Appendix A6.1.5.4. Adverse events from completed clinical studies. Relevant safety summary tables from clinical study reports are compiled in this appendix for convenience purpose.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

TABLE OF CONTENT

1. Adverse Events Reported in Single-use Clinical Studies – THS Regular 4
2. Adverse Events Reported in Single-use Clinical Studies – THS Menthol 8
3. Adverse Events Reported in 5-day Clinical Studies – THS Regular 11
4. Adverse Events Reported in 3-month Clinical Studies – Confinement Period - THS Menthol 14
5. Adverse Events Reported in 3-month Clinical Studies – Ambulatory Period - THS Menthol 18

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

TABLE OF TABLES

Table 1 ZRHR-PK-01-EU. Summary of Adverse Events by SOC and PT 4
Table 2 ZRHR-PK-01-EU. Summary of Adverse Events Related to Investigational Product and Reference Point Product by SOC and PT 5
Table 3 ZRHR-PK-02-JP. Summary of Adverse Events by SOC and PT 6
Table 4 ZRHR-PK-02-JP. Summary of Adverse Events Related to Investigational Product and Reference Point Product by SOC and PT 7
Table 5 ZRHM-PK-05-JP. Summary of Adverse Events by SOC and PT 8
Table 6 ZRHM-PK-06-US. Summary of Adverse Events by SOC and PT 9
Table 7 ZRHM-PK-06-US. Summary of Adverse Events Related to Investigational Product and Reference Point Product by SOC and PT 10
Table 8 ZRHR-REXC-03-EU. Summary of Adverse Events by SOC and PT 11
Table 9 ZRHR-REXC-03-EU. Summary of Adverse Events (PT) Related to Investigational Product 13
Table 10 ZRHR-REXC-04-JP. Summary of Adverse Events by SOC and PT 13
Table 11 ZRHM-REXA-07-JP. Summary of Adverse Events by SOC and PT – Confinement Period 14
Table 12 ZRHM-REXA-08-US. Summary of Adverse Events by SOC and PT - Confinement Period 15
Table 13 ZRHM-REXA-07-JP. Summary of Adverse Events by SOC and PT – Ambulatory Period 18
Table 14 ZRHM-REXA-07-JP. Summary of Adverse Events by SOC and PT - Safety Follow-up Period 19
Table 15 ZRHM-REXA-08-US. Summary of Adverse Events by SOC and PT - Ambulatory Period 20
Table 16 ZRHM-REXA-08-US. Summary of Adverse Events by SOC and PT - Safety Follow-Up Period 22

