voice and was diagnosed with allergy and Laryngeal oedema. The severity of the events was reported as moderate. Unspecified antihistamines were administered due to the events and a positive dechallenge was reported. The events were assessed as related to the usage of the product.

As mentioned in Section 14, the AE Rash showed a 3 fold increase in the reporting rate comparing cumulative data up to 31-Dec-2016 to those up to 31-Dec-2017 being so assessed as a new open signal. During the reporting period of this SUR a total of 39 AEs of Rash have been received from 39 ICSRs. One AE was assessed as serious (case PMI002404). The SAE of Rash occurred in an 8 month-old male child who swallowed a used heating-type cigarette (amount reported as one stick) and was taken to a hospital. Gastric lavage was reported as treatment administered at the medical institution due to the events. The outcome of the event was not reported. PMI will continue regular monitoring activities of the events of Rash upon THS products use to ensure the ongoing evaluation of new safety information.

Taken together the new information received during the period covered by this SUR does not support an update of the characterization of the risk of Hypersensitivity upon THS products use, nevertheless PMI will attentively monitor the occurrence of the events of Rash upon THS products use.

15.3.1.2 Accidental exposure to product by Child

A search covering the period from 01-Jan-2017 to the DLP of this SUR (31-Dec-2017) was performed in the global safety database to retrieve data related to accidental exposure to THS products by child. The electronic search included SAEs and non-serious AEs of accidental exposure (PTs: Accidental exposure to product; Accidental exposure to product by child) from all sources for all THS products occurring in subjects of age <18 years old and belonging to the age groups adolescent, child, infant, and neonate.

During the review period of this SUR, a total of 1132 ICSRs have been received reporting 1125 AEs of Accidental exposure to product by child (1106 non-serious and 19 serious) and seven AEs of Accidental exposure to product (all non-serious and referred to children). Out of the total AEs related to Accidental exposure, 99.9% (n= 1131) have been received from Japan and 0.1% (n=1) from Greece.

In the majority of ICSRs reporting accidental exposure to product no health-related events were co-reported (No adverse event, n=930). The most frequently (>1%) health-related events co-reported with children exposition to THS products were: Vomiting (11.57%, n=131, 9 serious and 122 non-serious), Pallor (1.77%, n=20, 4 serious and 16 non-serious), and Nausea (1.24%, n= 14, 1 serious and 13 non-serious).

Accidental exposure to THS products was reported as ingestion in all reported cases. The verbatim included the wording ingestion/swallowing of EHTPs or filters, drinking liquids with EHTPs discarded, or licking EHTPs. Information provided in these ICSRs is scarce and did not allow an appropriate medical assessment.

Out of the 1132 ICSRs regarding accidental exposure to THS products by children, 19 reported SAEs: 14 medically serious with Vomiting, Malaise and Pallor as the most represented SAEs (Vomiting n=6, Malaise n=2, Pallor n=2); five which required hospitalization with Vomiting and Pallor as the most represented SAEs (Vomiting n=3, Pallor n=2). For none of the SAEs the outcome was known at the time of reporting.

As described in the *IQOS with HeatSticks* SPI version 3.0 dated 08-Nov-2017, Vomiting, Nausea, Pallor, and Malaise are signs and symptoms of nicotine intoxication which may potentially occur upon the accidental ingestion of EHTP. The evaluation of the new information received during the period covered by this SUR does not support an update of the characterization of the risk Accidental exposure to product by Child.

15.3.1.3 Burning sensation (during hot and humid weather conditions)

A search covering the period from 01-Jan-2017 to the DLP of this SUR (31-Dec-2017) was performed in the global safety database to retrieve data related to Burning sensation (during hot and humid weather conditions) upon THS products use. The search criteria was a list of

selected MedDRA PTs as follows: Burning sensation, Burning sensation mucosal, and Skin burning sensation.

The electronic search included all SAEs and non-serious events from all sources for all THS products.

During the review period of this SUR a total of 23 AEs (all non-serious) have been received in 23 ICSRs. The retrieved AEs were: Burning sensation (n=22) and Burning sensation mucosal (n=1).

All consumers were adults, 47.83% (n= 11) were male and 39.13% (n= 9) female. The gender was not reported in 13.4% (n=3) of cases.

AEs affecting face and mucosa (8.70%, n=2) might have been caused by too hot aerosol. For 91.30% (n=21) of the AEs the burning sensation affected site was not specified. Information regarding these cases is scarce and did not allow a deep root cause analysis of the burning sensation events.

The evaluation of the new information received during the period covered by this SUR does not support an update of the characterization of the risk Burning sensation (during hot and humid weather conditions).

15.3.2 New information on Important Potential Risks

15.3.2.1 Thermal Burn

A search covering the period from 01-Jan-2017 to the DLP of this SUR (31-Dec-2017) was performed in the global safety database to retrieve data related to Thermal Burn upon THS products use. The search criteria was a list of selected MedDRA PTs as follows: Airway burns, Burn oesophageal, Burn of internal organs, Burn oral cavity, Burns first degree, Burns fourth degree, Burns second degree, Burns third degree, Eye burns, and Thermal burn.

During the review period of this SUR a total of 703 AEs (all non-serious) have been received in 668 ICSRs. The retrieved AEs were: Thermal burn (n=557), Burn oral cavity (n=131), Burn oesophageal (n=10), Airway burns (n=2), Burns second degree (n=2), and Burns first degree (n=1).

The vast majority of the consumers were adults (98.29%, n=691), out of them 54.91% (n= 386) were males and 40.68% (n= 286) females. The gender was not reported in 4.41% (n=31) of cases.

AEs affecting the lips, tongue, and mouth (61.88%, n=435), oral cavity (9.39%, n= 66), oesophagus (1.42%, n=10), and face (0.14%, n=1) might have been caused by too hot aerosol. For 16.36% (n=115) of the AEs the affected site was not specified; AEs affecting fingers and/or hands (10.67%, n=75) and foot (0.14%, n=1) might be due to too hot device.

Information regarding these cases is scarce and did not allow a deep root cause analysis of the thermal burn events.

15.3.3 Update on missing information

15.3.3.1 Pregnancy and Lactation

A search covering the period from 01-Jan-2017 to the DLP of this SUR (31-Dec-2017) was performed in the global safety database to retrieve data related to pregnancy and lactation. The electronic search for pregnancy reports included all SAEs and non-serious adverse events from all sources and was carried out under the MedDRA SOC Pregnancy, puerperium and perinatal conditions and the SMQ Neonatal exposures via breast milk.

During the review period of this SUR, one spontaneous non-serious AE of exposure during pregnancy was reported in the United States (case PMI002058). The health-related events co-reported with the exposure during pregnancy to THS products were Dizziness and Nausea both assessed as moderate and non-serious and resolved at the time of reporting. The exposure (occupational exposure) in a 37 year-old 31weeks and 2 days pregnant woman part of PMI study ZRHR-ERS-09-US staff while she was physically counting the left over THS units in preparation for return to depot. The pregnancy had a successful outcome.

15.4 Characterization of Important Identified Risks

15.4.1.1 Hypersensitivity

Worldwide, the prevalence of allergic diseases has increased substantially in the last few decades[8,9]. One possible reason for such an increase might be the changing exposure to known and unknown risk factors[10] such as smoking. An increased risk of allergic diseases among individuals exposed to tobacco smoke is biologically plausible as smoking is known to facilitate sensitization to perennial indoor allergens, such as those caused by furry animals, as well as to some outdoor allergens such as pollen[11]. Smoking augments nasal responses to allergen in atopic subjects and increases IgE, immunoglobulin G4 (IgG4), and postallergen histamine levels in nasal lavage fluid[12,13]. Tobacco smoke has a number of harmful effects on the immune system,[14] *e.g.* on humoral and cellular immunity. The putative direct effect of tobacco smoke on the skin is unclear,[15] but smoke might directly impair skin-barrier function via the effects of reactive oxygen species on keratinocytes[16,17]. Several studies have assessed the association between smoking exposure and allergic diseases[18]. Nicotine replacement therapies (NRT) based on nasal inhalation of nicotine also showed hypersensitivity as a common (≥1/100, <1/10) undesirable effect (e.g. Nicorette Inhalator). The *IQOS with HeatSticks* SPI version 3.0 dated 08-Nov-2017, mentions that Hypersensitivity reactions may occur in users of THS products, in particular in those with a

past medical history of allergic condition, such as food, pet or dust allergies. In case of signs and symptoms that may indicate a serious allergic reaction, users should stop using THS products and contact their physician immediately.

To characterize this risk, a cumulative search from the IBD (04-Nov-2014) to the DLP of this SUR (31-Dec-2017) was performed in the global safety database to retrieve data on Hypersensitivity. The electronic search for Hypersensitivity included all SAEs and non-serious adverse events from all sources and for all THS products carried out under the MedDRA version 20.1 SMQ Hypersensitivity (narrow).

During the review period of this SUR, a total of 356 AEs of Hypersensitivity to THS products use (15 serious and 341 non-serious) have been received in 321 ICSRs. The 15 SAEs were: Hypersensitivity (n=6), Angioedema (n=4), Rash Generalized (n=2), Rash, Urticaria, and Laryngeal oedema (n=1 each). Out of the 15 SAEs, three were life-threatening (Hypersensitivity n=2 and Angioedema n=1) and were resolved at the time of reporting; three SAEs required hospitalization: Hypersensitivity n=2, resolved at the time of reporting and Rash Generalized (n=1) not resolved. All the other SAEs were assessed as medically serious, the outcome of four SAEs was unknown (Hypersensitivity, n=2; Rash and Urticaria n=1 each) all the rest of the SAEs were resolved at the time of reporting.

Cumulatively, the information received on the risk of Hypersensitivity reactions upon THS products use did not show a modified trend in the number of cases received, or impact on the individual or public health throughout the period going from the IBD and the DLP of this SUR. PMI will continue regular monitoring activities of the events of Hypersensitivity upon THS products use to ensure the ongoing evaluation of new safety information.

15.4.1.2 Accidental exposure to product by Child

Unintentional ingestion of tobacco products is a major reason for infant and child toxic exposures all over the world. A European retrospective study published in 2017 reported the outcomes of e-cigarette exposure incidents reported to 10 Poison Centers[32]. Out of 277 incidents analysed, unintentional exposure was the most frequently cited type of exposure (71.3%). Among all analysed poisoning incidents, 42.7% were among the children population. Exposure via ingestion was more frequent among paediatric patients (≤5 years) compared with children of 6–18 years and adults (87.0% vs. 59.3% vs. 57.6% $p < 0.001$)[32]. Similar results have been shown by a retrospective analysis of exposures associated with nicotine and tobacco products among children younger than 6 years old conducted in the United States[33,34]. Chewing tobacco (67.3%) and snuff (25.0%) accounted for most of the other tobacco product exposures[33]. Most children were exposed through ingestion (95.5%) or multiple routes including ingestion (2.8%), and only 1.7% through non-ingestion routes[33]. Infants are susceptible to accidental tobacco ingestion because of a natural curiosity and a tendency for oral exploration[35,36]. As taste discrimination develops, young children may be more attracted to flavoured tobacco products[37]. Ingestion of as little as 1 mg of nicotine by a

small child can produce symptoms such as nausea and vomiting[38]. Severe toxic effects of nicotine ingestion may include weakness, convulsions, unresponsiveness, and impaired respiration and ultimately may lead to respiratory arrest and death[38].

As described in the *IQOS with HeatSticks* SPI version 3 dated 08-Nov-2017 toxic effects of nicotine develop rapidly following acute overdose. The current data indicate that more than 500mg (6 to 7mg/kg) of acute oral nicotine is an accurate estimate of the acute lethal oral dose in adults. One EHTP contains, in average, 5 – 6mg of nicotine. The accidental ingestion of EHTP may potentially cause signs and symptoms of nicotine intoxication such as: nausea, hyper-salivation, abdominal pain, vomiting, diarrhoea, cold sweat, headache, dizziness, hearing and visual disturbances, mental confusion, tremor, weakness, weak analgesia, increase of respiratory reflex and coughing, increased bronchial secretions, increase in heart rate and blood pressure. THS products should be kept away from children. In case of accidental ingestion by children a physician should be contacted immediately.

To characterize the risk of Accidental exposure to product by Child, a cumulative search from the IBD (04-Nov-2014) until the DLP of this SUR (31-Dec-2017) was performed in the global safety database to retrieve data on accidental exposure to all THS products by child. The electronic search included all SAEs and non-serious adverse events of accidental exposure from all sources in subjects of age <18 years old and belonging to the age groups adolescent, child, infant, and neonate.

Out of the 1461 ICSRs regarding accidental exposure to THS products by children, 30 reported health-related issues assessed as serious: 22 reporting events medically serious with Vomiting, Pallor, and Malaise as the most represented SAEs (Vomiting n=10, Pallor n=2, Malaise n=2); eight reporting events which required hospitalization with Pallor and Vomiting as the most represented SAEs (Pallor n=5, Vomiting n=4).

Cumulatively, the information received on the risk of accidental exposure by child to THS products use did not show a modified trend in the number of cases received, or impact on the individual or public health throughout the period going from the IBD to the DLP of this SUR. PMI will continue regular monitoring activities of all the reported events of accidental exposure to THS products by child to assure the ongoing evaluation of new safety information.

15.4.1.3 Burning sensation (during hot and humid weather conditions)

The identified risk of burning sensation (during hot and humid weather conditions) upon THS products use is linked to the emission of hot aerosol from the device. The water in the aerosol increases heat transfer properties and, under hot and humid weather conditions, may intensify the feeling of a higher temperature of the aerosol. One CAPAs entitled "*Warm aerosol understanding and mitigation*" (Section 3) was finalized to investigate cases received regarding the burning lips from hot aerosol. Measures to prevent the hot aerosol sensation and battery leakage under high humidity conditions were implemented. As mentioned in the

IQOS with HeatSticks SPI version 3.0 dated 08-Nov-2017 THS products, users are encouraged to keep the products in a dry environment and prevent them from exposure to high humidity to help avoid the sensation of hot aerosol when using THS products.

To characterize the risk of burning sensation (during hot and humid weather conditions) a cumulative search from the IBD (04-Nov-2014) until the DLP of this SUR (31-Dec-2017) was performed in the global safety database to retrieve data on burning sensation due to the use of all THS products. A list of selected MedDRA PTs has been used in the search strategy: Burning sensation, Burning sensation mucosal, and Skin burning sensation.

The electronic search included all SAEs and non-serious events from all sources for all THS products.

Using this search strategy, a total of 26 AEs (all non-serious) of Burning sensation (during hot and humid weather conditions) using THS products use have been received in 26 ICSRs. The retrieved AEs were: Burning sensation (n=25) and Burning sensation mucosal (n=1).

All the consumers were adults, 53.85% (n= 14) were male and 34.62% (n= 9) female. The gender was not reported in 11.54% (n=3) of cases.

AEs affecting face and mucosa (7.69%, n=2) might have been caused by too hot aerosol. For 92.31% (n=24) of the AEs the burning sensation affected site was not specified. Information regarding these cases is scarce and did not allow a deep root cause analysis of the burning sensation events.

Cumulatively, the information received on the risk of Burning sensation (during hot and humid weather conditions) using THS products did not show a different trend in the number of cases received, or impact on the individual or public health throughout the period going from the IBD and the DLP of this SUR. PMI will continue regular monitoring activities on this risk to ensure the ongoing evaluation of new safety information.

15.4.1.4 Pregnancy and Lactation

All over the world, public health institutes recommends that mothers should quit using tobacco products whilst pregnant[42] being nowadays clear that maternal smoking affects foetal wellbeing and growth[43,44]. Indeed, nicotine is able to cross the placenta and therefore may affect foetal development [45]. As pregnancy and lactation constitute exclusion criteria and reason for immediate withdrawal in all completed and ongoing clinical and pre-marketing studies for THS products, its use has not been tested in pregnant and breastfeeding women. An appropriate characterization of the risks to which pregnant women are exposed while using *I* THS products might only be achieved through a long term monitoring of spontaneous cases reporting AEs associated with THS products usage within this population. Based on the current knowledge and as described in the *IQOS with HeatSticks* SPI version 3.0 dated

08-Nov-2017 pregnant and breastfeeding women should be advised against the use of THS products.

To characterize the risk associated to the use of THS products during pregnancy and lactation a cumulative search from the IBD (04-Nov-2014) until the DLP of this SUR (31-Dec-2017) was performed in the global safety database. The electronic search for pregnancy reports included all SAEs and non-serious events from all sources and was carried out under the MedDRA SOC Pregnancy, puerperium and perinatal conditions and the SMQ Neonatal exposures via breast milk.

A total of 5 ICSR (4 from studies and 1 spontaneous) reporting 4 non-serious AE of Exposure during pregnancy and 1 Maternal exposure with timing unspecified were reported. The co-reported health-related events were Dizziness, Nausea, and Occupational exposure to product, all non-serious and resolved at the time of reporting.

Cumulatively, the information received on the risk associated to the Exposure during Pregnancy and lactation to THS products did not show a modified trend in the number of cases, or impact on the individual or public health throughout the period going from the IBD and the DLP of this SUR. PMI will continue regular monitoring activities of these events to assure the ongoing evaluation of new safety information.

16 MARKET SPECIFIC SAFETY SUMMARY

If applicable a brief safety summary of Post-Market tabulated data is presented in Appendix 6 for Market Specific requests.

17 CONCLUSIONS AND ACTIONS

This SUR covers all relevant safety data received for THS products during the period from 01-Jan-2017 to 31-Dec-2017.

The evaluation of the new information received during the period covered by this SUR did not support an update of the characterization of the identified risks and missing information. Cumulatively, the information received on important identified and potential risks and missing information did not show a modified trend in the number of cases received, or impact on the individual or public health throughout the period going from the IBD until the DLP of this SUR. PMI will continue regular monitoring activities to assure the ongoing evaluation of new safety information. Taken together, the data presented in this report did not lead to any safety-related action.

The evaluation of information presented in this SUR, including data from Post-marketing Safety Surveillance (spontaneous reports) and from published literature, showed three new signals: Rash, Acne and Chest discomfort. PMI will perform monitoring activities to evaluate new safety information in order to close or refute these signals.

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19 APPENDICES

19.1 Appendix 1: Reference Safety Information

19.1.1 Appendix 1a: THS 2.2 Regular Investigator Brochure (IB) version 6.0 dated 16-Aug-2016

PMI RESEARCH & DEVELOPMENT

Investigator's Brochure

THS 2.2 Regular

Sponsor:	Philip Morris Products S.A., Research & Development
Version:	Final
Edition Number:	Edition 6
Release Date:	17 August 2016
Previous Release Date:	27 April 2015

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ABBREVIATIONS AND ACRONYMS

1-OHP	1-hydroxypyrene
2-NA	2-aminonaphthalene
3-HPMA	3-hydroxypropylmercapturic acid
3R4F	Kentucky 3R4F Reference Research Cigarette
4-ABP	4-aminobiphenyl
AE	Adverse event
BoExp	Biomarker(s) of exposure
CC	Conventional or combustible cigarette
CEMA	2-cyanoethylmercapturic acid
CI	Confidence interval
Cmax	Maximum concentration
CO	Carbon monoxide
COHb	Carboxyhemoglobin
Creat	Creatinine
CYP1A2	Cytochrome P450 1A2
ECG	Electrocardiogram
EHCSS	Electrically Heated Cigarette Smoking System
FDA	U.S. Food and Drug Administration
FD&C Act	The Federal Food, Drug, and Cosmetic Act
GVP	Gas vapor phase
HCI	Health Canada Intense
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
HPHCs	Harmful and potentially harmful constituents
ICH	International Conference on Harmonization
ISO	International Organization for Standardization
MHBMA	Monohydroxybutenyl mercapturic acid
MLA	Mouse lymphoma TK assay

MRTP	Modified risk tobacco product
NEQ	Nicotine equivalents
NFDPM	Nicotine free dry particulate matter
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
N/M	Not measured
NRT	Nicotine replacement therapy
NRU	Neutral red uptake assay
OECD	Organisation for Economic Co-operation and Development
o-tol	*o*-toluidine
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PMI	Philip Morris International
QSU	Questionnaire of Smoking Urges
RH	Relative humidity
SAE	Serious adverse event
S-PMA	S-phenylmercapturic acid
THD	Tobacco Heating Device
THS	Tobacco Heating System
TPM	Total particulate matter
t_{max}	Time to the maximum concentration
WHO	World Health Organization

1 SUMMARY

Philip Morris International (PMI) develops, assesses and commercializes a portfolio of innovative products that have the potential to reduce the risk of smoking-related diseases in comparison to combustible cigarettes (CC). Our dual objectives are to develop products that (1) significantly reduce the risk of smoking-related disease compared to continued smoking of combustible cigarettes and (2) are accepted by smokers as substitutes for combustible cigarettes.

Many harmful and potentially harmful constituents (HPHCs) in cigarette smoke are primarily formed due to the burning of tobacco [1]. Thus, lowering the temperature and heating the tobacco instead of burning it can substantially reduce levels of HPHCs. PMI's Tobacco Heating System (THS) is a novel tobacco heating system that heats a specifically designed tobacco stick within a precisely controlled temperature range (far lower temperatures than CC) rather than burning it. THS replicates the ritual of smoking but without combustion.

1.1 Description of the Product

Several menthol and non-menthol variants of the THS are available. This IB focuses on the non-menthol variants of THS 2.2, also referred as THS 2.2 Regular.

THS 2.2 is comprised of three main components: (1) the THS Tobacco Stick, which is a single-use consumable item, (2) the Holder, which provides the power source for a single use and heating control electronics, and (3) the Charger, which enables the Holder to be recharged.

To use THS 2.2, the consumer inserts the THS Tobacco Stick into the Holder to pre-heat it. Thereafter, the aerosol generated by the heating process is inhaled by placing the lips on the mouthpiece filter and drawing air through the THS Tobacco Stick. During use, the THS Tobacco Stick is heated according to a controlled temperature profile within the Holder, tobacco is heated without combustion. The temperature at which the Tobacco Stick is heated was further reduced to less than 350 °C in the current version, THS 2.2.

1.2 Non-Clinical Studies

The non-clinical assessment of THS 2.2 supported the initiation of the clinical studies described in this Investigator's Brochure. No new or increased toxicological hazard in the THS aerosol was detected compared with CC smoke. Chemical analysis confirmed that THS 2.2 aerosol has significantly lower levels of HPHCs than CC smoke. The biological activity of THS 2.2 aerosol was tested *in vitro* and *in vivo*. A number of *in vitro* assays were performed to assess the cytotoxicity and genotoxicity of the total particulate matter (TPM) and gas vapor phase (GVP) fractions of the aerosol. The subchronic toxicity of the aerosol *in vivo* was evaluated in a 90-day inhalation study in rats. *In vitro* and *in vivo* results corroborated the concept that the absence of combustion, when heating tobacco instead of burning it, substantially reduces toxic effects.

