



PMI RESEARCH & DEVELOPMENT

THS Additional Safety Data Report

Tobacco Heating System / iQOS

Appendix 1 CIOMS/MedWatch reports for SAE Individual Case Safety reports from clinical studies

Report Number: PMI_SURV_2016_SSR03

Sponsor: Philip Morris Products S.A.
PMI Research & Development
Quai Jeanrenaud 5
2000 Neuchâtel, Switzerland

Version: Final 1.0

Date: 12 May 2016

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U.S. Department of Health and Human Services
Food and Drug AdministrationFor use by user-facilities,
importers, distributors and manufacturers
for MANDATORY reporting

MEDWATCH

FORM FDA 3500A (10/05)

Page 1 of 5

Mfr Report #	US-PMI-PMI000007
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b) (6) In confidence	2. Age at Time of Event: 36 year or _____ Date of Birth: (b) (6)	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight ____ lbs or 105 kgs
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: _____ (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage			
<input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect			
<input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events)			
<input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)	4. Date of This Report (mm/dd/yyyy) 02/26/2015		
5. Describe Event or Problem Continued...			
6. Relevant Tests/Laboratory Data, Including Dates Continued...			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) #1. Type 2 diabetes mellitus (2008 ;) #2. Insulin-dependent diabetes mellitus (;) #3. Diabetic ketoacidosis (2013 ; 2013) #4. ADHD (;) #5. ADD (;) #6. Thalassemia (;) #7. Reye's syndrome (;) #8. Leukocytosis (;) #9. Bilateral salpingo-oophorectomy (;) #10. Ovarian cancer (;)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) #1 Tobacco Heating System 2.2 menthol () #2			
2. Dose, Frequency & Route Used #1 Used only once ;Respirat #2		3. Therapy Dates (If unknown, give duration from/to (or best estimate) #1 02/11/2014 ; 02/11/2014 #2	
4. Diagnosis for Use (Indication) #1 Tobacco user (17.1) #2		5. Event Abated After Use Stopped or Dose Reduced? #1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply #2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot # #1 #2	7. Exp. Date #1 #2	8. Event Reappeared After Reintroduction? #1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply #2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) #1. METFORMIN (2008 ; unknown) #2. GLUCOSE (2013 ; unknown)			

D. SUSPECT MEDICAL DEVICE			
1. Brand Name			
2. Common Device Name			
3. Manufacturer Name, City and State			
4. Model #	Lot #	5. Operator of Device <input type="checkbox"/> Health Professional <input type="checkbox"/> Lay User/Patient <input type="checkbox"/> Other: _____	
Catalog #	Expiration Date (mm/dd/yyyy)		
Serial #	Other #		
6. If Implanted, Give Date (mm/dd/yyyy)		7. If Explanted, Give Date (mm/dd/yyyy)	
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? <input type="checkbox"/> Yes <input type="checkbox"/> No			
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor			
10. Device Available for Evaluation? (Do not send to FDA) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Returned to Manufacturer on: _____ (mm/dd/yyyy)			
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			

E. INITIAL REPORTER			
1. Name and Address		Phone # (b) (6)	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
3. Occupation Dr		4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk.	

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

PLEASE TYPE OR USE BLACK INK

MEDWATCH

FORM FDA 3500A (10/05) (continued)

Page 2 of 5

FDA USE ONLY

F. FOR USE BY USER FACILITY/IMPORTER (Devices Only)

1. Check One <input type="checkbox"/> User Facility <input type="checkbox"/> Importer		2. UF/Importer Report Number	
3. User Facility or Importer Name/Address			
4. Contact Person		5. Phone Number	
6. Date User Facility or Importer Became Aware of Event (mm/dd/yyyy)		8. Date of This Report (mm/dd/yyyy)	
7. Type of Report <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up # _____			
9. Approximate Age of Device		10. Event Problem Codes (Refer to coding manual)	
		Patient Code _____ - _____ - _____ Device Code _____ - _____ - _____	
11. Report Sent to FDA? <input type="checkbox"/> Yes _____ (mm/dd/yyyy) <input type="checkbox"/> No		12. Location Where Event Occurred <input type="checkbox"/> Hospital <input type="checkbox"/> Outpatient Diagnostic Facility <input type="checkbox"/> Home <input type="checkbox"/> Ambulatory Surgical Facility <input type="checkbox"/> Nursing Home <input type="checkbox"/> Outpatient Treatment Facility <input type="checkbox"/> Other: _____ (Specify)	
13. Report Sent to Manufacturer? <input type="checkbox"/> Yes _____ (mm/dd/yyyy) <input type="checkbox"/> No			
14. Manufacturer Name/Address			

G. ALL MANUFACTURERS

1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jeanrenaud 5 Neuchâtel 2000 SWITZERLAND		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 02/14/2014		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
6. If IND, Give Protocol #		5. (A)NDA # _____ IND # _____ STN # _____ PMA/510(k) # _____ Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
7. Type of Report (Check all that apply) <input checked="" type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up # _____			
9. Manufacturer Report Number US-PMI-PMI000007		8. Adverse Event Term(s) #1. Diabetic ketoacidosis (17.1) Continued...	

H. DEVICE MANUFACTURERS ONLY

1. Type of Reportable Event <input type="checkbox"/> Death <input type="checkbox"/> Serious Injury <input type="checkbox"/> Malfunction <input type="checkbox"/> Other: _____		2. If Follow-up, What Type? <input type="checkbox"/> Correction <input type="checkbox"/> Additional Information <input type="checkbox"/> Response to FDA Request <input type="checkbox"/> Device Evaluation	
3. Device Evaluated by Manufacturer? <input type="checkbox"/> Not Returned to Manufacturer <input type="checkbox"/> Yes <input type="checkbox"/> Evaluation Summary Attached <input type="checkbox"/> No (Attach page to explain why not) or provide code: _____		4. Device Manufacture Date (mm/yyyy)	
		5. Labeled for Single Use? <input type="checkbox"/> Yes <input type="checkbox"/> No	
6. Evaluation Codes (Refer to coding manual)			
Method _____ - _____ - _____ - _____ Results _____ - _____ - _____ - _____ Conclusions _____ - _____ - _____ - _____			
7. If Remedial Action Initiated, Check Type <input type="checkbox"/> Recall <input type="checkbox"/> Notification <input type="checkbox"/> Repair <input type="checkbox"/> Inspection <input type="checkbox"/> Replace <input type="checkbox"/> Patient Monitoring <input type="checkbox"/> Relabeling <input type="checkbox"/> Modification/Adjustment <input type="checkbox"/> Other: _____		8. Usage of Device <input type="checkbox"/> Initial Use of Device <input type="checkbox"/> Reuse <input type="checkbox"/> Unknown	
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:			

10. ☐ Additional Manufacturer Narrative and / or 11. ☐ Corrected Data

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page (1)

C2 continued ...

#1. Used only once ;Respiratory(inhalation)

B5 continued

Patient: 1119

Verbatim: Diabetic ketoacidosis precipitated by sinusitis

Study ZRHM-REXA-08-US: A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting.

INITIAL INFORMATION RECEIVED ON 14-FEB-2014 AND FOLLOW-UP INFORMATION RECEIVED ON 18-FEB-2014, 21-FEB-2014 AND 25-FEB-2014:

This report was received from an investigator and concerned a 36-year-old female subject (subject ID 1119, height 175 cm, weight 105 kg) who was enrolled in the above mentioned study.

The subject's medical history included diabetes mellitus type II, since 2008. The subject had no other relevant medical history and no history of sinus infection.

Concomitant medication included metformin 1000 mg twice a day, oral since 2008 for diabetes mellitus type II (information reported by the subject at screening and at check-in). The subject also reported later to a member of the investigational site that she occasionally took her metformin 3-4 times a day.

The subject used the Tobacco Heating System (THS) 2.2 Menthol (Batch number B-08545) only once on 11-Feb-2014 at around 16:24. She actually used the product trial at the end of screening period, before randomization. This is why the subject used it only once. On (b) (6), the subject developed sinus infection and was hospitalized on the same day. The event was considered to be moderate in intensity. Additionally, the subject experienced headache, emesis and nausea on 12-Feb-2014: these three events were non-serious and emesis/nausea resolved on 12-Feb-2014. The subject was kept for observation due to sugar levels being uncontrolled. The subject was discharged on (b) (6).

The subject recovered from her sinus infection on 22-Feb-2014.

The subject was discontinued from the study on 12-Feb-2014 for not being compliant with her concomitant medication (metformin).

The investigator considered the event of sinus infection to be unrelated to the investigational product and attributed the event to 'basis disease/pre-existing condition'.

FOLLOW-UP INFORMATION RECEIVED ON 19-MAR-2014:

The review of the hospital records showed that the subject was hospitalised due to sinus infection which precipitated diabetic ketoacidosis. Thus the SAE term was changed from 'Hospitalization/Sinus infection' to 'Diabetic ketoacidosis precipitated by sinusitis'. The event was considered to be moderate in intensity and at the time of this follow-up report, the subject was recovering from the event.

The subject's medical history included diabetes mellitus type II, since 2008 (as previously reported by the subject) / insulin-dependent diabetes mellitus (as per hospital records). The hospital records showed that the subject had a previous history of diabetic ketoacidosis approximately one year ago and that she had a subcutaneous insulin pump which she stopped on the morning of 12-Feb-2014. None of this was mentioned by the subject when she was interviewed at the site while obtaining information on her past medical history. Concomitant medication also included metformin 2000 mg daily, oral since 2008 for diabetes and glucose tablet 4 grams daily, oral since 2013 for low blood sugar.

The investigational site attempted to contact the subject to inquire about the information in the medical records, however, the telephone call was abruptly ended. The site was going to continue to make attempts to contact the subject but it appeared that the subject deliberately withheld very important health information.

During her hospitalisation, the subject received the following treatments: oral ondansetron hydrochloride (4

page (2)

mg as needed every 6 hours as needed, for nausea on 12-Feb-2014), prochlorperazine (rectal suppository, 25 mg daily, for nausea/vomiting on 12-Feb-2014), IV metoclopramide hydrochloride (10 mg daily, for nausea/vomiting on 12-Feb-2014), oral acetaminophen (650 mg every 6 hours as needed, for headache between 12-Feb-2014 and 13-Feb-2014), IV morphine sulphate (2 mg every 2 hours as needed, for sinus pain/headache on 12-Feb-2014), oral acetaminophen/hydrocodone (325mg/5mg every 4 hours as needed, for sinus pain/headache between 12-Feb-2014 and 14-Feb-2014), oral zolpidem tartrate (5 mg daily, for insomnia on 12-Feb-2014), oral temazepam (15 mg daily, for insomnia on 12-Feb-2014), oral docusate sodium (100 mg daily, for constipation on 12-Feb-2014), oral magnesium hydroxide (30 mL daily, for severe constipation on 12-Feb-2014), oral aluminum/magnesium/simethicone (30 mL every 6 hours as needed, for dyspepsia on 12-Feb-2014), oral calcium carbonate (1000 mg, for dyspepsia on 12-Feb-2014), IV pantoprazole (40 mg daily, for dyspepsia on 12-Feb-2014), subcutaneous insulin Novolin (as per sliding scale, for diabetes between 12-Feb-2014 and 13-Feb-2014), subcutaneous insulin Novolog (10 units daily, for diabetes between 13-Feb-2014 and 14-Feb-2014), oral azithromycin (500 mg daily, for sinus infection between 13-Feb-2014 and 14-Feb-2014), oral loratadine (10 mg daily, for sinus infection between 13-Feb-2014 and 14-Feb-2014), Flonase (fluticasone propionate, by nostril route, 2 sprays daily, for sinus infection between 13-Feb-2014 and 14-Feb-2014) and subcutaneous enoxaparin sodium (40 mg daily, for unknown indication between 12-Feb-2014 and 14-Feb-2014).

The investigator considered the event of diabetic ketoacidosis precipitated by sinusitis to be unrelated to the investigational product and attributed the event to 'basis disease/pre-existing condition'.

FOLLOW-UP INFORMATION RECEIVED ON 08-APR-2014:

The subject recovered from her diabetic ketoacidosis on 14-Feb-2014. No further information regarding the subject's insulin treatment was available. She did not report to the investigational site that she was using an insulin pump and this information was discovered in her hospital records.

FOLLOW-UP INFORMATION RECEIVED ON 12-SEP-2014:

The subject's medical history included attention deficit disorder with hyperactivity, attention deficit disorder, thalassemia, Reye's syndrome, leukocytosis, bilateral salpingo-oophorectomy and ovarian cancer.

FOLLOW-UP INFORMATION RECEIVED ON 17-FEB-2015:

Following SAE reconciliation, the intensity of the reported events was changed from 'moderate' to 'severe' and the action taken was changed from 'Subject discontinued study' to 'No action taken'.

This case is considered satisfactorily documented - no further follow-up requested.

Sender Comment: Company comment: Not related. In line with the investigator's assessment, the reported events are judged to be due to the subject's underlying condition.

B6 continued

#1. Venous blood pH decreased | 12-FEB-2014 | 7.25 (Time: 17:40) | N/A | 7.36 | 7.4 ;

#2. PCO2 | 12-FEB-2014 | 40 (Time: 17:40) | mmHg | 44 | 48 ;

#3. PO2 | 12-FEB-2014 | 31 (Time: 17:40) | mmHg | 35 | 40 ;

#4. Bicarbonate | 12-FEB-2014 | 17 (Time: 17:40) | mmol/L | 22 | 26 ;

#5. Venous oxygen saturation | 12-FEB-2014 | 58 (Time 17:40) | % | 70 | 76 ;

#6. Glucose | 12-FEB-2014 | 112 (Time 15:50) | mg/dL | 74 | 106 ;

#7. Glucose | 12-FEB-2014 | 123 (Time 17:50) | mg/dL | 74 | 106 ;

#8. Glucose | 12-FEB-2014 | 166 (Time 18:42) | mg/dL | 74 | 106 ;

MedWatch FDA35000: Continue.....

page (3)

B6 continued

#9. Glucose | 12-FEB-2014 | 226 (Time: 20:05) | mg/dL | 74 | 106 ;
#10. Glucose | 12-FEB-2014 | 238 (Time: 21:06) | mg/dL | 74 | 106 ;
#11. Glucose | 12-FEB-2014 | 295 (Time 21:45) | mg/dL | 74 | 106 ;
#12. Glucose | 12-FEB-2014 | 395 (Time 22:35) | mg/dL | 74 | 106 ;
#13. Glucose | 12-FEB-2014 | 242 (Time: 23:30) | mg/dL | 74 | 106 ;
#14. Glucose | 12-FEB-2014 | 378 (Time 00:50) | mg/dL | 74 | 106 ;
#15. Glucose | 13-FEB-2014 | 450 (Time 02:24) | mg/dL | 74 | 106 ;
#16. Glucose | 13-FEB-2014 | 438 (Time: 06:56) | mg/dL | 74 | 106 ;
#17. Glucose | 13-FEB-2014 | 330 (Time: 12:17) | mg/dL | 74 | 106 ;
#18. Glucose | 13-FEB-2014 | 345 (Time 21:20) | mg/dL | 74 | 106 ;
#19. Betahydroxybutyrate | 12-FEB-2014 | 3.50 (Time 15:50) | mmol/L | 0.00 | 0.39 ;
#20. Hemoglobin A1C increased | 13-FEB-2013 | 10.5 (Time: 06:56) | % | 4.3 | 6.0 ;
#21. WBC | 12-FEB-2014 | 17.9 (time: 15:50) | 10*3/iL | 4.0 | 11.0 ;
#22. Base excess | 12-FEB-2014 | -8.9 (Time: 17:40) | mmol/L | -2 | 2 ;

G8 continued

#2. Sinusitis (17.1)

MedWatch FDA35000: END of Continue.....

MEDWATCH
3500A Facsimile

Page 1 of 7

Mfr Report #	PMI000350
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event: 62 Years or Date of Birth: (b) (6)	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 161.4 lbs or 73.2 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input checked="" type="checkbox"/> Life-threatening (mm/dd/yyyy) <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 02/17/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Metastatic small bowel tumors [Metastases to small intestine] Severe anemia [Anaemia] Case Description: Verbatim: Severe Anemia, Metastatic Small Bowel Tumors. Clinical study ZRHR-ERS-09-US: A randomised, 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. INITIAL INFORMATION RECEIVED ON 20-OCT-2015: This report was received from an investigator and concerned a 62-year-old Caucasian female subject (Initials (b) ID continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates Tests were performed including esophagogastroduodenoscopy (EGD), colonoscopy and Computed tomography (CT) of the abdomen/pelvis. CT scan of the brain and lungs were clear. 08-OCT-2015: Large platelets 1+ (abnormal) - Reference range: negative; Anisocytosis 1+ (abnormal) - Reference range: negative; continued in additional info section...			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 --/--/1959 to --/--/1959 Historical Condition, (Continued) #2 --/--/1959 to --/--/1959 Procedure, (Continued) #3 --/--/1985 to --/--/1985 Historical Condition, (Continued) continued in additional info section...			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. Tobacco Heating System 2.2 (N/A) N/A			
#2. Conventional cigarette (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. UNK, Respiratory		#1. 09/01/2015 to 10/07/2015	
#2. UNK, Respiratory		#2. --/--/1974 to UNK	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1. B-17724	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND			
4. Date Received by Manufacturer (mm/dd/yyyy) 02/09/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #3			
9. Manufacturer Report Number PMI000350		8. Adverse Event Term(s) Metastases to small intestine, Anaemia	
E. INITIAL REPORTER			
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Physician	
		4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 7

Mfr Report #	PMI000350
UF/Importer Report #	
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Number: 04260, Randomisation Number: 20403, weight: 73.2 kg, height: 152 cm) who had been enrolled in the above mentioned clinical study.

The subject's relevant medical history included intermittent sinus headaches since 1990, high cholesterol (with controlled diet) since 1995, mild insomnia since 2014 and post-menopausal status since 2000. The subject's past medical history included tonsillitis and tonsillectomy in 1959, and Chlamydia in 1985. Concomitant medication was not provided.

The subject was randomized to the Tobacco Heating System 2.2 (THS 2.2) group (batch B-17724) and started using the product on 01-Sep-2015.

On 04-Oct-2015, the subject had felt light-headed and weak. Melena was observed. On (b) (6) the subject was seen by a gastroenterologist and was referred for hospitalization. The subject was admitted to the Intensive Care Unit on the same day: severe anemia was observed with decreased hemoglobin to lowest level of 3.7 (units not provided). Several PBRCs (packed red blood cells) were transfused. Tests were performed including esophagogastroduodenoscopy (EGD), colonoscopy and computed tomography (CT) of the abdomen/pelvis. The subject was diagnosed with non-operable small bowel tumors. Diagnosis of rare neuroendocrine tumors was made. Computed tomography (CT) scan of the brain and lungs was clear.

