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PMI RESEARCH & DEVELOPMENT

Safety Summary Report

Passive Safety Surveillance for Perception & Behavior Assessment Study n° THS-PBA-07-US

Report Number:	PMI_SURV_2016_SSR02
Study Title:	Actual Use Study of THS 2.2 – THS-PBA-07-US
Study ID:	THS-PBA-07-US
Safety ID	THS-PBA-07-US_PSS
Products Name:	Tobacco Heating System 2.2 / Regular and Menthol
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EXECUTIVE SUMMARY

The Actual Use Study of THS 2.2 – THS-PBA-07-US was conducted by Philip Morris International (PMI) to investigate the consumer perception and behavior in relation to Investigational Tobacco Product (ITP), herein referred to as Tobacco Heating System (THS) 2.2 products. THS-PBA-07-US study was conducted in the United States (US) from September 2015 to February 2016. PMI THS products are not yet available on the US market.

THS 2.2 is comprised of a device commercialized (in some countries outside the US) under the brand name "*iQOS*" and THS Tobacco Sticks branded as "*HeatSticks*" designed to be exclusively used with the *iQOS* device. Therefore, in the context of this study, the terminology of "the *iQOS* system" was used to describe "THS 2.2" and "*HeatSticks*" was used to describe "THS Tobacco Sticks".

The purpose of this study was to investigate how US adult daily smokers of Conventional Cigarettes (CC) actually use the tobacco sticks in a near to real-world conditions environment. The Actual Use Study of the *iQOS* system involved an assessment of participant-reported stick-by-stick consumption of tobacco sticks and of CC and product use behaviors. Participants were able to consume CC and other tobacco products *ad libitum*. Adverse events spontaneously reported by study participants were collected using a passive safety surveillance methodology. This document summarizes only the results from the passive safety surveillance.

The study design included one-week baseline assessment period, six-week observational period, one-week close-out period and a 30-day follow-up interview. The main topic covered in these interviews was the documentation of tobacco and nicotine-containing products use after six-week exposure/use of tobacco sticks.

Participants were adult smokers (18 years of age or above), daily smokers of regular and/or menthol CC.

The planned study sample was approximately 1'300 participants, however 1'336 participants were enrolled in the study. Of these, the safety population exposed to the product use included 1'158 participants which tested at least one THS tobacco stick and their data were valid for safety analysis.

Adverse Events (AEs) and pregnancy reports were spontaneously reported to the hotline operators and interviewers during the study period and until the 30-day follow up interview was completed for the last study participant.

A total of 48 case reports were received from THS-PBA-US-07 study, from which 8 cases (16.7%) were assessed as serious and 40 cases (83.3%) were assessed as non-serious.

A total of 121 AEs in 48 cases were spontaneously reported during the study (reporting rate of 4.14%.), of which 19.01% (23/121) were assessed as listed and 65.29% (79/121) as unlisted health-related AEs, respectively, according to the current Reference Safety Information. Listedness was not applicable to 19 AEs, all related to product quality issues (19/121, 15.70%).

No safety concerns emerged based on the information received during this Perception and Behavior Study about the safety profile of THS 2.2 Regular (Dorado II / Ron) and THS 2.2 Menthol (Dorado I /Vinny Low Menthol).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

Table 1 Abbreviations

AE	Adverse Event
CC	Conventional Cigarette
ISDCF	Individual Safety Data Collection Form
MedDRA	Medical Dictionary for Regulatory Activities
PBA	Perception and Behavior Assessment
PMI	Philip Morris International
PMI-PSSD	Philip Morris International-Product Safety Surveillance Department
PT	Preferred Term (MedDRA)
RSI	Reference Safety Information
SAE	Serious Adverse Event
SMP	Safety Management Plan
SOC	System Organ Class (MedDRA)
THS 2.2	Tobacco Heating System (Version) 2.2
(b)	(b) (4)
US	United States

Definitions

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).
Safety Population/Participant	Participants who have signed the Informed Consent Form and have tried the Investigational Tobacco Product at least once (who tested at least one tobacco stick).
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 (FDA 2012: MRTPA Draft Guidance).

1 STUDY DESCRIPTION

1.1 Perception and Behavior Assessment Study Objectives

The Actual Use Study THS-PBA-07-US (THS-PBA-07-US) was conducted by PMI to study consumer perception and behavior in relation to Tobacco Heating System (THS) 2.2 products.

