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PMI RESEARCH & DEVELOPMENT

Safety Update Report
Tobacco Heating System 2.2 Regular

Report Number:	PMI_SURV_2015_SUR01
Period Covered:	01 May 2014 to 30 April 2015
Product Name:	Tobacco Heating System 2.2 Regular
Sponsor:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	Final v1.0
Date:	25 June 2015
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EXECUTIVE SUMMARY

This is the second safety update report (SUR) on Tobacco Heating System 2.2 Regular (THS 2.2 Regular, herein referred to as THS 2.2), summarizing relevant safety data received by Philip Morris International (PMI) within the period from 01 May 2014 to 30 April 2015 and which is compiled according to the International Conference on Harmonisation guideline ICH-E2F.

THS 2.2 is test marketed in Nagoya (Japan) since 04 Nov 2014 and in Milan (Italy) since 20 Nov 2014.

There were three completed clinical studies and two ongoing clinical studies with THS 2.2 during the review period of this report.

Cumulatively, in the five clinical trials sponsored by PMI, approximately 342 subjects have been exposed to THS 2.2.

During the period of this report, the consumer exposure to THS 2.2 in the market research studies (pre-marketing safety surveillance) was about 3502 consumers. The number of consumers of THS 2.2 in the post-market setting (post-marketing passive safety surveillance) is estimated to be around 17’000.

During the period under review, one serious case (including 3 serious adverse events (SAEs)) and 182 non-serious cases (including 350 Adverse events (AEs)) were reported in the Company safety database from clinical studies, pre-market studies and post-market safety surveillance to PMI or any affiliate involving THS 2.2. Additionally, 280 non-serious AEs were reported from completed clinical studies according to correcponding clinical study reports.

During the review period the Reference safety information (RSI) was updated. The current RSI (Investigator’s Brochure Edition 5.0, dated 27 Apr 2015) adequately reflects the product`s safety profile.

Based on the currently available information from ongoing and completed clinical studies, and from pre-market studies and post-marketing safety surveillance, exposure to THS 2.2 did not raise any new safety concerns in the adult smokers.

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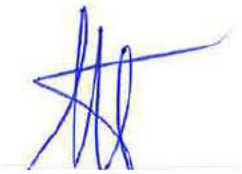
LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

EC	Ethical Committee
AE	Adverse event
BALF	Bronchoalveolar lavage fluid
DIBD	Development international birth date
DLP	Data lock point
HC	Heated cigarette
HPHC	Harmful and potentially harmful constituent
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICSR	Individual case safety report
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NNS	Nicotine nasal spray
PK/PD	Pharmacokinetic/Pharmacodynamic
PMI	Philip Morris International
PT	Preferred term
RSI	Reference safety information
SAE	Serious adverse event
SOC	System organ class
SUR	Safety update report
THS 2.2	Tobacco Heating System 2.2
UK	United Kingdom
WOT	Whole offer test

SIGNATURES

Name / Function / Company	Date	Signature
John Magnette, MD, DipPharmMed, FFPM Manager Product Surveillance Philip Morris Products S.A.	25 June 2015	
Frank Lüdicke, MD Director Product Assessment and Scientific Substantiation Philip Morris Products S.A.	25 June 2015	

1 INTRODUCTION

This is the second safety update report (SUR) on Tobacco Heating System 2.2 Regular (THS 2.2 Regular, herein referred to as THS 2.2), summarizing relevant safety data received by Philip Morris International (PMI, herein referred to as the Company) within the period from 01 May 2014 to 30 April 2015 and which is compiled according to the ICH-E2F guideline.

The Development international birth date (DIBD) of the THS 2.2 is 30 April 2013, based on the date of the first ethics committee approval for the first clinical study (17 May 2013).

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. THS 2.2 belongs to the tobacco products category called by the Company as the Heat-not-Burnt tobacco product class.

To use the 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 around the filter and drawing air through the THS Tobacco Stick. During use, the THS Tobacco Stick is heated according to a carefully controlled temperature profile within the holder to heat the tobacco without combustion while at the same time providing an acceptable consumer experience in a consistent manner.

When testing earlier development versions of THS in clinical studies, subjects were able to substantially reduce their exposure to selected Harmful and potentially harmful constituents (HPHCs). However, consumer acceptance of those product versions was low, in part due to their design features. Based on this experience, THS has been improved and the temperature at which the Tobacco Stick is heated was further reduced to less than 350 °C in the current version, THS 2.2.