1.3 Product Experience in Humans

Several clinical studies were conducted on earlier development versions of THS 2.2, in Europe, Asia, Africa and the United States. The present IB reports the results of clinical studies conducted with THS 2.2 Regular which showed a consistent reduction in the Biomarkers of Exposure (BoExp) levels to 15 HPHCs in THS 2.2 Regular users compared to smokers continuing CC. Importantly, the magnitude of reductions when using THS 2.2 were comparable to those observed when smokers stopped smoking CC.

Two PK studies (single use) and two reduced exposure studies (5 day exposure *ad libitum*) showed that participants using THS 2.2 Regular reached nicotine levels similar to CC smoking. The nicotine uptake as well as reduction of urge-to-smoke reduction were found to be comparable to CC, thus THS 2.2 Regular offered an experience close to what smokers can expect when smoking CC. This is considered critical for adult smokers acceptance in order to offer THS as a suitable alternative to CC in the context of harm reduction strategy.

Variants of THS 2.2 Regular and THS Menthol are now marketed in several countries outside the United States.

The safety data of THS 2.2 Regular and THS Menthol reported in this IB are derived from the clinical assessment program in combination with the safety data from pre-marketing passive safety surveillance with various THS variants and post-marketing passive safety surveillance which has been put in place for THS. So far, no safety concerns for any of the variants of THS tested, including its predecessors have been revealed.

2 INTRODUCTION

2.1 Tobacco Harm Reduction

PMI's approach to harm reduction for current smokers is to develop innovative products, such as THS 2.2, to reduce the risk of tobacco-related diseases compared to CC by reducing or eliminating, to the extent possible, HPHCs in THS 2.2 aerosol. There is no 'safe' tobacco product and the best way to reduce the adverse health consequences of smoking is to quit tobacco use.

The Tobacco Advisory Group of the Royal College of Physicians opined in 2007 that "if nicotine could be provided in a form that is *acceptable and effective as a cigarette substitute*, millions of lives could be saved" [2]. The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act [3] in the US, embraces this concept. Section 911 of the FD&C Act establishes two distinct pathways for approving the marketing, sale, and distribution of MRTP. Section 911(g)(1) permits approval of a "Reduced Risk" MRTP if the manufacturer demonstrates that the product, as actually used, significantly reduces the risk of tobacco-related diseases in individual tobacco users as compared to CC and will benefit the health of the population as a whole. Section 911(g)(2) permits approval of a "Reduced Exposure" MRTP if the manufacturer demonstrates that the product reduces exposure to HPHCs and there is a reasonable likelihood that subsequent studies will demonstrate a measurable and substantial reduction in morbidity or mortality among individual tobacco users [4].

PMI intends to utilize smoking cessation/abstinence as the benchmark for assessing THS 2.2 risk reduction potential. PMI has conducted and plans to conduct more clinical studies with THS 2.2, to measure changes in blood chemistry, risk factors and health effects in smokers who switch to THS 2.2, and to compare those changes to those observed in smokers who continue smoking and in smokers who cease using tobacco products.

Finally, the impact on population harm should take into account the potential benefit to the population that the MRTP could bring. The FD&C Act indicates that individuals and the population as a whole would benefit from the introduction of an MRTP. PMI scientific assessment program is expected to generate evidence regarding the effect of a MRTP availability and marketing on tobacco product initiation, cessation, dual use, and relapse, in both individual smokers and in the population as a whole. A summary of the underlying principles of PMIscientific assessment is outlined in Table 1.

Table 1 Risk Assessment of MRTPs

Evidence	Assessments	Objectives
Hazard characterization	Physical and chemical comparison of the candidate MRTP aerosol to CC smoke	To demonstrate that the candidate MRTP aerosol contains lower levels of HPHCs than CC smoke
Toxicological evidence	*In vitro* and *in vivo* toxicological assays that can serve to demonstrate that the candidate MRTP is toxicologically less hazardous than CC in a way that may have clinical relevance	To demonstrate that the candidate MRTP aerosol is less biologically active than CC smoke and can reveal a dose response relationship
Exposure assessment	Clinical evidence that adult smokers who switch from CC to the candidate MRTP significantly reduce their levels of biomarkers of exposure (BoExp), which provide direct, quantitative evidence of the presence of exposure to HPHCs or their metabolites in the body	To provide evidence in exposure studies that subjects who switch to the candidate MRTP have lower levels of all BoExp than those who smoke CC To evaluate how measured exposure reductions compare with levels of reductions observed in subjects who cease using tobacco products altogether
Biological and functional effects	Clinical evidence from short- to long-term ambulatory clinical studies conducted under conditions of real world use of exposure reduction, and measurement of functional changes in subjects who switch from CC to a candidate MRTP. If observed changes in subjects are similar to the short- and long-term changes seen following smoking cessation, claims for candidate MRTP of reduced reduced disease risk, when compared to smoking cigarettes could be supported	To assess indicators of "exposure response", including established risk factors for smoking related diseases To compare exposure reductions, risk factor, molecular and functional changes in smokers who switch to the candidate MRTP with the changes observed in smokers who cease using tobacco products

Evidence	Assessments	Objectives
Risk characterization	Clinical, behavioral and post-market studies concerning the impact of the candidate MRTP on consumer perception, behavior, and health	To survey patterns of tobacco product consumption, perception, and understanding among adult smokers, never smokers, candidate MRTP users, and former smokers before and after a candidate MRTP is marketed

Randomized clinical studies are a central component of the THS assessment program and will advance the scientific evidence that the new candidate MRTP modifies the risk profile compared to CC use. This Investigator's Brochure supports the THS 2.2 clinical assessment program that comprises three types of clinical studies conducted on both THS 2.2 Regular and its Menthol variants:

1. Pharmacokinetic/Pharmacodynamic (PK/PD) studies.

2a. Reduced Exposure studies in confinement (up to 5 days of exposure to THS 2.2).

2b. Reduced Exposure studies in confinement with an ambulatory period (up to three months of exposure to THS 2.2).

3. Exposure Response study in ambulatory conditions (6 months of exposure to THS 2.2), followed by a 6-month extension study for subjects who agreed to extend duration of product use. A 1 year smoking cessation study was conducted in parallel to be used as a point of comparison.

The present IB intends to report clinical results on THS 2.2 Regular and provides guidance to Investigator regarding safety data (Section 6.5). The IB covers all clinical studies conducted on THS 2.2 Regular and its Menthol variants and details safety data collected from the pre-marketing and post-marketing passive safety surveillance which have been put in place for THS. Additionally, the PMI perception and behavior assessment (PBA) program studies how adult smokers of CC use THS 2.2 in a close to real-world conditions environment. Results will be made available when the study report is completed. Considering THS 2.2 is currently commercialized in a number of countries and whole offer tests as well as post-marketing studies are being conducted, it is important to have an understanding of the use and risk characterization of THS 2.2 at a larger scale level.

2.2 The Tobacco Heating System

The development of Electrically Heated Cigarette Smoking System (EHCSS) started in the 1990s, and since then, PMI has continuously improved the principle of heating versus burning tobacco in order to substantially reduce the exposure to HPHCs with THS. These developments have been ongoing through different versions and focused on:

1. Decreased formation of HPHCs by reducing and controlling the heating temperature.
2. Improved taste to the point where smokers are prepared to accept the candidate MRTP as a replacement for CC.
3. Improved convenience in use and handling.

Table 2 Evolution of the Electrically Tobacco Heating System Development

Name of the Product	Development and Commercial Status	Key Characteristics	Improvements	Aerosol Chemistry
EHCSS Series JLI	Middle of 1990s. The EHCSS Series JLI was test marketed in Richmond (USA) in 2002 as Accord® and in Osaka, Japan in 2002 as Oasis®	Energy control of the heating blades External Tobacco Stick heating Tobacco Stick design using coated cast leaf tobacco Usage limited to 8 puffs per Stick Peak temperature of the tobacco material ~ 550°C	Substantially reduced CO delivery compared to CC Sidestream smoke significantly reduced compared to CC	↓HPHC yield relative to CC
EHCSS Series K6 (also referred to as THS 1.0)	EHCSS Series K6 (THS 1.0) was test marketed in Australia and Switzerland in 2006	Change from Series JLI: Addition of a highly activated carbon filter	Improved consumer acceptability compared with the earlier versions Reduced yields of GVP HPHCs compared to EHCSS Series JLI	↓HPHC yield relative to CC
THS 2.0	Development timing 2007-2010. No commercial or marketing activity	Temperature control of the heating blade Internal THS Tobacco Stick heating THS Tobacco Stick design using shredded cast leaf tobacco Usage limited to 6 minutes Heating blade temperature of 375°C	Overall reduction of HPHC delivery compared to THS 1.0 Consumer acceptability improved (taste and ergonomics)	↓HPHC yield relative to CC ↓HPHC yield relative to THS 1.0

Name of the Product	Development and Commercial Status	Key Characteristics	Improvements	Aerosol Chemistry
		Significant device size reduction and introduction of a two-piece system including a Charger and Holder		
THS 2.1	Development in 2011	Changes from THS 2.0: Introduction of blend FR1 [1] THS Tobacco Stick design using crimped cast leaf tobacco	Increased manufacturing consistency Improved consistency of sensory experience	↓HPHC yield relative to CC Comparable HPHC yield to THS 2.0
THS 2.2	Development from 2011	Changes from THS 2.1: Optimized heater blade temperature profile and (b) (4) compared to THS 2.1	Improved puff by puff consistency and sensory satisfaction compared to THS 2.1	↓HPHC yield relative to CC Comparable HPHC yield to THS 2.0 and 2.1
		Change of tobacco blend from FR1 to Dorado II [2]. Blends demonstrated to be equivalent through a comparability protocol [5].	Blend sustainability for commercial manufacturing	Aerosol chemistry directly comparable to former blend, but very minor changes in the Tobacco Plug composition, aerosol fractions and Bill of Material

[1] Blend FR1 was used in THS versions described in the IB editions 1, 2 and 3

[2] Blend Dorado II was used in THS versions described in the IB edition 4, 5 and 6

The concept that lowering the temperature can effectively reduce the levels of HPHCs was confirmed early in tests using the first versions of the THS technology. It was also shown that such reduction in HPHCs leads to lower levels of BoExp in smokers who switched to THS and was instrumental to the decision to further develop the EHCSS.

A significant design change was made with the introduction of a two piece system of a Charger and Holder with THS 2.0, which was expected to have better user acceptance than the somewhat bulky, single piece THS 1.0 device. The temperature control and optimization was achieved through heating the THS Tobacco Stick internally instead of externally and optimal electronic control of the heating blade temperature, (b) (4)

(b) (4) (Table 2). THS has been launched under the brand name of *iQOS* in 2014 in several markets outside the United States.

3 DESCRIPTION OF THE PRODUCT

THS 2.2 has three distinct components, which perform different functions during use:

- A THS Tobacco Stick, which contains the tobacco plug.
- A Holder into which the THS Tobacco Stick is inserted.
- The Charger which is used to recharge the Holder after each use.

These three components are shown in Figure 1.

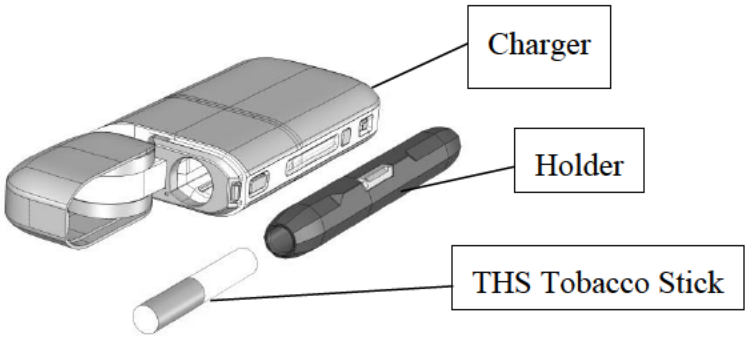

Figure 1 The Three Components of THS 2.2

3.1 The Product Components

3.1.1 The Holder

The Holder comprises 4 major components (Figure 2):

- The Casing.
- The Heater element, which is a glass-coated metallic resistive element through which electricity is passed to create the heating (heating blade).
- Control Electronics, which ensure the temperature control of the heating element and continuously measure the element temperature, allowing overheating to be detected and inhibited.
- A Battery, which stores sufficient power for a single THS Tobacco Stick use.

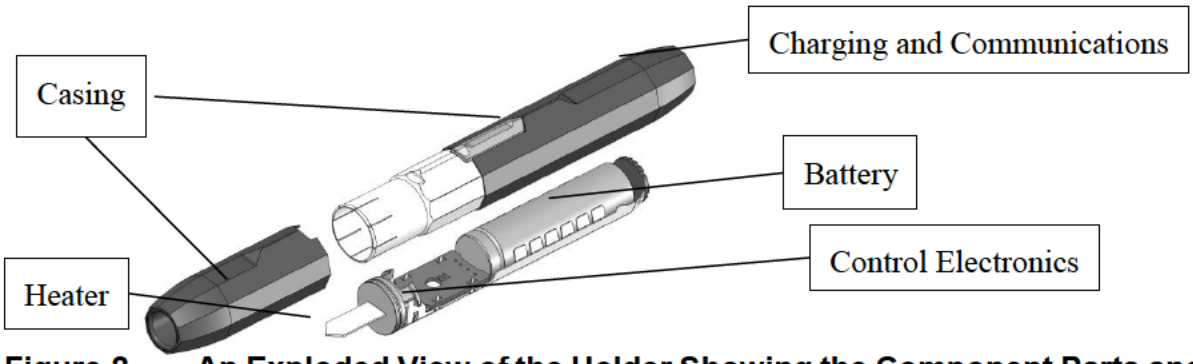

Figure 2 An Exploded View of the Holder Showing the Component Parts and Assemblies

3.1.2 The Charger

The Charger (Figure 3) is designed to be portable (approximately the size of a pack of CC) and to recharge the Holder. The Electronics regulate both the charging of the Holder battery from the Charger battery and the charging of the Charger battery from an external power source.

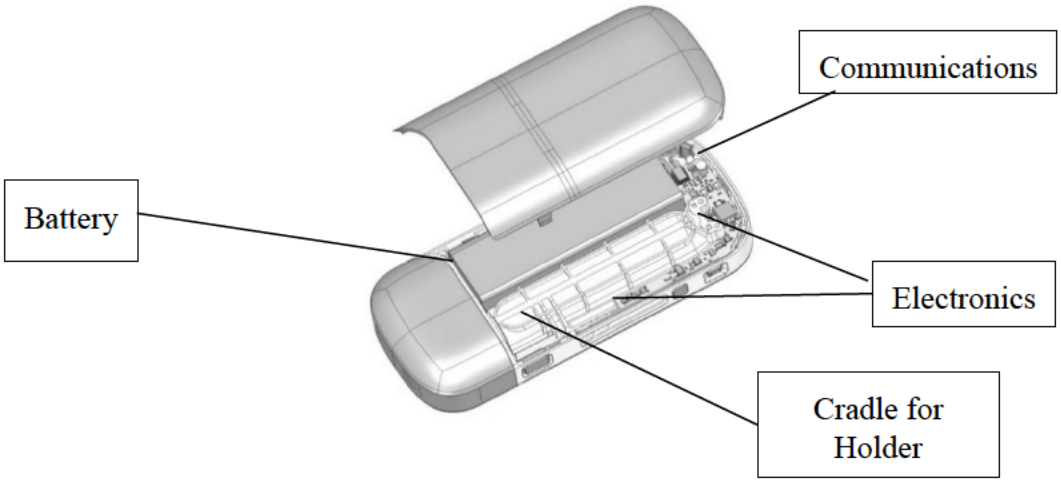

Figure 3 An Exploded View of the Charger

3.1.3 The THS Tobacco Stick

The THS Tobacco Stick is similar in basic design to a CC, but is shorter, contains less tobacco material and has an additional filter section. The THS Tobacco Stick comprises a number of elements (Figure 4):

- A Tobacco Plug manufactured from crimped, cast-leaf tobacco. Glycerin is added to the cast-leaf to facilitate aerosolization.

- A Hollow Acetate Tube which acts as a mechanical spacer between the tobacco plug and the first filter.
- A Polymer-Film Filter, which reduces primarily phenol.
- A low-density cellulose acetate Mouth Piece Filter.
- The Outer and Tipping Papers (standard papers used in CC).
- The Mouth Piece Filter.

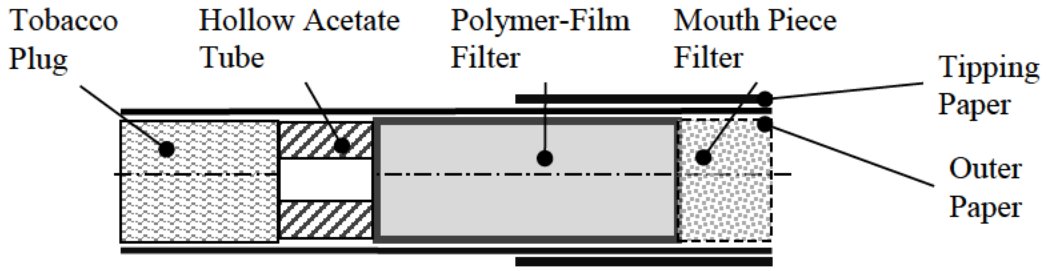

Figure 4 A Cross-Sectional Diagram of the THS Tobacco Stick

3.1.3.1 Bill of Materials

The THS Tobacco Stick is made up of elements that include those used in CCs and some new elements which have been developed specifically for the THS Tobacco Stick. All materials have been evaluated with regards to their toxicological potential and have been approved for use.

The overall composition of the THS Tobacco Stick is as shown in Table 3.

Table 3 Bill of Materials for the THS Tobacco Stick

Component	Approximate % of Total Weight [1]
Tobacco Plug	40%
Hollow Acetate Tube	10%
Polymer-film Filter	37%
Mouth Piece Filter	7%
Outer Paper	3%
Tipping Paper	2%
Adhesives	1%
Total	100%

[1] Values in this table are representative. They may slightly vary from batch to batch.

The average weights in the Bill of Materials may slightly differ from batch to batch. Only batches within specifications are released for use.

3.1.3.2 The Tobacco Plug

The tobacco plug is made from the materials shown in Table 4. Nicotine content is 4.3 – 5.4 mg per Tobacco Stick.

Table 4 Tobacco Plug Composition

Component	Approximate % of Total Weight [1]
Tobacco	64%
Glycerin (pharmaceutical grade)	17 %
Water	11.5%
Wrapper	2.6%
Guar (food grade, E412)	2.5%
Fibers	1.7%
Propylene Glycol	0.82%
Ethanol	<< 1.0%
Flavors	0.05%
Total	100%

[1] Values in this table are representative. They may slightly vary from batch to batch

The average weights in the Tobacco Plug composition may slightly differ from batch to batch. Only batches within specifications are released for use.

3.1.3.3 Aerosol Fractions Determined by International Organization for Standardization (ISO) and Health Canada Methods

Many countries require cigarette manufacturers to print the per cigarette yields of tar, nicotine, and carbon monoxide (CO) on the outside of the packaging. Per cigarette/Tobacco Stick tar, nicotine, and carbon monoxide yields are normally determined by standardized test methods. The most widely used test method is ISO 4387. PMI has developed a modified version of this method, which improves the determination of tar in products with high water content, which is typical for heated tobacco products [6]. Another method is the more intensive smoking method, Health Canada Intense (HCI) [7].

Table 5 lists ISO and HCI reported values:

Table 5 Reported Aerosol Fractions for the THS Tobacco Sticks

Constituent (mg/THS Tobacco Stick)	ISO [1]	Health Canada Intense regime [2]
/NFDPM [3]	3.44	10.48
Nicotine	0.45	1.30
Carbon monoxide	0.17	0.51

[1] International Organization for Standardization ISO machine-smoking regimen. The analytical method has been modified to avoid inaccuracies as a result of condensation from high water-content aerosols.

[2] Health Canada Intense machine-smoking regimen (55 mL puff volume, 2-second puff duration, 30-second inter-puff interval) [7]. Data collected 11/11/2014, product reference CONS.01938.RD(2)/B-13063, blend Dorado II.

[3] NFDPM: nicotine free dry particulate matter

3.2 Product Use

To use THS 2.2, the THS Tobacco Stick is inserted into the Holder. The heating of the THS Tobacco Stick is initiated by pressing the button on the Holder and an LED indicates when the initial heating process is complete.

Once initial heating is complete, the product is used in much the same way as a CC:

- The user draws air through the THS Tobacco Stick.
- This initiates the use heating cycle, which follows a puff-by-puff heating profile designed to provide a consistent user experience throughout use.

- The Holder and THS Tobacco Stick can deliver up to 14 puffs over a period of approximately 6 minutes.
- Once this cycle is complete, the Holder must be recharged and a new THS Tobacco Stick must be used.

In use, the Holder/THS Tobacco Stick combination can be held and used in a manner very similar to a CC. Detailed user manuals are provided to study sites and subjects.

3.3 Product Stability

Stability tests have been performed under three sets of 12 month storage conditions. The conditions are a) 60% relative humidity (RH), 22°C, b) 35% RH, 30°C, and c) 75% RH, 30°C. The levels of nicotine, tar, carbon monoxide, glycerin, 29 other HPHCs and 3 flavor markers were measured as well as aerosol droplet size characteristics, the basic physical characteristics of the THS Tobacco Stick, and a qualitative sensorial assessment. (b) (4)

Under condition b) the stability of TPM can be proven only until 7 months. Water and glycerin showed a consistent reduction with time, but remained within specification as did all other measurements. (b) (4)

At 6 months the stability of TPM can be proven only until 6 months, and the stability of glycerin can be proven until 9 months. Other parameters showed some variation but remained within specification [8].

The conclusion is that under normal usage conditions the THS Tobacco Sticks show some variation, but deliveries of HPHCs and general performance remain consistent over a period of 12 months.

4 NON-CLINICAL STUDIES

As described in section 1.1, the THS product consists of a THS Tobacco Stick and a THS Tobacco Stick Holder that is a separate component in which the THS Tobacco Stick is inserted in order to heat it and generate an inhalable aerosol. The initial step in the toxicological assessment process is the qualification of the materials and ingredients used in the manufacturing of the THS Tobacco Stick disclosed in the bill of material (Table 3). The qualification of the materials used in the Holder, the packaging materials and the indirect materials used in the manufacturing process are also included in the toxicological assessment process. The materials and ingredients mentioned above were toxicologically assessed and approved for their intended use.

The next step consists of the toxicological assessment of the aerosol generated from the heated THS Tobacco Stick on puffing. The endpoints for the *in vitro* part of the aerosol assessment include cytotoxicity and genotoxicity. For cytotoxicity, the neutral red uptake (NRU) assay is used, while for genotoxicity, gene mutation induced by the aerosol in bacterial and mammalian cells are evaluated with the Ames and the mouse lymphoma assay (MLA), respectively. The *in vivo* toxicological assessment includes a 90-day aerosol inhalation study in rats.

The main studies conducted for non-clinical evaluation of THS 2.2 are summarized in Table 6.