The THS-PBA-07-US study focused on how United States (US) adult current daily smokers of conventional cigarettes (CC) use the *iQOS* system under near to real world conditions. In particular, the study assessed the quantities of CC and of tobacco sticks consumed by individual participants over time. The Actual Use Study of the *iQOS* system involved an assessment of participant-reported stick-by-stick consumption of tobacco sticks and of CC and product use behaviors. Participants were able to consume CC and other tobacco products *ad libitum*.

Each participant took part in this study for a total of eight weeks after the recruitment period: one-week baseline period followed by six-week observational period followed by one-week close out period. Within the study design, there was a baseline assessment period, an observational period, a close out period, and a 30-day follow-up interview which took place 30 days - 60 days after the start of the close out period to document tobacco and nicotine-containing products (electronic e-cigarettes, Nicotine Replacement Therapies products) use after six-week exposure/use of tobacco sticks (i.e. observational period).

THS 2.2 is comprised of a device commercialized (in several countries outside the US) under the brand name "*iQOS*" and THS tobacco sticks branded as "*HeatSticks*" designed to be exclusively used with the *iQOS* device. Therefore, in the context of this study, the terminology of "the *iQOS* system" was used to describe "THS 2.2" and "*HeatSticks*" was used to describe "THS Tobacco Sticks".

1.2 Study Population

The study surveillance population included 1'336 participants enrolled in the study. The safety population included 1'158 study participants who used at least one tobacco stick.

Participants were adult smokers (18 years of age or above or the minimum local or state legal smoking age and above, whichever was higher), which were daily smokers of regular and/or menthol CC with no intention of quitting within the 30 days (current daily smoker is defined as an individual who has smoked at least 100 cigarettes in his/her lifetime and was smoking at least one regular or menthol CC (no brand restrictions) per day, disregarding religious fasting).

1.3 Investigational Tobacco Products

Two Tobacco Heating System (THS) 2.2 product variants were used in this study:

- THS 2.2 Regular (Dorado II / Ron) (i.e. *HeatStick* regular)
- THS 2.2 Menthol (Dorado I / Vinny Low Menthol) (i.e. *HeatStick* menthol)

1.4 Passive Safety Surveillance

The scope of the passive safety surveillance part of THS-PBA-07-US actual use study was the collection and the assessment of adverse events (AEs) and pregnancies spontaneously reported by study participants, including those captured in open-ended questionnaires (see Appendix 2).

1.5 Study Organization

The study was conducted in United States. The details of the study organization are presented in the Safety Management Plan (SMP) (see Appendix 2).

1.6 Study Timelines

The study timelines are presented in Table 2 below:

Table 2 THS-PBA-US-07 Study Timelines

Timelines	Dates
First Subject In	21 September 2015
iQOS system usage start date	29 September 2015
Observational period data collection completed	21 December 2015
Last Subject Out (for which the final interview was performed)	07 January 2016
Last day of the 30-day follow up interview	03 February 2016
Closure of the hotline	18 February 2016

Note: The observational period data collection was completed by 21 December 2015 for all subjects, except one subject which final interview took place on 07 January 2016.

2 SAFETY DATA HANDLING

The details of the safety data handling are presented in the SMP (see Appendix 2).

2.1 Collection

Day 0 is defined as the day of first awareness of an AE by PMI employee or designee (e.g., call center operators, interviewers or site staff).

2.1.1 Adverse Events Passively Collected Through ISDCFs

Adverse events were passively collected by the hotline operators and interviewers as per the SMP. Data collection forms included:

- Individual Safety Data Collection Forms (ISDCFs)
- Pregnancy forms
- Open-ended questionnaires

The hotline operators were trained to record and forward all adverse event and pregnancy reports to PMI's Safety Service Provider ((b) (4), (b) (4)) by fax or e-mail within 24 hours of first awareness using the ISDCF / Pregnancy forms.

AEs and pregnancy reports were collected by the hotline operators and by interviewers during the study period and until the 30-day follow up interview was completed for the last study participant.

2.1.2 End-of-Study Health Problems Listing

At the end of the study, the PMI Product Safety Surveillance Department (PMI-PSSD) sent to (b) (4) the end-of-study listing of spontaneously reported health problems in follow-up study questionnaires.