2 WORLDWIDE STATUS

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

THS 2.2 is test marketed in Nagoya (Japan) since 04 Nov 2014 and in Milan (Italy) since 20 Nov 2014.

3 ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS

No specific actions have been taken by the Regulatory Authorities, by the sponsor Company, by data monitoring committees or ethics committees that had an impact on the conduct of a specific clinical study(ies) or on the overall clinical development programmes for THS 2.2 during the period covered by this report.

4 CHANGES TO REFERENCE SAFETY INFORMATION

The Reference safety information (RSI) for THS 2.2 at the beginning of the SUR review period was the Investigator's Brochure (IB) Edition 3.0, dated 14 April 2014.

During the review period, there have been changes to the RSI (Appendix A).

The IB Edition 5.0, dated 27 Apr 2015 served as the RSI for this SUR (Appendix A).

5 INVENTORY OF CLINICAL STUDIES ONGOING AND COMPLETED DURING THE REPORTING PERIOD

During the reporting period covered by this SUR the following two clinical studies were **ongoing**:

- ZRHR-REXC-04-JP: reduced exposure, 1-week clinical study.

A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching from conventional cigarettes to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to smokers continuing to use conventional cigarettes for 5 days in confinement. The clinical study report for this study is not yet available.

- ZRHR-ERS-09-US: biological and functional changes in healthy smokers after switching to THS 2.2 for 26 weeks.

A 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 conventional cigarettes for 26 weeks in an ambulatory setting. This study is currently in its subjects' recruitment phase.

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

- ZRHR-PK-01-EU: pharmacokinetic/pharmacodynamics (PK/PD) single use clinical study

A single-centre, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 (THS 2.2) following single use in smoking, healthy subjects compared to conventional cigarettes and nicotine nasal spray (NNS).

- ZRHR-PK-02-JP: pharmacokinetic/pharmacodynamics (PK/PD) single use clinical study

A single-centre, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 (THS 2.2) following single use in smoking, healthy subjects compared to conventional cigarettes and nicotine 2mg gum.

- ZRHR-REXC-03-EU: reduced exposure, 1-week clinical study

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

The tables presented in Appendix B contain more detailed information on these clinical studies.

6 ESTIMATED CUMULATIVE EXPOSURE

6.1 Cumulative Subject Exposure in the Development Program

Cumulatively, in the five clinical studies sponsored by the Company, approximately 342 subjects have been exposed to THS 2.2 (see Appendix B).

The typical demographic characteristics of the population for the five listed clinical studies are as follows:

- Healthy male and female adult smokers, Caucasian and Japanese, aged 21 to 65 years old.
- Smoking at least 10 commercially available non-menthol conventional cigarettes per day for at least the last four weeks before inclusion, with smoking history of three years or more.
- For study ZRHR-ERS-09-US, subjects were required to be aged at least 30 years old.

6.2 Consumer Exposure from Pre-Marketing Experience

During the period of this report (covering from 01 May 2014 to 30 Apr 2015), passive safety surveillance was implemented in 5 market research studies (pre-marketing safety surveillance). The consumer exposure to THS 2.2 in these market research studies was about 3502 consumers (market research respondents) (see details in Table 1).

Table 1 Consumer Exposure toTHS 2.2 in the Pre-Market Passive Safety Surveillance

	BT1 Italy	WOT2 Italy	WOT1 Germany	WOT1 Switzerland	WOT1 Korea	Total
Consumer exposure to THS 2.2	675	928	593	344	962	3502

BT: Blend Test in market research settings

WOT: Whole offer test in market research settings

6.3 Consumer Exposure from Post-Marketing Experience

During the period of this report (covering from 01 May 2014 to 30 Apr 2015), the total number of consumer exposed to THS 2.2 in markets is estimated to be approximately 17'000, based on number of THS 2.2 devices and proportion of non-menthol tobacco sticks (also called Marlboro flavor or "regular" flavor) sold during the period of November 2014 (date of 1st launch) and April 2015 in the test market in Japan and Italy.

7 DATA IN LINE LISTINGS AND SUMMARY TABULATIONS

Line listings and summary tabulations presented in this safety update report were generated from the Company safety database. The company safety database includes all AEs reported from pre-and post-marketing safety surveillance as well as SAEs reported from clinical studies.