Table 6 Non-Clinical Assessment of THS 2.2

Test System	Smoke Generation Regimen	THS Tobacco Sticks Tested	Study Report Number
Smoke chemistry	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/Cast Leaf – CL/Flavor/Reynaldo	RLS-ZRH-2012-252
NRU	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/CAST LEAF – CL/Flavor/Reynaldo	RLS-ZRH-2012-249
Ames	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/CAST LEAF – CL/Flavor/Reynaldo	RLS-ZRH-2013-15
MLA	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/Cast Leaf – CL/Flavor/Reynaldo	RLS-ZRH-2012-315
90-Day inhalation study	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/Cast Leaf – CL/Flavor/Reynaldo	15006

4.1 Constituent Analysis of the THS Aerosol

The following criteria have been used consistently through the THS development program for the selection of scientifically meaningful HPHC aerosol to be monitored:

1. Priority toxicants in tobacco smoke as listed by regulatory bodies, or proposed by cognizant authorities (Food and Drug Administration (FDA) [4], World Health Organization (WHO) [9], Health Canada [10]).
2. HPHCs with established BoExp in human (smoke/aerosol constituents or metabolites).
3. HPHCs which are predominantly formed below 400°C.
4. HPHCs which are predominantly formed above 400°C.

4.1.1 Reduction of HPHCs in THS 2.2 vs. 3R4F

Heating instead of burning tobacco excludes many constituents from forming as a result of tobacco combustion. By only heating the tobacco, the number and concentration of HPHCs in the aerosol are further reduced as compared to the 3R4F reference cigarette. University of Kentucky 3R4F reference cigarette (ISO tar 7.8 mg; nicotine 0.74 mg; CO 10.7 mg) serves as an international standard for research purposes and provides a basis for comparing data collected in various laboratories. The 3R4F reference cigarettes are the third production run and are considered to be representative of the US market cigarettes [11].

The constituents generated under HCI by THS 2.2 aerosol are qualitatively and quantitatively significantly reduced compared to the HPHCs measured for 3R4F reference cigarette on an equal nicotine basis (Figure 5).

4.1.2 Product and Design Evolution

With THS 1.0, THS Tobacco Sticks were heated up to 500 °C, and subsequent developments enabled lowering the temperature for the THS 2.2 system to no more than 350 °C. When compared to its predecessors, THS 2.2 showed on a nicotine equivalent basis, similar or reduced levels of HPHCs in the generated aerosol.

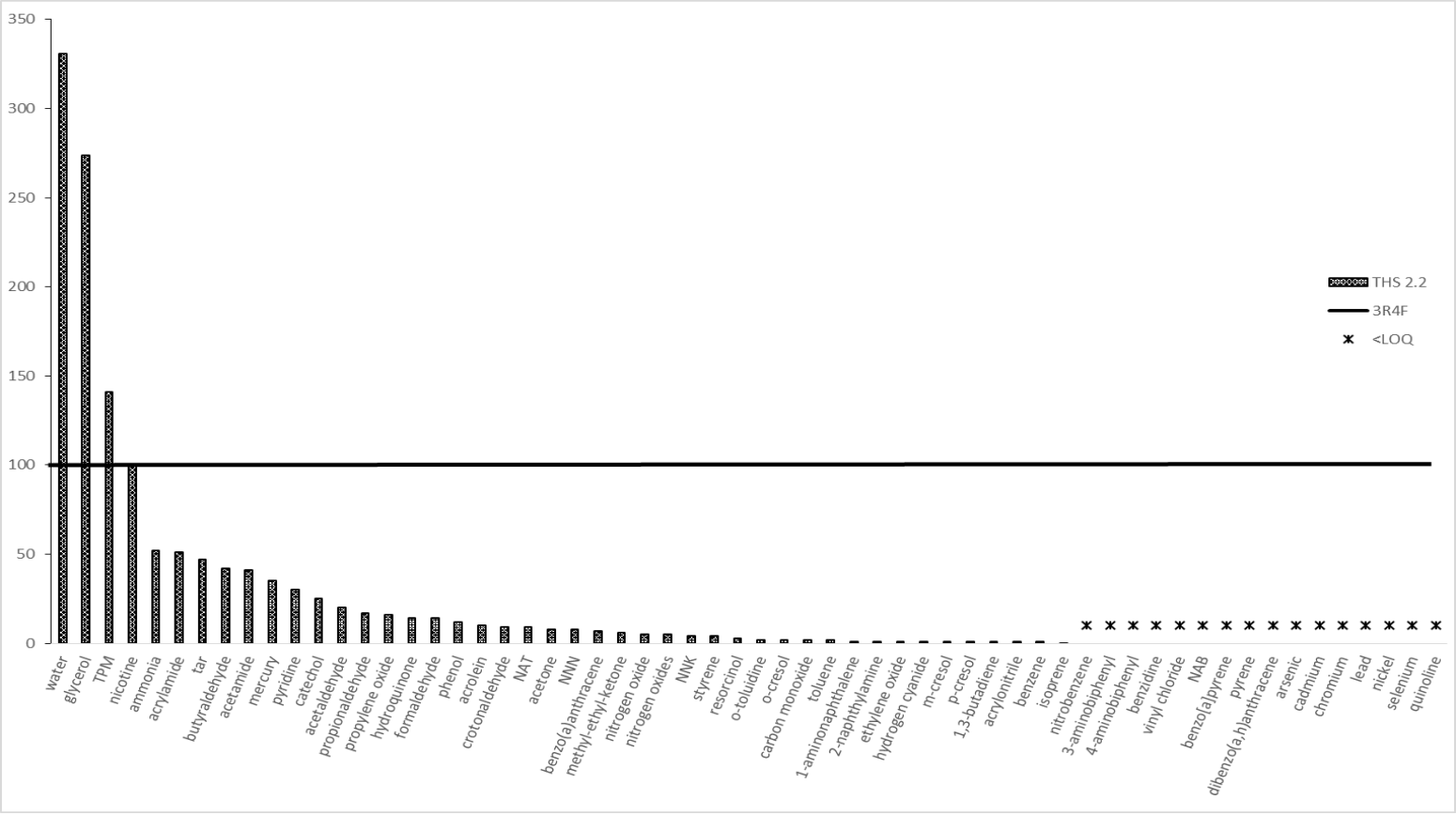

Figure 5 Comparison of Constituents of THS 2.2 to those from 3R4F, on a per mg Nicotine Basis (Constituents of 3R4F Set to 100%)

4.2 *In Vitro* Toxicology

4.2.1 Neutral Red Uptake Assay

The neutral red uptake *in vitro* cytotoxicity assay (NRU) has been widely used and accepted by the chemical and pharmaceutical industry, and by regulatory authorities, as a screening method to determine the cytotoxicity of compounds [12, 13]. It is known to be responsive to both the particle phase of CC smoke and to the GVP [14], and it can discriminate between different CC tobacco types [15, 16]. The assay is a well-established, reproducible, and standardized short-term test that responds to cytotoxic compounds in a dynamic range of five orders of magnitude [17].

On an equal nicotine basis, the cytotoxicity of TPM and GVP for THS 2.2 was lower than that from 3R4F reference cigarette when smoked under Health Canada Intense (HCI) machine-smoking regimen conditions (Figure 6).

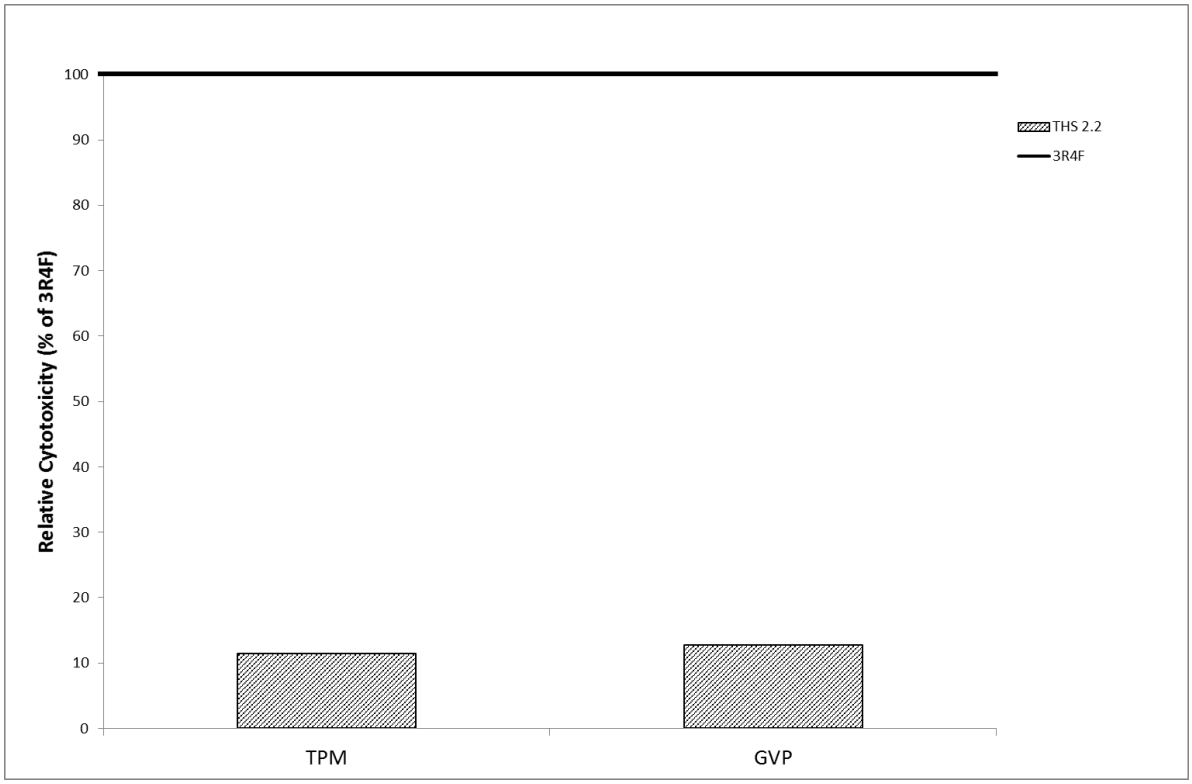

Figure 6 Relative cytotoxicity in Neutral Red Uptake Assay of TPM and GVP of THS 2.2 compared to 3R4F smoked under HCI, on an Equal Nicotine Basis

4.2.2 Genotoxicity Studies

4.2.2.1 Bacterial Reverse Mutation Test

The Salmonella reverse mutation assay (Ames assay) is recommended both by the Organisation for Economic Co-operation and Development (OECD) and International Conference on Harmonization (ICH), as part of the standard testing battery for genotoxicity [18, 19]. The Ames test can detect and discriminate the mutagenic activity of different types of CC [14, 20] with different filter ventilation, filter efficiency, and paper porosity [21], and different tobacco types and CC smoke fractions [22]. The Ames assay is sensitive to TPM from CC smoke, but the sensitivity depends on the strain and the presence or absence of a metabolic activation system (S9). The strains that are the most sensitive toward TPM are TA98, TA100 and TA1537 with S9 (TA98>TA100>TA1537). TA98, TA100 and TA1537 without S9 and TA1535 with S9 show only marginal response. TA102 with and without S9 and TA1535 without S9 are not responsive to TPM [23].

The TPM (up to 2.5 mg/plate) and the GVP (up to 3.0 mg/plate) from THS 2.2 did not show any mutagenic activity in the different strains tested in presence or absence of S9 (data not shown). The TPM (from 50 µg/plate) and the GVP (from 200 µg/plate) from 3R4F were however reported as mutagenic in absence and presence of S9.

4.2.2.2 Mouse Lymphoma TK Assay

The mouse lymphoma TK assay (MLA) is recommended both by the OECD [24] and ICH [18], as part of the standard testing battery for genotoxicity. MLA measures the induction of forward mutations at the tk-locus in L5178Y/tk+/-3.7.2C mouse lymphoma cells. The response to TPM is in general very low, only up to a 3- to 5-fold increase over the background mutant frequency [25, 26], but the assay can nevertheless discriminate the mutagenic activity of different tobacco types [27].

On a nicotine equivalent basis, the relative mutagenicity of TPM and GVP from THS 2.2 was substantially lower than 3R4F with or without metabolic activation (S9) (Figure 7).

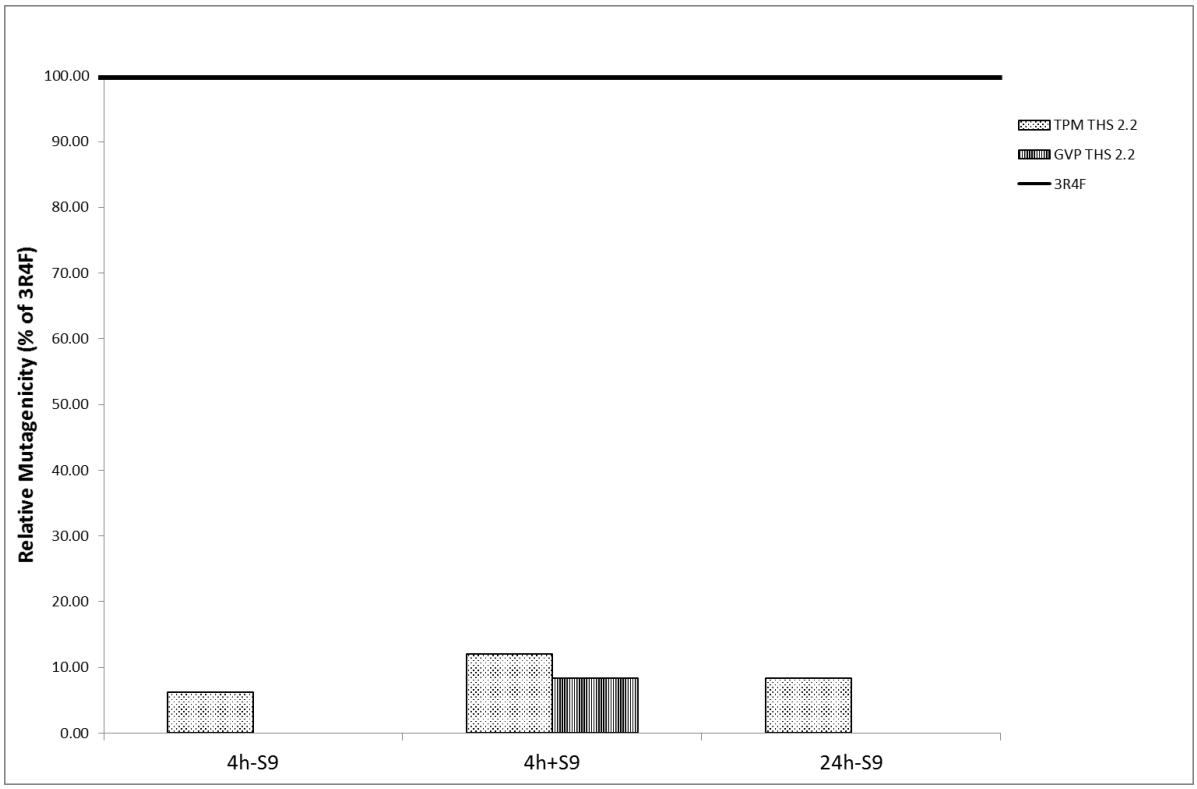

Figure 7 Relative Mutagenicity in MLA of TPM and GVP of THS 2.2 Compared to 3R4F Smoked Under HCI, on an Equal Nicotine Basis, with and without S9 Metabolic Activation

4.3 *In Vivo* Toxicology

4.3.1 90-Day Rat Inhalation Study

Previous studies showed that a 90-day rat inhalation study is a suitable model for the detection of diluted mainstream smoke-related changes in systemic toxicity and histopathology of the respiratory tract [20, 28, 29]. The inhalation toxicity of THS 2.2 was investigated after sub-chronic exposure to the mainstream aerosol. The biological activities of the THS 2.2 aerosol were compared with those of 3R4F. The toxicological activity was determined in basic conformity with OECD guideline 413 with regard to the following parameters: body weight, food consumption, ophthalmologic changes, clinical observations, clinical chemical and hematological parameters, gross pathological observations, organ weights, and histopathological changes in the respiratory tract [30].

Aerosol generation was reproducible throughout the exposure period and the THS 2.2 Regular aerosol was demonstrated to be efficiently taken up by the animals as indicated by the biomonitoring parameters. Results of carboxyhemoglobin, nicotine and other urinary aerosol constituent metabolites correlated well with the constituents concentrations in the test atmospheres.

The overall evaluation of the data, summarized in Table 7, indicates that exposure to THS 2.2 aerosol induces less inflammation and fewer degenerative changes to the respiratory tract organs and does not result in additional hazards to those presented by smoking CC.

Table 7 Systemic Toxicity and Histopathology of Male and Female Rats Exposed to Mainstream Smoke from 3R4F and Mainstream Aerosol form THS 2.2 in a 90-Day Inhalation Study

Findings [1]	3R4F	THS 2.2
Death	No death related to exposure up to 23 µg/L nicotine in test atmosphere	No death related to exposure up to 50 µg/L nicotine in test atmosphere.
Body weight	Reduced body weight gain.	Reduced body weight gain but less pronounced compared to 3R4F.
Organ weight	Dose-dependent increase of lung, larynx and trachea weight. Increase of liver weight at 23 µg/L nicotine. Increase of adrenal gland weight. Dose-dependent decrease of thymus and uterus weight.	Increase in lung, larynx and trachea weight less pronounced when compared to 3R4F. Increase of liver weight at 23 and 50 µg/L nicotine. Increase of adrenal gland weight. Decrease in thymus weight less pronounced than 3R4F. Dose-dependent decrease of uterus weight.
Respiratory physiology	Dose-dependent reduction in respiratory minute volume.	No change in respiratory minute volume.
Lung inflammation	Dose-dependent increase in immune cell counts present in bronchoalveolar lavage.	Minimal increase in immune cell counts present in bronchoalveolar lavage.
Clinical Chemistry	Dose-dependent increase in liver enzymes.	Dose-dependent increase in liver enzymes.

Findings [1]	3R4F	THS 2.2
Histopathology	Nose: Reserve cell hyperplasia of the respiratory epithelium. Squamous epithelial metaplasia of the respiratory epithelium and olfactory epithelium. Ulceration and atrophy of olfactory epithelium. Larynx: Squamous epithelial metaplasia at base and distal base of epiglottis. Hyperplasia of squamous epithelium of vocal folds. Epithelial thickness at the floor of the larynx and at the lower medial region of vocal cords. Tracheal ring and bifurcation: Reserve cell hyperplasia. Goblet cell hyperplasia at tracheal epithelium. Lung: Presence of macrophages with and without yellow pigmentation in the alveolar lumen. Presence of neutrophilic granulocytes in the alveolar lumen. Goblet cell hyperplasia at the main bronchus.	Significantly decreased histopathological changes compared to 3R4F.

[1] Study was performed in rats according to OECD TG 413 (2009); 90-day inhalation period, exposure for 6 h/d, 5 d/wk. Groups: sham, low, medium and high nicotine both for CC and THS 2.2. Three groups (sham, high CC and high THS 2.2) were kept for a 42 days post-inhalation period.

In conclusion, exposure to the mainstream aerosol from THS 2.2 Regular did not cause additional toxicity when compared to the smoke from the 3R4F reference cigarette. Moreover, the overall biological activity of the THS 2.2 Regular aerosol with respect to the toxicity on respiratory tract organs was significantly decreased in comparison to 3R4F cigarette smoke.

4.4 Conclusions

By heating instead of burning tobacco, the aerosol composition of the THS Tobacco Stick becomes less complex than CC smoke, and measured HPHCs are either substantially reduced or undetectable. It is, however, acknowledged that not all possible HPHCs in CC smoke are known and can be analytically measured.

Even if the contribution of a single constituent to the induction of a smoking related disease is not known and needs to be further investigated, it is reasonable to assume that exposure to a less complex mixture and a substantial reduction in the measured HPHCs leads to a reduced toxicological hazard compared to CC smoke.

THS 1.0 and 2.1 were improved in design and features for consumer use. The heating profile was further optimized and controlled and the heating temperature was decreased. These

changes resulted in even greater reductions of the levels of some HPHCs present in THS 2.2 aerosol compared to former versions, leading to reduced *in vitro* cytotoxicity and genotoxicity in standard biological assays.

Furthermore, the 90-day inhalation studies in rats revealed less toxicological effects in the respiratory tract from exposure to THS 2.2 aerosol compared with exposure to CC smoke.

In summary, the results of chemical, in *vitro* and *in vivo* toxicological assessment of THS 2.2 and consistent results throughout the evolution of the THS support the conclusion that adult smokers switching to THS 2.2 in clinical studies will not be exposed to new or increased hazard compared to continuous CC use.

5 PRODUCT EXPERIENCE IN CURRENT SMOKERS

Several clinical studies with THS have been conducted by PMI and Philip Morris USA from 2004 to 2008. Extensive data are available for THS 1.0, the EHCSS Series K6, and its predecessors, EHCSS Series E4 and EHCSS Series JLI. The clinical experience ranged from short-term studies in confinement to long-term studies in an ambulatory setting. In 2012, PMI conducted two exploratory clinical studies; one short-term PK/PD and one Reduced Exposure with THS 2.1.

PMI's phased approach includes first assessing THS 2.2 in relatively short-term studies and then gradually expanding the duration and resemblance to actual use in real world conditions in the global clinical THS development program. The list of all clinical studies performed with THS 2.2 using Regular or Menthol Tobacco Sticks is provided in Table 8. The conduct phase of all studies, except ZRHR-ERS-09-US and ZRHR-ERS-09-EXT-US, is completed and results of the studies with THS 2.2 Regular are now summarized in this edition of the IB (section 5). A summary of the safety findings are reported for the studies with both THS 2.2 Regular and Menthol (section 5).

All clinical studies were conducted in accordance with the Declaration of Helsinki that was effective at the time of each conducted study and were approved by an Ethic Committee. They were conducted following the Good Clinical Practice guideline [31].

Table 8 List of PMI's Clinical Studies Conducted With THS 2.2 Regular or Menthol

Study Code	Variant	Country	Exposure Duration	N [1]	Study Type	ClinicalTrial.gov Identifier Status
ZRHR-PK-01-EU	THS 2.2 Regular	UK	Single use	62	PK/PD	NCT01967732 Completed
ZRHR-PK-02-JP	THS 2.2 Regular	JP	Single use	62	PK/PD	NCT01959607 Completed
ZRHM-PK-05-JP	THS 2.2 Menthol	JP	Single use	62	PK/PD	NCT0196770 Completed
ZRHM-PK-06-US	THS 2.2 Menthol	US	Single use	62	PK/PD	NCT01967719 Completed
ZRHR-REXC-03-EU	THS 2.2 Regular	PL	5 days	160	Reduced Exposure (Confinement)	NCT01959932 Completed

Study Code	Variant	Country	Exposure Duration	N [1]	Study Type	ClinicalTrial.gov Identifier Status
ZRHR-REXC-04-JP	THS 2.2 Regular	JP	5 days	160	Reduced Exposure (Confinement)	NCT01970982 Completed
ZRHM-REXA-07-JP	THS 2.2 Menthol	JP	90 days	160	Reduced Exposure (Confinement and ambulatory)	NCT01970995 Completed
ZRHM-REXA-08-US	THS 2.2 Menthol	US	90 days	160	Reduced Exposure (confinement and ambulatory)	NCT01989156 Completed
ZRHR-ERS-09-US	THS 2.2 Regular	US	26 weeks	950 [2]	Reduced Exposure (ambulatory)	NCT02396381 Ongoing
ZRHR-ERS-09-EXT-US	THS 2.2 Regular	US	26 weeks	665 [3]	Reduced Exposure (ambulatory)	NCT02649556 Ongoing

[1] Number of randomized subjects

[2] Targeted number of subjects

[3] Targeted number of subjects (i.e. 30% of the N in ZRHR-ERS-09-US)

5.1 PK/PD Clinical Studies with THS 2.2 Regular

Studies ZRHR-PK-01-EU and ZRHR-PK-02-JP were randomized, controlled, crossover studies investigating the nicotine PK profile and safety data of THS 2.2 following singe use in smoking healthy subjects compared to CC and nicotine nasal spray (NNS) or nicotine gum.