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

1. Adverse Events Reported in Single-use Clinical Studies – THS Regular

Table 1 ZRHR-PK-01-EU. Summary of Adverse Events by SOC and PT

System Organ Class (SOC) Preferred Term (PT)	Sequence				
	THS 2.2 - CC (N=22)	CC - THS 2.2 (N=22)	THS 2.2 - NNS (N=9)	NNS - THS 2.2 (N=9)	Overall Safety (N=62)
Number (%) subjects with any AEs	10 (45.5%)	7 (31.8%)	4 (44.4%)	2 (22.2%)	23 (37.1%)
Nervous system disorders	8 (36.4%)	6 (27.3%)	3 (33.3%)	1 (11.1%)	18 (29.0%)
Dizziness	5 (22.7%)	1 (4.5%)	0	1 (11.1%)	7 (11.3%)
Headache	3 (13.6%)	2 (9.1%)	1 (11.1%)	0	6 (9.7%)
Presyncope	1 (4.5%)	3 (13.6%)	2 (22.2%)	0	6 (9.7%)
Dysgeusia	1 (4.5%)	0	0	0	1 (1.6%)
Gastrointestinal disorders	4 (18.2%)	2 (9.1%)	0	0	6 (9.7%)
Nausea	2 (9.1%)	1 (4.5%)	0	0	3 (4.8%)
Vomiting	1 (4.5%)	2 (9.1%)	0	0	3 (4.8%)
Constipation	1 (4.5%)	0	0	0	1 (1.6%)
Dyspepsia	1 (4.5%)	0	0	0	1 (1.6%)
Musculoskeletal and connective tissue disorders	2 (9.1%)	0	0	1 (11.1%)	3 (4.8%)
Muscle spasms	1 (4.5%)	0	0	1 (11.1%)	2 (3.2%)
Musculoskeletal pain	1 (4.5%)	0	0	0	1 (1.6%)
Vascular disorders	1 (4.5%)	0	1 (11.1%)	0	2 (3.2%)
Pallor	1 (4.5%)	0	1 (11.1%)	0	2 (3.2%)
Renal and urinary disorders	0	0	0	1 (11.1%)	1 (1.6%)
Haematuria	0	0	0	1 (11.1%)	1 (1.6%)
Reproductive system and breast disorders	0	1 (4.5%)	0	0	1 (1.6%)
Dysmenorrhoea	0	1 (4.5%)	0	0	1 (1.6%)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (11.1%)	1 (1.6%)
Cough	0	0	0	1 (11.1%)	1 (1.6%)
Skin and subcutaneous tissue disorders	1 (4.5%)	0	0	0	1 (1.6%)
Rash	1 (4.5%)	0	0	0	1 (1.6%)

Abbreviations: AE = adverse event; CC = conventional cigarette; N = number of subjects; NNS = nicotine nasal spray; THS 2.2 = Tobacco Heating System 2.2.
Terms coded using MedDRA® Version 16.0.
Percentages were calculated using the N of subjects in the column headers.
Data Source: Study ZRHR-PK-01-EU Clinical study report Appendix 15, Table 15.2.6.2.1.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 2 **ZRHR-PK-01-EU. Summary of Adverse Events Related to Investigational Product and Reference Point Product by SOC and PT**

Preferred Term	Sequence				
	THS 2.2 - CC (N=22)	CC - THS 2.2 (N=22)	THS 2.2 - NNS (N=9)	NNS - THS 2.2 (N=9)	Overall Safety (N=62)
Number (%) subjects with any AEs related to IP	4 (18.2%)	4 (18.2%)	3 (33.3%)	1 (11.1%)	12 (19.4%)
Presyncope	1 (4.5%)	3 (13.6%)	2 (22.2%)	0	6 (9.7%)
Dizziness	3 (13.6%)	1 (4.5%)	0	1 (11.1%)	5 (8.1%)
Nausea	0	1 (4.5%)	0	0	1 (1.6%)
Vomiting	0	1 (4.5%)	0	0	1 (1.6%)
Pallor	0	0	1 (11.1%)	0	1 (1.6%)
Number (%) subjects with any AEs related to NNS	0	0	0	0	0

Abbreviations: AE = adverse event; CC = conventional cigarette; IP = investigational product; N = number of subjects; NNS = nicotine nasal spray; THS 2.2 = Tobacco Heating System 2.2.
Terms coded using MedDRA® Version 16.0.
Percentages were calculated using the N of subjects in the column headers.
Data Source: Study ZRHR-PK-01-EU Clinical study report Appendix 15, Table 15.2.6.3.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 3 ZRHR-PK-02-JP. Summary of Adverse Events by SOC and PT