On (b) (6), the subject was discharged from the hospital and was to be followed-up with an oncologist. The event of severe anemia was considered resolved on the same day.

As a result of the events, the use of THS 2.2 was permanently discontinued on unspecified date.

The investigator considered the events of severe anemia and small bowel tumors to be severe in intensity and not related to the use with THS 2.2.

FOLLOW UP INFORMATION RECEIVED ON 04-NOV-2015 AND 06-NOV-2015:

The subject started smoking 41 years ago, since 1974. She had smoked on average 20 conventional cigarettes a day. At the time of this follow-up, co-medications were unknown.

Following randomisation to the Tobacco Heating System 2.2 (THS 2.2) group, the subject smoked 2 to 4 conventional cigarettes a day.

On 11-Oct-2015, a CT enterography was performed with the following result: enlarged upper abdominal lymph nodes around the proximal small bowel loops and in the retroperitoneum consistent with metastasis. Small nodule inferior to the spleen in the left upper quadrant also worrisome for metastasis. Enlarged lymph nodes abutting proximal jejunal loops. Suspicious wall thickening involving the gastroesophageal region. Bilateral renal cysts. Multiple hepatic hypodense lesions probably represent cysts. Bilateral adrenal adenomas or adenomatous hyperplasia.

On 13-Oct-2015, a CT Abdomen was performed with the following result: multiple large, necrotic lymph nodes in the lesser sac and retroperitoneum compatible with metastases. The source of these metastases was not identified on this exam. This might be due to a gastric mass.

Additional laboratory test results were received.

The reported term was changed from 'Small bowel tumors' to 'Metastatic small bowel'. It was also clarified that the type of anaemia was hemorrhagic. The subject had no risk factors for the reported events of Metastatic small bowel and Severe anaemia. Light-headed feeling, weakness and melena were considered as signs and symptoms of the Severe anaemia.

The subject stopped using the THS on 07-Oct-2015 and discontinued from the study on the same day.

At the time of this follow-up, it was unknown whether treatment was planned or administered to the subject for her tumors.

FOLLOW UP INFORMATION RECEIVED ON 19-JAN-2016:

The investigator considered the reported events of Severe anemia and Metastatic small bowel tumors to be unrelated to the consumption of conventional cigarettes.

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 3 of 7

Mfr Report #	PMI000350
UF/Importer Report #	
	FDA Use Only

It was confirmed that the 'bilateral renal cysts', 'multiple hepatic hypodense lesions probably represent cysts', 'bilateral adrenal adenomas or adenomatous hyperplasia' should not be considered as additional SAEs.

The subject declined to provide further information on her status.

FOLLOW UP INFORMATION RECEIVED ON 09-FEB-2016:

The investigator considered the reported events of Severe anemia and Metastatic small bowel tumors to be not related to study procedures.

No further information is expected. Case closed.

Case Comment:

Metastases to small intestine and Anaemia were assessed as serious, due to being life-threatening, requiring hospitalisation, or its prolongation.

Metastases to small intestine and Anaemia are unexpected, according to the Investigator's Brochure.

The Investigator has assessed these adverse events as not related to the use of THS 2.2 or to the conventional cigarette smoking or to study procedures.

Considering the implausible temporal relationship (i.e. the metastatic small bowel tumours were reportedly detected several weeks after enrolment in this study and starting using THS 2.2), and in agreement with the Investigator's causality assessment, the Metastases to small intestine is assessed as not related to the use of THS 2.2 or to study procedures. Although the primary tumour was not identified, a potential causal relationship between this patient's long history of conventional cigarette smoking and the now detected metastatic malignancy cannot be excluded and, therefore, is assessed as possible.

The reported severe Anemia, confirmed to be hemorrhagic (melena was reportedly observed), was most likely a consequence of the blood loss associated with the detected intestinal tumours. Therefore, in agreement with the Investigator's causality assessment, Anaemia is also assessed as not related to the use of THS 2.2 or to the conventional cigarette smoking or to study procedures.

B6. RELEVANT TESTS (Continued)

Schistocytes 1+ (abnormal) - Reference range: negative; Polychromasia 1+ (abnormal) - Reference range: negative; Poikilocytosis 1+ (abnormal) - Reference range: negative; Hypochromasia 2+ (abnormal) - Reference range: negative

10-OCT-2015: Colonoscopy

10-OCT-2015: UA Blood : 2+ (abnormal) - Reference range: negative

11-OCT-2015: CT Enterography showed enlarged upper abdominal lymph nodes around the proximal small bowel loops and in the retroperitoneum consistent with metastasis. Small nodule inferior to the spleen in the left upper quadrant also worrisome for metastasis. Enlarged lymph nodes abutting proximal jejunal loops. Suspicious wall thickening involving the gastroesophageal region. Bilateral renal cysts. Multiple hepatic hypodense lesions probably represent cysts. Bilateral adrenal adenomas or adenomatous hyperplasia.

13-OCT-2015: Clinical history and diagnosis : GI bleeding, abnormal CT scan in the abdomen, anemia

13-OCT-2015: Path 1st specimen instructions : jejunal mass

13-OCT-2015: CT Abdomen showed multiple large, necrotic lymph nodes in the lesser sac and retroperitoneum compatible with metastases. The source of these metastases is not identified on this exam. This may be due to a gastric mass. Asymmetric nodularity of the skin of the perineum. Stable bilateral adrenal nodules. Liver and renal cysts.

14-OCT-2015: Prot Elec Interp - Hypoproteinemia and hypoalbuminemia

15-OCT-2015: Chromogranin A / Results : 2081 ng/mL / Reference Range : 0 ng/mL - 95 ng/mL

15-OCT-2015: Direct Coombs Poly: Negative

15-OCT-2015: CT Brain showed no acute intracranial abnormality. Essentially unremarkable exam. No abnormal enhancement.

15-OCT-2015: CT Chest showed no evidence of metastatic disease in the thorax. No change in the upper abdomen.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	10/14/2015	Blood albumin depressed g/dL	2.84	5.71 4.10

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 4 of 7

Mfr Report #	PMI000350
UF/Importer Report #	
	FDA Use Only

2	10/14/2015	Blood albumin depressed g/dL	3.1	5.5 3.2
3	10/08/2015	Creatinine renal clearance depressed mL/min	38.27	
4	10/09/2015	Creatinine renal clearance depressed mL/min	42.73	
5	10/10/2015	Creatinine renal clearance depressed mL/min	47.84	
6	10/13/2015	Creatinine renal clearance depressed mL/min	45.85	
7	10/14/2015	Creatinine renal clearance depressed mL/min	49.46	
8	10/14/2015	Electrophoresis protein depressed g/dL	5.0	8.0 6.5
9	10/08/2015	Haematocrit depressed Critical value	11.7 %	45.5 34.3
10	10/09/2015	Haematocrit depressed	25.4 %	45.5 34.3
11	10/10/2015	Haematocrit depressed	25 %	45.5 34.3
12	10/11/2015	Haematocrit depressed	23.9 %	45.5 34.3
13	10/12/2015	Haematocrit depressed	23.9 %	45.5 34.3
14	10/14/2015	Haematocrit depressed	24.9 %	45.5 34.3
15	10/16/2015	Haematocrit depressed	29.3 %	45.5 34.3
16	10/08/2015	Haemoglobin depressed g/dL (Critical value)	3.7	14.7 11.4
17	10/09/2015	Haemoglobin depressed g/dL	8.7	14.7 11.4
18	10/10/2015	Haemoglobin depressed g/dL	8.4	14.7 11.4

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 5 of 7

Mfr Report #	PMI000350
UF/Importer Report #	
	FDA Use Only

19	10/11/2015	Haemoglobin depressed g/dL	7.9	14.7 11.4
20	10/12/2015	Haemoglobin depressed g/dL	7.7	14.7 11.4
21	10/14/2015	Haemoglobin depressed g/dL	7.9	14.7 11.4
22	10/16/2015	Haemoglobin depressed g/dL	9.1	14.7 11.4
23	10/15/2015	Haptoglobin elevated mg/dL	379	200 30
24	10/08/2015	Lymphocyte count depressed	20 %	45 20.5
25	10/08/2015	Monocyte count increased elevated 10 ³ /uL	1.54	0.80 0.00
26	10/08/2015	Neutrophil count elevated 10 ³ /uL	10.44	7.50 1.5
27	10/08/2015	Platelet count elevated 10 ³ /uL	388	361 139
28	10/16/2015	Platelet count elevated 10 ³ /uL	430	361 139
29	10/14/2015	Protein total depressed g/dL	5.7	8.0 6.5
30	10/08/2015	Red blood cell count depressed 10 ⁶ /uL	1.27	5.00 3.75
31	10/09/2015	Red blood cell count depressed 10 ⁶ /uL	2.95	5.00 3.75
32	10/10/2015	Red blood cell count depressed 10 ⁶ /uL	2.84	5.00 3.75
33	10/11/2015	Red blood cell count depressed 10 ⁶ /uL	2.66	5.00 3.75

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 6 of 7

Mfr Report #	PMI000350
UF/Importer Report #	
	FDA Use Only

34	10/12/2015	Red blood cell count depressed 10 ⁶ /uL	2.58	5.00 3.75
35	10/14/2015	Red blood cell count depressed 10 ⁶ /uL	2.68	5.00 3.75
36	10/16/2015	Red blood cell count depressed 10 ⁶ /uL	3.14	5.00 3.75
37	10/15/2015	Reticulocyte count elevated 10 ⁹ /L	227.5	125 38
38	10/15/2015	Reticulocyte count elevated	7.2 %	1.9 0.6
39	10/15/2015	Serum ferritin elevated ng/mL	610	307 11
40	10/08/2015	Transferrin saturation depressed	4 %	44 30
41	10/08/2015	White blood cell count elevated 10 ³ /uL	15.06	10.50 4.40
42	10/09/2015	White blood cell count elevated 10 ³ /uL	12.32	10.50 4.40
43	10/10/2015	White blood cell count elevated 10 ³ /uL	16.14	10.50 4.40
44	10/11/2015	White blood cell count elevated 10 ³ /uL	13.56	10.50 4.40
45	10/12/2015	White blood cell count elevated 10 ³ /uL	14.08	10.50 4.40
46	10/14/2015	White blood cell count elevated 10 ³ /uL	13.63	10.50 4.40
47	10/16/2015	White blood cell count elevated 10 ³ /uL	11.60	10.50 4.40
48	10/10/2015	White blood cells urine positive elevated /HPF	27	4 0

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 7 of 7

Mfr Report #	PMI000350
UF/Importer Report #	
	FDA Use Only

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	--/--/1959 --/--/1959	Historical Condition Tonsillitis	clinically insignificant
2	--/--/1959 --/--/1959	Procedure Tonsillectomy	clinically insignificant
3	--/--/1985 --/--/1985	Historical Condition Chlamydial infection	clinically insignificant
4	--/--/1990 Ongoing	Current Condition Sinus headache	intermittent, clinically insignificant
5	--/--/1995 Ongoing	Current Condition Blood cholesterol increased	clinically insignificant, controlled with diet
6	--/--/2000 Ongoing	Current Condition Postmenopause	clinically insignificant. Last menstrual period in 2000.
7	--/--/2014 Ongoing	Current Condition Insomnia	clinically insignificant
8	Ongoing	Current Condition Tobacco user	Started smoking 41 years ago (since 1974) and smoked on average 20 conventional cigarettes per day.

MEDWATCH
3500A Facsimile

Page 1 of 6

Mfr Report #	PMI000360
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event: 56 Years or Date of Birth: (b) (6)	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 170.0 lbs or 77.1 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 02/12/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Urosepsis [Urosepsis] Acute pyelonephritis [Pyelonephritis acute] Nephrolithiasis [Nephrolithiasis] Case Description: Verbatim: Sepsis, Acute pyelonephritis, Nephrolithiasis (previously reported as Kidney stone, Kidney infection). Clinical study ZRHR-ERS-09-US: A randomised, 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. INITIAL INFORMATION RECEIVED ON 26-OCT-2015: continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates Gastrointestinal: tenderness: mild, generalized, worst in lower left quadrant (LLQ). 30-Sep-2015: US venous duplex bilateral: no evidence of deep venous thrombus (in the bilateral lower extremities). LABORATORY DATA #1 09/29/2015 Alanine aminotransferase (continued) continued in additional info section...			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 --/--/1974 to Ongoing, Current Condition, Tobacco user (Regularly, smokes about a pack every 3 days.(Continued)) #2 Historical Condition, Scar excision #3 Historical Condition, Caesarean section (three times) #4 Ongoing, Current Condition, Dermatitis contact (Causes rash)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. Conventional cigarette (N/A) N/A			
#2. Tobacco Heating System 2.2 (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. UNK, Respiratory		#1. --/--/1974 to Ongoing	
#2. UNK, Respiratory		#2. 08/19/2015 to 08/23/2015	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1.	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND			
4. Date Received by Manufacturer (mm/dd/yyyy) 02/03/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-US		3. Report Source (Check all that apply)	
7. Type of Report (Check all that apply)		<input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #3			
9. Manufacturer Report Number PMI000360		8. Adverse Event Term(s) Urosepsis, Pyelonephritis acute, Nephrolithiasis	
E. INITIAL REPORTER			
1. Name and Address		Phone # Withheld	
UNITED STATES Name and address withheld.			
2. Health Professional?		3. Occupation Physician	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
		4. Initial Reporter Also Sent Report to FDA	
		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 6

Mfr Report #	PMI000360
UF/Importer Report #	
	FDA Use Only

ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

This report was received from an investigator and concerned a 56-year-old Caucasian female subject (Initials (b) (6) ID Number: 01094, Randomisation Number: 20295, weight: 77.1 kg, height: 173 cm) who had been enrolled in the above mentioned clinical study.

The subject's relevant medical history and concomitant medications were not provided.

Tobacco Heating System 2.2 (THS 2.2) was dispensed to the subject on 18-Aug-2015 and she used THS between 19-Aug-2015 and 24-Aug-2015.

The subject was subsequently randomized to the conventional cigarettes arm.

The subject went to the hospital on (b) (6) for lower back pain that began on 23-Sep-2015 at 07:00. The subject was admitted on the same day and hospitalized until (b) (6). She was diagnosed with kidney stone and kidney infection. Both reported events were considered as severe in intensity.

The subject did not stop smoking and was not discontinued from the study due to the occurrence of these events.

At the time of this report, the outcome of both reported events was unknown.

The investigator considered both events of kidney stone and kidney infection to be not related to the use of THS 2.2. The Investigator also considered the event of kidney infection to be not related to the use of conventional cigarettes and the event of kidney stone to be possibly related to the use of conventional cigarettes.

FOLLOW-UP INFORMATION RECEIVED ON 11-NOV-2015 and 13-NOV-2015:

The subject smoked since 1974 and her average consumption was 10 conventional cigarettes per day since she started smoking. Her medical history included allergy to adhesive bandage (causes rash), C-section (three times) and surgery after C-section for scar tissue. She was also identified as having a risk for venous thromboembolism (VTE). She drank alcohol occasionally.

She used Tobacco Heating System 2.2 (THS 2.2) between 19-Aug-2015 and 23-Aug-2015.

The subject was randomized to the conventional cigarettes arm on 24-Aug-2015.

Approximately a week prior to admission, she developed fevers, chills and back pain. She was found to have sepsis present on admission. She also had other multiple complaints including no bowel movement for 2 weeks, abdominal pain, nausea, vomiting, headache, shortness of breath (which later on improved and was possibly related to sepsis) and atypical chest pain. There was evidence of leukocytosis, tachycardia, tachypnea (secondary to acute pyelonephritis), hyponatremia, hypokalaemia and transaminitis. She was also found to have a kidney stone with hydronephrosis. She was hospitalised for acute pyelonephritis, sepsis (secondary to pyelonephritis) and nephrolithiasis (with mild hydronephrosis and hydroureter) on (b) (6) at 22:55. The events were considered to be severe in intensity.

On 29-Sep-2015, an abdomen and pelvis CT showed a 5-mm calculus/stone at the left ureterovesical junction (UVJ) associated with mild hydronephrosis and hydroureter, as well as abnormal patchy enhancement of the left kidney likely reflecting nephritis.

During her hospitalisation, the subject was administered IV fluids, IV antibiotics and pain medications, which included IV sodium chloride 0.9%, IV Toradol (ketorolac), IV Zofran (ondansetron), IV morphine, IV fentanyl, IV or oral potassium chloride, IV metronidazole, IV Levaquin (levofloxacin), oral Colace (docusate), IV magnesium sulphate, IV sodium phosphate, oral lactulose, subcutaneous enoxaparin, oral Percocet 5/325 (acetaminophen/oxycodone), IV midazolam, IV propofol, IV lidocaine, IV Ancef (cefazolin) and IV dexamethasone.

On 02-Oct-2015, she underwent cystoscopy (with left retrograde pyelogram) and left ureteroscopy, showing spontaneous passage of left ureteral calculus.

During her hospitalisation, she complained of some difficulty in breathing. A D-dimer was checked and was elevated. Therefore, the ultrasound of bilateral lower extremities was done as well as a V/Q scan and both were negative.

She was discharged on (b) (6) with the following medications: Percocet (acetaminophen/ oxycodone) as needed for pain, oral Colace (docusate) 100 mg twice a day and oral Levaquin (levofloxacin) 500 mg daily for 7 days. The events resolved on

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 3 of 6

Mfr Report #	PMI000360
UF/Importer Report #	
	FDA Use Only

09-Oct-2015.

The investigator considered the reported events of Sepsis, Acute pyelonephritis and Nephrolithiasis to be not related to the use of THS 2.2.

FOLLOW-UP INFORMATION RECEIVED ON 12-JAN-2016:

Based on the subject's medical history, she did not have previous episodes of nephrolithiasis, acute pyelonephritis or sepsis and she did not have risk factors for nephrolithiasis or sepsis. It was added that being female is a known risk factor for urinary tract infections, including pyelonephritis.

The subject was not taking any concomitant medications at the time of the occurrence.

The reported event of 'Sepsis' was updated to 'Urosepsis'.

The investigator considered the reported event of Sepsis/Urosepsis to be related to the use of conventional cigarettes.