In the ZRHR-PK-01-EU study, amount of plasma nicotine absorbed expressed as C_{max} and $AUC_{0\text{-}last}$ was lower (22 and 25% respectively) for THS 2.2 compared to CC, while they were comparable in the ZRHR-PK-02-JP study (Table 9). Time to Maximal concentration (t_{max}) of nicotine was reached after six minutes for both tobacco products, in each study. In ZRHR-PK-01-EU, THS 2.2 C_{max} was 3 times higher than that of NNS, with a comparable time to Maximum concentration (t_{max} of 7 minutes for THS 2.2 and 8 minutes for NNS). In ZRHR-PK-02-JP, the nicotine absorption was higher and faster (t_{max} of 6 vs 36 minutes, respectively) following THS 2.2 use compared to nicotine gum.

Table 9 AUC and Cmax Analysis of Nicotine Plasma Concentrations After Single Use of THS 2.2 and CC

	Study	THS Geometric Mean	CC Geometric Mean	Ratio	95% CI Lower bound	95% CI Upper bound	Precision (%)
C_{max} [ng/mL]	PK-01-EU	9.62	12.42	77.43	62.69	95.63	18.20
	PK-02-JP	14.30	13.82	103.50	84.94	126.11	22.61
$AUC_{(0\text{-last})}$ [ng/mL]	PK-01-EU	15.10	20.28	74.47	61.52	90.14	15.67
	PK-02-JP	23.75	24.66	96.34	85.10	109.07	12.72

The total urge-to-smoke score profile over 12 hours post start of product use, as assessed by the brief questionnaire of smoking urges (QSU-brief) [32], was similar across studies following THS 2.2 and CC use, with comparable maximum reduction from baseline observed 15 minutes after that start of product use for both products in the two studies. The total urge-to-smoke score profile over 12 hours post start of product use was similar following THS 2.2 and NNS use in ZRHR-PK-01-EU, but was different between THS 2.2 and NRT gum during the first 2-4 hours post-product use in ZRHR-PK-02-JP with lower total urge-to-smoke score for THS 2.2.

5.2 Reduced Exposure Clinical Studies with THS 2.2 Regular

5.2.1 Biomarkers of Exposure

PMI has established validated analytical methods to measure BoExp to 16 HPHCs in addition to nicotine, selected mainly from the FDA abbreviated list of 18 HPHCs [4, 33], but also from the WHO initial list of toxicants [9], in order to demonstrate reduced exposure in subjects using THS 2.2 as compared to when smoking CC. The BoExp assessed in PMI clinical studies cover all five major risks stipulated by FDA including carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, and addiction potential [4]. Exposure to nicotine is presented in Section 5.2.3.

The two ZRHR-REXC-03-EU and ZRHR-REXC-04-JP were randomized, open-label, 3-arm, parallel group *ad libitum* product use studies, comparing levels of reductions in BoExps to 16 HPHCs in smoking, healthy subject switching to THS 2.2 with subjects continuing to use conventional cigarettes or stopping smoking. Subjects were confined in a controlled environment for nine days, with the exposure or abstinence period lasting for 5 days.

At the end of the two studies, on day 5, the levels of 15 BoExps were reduced by at least 47% (3-HPMA) and up to 96% (1-NA) (Table 10). The reductions from baseline were comparable between the THS and SA arms (Figure 8). There was no notable difference in S-BMA levels

between the CC, THS 2.2 and smoking abstention groups. It would appear that although S-BMA has been described as being a valuable BoExp to measure occupational exposure to toluene [34, 35], this BoExp is not a "fit-for-purpose" BoExp to measure exposure to toluene when the goal is to discriminate smokers from non-smokers.

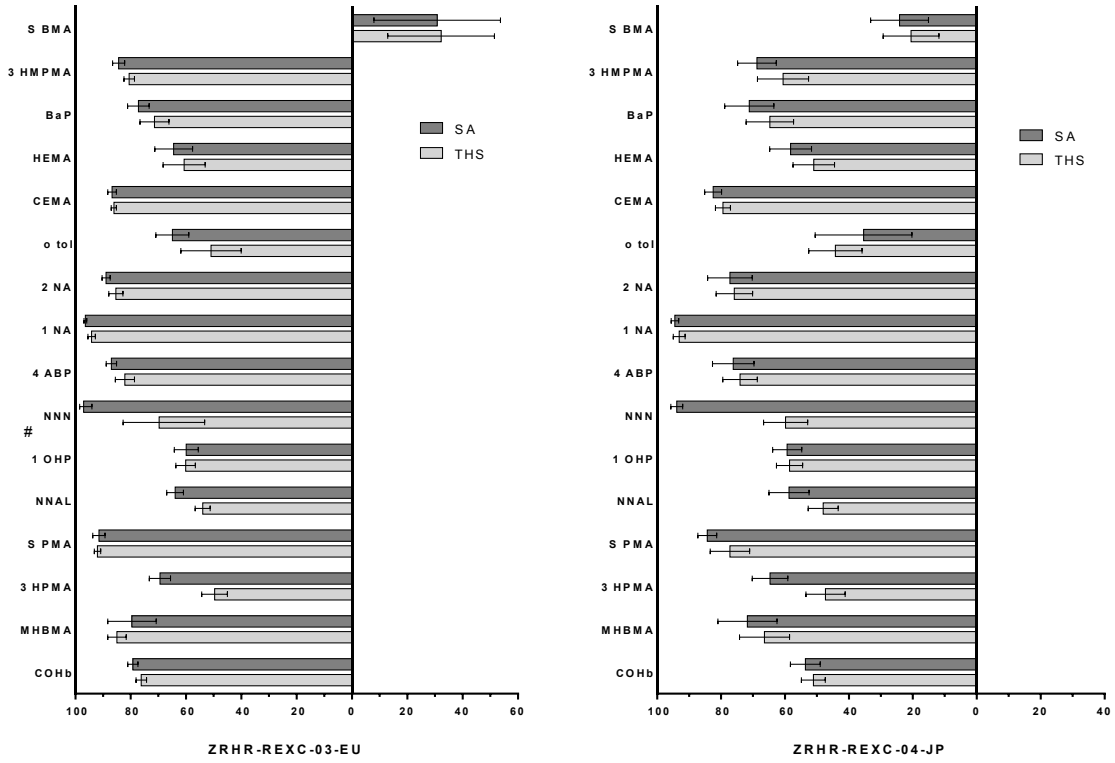

Figure 8 Percent Changes from Baseline and 95% CI in Biomarkers of Exposure in THS 2.2 Regular at Day 5 of the Two Reduced Exposure Studies

Carboxyhemoglobin (COHb), monohydroxybutenyl-mercapturic acid (MHBMA), 3-hydroxypropyl-mercapturic acid (3-HPMA), S-phenyl-mercapturic acid (S-PMA), (7) total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), total 1-hydroxypyrene (1-OHP), total N-nitrosonornicotine (NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), o-toluidine (o-tol), 2-cyanoethylmercapturic acid (CEMA), hydroxyethylmercapturic acid (HEMA), hydroxy-benzo[a]pyrene (BaP), 3-hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA), S-benzyl mercapturic acid (S-BMA), nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide.

Change from Baseline was calculated from the median value

Table 10 Biomarkers of Exposure after Switching to THS 2.2 – Levels of Reduction Compared to CC Smoking at Day 5

HPHC (organ class toxicity)	Acrolein (RT, CT)	Pyrene Surrogate for PAH	NNK (CA)	Benzene (CA, CT, RDT)	CO (RDT, CT)	1,3-Butadiene (CA, RT, RDT)	4-Aminobiphenyl (CA)	o-Toluidine (CA)	Crotonaldehyde (CA)	1-Aminonaphthalene (CA)	2-Aminonaphthalene (CA)	Acrylonitrile (CA, RT)	B[a]P (CA, RT)	Ethylene oxide (CA, RT, RDT)	NNN (CA)	Toluene (RT, RDT)
BoExp	**3-HPMA[1]**	**1-OHP[2]**	**Total NNAL[3]**	**S-PMA[4]**	**COHb[5]**	**MHBMA[6]**	**4-ABP[7]**	**o-TOL[8]**	**3-HMPMA[9]**	**1-NA[10]**	**2-NA[11]**	**CEMA[12]**	**3-OH-B[a]P[13]**	**HEMA[14]**	**Total NNN[15]**	**S-BMA[16]**
ZRHR-REXC-03-EU	-58%	-56%	-56 %	-94%	-77 %	-92%	-85 %	-58%	-77%	-96%	-88%	-87%	-73%	-68%	-76%	+10%
ZRHR-REXC-04-JP	-47%	-54%	-51 %	-84%	-53 %	-77%	-82 %	-49%	-62%	-96%	-82%	-79%	-70%	-54%	-70%	-16%

(1) 3-hydroxypropyl-mercapturic acid; (2) total 1-hydroxypyrene, (3) total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, (4) S-phenyl-mercapturic acid, (5) carboxyhemoglobin, (6) monohydroxybutenyl-mercapturic acid, (7) 4-aminobiphenyl, (8) o-toluidine, (9) 3-hydroxy-1-methylpropyl-mercapturic acid, (10) 1-aminonaphthalene, (11) 2-aminonaphthalene, (12) 2-cyanoethylmercapturic acid, (13) 3-hydroxy-benzo[a]pyrene, (14) 2-hydroxyethylmercapturic acid, (15) Total N-nitrosonornicotine, (16) S-benzylmercapturic acid; Organ class toxicity as defined by FDA [4]: AD: addictive; CA: carcinogen; CT: cardiovascular toxicant; RDT: reproductive and developmental toxicant; RT: respiratory toxicant. BoExp for addiction potential (AD) "Nicotine" and its metabolites is measured in each study

5.2.2 Product Consumption and Subjective Effects

In the ZRHR-REXC-03-EU study, the average number of THS Tobacco Sticks consumed increased from 16.0 CC/day at baseline to 20.7 THS Tobacco sticks/day at Day 5. In the CC arm, the number of CC consumed daily remained stable (16.2 CC/day at baseline and 16.5 CC/day at Day 5). The number of THS Tobacco Sticks increased from baseline to Day 5 while the NEQ concentration adjusted to creatinine remained comparable throughout the study (section 5.2.3).

In the ZRHR-REXC-04-JP study, the number of THS Tobacco Sticks consumed in the THS 2.2 arm decreased from baseline to Day 1, with a daily consumption from Day 2 onwards comparable to baseline (10.3 cigarettes/day). In the CC arm, daily consumption increased from baseline (10.5 cigarettes/day) to Day 5 (12.5 cigarettes/day). In addition, product consumption was consistently higher in CC compared to THS. Despite the change in the number of THS Tobacco Sticks from baseline to Day 5, the exposure of subjects to nicotine remained comparable between the CC and THS arms (section 5.2.3).

There were no notable differences between the urge-to-smoke total scores for THS compared to CC in the two studies.

The difference of consumption of THS Tobacco Sticks as compared to CC, and potentially of subjective effects, likely reflects an adaptation process due to switching from CC to THS 2.2. Also, different sensorial characteristics compared to the subjects' preferred CC brand can contribute to the change in consumption pattern and product satisfaction.

5.2.3 Nicotine Equivalents (NEQ)

Excretion of nicotine and its metabolites in urine are well-established tobacco-specific BoExp to nicotine [36]. On a quantitative basis, the measured concentration of the molar sum of nicotine, cotinine, trans-3'-hydroxycotinine, and their respective glucuronide conjugates, expressed as NEQ in 24-h urine, provides an estimate of up to ~85% of total nicotine uptake and excretion in smokers [37].

The profiles of NEQ levels were overall comparable between the THS and CC arms, with differences mainly observed during the first two days of the studies (Figure 9). NEQ levels were much higher in the European subjects than in the Japanese, explained by a difference in smoking behavior, as evidenced by higher product consumption in the European subjects at baseline (Figure 9).

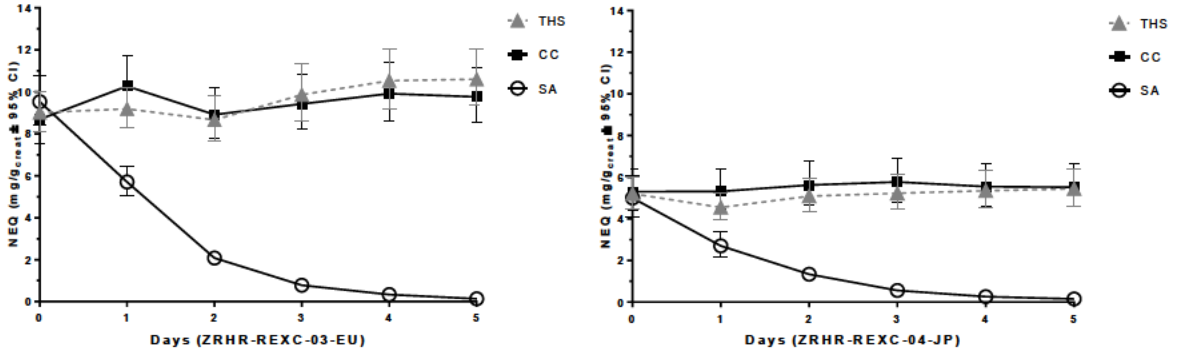

Figure 9 Urinary NEQ Levels Throughout the Studies (mg/g_{creat})

5.3 Adverse Events Reported During THS Clinical Studies

In order to provide comprehensive safety information, this section describes the most commonly reported adverse events during THS clinical studies with the Regular (non-menthol) flavor variant, as well as with the menthol flavor variant.

5.3.1 THS 1.0 and its earlier development versions

In total, around 655 subjects were exposed to THS 1.0 and its earlier development versions, namely EHCSS-K4 and EHCSS-JLI. Table 2 details the evolution of the Electrically Heated Cigarette Smoking System (EHCSS) development.

The most commonly reported AEs that were considered related to THS 1.0 or its earlier development versions were dry mouth, dry throat, lip ulceration, cough and diarrhea.

5.3.2 THS 2.1 Regular

In total, 75 subjects were exposed to THS 2.1. No Serious Adverse Events (SAEs) were reported for subjects exposed to THS 2.1. The most frequently reported AEs were nausea, headache, dizziness and presyncope in study ZRHX-PK-02 and increased blood triglycerides and oropharyngeal pain in study ZRHX-EX-01. Of note, a total of six presyncope events were experienced by five subjects (one subject after THS 2.1 exposure and four subjects after CC use) in study ZRHX-PK-02. It was suggested by the investigator that a light breakfast be allowed before product use in future studies to prevent such events.

5.3.3 THS 2.2 Regular and THS 2.2 Menthol

Among the 939 smokers enrolled in the so far completed clinical studies with THS 2.2 Regular and THS 2.2 Menthol, a total of 566 smokers were exposed to THS 2.2 Regular or THS 2.2 Menthol variant.

In the 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, a 36-year-old woman who stopped metformin treatment before the use of one THS Tobacco Stick.

Most commonly reported all-cause adverse events in the 5-day and 3-month studies are summarized in Table 11, Table 12, Table 13 and Table 14.

Table 11 Most commonly reported all-cause Adverse Events in ZRHR-REXC-03-EU (THS 2.2 Regular)

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
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%)

Table 12 Most commonly reported all-cause Adverse Events in ZRHR-REXC-04-JP (THS 2.2 Regular)

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
Blood triglycerides increased	2 (2.5%)	2 (5.0%)	-

Table 13 Most commonly reported all-cause Adverse Events in ZRHM-REXA-07-JP (THS 2.2 Menthol)

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
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%)

Table 14 Most commonly reported all-cause Adverse Events in ZRHR-REXA-08-US (THS 2.2 Menthol)

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
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%)

Investigational product-related adverse events reported in single use cross-over studies were nausea and vomiting, presyncope, dizziness, dysphoria, headache, pallor and hepatic function abnormal and they were all mild or moderate in severity (see also section 6.5). Apart from hepatic function abnormal, other THS-related AEs are symptoms which may be associated with mild nicotine overdose. The abnormal hepatic function was observed in one subject 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.

THS-related adverse events reported during 5-day and 3-month use were spirometry abnormal, cough, vertigo, carbon monoxide diffusion capacity decreased, diarrhea, dry mouth, hyperhidrosis, hypertriglyceridemia, musculoskeletal chest pain, myocardial ischemia, non – cardiac chest pain, oral pain and oropharyngeal pain. None of these AEs were severe in intensity. The myocardial ischemia was observed in a 38-year old subject (20-year smoking history and actual CC smoking >19 CC per day) included in a 5-day use study. At Day 6, interpretation of ECG data for this subject 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.

5.4 Pre-Market Experience

Since May 2014, PMI has implemented a study-specific passive safety surveillance mechanism in some field market research studies and in human studies part of the Perception and Behavior Assessment program, when THS was used. 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.

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.

As of 31-Dec-2015, a total of 5948 participants participated in several human studies utilizing a passive safety surveillance approach and 4079 used the THS regular variants, with overall 5.7% AEs reporting rate.

Most commonly reported AEs during passive surveillance in premarket studies as of 31-Dec-2015, are listed in Table 15.

Table 15 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%

In a systematic review and meta-analysis of 120 NRT clinical trials involving 177,390 individuals [38], a number of side effects were significant 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 odd 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.

Thus, 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.

5.5 Market Experience

THS Regular and Menthol variants are currently marketed in several countries outside USA since November 2014, and 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.

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

Since first THS marketing in November 2014 and up to 31-Dec-2015, a total of 174 THS (Regular or Menthol)-emergent AEs were spontaneously reported by consumers, corresponding to a reporting rate below 3 AEs per 10,000 consumers.

The ten most commonly reported THS (Regular and Menthol)-emergent AEs during post market passive surveillance are listed in Table 16.

Table 16 Ten Most Commonly Reported AEs from Postmarket Passive Safety Surveillance

Adverse Event Preferred Term	THS Regular and Menthol variants 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%

5.6 Conclusions

Several clinical studies were conducted on earlier development versions of THS 2.2, in Europe, Asia, Africa and the United States. The present IB reports the results of clinical studies conducted with THS 2.2 Regular which showed a consistent reduction in the BoExp levels to 15 HPHCs in users of THS 2.2 compared to smokers continuing CC. Importantly, the magnitude of reductions when using THS 2.2 were comparable to those observed when smokers stopped smoking CC. The results of the clinical studies in combination with the results of the non-clinical assessment, substantiate the principle of heating vs. burning tobacco, which was developed with the aim of reducing exposure to HPHCs in THS 2.2 aerosol.

Two PK studies (single use) and two reduced exposure studies (5 day exposure *ad libitum*) showed that participants using THS 2.2 Regular were able to reach nicotine levels similar to CC smoking. Product acceptability as measured by nicotine uptake and reduction of urge-to-smoke is comparable to CC, thus THS offered an experience close to what smokers expect when smoking CC.

From a medical judgement point of view, the observed adverse events associated or related to THS 2.2 indicates no higher or new safety risks than with CC.

In summary, the clinical study results support the ongoing comprehensive clinical assessment program with THS 2.2.

6 GUIDANCE FOR THE INVESTIGATOR

6.1 Target Populations

The target population for THS 2.2 is adult smokers.

6.2 Use of Product

To use THS 2.2, the consumer inserts the THS Tobacco Stick into the Holder to pre-heat it. Thereafter, the aerosol is inhaled by placing the lips on the THS Tobacco Stick mouthpiece and drawing air through the THS Tobacco Stick. Subjects need to be informed about the correct use of the product and the associated main unit. Once the Holder is switched on, the user can puff for approximately six minutes (although approximately 20 seconds of this six-minute period is for heating). The THS 2.2 Holder may warm up slightly when in use. A detailed user manual will be provided at the study sites and to subjects.

6.3 Product Variants

The THS 2.2 Holder, Charger, and accessories, which have been tested in non-clinical and clinical studies was THD Model 2.2. THS Tobacco Sticks are available in non-menthol and menthol options. This Investigator's Brochure describes the Regular variant of the THS Tobacco Sticks.

6.4 Warnings and Precautions

6.4.1 Smoking-related diseases

Although all results obtained to date show that heating instead of burning tobacco reduces the levels of HPHCs in THS aerosol compared to CC smoke, given the current state of knowledge of THS 2.2, it has not been demonstrated that THS products reduce the risk of developing smoking-related diseases compared to CC. Cigarette smoking causes cancer, pulmonary diseases, cardiovascular diseases, and many other related diseases. Smoking cessation has multiple benefits and is, by far, the best way to reduce any risks of developing such diseases.

Smoking-attributable morbidity and mortality reversibility upon smoking cessation is not immediate and takes years if not decades to return to the level of risk of a non-smoker [39]. As a consequence, the occurrence of these smoking-attributable diseases and their signs and symptoms are expected, as smoking has a very long half-life for effects.

6.4.2 Product use behavior

Based on the results of the clinical studies on nicotine absorption and exposure with THS 2.1 and THS 2.2, it can be expected that THS is similar to CC with regard to nicotine uptake when used *ad libitum*. Measures on subjective effects e.g., urge-to smoke, withdrawal symptoms,

product evaluation, illustrated that THS products offered a close experience to what was observed in smokers when smoking CC. Due to sensorial and technological differences between THS products and CC, smokers may adapt their product use behavior and consume more THS Tobacco Sticks than CC, without increase in overall nicotine exposure (section 5.1). The confinement setting, in which these studies were conducted, may also have an influence on product use behavior, explaining an increase in CC use.

6.4.3 Mild nicotine over-exposure

A smoker using THS 2.2 may experience transient symptoms suggesting mild nicotine 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, increased bronchial secretions, increase in heart rate and blood pressure) due to the stimulation of autonomic nervous system by nicotine.

Individuals who experience adverse events (suggesting mild nicotine intoxication) should be instructed to reduce their intensity of product use by increasing the interval between the use of a new THS Tobacco Stick, and/or by decreasing the number of puffs and/or the intensity of puffing.

Supportive treatment is directed toward the specific presenting complaint. The commonly seen vomiting can help to reduce absorption and is usually self-limited; treatment with anti-emetics is not recommended.