Line listings and summary tabulations for all non-serious AEs from clinical studies are reported separately, as part of each clinical study report. Only significant findings (if any) from clinical studies are reported in the SUR.

For the generation of line-listings and summary tabulations, Argus and BaseCon Pharmacovigilance databases were searched for individual case safety reports (ICSRs; also called "cases") reported from clinical studies, pre-market studies and post-market safety surveillance to PMI or any affiliate. Further details are described in section 7.2 and section 7.3.

Relevant safety findings from these sources are described in sections 8, 9, 10 and 11.

During the period under review, one serious case (from Argus database), and 182 non-serious cases (87 from Argus and 95 from BaseCon databases) were received by the Company for THS 2.2 (Appendix C).

7.1 Reference Information

The current version of Medical Dictionary for Regulatory Activities (MedDRA) has been used for the coding of AEs; as of May 2014, the version in use was 17.0 and as of November 2014 the version in use was 17.1. The line listings and the summary tabulations are sorted alphabetically by primary System organ class (SOC) and Preferred term (PT) level.

"Expectedness" for THS 2.2 is based on the IB that was available at the assessment date of the case (see Appendix A).

7.2 Line Listings of Serious and Non-Serious Adverse Events during the Reporting Period

The Company Safety Databases referred to above were searched for ICSRs received between 01 May 2014 and 30 Apr 2015, and meeting the criteria mentioned below:

- All ICSRs with **serious and non-serious** AEs (causality assessed as not reported/ related/ not related by either the reporter or the Company), from clinical studies, pre-market studies and post-market safety surveillance to PMI or any affiliate.

Appendix C includes the line-listings with all cases meeting the above-mentioned SUR inclusion criteria for the reporting period.

The line-listings contain all data required by the ICH guideline E2F (study identification, subject identification number, case number, country, reaction/event, etc.) and are sorted by SOC and PT. Each ICSR is included only once regardless of how many reactions/events were

reported; if there are more than one reactions/events, all of them are shown in the field "reaction" but the case just appears under the SOC corresponding to the most serious one.

7.3 Cumulative Summary Tabulations of Serious and Non-Serious Adverse Events

Cumulatively, there were three SAEs belonging to the same subject (one single case PMI000109) and 350 (149 from Argus and 201 from BaseCon databases) non-serious AEs reported up to the Data lock point of this SUR, for THS 2.2.

Cumulative summary tabulations in Appendix C are presented for the previous review period (from IBD to 30 April 2014) and from 01 may 2014 to the Data lock point (DLP) of this SUR (30 Apr 2015) and include all serious and non-serious AEs. The summary tabulations are sorted primarily by SOC and PT.

8 SIGNIFICANT FINDINGS FROM CLINICAL STUDIES DURING THE REPORTING PERIOD

8.1 Completed Clinical Studies

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

- **ZRHR-PK-01-EU:** A single-centre, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 (THS 2.2) following single use in smoking, healthy subjects compared to conventional cigarettes and nicotine nasal spray (NNS).

  Safety results: There were no SAEs or severe AEs reported in this study and no subjects discontinued from the study due to an AE. Overall, there were 39 AEs reported by 23 of the 62 subjects (37%) in the safety population, the majority of which were mild in severity. The frequency of AEs was greater for the THS 2.2 − CC sequence (21 AEs) compared to the CC − THS 2.2 (10 AEs), THS 2.2 – NNS (4 AEs), and NNS − THS 2.2 (4 AEs) sequences. The greater number of AEs in the THS 2.2 − CC sequence was partly due to 7 study procedure related AEs in 3 subjects which were not observed in any of the other sequences. The incidence of subjects reporting AEs was comparable between the THS 2.2 – CC and THS 2.2 – NNS sequences (44.4% to 45.5%) and was lower in the CC − THS 2.2 (31.8%) and NNS − THS 2.2 (22.2%) sequences. The most frequent AEs were dizziness (8 AEs), headache (6 AEs), presyncope (6 AEs), nausea (3 AEs), and vomiting (3 AEs). All other AEs were reported by 2 or fewer subjects and a maximum of 1 subject per sequence.

  During the study, 12 subjects experienced 14 AEs that were considered to be related to IP (THS 2.2 or CC) and none of the events were considered unexpected. No AEs were considered to be related to NNS use. No device events or malfunctions occurred during the study for any subject.