The investigator clarified that the following events were not considered separate serious adverse events: no bowel movement for 2 weeks, abdominal pain, nausea, vomiting, headache, shortness of breath, atypical chest pain, leukocytosis, tachycardia, tachypnea, hyponatremia, hypokalaemia and transaminitis.

FOLLOW-UP INFORMATION RECEIVED ON 03-FEB-2016:

The investigator considered the reported events of Urosepsis, Acute pyelonephritis, Nephrolithiasis to be not related to any of the study procedures.

No further information is expected. Case closed.

Case Comment:

Urosepsis, Pyelonephritis acute, and Nephrolithiasis were assessed as serious (requiring hospitalisation).

Urosepsis, Pyelonephritis acute, and Nephrolithiasis are unexpected adverse events, as per the Reference Safety Information (i.e. the IB).

In agreement with the Investigator's causality assessment, the Urosepsis and Nephrolithiasis are assessed as not related to the use of THS 2.2, but possibly related to this patient's smoking conventional cigarettes. Also in agreement with the Investigator's causality assessment, the Pyelonephritis acute is assessed as not related to the use of THS 2.2 or of conventional cigarettes, in this female patient. None of the Urosepsis, Pyelonephritis acute, and Nephrolithiasis adverse events was assessed as related to any of the study procedures, by the Investigator or by the Company. Of note, THS 2.2 was used for only five days, approximately one month before the onset of the adverse events, and the use of conventional cigarettes was not discontinued due to the events, which have all resolved.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	09/29/2015	Alanine aminotransferase elevated IU/L	80	46 10
2	09/30/2015	Alanine aminotransferase elevated IU/L	58	46 10
3	09/29/2015	Bacterial test	3+	
4	09/29/2015	Blood albumin	3.1	
5	09/29/2015	Blood culture No growth		

MEDWATCH

3500A Facsimile (Back)

(Continued)

Page 4 of 6

Mfr Report #	PMI000360
UF/Importer Report #	
	FDA Use Only

6	09/29/2015	Blood culture		
		No growth		
7	09/29/2015	Blood glucose elevated mg/dL	180	99 65
8	09/30/2015	Blood glucose elevated mg/dL	121	99 65
9	10/01/2015	Blood glucose elevated mg/dL	113	99 65
10	09/29/2015	Blood potassium mmol/L	2.8	
11	09/29/2015	Blood pressure measurement	138/80	
12	09/29/2015	Blood sodium depressed mmol/L	129	
13	09/29/2015	Blood urine Small		
14	09/29/2015	Body temperature Degrees Celsius	38.4	
15	09/29/2015	Body temperature Degrees Celsius	37	
16		Computerised tomogram		
17	09/29/2015	Computerised tomogram CT abdomen and pelvis showed a 5-mm calculus/stone at the left UVJ associated with mild hydronephrosis and hydroureter. Abnormal patchy enhancement of the left kidney likely reflected nephritis.		
18	09/29/2015	Culture urine cfu/ml Escherichia coli	>100,000	
19	09/29/2015	Electrocardiogram abnormal Reason: chest pain (atypical)		
20	09/29/2015	Heart rate	83	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 5 of 6

Mfr Report #	PMI000360
UF/Importer Report #	
	FDA Use Only

21	09/29/2015	Heart rate bpm	116	
22	09/29/2015	Lipase depressed IU/L	66	
23	09/29/2015	Neutrophil count elevated K/ul	12.8	7.8 1.5
24	09/30/2015	Neutrophil count elevated K/ul	10.4	7.8 1.5
25	10/01/2015	Neutrophil count elevated K/ul	9.4	7.8 1.5
26	09/29/2015	Oxygen saturation on room air	97 %	
27	09/29/2015	Protein urine mg/dL	100	
28	09/29/2015	Red blood cells urine /HPF	11-20	2 1
29	09/29/2015	Respiratory rate br/min	24	
30	09/29/2015	Respiratory rate	18	
31	09/29/2015	Urine abnormality /HPF	3+	1+
32	09/29/2015	Urine analysis Cloudy		
33	09/29/2015	Urine leukocyte esterase Large		
34		Ventilation/perfusion scan Showed low probability for PE and ultrasound of bilateral lower extremity showed no evidence of DVT.		
35	09/29/2015	White blood cell count elevated K/MM3	15.2	11.0 4.0

MEDWATCH

3500A Facsimile (Back)

(Continued)

Page 6 of 6

Mfr Report #	PMI000360
UF/Importer Report #	
	FDA Use Only

36	09/30/2015	White blood cell count elevated K/MM3	12.8	11.0 4.0
37	10/01/2015	White blood cell count elevated K/MM3	11.7	11.0 4.0
38	09/29/2015	White blood cells urine /HPF	>50	

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	--/--/1974	Current Condition	Regularly, smokes about a pack every 3 days. Average daily consumption is 10 since subject started smoking.
	Ongoing	Tobacco user	

MEDWATCH
3500A Facsimile

Page 1 of 3

Mfr Report #	PMI000369
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event: 37 Years or Date of Birth: (b) (6)	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 177.7 lbs or 80.6 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input checked="" type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 02/05/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Left thyroid papillary carcinoma with lymph node involvement [Papillary thyroid cancer] Case Description: Verbatim: Left thyroid papillary carcinoma with lymph node involvement (previously reported as Thyroidectomy) Clinical study ZRHR-ERS-09-US: A randomised, 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. INITIAL INFORMATION RECEIVED ON 02-NOV-2015: This report was received from an investigator and concerned a continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates Result of the surgical pathology report: Left node with calcified nodule showing atypical follicular architecture thyroid cells and adjacent fragment of lymph node with feature compatible with metastatic thyroid carcinoma; the pathologic stage was noted as pT3 pN1b. continued in additional info section...			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc) Race: Caucasian #1 --/--/1996 to Ongoing, Current Condition, Tobacco user (20 conventional cigarettes per day) #2 Ongoing, Current Condition, Neck pain (Cervical (C5-6 worse than C4-5)) #3 Ongoing, Current Condition, Intervertebral disc degeneration			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. Conventional cigarette (N/A) N/A			
#2. Tobacco Heating System 2.2 (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. UNK, Respiratory		#1. --/--/1996 to Ongoing	
#2. UNK, Respiratory		#2. 06/19/2015 to 06/25/2015	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1.	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 01/26/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #2			
9. Manufacturer Report Number PMI000369		8. Adverse Event Term(s) Papillary thyroid cancer	
E. INITIAL REPORTER			
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Physician	
		4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000369
UF/Importer Report #	
	FDA Use Only

ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

37-year-old male subject (Initials: (b) (6), ID Number: 12097, Randomisation Number: 10410, weight: 80.6 kg, height: 171 cm) who had been enrolled in the above mentioned clinical study.

The subject's relevant medical history was not provided. Concomitant medications included oral Robaxin (methocarbamol) at the dosage of 1500 mg daily from 14-Oct-2015 for pain, and oral hydrocodone/acetaminophen at the dosage of 7.5/325 mg daily from 14-Oct-2015 for pain.

The subject was randomized to the Tobacco Heating System 2.2 (THS 2.2) arm.

In early October 2015, the subject had a CT scan in preparation for neck surgery. Thyroid nodule was found and the subject was scheduled for thyroidectomy.

The subject was hospitalised and underwent thyroidectomy on (b) (6). It was reported that he was hospitalised for more than 24 hours. The subject recovered (b) (6).

The investigator considered the reported event of thyroidectomy to be not related to the use of THS 2.2.

FOLLOW-UP INFORMATION RECEIVED ON 11-NOV-2015 and 16-NOV-2015:

The subject had no relevant medical history. He started smoking in 1996 and he smoked 20 conventional cigarettes a day. His ethnicity was Caucasian.

The subject was randomized to the conventional cigarettes arm, on 25-Jun-2015 (not to the THS 2.2 arm, as previously recorded).

On 11-Sep-2015, the subject (who had a history of neck pain which was not considered as an additional serious adverse event) had an MRI (Magnetic Resonance Imaging) of the cervical spine: cervical degenerative changes were noted at C4-C5 and C5-C6, as well as a mass within the paraspinal soft tissue at the level of C5-C7. This mass had not been clinically noted prior to CT scan.

On 06-Oct-2015, the subject had a CT (Computerised Tomogram) scan in preparation for surgery for cervical degenerative disc disease, as well as for the detection of the cervical lymphadenopathy during the MRI. Presence of thyroid nodules was confirmed.

The subject underwent total thyroidectomy with left selective node dissection on (b) (6). The surgical pathology report provided the following diagnosis: left node with calcified nodule showing atypical follicular architecture thyroid cells and adjacent fragment of lymph node with feature compatible with metastatic thyroid carcinoma. The pathologic stage was noted as pT3 pN1b.

The event of left thyroid papillary carcinoma with lymph node involvement was considered to be severe in intensity and to be serious due to being medically important.

At the time of this follow-up, the event was still ongoing. Further treatment plans were going to be provided by the surgeons.

The Investigator considered the reported event of Left thyroid papillary carcinoma with lymph node involvement to be of unknown etiology / Other non-drug cause.

FOLLOW-UP INFORMATION RECEIVED ON 26-JAN-2016:

The subject used the THS 2.2 from 19-Jun-2015 to 25-Jun-2015 during the run-in period.

The subject was not taking any medications at the time the nodules were detected.

As the thyroid nodules were detected by MRI on 11-Sep-2015, the onset date of the reported carcinoma was changed from (b) (6) (date for thyroidectomy) to 11-Sep-2015 (date of detection by MRI).

The subject was hospitalized for thyroidectomy from (b) (6).

No aetiology was identified as the cause of the occurrence of the SAE of left thyroid papillary carcinoma with lymph node involvement.

At time of the report, the event was still ongoing.

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 3 of 3

Mfr Report #	PMI000369
UF/Importer Report #	
	FDA Use Only

The investigator considered the reported event of left thyroid papillary carcinoma with lymph node involvement to be not related to the use of THS 2.2, to the consumption of conventional cigarettes or to any of the study procedures.

Further information will be requested (Final outcome and resolution date, confirmation seriousness criteria as both hospitalisation and medically important).

Case Comment:

Papillary thyroid cancer was assessed as serious (medically important and hospitalisation).

Papillary thyroid cancer is unexpected, according to the Reference Safety Information (i.e. the Investigator's Brochure).

Considering the implausible temporal relationship (i.e. the thyroid nodules, which were then diagnosed as thyroid papillary carcinoma with lymph node involvement, were detected only less than three months later after the subject had used Tobacco Heating System 2.2 (THS 2.2) for only seven days), the Papillary thyroid cancer is assessed as not related to the use of THS 2.2.

Considering the current understanding of thyroid cancer's risk factors, and also in agreement with the Investigator's causality assessment, the Papillary thyroid cancer is assessed as not related to the subject's smoking conventional cigarettes and not related to any of study procedures.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	10/06/2015	Computerised tomogram		
		Thyroid nodules were found		
2	09/11/2015	Nuclear magnetic resonance imaging		
		Cervical degenerative changes at C4-C5 and C5-C6 + there is a mass at the level of C5-C7 within the paraspinal soft tissue.		

MEDWATCH
3500A Facsimile

Page 1 of 3

Mfr Report #	PMI000385
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event: 46 Years or Date of Birth: (b) (6)	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 175.5 lbs or 79.6 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 01/25/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Cervical osteophyte [Vertebral osteophyte] Cervical myelopathy [Cervical myelopathy] Case Description: Verbatim: Cervical osteophyte, Cervical myelopathy Clinical study ZRHR-ERS-09-US: A randomised, 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. INITIAL INFORMATION RECEIVED ON 09-NOV-2015: This report was received from an Investigator and concerned a 46-year-old male subject (Initials (b) ID Number: 14046, continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates 09-SEP-2015: MRI of the shoulder: Cervical osteophyte and cervical myelopathy were discovered.			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc) Race: Black #1 --/--/1991 to Ongoing Current Condition, (Continued) #2 --/--/1994 to Ongoing Current Condition, (Continued) #3 --/--/1994 to --/--/1994 Historical Condition, (Continued) continued in additional info section...			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) (Regimens Continued)			
#1. Conventional cigarette (N/A) N/A			
#2. Tobacco Heating System 2.2 (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 10 DF, qd, Respiratory		#1. --/--/1991 to 07/15/2015	
#2. UNK, Respiratory		#2. 07/07/2015 to 07/15/2015	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1.	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. B-17825	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 01/15/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #1			
9. Manufacturer Report Number PMI000385		8. Adverse Event Term(s) Vertebral osteophyte, Cervical myelopathy	
E. INITIAL REPORTER			
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Physician	
		4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000385
UF/Importer Report #	
	FDA Use Only

ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Randomisation Number: 10256, weight: 79.6 kg, height: 176 cm) who had been enrolled in the above mentioned clinical study.

The subject's medical history included seasonal allergies since 2005, nerve impingement (right elbow) between 1994 and 26-Jun-2015, grade 5 acromioclavicular (AC) separation right shoulder in 1994, intermittent right shoulder pain since 1994, herniated disc L5-S1 between 2000 and 2008, spinal fusion L5-S1 in 2008, back stiffness (secondary to fusion) since 2008, inguinal hernia between 2011 and 2012, inguinal hernia repair in 2012, and intermittent neck pain since 2013 (that the subject attributed to a 'crick in the neck' or 'sleeping wrong').

The subject used the Tobacco Heating System 2.2 (THS 2.2, batch number B-17825) between 07-Jul-2015 and 15-Jul-2015.

On 09-Sep-2015, the subject had an MRI (Magnetic Resonance Imaging) of his shoulder for ongoing shoulder pain. It was discovered that the subject had a cervical osteophyte and cervical myelopathy. These events were considered to be mild in intensity. The subject was not aware that he had these problems. His doctor recommended cervical disc replacement.

The subject took oral acetaminophen/oxycodone (325/5 mg) between 08-Oct-2015 and 29-Oct-2015 for intermittent right shoulder pain.

On (b) (6), the subject was hospitalized for surgery (cervical disc replacement). During his hospitalization, the subject received intravenous morphine (dosage unknown) on 29-Oct-2015 for post-operative pain secondary to disc replacement, oral docusate (dosage unknown) on 30-Oct-2015 for prophylaxis of constipation, oral senna (dosage unknown) on 30-Oct-2015 for prophylaxis of constipation, oral famotidine (dosage unknown) on 30-Oct-2015 for prophylaxis of stress ulcer, and cefazolin (dosage unknown) on 30-Oct-2015 for prophylaxis of infection.

The subject recovered on 29-Oct-2015 and was discharged on (b) (6) with oral Soma (carisoprodol) 1 tablet three times a day and oral acetaminophen/oxycodone (325/10 mg), both taken for post-operative pain secondary to disc replacement.

The subject was not withdrawn from the study due to the occurrence of these events.

The investigator considered the reported events of Cervical osteophyte and Cervical myelopathy to be not related to the use of THS 2.2 and attributed them to the subject's basic disease/pre-existing condition.

FOLLOW-UP INFORMATION RECEIVED ON 15-JAN-2016:

The subject was randomized to the Conventional Cigarettes arm on 16-JUL-2015.

The subject has been smoking since 1991 and his average consumption was 10 conventional cigarettes per day before randomization and 13 conventional cigarettes per day after randomization.

The subject's ethnicity is black.

The investigator considered the reported events of Cervical osteophyte and Cervical myelopathy to be unrelated to the use of THS, to the consumption of conventional cigarettes, or to the study procedures.

No further information is expected. Case closed.

Case Comment:

Vertebral osteophyte and Cervical myelopathy were assessed as serious (requiring hospitalisation).

Vertebral osteophyte and Cervical myelopathy are unexpected, according to the Reference Safety Information (i.e. Investigator's Brochure).

Considering the presence of alternative explanations (i.e. the medical history, including nerve impingement, acromioclavicular separation, and herniated disc requiring surgery, pointing to a mechanical, post-traumatic causation), and in agreement with the Investigator's causality assessment, the reported cervical osteophyte and cervical myelopathy are assessed as not related to the conventional cigarette smoking. Besides, considering the implausible temporal relationship (i.e. the reported adverse events were detected by MRI, which was performed to further investigate a pre-existing condition, a couple of months after enrolment and after using THS 2.2 for only nine days), the reported adverse events are assessed as not related to the use of THS 2.2 or to the study

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 3 of 3

Mfr Report #	PMI000385
UF/Importer Report #	
FDA Use Only	

procedures.

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	--/--/1991 Ongoing	Current Condition Tobacco user	
2	--/--/1994 Ongoing	Current Condition Musculoskeletal pain	
3	--/--/1994 --/--/1994	Historical Condition Joint dislocation	Grade 5 acromioclavicular (AC) separation right shoulder
4	--/--/1994 06/26/2015	Historical Condition Nerve compression	Nerve impingement (right elbow)
5	--/--/2000 --/--/2008	Historical Condition Intervertebral disc protrusion	Herniated disc L5-S1
6	--/--/2005 Ongoing	Current Condition Seasonal allergy	
7	--/--/2008 --/--/2008	Historical Condition Spinal fusion surgery	Spinal fusion L5-S1
8	--/--/2008 Ongoing	Current Condition Musculoskeletal stiffness	secondary to fusion
9	--/--/2011 --/--/2012	Historical Condition Inguinal hernia	
10	--/--/2012 --/--/2012	Procedure Inguinal hernia repair	
11	--/--/2013 Ongoing	Current Condition Neck pain	Intermittent neck pain since 2013 (that the subject attributed to a 'crick in the neck' or 'sleeping wrong')

Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#1 Conventional cigarette Regimen # 2	13 DF, qd, Respiratory	07/16/2015 to Ongoing		
#2 Tobacco Heating System 2.2 Regimen # 2	UNK			

MEDWATCH
3500A Facsimile

Page 1 of 3

Mfr Report #	PMI000452
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b) (6)	2. Age at Time of Event: 55 Years or Date of Birth: (b) (6)	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 148.4 lbs or 67.3 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input checked="" type="checkbox"/> Death: (b) (6) (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 04/22/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Death due to acute and chronic alcohol abuse [Alcohol abuse] Case Description: Verbatim: Death due to acute and chronic alcohol abuse. Clinical study ZRHR-ERS-09-US: 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. INITIAL INFORMATION RECEIVED ON 16-DEC-2015: This report was received from an investigator and concerned a 55-year-old male subject (Initials: (b) (6), ID Number: 04384, continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 12/17/2015 Blood ethanol (continued) #2 12/17/2015 Blood test (continued) #3 12/17/2015 Blood test (continued)			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc) Race: Caucasian #1 --/--/2005 to Ongoing, Current Condition, Tobacco user (Before randomization on average 40 CC daily) #2 Historical Condition, Alcohol abuse (History of chronic alcohol abuse in the past)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) (Regimens Continued)			
#1. Tobacco Heating System 2.2 (N/A) N/A			
#2. Conventional cigarette (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 20 DF, qd around, Respiratory		#1. 09/28/2015 to 10/06/2015	
#2. 40 DF, qd, Respiratory		#2. --/--/1970 to 10/06/2015	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1. B-(Continued)	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND			
4. Date Received by Manufacturer (mm/dd/yyyy) 04/13/2016		5. (A)NDA # IND # N/A STN # PMA/510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #3			
9. Manufacturer Report Number PMI000452		8. Adverse Event Term(s) Alcohol abuse	
E. INITIAL REPORTER			
1. Name and Address		Phone # Withheld	
UNITED STATES Name and address withheld.			
2. Health Professional?	3. Occupation Physician	4. Initial Reporter Also Sent Report to FDA	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000452
UF/Importer Report #	
	FDA Use Only

ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Randomisation Number: 10514, weight: 67.3 kg, height: 176.5 cm) who had been enrolled in the above mentioned clinical study.