See also section 6.8 on nicotine overdose.

6.4.4 Tobacco and nicotine withdrawal symptoms

Tobacco and nicotine withdrawal symptoms are common in smokers and were also reported by THS 2.2 users. Such symptoms can be even exacerbated in quitters. These symptoms usually emerge after a few hours after nicotine abstinence and reflect the imbalance in brain neurochemistry [40].

These symptoms can be clustered in affective, somatic and cognitive symptoms (Table 17) [41]. Soreness of throat and aphthous mouth ulcers are also listed as possible withdrawal symptoms [42].

Table 17 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

6.4.5 Hypersensitivity reactions

Few cases (<1%) of skin disorders (pruritus, rashes, erythema, urticaria) have been reported in the eight 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 during postmarket experience.

Skin disorders through local irritation or through hypersensitivity reactions in susceptible subjects have been reported with nicotine [43] and ingredients such as menthol [44], propylene glycol [45] and glycerol [46].

6.4.6 Smoke – Drug Interactions

The suppression of smoke-drug interactions in CC smokers switching completely to THS 2.2 and potential impact in some patients is described in Section 6.6.

6.4.7 Pregnancy and lactation

THS is not intended for use during pregnancy or for breastfeeding women. Pregnant or breastfeeding women should be advised to stop smoking. If pregnancy is detected during a clinical study sponsored by PMI, the study subject is to be discontinued from study and smoking cessation advice is to be provided.

6.5 Adverse Events

Based on the safety knowledge accumulated to date related to the use of THS products (for both the Regular and Menthol variants), Table 18 provides the list of reported AEs, ordered by frequency, which were assessed to be related to THS use during clinical studies and should be considered expected with the use of THS. Table 19 provides also a list of events which can be expected based on the nature of the product and its composition, its pattern of use and the over- or under-exposure to nicotine. The frequency classes mentioned in Table 18 are those used for medicinal products labeling in Europe. Frequencies below 1% are set as not known, as the overall THS-exposed population to date does not allow an accurate estimation of event frequencies below 1%, based on the rule of thumb used in pharmacovigilance (300 subjects

needed to estimate frequency of 1%). As only a small subset of THS-emergent AEs was assessed as related to THS, none of these THS-related AEs reached an incidence rate > 1%.

Table 18 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

Table 19 THS Expected AEs: 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
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

6.6 Smoke – Drug Interactions

It is established that smoking accelerates the metabolism of many drugs, particularly those primarily metabolized by CYP1A2. The CYP1A2 enzyme-inducing effects of cigarette smoke are thought to be related to exposure to polycyclic aromatic hydrocarbons (PAH) and other combustion products [47]. Levels of these HPHCs are significantly lower in THS 2.2 as compared to CC. This is not a THS-drug interaction but an effect similar to what is observed upon smoking cessation, namely a de-induction of CYP1A2, resulting from a decrease or absence of exposure to inducers such as PAH. A CYP1A2 activity decrease was observed in the ZRHR-REXC-03-US and ZRHR-REXC-04-JP studies (reduction of CYP1A2 activity of about 17% and 27% compared to baseline) in the THS arm after 5 days of use, similar to the decrease observed in the smoking abstinence arm. The magnitude of this effect appears to be similar to that observed following smoking cessation [48]. Therefore, smokers treated with drugs primarily metabolized by CYP1A2 and having a narrow therapeutic index (e.g., theophylline, olanzapine, clozapine, ropinirole) may need adjustment in the dosage regimen of these drugs.

6.7 Abuse and Dependence

Given current product knowledge, there is no reason to expect changes in abuse and dependence compared to that observed for CC.

6.8 Known Effects of Nicotine Overdose

Signs and symptoms suggesting mild nicotine intoxication are due to the stimulation of 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. Toxic effects of nicotine develop rapidly following acute overdose. One THS Tobacco Stick contains less than 6 mg nicotine. The acute lethal oral dose in adult humans is traditionally set at 60mg (ca 0.8mg/kg bodyweight) but this number is currently challenged as a number of nonfatal nicotine intoxications are hardly compatible with a lethal dose of 60mg. The current data indicate that more than 500mg (6 to 7mg/kg) of acute oral nicotine is a more accurate estimate of the acute lethal oral dose [49].

The gastric absorption of nicotine from tobacco taken by mouth is delayed because of slowed gastric emptying and the acidic environment in the stomach. As a result, vomiting caused by the central effect of the initially absorbed fraction may remove much of the tobacco remaining in the gastrointestinal tract. Signs and symptoms of acute nicotine intoxication include 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, increased bronchial secretions, increase in heart rate and blood pressure. Other subsequent conditions may also occur such as faintness, prostration, dyspnea, seizure, hypotension, weak, irregular, rapid pulse rate / transient cardiac standstill or paroxysmal atrial fibrillation [43]. Death may occur within a few minutes following severe nicotine overdose, usually as a result of respiratory failure secondary to paralysis of respiratory muscles [50].

Acute nicotine intoxication generally requires symptomatic and supportive care. There is no specific antidote for nicotine intoxication. Activated charcoal is recommended if patients present shortly after nicotine ingestion, owing to the possibility of nicotine-induced seizures, provided the risks do not outweigh the anticipated benefits. If a patient is vomiting, seizing, or has a decreased level of consciousness, there is a risk of pulmonary aspiration with charcoal administration. Alkaline solutions should be avoided. Treatment is supportive and includes support of respiration and control of convulsions. Atropine may be used to suppress features of parasympathomimetic stimulation [51].

6.9 Summary of Non-Clinical Studies

The non-clinical assessment of THS consisted of evaluating the toxicological risk associated with the use of this alternative product for tobacco consumption by adult smokers.

Aerosol chemistry showed that heating instead of burning tobacco substantially reduces exposure to HPHCs compared to CC.

In vitro studies demonstrated a decreased biological activity of THS generated aerosol compared to CC smoke. Cytotoxicity (NRU assay) was reduced by more than 80% in THS 2.2

compared to CC. The genotoxic activity in bacterial cells (Ames assay) and in mammalian cells (MLA) was decreased. No genotoxic activity could be detected in bacterial cells (Ames) with THS 2.2. The genotoxic activity in mammalian cells (MLA) was decreased between 80% and 90% with THS 2.2 in comparison to CC.

In vivo 90-day inhalation study performed with THS 2.2 demonstrated their lower toxicity compared to the exposure to CC.

The non-clinical assessment performed with THS, including the THS 2.2 version, supports the conclusion that subjects will not be exposed to increased or new hazards when compared to continued smoking of CC.

6.10 Summary of Clinical Studies

The results of clinical studies conducted with THS 2.2 Regular showed a consistent reduction in the BoExp levels to 15 HPHCs in smokers using THS 2.2 *ad libitum* compared to smokers continuing CC. Importantly, the magnitude of reductions when using THS 2.2 were comparable to those observed when smokers stopped smoking CC. In conclusion, the clinical assessment in combination with the results of the non-clinical assessment, substantiates a successful implementation and evolution of the principle of heating vs. burning tobacco to reduce exposure to HPHCs of THS.

In addition, the results of clinical studies with THS to date show that participants using THS were able to reach nicotine levels similar to CC smoking. The nicotine uptake as well as the reduction of urge-to-smoke were found comparable to CC, thus THS offered an experience close to what smokers can expect when smoking CC. This is considered critical for the acceptance of THS to be considered a suitable alternative to CC for adult smokers in the context of harm reduction strategy and conversion of CC smokers to THS2.2.

From a medical judgement point of view, the so far observed AEs associated with or related to THS 2.2 seems to be very similar with the safety profile of smoking cessation pharmacotherapies such as NRT, as reported in NRT clinical trials.

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8 SIGNATURE PAGE

Sponsor:	Philip Morris Products S.A., Research & Development Quai Jeanrenaud 5, Neuchâtel, Switzerland, 2000 Neuchatel, Switzerland
Product Name:	THS 2.2
Edition:	Edition 6
Version Number:	Final
Release Date:	27 April 2015
Previous Release Date:	17 August 2016

I, the undersigned, confirm that this Investigator's Brochure is accurate.

Signed: _____ Date: 17 Aug. 2016

John Magnette, MD, FFPM, DiPharmMed

Manager Product Surveillance

19.1.2 Appendix 1b: *IQOS with HeatSticks* Safety Product Information version 3 dated 08-Nov-2017

PMI RESEARCH & DEVELOPMENT

SUMMARY OF PRODUCT INFORMATION (SPI)

IQOS with HeatSticks

Company:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	3.0
Release Date:	08-November-2017
Replaces Previous Version:	Version 2.0
Previous Release Date:	09-June-2017

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LIST OF IN-TEXT FIGURES

ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
BoExp	Biomarker(s) of exposure
CC	Cigarette
CI	Confidence Interval
CYP1A2	Cytochrome P450 1A2
HAT	Hollow acetate tube
HCI	Health Canada Intense Smoking Regime
HPHCs	Harmful and Potentially Harmful Constituents
LED	Light Emitting Diode
NA	Not Analyzed
NAB	N-nitrosoanabasine
NAT	N-nitrosoanatabine
NFDPM	Nicotine-free dry particulate matter
NNN	N-nitrosonornicotine
NNK	4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone
PAH	Polycyclic Aromatic Hydrocarbon
PLA	Polylactic acid
PMI	Philip Morris International
SPI	Summary of Product Information
TPM	Total Particulate Matter

1 INTRODUCTION

IQOS with HeatSticks is a heat-not-burn tobacco product (also known as Tobacco Heating System) that heats tobacco without combustion. In comparison with cigarette smoke, the formation of harmful and potentially harmful constituents (HPHCs) is greatly reduced.

The results of clinical studies conducted on *IQOS* with HeatSticks have shown a consistent sustained reduction in the levels of biomarkers of exposure (BoExp) to selected HPHCs in participants that used the product ad libitum in comparison with those that continued smoking cigarettes (CC).

Importantly, the magnitude of reductions in the BoExp levels to selected HPHCs when using IQOS with HeatSticks were comparable to those observed when smokers stopped smoking CC [1].

The purpose of this Summary of Product Information (SPI) is to be the reference for professionals (e.g. researchers, health care providers) on how to use the product safely and effectively once it is commercially available in the market. In this way, the SPI will be the reference for safety and efficacy for conducting clinical studies once the product has been commercialized (e.g. for Investigator-Initiated Studies).

2 PRODUCT DESCRIPTION

2.1 Product Name

IQOS with HeatSticks

2.2 The *IQOS* with HeatSticks components

IQOS with HeatSticks is a system made up of three main components (see Figure 1): The Tobacco Stick (HeatStick), the Holder, and the Charger.

Figure 1 Picture of the components of *IQOS* with HeatSticks

2.2.1 The tobacco stick (HeatStick)

The tobacco stick or HeatStick, also known as HEETS (brand name), is designed to function with the Holder.

The HeatStick is made up of a tobacco plug, a hollow acetate tube (HAT), a polylactic acid (PLA) polymer-film filter, a mouth piece filter, and of outer and mouth-end papers (see Figure 2).

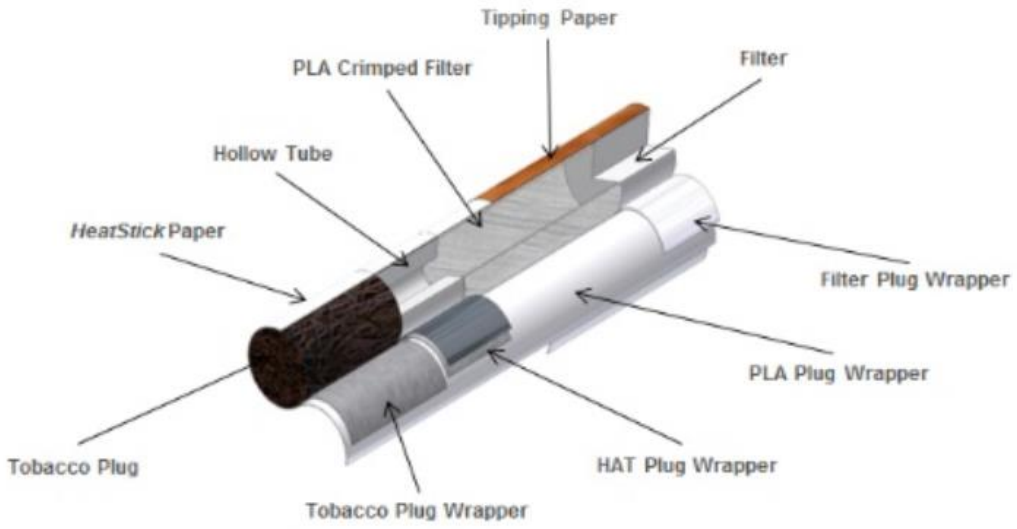

Figure 2 Picture of *IQOS* HeatStick

All the ingredients have been evaluated with regards to their toxicological potential and have been approved for use. The heatstick delivers nicotine naturally present in tobacco. The tobacco plug contains 5-6mg nicotine.

Table 1 shows, per product variant, the ingredients contained in the heatstick, in addition to blended tobacco.

Table 1 Ingredients[1] contained in the heatstick, in addition to blended tobacco

Category	Ingredient Name	Regular Variant	Menthol Variant
Tobacco Ingredient	Glycerol	x	x
Tobacco Ingredient	Water	x	x
Tobacco Ingredient	Guar Gum	x	x

[1] Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications

Source: https://www.fda.gov/TobaccoProducts/Labeling/MarketingandAdvertising/ucm546281 htm, accessed on 24-Oct-2017

Category	Ingredient Name	Regular Variant	Menthol Variant
Tobacco Ingredient	Cellulose	x	x
Tobacco Ingredient	Menthol		x
Tobacco Ingredient	Propylene Glycol	x	x
Tobacco Ingredient	Peppermint Oil		x
Tobacco Ingredient	Natural & Artificial Flavorings	x	x
Tobacco Plug Wrap Paper	Cellulose	x	x
Tobacco Plug Wrap Paper	Calcium Carbonate	x	x
Tobacco Plug Wrap Paper	Carboxymethylcellulose and its Sodium Salt	x	x
Tobacco Plug Adhesive	Ethylene-Vinyl Acetate Copolymer	x	x
Tobacco Plug Adhesive	Starch and/or Modified Starches	x	x
Tobacco Plug Adhesive	Propylene Glycol	x	x
Outer Paper	Cellulose	x	x
Outer Paper	Calcium Carbonate	x	x
Outer Paper	Epichlorhydrin Resin	x	
Outer Paper	Carboxymethylcellulose	x	x
Outer Paper	Guar Gum	x	
Outer Paper Adhesive	Ethylene-Vinyl Acetate Copolymer	x	x
Hollow Acetate Tube	Cellulose Acetate	x	x
Hollow Acetate Tube	Triacetin	x	x
Hollow Acetate Tube	Titanium Dioxide	x	x
Hollow Acetate Tube - Plugwrap Paper	Cellulose	x	x
Hollow Acetate Tube - Plugwrap Paper	Calcium Carbonate	x	x
Hollow Acetate Tube - Plugwrap Paper	Carboxymethylcellulose and its Sodium Salt	x	x
Hollow Acetate Tube - Adhesive	Polyvinyl Acetate	x	x
Hollow Acetate Tube - Adhesive	Hydroxyethylene - Vinyl Acetate Copolymer	x	x
Polylactic Acid Filter	Poly Lactic Resin	x	x
Polylactic Acid Filter	Cellulose Acetate		x
Polylactic Acid Filter	Menthol		x
Polylactic Acid Filter	Calcium Carbonate	x	x
Polylactic Acid Filter - Plug Wrap Paper	Cellulose	x	x
Polylactic Acid Filter - Plug Wrap Paper	Kaolin	x	x
Polylactic Acid Filter - Plug Wrap Paper	Rosin	x	x
Polylactic Acid Filter - Plug Wrap Paper	Optical Brightener	x	x
Polylactic Acid Filter - Adhesive	Polyvinyl Acetate	x	x

Category	Ingredient Name	Regular Variant	Menthol Variant
Polylactic Acid Filter - Adhesive	Ethylene-Vinyl Acetate Copolymer	x	x
Polylactic Acid Filter - Adhesive	Hydrocarbon Resin	x	x
Polylactic Acid Filter - Adhesive	Paraffin	x	x
Polylactic Acid Filter - Adhesive	Hydroxyethylene - Vinyl Acetate Copolymer	x	x
Polylactic Acid Filter - Adhesive	Polyisobutylene	x	x
Mouth Piece Filter	Cellulose Acetate	x	x
Mouth Piece Filter	Triacetin	x	x
Mouth Piece Filter	Titanium Dioxide	x	x
Mouth Piece Filter - Plug Wrap Paper	Cellulose	x	x
Mouth Piece Filter - Plug Wrap Paper	Rosin	x	x
Mouth Piece Filter - Plug Wrap Paper	Optical Brightener	x	x
Mouth Piece Filter - Plug Wrap Paper	Kaolin	x	x
Mouth Piece Filter - Adhesive	Polyvinyl Acetate	x	x
Mouth Piece Filter - Adhesive	Ethylene-Vinyl Acetate Copolymer	x	x
Mouth Piece Filter - Adhesive	Hydrocarbon Resin	x	x
Mouth Piece Filter - Adhesive	Paraffin	x	x
Mouth Piece Filter - Adhesive	Polyisobutylene	x	x
Mouth Piece Filter - Adhesive	Hydroxyethylene - Vinyl Acetate Copolymer	x	x
Tipping Paper	Cellulose	x	x
Tipping Paper	Calcium Carbonate	x	x
Tipping Paper	Kaolin	x	x
Tipping Paper	Titanium Dioxide	x	x
Tipping Paper	Starch and/or Modified Starches	x	x
Tipping Paper	Alkylketene Dimer	x	x
Tipping Paper	Epichlorhydrin Resin	x	x
Tipping Paper	Pigments	x	x
Tipping Paper - Adhesive	Ethylene-Vinyl Acetate Copolymer	x	x
Tipping Paper - Adhesive	Hydroxyethylene - Vinyl Acetate Copolymer	x	x

2.2.2 The Holder

The Holder is a slim electrical heating unit that heats the HeatStick in a controlled manner by using a heater blade.

The Holder stores enough energy for a single inhalation experience, delivering puffs over a period of about 6 minutes or 14 puffs (whichever comes first). A Light Emitting Diode (LED) indicates when the experience can start and when the experience ends.

Once this cycle is complete, the Holder must be recharged before a new HeatStick can be used.

2.2.3 The Charger

The power supply for the Holder is the Charger.

The Charger holds enough energy for approximately 20 uses of the Holder and can be recharged from household power.

The Charger stores the Holder when not in use, and provides a secure environment for the cleaning process of the heater blade.

2.3 Product Variants

Different *IQOS* with HeatSticks product variants are available on the market.

The HeatSticks are available in different tobacco blends/flavors options, including the Regular (non-Methol variant) and the Menthol variants.

2.4 *IQOS* with HeatSticks Aerosol

Table 2 shows the levels of a selected list of compounds and HPHCs found, under the Health Canada Intense (HCI) machine-smoking conditions[2], in the aerosol of the Regular and Menthol variants of *IQOS* with HeatSticks in comparison with the levels found in a 3R4F reference cigarette. The data show that *IQOS* with HeatSticks reduced the level of the majority of HPHCs by more than 90% compared to the reference cigarette [2, 3].

Table 2 Analytes yields from *IQOS* with HeatSticks (Regular and Menthol variants) and a cigarette (3R4F standard) obtained under HCI machine-smoking conditions

Parameter (Unit)	*IQOS* with HeatSticks (Regular)	*IQOS* with HeatSticks (Menthol)	Reference cigarette (3R4F)
	mean ± $CI_{95\%}$/stick	mean ± $CI_{95\%}$/stick	mean ± $CI_{95\%}$ /cigarette
TPM (mg/stick)	54.1 ± 2.4	53.8 ± 3.6	46.3 ± 2.9
Water (mg/stick)	39.4 ± 4.6	39.1 ± 3.6	13.3 ± 1.6
Nicotine (mg/stick)	1.26 ± 0.24	1.32 ± 0.11	2.09 ± 0.14
NFDPM[3] (mg/stick)	13.4 ± 2.8	13.4 ± 0.6	30.9 ± 1.9
Carbon monoxide (mg/stick)	0.598 ± 0.072	0.620 ± 0	30.7 ± 3.0
Benzo[a]pyrene (ng/stick)	1.19 ± 0.08	1.08 ± 0.09	13.7 ± 0.8
Menthol (mg/stick)	n.a.	2.98 ± 0.21	n.a.
Glycerol (mg/stick)	4.1 ± 1.07	4.59 ± 0.47	2.39 ± 0.15

[2] Puffing regime, first described by Health Canada, when taking one puff of 55 ml volume and 2 seconds duration every 30 s with 100 % of the ventilation zone on the cigarette filter blocked

[3] Nicotine-free dry particulate matter

Parameter (Unit)	*IQOS* with HeatSticks (Regular)	*IQOS* with HeatSticks (Menthol)	Reference cigarette (3R4F)
	mean ± $CI_{95\%}$ /stick	mean ± $CI_{95\%}$ /stick	mean ± $CI_{95\%}$ /cigarette
1-aminonaphthalene (ng/stick)	0.063 ± 0.006	<0.061	19.7 ± 1.6
2-aminonaphthalene (ng/stick)	<0.035	<0.035	14.8 ± 1.9
3-aminobiphenyl (ng/stick)	<0.013	<0.013	3.90 ± 0.42
4-aminobiphenyl (ng/stick)	<0.021	n.a.	3.13 ± 0.60
o-toluidine (ng/stick)	1.204 ± 0.149	0.868 ± 0.087	90.5 ± 3.1
Acetaldehyde (µg/stick)	213 ± 19	220 ± 22	1589 ± 76
Acetone (µg/stick)	33.8 ± 6.4	42.6 ± 8.1	729 ± 36
Acrolein (µg/stick)	9.44 ± 0.87	10.91 ± 2.98	193 ± 21
Butyraldehyde (µg/stick)	25.3 ± 2.7	26.4 ± 0.9	103.9 ± 8.3
Crotonaldehyde (µg/stick)	3.75 ± 0.34	4.15 ± 0.64	92.1 ± 13.2
Formaldehyde (µg/stick)	5.22 ± 0.24	6.19 ± 2.00	68.7 ± 7.8
Methyl ethyl ketone (µg/stick)	7.94 ± 0.75	10.19 ± 2.23	241 ± 16
Propionaldehyde (µg/stick)	13.6 ± 1.5	15.9 ± 2.2	147 ± 8
Acrylonitrile (µg/stick)	0.186 ± 0.028	0.196 ± 0.016	31.6 ± 2.3
1,3-butadiene (µg/stick)	0.319 ± 0.073	0.411 ± 0.093	91.8 ± 11.0
Benzene (µg/stick)	0.575 ± 0.072	0.628 ± 0.073	100.4 ± 2.8
Isoprene (µg/stick)	2.44 ± 0.50	2.63 ± 0.60	869 ± 50
Pyridine (µg/stick)	9.38 ± 0.95	10.08 ± 0.46	51.8 ± 7.5
Quinoline (µg/stick)	0.014 ± 0.002	0.010 ± 0.003	0.390 ± 0.101
Styrene (µg/stick)	0.672 ± 0.063	0.632 ± 0.079	28.9 ± 2.2
Toluene (µg/stick)	1.61 ± 0.17	1.67 ± 0.37	198.8 ± 10.9
Catechol (µg/stick)	16.4 ± 0.6	12.8 ± 1.3	88.7 ± 2.6