2.2 Validation

Upon receipt of an ISDCF, (b) (4) validated that the information received was legible/consistent and sent an acknowledgment of receipt by e-mail within one business day to the hotline operator and to PMI-PSSD. A unique reference number was allocated to each safety case by logging minimum information into the safety database.

2.3 Databasing

The responsible personnel at (b) (4) entered the safety information presented in ISDCFs into the safety database. The version 18.1 of the Medical Dictionary for Regulatory Activities (MedDRA) was used to code the reported adverse event terms. A case narrative (and a company comment for Serious Adverse Event (SAE) report only) was prepared. Quality Control (QC) of safety data processing was performed.

Each adverse event from the end-of-study health problems listing was processed in the same way as for ISDCFs. Each case was reviewed by a Safety Physician at (b) (4) according to valid (b) (4) procedural documents.

3 ACTUAL EXPOSURE

The planned study sample was approximately 1'300 participants, however 1'336 participants were enrolled in the study. Of these, the exposed safety population included 1'158 participants who tested at least one tobacco stick.

The actual exposure of safety population by product variant is presented in Table 3.

Table 3 Sample size per product variant

Product variant	Sample size
THS 2.2 Regular (Dorado II / Ron) only	441
THS 2.2 Menthol (Dorado I /Vinny Low Menthol) only	512
THS 2.2 Regular and THS 2.2 Menthol	205
Overall	**1'158**

3.1 Actual Exposure to THS Products

The typical demographic characteristics of the participants in study THS-PBA-07-US were male (51%) and female (49%) adult smokers, White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, aged 18 to 82 years old (see Appendix 3).

The detailed distribution of actual exposure of participants to THS product variants in this study by Gender, Age and Race is presented in Appendix 3. There is no apparent imbalance in product use per Gender or per Age. Use of only THS Menthol variant was more frequent in Black or African American participants (66.5%) than in White participants (35.0%).

4 ADVERSE EVENTS

A Summary Tabulation of Adverse Events (AEs) and the Line Listings of cases received from the study THS-PBA-07-US are presented in Appendix 4 and Appendix 5, respectively.

5 OVERALL SAFETY ASSESSMENT

5.1 Adverse Events Reporting Rate

Overall, a total of 121 AEs (102 non-serious and 19 serious) were reported in 48 individual cases during the study THS-PBA-07-US.

The overall reporting rate was 4.14%. The numbers of adverse events and cases per product variant are presented in Table 4. In 9 cases, participants used both THS 2.2 Regular and THS 2.2 Menthol product variants.

Table 4 Adverse Events per THS Product variant

Product variant	AEs (Cases)		Total AEs (Total Cases)	AE reporting rate %[1]
	Serious AEs (Cases)	Non-Serious AEs (Cases)		
THS 2.2 Regular (Dorado II / Ron) only	8 (2)	38 (14)	46 (16)	3.63 % (16/441)
THS 2.2 Menthol (Dorado I /Vinny Low Menthol) only	6 (5)	55 (18)	61 (23)	4.49 % (23/512)
THS 2.2 Regular and THS 2.2 Menthol	5 (1)	9 (8)	14 (9)	4.39 % (9/205)
Overall	**19 (8)**	**102 (40)**	**121 (48)**	**4.14 % (48 /1'158)**

[1] AE Reporting rate = Number of Cases / Number of exposed participants

The AE reporting rates were comparable across product variants, from 3.63% for THS 2.2 Regular to 4.49 % for THS 2.2 Menthol.

5.2 Most Frequent Reported Adverse Events

5.2.1 General Overview

The severity of the leading event was reported as Mild in 5 cases (10.40%), Moderate in 7 cases (14.58%), Severe in 6 cases (12.50%), and Unknown in 6 cases (12.50%). The severity was not reported in half of the total number of cases (24 cases, 50.0%).

The vast majority of AEs (84.30%; 102/121) was reported under the following six System Organ Classes (SOC): **General disorders and administration site conditions** (n=32), **Nervous system disorders** (n=23), **Gastrointestinal disorders** (n=19), **Injury, poisoning and procedural complications** (n=16), **Respiratory, thoracic and mediastinal disorders** (n=15), and **Infections and infestations** (n=12).

More than 50% of the AEs included in the SOC **General disorders and administration site conditions** were attributed to product quality issues (59.37 %, 19/32, see Section 5.5.1).