System Organ Class Preferred Term	Sequence				
	THS 2.2 - CC (N=22)	CC - THS 2.2 (N=22)	THS 2.2 - NRT gum (N=9)	NRT gum - THS 2.2 (N=9)	Overall Safety (N=65)
Number (%) subjects with any AEs	3 (13.6%)	3 (13.6%)	4 (44.4%)	1 (11.1%)	11 (16.9%)
Investigations	3 (13.6%)	1 (4.5%)	2 (22.2%)	0	6 (9.2%)
Blood triglycerides increased	1 (4.5%)	1 (4.5%)	0	0	2 (3.1%)
Haemoglobin decreased	1 (4.5%)	0	1 (11.1%)	0	2 (3.1%)
Blood bilirubin increased	0	0	1 (11.1%)	0	1 (1.5%)
Hepatic enzyme increased	1 (4.5%)	0	0	0	1 (1.5%)
Psychiatric disorders	0	1 (4.5%)	2 (22.2%)	0	3 (4.6%)
Dysphoria	0	1 (4.5%)	1 (11.1%)	0	2 (3.1%)
Tobacco withdrawal symptoms	0	0	1 (11.1%)	0	1 (1.5%)
Nervous system disorders	0	1 (4.5%)	0	1 (11.1%)	2 (3.1%)
Dizziness	0	1 (4.5%)	0	0	1 (1.5%)
Nervous system disorder	0	1 (4.5%)	0	0	1 (1.5%)
Tension headache	0	0	0	1 (11.1%)	1 (1.5%)
Hepatobiliary disorders	0	1 (4.5%)	0	0	1 (1.5%)
Hepatic function abnormal	0	1 (4.5%)	0	0	1 (1.5%)
Renal and urinary disorders	0	0	1 (11.1%)	0	1 (1.5%)
Calculus urinary	0	0	1 (11.1%)	0	1 (1.5%)

Abbreviations: AE = adverse event; CC = conventional cigarette; N = number of subjects; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.
Terms coded using MedDRA® version 16.0.
Percentages were calculated using the N of subjects in the column headers. None of the subjects who were exposed to THS 2.2 but not randomized reported an AE.
Data Source: Study ZRHR-PK-02-JP Clinical study report Appendix 15, Table 15.2.6.2.1.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 4 **ZRHR-PK-02-JP. Summary of Adverse Events Related to Investigational Product and Reference Point Product by SOC and PT**

	Sequence					
System Organ Class Preferred Term	**THS 2.2 - CC (N=22)**	**CC - THS 2.2 (N=22)**	**THS 2.2 - NRT gum (N=9)**	**NRT gum - THS 2.2 (N=9)**	**Exposed not Random-ized (N=3)**	**Overall Safety (N=65)**
Number (%) subjects with any AEs related to IP	0	2 (9.1%)	1 (11.1%)	0	0	3 (4.6%)
Psychiatric disorders	0	1 (4.5%)	1 (11.1%)	0	0	2 (3.1%)
Dysphoria	0	1 (4.5%)	1 (11.1%)	0	0	2 (3.1%)
Hepatobiliary disorders	0	1 (4.5%)	0	0	0	1 (1.5%)
Hepatic function abnormal	0	1 (4.5%)	0	0	0	1 (1.5%)
Number (%) subjects with any AEs related to NRT gum	0	0	0	0	0	0

Abbreviations: AE = adverse event; CC = conventional cigarette; IP = investigational product; N = number of subjects; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.
Terms coded using MedDRA® version 16.0.
Percentages were calculated using the N of subjects in the column headers.
Data Source: Study ZRHR-PK-02-JP Clinical study report Appendix 15, Table 15.2.6.3.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

2. Adverse Events Reported in Single-use Clinical Studies – THS Menthol

Table 5 ZRHM-PK-05-JP. Summary of Adverse Events by SOC and PT

System Organ Class Preferred term	Sequence					
	THS 2.2 Menthol - mCC (N=22)	mCC - THS 2.2 Menthol (N=22)	THS 2.2 Menthol - NRT gum (N=9)	NRT gum - THS 2.2 Menthol (N=9)	Exposed not randomized (N=11)	Overall Safety (N=73)
Number (%) subjects with any AEs	1 (4.5%)	2 (9.1%)	0	1 (11.1%)	0	4 (5.5%)
Investigations						
Bilirubin conjugated increased	0	1 (4.5%)	0	0	0	1 (1.4%)
Blood bilirubin increased	0	1 (4.5%)	0	0	0	1 (1.4%)
Hemoglobin decreased	0	0	0	1 (11.1%)	0	1 (1.4%)
Lymphocyte count increased	1 (4.5%)	0	0	0	0	1 (1.4%)