- **ZRHR-PK-02-JP:** A single-centre, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 (THS 2.2) following single use in smoking, healthy subjects compared to conventional cigarettes and nicotine 2mg gum.

  Safety results: There were no SAEs or severe AEs reported in this study and no subjects discontinued from the study due to an AE. Overall, there were 14 AEs reported by 11 of the 65 subjects (17%) in the safety population (which included 3 subjects who were enrolled but not randomized), the majority of which were mild in severity. The incidence of AEs in the THS 2.2 – CC, CC - THS 2.2, and NRT gum – THS 2.2 sequences were comparable (11% to 14%), while the incidence of AEs was higher in the THS 2.2 – NRT gum sequence (4 out of 9 subjects [44%]) than in the other sequences. This difference was mostly due to study procedure AEs (2 out of 9 subjects [22%]) whereas investigational product (IP) related AEs (1 subject [11%]) were in line with that seen in other sequences. The most frequent AEs were related to investigations and included

blood triglycerides increased, hemoglobin decreased, and dysphoria which were each reported by 2 subjects. All other AEs were reported by only 1 subject. During the study, 3 subjects experienced 3 AEs that were considered as related to IP. No AEs were considered to be related to NRT gum.

During THS 2.2 use, 2 subjects each experienced 1 device event or malfunction (a broken heater and a charging issue) which led to the replacement of the Tobacco Stick Holder. Neither of these events led to an AE. No SAEs or severe AEs were reported during this study, with the number of AEs being low and balanced across study sequences.

- **ZRHR-REXC-03-EU***:* A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement.

  Safety results: There were no SAEs reported in this study and no randomized subjects discontinued from the study due to an AE. Eight subjects were discontinued from the study prior to randomization following abnormal assessments on Day 0. A further subject was discontinued prior to randomization for having fragile veins. Overall, there were 227 AEs reported by 112 of the 169 subjects (66.3%) in the Safety population, most of which were mild or moderate in severity. Only 1 severe AE was reported which occurred in the CC arm, and was not considered to be related to IP use or study procedures. The incidence and frequency of AEs were comparable in the THS 2.2 (98 AEs in 50/80 subjects [62.5%]), the CC (63 AEs reported by 29/41 [70.7%] subjects), and the SA arms (49 AEs in 24/39 [61.5%] subjects). The most frequent AEs after THS 2.2 or CC exposure were headache, oropharyngeal pain, syncope, polyuria, and spirometry abnormal. The most frequent AEs after SA were headache, back pain, influenza-like illness, spirometry abnormal, abdominal distension, hypertriglyceridemia, polyuria, hypertension, and vertigo. The incidence of headache and spirometry abnormal were comparable between the THS 2.2, CC, and SA arms, the incidence of polyuria was higher in the THS 2.2 and CC arms, while syncope and oropharyngeal pain were not experienced by any subject in the SA arm. Only 26 of the 227 reported AEs were assessed as being related to THS 2.2 or CC use and were reported by 23 of the 130 subjects in the THS 2.2, CC, and enrolled not randomized arms (17.7%). The incidence of AEs assessed as related to IP use was comparable for the THS 2.2 (14/80 subjects [17.5%]) and CC arms (7/41 subjects [17.1%]). The most frequent AEs assessed as related to IP use were spirometry abnormal, syncope, COHb increased, cough, and vertigo. All other AEs assessed as related to IP use were reported by single subjects in the THS 2.2 arm only.
  During THS 2.2 use, 12 subjects experienced a total of 19 major device events or malfunctions which led to the replacement of the THS Tobacco Stick Holder or Charger. None of these events led to an AE.

In total, among these 3 clinical studies, a total of 280 AEs were reported in 146 subjects. No SAEs were reported. There were no significant findings from the completed clinical studies during the review period of this SUR.

8.2 Ongoing Clinical Studies

No clinically important relevant new safety finding was identified from ongoing clinical studies during the period of this SUR.

8.3 Long-Term Follow-up

No clinically important relevant new safety finding was identified from ongoing clinical studies during the period of this SUR.

9 SAFETY FINDINGS FROM PRE-MARKET SAFETY SURVEILLANCE

A total of 353 AEs were reported by 182 respondents amoung 3502 respondents having participated in the five market research respondents, with an overall reporting rate of 5.2 case reports per 100 market research respondents.