Frequency and distribution of AEs of most common health-related AEs by THS product variants are presented in Section 5.2.2.

5.2.2 Most Frequent Reported AEs by THS Product variants

The most frequent reported AEs/PTs (Preferred Term) were distributed among the two THS product variants as presented in Table 5.

Table 5 Distribution of Most Frequent AEs among THS Product variants

AE [PT][1]	Number of AEs (% of all AEs received by product variant)			Total AEs (All reported AEs)
	THS 2.2 Regular (Dorado II / Ron)	THS 2.2 Menthol (Dorado I /Vinny Low Menthol)	THS 2.2 Regular and THS 2.2 Menthol	
Headache	6 (13.04%)	6 (9.84%)	1 (7.14%)	13 (10.74%)
Malaise	3 (6.52%)	2 (3.28%)	2 (9.76%)	7 (5.78%)
Nausea	4 (8.70%)	2 (3.28%)	0	6 (5.00%)
Dizziness	2 (4.35%)	2 (3.28%)	0	4 (3.30%)
Abdominal discomfort	1 (2.17%)	1 (1.64%)	1 (7.14%)	3 (2.48%)
Oral discomfort	1 (2.17%)	2 (3.28%)	0	3 (2.48%)
Chest pain	1 (2.17%)	1 (1.64%)	1 (7.14%)	3 (2.48%)
Cough	0	2 (3.28%)	1 (7.14%)	3 (2.48%)
Throat irritation	1 (2.17%)	2 (3.28%)	0	3 (2.48%)
Total	**19 (41.30%)**	**20 (32.79%)**	**6 (42.86%)**	**45 (37.19%)**

[1] PT = Preferred Term

The most frequent reported AEs by PTs were Headache (n=13), Malaise (n=7), Nausea (n=6), Dizziness (n=4), Abdominal discomfort (n=3), Oral discomfort (n=3), Chest pain (n=3), Cough (n=3), and Throat irritation (n=3). In total, the most frequent PTs represents 37.19% (45/121) of the total number of AEs reported during the study for all THS product variants.

The event Headache was the most frequent reported AE in both THS 2.2 product variants investigated in the study (reported in 13 out of 48 cases), with a reporting rate of 10.74% from all AEs received. Other frequent reported AEs were Malaise, Nausea and Dizziness (overall reporting rates from 3.30% to 5.78%).

The frequency of most reported AEs is comparable between THS 2.2 product variants, except for Nausea which was reported two times more in participants using THS 2.2 Regular (Dorado II / Ron) and Cough reported mostly in participants which used THS 2.2 Menthol (Dorado I /Vinny Low Menthol).

Detailed information (severity, age, gender, and listedness) of most frequent reported AEs for THS 2.2 Regular and THS 2.2 Menthol is presented by System Organ Class (SOC) in Table 6 and Table 7, respectively.

Table 6 Details of Most Frequent AEs reported for THS 2.2 Regular (Dorado II / Ron)

SOC	Frequent PTs n AEs (% of all AEs received for the product variant)	Severity	Participants Age (years)/ Gender Male (M) / Female (F)	Listedness
Nervous system disorders	Headache 6 (13%)	Mild	41/M	Listed
		Moderate	34/M	
			57/F	
		Not reported	56/M	
			46/M	
			25/M	
	Dizziness 2 (4.3%)	Moderate	33/M	Listed
		Not reported	31/M	
Gastrointestinal disorders	Nausea 4 (8.7%)	Moderate	33/M	Listed
			27/F	
			57/F	
		Not reported	31/M	
General disorders and administration site conditions	Malaise 3 (6.5%)	Mild	49/M	Unlisted
		Moderate	33/M	
		Not reported	20/F	

Table 7 Details of Most Frequent AEs reported for THS 2.2 Menthol (Dorado I / Vinny Low Menthol)

SOC	Frequent PTs n AEs (% of all AEs received for the product variant)	Severity	Participants Age (years)/ Gender Male (M) / Female (F)	Listedness
Nervous system disorders	Headache 6 (9.8%)	Mild	41/M	Listed
		Moderate	34/M	
			57/F	
		Not reported	56/M	
			46/M	
			25/M	
	Dizziness 2 (3.3%)	Moderate	57/M	Listed
		Not reported	66/F	
General disorders and administration site conditions	Malaise 2 (3.3%)	Mild	49/M	Unlisted
		Moderate	33/M	
		Not reported	20/F	
Gastrointestinal disorders	Nausea 2 (3.3%)	Not reported	56/M	Listed
			66/F	
	Oral discomfort 2 (3.3%)	Mild	28/F	Unlisted
		Severe	51/F	
Respiratory, thoracic and mediastinal disorders	Cough 2 (3.3%)	Severe	51/F	Unlisted
		Not reported	53/F	
	Throat irritation 2 (3.3%)	Not reported	56/M	Unlisted
			53/F	