No medical history was reported.

No concomitant medication was reported.

The subject was randomized to the Tobacco Heating System 2.2 (THS 2.2) arm and started using the product on 28-Sep-2015 at 12:00. The subject ceased the use of THS 2.2 (Batch number B-17724 / B-17821) on 10-Dec-2015 at 20:40.

On an unknown date, the site was contacted by a detective from the police department of homicide in regard to this subject who died on (b) (6). The homicide investigation was ongoing, at the time of this report, and the medical examiner's report was going to be available in 8 to 12 weeks.

The subject was withdrawn from the study due to the occurrence of this event.

The Investigator considered the reported death to be unrelated to the use of the THS 2.2.

FOLLOW UP INFORMATION RECEIVED ON 19-JAN-2016:

The subject did not have any relevant medical history and was not taking any concomitant medications at the time of the event.

The subject started smoking conventional cigarettes 45 years ago, at the age of 10.

The subject smoked 40 conventional cigarettes daily before randomization.

The subject was randomized to THS arm on 07-Oct-2015.

The reason for the subject to stop using the THS five days before his death was unknown and, it was considered that the use of THS was discontinued due to the occurrence of the SAE.

At time of the report, the medical examiner's report was still pending and no further information was available.

The investigator considered the fatal SAE as not related to the use of THS, to the consumption of conventional cigarettes or to the study procedures.

FOLLOW UP INFORMATION RECEIVED ON 23-FEB-2016:

The subject was found dead on (b) (6) and an autopsy was conducted on 17-Dec-2015.

According to the autopsy report, the subject's cause of death was 'Acute and chronic alcohol abuse'. Consequently, the verbatim was updated to 'Death due to acute and chronic alcohol abuse'. The autopsy report also mentioned the following findings: acute alcohol intoxication, pulmonary edema and cerebral edema.

The autopsy report concluded that the death of this subject, who was found deceased in the bathtub at his residence, was due to acute and chronic alcohol abuse. Post-mortem toxicology revealed a level of ethanol (0.263 g/dL) not usually associated with death due to acute alcohol intoxication. However, there were no other significant findings at autopsy and the deceased did have a history of chronic alcohol abuse in the past. Medical records indicated that the deceased had been abstinent from alcohol but scene examination revealed the presence of alcoholic beverages. Witnesses stated that the deceased was found in the bathtub without his head submerged. The manner of death was accident.

FOLLOW-UP INFORMATION RECEIVED ON 13-APR-2016:

Before randomization, during the run-in period from 28-Sep-2015 to 06-Oct-2015, the subject used around 20 THS daily.

After randomization, the subject smoked between 0 to 12 conventional cigarettes daily and used between 7 to 27 THS daily.

On 17-Dec-2015, samples were taken. Blood nicotine level was at 27 ng/mL (reporting limit at 25 ng/mL and nicotine concentrations

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 3 of 3

Mfr Report #	PMI000452
UF/Importer Report #	
FDA Use Only	

from use of tobacco products and/or nicotine replacement therapy at 5-50 ng/mL). Blood cotinine level was at 380 ng/mL (reporting limit at 50 ng/mL and cotinine concentrations from use of tobacco products and/or nicotine replacement therapy at 100-1200 ng/mL).

No further information is expected. Case closed.

Case Comment:

Death due to acute and chronic alcohol abuse [Alcohol abuse] was assessed as serious (fatal outcome).

Alcohol abuse is unexpected, according to the Reference Safety Information (i.e. the Investigator's Brochure).

The Investigator considered the reported death due to acute and chronic alcohol abuse to be not related to the use of the THS 2.2, to the conventional cigarette smoking, or to the study procedures.

Based on the provided information, the use of THS 2.2 had been stopped, for an unknown reason, a few days prior to the fatal alcohol abuse. In agreement with the Investigator's causality assessment, the reported death due to acute and chronic alcohol abuse is assessed as not related to the use of THS 2.2, to the conventional cigarette smoking, or to the study procedures, in this male patient.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	12/17/2015	Blood ethanol elevated	0.263 g/dL	0.01
2	12/17/2015	Blood test	27 ng/mL	
		Reporting limit= 25 ng/mL, nicotine concentrations from use of tobacco products and/or nicotine replacement therapy: 5-50 ng/mL		
3	12/17/2015	Blood test	380 ng/mL	
		Reporting limit= 50 ng/mL, cotinine concentrations from use of tobacco products and/or nicotine replacement therapy: 100-1200 ng/mL		

C6. LOT# (Continued)

Suspect Medication #1: B-17724 / B-17821

Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#1 Tobacco Heating System 2.2 Regimen # 2	7 to 27 DF qd, Respiratory	10/07/2015 to 12/10/2015		
#2 Conventional cigarette Regimen # 2	0 to 12 DF, qd, Respiratory	10/07/2015 to 12/10/2015		

MEDWATCH
3500A Facsimile

Page 1 of 3

Mfr Report #	PMI000463
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event 44 Years or Date of Birth (b) (6)	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 137.4 lbs or 62.3 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 04/22/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Passed out and hit her head which caused a seizure and 5 day hospital stay [Loss of consciousness] Passed out and hit her head which caused a seizure and 5 day hospital stay [Head injury] Passed out and hit her head which caused a seizure and 5 day hospital stay [Seizure] Case Description: Verbatim: Passed out and hit her head which caused a seizure and 5 day hospital stay. Clinical study ZRHR-ERS-09-US: 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 continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 --/--/1986 to Ongoing Current Condition, (Continued) #2 Ongoing, Current Condition, Anaemia #3 Historical Condition, (Continued) #4 Ongoing, Current Condition, Hyperthyroidism			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. Tobacco Heating System 2.2 (N/A) N/A			
#2. Conventional cigarette (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 15-20 DF, qd, Respiratory		#1. 09/28/2015 to Ongoing	
#2. 20 DF, qd on (Continued)		#2. --/--/1986 to 10/04/2015	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1. B-17821	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
1) Synthroid (Levothyroxine sodium) --/--/1986 to ongoing			
2) Vitamin b12 (Cyanocobalamin) --/--/2007 to ongoing			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 04/11/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other: _____ _____ _____	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #2		9. Manufacturer Report Number PMI000463	
8. Adverse Event Term(s) Loss of consciousness, Head injury, Seizure			
E. INITIAL REPORTER			
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Physician	
4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk			

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000463
UF/Importer Report #	
	FDA Use Only

ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

conventional cigarettes for 26 weeks in an ambulatory setting.

INITIAL INFORMATION RECEIVED ON 22-DEC-2015:

This report was received from an investigator and concerned a 45-year-old female subject (Initials (b) (6)) ID Number: 09236, Randomisation Number: 20384, weight: 62.3 kg, height: 156 cm) who had been enrolled in the above mentioned clinical study.

The subject's medical history included hyperthyroidism and anemia. Concomitant medication included oral Synthroid (levothyroxine) at the dosage of 112 mcg daily since 1986 for hyperthyroidism and intramuscular vitamin B 12 (1 shot weekly) since 2007 for anemia.

The subject was randomized to the Tobacco Heating System 2.2 (THS 2.2) arm and started using the product on 28-Sep-2015 at 12:00.

The subject reported that she passed out while washing the dishes. She hit her head rather hard and began to seize. The subject was admitted to hospital on (b) (6) where she was monitored. She was administered oral divalproex ER at the dosage of 1000 mg daily from 10-Dec-2015 for the treatment of seizure. The subject recovered on (b) (6) and was discharged from hospital on the same day.

The subject was not withdrawn from the study due to the occurrence of these events and continued using THS 2.2 (Batch number B-17821) at the time of this report.

The Investigator considered the reported events to be unrelated to the use of the THS 2.2.

FOLLOW-UP INFORMATION RECEIVED ON 15-MAR-2016:

The subject started smoking when she was 16-year-old. Before randomization, the subject smoked on average 20 conventional cigarettes per day.

The subject was randomized to the THS arm on 05-Oct-2015. Since randomization, the subject smoked on average 5 to 10 conventional cigarettes per day.

It was reported that the subject experienced previous episodes of passing out, but not to this extreme. However, it had been a while since the last episode.

It was confirmed that the subject passed out, then fell, and had the seizure after the fall.

At the time of this report, the final diagnosis was unknown. The causes of loss of consciousness and of seizure were unknown. The results of relevant medical investigations were unknown. The type of underlying anaemia was unknown.

The Investigator considered the reported events to be unrelated to the consumption of conventional cigarettes and to the study procedures.

FOLLOW-UP INFORMATION RECEIVED ON 11-APR-2016:

The subject's birthdate was (b) (6)

The subject used 15 to 20 THS daily since randomization.

No action was taken with the conventional cigarettes due to the events.

No medical records were received. Thus, no clarifications were provided about the cause of loss of consciousness, the cause of seizure, the type of underlying anemia or the final diagnosis. No information was provided about any relevant medical investigations.

No follow-up information is expected. Case closed.

Case Comment:

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 3 of 3

Mfr Report #	PMI000463
UF/Importer Report #	
	FDA Use Only

Loss of consciousness, Head injury, and Seizure were assessed as serious (hospitalisation).

Loss of consciousness, Head injury, and Seizure are considered unexpected, according to the Reference Safety Information (i.e. the Investigator's Brochure).

The Investigator considered all reported adverse events as being not related to the use of the THS 2.2, to the conventional cigarette smoking, or to study procedures.

It was reported that the subject passed out while washing the dishes, hit her head, and then started having a seizure. Considering these circumstances and the presence of alternative explanations (i.e. previous episodes when the patient passed out; underlying hyperthyroidism, treated with levothyroxine, and anemia, treated with intramuscular vitamin B12), and in agreement with the Investigator's causality assessment, the Loss of consciousness, Head injury, and Seizure are assessed as not related to the use of THS 2.2, conventional cigarette smoking, or to study procedures. Of note, this subject, who had been a smoker of conventional cigarettes, continued the use of THS 2.2.

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	--/--/1986	Current Condition	Subject was 16 years old when she began smoking. Before randomization, the subject smoked on average 20 conventional cigarettes per day. Since randomization, the subject smoked on average 5 to 10 conventional cigarettes per day.
	Ongoing	Tobacco user	
3		Historical Condition	The subject experienced previous episodes of passing out but not to this extreme.
		Loss of consciousness	

C2. DOSE, FREQUENCY & ROUTE USED (Continued)

Suspect Medication #2: 20 DF, qd on average, Respiratory

Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#2 Conventional cigarette Regimen # 2	5-10 cigarettes per day, Respiratory	10/05/2015 to Ongoing		

MEDWATCH
3500A Facsimile

Page 1 of 3

Mfr Report #	PMI000466
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event: 47 Years or Date of Birth: (b) (6)	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 173.3 lbs or 78.6 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input type="checkbox"/> Hospitalization - initial or prolonged <input checked="" type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 01/29/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Head injury secondary to fall [Head injury]			
Case Description: Verbatim: Head injury secondary to fall.			
Clinical study ZRHR-ERS-09-US: 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.			
INITIAL INFORMATION RECEIVED ON 05-JAN-2016:			
This report was received from an Investigator, and it concerned a 47-year-old male subject (Initials (b)), ID continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc) Race: Caucasian #1 -/2001 to Ongoing, Current Condition, Tobacco user (On average 10 CC daily)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. No study product (No study product) N/A			
#2. Conventional cigarette (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1.		#1.	
#2. 10 DF, qd, Respiratory		#2. -/2001 to UNK	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1.		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1.	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND			
4. Date Received by Manufacturer (mm/dd/yyyy) 01/20/2016		5. (A)NDA # IND # N/A STN # PMA/510(k) #	
6. If IND, Give Protocol # ZRHR-ERS-09-US		3. Report Source (Check all that apply)	
7. Type of Report (Check all that apply)		<input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #1		<input type="checkbox"/> Combination Product <input type="checkbox"/> Yes <input type="checkbox"/> Pre-1938 <input type="checkbox"/> Yes <input type="checkbox"/> OTC Product <input type="checkbox"/> Yes	
9. Manufacturer Report Number PMI000466		8. Adverse Event Term(s) Head injury	
E. INITIAL REPORTER			
1. Name and Address		Phone # Withheld	
UNITED STATES Name and address withheld.			
2. Health Professional?	3. Occupation Physician	4. Initial Reporter Also Sent Report to FDA	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000466
UF/Importer Report #	
	FDA Use Only

ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Number: 04647, weight: 78.6 kg, height: 182 cm) who had been enrolled in the above mentioned clinical study.

No medical history was reported.

No concomitant medication was reported.

At the time of this report, the subject had not been randomized yet, and no investigational product was assigned.

On (b) (6) the subject slipped and fell at work. He hit his head. No loss of consciousness was observed. On the same day, the subject was hospitalized for observation. This event was considered to be moderate in intensity.

On (b) (6), the subject was discharged from the hospital. Medical records were requested.

The subject was not withdrawn from the study due to the occurrence of this event.

At the time of this report, the subject was recovering.

The Investigator considered the reported head injury secondary to fall to be unrelated to the use of the THS 2.2 (no investigational product was assigned to the subject, as the subject had not been yet randomized, at the time of the event).

FOLLOW UP INFORMATION RECEIVED ON 20-JAN-2016:

The subject started smoking conventional cigarettes 15 years ago.

The subject reported smoking approximately 10 cigarettes per day.

The subject did not have any relevant medical history. No concomitant medications taken at the time of the event were reported.

The subject was only screened at the time of the event.

The subject reported that he had only been in the hospital for a couple of hours for observation in the emergency department and was not admitted to hospital.

The subject reported being given an intravenous treatment at the hospital, but did not know what he was given.

At the time of this follow-up, the investigational site had not been able to contact the subject to retrieve his hospital records.

The subject recovered from the event on an unknown date.

The investigator considered the reported head injury secondary to fall to be unrelated to the consumption of conventional cigarettes or to the study procedures.

The event of fall was not considered as an additional SAE.

Additional information will be requested (As it was reported that there was no hospitalisation (admission into hospital, overnight stay), please confirm whether the AE Head injury is still considered serious (SAE); if so, please provide the seriousness criterion (now, medically significant is recorded in the safety database), Resolution date).

Case Comment:

Head injury was assessed as serious (medically significant).

Head injury is unexpected, as per the Reference Safety Information (i.e. the Investigator's Brochure).

The Investigator considered the reported adverse event as being not related to the use of the THS 2.2, as the adverse event occurred during screening. It was reported that, while being at work, the subject slipped and fell. Considering that the adverse event occurred before any use of THS 2.2, and in agreement with the Investigator's causality assessment, the Head injury is assessed as not related to the use of THS 2.2. Based on the reported circumstances, and also in agreement with the Investigator's causality

MEDWATCH

3500A Facsimile (Back)

(Continued)

Page 3 of 3

Mfr Report #	PMI000466
UF/Importer Report #	
	FDA Use Only

assessment, the Head injury is also assessed as not related to the conventional cigarette smoking or to study procedures, in this case.

MEDWATCH
3500A Facsimile

Page 1 of 4

Mfr Report #	PMI000467
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event: 57 Years or Date of Birth: (b) (6)	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 199.6 lbs or 90.5 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 04/22/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Methicillin-resistant Staphylococcus aureus cellulitis of right foot [Cellulitis staphylococcal]			
Case Description: Verbatim: Methicillin-resistant Staphylococcus Aureus cellulitis of right foot (initially reported as Cellulitis right 4th and 5th toes and then Staphylococcus Aureus cellulitis of foot (right)).			
Clinical study ZRHR-ERS-09-EXT-US: A 26 week extension study to determine the biological and functional changes in healthy smokers who switched from conventional cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study.			
continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates Blood and wound cultures were positive for Staphylococcus 10-Dec-2015: Gram stain (source: 5th toe right): rare WBCs and many gram positive cocci in pairs and clusters 11-Dec-2015: Blood culture PCR: methicillin (oxacillin) resistant coagulase negative staphylococcus. Possible blood culture continued in additional info section...			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 03/17/1958 to 05/--/1973 Historical Condition, (Continued) #2 05/--/1973 to 05/--/1973 Procedure, (Continued) #3 --/--/1979 to Ongoing Current Condition, (Continued) #4 11/01/2015 to Ongoing Current Condition, (Continued)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. Conventional cigarette (N/A) N/A			
#2. Tobacco Heating System 2.2 (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 35 DF, qd, Respiratory		#1. --/--/1979 to Ongoing	
#2. UNK, Respiratory		#2. 04/30/2015 to 05/11/2015	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1.	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. B17724	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND			
4. Date Received by Manufacturer (mm/dd/yyyy) 04/11/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-EXT-US		3. Report Source (Check all that apply)	
7. Type of Report (Check all that apply)		<input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #4			
9. Manufacturer Report Number PMI000467		8. Adverse Event Term(s) Cellulitis staphylococcal	
E. INITIAL REPORTER			
1. Name and Address		Phone # Withheld	
UNITED STATES Name and address withheld.			
2. Health Professional?	3. Occupation Physician	4. Initial Reporter Also Sent Report to FDA	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 4

Mfr Report #	PMI000467
UF/Importer Report #	
	FDA Use Only

ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)****INITIAL INFORMATION RECEIVED ON 07-JAN-2016:**

This report was received from an Investigator and concerned a 57-year-old Caucasian male subject (Initials (b) ID Number: 14018, Randomization Number: 10247, weight: 90.5 kg, height: 183 cm) who had been enrolled in the above mentioned clinical study.

No relevant medical history was reported. No concomitant medication was reported.