Abbreviations: AE = adverse event; mCC = menthol conventional cigarette; N = number of subjects; NRT gum = nicotine replacement therapy gum; THS 2.2 = Tobacco Heating System 2.2.
Terms coded using MedDRA® version 16.0.
Percentages were calculated using the N of subjects in the column headers.
Data Source: Study ZRHM-PK-05-JP Clinical study report Appendix 15, Table 15.2.6.2.1.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 6 ZRHM-PK-06-US. Summary of Adverse Events by SOC and PT

System Organ Class Preferred term	Sequence THS 2.2 Menthol - mCC (N=22)	mCC - THS 2.2 Menthol (N=22)	THS 2.2 Menthol - NNS (N=9)	NNS - THS 2.2 Menthol (N=9)	Overall Safety (N=64)
Number (%) subjects with any AEs	7 (31.8%)	7 (31.8%)	3 (33.3%)	2 (22.2%)	19 (29.7%)
Nervous system disorders	5 (22.7%)	3 (13.6%)	1 (11.1%)	0	9 (14.1%)
Headache	5 (22.7%)	2 (9.1%)	0	0	7 (10.9%)
Dizziness	0	1 (4.5%)	1 (11.1%)	0	2 (3.1%)
Gastrointestinal disorders	1 (4.5%)	1 (4.5%)	1 (11.1%)	1 (11.1%)	4 (6.3%)
Vomiting	1 (4.5%)	1 (4.5%)	1 (11.1%)	0	3 (4.7%)
Nausea	1 (4.5%)	0	1 (11.1%)	0	2 (3.1%)
Toothache	0	0	0	1 (11.1%)	1 (1.6%)
Respiratory, thoracic, and mediastinal disorders	1 (4.5%)	2 (9.1%)	1 (11.1%)	0	4 (6.3%)
Nasal congestion	0	2 (9.1%)	1 (11.1%)	0	3 (4.7%)
Sneezing	1 (4.5%)	0	0	0	1 (1.6%)
Infections and infestations	1 (4.5%)	1 (4.5%)	0	1 (11.1%)	3 (4.7%)
Hordeolum	1 (4.5%)	0	0	0	1 (1.6%)
Upper respiratory tract infection	0	0	0	1 (11.1%)	1 (1.6%)
Viral upper respiratory tract infection	0	1 (4.5%)	0	0	1 (1.6%)
Investigations	0	2 (9.1%)	0	0	2 (3.1%)
Spirometry abnormal	0	2 (9.1%)	0	0	2 (3.1%)
Skin and subcutaneous tissue disorders	1 (4.5%)	0	1 (11.1%)	0	2 (3.1%)
Rash	1 (4.5%)	0	1 (11.1%)	0	2 (3.1%)
Eye disorders	0	0	1 (11.1%)	0	1 (1.6%)
Eye pruritus	0	0	1 (11.1%)	0	1 (1.6%)
Ocular hyperemia	0	0	1 (11.1%)	0	1 (1.6%)

Abbreviations: AE = adverse event; mCC = menthol conventional cigarette; N = number of subjects; NNS = nicotine nasal spray; THS 2.2 = Tobacco Heating System 2.2.
Terms coded using MedDRA version 16.0.
Percentages were calculated using the N of subjects in the column headers. None of the subjects who were exposed to THS 2.2 but not randomized reported an AE.
Data Source: Study ZRHM-PK06-US Clinical study report Appendix 15, Table 15.2.6.2.1.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 7 **ZRHM-PK-06-US. Summary of Adverse Events Related to Investigational Product and Reference Point Product by SOC and PT**