According to the Reference Safety Information (RSI, Investigator Brochure (IB) edition 5.0 (dated 27 Apr 2015) for THS 2.2 Regular) and the Investigator Brochure edition 3.0 (dated 27 Apr 2015) for THS 2.2 Menthol), the events of Headache, Dizzinees and Nausea were considered listed (associated to the use of THS 2.2 Regular and THS 2.2 Menthol). All the other health-related AEs (e.g., Malaise, Oral discomfort, Cough, Throat irritation) were assessed as unlisted according to the RSI.

Overall, the proportion of listed AEs and unlisted AEs was 19.01% (23/121) and 65.29% (79/121) of the total AEs, respectively. Listedness is not applicable to 19 AEs related to product quality issues (19/121, 15.70%, see Section 5.5.1).

5.3 Serious Adverse Events

Eight cases (of 16.67% total) reporting 19 serious AEs (15.70% of total AEs) were assessed as serious (see Table 8). A short description of serious events by case report is presented in Section 5.3.1.

Table 8 Serious Adverse Events received during THS-PBA-07-US Study

Case ID	Subject ID	THS product	SAE Criteria	SAEs [PTs]
PMI000347	200851	Regular	Hospitalisation	Road traffic accident, Concussion, Joint injury, Muscle strain, Skin abrasion
PMI000365	209653	Menthol	Hospitalisation	Hospitalisation
PMI000367	654390	Regular Menthol	Hospitalisation	Accident, Limb Injury, Skeletal injury, Osteomyelitis, Nerve injury
PMI000381	821416	Menthol	Hospitalisation	Head injury
PMI000394	652030	Regular	Hospitalisation	Sepsis, Cholecystitis infective, Pneumonia
PMI000404	656993	Menthol	Hospitalisation, Important Medical Event	Bronchitis, Ear infection
PMI000409	184377	Menthol	Important Medical Event	Tonsillar cyst
PMI000410	759911	Menthol	Hospitalisation	Adverse Event

5.3.1 Safety Assessment of Serious Events

- **Case PMI000347:** A 31-year old male was hit by a car while cycling and experienced concussion, joint injury, muscle strain, skin abrasion, nausea and dizziness. The participant smoked on average 10 cigarettes per day. He had a road accident 6 days after he started using the THS 2.2 Regular (Dorado II / Ron). The events were reported as ongoing, except nausea and dizziness that were resolved at the time of the report. No further information was available.

  Company Comment: The Road traffic accident, Concussion, Joint injury, Muscle strain, and Skin abrasion were assessed as serious, due to requiring hospitalization. Nausea and Dizziness were assessed as non-serious. Road traffic accident, Concussion, Joint injury, Muscle strain, and Skin abrasion are unlisted, whereas Nausea and Dizziness are listed, as per the RSI (IB). Based on the information (i.e. the participant was reportedly feeling fine before the accident; the participant was hit by a turning car, while cycling) provided in this report, the Road traffic accident and the directly derived adverse events (i.e. Concussion, Joint injury, Muscle strain, Skin abrasion), as well as the transient Nausea and Dizziness experienced while on treatment with Percocet initiated during hospitalisation, were assessed as not related to the use of THS 2.2 Regular (Dorado II / Ron). Of note, the product use was restarted 12 days after the discharge from hospital.

- **Case PMI000365**: Hospitalisation was reported by a 43-year old male daily smoker of an average of 8 cigarettes per day. One week after starting using THS 2.2 Menthol (Dorado I /Vinny Low Menthol), the participant was hospitalized for unspecified health-related reasons. The event resolved after one week. Medical history, relevant investigations and treatment received were not reported. As per the participant, the event was not related to the use of THS product. The participant used the product every day, and used 4 tobacco sticks and 7 cigarettes on the day of event (conflictual information as it was reported as well he stopped smoking on the day of event). Rechallenge was reported as negative.