During the review period of this SUR, one passive safety surveillance for market research study entitled P1_WOT1_DE, was completed and safety summary report finalized.

Study P1_WOT1_DE_PSS conducted in Germany, started on 17 Sep 2014 and was terminated on 04 Nov 2014 (Closure of the hotline). Two product variants were used (same blend/flour) with two different tipping papers:

- THS 2.2 Regular (Dorado II / Ron) – cork tipping paper
- THS 2.2 Regular (Dorado II / Ron) – half white tipping paper

Safety results: Altogether throughout the study, 42 events were reported (29 reported from respondents using the half white tipping paper heatsticks and 13 from respondents using the cork tipping paper heatsticks), mostly clustering in the MedDRA System organ class (SOC) Gastrointestinal disorders (n=14) with the leading event of nausea (n=8), in the SOC Nervous system disorders (n=12) with the leading event of headache (n=8) and in the SOC General disorders and administration site conditions (n=10) with the leading event of malaise (n=4). According to the Investigator's Brochure (for THS 2.2, Edition 4, issued 24-Nov-2014), the following events (PTs) were expected: headache, nausea, dizziness, vomiting and oropharyngeal pain. The following events (PTs) were unexpected: abdominal discomfort, aversion, dysgeusia, malaise, oral pruritus, oral discomfort, chest discomfort, bronchitis, eye irritation and nasal discomfort. Additionally, the following terms (PTs) were reported: product taste abnormal, product odour abnormal, device malfunction and wrong technique in product usage process.

No specific observations were made based on the information received. There was limited information to assess causality. No safety issues/concerns emerged from the adverse event reports received from this pre-market research study.

Of note, during the review period of this SUR, four passive safety surveillance for market research studies were considered as not completed (safety summary reports were not finalized). They are briefly mentioned below,

Study P1_BT1_IT_PSS conducted in Italy, started on 14 May 2014 and ended on 17 Jun 2014 (Closure of the hotline). Five product variants were used:

- THS 2.2 Regular (Ron)
- THS 2.2 Regular (Dorado I / Fitz)
- THS 2.2 Regular (Dorado II / Ron)
- THS 2.2 Regular (Dorado II / Albertino)
- THS 2.2 Menthol (Mint Veronica)

Study P1_WOT1_CH_PSS conducted in Switzerland, started on 29 Oct 2014 and ended on 26 Dec 2014. Two product variants with the same tipping paper were used:

- THS 2.2 Regular (Dorado II / Ron) – half white tipping paper
- THS 2.2 Menthol (Vinny / Ron) – half white tipping paper

Study P1_WOT1_KO_PSS conducted in South Korea, started on 10 Apr 2015 and ended on 5 Jun 2015 (Closure of the hotline, outsite of the review period). Three product variants with the same tipping paper were used :

- THS 2.2 Regular (Dorado II / Fitz)
- THS 2.2 Regular (Ginebra / Fitz)
- THS 2.2 Menthol (Dorado I / Vinny low menthol)

Study P1_WOT2_IT_PSS conducted in Italy, started on 05 Nov 2014 and ended on 16 Jan 2015 (Closure of the hotline). Two product variants with the same tipping paper were used:

- THS 2.2 Regular (Dorado II / Ron) – half-white tipping paper
- THS 2.2 Menthol (Vinny / Ron) – half-white tipping paper

10 OTHER CLINICAL TRIAL / STUDY SAFETY INFORMATION

Not applicable.

11 SAFETY FINDINGS FROM POST- MARKETING EXPERIENCE

During the reporting period, a total of 8 non-serious AEs (and no SAEs) were spontaneously reported by 4 consumers, with an estimated reporting rate of 2.4 cases per 10’000 consumers.

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

12 NON-CLINICAL DATA

During the reporting period, smoke chemistry information was updated as mentioned in Appendix A. There were no new *in vitro* or *in vivo* THS studies. There were no new THS 2.2 non-clinical data raising safety concerns.

13 LITERATURE

A literature search has been performed in two major literature databases Medline and Embase. Two searches were performed using the following search terms "iQOS" and "Heat* AND tobacco AND (product OR cigarette)" in 2014 and 2015.

First search with "iQOS" exact product name did not return any hit in any database.

Second search string returned 117 results in Embase and 39 in Medline. Articles only related to electronic cigarettes and not heated tobacco were discarded.

In spite of the large number of publications retrieved during this search, no one addressed new safety issues regarding the use of heated tobacco.