System Organ Class Preferred term	Sequence					
	THS 2.2 Menthol - mCC (N=22)	mCC - THS 2.2 Menthol (N=22)	THS 2.2 Menthol - NNS (N=9)	NNS - THS 2.2 Menthol (N=9)	Exposed not randomized (N=2)	Overall Safety (N=64)
Number (%) subjects with any AEs related to IP	2 (9.1%)	1 (4.5%)	1 (11.1%)	0	0	4 (6.3%)
Nervous system disorders	1 (4.5%)	0	0	0	0	1 (1.6%)
Headache	1 (4.5%)	0	0	0	0	1 (1.6%)
Gastrointestinal disorders	1 (4.5%)	1 (4.5%)	1 (11.1%)	0	0	3 (4.7%)
Vomiting	1 (4.5%)	1 (4.5%)	0	0	0	2 (3.1%)
Nausea	1 (4.5%)	0	1 (11.1%)	0	0	2 (3.1%)
Number (%) subjects with any AEs related to NNS	1 (4.5%)	0	0	0	0	1 (1.6%)
Respiratory, thoracic, and mediastinal disorders	1 (4.5%)	0	0	0	0	1 (1.6%)
Sneezing	1 (4.5%)	0	0	0	0	1 (1.6%)

Abbreviations: AE = adverse event; IP = investigational product; mCC = menthol conventional cigarette; N = number of subjects; NNS = nicotine nasal spray; THS 2.2 = Tobacco Heating System 2.2.
Terms coded using MedDRA version 16.0.
Percentages were calculated using the N of subjects in the column headers.
Data Source: Study ZRHM-PK06-US Clinical study report Appendix 15, Table 15.2.6.3.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

3. Adverse Events Reported in 5-day Clinical Studies – THS Regular

Table 8 ZRHR-REXC-03-EU. Summary of Adverse Events by SOC and PT

System Organ Class Preferred Term	Study Arm THS 2.2 (N=80)	CC (N=41)	SA (N=39)	Exposed not Randomized (N=9)	Overall Safety (N=169)
Number (%) subjects with any AEs	50 (62.5%)	29 (70.7%)	24 (61.5%)	9 (100%)	112 (66.3%)
Nervous system disorders	27 (33.8%)	19 (46.3%)	13 (33.3%)	3 (33.3%)	62 (36.7%)
Headache	24 (30.0%)	16 (39.0%)	13 (33.3%)	3 (33.3%)	56 (33.1%)
Syncope	6 (7.5%)	4 (9.8%)	0	0	10 (5.9%)
Investigations	7 (8.8%)	6 (14.6%)	3 (7.7%)	3 (33.3%)	19 (11.2%)
Spirometry abnormal	4 (5.0%)	3 (7.3%)	2 (5.1%)	3 (33.3%)	12 (7.1%)
Lymphocyte count increased	1 (1.3%)	0	1 (2.6%)	1 (11.1%)	3 (1.8%)
Carboxyhaemoglobin increased	0	2 (4.9%)	0	0	2 (1.2%)
Blood bilirubin increased	1 (1.3%)	0	0	0	1 (0.6%)
Eosinophil count increased	1 (1.3%)	0	0	0	1 (0.6%)
Neutrophil count decreased	0	1 (2.4%)	0	0	1 (0.6%)
Gastrointestinal disorders	7 (8.8%)	5 (12.2%)	3 (7.7%)	2 (22.2%)	17 (10.1%)
Constipation	3 (3.8%)	2 (4.9%)	0	1 (11.1%)	6 (3.6%)
Toothache	1 (1.3%)	1 (2.4%)	0	1 (11.1%)	3 (1.8%)
Abdominal distension	0	0	2 (5.1%)	0	2 (1.2%)
Gastrooesophageal reflux disease	0	2 (4.9%)	0	0	2 (1.2%)
Mouth ulceration	2 (2.5%)	0	0	0	2 (1.2%)
Abdominal pain upper	0	0	1 (2.6%)	0	1 (0.6%)
Nausea	0	0	1 (2.6%)	0	1 (0.6%)
Oral pain	1 (1.3%)	0	0	0	1 (0.6%)
Vomiting	0	0	1 (2.6%)	0	1 (0.6%)
Respiratory, thoracic, and mediastinal disorders	10 (12.5%)	4 (9.8%)	0	1 (11.1%)	15 (8.9%)
Oropharyngeal pain	7 (8.8%)	3 (7.3%)	0	0	10 (5.9%)
Cough	3 (3.8%)	0	0	1 (11.1%)	4 (2.4%)
Epistaxis	0	1 (2.4%)	0	0	1 (0.6%)
Metabolism and nutrition disorders	4 (5.0%)	3 (7.3%)	4 (10.3%)	2 (22.2%)	13 (7.7%)
Hypertriglyceridaemia	3 (3.8%)	2 (4.9%)	2 (5.1%)	0	7 (4.1%)
Hypercholesterolaemia	0	1 (2.4%)	1 (2.6%)	0	2 (1.2%)
Hyperglycaemia	0	0	1 (2.6%)	1 (11.1%)	2 (1.2%)
Hyperkalaemia	1 (1.3%)	0	0	1 (11.1%)	2 (1.2%)
Renal and urinary disorders	7 (8.8%)	4 (9.8%)	2 (5.1%)	0	13 (7.7%)
Polyuria	6 (7.5%)	4 (9.8%)	2 (5.1%)	0	12 (7.1%)
Leukocyturia	1 (1.3%)	0	0	0	1 (0.6%)
Musculoskeletal and connective tissue disorders	6 (7.5%)	2 (4.9%)	4 (10.3%)	0	12 (7.1%)
Back pain	3 (3.8%)	2 (4.9%)	3 (7.7%)	0	8 (4.7%)
Arthralgia	1 (1.3%)	0	0	0	1 (0.6%)
Musculoskeletal chest pain	1 (1.3%)	0	0	0	1 (0.6%)
Myalgia	0	0	1 (2.6%)	0	1 (0.6%)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