  Company Comment: Hospitalization was assessed as serious.Hospitalization is unlisted for THS 2.2 Menthol, as per RSI. Hospitalisation is not an adverse event per se. In this case, the reason for hospitalisation, which would potentially be the actual adverse event, was vaguely provided as health problems, which were assessed by the reporter as being not related to the product in question. The information provided in this report with regard to the medical history, relevant investigations, and treatment received during hospitalisation, is also limited. Based on reporter's causality assessment, the Hospitalisation was assessed as not related to the use of THS 2.2 Menthol, in this participant, who had been a smoker of conventional cigarettes.

- **Case PMI000367**: A 51-year old female experienced limb injury, skeletal injury, osteomyelitis and nerve injury after being involved in an accident. She smoked on average 10-20 cigarettes per day. The participant used both THS 2.2 product variants on a daily basis. She had an accident and she was hospitalised one week after starting using THS products. The outcome of the events was unknown at the time of the report. No further information was available.

Company Comment: The Accident, Limb injury, Lower limb fracture, Osteomyelitis, and Nerve injury were assessed as serious, due to requiring hospitalization. Accident, Limb injury, Lower limb fracture, Osteomyelitis, and Nerve injury are unlisted for THS 2.2 Menthol and THS 2.2 Regular, as per the RSI. Considering the circumstances provided in this report, the Accident and the ensuing adverse events (i.e. Limb injury, Lower limb fracture, Osteomyelitis, Nerve injury) were assessed as not related to the use of the products, in this participant, who had been a smoker of conventional cigarettes.

- **Case PMI000381:** Head injury, Hypotension, Loss of consciousness, Dizziness and Device defective were reported in a 57-year old male. The participant was a daily smoker of approximately 15 cigarettes per day. After three weeks of using THS 2.2 Menthol (Dorado I /Vinny Low Menthol), he was involved in a fight during which he was hit with a baseball bat over the head. He has been hospitalised on the same day. On the day of the event, he used 15 cigarettes and he reported not to remember about the tobacco sticks use. The participant stopped the use of THS 2.2. Menthol due to device defective. At the time of the reporting, the events were not resolved. No further information was available.

  Company Comment: The Head injury was assessed as serious, due to requiring hospitalization. The Hypotension, Loss of consciousness, Dizziness, and Device defective were assessed as non-serious, based on the provided information. Head injury, Hypotension, and Loss of consciousness (described as blackout) are considered unlisted, as per the RSI. Dizziness is listed, as per the IB. Listedness and causality assessments are not applicable for Device defective. The information provided in this non-medically confirmed report was limited. It was reported that the Head injury was the results of a blow to the head sustained during a fight. Therefore, the Head injury was assessed as not related to the use of Tobacco Heating System (THS) 2.2. Although Hypotension, Loss of consciousness, and Dizziness were reportedly following the Head injury, and despite their persistence even after stopping the use of product (due to Device defective), considering the current knowledge on the product in question, the causality relationship between the use of THS 2.2 and Hypotension, Loss of consciousness, and Dizziness cannot be excluded and, therefore, was assessed as related.

- **Case PMI000394**: A 52-year old male was hospitalized for Sepsis and Cholecystitis infective. He was a daily smoker of approximately 10-15 cigarettes per day. Medical history included high blood pressure and high cholesterol. The participant was taking multiple concomitant medications. The time interval between starting using THS 2.2 and the occurrence of the events was not reported. He stopped smoking cigarettes and using THS 2.2 on the day of admission to the hospital. The participant reported that he had underwent a cholecystectomy. He stated he got Pneumonia in the hospital (due to intubation), COPD (Chronic Obtructive Pulmonary Disease), Decubitus ulcer and Frequent bowel movements. Sepsis and Pneumonia were resolved and the other events were ongoing at the time of the report. The THS 2.2 use was not re-started. No further information was available.