The subject used the Tobacco Heating System 2.2 (THS 2.2) (batch number: B17724) between 30-Apr-2015 and 11-May-2015. The subject was subsequently randomized to the Conventional Cigarette arm on an unknown date.

On 12-Dec-2015, the subject stated that he noticed that his 4th and 5th toes on his right foot were red and painful. It became worse as his right foot was swollen, red and painful. On (b) (6), the subject went to the Emergency Room (ER), where he was admitted to the hospital for the cellulitis of his 4th and 5th toes. He stayed in the hospital for 6 days, where he was treated with intravenous antibiotics and intravenous pain medications.

On (b) (6), he was discharged with oral antibiotics (sulfamethoxazole/trimethoprim) for the cellulitis, and was going to follow-up with his primary or wound care doctor. However, the subject stated that he had not followed up with his doctor, but he was going to try to get an appointment as soon as possible. Medical records were pending.

This event was considered to be severe in intensity.

The subject was not withdrawn from the study due to the occurrence of this event.

At the time of this report, the subject stated that he was back to normal and all symptoms were resolved on 01-Jan-2016. The reporter stated that the subject recovered with (unspecified) sequelae.

The Investigator considered the reported cellulitis to be unrelated to the use of THS 2.2 and conventional cigarettes.

FOLLOW-UP INFORMATION RECEIVED ON 25-JAN-2016 and 28-JAN-2016:

It was clarified that the subject was taking part in the extension clinical study ZRHR-ERS-09-EXT-US (A 26 week extension study to determine the biological and functional changes in healthy smokers who switched from conventional cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study) when the SAE occurred.

During his stay in the hospital, the subject was treated with intravenous antibiotics and pain medications for 3 days.

No action was taken regarding the use of the study product.

On 22-Jan-2016, the subject withdrew from the study, as per his personal decision.

The Investigator considered the reported cellulitis to be unrelated to the use of the study product and unrelated to study procedures.

FOLLOW-UP INFORMATION RECEIVED ON 10-FEB-2016:

The subject's medical history included Hirschsprung disease from 17-Mar-1958 to May-1973, lower intestine dissection/repair in May 1973 and spider bite on his back since 01-Nov-2015. The subject had no history of previous episodes of cellulitis.

The subject started smoking in 1979 and his consumption was 35 conventional cigarettes daily.

The subject was randomized to the Conventional Cigarette arm on 12-May-2015.

Approximately 1 week before going to the ER, the subject noticed that he had a small cut between his fourth and fifth toes that started draining. He was cleaning it at home using over-the-counter (OTC) medication; however, the morning of going to the ER, he woke up with significant increased swelling of his entire right foot with redness and pain escalating to his ankle.

MEDWATCH

3500A Facsimile (Back)

(Continued)

Page 3 of 4

Mfr Report #	PMI000467
UF/Importer Report #	
	FDA Use Only

The subject was able to continue to smoke during his hospitalization.

Blood and wound cultures were positive for Staphylococcus Aureus.

The subject was administered the following treatments: intravenous piperacillin/tazobactam/sodium chloride 100ml and intravenous vancomycin hydrochloride 250ml for cellulitis of right foot on 10-Dec-2015; intravenous morphine sulfate 4mg for pain 10-Dec-2015; intravenous sodium chloride 1000ml for hydration on 10-Dec-2015; intravenous ondansetron hydrochloride 4mg for Hirschsprung disease on 10-Dec-2015; Lovenox (enoxaparine, dose unknown) for prophylaxis of deep venous thrombosis on 10-Dec-2015 and topical miconazole powder for Tinea pedis on 10-Dec-2015.

The subject was given oral sulfamethoxazole/trimethoprim at the dosage of 800mg/16mg twice daily from 22-Dec-2015 to 15-Jan-2016. The subject was also given the instruction to have elevation of his right lower extremity. The subject was sent for 'wound care instructions'.

The subject stated that his foot resolved on 01-Jan-2016.

The Investigator considered the reported cellulitis to be unrelated to the use of THS 2.2 or consumption of conventional cigarettes, and unrelated to study procedures.

FOLLOW-UP INFORMATION RECEIVED ON 21-MAR-2016:

Regarding the subject's medical history, the subject denied ever having Tinea Pedis.

The Investigator agreed to change the SAE verbatim to 'Staphylococcus Aureus cellulitis of foot (right)'.

It was clarified that the IV medications were administered when the subject was in the Emergency Room, before admission.

It was clarified that the treatment with ondansetron hydrochloride was administered to the subject for the prophylaxis of Hirschsprung disease.

The blood and wound cultures were positive: Gram stain (source: 5th toe right) performed on 10-Dec-2015 showed rare WBCs and many gram positive cocci in pairs and clusters; Blood culture (PCR) performed on 11-Dec-2015 showed methicillin (oxacillin) resistant coagulase negative staphylococcus (possible blood culture contaminant was noted); Wound culture performed on 12-Dec-2015 showed methicillin resistant Staphylococcus Aureus (heavy growth); Blood culture performed on 15-Dec-2015 showed no growth after 5 days; Blood culture performed on 17-Dec-2015 showed coag-negative staph species (bacterial growth suggestive of a skin contaminant was noted).

The subject recovered from the event (without sequelae).

FOLLOW-UP INFORMATION RECEIVED ON 11-APR-2016:

The SAE verbatim was updated from 'Staphylococcus Aureus cellulitis of foot (right)' to 'Methicillin-resistant Staphylococcus Aureus cellulitis of right foot'.

The start date of the event was updated to 10-Dec-2015 (as the subject received IV medications for his cellulitis on that date).

The 'blood cultures positive for methicillin (oxacillin) resistant coagulase negative Staphylococcus' was not considered as an additional SAE.

No follow-information is expected. Case closed.

Case Comment:

Cellulitis staphylococcal was assessed as serious (hospitalisation).

Cellulitis staphylococcal is unexpected, as per the Reference Safety Information (i.e. the Investigator's Brochure).

The Investigator considered the reported methicillin-resistant Staphylococcus aureus cellulitis of right foot as being not related to the use of THS 2.2, smoking of conventional cigarettes, or to study procedures.

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3500A Facsimile (Back) (Continued)

Page 4 of 4

Mfr Report #	PMI000467
UF/Importer Report #	
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In agreement with the Investigator's causality assessment, the reported methicillin-resistant *Staphylococcus aureus* cellulitis of right foot is assessed as not related to the use of THS 2.2, smoking of conventional cigarettes, or to study procedures, in this subject. Of note, the adverse event occurred more than six months after the last THS 2.2 use.

B6. RELEVANT TESTS (Continued)

contaminant

12-Dec-2015: Wound culture: Methicillin resistant *Staphylococcus Aureus* (heavy growth)

15-Dec-2015: Blood culture: no growth detected after 5 days

17-Dec-2015: Blood culture: coag-negative staph species (bacterial growth suggestive of a skin contaminant)

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	03/17/1958 05/--/1973	Historical Condition Congenital megacolon	
2	05/--/1973 05/--/1973	Procedure Gastrointestinal surgery	Lower intestine dissection/repair
3	--/--/1979 Ongoing	Current Condition Tobacco user	35 cigarettes/day
4	11/01/2015 Ongoing	Current Condition Arthropod bite	spider bite on the back

MEDWATCH
3500A Facsimile

Page 1 of 2

Mfr Report #	PMI000470
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event: 51 Years or Date of Birth: (b) (6)	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 162.9 lbs or 73.9 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 01/25/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Left forearm laceration [Laceration]			
Case Description: Verbatim: Left forearm laceration			
Clinical study ZRHR-ERS-09-EXT-US: A 26 week extension study to determine the biological and functional changes in healthy smokers who switched from conventional cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study.			
INITIAL INFORMATION RECEIVED ON 14-JAN-2016:			
This report was received from an Investigator and concerned a 51-year-old Black male subject (Initials (b)), ID Number: continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc) Race: Black #1 Ongoing, Current Condition, Tobacco user			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) (Regimens Continued)			
#1. Tobacco Heating System 2.2 (N/A) N/A			
#2. Conventional cigarette (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. UNK, Respiratory		#1. 07/15/2015 to 01/01/2016	
#2. , Respiratory		#2.	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1. 17821	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND			
4. Date Received by Manufacturer (mm/dd/yyyy) 01/14/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-EXT-US		3. Report Source (Check all that apply)	
7. Type of Report (Check all that apply)		<input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input checked="" type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> Follow-up #			
9. Manufacturer Report Number PMI000470		8. Adverse Event Term(s) Laceration	
E. INITIAL REPORTER			
1. Name and Address		Phone # Withheld	
UNITED STATES Name and address withheld.			
2. Health Professional?		3. Occupation Physician	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
		4. Initial Reporter Also Sent Report to FDA	
		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 2

Mfr Report #	PMI000470
UF/Importer Report #	
FDA Use Only	

ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

04189, Randomization Number: 10435, weight: 73.9 kg, height: 171 cm) who had been enrolled in the above mentioned clinical study.

Relevant medical history and concomitant medications were not reported.

The subject was randomized to the Tobacco Heating System 2.2 (THS 2.2) arm and started using the product (batch number 17821) on 15-JUL-2015.

On (b) (6) at 03:00 am, the subject slipped and fell cutting his left forearm on broken glass. On the same day, he went to the Emergency Room and was taken to the Operating Room at 05:00 am for repair, foreign body removal and muscle/ skin repair. Following the fall, the subject experienced a left 5th digit's loss of flexor tendon flexion, and a visit to see a specialist was planned. The subject received antibiotics and narcotics: oral cephalexin at the dosage of 2000 (unit unknown) daily from 02-JAN-2016 to 11-JAN-2016 and oral oxycodone at the dosage of 5/325 (unit unknown) daily from 04-JAN-2016 to 07-JAN-2016. During his hospitalisation, the subject temporally stopped using THS for 48 hours between (b) (6) and (b) (6). On (b) (6) at 10:00, he was discharged from the hospital.

At the time of this report, the subject had finished his course of medications. The sutures were still present.

This event was considered to be moderate in intensity.

The subject was not withdrawn from the study due to the occurrence of this event.

At the time of this report, the subject was recovering.

The Investigator considered the reported event of left forearm laceration to be unrelated to the use of THS 2.2.

Additional information will be requested (Relevant medical history; Concomitant medications, if any; Start date for CC smoking; Daily consumption of CC before/after randomisation; Randomisation date; Daily use of THS; Confirmation on status of CC smoking during and after hospitalisation; Results of relevant tests/investigations; Clarification as to whether the loss of flexion in the left 5th finger's flexor muscle tendon was considered a separate SAE; Confirmation as to whether the causality assessment (i.e. not related) applies to both CC and THS; Causality assessment with regard to study procedures; Final outcome and resolution date).

Case Comment:

The Laceration was assessed as serious (hospitalisation).

Laceration is unexpected, as per the Reference Safety Information (i.e. the Investigator's Brochure).

The Investigator considered the reported left forearm laceration as being not related to the use of THS 2.2. The Investigator has not provided an assessment of causal relationship to conventional cigarettes.

It was reported that the subject slipped and fell, cutting his left forearm on broken glass, for which he underwent emergency surgery repair, foreign body removal, and muscle and skin repair. Considering the accidental circumstances, and in agreement with the Investigator's causality assessment, the reported left forearm laceration (also reportedly associated with loss of flexion in the left 5th finger's flexor muscle tendon) is assessed as not related to the use of THS 2.2 or to conventional cigarette smoking.

Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#1 Tobacco Heating System UNK, Respiratory 2.2 Regimen # 2		01/03/2016 to Ongoing		

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Mfr Report #	PMI000482
UF/Importer Report #	
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Page 1 of 3

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event 42 Years or Date of Birth (b) (6)	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 162.3 lbs or 73.6 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage			
<input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect			
<input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input checked="" type="checkbox"/> Other Serious (Important Medical Events)			
<input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 03/31/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Right breast cancer [Breast cancer] Case Description: Verbatim: Diagnosis of breast cancer Clinical study ZRHR-ERS-09-EXT-US: A 26 week extension study to determine the biological and functional changes in healthy smokers who switched from conventional cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study. INITIAL INFORMATION RECEIVED ON 02-FEB-2016: This report was received from an Investigator and concerned a 42-year-old Black and Caucasian female subject (Initials (b)) continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) #1 --/--/1994 to UNK, Historical Condition, Breast cyst (Benign fluid-filled cyst of the left breast) #2 --/--/1995 to 01/25/2016, Current Condition, Tobacco user (Before randomisation, the subject smoked 15 conventional cigarettes per day. After randomisation, she smoked 8 conventional cigarettes per day.)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) (Regimens Continued)			
#1. Conventional cigarette (N/A) N/A			
#2. Tobacco Heating System 2.2 (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 15 DF, UNK, Respiratory		#1. --/--/1995 to 05/19/2015	
#2. 7 DF, qd, Respiratory		#2. 05/14/2015 to 05/20/2015	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1.	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
1) Multivitamin (Vitamins nos) --/--/1995 to ongoing			
2) Biotin (Biotin) 12/--/2014 to 01/19/2016			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 03/21/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-EXT-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other: _____ _____ _____	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #2		8. Adverse Event Term(s) Breast cancer	
9. Manufacturer Report Number PMI000482			
E. INITIAL REPORTER			
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Physician	
		4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000482
UF/Importer Report #	
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

ID Number: 14030, Randomization Number: 20244, weight: 73.6 kg, height: 176 cm) who had been enrolled in the above mentioned clinical study.

Relevant medical history was not reported. The subject was taking the following concomitant medications for prophylaxis and nutritional supplement: oral multivitamin at the dosage of 1 tablet daily since 1995 (treatment still ongoing), oral Biotin at the dosage of 1 capsule daily since 2014 (treatment still ongoing) and oral maca root at the dosage of 2 capsules daily since Feb-2015 (treatment still ongoing).

The subject used Tobacco Heating System 2.2 (THS 2.2) from 14-May-2015 to 20-May-2015 during the run-in period. The subject was subsequently randomized to the Conventional Cigarettes arm on an unknown date.

On 15-Dec-2015, during visit 11, the subject reported that she had had a yearly exam on 10-Dec-2015 and a benign cyst on left breast was found. This was going to be followed-up with a mammogram; however, no information was available regarding that test. On 26-Jan-2016, the subject's husband reported that his wife was diagnosed with breast cancer and that surgery was planned on (b) (6) (but not confirmed). He stated that she was cutting back on smoking and would keep the investigational site updated on procedures to be done and other important information.

This event was considered to be severe in intensity and to be serious, reported as important medical event. It was not confirmed whether the planned surgery was going to be done as a in-patient or out-patient procedure.

The subject was withdrawn from the study due to the occurrence of this event, on 27-Jan-2016 (to be confirmed).

At the time of this report, the outcome of the event was unknown.

The Investigator considered the reported event of breast cancer to be unrelated to the use of THS 2.2.

At time of this report, multiple attempts (by phone calls and emails) were performed, but the investigational site was unable to get additional information.

FOLLOW-UP INFORMATION RECEIVED ON 16-FEB-2016:

The subject informed the site that she was diagnosed with right breast cancer on 18-Jan-2016. She was scheduled to have a mastectomy on (b) (6).

The subject reported that she was no longer taking Biotin or maca root, per her primary care physician's instructions, and that she discontinued both of them on 19-Jan-2016.

The subject reported to have had the mastectomy on (b) (6). She went to the hospital, around 7am, and was discharged on (b) (6), around 5pm. The subject reported that she had no complications and was already back to work. The subject reported that she took oral Tynelol 3, at the dosage of 1 tablet as necessary from 29-Jan-2016 to 31-Jan-2016, and oral Tramadol, at the dosage of 25 mg as necessary from 29-Jan-2016 to 02-Feb-2016, for post operative pain. She was also given antibiotics for preventing infection (she did not remember the name of the medications, at time of the report, but she would provide the site with the information on 15-Feb-2016).

The subject reported that she was no longer smoking and she took her last cigarette on 25-Jan-2016.

The subject reported that she might have to undergo chemotherapy. She was scheduled to meet with the oncology unit to receive further information. The subject's medical records regarding this matter were requested. The site was going to provide follow-up information once the documents were received.

The date of discontinuation from the study was updated to 12-Feb-2016.

FOLLOW-UP INFORMATION RECEIVED ON 21-MAR-2016:

The subject's medical history included benign fluid filled cysts of the left breast since 1994. The subject reported that it was the first time that something was found in her right breast.

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3500A Facsimile (Back) (Continued)

Page 3 of 3

Mfr Report #	PMI000482
UF/Importer Report #	
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The subject clarified that she took multivitamins for overall nutritional health purposes and not for the prevention of any medical condition. She took Biotin as nutritional supplement for healthy hair and nail growth, and maca root to help her burst her energy level as she worked a lot of hours.

The subject started smoking in 1995 and smoked 15 conventional cigarettes per day.

During the run-in period, the subject used seven THS 2.2 daily. The subject was randomized to the Conventional Cigarettes arm on 20-May-2015. After randomisation, she smoked 8 conventional cigarettes per day.

During her hospitalisation, she was treated with Tylenol 3 (paracetamol with codeine) and tramadol. Following discharge from hospital, the subject took sulfamethoxazole-trimethoprim (800mg/160mg) since 30-Jan-2016 at the dosage of 1 tablet twice a day.

At the time of this report, the event was ongoing.

The Investigator considered the reported breast cancer to be unrelated to the use of THS 2.2 or consumption of conventional cigarettes, and unrelated to study procedures.

Additional information will be requested (Clarification on treatment administered (i.e. whether/when mastectomy was performed, whether/when it required hospital admission, whether chemotherapy was started); SAE's current status, SAE's final outcome (e.g. resolved) and outcome date).

Case Comment:

The Breast cancer was assessed as serious (important medical event, hospitalisation required).

Breast cancer is unexpected, as per the Reference Safety Information (i.e. the Investigator's Brochure).

The Investigator considered the reported right breast cancer as being unrelated to the use of THS 2.2, conventional cigarette smoking, or to study procedures.

It was reported that THS 2.2 had been used for seven days, during the study run-in period, approximately seven months before the detection of breast cancer, in this female patient who had been a smoker of conventional cigarettes, and who had been concomitantly taking multivitamins, biotin, and oral maca root (both biotin and maca root have reportedly been discontinued, as per primary care physician's instructions, after the diagnosis of breast cancer). In agreement with the Investigator's causality assessment, the Breast cancer is assessed as being not related to the use of THS 2.2 or to study procedures. However, the Breast cancer is considered possibly related to the long history of conventional cigarette smoking, which has reportedly been discontinued a week after the diagnosis of breast cancer.

Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#1 Conventional cigarette Regimen # 2	8 DF, qd, Respiratory	05/20/2015 to 01/25/2016		
#1 Conventional cigarette Regimen # 3	UNK, Respiratory	UNK to 01/25/2016		

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Mfr Report #	PMI000500
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Page 1 of 4

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event 40 Years or Date of Birth (b) (6)	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 158.8 lbs or 72.0 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply) <input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 03/24/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Costochondritis with shortness of breath [Costochondritis] Case Description: Verbatim: Costochondritis with shortness of breath Clinical study ZRHR-ERS-09-EXT-US: A 26 week extension study to determine the biological and functional changes in healthy smokers who switched from conventional cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study. INITIAL INFORMATION RECEIVED ON 16-FEB-2016 and FOLLOW-UP INFORMATION RECEIVED on 17-FEB-2016: This report was received from an Investigator and concerned a 40-year-old female subject (Initials (b)), ID Number: 04202, continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates Tests performed on 12-Feb-2016 ECG: sinus tachycardia, Q wave lead III Respiratory test: air entry bilaterally equal, no crepitus, no rhonchi Chest x-ray and CTA chest: no evidence of pulmonary embolism. 5 mm pleura-based nodule in the right lower lobe continued in additional info section...			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 --/--/1978 to Ongoing Current Condition, (Continued) #2 --/--/1988 to Ongoing Current Condition, (Continued) #3 --/--/1995 to --/--/1995 Procedure, (Continued) continued in additional info section...			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) (Regimens Continued) #1. Tobacco Heating System 2.2 (N/A) N/A #2. Conventional cigarette (N/A) N/A			
2. Dose, Frequency & Route Used #1. 22 DF, qd, Respiratory #2. 20 DF, qd, Respiratory		3. Therapy Dates (if unknown, give duration) from/to (or best estimate) #1. 07/21/2015 to 02/16/2016 #2. --/--/1988 to 07/27/2015	
4. Diagnosis for Use (Indication) #1. Tobacco user (Tobacco user) #2. Tobacco user (Tobacco user)		5. Event Abated After Use Stopped or Dose Reduced? #1. <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Doesn't Apply #2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot # #1. 21534 #2.	7. Exp. Date #1. #2.	8. Event Reappeared After Reintroduction? #1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply #2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) 1) Acetaminophen (Paracetamol) 07/28/2015 to ongoing			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 03/14/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-EXT-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other: _____ _____ _____	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #1		8. Adverse Event Term(s) Costochondritis	
9. Manufacturer Report Number PMI000500			
E. INITIAL REPORTER			
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Physician	
		4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

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Page 2 of 4

Mfr Report #	PMI000500
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Randomization Number: 20390, weight: 72.0 kg, height: 159.5 cm) who had been enrolled in the above mentioned clinical study.

Relevant medical history included migraines episodes since 1978 (twice per year), bilateral tubal ligation on 1995, lower back surgery on 1995, herniated disc since 1995, familial history of breast cancer, familial history of cardiovascular disorder, familial history of diabetes. The subject was taking the following concomitant medications: oral Probioslim, at the dosage of 2 capsules since 8-Jun-2015 for supplementation, and oral acetaminophen (paracetamol), at the dosage 97.5 mg as necessary since 28-Jul-2015 for migraines. It was also reported that the subject had resigned from her job and that her financial/ family stress had increased.

The subject was randomized to the Tobacco Heating System 2.2 (THS 2.2) arm and started using the product (batch number 21534) on 21-Jul-2015.

On (b) (6), the subject began having right chest pain from back to front and, concomitantly, shortness of breath. On the same day, she went to Emergency Room (ER) and was admitted at the hospital. The subject was kept overnight in hospital for cardiac and pulmonary testing. Laboratory tests and X-rays chest Computed Tomography (CT) were performed. The chest CT showed the presence of a 5 mm pleura-based nodule in the right lower lobe, and a 5 mm breast nodule. No evidence of pulmonary embolism was detected. Coronary calcium scores were done and were negative for acute causes of pulmonary or cardiac disease. The electrocardiogram (ECG) showed a sinus tachycardia and Q wave lead III. The respiratory test showed air entry bilaterally equal, no crepitus, no rhonchi. CT coronary angio with contrast was performed: no coronary artery anomalies, no evidence of hypoperfusion or infarct, no pericardial thickening or effusion, no aneurysm or dissection of the aorta, no pulmonary effusion, no mass in the mediastinum, no acute fracture or destructive lesion of the osseous structures. CT Angio Chest Pulmonary Emboli was performed: no evidence of pulmonary embolus, 5 mm pleural-based nodule in the right lower lobe, nodular density in the lower outer quadrant of the right of the right breast.

Corrective treatments were administered to the subject: oral aspirin at the dosage of 162 mg from 11-Feb-2016 for chest pain (treatment still ongoing), intravenous Zofran (Ondansetron) at the dosage of 4 mg from 11-Feb-2016 to 12-Feb-2016 for chest pain and nausea, sublingual Nitrostat (nitroglycerin, dosage unknown) from 11-Feb-2016 to 12-Feb-2016 for chest pain. On (b) (6) the subject was discharged from the hospital with a presumptive diagnosis of musculoskeletal pain. She was told to take oral ibuprofen at the dosage of 800 mg as needed for pain for costochondritis from (b) (6) but no prescription was given. On (b) (6), she did take 1 dose of 200 mg of ibuprofen for a headache. She was still having some pain and shortness of breath.

It was reported that the subject interrupted the use of THS between 16-Feb-2016 and 17-Feb-2016.

This event was considered to be moderate in intensity and to be serious due to hospitalization.

The subject was not withdrawn from the study.

At the time of this report, the event was not resolved.

The Investigator considered the reported event of costochondritis with shortness of breath to be unrelated to the use of THS 2.2.

FOLLOW-UP INFORMATION RECEIVED ON 14-MAR-2016:

The subject started smoking in 1988. Before randomization, the subject smoked 20 conventional cigarettes per day.

The subject was randomized to the THS arm on 28-Jul-2015. Since randomization, the subject was using 22 THS sticks per day and was smoking 2 conventional cigarettes per day.

It was clarified that the shortness of breath was not the main reason for admission and was not a stand-alone Serious Adverse Event (SAE). The pain from the costochondritis was the main reason for admission and this caused the shortness of breath.

It was clarified that just one lung nodule was noticed, that was pleural-based. Neither pulmonary/pleural or breast nodules were considered as additional SAEs at the time of this report.

When the subject informed the site that she had gone to the Emergency Room with chest pain and shortness of breath, she was advised to stop THS until she was seen by the Investigator and her records could be reviewed. It was reported that the subject was under a lot of stress due to work issues and had not been sleeping well.

No action was taken regarding the conventional cigarettes.

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 3 of 4

Mfr Report #	PMI000500
UF/Importer Report #	
	FDA Use Only

The Investigator considered the reported event of costochondritis with shortness of breath to be unrelated to study procedures, to the use of THS, or to the consumption of conventional cigarettes.

At the time of the subject's last visit, the event was not resolved.

No follow-information is expected. Case closed.

Case Comment:

The Costochondritis was assessed as serious (hospitalisation required).

Costochondritis is unexpected, as per the Reference Safety Information (i.e. the Investigator's Brochure).

The Investigator considered the reported costochondritis with shortness of breath as being not related to the use of THS 2.2, to the consumption of conventional cigarettes, to study procedures/participation.

Considering the presence of alternative explanations (i.e. medical history, work-related stress), and in agreement with the Investigator's causality assessment, the reported costochondritis with shortness of breath is assessed as not related to the use of THS 2.2, which had been commenced approximately six months before, or to the study procedures. It is confirmed now that the shortness of breath was due to the costochondritis. In agreement with the Investigator's causality assessment, the reported costochondritis with shortness of breath is assessed as not related to conventional cigarette.

B6. RELEVANT TESTS (Continued)

CT coronary angio with contrast: no coronary artery anomalies, cardiac anatomy (no evidence of hypoperfusion or infarct, no pericardial thickening or effusion), Aorta (no aneurysm or dissection), no pulmonary effusion, Mediastinum: no mass, Osseous structures (no acute fracture or destructive lesion)

CT Angio Chest Pulmonary Emboli: no evidence of pulmonary embolus, 5mm pleural-based nodule in the right lower lobe, nodular density in the lower outer quadrant of the right of the right breast

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	02/12/2016	Electrocardiogram beats/min	102	
2	02/12/2016	Troponin	<0.01	

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	--/--/1978 Ongoing	Current Condition Migraine	Twice per year
2	--/--/1988 Ongoing	Current Condition Tobacco user	20 cigarettes per day before randomization and 2 cigarettes per day after randomization
3	--/--/1995 --/--/1995	Procedure Female sterilisation	
4	--/--/1995 --/--/1995	Historical Condition Intervertebral disc protrusion	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 4 of 4

Mfr Report #	PMI000500
UF/Importer Report #	
	FDA Use Only

5	--/--/1995 --/--/1995	Procedure Surgery
---	--------------------------	----------------------

6		Historical Condition Familial risk factor
---	--	--

7		Historical Condition Familial risk factor
---	--	--

8		Historical Condition Familial risk factor
---	--	--

9	Ongoing	Current Condition Family stress
---	---------	------------------------------------

10	Ongoing	Current Condition Stress at work
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Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#1 Tobacco Heating System 2.2 Regimen # 2	UNK, Respiratory	02/18/2016 to UNK		
#2 Conventional cigarette Regimen # 2	2 DF, qd, Respiratory	07/28/2015 to UNK		

MEDWATCH
3500A Facsimile

Page 1 of 3

Mfr Report #	PMI000507
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event 52 Years or Date of Birth (b) (6)	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 186.1 lbs or 84.4 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 04/05/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) mental health: suicidal ideation [Suicidal ideation] Case Description: Verbatim: Mental health: suicidal ideation Clinical study ZRHR-ERS-09-US: A randomised, 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. INITIAL INFORMATION RECEIVED ON 19-FEB-2016: This report was received from an investigator and concerned a 52-year-old female subject (Initials: (b), ID Number: 21035, continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 --/--/1975 to Ongoing, Current Condition, Tobacco user (The subject smoked on average 20 conventional cigarettes daily before and after randomization.) #2 --/--/2009 to --/--/2009, Historical Condition, Suicide attempt #3 --/--/2009 to Ongoing, Current Condition, Depression #4 Ongoing, Current Condition, Back pain			

C. SUSPECT PRODUCT(S)	
1. Name (Give labeled strength & mfr/labeler)	
#1. Conventional cigarette (N/A) N/A	
#2. Tobacco Heating System 2.2 (N/A) N/A	
2. Dose, Frequency & Route Used	3. Therapy Dates (if unknown, give duration) from/to (or best estimate)
#1. 20 UNK, UNK, Respiratory	#1. --/--/1975 to UNK
#2. UNK UNK, qd, Respiratory	#2. 01/18/2016 to 01/24/2016
4. Diagnosis for Use (Indication)	
#1. Tobacco user (Tobacco user)	
#2. Tobacco user (Tobacco user)	
6. Lot #	7. Exp. Date
#1.	#1.
#2. B-21530	#2.
9. NDC# or Unique ID	
5. Event Abated After Use Stopped or Dose Reduced?	
#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
8. Event Reappeared After Reintroduction?	
#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)	

G. ALL MANUFACTURERS	
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND	2. Phone Number
3. Report Source (Check all that apply)	
<input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
4. Date Received by Manufacturer (mm/dd/yyyy) 03/24/2016	5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes
6. If IND, Give Protocol # ZRHR-ERS-09-US	7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #1
9. Manufacturer Report Number PMI000507	8. Adverse Event Term(s) Suicidal ideation

E. INITIAL REPORTER			
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	3. Occupation Physician	4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000507
UF/Importer Report #	
	FDA Use Only

ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Randomisation Number: 20511, weight: 84.4 kg, height: 154 cm) who had been enrolled in the above mentioned clinical study.

The subject's relevant medical history included a previous suicide attempt that occurred in 2009, depression episodes (no further information) and back pain treated with oral Advil (bupropion) at the dosage of 800 mg daily from 2007 to 07-Jan-2016. The suicide attempt was not reported by the subject at the screening visit or any other visit until visit 5 on 19-Feb-2016. The subject started smoking before the start of the study.

The subject was randomized to the Tobacco Heating System 2.2 (THS 2.2) group (batch B-201530) and used the product from 18-Jan-2016 to 24-Jan-2016.

On 19-Feb-2016, the subject came in for visit 5 and reported having suicidal thoughts earlier that week. She related these thoughts to increased stress levels with work and finances. The subject stated that she voluntarily went to local Emergency Room (ER) to be evaluated. She was admitted to a local mental health facility for care and counseling. On 19-Feb-2016, at time of visit 5, the subject also admitted a previous history of depression and a suicidal attempt back in 2009. She had had intermittent therapy since then, but had not required medication. On 19-Feb-2016, the subject was stable and rational. It was reported that the event resolved on 18-Feb-2016. She stated that she would have her first follow-up with a counselor on Monday, 22-Feb-2016. Records from mental health facility were requested to gather further information on the event.

The Investigator considered the event of suicidal ideation to be severe in intensity and not related to the use with THS 2.2, but rather due to the subject's pre-existing health condition.

FOLLOW-UP INFORMATION RECEIVED ON 24-MAR-2016:

The subject's ethnicity was reported as Hispanic (considered as Caucasian).

The subject experienced depression since 2009 (no further information provided).

Apart from this event and the suicide attempt in 2009, the subject did not report any other previous episode of suicidal ideation.

The subject started smoking conventional cigarettes in 1975.

It was clarified that the subject was randomized to the conventional cigarette arm (and not in the THS arm).

The subject smoked on average 20 conventional cigarettes daily before and after randomization.

The subject was admitted in the mental health facility from (b) (6) to (b) (6) due to the event.

At the time of this follow-up, medical records were pending.

The investigator considered the event of suicidal ideation to be not related to the use with THS 2.2, or to the consumption of conventional cigarettes, or to any study procedures. The investigator considered the reported event to be due to the subject's pre-existing health condition.

Additional information will be requested (Please confirm whether the patient experienced any other mental health disturbance during the study; please confirm whether there had been any changes in the underlying depression's treatment, in the weeks/days prior to the occurrence of reported suicidal ideation; depression's current status and treatment; daily consumption of THS in run-in period; randomization date).

Case Comment:

Suicidal ideation was assessed as serious (required admission in to a mental health facility for care and counselling).

Suicidal ideation is unexpected, according to the Investigator's Brochure.

The Investigator has assessed this adverse event as not related to the use of THS 2.2, to conventional cigarette smoking, or to study procedures, considering it due to the subject's preexisting health condition.

The THS 2.2 had been used for seven days, approximately three weeks prior to the adverse event. Considering the existence of

MEDWATCH
3500A Facsimile (Back) **(Continued)**

Mfr Report #	PMI000507
UF/Importer Report #	
	FDA Use Only

alternative explanations (i.e. previous suicide attempt, pre-existing/underlying depression, recent work-related and financial stress), and in agreement with the Investigator's causality assessment, the reported suicidal ideation is assessed as not related to the use of THS 2.2, to the smoking of conventional cigarettes, or to any study procedure, in this female patient.

MEDWATCH
3500A Facsimile

Page 1 of 2

Mfr Report #	PMI000511
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event: 44 Years or Date of Birth: (b) (6)	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 166.3 lbs or 75.4 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 03/03/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Mycoplasma pneumonia [Pneumonia mycoplasma]			
Case Description: Verbatim: Mycoplasma pneumonia			
Clinical study ZRHR-ERS-09-US: A randomised, 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.			
INITIAL INFORMATION RECEIVED ON 23-FEB-2016:			
This report was received from an investigator and concerned a 44-year-old female subject (Initials (b) ID Number: 04267, continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc) Race: Black #1 Current Condition, Tobacco user			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) (Regimens Continued)			
#1. Tobacco Heating System 2.2 (N/A) N/A			
#2. Conventional cigarette (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. UNK, Respiratory		#1. 08/20/2015 to 02/14/2016	
#2. , Respiratory		#2.	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1. B-21530	#1.	#1. <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
1) Mucinex (Guaifenesin) 02/09/2016 to 02/14/2016			
2) Dextromethorphan (Dextromethorphan hydrobromide) continued in additional info section...			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND			
4. Date Received by Manufacturer (mm/dd/yyyy) 02/23/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-US		3. Report Source (Check all that apply)	
7. Type of Report (Check all that apply)		<input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input checked="" type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> Follow-up #			
9. Manufacturer Report Number PMI000511		8. Adverse Event Term(s) Pneumonia mycoplasma	
E. INITIAL REPORTER			
1. Name and Address		Phone # Withheld	
UNITED STATES Name and address withheld.			
2. Health Professional?		3. Occupation Physician	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
		4. Initial Reporter Also Sent Report to FDA	
		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 2

Mfr Report #	PMI000511
UF/Importer Report #	
FDA Use Only	

ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Randomisation Number: 20399, weight: 75.4 kg, height: 164 cm) who had been enrolled in the above mentioned clinical study.

No relevant medical history, at the time of the event, was reported. It was reported that the patient was taken the following treatments for mycoplasma pneumonia from 09-Feb-2016 to 14-Feb-2016: oral Mucinex (guaifenesin) at the dosage of 400mg, oral Dextromethorphan (dextromethorphan hydrobromide) at the dosage of 20mg, oral Phenylephrine at the dosage of 10mg.

The subject was randomized to the Tobacco Heating System 2.2 (THS 2.2) group (batch B-21530) and started using the product on 20-Aug-2015.

On an unknown date, the subject began experiencing respiratory symptoms of cough and congestion, after exposure to child and husband. She took over the counter medications but was not better. On (b) (6), she went to (b) (6) and was admitted with diagnostic of pneumonia. On the same day, the use of the product was interrupted. On (b) (6), the subject was discharged from the hospital. The subject was given medication in the hospital, but no post-discharge prescription was given. The hospital records were pending. It seems that the subject restarted using the product on 18-Feb-2016 (product interruption until 17-Feb-2016).

On 22-Feb-2016, the subject recovered from the event.

The investigator considered the event of mycoplasma pneumonia to be severe in intensity and not related to the use with THS 2.2.

Additional information will be requested: Relevant medical history (including other similar previous episodes) and other risk factors; Start date (or age) for conventional cigarettes (CC) smoking; Randomization date; Daily consumption of CC before/after randomisation; Clarification on whether the family members had also experienced Mycoplasma pneumoniae infection; Clarification on the pneumonia's onset date (i.e. the date when its first sign/symptom occurred), as the cough and congestion had reportedly occurred and been treated before the hospitalisation date; Results of relevant tests; Causality assessment with regard to CC and study procedures.