Parameter (Unit)	*IQOS* with HeatSticks (Regular)	*IQOS* with HeatSticks (Menthol)	Reference cigarette (3R4F)
	mean ± $CI_{95\%}$ /stick	mean ± $CI_{95\%}$ /stick	mean ± $CI_{95\%}$ /cigarette
o-cresol (µg/stick)	0.105 ± 0.017	0.059 ± 0.007	4.86 ± 0.50
m-cresol (µg/stick)	0.042 ± 0.006	0.032 ± 0.005	3.71 ± 0.34
p-cresol (µg/stick)	0.073 ± 0.009	0.042 ± 0.007	8.50 ± 0.78
Hydroquinone (µg/stick)	7.86 ± 0.63	6.21 ± 0.86	84.1 ± 3.3
Phenol (µg/stick)	1.51 ± 0.23	1.00 ± 0.17	13.2 ± 0.9
Resorcinol (µg/stick)	0.055 ± 0.013	0.036 ± 0.005	1.95 ± 0.55
Acetamide (µg/stick)	4.13 ± 0.21	3.43 ± 0.17	13.7 ± 0.7
Acrylamide (µg/stick)	2.27 ± 0.28	1.90 ± 0.12	5.3 ± 0.4
NAB (ng/stick)	3.52 ± 0.48	3.27 ± 0.15	34.1 ± 3.0
NAT (ng/stick)	22.3 ± 1.6	18.6 ± 2.9	300 ± 53
NNK (ng/stick)	10.1 ± 0.4	7.9 ± 1.1	257 ± 39
NNN (ng/stick)	10.3 ± 0.4	7.7 ± 1.0	268 ± 50
Ammonia (µg/stick)	15.6 ± 1.1	13.9 ± 1.1	39.2 ± 4.1
Hydrogen cyanide (µg/stick)	3.78 ± 0.44	5.57 ± 0.35	451 ± 47
Nitric oxide (µg/stick)	21.0 ± 8.1	18.4 ± 3.6	501 ± 33
Nitrogen oxides (µg/stick)	22.6 ± 8.8	19.4 ± 4.0	541 ± 74
Arsenic (ng/stick)	<1.13	<1.13	6.56 ± 0.46
Cadmium (ng/stick)	<0.350	<0.350	122 ± 12
Chromium (ng/stick	<0.17	0.44	2.70[a]
Lead (ng/stick)	<3.35	<3.35	25.1 ± 2.1
Mercury (ng/stick)	1.02 ± 0.05	1.12 ± 0.19	4.17 ± 0.74
Nickel (ng/stick)	<0.55	0.88	1.30[a]
Selenium (ng/stick)	<0.550	<0.550	1.43 ± 0.15
Ethylene oxide (µg/stick)	0.314 ± 0.011	0.273 ± 0.036	34.2 ± 3.6
Nitrobenzene (ng/stick)	0.092 ± 0.008	0.155 ± 0.004	0.55 ± 0.04

Parameter (Unit)	*IQOS* with HeatSticks (Regular)	*IQOS* with HeatSticks (Menthol)	Reference cigarette (3R4F)
	mean ± $CI_{95\%}$/stick	mean ± $CI_{95\%}$/stick	mean ± $CI_{95\%}$ /cigarette
Propylene oxide (µg/stick)	0.175 ± 0.03	0.14 ± 0.019	1.72 ± 0.16
Vinyl chloride (ng/stick)	<3.47	<3.47	95.3 ± 12.3
Benz[*a*]anthracene (ng/stick)	2.58 ± 0.17	2.50 ± 0.06	26.6 ± 1.7
Dibenz[*a,h*]anthracene (ng/stick)	<0.100	<0.100	1.79 ± 0.14
Pyrene (ng/stick)	7.93 ± 0.78	7.71 ± 0.63	87.3 ± 4.1

CI is the confidence interval of the mean,
n.a.: not analyzed.
<: median lower than the limit of quantitation, in this case LOQ is given.
If at least one value is below the LOQ, the median is given and the CI is not mentioned.
[a] CI not calculated.

3 PRODUCT PARTICULARS

3.1 Target Population

The intended population for *IQOS* with HeatSticks products is legal age adult smokers who would otherwise continue to smoke.

3.2 Product Use

To use *IQOS* with HeatSticks, the consumer inserts the HeatStick into the Holder to pre-heat it. Thereafter, the aerosol is inhaled by placing the lips on the HeatStick mouthpiece and drawing air through it.

IQOS with HeatSticks should not be used if the *IQOS* device appears damaged, has been exposed to excessive heat or moisture or if its batteries appear to be leaking.

The Holder may warm up slightly when in use.

Further details for use are provided in the *IQOS* with HeatSticks User Guide.

3.3 Warnings and Precautions

To reduce the risk of injury, *IQOS* with HeatSticks products shall always be used in accordance with the manufacturer's instructions (see *IQOS* with HeatSticks User Guide).

Pregnant or breastfeeding women should be advised against the use of *IQOS* with HeatSticks.

3.3.1 Specific Risks that Lead to a Precaution for Use

3.3.1.1 Hypersensitivity

Hypersensitivity reactions may occur in users of *IQOS* with HeatSticks, in particular in users with a past medical history of allergic condition, such as food, pet or dust allergies. In case of signs and symptoms that may indicate a serious allergic reaction, users should be instructed to stop using *IQOS* with HeatSticks and contact a physician immediately.

3.3.1.2 Risk of Accidental Ingestion by Children

IQOS with HeatSticks shall be kept away from children at all times and ensure they do not play with this product. The accidental ingestion of HeatSticks may potentially cause signs and symptoms of nicotine intoxication (see Section 3.6). In case of accidental ingestion by children, users of *IQOS* with HeatSticks should be instructed to contact a physician immediately.

3.3.1.3 Sensation of Hot Aerosol during Hot and Humid Weather Conditions

The water in the aerosol increases heat transfer properties and, under hot and humid weather conditions, may intensify the feeling of a higher temperature of the aerosol. *IQOS* with HeatSticks users are encouraged to keep *IQOS* with HeatSticks in a dry environment and prevent them from exposure to high humidity to help avoid the sensation of hot aerosol when using *IQOS* with HeatSticks. If users continue to experience discomfort, they should be advised against further usage of *IQOS* with HeatSticks in hot conditions during periods of high humidity and should be advised to contact a physician.

3.3.2 Risks Associated with Starting Using the Product

IQOS with HeatSticks contains nicotine, which is addictive.

Due to the stimulation effects of nicotine of autonomic nervous system, the users of *IQOS* with HeatSticks may experience the following transient signs and symptoms: 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, increased bronchial secretions, increase in heart rate and blood pressure. Users who experience those signs/symptoms should be instructed to reduce the product use by increasing the interval between single inhalation experiences, and/or by decreasing the number of puffs and/or the intensity of puffing.

3.3.3 Risks Associated with Nicotine Withdrawal

Users of *IQOS* with HeatSticks that stop using the product may experience nicotine withdrawal symptoms. These symptoms usually emerge a few hours after nicotine abstinence and reflect the imbalance in brain neurochemistry.

Nicotine withdrawal symptoms can be clustered as affective (irritability, anger, frustration, anxiety, depressed mood, insomnia, dysphoria, hyperalgesia, impatient, restlessness, nightmares), somatic (tremors, bradycardia, gastrointestinal discomfort, nausea, constipation, increased appetite, hungry, weight gain, coughing, dizziness, sore throat, mouth ulcer) or cognitive (difficulty concentrating, impaired memory).

3.4 Interactions

3.4.1 Smoke-Drug Interactions

It is established that tobacco exposure/use accelerates the metabolism of many drugs, particularly those primarily metabolized by Cytochrome P450 1A2 (CYP1A2). The CYP1A2 enzyme-inducing effects of cigarette smoke are thought to be related to exposure to polycyclic aromatic hydrocarbons (PAHs) and other combustion by products. The levels of these HPHCs are significantly lower in *IQOS* with HeatSticks products as compared to CC. Consequently, the reduction of PAHs levels may impact CYP1A2 activity. This is not an *IQOS* with HeatSticks drug interaction but an effect similar to what is observed upon smoking cessation, namely a de-induction of CYP1A2, resulting from a decrease or absence of exposure to inducers such as PAH. Therefore, smokers treated with drugs primarily metabolized by CYP1A2 and having a narrow therapeutic index (e.g., theophylline, olanzapine, clozapine, ropinirole) may need adjustment in the dosage regimen of these drugs, when switching from smoking CC to *IQOS* with HeatSticks use.

3.5 Undesirable Events

3.5.1 Summary of Safety Profile

Hypersensitivity reactions may occur in users of *IQOS* with HeatSticks, in particular in users with a past medical history of allergic conditions, such as food, pet or dust allergies (see specific warnings and precautions in section 3.3.1.1).

The accidental ingestion of HeatSticks by children may potentially cause signs and symptoms of nicotine intoxication (see specific warnings and precautions in section 3.3.1.2).

When using *IQOS* with HeatSticks during hot and humid weather conditions, consumers may experience sensation of hot aerosol (see specific warnings and precautions in section 3.3.1.3).

As a class effect observed in other nicotine-containing products, *IQOS* with HeatSticks may cause some common nicotine-related signs and symptoms when starting using the product (see specific warnings and precautions in section 3.3.2)

Nicotine withdrawal symptoms may occur when stopping using *IQOS* with HeatSticks. These symptoms usually emerge a few hours after nicotine abstinence (see specific warnings and precautions in section 3.3.3)

3.5.2 Risks Associated with the use *IQOS* with HeatSticks

For the purpose of this document, the list of risks in Table 2 and Table 3 are to be considered expected with *IQOS* with HeatSticks use.

3.5.2.1 Identified Risks

Table 3 provides the list of identified risks associated with the use *IQOS* with HeatSticks based on clinical studies and post-market experience.

Table 3 List of Identified Risks with IQOS with HeatSticks use

System Organ Class	Risk (Preferred term)
Immune System Disorders	- Hypersensitivity
General disorders and administration site conditions	- Burning sensation
Injury, poisoning and procedural complications	- Accidental exposure to product by child

3.5.2.2 Class Effect Risks

Table 4 provides the list of class effect risks with *IQOS* with HeatSticks use, based on safety information from other nicotine containing products such as Nicotine Replacement Therapy (NRT)[4].

Table 4 List of Class Effect Risks with Nicotine Use

System Organ Class	Risk (Preferred Term)
Immune System Disorders	- Anaphylactic reaction
Psychiatric disorders	- Abnormal dreams - Agitation - Anxiety - Concentration impaired - Insomnia - Mood altered
Nervous System Disorders	- Headache - Dizziness - Dysgeusia - Paraesthesia
Eye Disorders	- Blurred Vision - Lacrimation increased

[4] Nicorette® 15mg Inhalator, McNeil Products Ltd

Source: http://www.medicines.org.uk/emc/medicine/24853/SPC/Nicorette+15mg+Inhalator, accessed on 13-Oct-2017

Nicotinell TTS 20, GlaxoSmithKline Consumer Healthcare

Source: http://www.medicines.org.uk/emc/medicine/20063/SPC/Nicotinell+TTS+20, accessed on 13-Oct-2017

Cardiac Disorders	- Palpitations - Tachycardia - Reversible atrial fibrillation
Vascular Disorders	- Flushing - Hypertension
Respiratory, Thoracic and Mediastinal Disorders	- Cough - Throat irritation - Nasal Congestion - Bronchospasm - Dysphonia - Dyspnoea - Sneezing - Throat tightness
Gastrointestinal Disorders	- Nausea - Stomatitis - Hiccups - Abdominal pain - Diarrhoea - Dry mouth - Dyspepsia - Flatulence - Salivary hypersecretion - Vomiting - Eructation - Glossitis - Oral mucosal blistering and exfoliation - Paraesthesia oral - Dysphagia - Hypoaesthesia oral - Retching - Dry throat - Gastrointestinal discomfort - Lip pain
Skin and Subcutaneous Tissue Disorders	- Hyperhidrosis - Pruritus - Rash - Urticaria - Angioedema - Erythema

Musculoskeletal and Connective Tissue Disorders	- Muscle tightness
General Disorders and Administration Site Conditions	- Fatigue - Asthenia - Chest discomfort and pain - Malaise

3.6 Nicotine Overdose

Signs and symptoms suggesting nicotine intoxication are due to the stimulation of autonomic nervous system by nicotine and can occur if *IQOS* with HeatSticks is used in excess, or ingested (e.g. accidentally by children)

Toxic effects of nicotine develop rapidly following acute overdose. The current data indicate that more than 500mg (6 to 7mg/kg) of acute oral nicotine is an accurate estimate of the acute lethal oral dose in adults [4]. One HeatStick contains, in average, 5 – 6mg of nicotine.

Signs and symptoms of acute nicotine intoxication include 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, increased bronchial secretions, increase in heart rate and blood pressure.

Other subsequent conditions may also occur such as faintness, prostration, dyspnea, seizure, hypotension, weak, irregular, rapid pulse rate / transient cardiac standstill or paroxysmal atrial fibrillation. Death may occur within a few minutes following severe nicotine overdose, usually as a result of respiratory failure secondary to paralysis of respiratory muscles.

Acute nicotine intoxication generally requires symptomatic and supportive care. There is no specific antidote for nicotine intoxication. Activated charcoal is recommended if patients are presented shortly after nicotine ingestion, owing to the possibility of nicotine-induced seizures, provided the risks do not outweigh the anticipated benefits. If a patient is vomiting, seizing, or has a decreased level of consciousness, there is a risk of pulmonary aspiration with charcoal administration. Alkaline solutions should be avoided. Treatment is supportive and includes support of respiration and control of convulsions. Atropine may be used to suppress features of parasympathomimetic stimulation.

The commonly seen vomiting can help to reduce absorption and is usually self-limited, therefore treatment with anti-emetics is not recommended in case of product ingestion.

4 PRODUCT PERFORMANCE

4.1 Pharmacokinetic and Pharmacodynamic properties

Following single use of *IQOS* with HeatSticks, clinical studies showed that the average nicotine plasma concentrations peaked around 10 to 14 ng/mL in around 6 minutes and that the terminal half-life of nicotine was around 2 to 4 hours[5] [5].

The results of clinical studies with *IQOS* with HeatSticks to date also have shown that the users of the product were able to reach nicotine levels similar to those achieved by CC smoking, suggesting that that nicotine exposure of *IQOS* with HeatSticks is similar to CC, after a period of adaptation to product use which can take several weeks.

Product acceptability as measured by nicotine uptake and reduction of urge-to-smoke was comparable to CC, thus *IQOS* with HeatSticks offers an experience close to what smokers expect when smoking CC [6, 7].

4.2 Summary of Safety Aspects from Non-Clinical Studies

No new or increased toxicological hazard in the *IQOS* with HeatSticks aerosol was detected compared with CC smoke.

Chemical analysis confirmed that *IQOS* with HeatSticks aerosol has significantly lower levels of HPHCs than CC smoke (see Section 2.4).

The biological activity of *IQOS* with HeatSticks aerosol was tested in vitro and in vivo. In vitro studies demonstrated a decreased biological activity of *IQOS* with HeatSticks generated aerosol compared with CC smoke. The cytotoxicity (neutral red uptake assay) was reduced by more than 80% in *IQOS* with HeatSticks when compared to CC. The genotoxic activity in bacterial cells (Ames assay) and in mammalian cells was decreased for *IQOS* with HeatSticks products compared to CC [2]. In vivo 90-day inhalation study performed with *IQOS* with HeatSticks demonstrated a lower toxicity compared to the exposure to CC [8-10].

The non-clinical assessment performed with *IQOS* with HeatSticks supports the conclusion that users of *IQOS* with HeatSticks will not be exposed to increased or new hazards when using *IQOS* with HeatSticks compared with continued smoking.

5 DATE OF FIRST MARKET LAUNCH

04-Nov-2014 (Japan)

6 DATE OF REVISION OF THE TEXT

08-November-2017

[5] Appendix 9 and 10 of Platform 1's Scientific Dossier submitted in line with EU's Tobacco Products Directive. Source: https://www.pmiscience.com/news/platform-1%E2%80%99s-scientific-dossier-submitted-line-eu%E2%80%99s-tobacco-products-directive. Accessed on 19-Apr-2017.

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19.1.3 Appendix 1c: THS Regular and Menthol Safety Core Data Sheet (SCDS) version 2 dated 18-Aug-2016

PMI RESEARCH & DEVELOPMENT

Safety Core Data Sheet

Tobacco Heating System (THS)

Sponsor:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	v 2.0
Release Date:	18-Aug-2016
Author:	Nicoleta Ciuria Senior Medical Safety Associate Philip Morris Products S.A
Reviewed and approved by:	John Magnette, MD, DipPharmMed, FFPM Manager, Product Safety Surveillance Philip Morris Products S.A.

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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 (FDA 2012: MRTPA Draft Guidance).
AER	Adverse Event Report
CC	Conventional Cigarettes
CYP1A2	Cytochrome P450 1A2
DSM	Diagnostic and Statistical Manual of Mental Disorders
FDA	Food and Drug Administration
HPHC	Harmful and Potentially Harmful Constituents
ICSR	Individual Case Safety Report
iQOS system	iQOS is the brand name of THS
MedDRA	Medical Dictionary for Regulatory Activities
MIA	Menthol In Aerosol
NA	Not Applicable
NRT	Nicotine Replacement Therapy
PMI	Philip Morris International
PT	Preferred Term (MedDRA)
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.
SOC	System Organ Class (MedDRA)
THS	Tobacco Heating System
USA	United States of America

1 PRODUCT NAME

Tobacco Heating System (THS), *iQOS*

2 PRODUCT DESCRIPTION

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.

(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.

Nicotine content is 4.5-4.7 mg per Tobacco Stick. For the list of ingredients, see Section 8.1.

3 INTENDED USE

The target population for THS products is adult smokers.

4 PRODUCT USE

To use THS, the consumer inserts the THS Tobacco Stick into the Holder to pre-heat it. Thereafter, the aerosol is inhaled by placing the lips on the THS Tobacco Stick mouthpiece and drawing air through the THS Tobacco Stick. Once the Holder is switched on, the user can puff for approximately six minutes (although approximately 20 seconds of this six-minute period is for heating). The THS Holder may warm up slightly when in use.

5 PRODUCT VERSIONS AND VARIANTS

Different THS product versions and variants are available.
THS Tobacco Sticks are available in different tobacco blends and flavors options.

6 WARNINGS AND PRECAUTIONS

- The review of THS human safety data at hand indicates that there is no safety signal suggesting new or increased risks in smokers switching from conventional cigarettes (CC) to THS as compared to smokers continuing smoking CC.
- Depending on the history of conventional cigarette smoking (duration and intensity of smoking) and the age of switching from cigarette smoking 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.

- In the context of safety, the term "smoking" means smoking of CC or other combusted tobacco products (e.g., cigarillos, pipes, cigares).
- Use of THS should be avoided during pregnancy and breastfeeding. Safety of THS in patients (e.g., smokers suffering from cardiovascular diseases, respiratory diseases or diabetes mellitus switching to THS) remains to be established.
- For details on foreseeable risks on THS use and exposure, see Section 7.3 and Table 3.
- THS should be kept out of reach of children and pets.
- 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-attributable morbidity (and corresponding signs and symptoms) and mortality may occur

7 SAFETY

7.1 Clinical Studies Experience

7.1.1 Expected Adverse Events (AEs) from Clinical Studies

Table 1 provides the list of reported adverse events which were assessed to be related to all variants of THS use during clinical studies.

Table 1 THS-related Adverse Events from Clinical Studies

System Organ Class (SOC)	Incidence[1]	THS-related Adverse Events (Preferred Terms - PTs)
None	Very common	None
None	Common	None
Cardiac disorders	Not known	Myocardial ischemia
Ear and labyrinth disorders	Not known	Vertigo
Gastrointestinal disorders	Not known	Nausea, Vomiting, Oral pain, Diarrhea, Dry mouth, Salivary hypersecretion
General disorders and administration site conditions	Not known	Non-cardiac chest pain
Hepatobiliary disorders	Not known	Hepatic function abnormal
Investigations	Not known	Carbon monoxide diffusion capacity decreased, Spirometry abnormal
Metabolism and nutrition disorders	Not known	Hypertriglyceridemia
Musculoskeletal and connective tissue disorders	Not known	Pallor, Musculoskeletal chest pain
Nervous system disorders	Not known	Headache, Dizziness, Presyncope, Syncope
Psychiatric disorders	Not known	Dysphoria
Respiratory, thoracic and mediastinal disorders	Not known	Cough, Upper airway cough syndrome, Oropharyngeal pain, Sneezing
Skin and subcutaneous tissue disorders	Not known	Hyperhidrosis

[1] Very common: (≥1/10), Common (≥1/100 to <1/10), Not known: incidence below 1% are set as not known as the overall THS-exposed population 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%).

7.2 Passive Safety Surveillance Experience

7.2.1 Expected Adverse Events from Passive Safety Surveillance Experience

All AEs spontaneously reported during passive safety surveillance activities for all THS product variants are listed in Table 2. The reporting rate was very low for all the AEs associated (suspected to be related) with THS use from passive safety surveillance.

Table 2 AEs Associated (suspected to be related) with THS Use from Passive Safety Surveillance

System Organ Class (SOC)	Adverse Events (PTs)
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 odour 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

System Organ Class (SOC)	Adverse Events (PTs)
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

7.3 Other Foreseeable Risks

Signs and symptoms suggesting mild nicotine intoxication are due to the stimulation of autonomic nervous system by nicotine and can be observed with too intense use of THS by consumers, accidental poisoning (e.g. child poisoning) or intentional poisoning. More intense symptoms are associated with higher level of nicotine and are due to secondary depression of the autonomic nervous system; severe nicotine intoxication is not expected under normal use conditions by adult [smokers] (see Section 7.4.2).

Tobacco and nicotine withdrawal symptoms are common in smokers and abstainers were also reported by THS users. These symptoms usually emerge a few hours after nicotine abstinence and reflect the imbalance in brain neurochemistry. These clinical manifestations can be clustered in affective, somatic and cognitive symptoms. Seven of these are considered primary symptoms (*in italic in the table*) for the Diagnostic and Statistical Manual of Mental Disorders, Edition 5 (DSM-5) diagnosis of nicotine withdrawal symptoms. Soreness of throat and aphthous mouth ulcers are also listed as possible withdrawal symptoms.

Table 3 provides also 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.

Table 3 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
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

7.4 Use In Special Groups and Situations

7.4.1 Use in Pregnancy and Lactation

THS shares at least the same risks as nicotine and Nicotine Replacement Therapy (NRT) products when used during pregnancy and breast feeding, and is expected to be at a higher risk than NRT due to the nature of the THS aerosol from heated tobacco, 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 (see Section 6 Warnings and Precautions).