Company Comment: The Sepsis and Cholecystitis infective were assessed as serious, due to requiring hospitalization. Pneumonia was assessed as serious, due to being considered a medically important event, requiring intervention. Chronic obstructive pulmonary disease, Decubitus ulcer, and Frequent bowel movements were assessed as non-serious, based on the provided information. Sepsis, Cholecystitis infective, Pneumonia, Decubitus ulcer, Chronic obstructive pulmonary disease, and Frequent bowel movements are unlisted, as per the RSI. The Sepsis was likely a consequence of the Cholecystitis infective (described as gallbladder gangrene, requiring open cholecystectomy). Considering the current knowledge on the product in question, the Sepsis and Cholecystitis infective were assessed as not related to the use of THS 2.2 Regular. Despite the presence of alternative explanations (i.e. medical history, multiple concomitant medications, hospital environment, recent septic episode), the causal relationships between the use of THS 2.2 Regular and Pneumonia (in this case, nosocomial pneumonia) cannot be completely excluded and, therefore, was assessed as possible. It was reported that the Chronic obstructive pulmonary disease (COPD) was diagnosed about a month after this patient, who had been a smoker of conventional cigarettes, started using the THS 2.2. Considering this implausible temporal sequence, the COPD was assessed as not related to THS 2.2. A clear alternative explanation (i.e. inappropriate care during hospitalisation) was provided for the occurrence of the decubitus ulcers. As well, the Increased bowel frequency were reportedly due to the use of concomitant probiotics. Therefore, Decubitus ulcer and Increased bowel frequency are assessed as not related to the use of THS 2.2 Regular.

- **Case PMI000404:** Bronchitis, Ear infection, Nerve injury, Neuralgia, Hyperaesthesia and Respiratory fume inhalation disorder were reported in a 48-year old female. The participant smoked 1-7 cigarettes per week. She started using the THS 2.2 Menthol occasionally. Bronchitis and ear infection (assessed as medically important events) have been diagnosed after reportedly inhaling smoke with chemicals from a fire occurring near her house. The participant continued to use THS 2.2 Menthol during the reported events. The outcome of events was reported as recovered.

  Company Comment: The Bronchitis and Ear infection were conservatively assessed as serious, due to the reported visit to hospital and required antibiotic treatment (i.e. medically important event, intervention). Nerve injury, Neuralgia, Hyperaesthesia, Respiratory fume inhalation disorder, and Device difficult to use were assessed as non-serious. Bronchitis, Ear infection, Nerve injury, Neuralgia, Hyperaesthesia, Respiratory fume inhalation disorder, and Device difficult to use are unlisted, as per the RSI. The information provided in this non-medically confirmed report is limited and unclear, particularly regarding the relevant medical history, respective adverse events' onset well as the THS 2.2 usage dates. Although the Bronchitis and Ear infection were diagnosed after reportedly inhaling smoke with chemicals from a fire occurred near her house, the causal relationship between the use of THS 2.2. Menthol and these two adverse events cannot be completely ruled out and, therefore, was assessed as possible. Of note, the subject, who had been a smoker of conventional cigarettes, used the product in question only occasionally. Although she continued to

use the product during her acute bronchitis and ear infection, these adverse events resolved.

- **Case PMI000409:** A 36-year old female developed Tonsillar cyst and experienced Oropharyngeal pain. She was a daily smoker of approximately 8 cigarettes per day. The temporal relationship cannot be accurately assessed, as the start date of THS 2.2 Menthol (Dorado I /Vinny Low Menthol) product was not provided. The participant stopped using the product upon occurrence of the events. The tonsillar cyst might have been associated with the reported seasonal sore throat. The participant underwent a surgery of tonsils. The outcome was unknown at the time of the report.

  Company Comment: The Tonsillar cyst was assessed as serious (medically important, requiring drainage). The Oropharyngeal pain was assessed as non-serious. Tonsillar cyst is unlisted, whereas Oropharyngeal pain is listed, as per the RSI. The information provided in this non-medically confirmed report is limited. The temporal relationship cannot be accurately assessed, as the product usage start date was not provided. Judging by the pharmacological treatment (i.e. unspecified antibiotics) administered for the Tonsillar cyst, one may deduce that it was infectious cyst, which may had been associated with the reported seasonal sore throat. Considering the current knowledge on the product in question, the causality relationship between the use of THS 2.2 and Tonsillar cyst and Oropharyngeal pain cannot be excluded and, therefore, was assessed as related. Of note, the subject had been a smoker of conventional cigarettes.

- **Case PMI000410:** Adverse event (health problem) was reported in a 46-year old male, daily smoker of an average of 8 cigarettes per day. The participant was hospitalized for an unspecified health problem 12 days after starting using THS 2.2 Menthol (Dorado I /Vinny Low Menthol). The adverse event resolved. The action taken with the THS 2.2. product was not reported. No other information was available.