Case Comment:

Pneumonia mycoplasmal was assessed as serious (hospitalisation required).

Pneumonia mycoplasmal is unexpected, according to the Investigator's Brochure.

The Investigator has assessed this adverse event as not related to the use of THS 2.2. The Investigator did not provide an assessment of relatedness to conventional cigarette smoking or study procedures.

In agreement with the Investigator's causality assessment, the reported mycoplasma pneumonia is assessed as not related to the use of THS 2.2. A causal relationship between conventional cigarette smoking and the reported mycoplasma pneumonia cannot be excluded and, therefore, is assessed as possible.

C10. CONCOMITANT MEDICAL PRODUCTS (Continued)

02/09/2016 to 02/14/2016

3) Phenylephrine (Phenylephrine hydrochloride) 02/09/2016 to 02/14/2016

Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#1 Tobacco Heating System UNK, Respiratory 2.2 Regimen # 2		02/18/2016 to UNK		

MEDWATCH
3500A Facsimile

Page 1 of 2

Mfr Report #	PMI000514
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event: 33 Years or Date of Birth: (b) (6)	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 177.3 lbs or 80.4 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 03/07/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Hospitalisation for 24 hours due to acute grief reaction secondary to death of infant son [Grief reaction] Case Description: Verbatim: Hospitalisation for 24 hours due to acute grief reaction secondary to death of infant son Clinical study ZRHR-ERS-09-US: A randomised, 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. INITIAL INFORMATION RECEIVED ON 25-FEB-2016: continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 Ongoing, Current Condition, Tobacco user			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. Conventional cigarette (N/A) N/A			
#2. Tobacco Heating System 2.2 (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. UNK, Respiratory		#1.	
#2. UNK, Respiratory		#2. 10/15/2015 to 10/21/2015	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1.	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 02/25/2016		5. (A)NDA # IND # N/A STN # PMA/510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input checked="" type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> Follow-up #			
9. Manufacturer Report Number PMI000514		8. Adverse Event Term(s) Grief reaction	
E. INITIAL REPORTER			
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Physician	
		4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

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Page 2 of 2

Mfr Report #	PMI000514
UF/Importer Report #	
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

This report was received from an investigator and concerned a 33-year-old Caucasian male subject (Initials: RLH, ID Number: 04410, Randomisation Number: 10525, weight: 80.4 kg, height: 185 cm) who had been enrolled in the above mentioned clinical study.

Medical history and concomitant medication taken at the time of the event were not reported.

The subject used the THS 2.2 between 15-Oct-2015 and 21-Oct-2015. It seems that the subject was subsequently randomized to the Conventional Cigarette arm (confirmation will be requested).

On (b) (6), the subject's son died from emergency surgery. The subject had an acute episode of grief related to this situation. The subject was participating in the Army reserve training. On (b) (6), the Army reserve sent him to the emergency room to be evaluated. The subject was hospitalized for 24 hours for observation of acute grief reaction. On 07-Feb-2016, the subject was administered oral Ativan (lorazepam) at the dosage of 0.5 mg daily for acute depression. On (b) (6), the subject was discharged from hospital with follow-up grief counseling for him and his family. The subject did not continue any other medications after his discharge.

On 08-Feb-2016, the subject recovered from the event.

The investigator considered the event of grief reaction to be mild in intensity and not related to the use of THS 2.2.

Additional information will be requested (Medical history, including signs/symptoms of depression; co-medications; clarification/confirmation regarding randomization arm; randomization date; start date (or age) for CC smoking; amount of daily CC consumption; daily THS consumption, during run-in period; results of relevant medical investigations/exams; whether the reported description of "acute depression" should be considered as a diagnosis and, hence, as a replacement of "acute grief reaction" or as an additional SAE; was the use of CC stopped during hospitalisation and re-started following hospital discharge; confirmation as to whether the provided causality assessment also applies to CC; causality assessment with regards to study procedures).

Case Comment:

Grief reaction was assessed as serious (hospitalisation required).

Grief reaction is unexpected, according to the Investigator's Brochure.

The Investigator has assessed this adverse event as being not related to the use of THS 2.2. The Investigator did not provide causality assessment regarding conventional cigarettes and study procedures.

Considering the implausible temporal relationship (i.e. THS 2.2 had been used for a week, more than three months before the event), and in agreement with the Investigator's causality assessment, the reported grief reaction (also described as acute depression) is assessed as not related to the use of THS 2.2. Considering also the reported circumstances (i.e. death of the patient's infant son, three days prior to the reported acute grief reaction), the Grief reaction is assessed as not related to the conventional cigarette smoking or to study procedures.

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Mfr Report #	PMI000518
UF/Importer Report #	
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Page 1 of 3

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event 56 Years or Date of Birth (b) (6)	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 264.6 lbs or 120.0 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply) <input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 04/22/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Epiglottitis [Epiglottitis] Case Description: Verbatim: Epiglottitis (previously reported as Severe throat infection) Clinical study ZRHR-ERS-09-EXT-US: A 26 week extension study to determine the biological and functional changes in healthy smokers who switched from conventional cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study. INITIAL INFORMATION RECEIVED ON 01-MAR-2016: This report was received from an investigator and concerned a 56-year-old Caucasian male subject (Initials (b) ID continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 White blood cell count 13.3 (Continued)			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 --/--/1967 to --/--/1967 Procedure, (Continued) #2 --/--/1971 to Ongoing Current Condition, (Continued) #3 01/--/2015 to Ongoing Current Condition, (Continued)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) (Regimens Continued) #1. Tobacco Heating System 2.2 (N/A) N/A #2. Conventional cigarette (N/A) N/A			
2. Dose, Frequency & Route Used #1. 30-35 DF qd, Respiratory #2. 20 DF, qd, Respiratory		3. Therapy Dates (if unknown, give duration) from/to (or best estimate) #1. 06/26/2015 to 02/27/2016 #2. --/--/1971 to 06/25/2015	
4. Diagnosis for Use (Indication) #1. Tobacco user (Tobacco user) #2. Tobacco user (Tobacco user)		5. Event Abated After Use Stopped or Dose Reduced? #1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply #2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot # #1. B-21534 #2.	7. Exp. Date #1. #2.	8. Event Reappeared After Reintroduction? #1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply #2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) 1) Omeprazole (Omeprazole) 06/--/2015 to ongoing			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 04/11/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-EXT-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other: _____ _____ _____	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #2		9. Manufacturer Report Number PMI000518	
8. Adverse Event Term(s) Epiglottitis			
E. INITIAL REPORTER			
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Physician	
4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk			

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3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000518
UF/Importer Report #	
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Number: 09134, Randomisation Number: 10401, weight: 120 kg, height: 190 cm) who had been enrolled in the above mentioned clinical study.

the subject's medical history included gastroesophageal reflux disease (GERD) diagnosed in January 2015 and appendectomy in 1967. At the time of the event, the subject was taking oral omeprazole at the dosage of 40 mg daily, since June 2015, for GERD.

The subject was randomized to the THS 2.2 arm and started using the product (batch number B-21534) on 26-Jun-2015.

On (b) (6), the subject was hospitalized due to a severe throat infection. During a call to the investigational site, the subject stated that he was going to be released from the hospital on (b) (6). The subject was going to have an unspecified appointment. Medical records were going to be requested.

At the time of this initial report, the event was not resolved.

The investigator considered the event of throat infection to be severe in intensity and not related to the use of THS 2.2.

FOLLOW-UP INFORMATION RECEIVED ON 14-MAR-2016:

It was clarified that the subject was enrolled in the clinical study ZRHR-ERS-09-EXT-US (and not in the clinical study ZRHR-ERS-09-US as previously reported).

FOLLOW-UP INFORMATION RECEIVED ON 15-MAR-2016:

It was reported that the subject did not have any relevant medical history or risk factors.

The subject started smoking in 1971. Before randomization, the subject smoked on average 20 conventional cigarettes per day.

The subject was randomized to THS arm on 03-Jul-2015. After randomization, the subject used on average 30 to 35 THS per day (reportedly 'since January 2016') and smoked on average 4 conventional cigarettes per day (reportedly 'since January 2016'). The date of the latest THS used and conventional cigarette smoked before the onset of throat infection was 27-Feb-2016.

It was confirmed that the onset of first signs/symptoms of the throat infection was on (b) (6). The severity of the event was reported as severe as per subject's verbal communication and in line with the medical records which stated that the event was considered as 'epiglottitis'. It was reported that there were no relevant circumstances leading up to the occurrence of throat infection. During hospitalization, white blood cell count was elevated at 13.3 (reference range 4.0 - 10.0, unit not provided). The infectious agent was not identified by the hospital staff. The subject was treated in the hospital with Intravenous Solumedrol (methylprednisolone), intravenous Unasyn (ampicillin-sulbactam) and (unspecified) intravenous bolus.

During the hospitalization, the subject did not smoke anything and he re-started smoking on 28-Feb-2016 or 01-Mar-2016 (reportedly). The subject was discharged on (b) (6).

The event of throat infection resolved on 07-Mar-2016.

The investigator considered the event of throat infection to be not related to the use of THS 2.2, to the consumption of conventional cigarettes, or to the study procedures.

FOLLOW-UP INFORMATION RECEIVED ON 11-APR-2016:

The verbatim was updated to 'Epiglottitis'.

The subject used about 30 to 35 THS daily and smoked about 2 to 6 conventional cigarettes daily between 26-Jun-2015 and Jan-2016.

The use of THS and smoking of conventional cigarettes was restarted after discharge, on 02-Mar-2016.

The event did not re-occur after restarting THS and conventional cigarettes.

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 3 of 3

Mfr Report #	PMI000518
UF/Importer Report #	
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Additional information will be requested (Clarification on the amount of THS and CCs used after discharge; Confirmation on the amount of 20 CCs smoked daily between 1971 to 26-Jun-2015; Confirmation on the amount of 2 to 6 CCs smoked daily between 26-Jun-2015 to Jan-2016; Confirmation on the amount of 4 CCs smoked daily from Jan-2016 to 27-Feb-2016; Confirmation that new event of epiglottitis is assessed as not related to the use of THS 2.2, the conventional cigarette smoking, or to the study procedures).

Case Comment:

Epiglottitis was assessed as serious (hospitalisation required).

Epiglottitis is unexpected, according to the Reference Safety Information (i.e. the Investigator's Brochure).

The Investigator assessed the reported epiglottitis as being not related to the use of THS 2.2, to the consumption of conventional cigarettes, or to the study procedures.

In agreement with the Investigator's causality assessment, the reported epiglottitis is assessed as not related to the use of THS 2.2, the conventional cigarette smoking, or to the study procedures. Of note, the epiglottitis did not reoccur after restarting THS and conventional cigarettes.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		White blood cell count elevated	13.3	10 4

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	--/--/1967 --/--/1967	Procedure Appendectomy	
2	--/--/1971	Current Condition	Before randomization, the subject smoked on average 20 conventional cigarettes per day. He smoked on average 4 conventional cigarettes per day, reportedly 'since January 2016'.
	Ongoing	Tobacco user	
3	01/--/2015 Ongoing	Current Condition Gastroesophageal reflux disease	

Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#1 Tobacco Heating System 2.2 Regimen # 2	UNK, Respiratory	03/02/2016 to Ongoing	B-21534	
#2 Conventional cigarette Regimen # 2	2-6 DF qd, Respiratory	06/26/2015 to 01/--/2016		
#2 Conventional cigarette Regimen # 3	4 DF, qd, Respiratory	01/--/2016 to 02/27/2016		
#2 Conventional cigarette Regimen # 4	UNK, Respiratory	03/02/2016 to Ongoing		

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Mfr Report #	PMI000551
UF/Importer Report #	
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Page 1 of 3

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event 38 Years or Date of Birth (b) (6)	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 169.6 lbs or 76.9 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply) <input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 04/22/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Influenza [Influenza] Case Description: Verbatim: Influenza (initially reported as productive cough, generalised myalgia, fever, nausea and vomit) Clinical study ZRHR-ERS-09-EXT-US: A 26 week extension study to determine the biological and functional changes in healthy smokers who switched from conventional cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study. INITIAL INFORMATION RECEIVED ON 14-MAR-2016: This report was received from an Investigator and concerned a 38-year-old Caucasian male subject (Initials: (b) ID continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 --/--/1995 to UNK Current Condition, (Continued) #2 01/16/2015 to 01/19/2015 Historical Condition, (Continued) #3 09/--/2015 to UNK Historical Condition, (Continued)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) (Regimens Continued)			
#1. Tobacco Heating System 2.2 (N/A) N/A			
#2. Conventional cigarette (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 45.8 DF, qd, Respiratory		#1. 07/07/2015 to 03/12/2016	
#2. average of 30-39 (Continued)		#2. --/--/1995 to --/--/2014	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1.	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 04/12/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-EXT-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other: _____ _____ _____	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #1		9. Manufacturer Report Number PMI000551	
9. Manufacturer Report Number PMI000551		8. Adverse Event Term(s) Influenza	
E. INITIAL REPORTER			
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Physician	
4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk			

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3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000551
UF/Importer Report #	
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Number: 01073, Randomisation Number: 10299, weight: 76.9 kg, height: 163 cm) who had been enrolled in the above mentioned clinical study.

The subject's medical history included hospitalisation for diverticulitis between (b) (6) (no surgery performed) and left ankle sprain in September 2015 treated with Toradol (ketorolac), Percocet (acetaminophen/oxycodone) and aspirin. The subject had been smoking since 1995 (1.5 packs a day, 30-39 cigarettes per day). His family history included heart disease. Concomitant medications were not reported.

The subject was randomized to the THS 2.2 arm (to be confirmed) and started using the product on 07-Jul-2015.

On (b) (6) at 10:00, the subject was hospitalized with the flu and his symptoms consisted of a productive cough, generalised myalgia, nausea, fever and vomiting. He was treated with oral Tamiflu (oseltamivir) 75 mg and oral Toradol (ketorolac) 10 mg on 13-Mar-2016 and 14-Mar-2016 for generalised myalgia. The subject was discharged from hospital on (b) (6) with the following prescriptions: Tamiflu and Toradol.

No action was taken with regards to the THS 2.2. The subject did not discontinue from the study due to the occurrence of these events.

At time of the report, the events were resolving.

The investigator considered the events of productive cough, generalised myalgia, nausea, fever and vomit to be severe in intensity and not related to the use of THS 2.2.

FOLLOW-UP INFORMATION RECEIVED ON 12-APR-2016 AND 13-APR-2016:

The subject reported smoking an average of 30 cigarettes per day over the last year.

The subject was randomized to THS arm on 13-Jul-2015.

The subject did not report smoking conventional cigarettes after randomization.

The average daily use of THS in the extension portion of the study was 45.8 THS sticks.

The final diagnosis at hospital discharge was Influenza A and dehydration. The verbatim was updated from 'Productive cough, generalised myalgia, fever, nausea and vomit' to 'Influenza'.

The onset date of the first signs/symptoms was on (b) (6) at 10:00.

The subject was admitted to hospital on (b) (6) at 06:18.

THS was stopped during hospitalization on (b) (6). The product was re-started at discharge on (b) (6).

The subject was discharged from hospital with prescriptions for fever and generalized myalgia. He was treated with oral Tamiflu (oseltamivir) 75 mg from 13-Mar-2016 to 17-Mar-2016 for fever and oral Toradol (ketorolac) 10 mg on 13-Mar-2016 and 14-Mar-2016 for generalised myalgia.

The event resolved on 15-Mar-2016 at 18:00.

The Investigator considered the event of influenza to be not related to the use of THS 2.2, to the consumption of conventional cigarettes and to the study procedures.

Additional information will be requested (Confirm whether 'dehydration' should be considered as an additional SAE).

Case Comment:

Influenza was assessed as serious (hospitalisation required).

Influenza is unexpected, according to the Reference Safety Information (i.e. the Investigator's Brochure).

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3500A Facsimile (Back) (Continued)

Page 3 of 3

Mfr Report #	PMI000551
UF/Importer Report #	
	FDA Use Only

The Investigator assessed Influenza as being not related to the use of THS 2.2, the conventional cigarette smoking, or to the study procedures.

In agreement with the Investigator's causality assessment, Influenza, which likely was an intercurrent viral infection (influenza A was mentioned in the report) occurred approximately eight months after starting the use of THS 2.2, is assessed as being not related to the use of THS 2.2, the conventional cigarette smoking, or to the study procedures. Of note, the use of THS 2.2. was restarted after hospital discharge, but before the resolution of Influenza.

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	--/--/1995	Current Condition	1.5 pack (30-39 cigarettes) per day, and an average of 30 cigarettes per day over the last year of smoking, reported at screening. No cigarette smoking after randomization on 13-Jul-2015.
	UNK	smoker	
2	01/16/2015 01/19/2015	Historical Condition Diverticulitis	Hospitalized (no surgery performed)
3	09/--/2015 UNK	Historical Condition Ligament sprain	

C2. DOSE, FREQUENCY & ROUTE USED (Continued)

Suspect Medication #2: average of 30-39 DF per day, Respiratory

Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#1 Tobacco Heating System 2.2 Regimen # 2	UNK, Respiratory	03/13/2016 to Ongoing		
#2 Conventional cigarette Regimen # 2	30 DF, qd, Respiratory	--/--/2014 to 07/12/2015		

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Page 1 of 3

Mfr Report #	PMI000553
UF/Importer Report #	
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A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event: 61 Years or Date of Birth: (b) (6)	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 148.6 lbs or 67.4 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 04/22/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Worsening of infected tooth bottom right molar [Tooth infection]			
Case Description: Verbatim: Worsening of infected tooth bottom right molar			
Clinical study ZRHR-ERS-09-US: A randomised, 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.			
INITIAL INFORMATION RECEIVED ON 14-MAR-2016: This report was received from an Investigator and concerned a 61-year-old African American female subject (Initials (b)) continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc) Race: Black #1 --/--/1985 to Ongoing, Current Condition, Tobacco user (On average 10 conventional cigarettes daily)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. Conventional cigarette (N/A) N/A			
#2. Tobacco Heating System 2.2 (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 10 DF, qd, Respiratory		#1. --/--/1985 to Ongoing	
#2. Total of 49 THS, Respiratory		#2. 09/08/2015 to 09/21/2015	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1.	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
1) Potassium (Potassium) --/--/2010 to ongoing			
2) Vitamin D3 (Calecaliferol) 10/06/2015 to UNK			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND			
4. Date Received by Manufacturer (mm/dd/yyyy) 04/13/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-US		3. Report Source (Check all that apply)	
7. Type of Report (Check all that apply)		<input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #1			
9. Manufacturer Report Number PMI000553		8. Adverse Event Term(s) Tooth infection	
E. INITIAL REPORTER			
1. Name and Address		Phone # Withheld	
UNITED STATES Name and address withheld.			
2. Health Professional?		3. Occupation Physician	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
		4. Initial Reporter Also Sent Report to FDA	
		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

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3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000553
UF/Importer Report #	
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

ID Number: 10043, Randomisation Number: 20201, weight: 67.4 kg, height: 158 cm) who had been enrolled in the above mentioned clinical study.