In addition, no relevant new safety findings were identified from unpublished manuscripts and presentations at scientific meetings.

13.1 Literature from Same Class Heat-not-Burn Tobacco Products

In a recent article, Fujimoto et al. (2015), compared the biological effects of heated cigarette (HC) to those of Reference (3R4F) cigarettes, using nose-only 5-week and 13-week inhalation studies. In the 13-week study, Sprague-Dawley rats were necropsied following exposure to mainstream smoke from each cigarette at 200, 600 or 1000 µg wet total particulate matter/L for 1 h/day, 7 days/week or following a 13-week recovery period. Histopathological changes in the respiratory tract were significantly lesser in HC groups; e.g. respiratory epithelial hyperplasia in the nasal cavity and accumulation of pigmented macrophages in alveoli. After a 13-week recovery, the lesions have completely or partially regressed, except for accumulation of pigmented macrophages in alveoli, in both HC and 3R4F groups. In the 5-week study, Sprague-Dawley rats were necropsied following exposure to mainstream smoke of either cigarette at 600 or 1000 µg wet total particulate matter/L for 1 h, two times/day (with 30 min interval), 7 days/week or following a 4-week recovery period. Bronchoalveolar lavage fluid (BALF) analysis of neutrophil percentages and enzyme levels like γ-GT, ALP and LDH indicated that pulmonary inflammation was significantly less in HC groups compared to 3R4F groups. The authors concluded that, based on the BALF parameters and histopathology, HC demonstrated significantly lower biological effects compared to combustible (3R4F) cigarettes.

13.2 THS 2.2 Literature

None of the articles retrieved as per the above-cited criteria contained safety findings related to THS 2.2.

14 OTHER SAFETY UPDATE REPORTS

A separate safety update report for the menthol version of THS 2.2 is in preparation.

15 REGION-SPECIFIC INFORMATION

Not applicable.

16 LATE-BREAKING INFORMATION

After the DLP of this SUR (30 Apr 2015), one ICSR (PMI000128) initially received on 03 May 2015 as non-serious, was upgraded to serious upon additional follow-up information received on 21 May 2015.

Of note, this case is presented below in more details as it was not part of the line-listings (Appendix C) with all cases received for THS 2.2 during the reporting period (from 01 May 2014 to 30 April 2015).

This case concerns a 40-year-old male subject who was enrolled in the pre-market research study P1_WOT1_KO (Whole offer test – Quantitative) and experienced the events *Injury associated with device*, *Thermal burn* and *Device battery issue* while using THS 2.2 Regular and THS 2.2 Menthol. *The Injury associated with device* and *Thermal burn* were assessed as serious (medically significant). *The Device battery issue* was assessed as non-serious. The causality and listedness assessments are not applicable for *Device battery issue*.

Company comment: There is limited information in this case. However, considering the temporal relationship and the knowledge about the products, the Company assessed the reported AEs as related to the use of the THS 2.2 Regular and THS 2.2 Menthol. The device from this subject is currently under investigation by the Company.

17 OVERALL SAFETY ASSESSMENT

Based on the currently available information from ongoing and completed clinical studies, from pre-market studies and post-market safety surveillance, the exposure to THS 2.2 raised no safety concerns in the adult smokers.

18 SUMMARY OF IMPORTANT RISKS

The information received from clinical studies, from pre-market studies and post-market safety surveillance during the reporting period does not suggest any safety concerns or new emerged health related risk associated with the exposure to the THS 2.2 as compared to combustible cigarettes.

19 CONCLUSIONS

This SUR covers all relevant safety data received for THS 2.2 during the period from 01 May 2014 to 30 Apr 2015.

Based on the data received for THS 2.2, no new safety concerns were raised regarding the exposure to THS 2.2 by adult smokers.

20 REFERENCE LIST

Fujimoto H, Tsuji H, Okubo C, Fukuda I, Nishino T, Lee KM, Renne R, Yoshimura H. Biological responses in rats exposed to mainstream smoke from a heated cigarette compared to a conventional reference cigarette. Inhal Toxicol. 2015 May; 13:1-13.

21 APPENDICES

Appendix A – Reference Safety Information

Appendix B – Description of Ongoing and Completed Clinical Studies

Appendix C – Line Listings and Summary Tabulations of Adverse Events

Appendix D – Scientific Abstracts