System Organ Class Preferred Term	Study Arm THS 2.2 (N=80)	CC (N=41)	SA (N=39)	Exposed not Randomized (N=9)	Overall Safety (N=169)
Pain in extremity	1 (1.3%)	0	0	0	1 (0.6%)
Vascular disorders	3 (3.8%)	2 (4.9%)	3 (7.7%)	2 (22.2%)	10 (5.9%)
Hypertension	1 (1.3%)	1 (2.4%)	2 (5.1%)	2 (22.2%)	6 (3.6%)
Hypotension	2 (2.5%)	1 (2.4%)	1 (2.6%)	0	4 (2.4%)
Infections and infestations	4 (5.0%)	2 (4.9%)	1 (2.6%)	0	7 (4.1%)
Nasopharyngitis	3 (3.8%)	1 (2.4%)	1 (2.6%)	0	5 (3.0%)
Herpes virus infection	0	1 (2.4%)	0	0	1 (0.6%)
Urinary tract infection	1 (1.3%)	0	0	0	1 (0.6%)
General disorders and administration site conditions	2 (2.5%)	1 (2.4%)	3 (7.7%)	0	6 (3.6%)
Influenza like illness	0	1 (2.4%)	3 (7.7%)	0	4 (2.4%)
Vessel puncture site reaction	2 (2.5%)	0	0	0	2 (1.2%)
Ear and labyrinth disorders	3 (3.8%)	0	2 (5.1%)	0	5 (3.0%)
Vertigo	3 (3.8%)	0	2 (5.1%)	0	5 (3.0%)
Reproductive system and breast disorders	3 (3.8%)	1 (2.4%)	1 (2.6%)	0	5 (3.0%)
Dysmenorrhoea	3 (3.8%)	1 (2.4%)	1 (2.6%)	0	5 (3.0%)
Cardiac disorders	1 (1.3%)	2 (4.9%)	0	1 (11.1%)	4 (2.4%)
Tachycardia	0	2 (4.9%)	0	0	2 (1.2%)
Myocardial ischaemia	1 (1.3%)	0	0	0	1 (0.6%)
Ventricular extrasystoles	0	0	0	1 (11.1%)	1 (0.6%)
Blood and lymphatic disorders	0	0	0	2 (22.2%)	2 (1.2%)
Leukocytosis	0	0	0	2 (22.2%)	2 (1.2%)
Eye disorders	0	0	1 (2.6%)	0	1 (0.6%)
Conjunctivitis	0	0	1 (2.6%)	0	1 (0.6%)
Hepatobiliary disorders	1 (1.3%)	0	0	0	1 (0.6%)
Hyperbilirubinaemia	1 (1.3%)	0	0	0	1 (0.6%)
Psychiatric disorders	0	0	1 (2.6%)	0	1 (0.6%)
Nicotine dependence	0	0	1 (2.6%)	0	1 (0.6%)
Skin and subcutaneous tissue disorders	1 (1.3%)	0	0	0	1 (0.6%)
Hyperhidrosis	1 (1.3%)	0	0	0	1 (0.6%)