The subject had no relevant medical history. Concomitant medications included oral potassium 1000 mg daily since 2010 as supplement and oral vitamin D3 1000 mg daily since 06-Oct-2015 as supplement.

The subject used the THS 2.2 between 08-Sep-2015 and 21-Sep-2015.

The subject reported that she experienced a major tooth infection on her bottom right molar on 07-Feb-2016. The subject was treated (outpatient) with oral clindamycin 150 mg four times a day since 10-Feb-2016, oral meloxicam 7.5 mg daily between 11-Feb-2016 and 13-Mar-2016 and hydrocodone/acetaminophen every 4 hours as needed between 10-Feb-2016 and 13-Mar-2016. She was subsequently admitted into the hospital for worsening of this same tooth infection between (b) (6). An interior bacterial infection was unmasked and surgery was required. The subject had an abscess lancing inside and outside underneath her jaw. The subject was treated with oral tramadol 50 mg every 6 hours as needed from 02-Mar-2016.

The subject returned to the hospital on (b) (6) to have another abscess lancing procedure done (outpatient surgery). The subject was treated with oral metronidazole 500 mg twice a day from (b) (6).

The subject recovered from the event on 02-Mar-2016. The subject did not discontinue from the study due to the occurrence of this event.

The Investigator considered the event of worsening of infected tooth bottom right molar to be severe in intensity and not related to the use of THS 2.2.

FOLLOW-UP INFORMATION RECEIVED ON 13-APR-2016:

The subject started smoking in 1985, on average 10 conventional cigarettes per day.

During the run-in period, the subject used 49 tobacco sticks over the duration of 12 days.

The subject was randomized to the conventional cigarettes arm on 21-Sep-2015.

It was clarified that the patient had an infection in the bottom right molar. As the pain and the infection worsened over time, the patient went to the emergency department. The worsening was the reason for the event to become serious.

The subject did not stop smoking conventional cigarettes due to the occurrence of the event.

It was considered that the serious event ended once the subject was discharged.

The 'tooth abscess requiring lancing' was not considered as an additional serious adverse event. This was an outpatient procedure.

The Investigator considered the event of worsening of infected tooth bottom right molar to be not related to the use of THS 2.2 or to study procedures but related to the consumption of conventional cigarettes.

No follow-up information is expected. Case closed.

Case Comment:

Tooth infection was assessed as serious (hospitalisation required).

Tooth infection is unexpected, according to the Investigator's Brochure.

The Investigator assessed the reported worsening of infected tooth bottom right molar as being not related to the use of THS 2.2 or to study procedures. The Investigator assessed the event as being related to conventional cigarette smoking.

The subject had used THS 2.2 for two weeks, approximately five months before she reportedly developed a major tooth infection in a bottom right molar, whose subsequent worsening required hospitalisation. Considering the implausible temporal relationship, and in agreement with the Investigator's causality assessment, the reported Tooth infection is assessed as not related to the use of THS 2.2

MEDWATCH

3500A Facsimile (Back)

(Continued)

Page 3 of 3

Mir Report #	PMI000553
UF/Importer Report #	
	FDA Use Only

and to study procedures. A causal relationship between the conventional cigarette smoking and Tooth infection cannot be excluded and, therefore, is assessed as possible.

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Mfr Report #	PMI000559
UF/Importer Report #	
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Page 1 of 3

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event 50 Years or Date of Birth (b) (6)	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 205.7 lbs or 93.3 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply) <input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening (mm/dd/yyyy) <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 04/27/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) High triglycerides [Blood triglycerides increased] Case Description: Verbatim: High triglycerides Clinical study ZRHR-ERS-09-EXT-US: A 26 week extension study to determine the biological and functional changes in healthy smokers who switched from conventional cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study. INITIAL INFORMATION RECEIVED ON 21-MAR-2016: This report was received from an Investigator and concerned a 50-year-old African American male subject (Initials: (b) , ID continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 06/30/2015 Blood glucose (continued) #2 10/16/2015 Blood glucose (continued) #3 01/15/2016 Blood glucose (continued) #4 06/30/2015 Blood triglycerides (continued) #5 10/16/2015 Blood triglycerides (continued) #6 01/15/2016 Blood triglycerides (continued)			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Black #1 --/--/1985 to UNK, Current Condition, Tobacco user (On average, 15 conventional cigarettes daily) #2 05/28/2015 to UNK, Current Condition, Blood triglycerides increased #3 #4			

Form Generated by Argus Safety Web v6.0.3

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) (Regimens Continued)			
#1. Conventional cigarette (N/A) N/A			
#2. Tobacco Heating System 2.2 (N/A) N/A			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 15 DF, qd, Respiratory		#1. --/--/1985 to 07/06/2015	
#2. 25 DF, qd, Respiratory		#2. 06/30/2015 to 07/07/2015	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Tobacco user (Tobacco user)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2. Tobacco user (Tobacco user)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1.	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 04/15/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-EXT-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other: _____ _____ _____	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #1		9. Manufacturer Report Number PMI000559	
8. Adverse Event Term(s) Blood triglycerides increased		E. INITIAL REPORTER	
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Physician	
4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk			

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000559
UF/Importer Report #	
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Number: 07040, Randomization Number: 10036, weight: 93.3 kg, height: 173.9 cm) who had been enrolled in the above mentioned clinical study.

It was reported that, at Visit 10 on 15-Jan-2016, the subject presented with a triglycerides level of 1446 (normal range: 55 - 327; unit not provided) and a glucose level of 318 (normal range: 70 -100; unit not provided).

No relevant medical history was reported. The subject was not taking any concomitant medications.

The subject used Tobacco Heating System 2.2 (THS 2.2) from 30-Jun-2015 at 08:00 to 07-Jul-2015.

On (b) (6), the subject was admitted to the hospital for high triglycerides and he stayed in the hospital between (b) (6) and (b) (6). The subject reported that he was given no medication but he was told to rest and stay away from fatty food. Medical records were requested.

The event resolved on 21-Mar-2016. No action was taken with the study product.

The Investigator considered the reported event of high triglycerides to be unrelated to the use of THS 2.2.

FOLLOW-UP INFORMATION RECEIVED ON 15-APR-2016:

The subject started smoking in 1985, on average 15 conventional cigarettes daily.

The subject already experienced an episode of high triglycerides on 28-May-2015.

During the run-in period, the subject used on average 25 THS sticks daily.

The subject was randomized to the conventional cigarette arm on 07-Jul-2015. After randomization, the subject smoked on average 15 conventional cigarettes daily.

Triglycerides and glucose levels fluctuated through the study. Triglycerides level was noted to be 3023 mg/dL on 30-Jun-2015, 223 mg/dL on 16-Oct-2015, and 1446 mg/dL on 15-Jan-2016. Glucose level was noted to be 285 mg/dL on 30-Jun-2015, 108 mg/dL on 16-Oct-2015, and 318 mg/dL on 15-Jan-2016. No treatment was administered to the subject due to the reported event.

The subject reported being dehydrated and experiencing vomiting. This was the reason the subject went to the hospital. The subject was administered unspecified fluids at the hospital for his dehydration. Medical records were requested.

The subject was not discontinued from the study (as per decision of the Investigator, who recommended that the subject should stay in the study).

The glucose level of 318 mg/dL was not considered as an additional SAE.

The Investigator considered the reported event of high triglycerides to be unrelated to the use of THS 2.2 and to the consumption of conventional cigarettes. The investigator did not provide causality assessment regarding study procedures.

Additional information will be requested (Please confirm the following: Whether detection of triglycerides of 3023 mg/dL (on 30-Jun-2015) occurred during subject's participation in the main study (ZRHR-ERS-09-US), and whether it was considered/reported as an SAE in that study; Whether the subject had had a medical history of high and/or fluctuating triglyceride level before enrolment in the main study (ZRHR-ERS-09-US); Whether, based on the subject's medical history and underlying/pre-existent conditions, the currently reported triglycerides level of 1446 mg/dL (on 15-Jan-2016) is still considered an AE; if so, please confirm its seriousness criterion; Whether vomiting or dehydration (requiring hospitalisation on (b) (6)) was considered as an SAE; if so, please provide relevant details (including onset, causality, outcome); Action taken with CC; Event intensity/severity; Causality assessment regarding study procedures).

Case Comment:

Blood triglycerides increased was assessed as serious (hospitalisation required, as per initial report).

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 3 of 3

Mfr Report #	PMI000559
UF/Importer Report #	
	FDA Use Only

Blood triglycerides increased is unexpected, as per the Reference Safety Information (i.e. the Investigator's Brochure).

The Investigator considered the Blood triglycerides increased as being not related to the use of THS 2.2 or to conventional cigarette smoking. The Investigator has not provided an assessment of causal relationship to study procedures.

It was reported that triglycerides and glucose levels fluctuated both before and throughout this study, with even higher triglyceride levels seen before this reported episode. The now reported high triglyceride level (i.e. 1446 mg/dL) was actually measured approximately two months before the patient was reportedly hospitalised for experiencing vomiting and being dehydrated. In agreement with the Investigator's causality assessment, the Blood triglycerides increased is assessed as not related to the use of THS. 2.2, which was only used for eight days, approximately six months prior to the episode of elevated triglycerides and glucose level reported in this case. A causal relationship (or a contributory role) between the long history of conventional cigarette smoking and Blood triglycerides increased cannot be excluded, and is therefore assessed as possible.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	06/30/2015	Blood glucose	285 mg/dL	100 70
2	10/16/2015	Blood glucose	108 mg/dL	100 70
3	01/15/2016	Blood glucose	318 mg/dL	100 70
4	06/30/2015	Blood triglycerides	3023 mg/dL	327 55
5	10/16/2015	Blood triglycerides	223 mg/dL	327 55
6	01/15/2016	Blood triglycerides	1446 mg/dL	327 55

Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#1 Conventional cigarette Regimen # 2	15 DF, qd, Respiratory	07/07/2015 to UNK		

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Mfr Report #	PMI000627
UF/Importer Report #	
FDA Use Only	

Page 1 of 3

A. PATIENT INFORMATION			
1. Patient Identifier (b)	2. Age at Time of Event 61 Years or Date of Birth (b) (6)	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 182.4 lbs or 82.7 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply) <input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital Anomaly/Birth Defect <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Other Serious (Important Medical Events) <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) (b) (6)		4. Date of This Report (mm/dd/yyyy) 05/02/2016	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Appendicitis [Appendicitis] Case Description: Verbatim: Appendicitis Clinical study ZRHR-ERS-09-EXT-US: A 26 week extension study to determine the biological and functional changes in healthy smokers who switched from conventional cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study. INITIAL INFORMATION RECEIVED ON 22-APR-2016: This report was received from an Investigator and concerned a 61-year-old Caucasian female subject (Initials (b)), ID continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 01/--/1970 to 07/--/1970 Historical Condition, (Continued) #2 03/--/1970 to 03/--/1970 Historical Condition, (Continued) #3 --/--/1990 to Ongoing Current Condition, (Continued) continued in additional info section...			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) #1. Tobacco Heating System 2.2 (N/A) N/A #2. Conventional cigarette (N/A) N/A			
2. Dose, Frequency & Route Used #1. UNK, Respiratory #2. 15-19 DF daily, Respiratory		3. Therapy Dates (if unknown, give duration) from/to (or best estimate) #1. UNK to 04/05/2016 #2. --/--/1990 to UNK	
4. Diagnosis for Use (Indication) #1. Tobacco user (Tobacco user) #2. Tobacco user (Tobacco user)		5. Event Abated After Use Stopped or Dose Reduced? #1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply #2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot # #1. B-21534 #2.	7. Exp. Date #1. #2.	8. Event Reappeared After Reintroduction? #1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply #2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) 1) Centrum (Ascorbic acid, Biotin, Calcium pantothenate, Cyanocobalamin, Ergocalciferol, Iron, Nicotinamide, continued in additional info section...			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Philip Morris Products S.A. Quai Jean Renaud 5 Neuchâtel, 2000 SWITZERLAND		2. Phone Number	
4. Date Received by Manufacturer (mm/dd/yyyy) 04/22/2016		5. (A)NDA # IND # N/A STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # ZRHR-ERS-09-EXT-US		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other: _____ _____ _____	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input checked="" type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> Follow-up # _____		8. Adverse Event Term(s) Appendicitis	
9. Manufacturer Report Number PMI000627			
E. INITIAL REPORTER			
1. Name and Address UNITED STATES Name and address withheld.		Phone # Withheld	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		3. Occupation Physician	
		4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk	

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 3

Mfr Report #	PMI000627
UF/Importer Report #	
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Number: 01046, Randomization Number: 20291, weight: 82.7 kg, height: 165 cm) who had been enrolled in the above mentioned clinical study.

The subject's medical history included: mononucleosis from Jan-1970 to Jul-1970; hospitalization in Mar-1970 for false appendicitis which did not require surgery; back problems / pain since 1997 due to mild degenerative disc T3 and C4 caused by an automobile accident; Sexual abstinence since Sep-1999; athlete's foot (both) since 01-Jun-2009 treated with topical cream fluocinonide 1mg as needed from 2014 to 30-Apr-2015; menopause since 2010; nasal congestion due to spring and fall allergies since 2010 (treated with oral Equate (diphenhydramine) 25 mg as needed from 2014 to 30-Apr-2015 as well as once on 28-Jul-2015 and as needed from 30-Jan-2016 to 29-Mar-2016 and, oral acetaminophen/dextromethorphan HBR/ phenylephrine HCL 650/20/10 mg daily from 26-Nov-2015 to 27-Nov-2015, oral cetirizine 10 mg once daily from 24-Feb-2016 to 01-Mar-2016); fracture of the distal radius left wrist on 23-Dec-2014 due to a fall; and generalised headaches treated with oral aspirin 650 mg once daily on 23-24-25-Nov-2015.

The subject was taking the following concomitant medication: oral Centrum Chewables (multivitamins, 1 tablet daily) since 15-Jan-2016 for general health.

It was reported that the subject started smoking in 1990, on average 15-19 conventional cigarettes daily. The subject used Tobacco Heating System 2.2 (THS 2.2) (batch number B-21534) from an unknown date up to 05-Apr-2016. It seems that the subject was randomized to the conventional cigarette arm (clarification will be requested).

On (b) (6), the subject was admitted to the hospital for severe appendicitis. The subject reported that she did not have appendectomy, as there was too much swelling to have surgery done at this time. The subject was expecting to be discharged from hospital on (b) (6). The subject reported ongoing non-serious events of dry throat, dry mouth, increased urinary frequency, decreased appetite, generalized arthralgia, nausea and upper abdominal pain. She reported that her nasal congestion was not worse than prior episodes and stated that she had not smoked since her symptoms began.

At time of the report, the event of appendicitis was not resolved.

The subject was not discontinued from the study.

The Investigator considered the reported event of appendicitis to be unrelated to the use of THS 2.2.

Additional information will be requested (Study enrolment and randomisation dates; Confirmation on randomisation to CC arm; Daily consumption of CC before/after randomisation; Start date and daily use of THS during the run-in period, as applicable; Confirmation of reason for stopping the use of THS on 05-Apr-2016; Onset date for first signs and symptoms of reported appendicitis (please consider recording that date as the SAE's onset date, instead of hospitalisation date, if different); Results of relevant investigations; Type of appendicitis; Treatment required/administered for the SAE; Action taken with conventional cigarettes due to the SAE; SAE's outcome and outcome/resolution date; Hospital discharge date; Confirmation as to whether the causality assessment (i.e. not related) applies to both CC and THS; Causality assessment to study procedures).

Case Comment:

Appendicitis was assessed as serious (hospitalization required).

Appendicitis is unexpected, as per the Reference Safety Information (i.e. the Investigator's Brochure).

The Investigator considered the reported appendicitis as being not related to the use of THS 2.2. The Investigator has not provided an assessment of causal relationship to conventional cigarette smoking or to study procedures.

Considering the implausible temporal sequence (i.e. THS 2.2 was not used in the last 10 days before the reported adverse event), and in agreement with the Investigator's causality assessment, the reported appendicitis is assessed as not related to the use of THS 2.2. The Company has assessed the reported appendicitis as also being not related to the conventional cigarette smoking. Of note, at the time of reporting, no surgery had been performed for the reported appendicitis; the patient had reportedly had an episode of false appendicitis, which did not require surgery, approximately 45 years before this report.

B7. OTHER RELEVANT HISTORY

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 3 of 3

Mfr Report #	PMI000627
UF/Importer Report #	
	FDA Use Only

#	Start/Stop Date	Condition Type / Condition	Notes
1	01/--/1970 07/--/1970	Historical Condition Mononucleosis syndrome	
2	03/--/1970 03/--/1970	Historical Condition Hospitalisation	Hospitalised for false appendicitis. Resolved. No surgery required.
3	--/--/1990 Ongoing	Current Condition Tobacco user	15-19 cigarettes daily
4	--/--/1997 UNK	Current Condition Intervertebral disc degeneration	Mild degenerative disc T3 and C4 caused by an automobile accident
5	--/--/1997 UNK	Current Condition Back pain	Back problems / Pain Mild degenerative disc T3 and C4 - Auto accident
6	09/--/1999 Ongoing	Current Condition Non-consummation	
7	06/01/2009 Ongoing	Current Condition Tinea pedis	Athlete's foot (both)
8	--/--/2010 UNK	Historical Condition Nasal congestion	Spring and fall allergy
9	--/--/2010 Ongoing	Current Condition Menopause	
10	12/23/2014 UNK	Historical Condition Wrist fracture	Distal radius left wrist (fell down) - Fracture left wrist
11		Historical Condition Headache	
12		Historical Condition Road traffic accident	

C10. CONCOMITANT MEDICAL PRODUCTS (Continued)

Pyridoxine hydrochloride, Retinol, Riboflavin, Thiamine hydrochloride, Tocopheryl acetate) 01/15/2016 to ongoing