7.4.2 Nicotine Over-exposure

Signs and symptoms suggesting mild nicotine intoxication are due to the stimulation of autonomic nervous system by nicotine and can be observed with too intense use of THS by consumers, accidental poisoning (e.g. child poisoning) or intentional poisoning.

More intense symptoms are associated with higher level of nicotine and are due to secondary depression of the autonomic nervous system; severe nicotine intoxication is not expected under normal use conditions by adult [smokers]. Table 4 provides a list of potential adverse events associated with severe nicotine intoxication.

Table 4 Foreseeable Risks associated with Nicotine Over-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 use conditions by adults] 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.

7.4.3 Abuse Liability

THS tobacco sticks contain nicotine, which is a highly addictive substance.

8 PRODUCTS PARTICULARS

8.1 List of Ingredients in Tobacco Plug

Glycerin, Water, Wrapper, Guar, Fibers, Propylene Glycol, Ethanol, Flavours.

8.2 Product Stability

Under normal usage conditions the THS Tobacco Sticks, deliveries of harmful and potentially harmful constituents (HPHC) and general performance remain consistent over a period of 12 months for THS Regular and over a period of 6 months for THS Menthol.

9 SPONSOR

Philip Morris Products S.A.
PMI Reduced Risk Products
Quai Jeanrenaud 5
2000 Neuchâtel, Switzerland

10 DATE OF FIRST MARKET LAUNCH

04 Nov 2014

11 REVISION HISTORY

Table 5 Revision History

Version N°	Major/Minor Change[1]	Release Date	Description of Change
1.0	Initial Document	09-Jun-2016	Original Issue Source: Section 6.1.5 Human Safety for THS Products MRTPA Dossier (May 2016)
2.0	Major Change	18-Aug-2016	Addition of section 7.4.2 Nicotine Over-exposure

[1] Types of Change: Major Change (e.g., version 1.0 to 2.0) is required for changes in the safety profile of the Product; Minor Change (e.g., version 1.0 to 1.1) is required for changes in Product's description not affecting the safety profile of the Product.

19.2 Appendix 2: Cumulative and Interval Summary Tabulations

19.2.1 Appendix 2a: Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

MedDRA System Organ Class	MedDRA Preferred Term	CC[1]	THS[2] 2.2	Total
Blood and lymphatic system disorders	Anaemia	1		1
Cardiac disorders	Acute myocardial infarction		1	1
Gastrointestinal disorders	Pancreatitis chronic	1		1
General disorders and administration site conditions	Death		1	1
Infections and infestations	Appendicitis	1		1
	Cellulitis	1		1
	Cellulitis staphylococcal	1		1
	Epiglottitis	1		1
	Influenza	1		1
	Peritonitis	1		1
	Pneumonia mycoplasmal		1	1
	Pyelonephritis acute	2		2
	Sinusitis		1	1
	Tooth infection	1		1
	Urosepsis		1	1
Injury, poisoning and procedural complications	Clavicle fracture	1		1
	Foot fracture	1		1
	Head injury		1	1
	Hip fracture		1	1
	Laceration	1		1
	Multiple fractures		1	1
	Pulmonary contusion	1		1
	Rib fracture	1		1
	Traumatic haemothorax		1	1
Metabolism and nutrition disorders	Diabetic ketoacidosis		1	1
Musculoskeletal and connective tissue disorders	Costochondritis	1		1
	Vertebral osteophyte	1		1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer		1	1
	Intestinal metastasis		1	1
	Papillary thyroid cancer		1	1
Nervous system disorders	Myelopathy	1		1
	Seizure		1	1
	Transient ischaemic attack		1	1

MedDRA System Organ Class	MedDRA Preferred Term	CC[1]	THS[2] 2.2	Total
Psychiatric disorders	Adjustment disorder with depressed mood	1		1
	Alcohol abuse		1	1
	Completed suicide		1	1
	Suicidal ideation	1		1
Renal and urinary disorders	Nephrolithiasis	1		1
Reproductive system and breast disorders	Menorrhagia		1	1
Respiratory, thoracic and mediastinal disorders	Pleural effusion	1		1
	Pneumonia aspiration		1	1
Social circumstances	Bereavement	1		1
Vascular disorders	Peripheral ischaemia		1	1
Total		24	20	44

[1] Conventional Cigarettes
[2] Tobacco Heating System

19.2.2 Appendix 2b: Cumulative Summary Tabulations of Serious Adverse Events from Passive Surveillance Pre-Market Studies

System Organ Class	Preferred Term	THS 2.2	THS 2.4	Total
General disorders and administration site conditions	Adverse event	1		1
	Injury associated with device	1		1
Infections and infestations	Bronchitis	1		1
	Cholecystitis infective	1		1
	Ear infection	1		1
	Osteomyelitis	1		1
	Pneumonia	1	1	2
	Sepsis	1		1
Injury, poisoning and procedural complications	Accident	1		1
	Concussion	1		1
	Fall	1		1
	Head injury	1		1
	Joint injury	1		1
	Limb injury	1		1
	Muscle strain	1		1
	Nerve injury	1		1
	Road traffic accident	1		1
	Skeletal injury	1		1
	Skin abrasion	1		1
	Thermal burn	1		1
Musculoskeletal and connective tissue disorders	Spinal disorder	1		1
	Spinal pain	1		1
Respiratory, thoracic and mediastinal disorders	Tonsillar cyst	1		1
Surgical and medical procedures	Hospitalization	1		1
Total		24	1	25

19.2.3 Appendix 2c: Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Events from Post-Marketing Experience

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
Blood and lymphatic system disorders	Anaemia		1			1
	Lymph node pain	2	2			2
	Lymphadenopathy	8	8			8
Blood and lymphatic system disorders Total		**10**	**11**			**11**
Cardiac disorders	Angina pectoris		2	8	8	10
	Arrhythmia	2	2	2	2	4
	Cardiac discomfort	9	9			9
	Cardiac disorder	1	5		2	7
	Cardiovascular disorder		1			1
	Cyanosis	2	2			2
	Myocardial infarction			3	3	3
	Myocardial ischaemia			1	1	1
	Palpitations	20	25	1	1	26
	Pericarditis			1	1	1
	Tachyarrhythmia			1	1	1
	Tachycardia	14	20	2	2	22
Cardiac disorders Total		**52**	**66**	**20**	**21**	**87**
Ear and labyrinth disorders	Ear discomfort		1			1
	Ear pain	1	2			2
	Hypoacusis		3			3
	Motion sickness	3	3			3
	Tinnitus	4	5			5
	Vertigo	19	22			22
Ear and labyrinth disorders Total		**27**	**36**			**36**
Endocrine disorders	Thyroid disorder	1	1			1
	Thyroid pain	1	1			1
Endocrine disorders Total		**2**	**2**			**2**
Eye disorders	Accommodation disorder		1			1
	Asthenopia	1	1			1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Blepharospasm	2	2			2
	Chromatopsia		1			1
	Dark circles under eyes	1	1			1
	Dry eye	6	6			6
	Excessive eye blinking	1	1			1
	Eye discharge	1	1			1
	Eye disorder	1	1			1
	Eye haemorrhage	1	1			1
	Eye inflammation	1	1			1
	Eye irritation	1	1			1
	Eye pain	8	12			12
	Eye paraesthesia	1	1			1
	Eye pruritus	4	5			5
	Eye swelling	8	9			9
	Lacrimation increased	2	3			3
	Metamorphopsia	1	2			2
	Ocular discomfort	1	2			2
	Ocular hyperaemia	7	7			7
	Photophobia	1	2			2
	Vision blurred	2	3			3
	Visual impairment	4	6			6
	Xerophthalmia	1	1			1
Eye disorders Total		**56**	**71**			**71**
Gastrointestinal disorders	Abdominal discomfort	37	40			40
	Abdominal distension	10	15			15
	Abdominal pain	10	15			15
	Abdominal pain lower	2	2			2
	Abdominal pain upper	56	66		1	67
	Abnormal faeces	1	2			2
	Allergic stomatitis	1	1			1
	Aphthous ulcer	17	19			19
	Aptyalism	1	1			1
	Breath odour	7	7			7

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Buccal mucosal roughening	1	3			3
	Cardiospasm	1	1			1
	Change of bowel habit	1	1			1
	Chapped lips	7	8			8
	Cheilitis	12	18			18
	Constipation	5	11			11
	Dental discomfort	2	3			3
	Dental paraesthesia	1	1			1
	Dental plaque	1	1			1
	Diarrhoea	16	19			19
	Dry mouth	79	88			88
	Duodenal ulcer	1	1			1
	Dyspepsia	65	72	1	1	73
	Dysphagia	11	13			13
	Enlarged uvula	1	2			2
	Epigastric discomfort		1			1
	Eructation	4	5			5
	Faeces discoloured	1	1			1
	Faeces soft	1	1			1
	Flatulence	3	9			9
	Functional gastrointestinal disorder	1	1			1
	Gastric dilatation	1	1			1
	Gastric disorder	2	4			4
	Gastric ulcer			1	1	1
	Gastritis	3	3			3
	Gastrointestinal disorder	3	3			3
	Gastrointestinal motility disorder		1			1
	Gastrointestinal sounds abnormal	1	1			1
	Gastrooesophageal reflux disease	7	8			8
	Gingival bleeding	26	29			29
	Gingival blister	3	4			4
	Gingival discolouration	1	1			1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Gingival discomfort	2	4			4
	Gingival disorder	7	8	1	1	9
	Gingival pain	21	22			22
	Gingival swelling	10	12			12
	Glossitis	10	14			14
	Glossodynia	64	80			80
	Haematochezia			1	1	1
	Hyperchlorhydria	2	2			2
	Hypoaesthesia oral	18	30			30
	Irritable bowel syndrome	1	1			1
	Lip blister	88	122			122
	Lip discolouration	14	16			16
	Lip disorder	4	6			6
	Lip dry	11	13			13
	Lip erythema	33	41			41
	Lip exfoliation	27	52			52
	Lip haemorrhage	6	8			8
	Lip pain	86	120			120
	Lip swelling	47	65			65
	Lip ulceration	1	4			4
	Loose tooth	1	1			1
	Mouth haemorrhage	9	11			11
	Mouth swelling	6	7			7
	Mouth ulceration	40	60			60
	Nausea	412	484	3	3	487
	Noninfective gingivitis	1	5			5
	Odynophagia	5	9			9
	Oesophageal dilatation	1	1			1
	Oesophageal discomfort	4	4			4
	Oesophageal disorder	1	1			1
	Oesophageal pain	4	5	1	1	6
	Oesophageal rupture	1	1			1
	Oral discomfort	92	111			111

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Oral disorder	2	3			3
	Oral mucosal blistering	15	25			25
	Oral mucosal discolouration	3	6			6
	Oral mucosal eruption	1	1			1
	Oral mucosal erythema	2	4			4
	Oral mucosal exfoliation	7	8			8
	Oral pain	47	66			66
	Oral pruritus	5	6			6
	Palatal disorder	3	3			3
	Palatal swelling	1	1			1
	Paraesthesia oral	35	46			46
	Pigmentation lip	1	1			1
	Plicated tongue	1	1			1
	Retching	11	12			12
	Saliva discolouration	4	4			4
	Salivary gland enlargement	1	1			1
	Salivary gland pain	1	1			1
	Salivary hypersecretion	6	8			8
	Sensitivity of teeth	2	2			2
	Stomatitis	52	60			60
	Swollen tongue	14	17			17
	Tongue blistering	9	11			11
	Tongue discolouration	2	2			2
	Tongue discomfort	19	41			41
	Tongue disorder	5	11			11
	Tongue dry	2	2			2
	Tongue eruption	6	7			7
	Tongue erythema	11	13			13
	Tongue exfoliation	1	1			1
	Tongue pruritus	1	1			1
	Tongue ulceration	2	2			2
	Tooth discolouration	3	3			3

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Tooth disorder	5	5			5
	Tooth loss			1	1	1
	Toothache	17	20			20
	Vomiting	223	281	10	15	296
Gastrointestinal disorders Total		**1952**	**2479**	**20**	**25**	**2504**
General disorders and administration site conditions	Adverse drug reaction	1	1			1
	Adverse event	22	33			33
	Adverse reaction	4	6			6
	Alcohol interaction	2	2	2		2
	Asthenia	25	34	1	2	36
	Chest discomfort	117	134		2	136
	Chest pain	94	108			108
	Chills	5	5	1		5
	Condition aggravated	12	13		1	14
	Crying	4	7		1	8
	Cyst	2	2			2
	Device intolerance	1	1	1		1
	Discomfort	43	55		1	56
	Face oedema	1	1	2		1
	Facial pain		1			1
	Fatigue	26	33	1	1	34
	Feeling abnormal	57	70			70
	Feeling cold	2	2			2
	Feeling drunk	1	3			3
	Feeling hot	11	16			16
	Feeling jittery	1	1			1
	Feeling of relaxation	1	1			1
	Food interaction		1			1
	Gait disturbance	1	3			3
	Gait inability	1	1			1
	General physical health deterioration	9	11		1	12
	Generalised oedema			1	1	1
	Hangover	1	1			1
	Hernia		1			1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Hunger	3	3			3
	Ill-defined disorder	18	18			18
	Inflammation	6	7			7
	Injury associated with device	2	2			2
	Malaise	228	276	3	4	280
	Mucosal dryness	4	5			5
	Mucosal induration		1			1
	Mucosal inflammation	1	2			2
	No adverse event	981	1270			1270
	Nodule	1	1			1
	Non-cardiac chest pain	2	2			2
	Oedema	1	1			1
	Pain	42	52	1	1	53
	Peripheral swelling	2	6			6
	Polyp	1	1			1
	Product intolerance	3	3			3
	Pyrexia	13	18	1	1	19
	Secretion discharge	7	7			7
	Sensation of blood flow		1			1
	Sensation of foreign body	46	54			54
	Sense of oppression	1	1			1
	Sensitivity to weather change	1	1			1
	Sluggishness	1	2			2
	Swelling	3	4	1	1	5
	Thirst	11	11			11
	Tobacco interaction	1	1			1
	Unevaluable event	33	46			46
	Withdrawal syndrome	2	2			2
General disorders and administration		**1858**	**2345**	**13**	**17**	**2362**

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
site conditions Total						
Hepatobiliary disorders	Gallbladder disorder	1	1			1
	Hepatic pain	2	2			2
	Hepatomegaly	1	1			1
	Liver disorder	1	1			1
Hepatobiliary disorders Total		**5**	**5**			**5**
Immune system disorders	Allergic oedema	1	1			1
	Allergy to chemicals	1	1	1	1	2
	Allergy to metals	1	1			1
	Device allergy	2	2			2
	Hypersensitivity	72	85	4	6	91
	Immune system disorder	1	1			1
Immune system disorders Total		**78**	**91**	**5**	**7**	**98**
Infections and infestations	Abscess oral		1			1
	Bronchiolitis	1	1			1
	Bronchitis	4	5	1	2	7
	Conjunctivitis	2	2			2
	Furuncle	1	1			1
	Gastroenteritis	1	1			1
	Gingival abscess		1			1
	Gingivitis	6	6			6
	Herpes virus infection	1	1			1
	Infection	2	2			2
	Influenza	5	6			6
	Laryngitis	2	2	1	1	3
	Lip infection	1	1			1
	Lower respiratory tract infection	1	1			1
	Nasopharyngitis	23	27			27
	Oral candidiasis	1	2			2
	Oral fungal infection	1	1			1
	Oral herpes	4	5			5
	Oral infection	1	1			1
	Oral pustule		1			1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Peritonsillar abscess			2	2	2
	Pharyngitis	13	15	1	1	16
	Pneumonia			4	6	6
	Purulent discharge	1	1			1
	Respiratory tract infection			1	1	1
	Rhinitis	6	7			7
	Sinusitis	1	1			1
	Tongue abscess	1	1			1
	Tonsillitis	9	11			11
	Viral infection	1	1			1
Infections and infestations Total		**89**	**105**	**10**	**13**	**118**
Injury, poisoning and procedural complications	Accidental exposure to product	82	120	2	2	122
	Accidental exposure to product by child	1109	1427	19	30	1457
	Accidental exposure to product packaging by child	1	1			1
	Airway burns	2	2			2
	Alcohol poisoning	1	1			1
	Burn oesophageal	10	12			12
	Burn oral cavity	131	160			160
	Burns first degree	1	1			1
	Burns second degree	2	4			4
	Device difficult to use	26	32			32
	Device use error	1	1			1
	Device use issue	1	6			6
	Electric shock	3	3			3
	Exposure during pregnancy	1	1			1
	Fall	1	1			1
	Foreign body in eye		1			1
	Foreign body in gastrointestinal tract	1	1			1
	Gingival injury	1	1			1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Incorrect route of drug administration	1	1			1
	Injury	6	7			7
	Joint dislocation	1	1			1
	Limb injury	1	2			2
	Lip injury	7	7			7
	Mouth injury	5	5			5
	Muscle injury			1	1	1
	Occupational exposure to product	1	5			5
	Poisoning	1	1	1	1	2
	Product use complaint	3	3			3
	Product use issue	4	4			4
	R b fracture			1	1	1
	Scar	3	3			3
	Scratch	1	1			1
	Skin injury	2	2			2
	Thermal burn	557	720			720
	Thermal burns of eye		1			1
	Tobacco poisoning	7	9			9
	Tongue injury	1	1			1
	Tooth injury	1	1			1
	Wound	3	4			4
	Wound complication		2			2
	Wound haemorrhage	1	1			1
	Wrong technique in device usage process	2	5			5
	Wrong technique in product usage process		1			1
Injury, poisoning and procedural complications Total		**1982**	**2562**	**24**	**35**	**2597**
Investigations	Blood aluminium increased	1	1			1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Blood glucose increased	2	2			2
	Blood pressure abnormal	1	1			1
	Blood pressure decreased	3	3			3
	Blood pressure increased	40	44		2	46
	Body temperature increased	2	4			4
	Breath sounds abnormal	1	1	1	1	2
	Chest X-ray abnormal	1	1			1
	General physical condition abnormal	3	3			3
	Heart rate abnormal	1	1			1
	Heart rate increased	29	36	1	1	37
	Hepatic enzyme increased	1	1			1
	Intraocular pressure increased	1	1			1
	Lymph node palpable	1	1			1
	Oxygen saturation decreased	1	1			1
	Oxygen saturation increased	1	1			1
	Respiratory rate decreased				1	1
	Respiratory rate increased	2	2			2
	Weight decreased	2	2			2
	Weight increased	8	10			10
	White blood cell count increased	1	1			1
Investigations Total		**102**	**117**	**2**	**5**	**122**
Metabolism and nutrition disorders	Acidosis	1	1			1
	Decreased appetite	5	7			7
	Dehydration	2	2			2
	Diabetes mellitus	1	2	1	1	3
	Feeding disorder	2	1			1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Increased appetite	1	2			2
Metabolism and nutrition disorders Total		**11**	**15**	**1**	**1**	**16**
Musculoskeletal and connective tissue disorders	Arthralgia	2	2			2
	Back pain	1	2			2
	Bone pain	1	1			1
	Limb discomfort	1	1			1
	Muscle spasms	1	3	1	1	4
	Muscle twitching	2	3			3
	Musculoskeletal chest pain	1	2			2
	Musculoskeletal discomfort	1	3			3
	Musculoskeletal disorder	1	1			1
	Musculoskeletal pain	2	2			2
	Musculoskeletal stiffness	6	7			7
	Neck pain	10	12			12
	Pain in extremity	11	12			12
	Pain in jaw	1	2			2
Musculoskeletal and connective tissue disorders Total		**41**	**53**	**1**	**1**	**54**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Laryngeal papilloma		1			1
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Total			**1**			**1**
Nervous system disorders	Ageusia	2	2			2
	Altered state of consciousness	1	1			1
	Amnesia	1	1			1
	Anosmia	1	1			1
	Aphonia	18	22			22
	Ataxia	1	1			1
	Autonomic nervous system imbalance	1	1	1	1	2

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Balance disorder	1	5	1	1	6
	Burning sensation	22	25			25
	Burning sensation mucosal	1	1			1
	Cerebral hypoperfusion			1	1	1
	Cerebrovascular accident			1	1	1
	Coordination abnormal		1			1
	Disturbance in attention	1	2			2
	Dizziness	318	361			361
	Dizziness postural	1	1			1
	Drooling		1		1	2
	Dysgeusia	53	74			74
	Dysgraphia	1	1			1
	Dysstasia	1	1			1
	Facial paralysis			1	1	1
	Facial spasm	1	1			1
	Hand-eye coordination impaired		1			1
	Head discomfort	4	6			6
	Headache	464	526			526
	Hyperaesthesia	1	1			1
	Hypersomnia	2	3			3
	Hypoaesthesia	12	14	1	1	15
	Hypogeusia	2	2			2
	Hypokinesia		1			1
	Lethargy	3	3			3
	Loss of consciousness			3	4	4
	Memory impairment	3	4	1	1	5
	Migraine	12	12			12
	Migraine with aura	1	1			1
	Movement disorder		1			1
	Neuralgia	1	1		1	2
	Neurological symptom	1	1			1
	Paraesthesia	8	8			8

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Parosmia	2	4			4
	Poor quality sleep	2	2			2
	Presyncope	2	2			2
	Reflexes abnormal	1	1			1
	Seizure				1	1
	Sensory disturbance	1	1			1
	Somnolence	10	11			11
	Speech disorder	2	3			3
	Syncope	4	5		1	6
	Tension headache	2	3			3
	Thermohypoaesthesia	2	2			2
	Tremor	14	17			17
	Visual perseveration	1	1			1
Nervous system disorders Total		**982**	**1140**		**11**	**1155**
Product issues	Device battery explosion	1	1			1
	Device battery issue	1	2			2
	Device breakage	3	3			3
	Device catching fire	1	1			1
	Device colour issue	1	1			1
	Device damage	7	8			8
	Device defective	8	9			9
	Device electrical finding	1	1			1
	Device issue	76	316			316
	Device leakage	9	9			9
	Device malfunction	17	23			23
	Device physical property issue	652	661			661
	Product caught fire	6	6			6
	Product colour issue	1	1			1
	Product odour abnormal	49	65			65
	Product physical issue	3	6			6