  Company Comment: The unspecified Adverse event was assessed as serious (due to hospitalization). Adverse event (not further unspecified, in this report) is considered unlisted for THS 2.2 Menthol, as per the RSI. The information provided in this report is limited, particularly regarding to the patient's unspecified health problem, the reason and dates of hospitalisation, and the action taken with the product. However, considering the plausible temporal relationship, a causal relationship between the use of THS 2.2 Menthol and the reported event cannot be excluded and, therefore, was assessed as possible.

5.3.2 Submission to Competent Authorities

As per the SMP, the initial 15-day reports were submitted to the Food and Drug Administration (FDA, Center for Tobacco Products). The Index of 15-day Reports from THS-PBA-07-US study submitted to FDA is presented by SOC in Appendix 6.

5.4 Other Significant Events

Pregnancy and lactation were exclusion criteria and reason for immediate withdrawal in the behavioral study THS-PBA-07-US and based on self-reporting at screening and during the study.

One pregnancy case with THS exposure was spontaneously reported in a 30-year-old female (**Case PMI000483**). The participant regularly smoked on average 2 conventional cigarettes per day. She used THS Regular and THS Menthol from Sep 2015 to Dec 2015. THS was stopped on an unknown day in Dec 2015. The last date recorded in the e-Diary for THS usage was 08 Dec 2015. First day of last menstrual period was reported as occurred in the "middle of Dec 2015". On 10 Jan 2016, during the visit to her HCP, the pregnancy has been medically confirmed. The estimated delivery date was reported as 28 Aug 2016. No other adverse events were reported in this case. *Maternal exposure timing unspecified* was assessed as non-serious event. Expectedness and causality assessment are not applicable for *Maternal exposure timing unspecified.* However, expectedness for this event has been captured as unlisted, by default, in the safety database. As per the protocol, the pregnancy will be followed-up until an outcome is reached.

5.5 Other Findings

5.5.1 Product Quality Issues Associated with AEs

Product quality issues associated with AEs were reported during the the course of passive safety surveillance in 35.42 % of cases (17/48), resulting in 19 corresponding AEs (15.70%, 19/121). All these AEs were assessed as non-serious (see details in Table 9).

Table 9 Product Quality Issues Associated with AEs

PT	N
Device difficult to use	6
Product quality issue (unspecified)	5
Device issue	4
Product taste abnormal	2
Device defective	1
Product odour abnormal	1
Product taste abnormal	2
Total	**19 (15.70%)**

All product quality issues were associated with non-serious cases/events except for two serious cases: PMI000381 in which the device had broken due to unknown cause and case PMI 000404 in which the participant found difficult to use the device due to pain in hand and arm. These two SAEs are not related to the reported product quality issues.

The information received from the AEs associated with product quality issues does not suggest any safety concern or health related risk associated with the use of the device.

5.5.2 Other Clinically Significant Findings

No significant clusters of AEs were identified in the remaining AEs reported in this study.

Overall, no specific safety observations could be made based on the information received on THS products used in THS-PBA-07-US study.

6 CONCLUSIONS

Among the participants who entered the THS-PBA-07-US study, the exposed safety population included 1’158 participants who tested at least one tobacco stick.

A total of 121 AEs in 48 cases were spontaneously reported during the study (reporting rate of 4.14%.), of which 19.01% (23/121) were listed and 65.29% (79/121) were unlisted health-related AEs, respectively. Listedness was not applicable to 19 AEs related to product quality issues (19/121, 15.70%). Eight cases were assessed as serious and 40 cases were assessed as non-serious.

No safety concerns emerged based on the information received during this Perception and Behavior Study about the safety profile of THS 2.2 Regular (Dorado II / Ron) and THS 2.2 Menthol (Dorado I / Vinny Low Menthol).

7 REFERENCES

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

8 REVISION HISTORY

Version Number	Description of change (including reason for change)	Type of change
1.0	Original issue	1
2.0	• Section 5.3 Serious Adverse Events Table 8 and Appendix 6: Subject ID corrected from ID 759991 to ID 759911 (typographical error) • Addition of Section 8 Revision History (to reflect the SUR changes from version 1.0 to version 2.0)	1

1. Major change/new version; 2. Minor change.

9 APPENDICES