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Product quality issue	129	152			152
	Product substitution issue	1	1			1
	Product taste abnormal	59	74			74
Product issues Total		**1025**	**1340**			**1340**
Psychiatric disorders	Agitation	6	8			8
	Anger	1	1			1
	Anxiety	7	8			8
	Aversion	1	1			1
	Behavioral addiction	1	1			1
	Confusional state	2	2			2
	Daydreaming	1	1			1
	Decreased eye contact	1	1	1	1	2
	Dependence	1	1			1
	Depressed mood	1	2			2
	Depression	1	1			1
	Disorientation	6	6			6
	Eating disorder	1	2			2
	Euphoric mood	1	1			1
	Insomnia	12	14			14
	Irritability	3	6			6
	Mental disorder	1	1		1	2
	Mental status changes	1	1			1
	Middle insomnia	1	1			1
	Mood altered	11	17			17
	Nervousness	2	3			3
	Nicotine dependence	2	4			4
	Nightmare	1	1			1
	Panic attack	5	5			5
	Panic reaction		1			1
	Restlessness		1			1
	Sleep disorder	2	2	1	1	3
	Sleep disorder due to general medical condition, insomnia type		1			1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Speech sound disorder		1			1
	Stress	1	1			1
	Tension	3	3			3
	Tobacco withdrawal symptoms	1	1			1
Psychiatric disorders Total		**77**	**100**	**2**	**3**	**103**
Renal and urinary disorders	Polyuria	1	1			1
	Renal pain	1	1			1
Renal and urinary disorders Total		**2**	**2**			**2**
Respiratory, thoracic and mediastinal disorders	Allergic cough	4	4			4
	Asphyxia			10	11	11
	Asthma	22	25	2	2	27
	Asthmatic crisis			1	1	1
	Bronchial disorder	3	4			4
	Bronchial irritation	1	1			1
	Bronchitis chronic	3	3			3
	Catarrh	1	2			2
	Choking	2	4	16	16	20
	Choking sensation	27	30			30
	Cough	630	736	1	1	737
	Cough decreased	1	1			1
	Diaphragmatic disorder	1	1			1
	Dry throat	111	126			126
	Dysphonia	60	72			72
	Dyspnoea	119	144	3	4	148
	Emphysema	1	1			1
	Eosinophilic pneumonia acute				1	1
	Epistaxis	5	6	1	1	7
	Haemoptysis	4	11			11
	Hiccups	18	18			18
	Increased upper airway secretion	3	4			4
	Increased viscosity of bronchial secretion		1			1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Laryngeal discomfort	12	23			23
	Laryngeal oedema		1	1	1	2
	Laryngeal pain	6	7			7
	Laryngospasm	1	1			1
	Lung disorder	21	23	1	1	24
	Nasal congestion	10	11			11
	Nasal discharge discolouration	1	1			1
	Nasal discomfort	7	8			8
	Nasal dryness	7	8			8
	Nasal obstruction		1			1
	Nasal oedema	1	1			1
	Nasal pruritus		1			1
	Oropharyngeal blistering	1	3			3
	Oropharyngeal discomfort	38	50			50
	Oropharyngeal pain	414	502			502
	Oropharyngeal swelling	1	2			2
	Painful respiration	1	1			1
	Pharyngeal disorder	7	8			8
	Pharyngeal erythema	5	7			7
	Pharyngeal haemorrhage	3	5	1	1	6
	Pharyngeal hypoaesthesia	3	4			4
	Pharyngeal inflammation	5	9			9
	Pharyngeal oedema	39	45			45
	Pharyngeal paraesthesia	10	11			11
	Pneumothorax			1	1	1
	Productive cough	70	86			86
	Pulmonary congestion	3	4			4
	Pulmonary oedema			1	1	1
	Pulmonary pain	40	48			48
	Rales	1	1			1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Respiration abnormal	3	3			3
	Respiratory disorder	5	6			6
	Respiratory tract congestion			1	1	1
	Respiratory tract irritation	5	11			11
	Rhinalgia	2	5			5
	Rhinorrhoea	3	6			6
	Rhonchi	1	1			1
	Sinus congestion	1	1			1
	Sinus disorder	2	2			2
	Sneezing	11	12			12
	Snoring	1	1			1
	Sputum discoloured	2	2			2
	Sputum increased	4	4			4
	Sputum retention	2	2			2
	Suffocation feeling	22	25			25
	Throat clearing	1	1			1
	Throat irritation	289	347			347
	Throat lesion	1	1			1
	Throat tightness	16	23			23
	Tonsillar disorder	1	2			2
	Tonsillar haemorrhage		1			1
	Tonsillar hypertrophy	6	8			8
	Tonsillar inflammation	4	4			4
	Tonsillar ulcer		1			1
	Tracheal disorder	1	1			1
	Tracheal pain	1	2			2
	Upper respiratory tract congestion	3	3			3
	Upper respiratory tract irritation	2	2			2
	Vocal cord disorder	3	3			3
	Vocal cord inflammation		1			1
	Vocal cord thickening	1	1			1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Wheezing	6	7			7
Respiratory, thoracic and mediastinal disorders Total		**2122**	**2555**	**40**	**43**	**2598**
Skin and subcutaneous tissue disorders	Acne	24	24			24
	Acne varioliformis	1	1			1
	Angioedema			3	4	4
	Blister	38	48			48
	Blister rupture		1			1
	Blood blister		1			1
	Cold sweat	8	10			10
	Dermatitis	1	1			1
	Dermatitis acneiform	1	1			1
	Dermatitis allergic	2	2			2
	Dermatitis atopic	1	1			1
	Dry skin	2	5			5
	Eczema	2	2			2
	Erythema	14	21			21
	Hair disorder	1	1			1
	Hyperhidrosis	10	12			12
	Miliaria	1	1			1
	Nail hypertrophy	1	1			1
	Pain of skin	1	2			2
	Pruritus	28	36	2	2	38
	Pruritus generalised	9	12		1	13
	Rash	38	41	1	1	42
	Rash erythematous	4	4			4
	Rash generalised	14	15	1	2	17
	Rash macular	1	1			1
	Rash papular	2	2			2
	Rash pruritic	3	4			4
	Rosacea	1	1			1
	Scab	3	5			5
	Sebaceous gland disorder	1	1			1
	Skin discolouration	4	4			4
	Skin disorder	7	7			7

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
	Skin exfoliation	6	11			11
	Skin haemorrhage	1	1			1
	Skin irritation	5	5	1	1	6
	Skin lesion		1			1
	Skin odour abnormal	2	3			3
	Skin reaction		1			1
	Solar lentigo	1	1			1
	Swelling face	3	3			3
	Urticaria	10	14		1	15
Skin and subcutaneous tissue disorders Total		**251**	**308**	**8**	**12**	**320**
Social circumstances	Impaired driving ability	1	1			1
	Passive smoking	7	14			14
Social circumstances Total		**8**	**15**			**15**
Surgical and medical procedures	Nerve block	1	1			1
	Surgery			1	1	1
Surgical and medical procedures Total		**1**	**1**	**1**	**1**	**2**
Vascular disorders	Angiopathy	1	1			1
	Blood pressure fluctuation	1	1			1
	Flushing	1	2			2
	Haematoma	1	1			1
	Haemorrhage	1	1			1
	Hypertension	6	7			7
	Hypertensive crisis	1	1			1
	Hypotension	1	2			2
	Internal haemorrhage			1	1	1
	Pallor	17	20	4	7	27
	Peripheral vascular disorder		1			1
	Poor peripheral circulation		1			1
	Vasospasm			1	1	1
	Venous occlusion			1	1	1

MedDRASOC	MedDRA PT	Non-serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
Vascular disorders Total		**31**	**39**	**6**	**9**	**48**
Total		**10764**	**13459**	**164**	**208**	**13667**

19.3 Appendix 3: Tabular Summary of Safety Signals

Signal term	**Date detected**	**Status (ongoing or closed)**	**Date closed (for closed signals)**	**Source of signal**	**Reason for evaluation & summary of key data**	**Method of signal evaluation**	**Action(s) taken or planned**
Acne	31-Dec-2017	Ongoing	*NA*	Global safety database	Increased reporting rate	Qualitative and quantitative	Monitoring activities
Chest discomfort	31-Dec-2017	Ongoing	*NA*	Global safety database	Increased reporting rate	Qualitative and quantitative	Monitoring activities
Rash	31-Dec-2017	Ongoing	*NA*	Global safety database	Increased reporting rate	Qualitative and quantitative	Monitoring activities

19.4 Appendix 4: Listing of Interventional and Non-Interventional Studies during the Reporting interval

ZRHR-ERS-09-US	Randomized, controlled, 2-arm parallel group, multi-center study, to evaluate biological and functional changes in healthy smokers switching to Tobacco Heating System 2.2 (THS 2.2) compared to continuing smoking CC for 26 weeks in an ambulatory setting.	United States	12-March-2015	Ongoing
ZRHR-ERS-09-US-EXT	26 week extension study to ZRHR-ERS-09-US.	United States	30-Sept-2015	Ongoing
P1-OHS-01-JP	6-month randomized, controlled, open-label, 2-arm parallel group, multicenter study to evaluate the effect of switching from cigarette smoking to the use of THS products in smokers with generalized	Japan	09-Nov-2017	Ongoing

	chronic periodontitis on the response to mechanical periodontal treatment and oral health status.			
P1_COT_DK	4 weeks ad libitum home usage of the THS 2.4 Regular and Menthol, aiming to understand the perception and adoption of the new products offer.	Denmark	05-Sept-2016	Completed

19.5 Appendix 5: Signature Page

PMI SURV 2018 SUR01

Period Covered: 01-~~Jan~~-2017~~to~~ 31-Dec-2017

Electrically Heated Tobacco Product (EHTP) and Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS)

Justification	**Name/*Title***	**Signature**	**Date**
Author	Ilenia D'Errico/*Scientist Product Surveillance*		09-May-2018
Medical Review	Nicolas Blanc/*Manager Medical Operations*		09-May-2018
Medical Review and Approval	Prieto Luis/*Director Population Risk Assessment*		09-May-2018
Medical Review and Approval	Frank Luedicke/*Chief Medical Officer*		09/May/2018

19.6 Appendix 6: Market Specific Appendices

Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Events from the US Post-Marketing Experience

Up to the DLP of this SUR THS products were not marketed in US.

Table 19-1 Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Events from the US Post-Marketing Experience

MedDRASOC	MedDRA PT	Non-Serious		Serious		Total
		Interval	Cumulative	Interval	Cumulative	
NA	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*

20 SUPPLEMENT 1: SERIOUS UNEXPECTED ADVERSE EVENTS REPORTED FOR THS PRODUCTS AFTER DLP

In order to provide the most recent information regarding safety matters to competent authorities, PMI is introducing a Supplement to the current SUR listing all Serious Unexpected Adverse Events reported for THS products from 01-Jan-2018 to 31-Mar-2018. The cases are presented in Table 20-1 organized by MedDRA SOCs (PTs are listed in alphabetical order and case IDs in chronological order; a brief summary for each case is also presented).

Table 20-1 Serious Unexpected Adverse Events reported for THS products **from 01-Jan-2018 to 31-Mar-2018**

SOCs	PTs	Case ID	Summary
Cardiac disorders (n=14)	Angina pectoris (n=6)	PMI008994	Case PMI008994 concerns a 25-years-old male who used 3 THS heat-sticks. The verbatim reported was “piercing pain in the heart”, corresponding to the MedDRA coding “Angina pectoris”. No consumer’ medical history was provided. The severity of the event was moderate. The event improved when the use of the product was stopped.
		PMI009634	Case PMI009634 concerns a female (unknown age) with unreported THS usage habits. The verbatim reported was “stinging pain in the heart”, corresponding to the MedDRA coding “Angina pectoris”. No consumer’ medical history was provided. The severity and the outcome of the event were not reported.
		PMI009709	Case PMI009709 concerns a 42-years-old female who was daily using THS (3 units per day). The verbatim reported was “heart pain”, corresponding to the MedDRA coding “Angina pectoris”. No consumer’ medical history was provided. The severity of the event was mild. The event improved when the use of the product was stopped and

SOCs	PTs	Case ID	Summary
			occurred again when the product was restarted.
		PMI009711	Case PMI009711 concerns a 22-years-old male who was daily using the product (20 units per day). The verbatim reported was "heart pain", corresponding to the MedDRA coding "Angina pectoris". No consumer' medical history was provided. The event was assessed as severe and improved when the use of the product was stopped.
		PMI010494	Case PMI010494 concerns a 53-years-old male with unreported THS usage habits. The verbatim reported was "heart ache", corresponding to the MedDRA coding "Angina pectoris". No consumer' medical history was provided. The severity and the outcome of the event were not reported.
		PMI010539	Case PMI010539 concerns a 53-years-old male with unreported THS usage habits. The verbatim reported was "stabbing pain over the heart", corresponding to the MedDRA coding "Angina pectoris". No consumer' medical history was provided. The severity and the outcome of the event were not reported.
	Arrhythmia (n=5)	PMI007213	Case PMI007213 concerns a 62-years-old female with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
		PMI007569	Case PMI007569 concerns an adult consumer (age and gender unknown) with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
		PMI008638	Case PMI008638 concerns a 47-years-old female with unreported THS usage habits. No consumer' medical history was provided.

SOCs	PTs	Case ID	Summary
			The severity and the outcome of the event were not reported.
		PMI008909	Case PMI008909 concerns a 44-years-old male with occasional use of THS (3 units per week). No consumer' medical history was provided. The event was reported as severe and improved when the use of the product was stopped. At the time of reporting the event was not resolved.
		PMI009410	Case PMI009410 concerns a 40-years-old female with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
	Myocardial infarction (n=2)	PMI008918	Case PMI008918 concerns a 41-years-old male with unreported THS usage habits. The verbatim reported was "heart attack", corresponding to the MedDRA coding "Myocardial infarction". No consumer' medical history was provided. The severity and the outcome of the event were not reported.
		PMI010337	Case PMI010337 concerns a 39-years-old male with unreported details on THS usage habits. No consumer's medical history was provided. The severity of the event was not reported. PMI became aware of this report from descriptions in a number of non-company sponsored digital media where the alleged wife of the consumer posted that the consumer died due to a heart attack. No medical confirmation was provided. This is the first spontaneous report of its kind the company picked up from non-PMI sponsored social media, and there are a number of uncertainties regarding the robustness of the information.
	Pericarditis (n=1)	PMI007264	Case PMI007264 concerns a 37-years-old male who consumed a total of 4 packs of HeatSticks prior to the event. No consumer' medical history was provided. The severity

SOCs	PTs	Case ID	Summary
			and the outcome of the event were not reported.
Eye disorders (n=2)	Blindness transient (n=1)	PMI008637	Case PMI008637 concerns a 19-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
	Eye haemorrhage (n=1)	PMI010076	Case PMI010076 concerns a 38-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity was not reported. At the time of reporting the event was resolved.
Gastrointestinal disorders (n=2)	Haematemesis (n=1)	PMI007451	Case PMI007451 concerns a 49-years-old male who was daily using THS (10 to 13 units per day). The consumer had a medical history of Hepatitis B and no chronic diseases. The severity of the event was mild and improved when the use of the product was stopped.
	Oral pain (n=1)	PMI009563	Case PMI009563 concerns a consumer (unknown age and gender) with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
General disorders and administration site conditions (n=2)	Feeling abnormal (n=1)	PMI009722	Case PMI009722 concerns a 39-years-old female with unreported THS usage habits. The consumer medical history included thrombosis of the legs. The severity and the outcome of the event were not reported.
	Ill-defined disorder (n=1)	PMI007786	Case PMI007786 concerns a 59-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
Infections and infestations	Bronchitis (n=1)	PMI009204	Case PMI009204 concerns a 41-years-old male with unreported THS usage habits. No consumer' medical history was provided.

SOCs	PTs	Case ID	Summary
(n=7)			The severity and the outcome of the event were not reported.
	Pneumonia (n=4)	PMI007293	Case PMI007293 concerns a 51-years-old female with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
		PMI007881	Case PMI007881 concerns a 25-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
		PMI009070	Case PMI009070 concerns a 34-years-old male with daily THS usage (6 units per day). No consumer' medical history was provided. The event was considered severe and required medical advice. Antibiotics were administered due to the event. The event did not improve when the use of the product was stopped. At the time of reporting the event was not resolved.
		PMI009719	Case PMI009719 concerns a 68-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
	Pneumonia viral (n=1)	PMI009968	Case PMI009968 concerns a consumer (unknown age and gender) with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
	Sinusitis (n=1)	PMI009631	Case PMI009631 concerns a 42-years-old female with a daily THS usage (average 15 units per day). No consumer' medical history was provided. The event was considered severe and required medical advice. Antibiotics were prescribed due to the event. At the time of reporting the event was not resolved.

SOCs	PTs	Case ID	Summary
Injury, poisoning and procedural complications (n=1)	Accidental exposure to product (n=1)	PMI007447	Case PMI007447 concerns a 49-years-old male with unreported THS usage habits. The consumer forgot he had put a used heatstick in a coffee cup and drank from the cup, leading to oropharyngeal discomfort. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
Metabolism and nutrition disorders (n=1)	Diabetes mellitus (n=1)	PMI007567	Case PMI007567 concerns a 40-years-old male with unreported THS usage habits. The consumer had no medical history of Diabetes. The severity and the outcome of the event were not reported.
Nervous system disorders (n=7)	Cerebral haemorrhage (n=1)	PMI007786	Case PMI007786 concerns a 59-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the events were not reported.
	Cerebrovascular accident (n=2)	PMI007786	
		PMI007980	Case PMI007980 concerns an adult consumer (unknown age and gender) with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
	Depressed level of consciousness (n=1)	PMI007816	Case PMI007816 concerns a 1-year-old male child who was accidentally exposed to THS. The medical history included developmental retard and hearing loss. The child ate used heating-type cigarettes and was treated with infusion solution. The severity and the outcome of the event were not reported.
	Epilepsy (n=1)	PMI007483	Case PMI007483 concerns an adult male (unknown age) with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
	Facial paralysis (n=1)	PMI009152	Case PMI009152 concerns a 21-years-old male with daily THS usage (10 units per day). No consumer' medical history was

SOCs	PTs	Case ID	Summary
			provided. The severity of the event was moderate. Unspecified treatment was administered due to the event. The event improved when product use was stopped but at the time of reporting was not resolved.
	Paralysis (n=1)	PMI010087	Case PMI010087 concerns a 45-years-old male with unreported THS usage habits. The consumer reported that he developed infection in his ears after using the IQOS which caused paralysis on his face. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
Respiratory, thoracic and mediastinal disorders (n=20)	Asphyxia (n=2)	PMI007881	Case PMI007881 concerns a 25-years-old male with unreported THS usage habits. The consumer reported that IQOS suffocates him, corresponding to the MedDRA coding "Asphyxia". No consumer' medical history was provided. The severity and the outcome of the event were not reported.
		PMI010375	Case PMI010375 concerns a 56-years-old male with unreported THS usage habits. The consumer reported that IQOS suffocates him, corresponding to the MedDRA coding "Asphyxia". The medical history included pacemaker implantation. The severity and the outcome of the event were not reported.
	Choking (n=12)	PMI007880	Case PMI007880 concerns a 51-years-old female with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported. Company comment: The reported choking event is not supported by evidence of mechanical obstruction. This event refer most likely to a sensation of chocking.
		PMI007978	Case PMI007978 concerns a 71-years-old male with unreported THS usage habits. No consumer' medical history was provided.

SOCs	PTs	Case ID	Summary
			The severity and the outcome of the event were not reported. Company comment: The reported choking event is not supported by evidence of mechanical obstruction. This event refer most likely to a sensation of chocking.
		PMI008137	Case PMI008137 concerns a 36-years-old female with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported. Company comment: The reported choking event is not supported by evidence of mechanical obstruction. This event refer most likely to a sensation of chocking.
		PMI008312	Case PMI008312 concerns a 21-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported. Company comment: The reported choking event is not supported by evidence of mechanical obstruction. This event refer most likely to a sensation of chocking.
		PMI008478	Case PMI008478 concerns a 41-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported. Company comment: The reported choking event is not supported by evidence of mechanical obstruction. This event refer most likely to a sensation of chocking.
		PMI008479	Case PMI008479 concerns a 44-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.

SOCs	PTs	Case ID	Summary
			Company comment: The reported choking event is not supported by evidence of mechanical obstruction. This event refer most likely to a sensation of chocking.
		PMI008480	Case PMI008480 concerns a 53-years-old female with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported. Company comment: The reported choking event is not supported by evidence of mechanical obstruction. This event refer most likely to a sensation of chocking.
		PMI008639	Case PMI008639 concerns a 24-years-old female with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported. Company comment: The reported choking event is not supported by evidence of mechanical obstruction. This event refer most likely to a sensation of chocking.
		PMI008904	Case PMI008904 concerns a 28-years-old female with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported. Company comment: The reported choking event is not supported by evidence of mechanical obstruction. This event refer most likely to a sensation of chocking.
		PMI008917	Case PMI008917 concerns a 29-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported. Company comment: The reported choking event is not supported by evidence of

SOCs	PTs	Case ID	Summary
			mechanical obstruction. This event refer most likely to a sensation of chocking.
		PMI009218	Case PMI009218 concerns a 71-years-old female with unreported THS usage habits. The medical history included asthma. The severity and the outcome of the event were not reported. Company comment: The reported choking event is not supported by evidence of mechanical obstruction. This event refer most likely to a sensation of chocking.
		PMI009723	Case PMI009723 concerns a 65-years-old male with unreported THS usage habits. The medical history included asthma. The severity and the outcome of the event were not reported. Company comment: The reported choking event is not supported by evidence of mechanical obstruction. This event refer most likely to a sensation of chocking.
	Lung disorder (n=1)	PMI007700	Case PMI007700 concerns a 19-years-old female with a daily THS usage (20 units per day). The medical history included asthma. The severity of the event was moderate and at the time of reporting was resolved.
	Oropharyngeal discomfort (n=1)	PMI007447	Case PMI007447 concerns a 49-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
	Pharyngeal haemorrhage (n=2)	PMI009050	Case PMI009050 concerns a 43-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
		PMI009111	Case PMI009111 concerns a 27-years-old male with unreported THS usage habits. No consumer' medical history was provided.

SOCs	PTs	Case ID	Summary
			The severity and the outcome of the event were not reported.
	Pulmonary oedema (n=2)	PMI007984	Case PMI007984 concerns a 30-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
		PMI009144	Case PMI009144 concerns an adult consumer (unknown age and gender) with unreported THS usage habits. The consumer reported that when he/she used iQOS, his/her lungs filled with fluid, corresponding to the MedDRA coding "Pulmonary oedema". No consumer' medical history was provided. The severity and the outcome of the event were not reported.
Vascular disorders (n=2)	Haemorrhage (n=1)	PMI009612	Case PMI009612 concerns a 35-years-old male with unreported THS usage habits. No consumer' medical history was provided. The severity and the outcome of the event were not reported.
	Pallor (n=1)	PMI007816	Case PMI007816 concerns a 1-year-old male child who was accidentally exposed to THS. The medical history included developmental retard and hearing loss. The child ate used heating-type cigarettes and was treated with infusion solution. The severity and the outcome of the event were not reported.

Company comment: The cases presented in the table above were poorly documented and not confirmed by Health Care Professionals. For the vast majority of cases no consumer medical history was provided and no information regarding treatments administration following the occurrence of the event was reported. The action taken with the product use was also not provided. Thus, given the paucity of information a causal role of the product in the occurrence of the serious unexpected events could not be medically assessed. The information received after DLP of this SUR (from 01-Jan-2018 to 31-Mar-2018) did not support an update of the Safety profile of THS products.