Abbreviations: AE = adverse event; CC = conventional cigarette; N = number of subjects; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.
Terms coded using MedDRA® version 16.0.
Percentages were calculated using the N of subjects in the column headers.
Data Source: Study ZRHR-REXC-03-EU Clinical study report Appendix 15, Table 15.2.6.2.1.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 9 ZRHR-REXC-03-EU. Summary of Adverse Events (PT) Related to Investigational Product

Preferred Term	Study Arm				
	THS 2.2 (N=80)	CC (N=41)	SA (N=39)	Exposed not Randomized (N=9)	Overall Safety (N=169)
Number (%) subjects with any AEs related to IP	14 (17.5%)	7 (17.1%)	0	2 (22.2%)	23 (13.6%)
Spirometry abnormal	4 (5.0%)	3 (7.3%)	0	2 (22.2%)	9 (5.3%)
Syncope	1 (1.3%)	2 (4.9%)	0	0	3 (1.8%)
Carboxyhaemoglobin increased	0	2 (4.9%)	0	0	2 (1.2%)
Cough	2 (2.5%)	0	0	0	2 (1.2%)
Vertigo	2 (2.5%)	0	0	0	2 (1.2%)
Oral pain	1 (1.3%)	0	0	0	1 (0.6%)
Oropharyngeal pain	1 (1.3%)	0	0	0	1 (0.6%)
Hypertriglyceridaemia	1 (1.3%)	0	0	0	1 (0.6%)
Musculoskeletal chest pain	1 (1.3%)	0	0	0	1 (0.6%)
Myocardial ischaemia	1 (1.3%)	0	0	0	1 (0.6%)
Hyperhidrosis	1 (1.3%)	0	0	0	1 (0.6%)

Abbreviations: AE = adverse event; CC = conventional cigarette; IP = investigational product; N = number of subjects; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.
Terms coded using MedDRA® version 16.0.
Percentages were calculated using the N of subjects in the column headers.
Data Source: : Study ZRHR-REXC-03-EU Clinical study report Appendix 15, Table 15.2.6.3.

Table 10 ZRHR-REXC-04-JP. Summary of Adverse Events by SOC and PT

System Organ Class Preferred Term	Study Arm				
	THS 2.2 (N=80)	CC (N=40)	SA (N=40)	Exposed Not Randomized (N=6)	Overall Safety (N=166)
Number (%) of subjects with any AEs	6 (7.5%)	3 (7.5%)	1 (2.5%)	0	10 (6.0%)
Investigations	6 (7.5%)	3 (7.5%)	1 (2.5%)	0	10 (6.0%)
Blood triglycerides increased	2 (2.5%)	2 (5.0%)	0	0	4 (2.4%)
Neutrophil count decreased	2 (2.5%)	1 (2.5%)	0	0	3 (1.8%)
Blood potassium decreased	1 (1.3%)	0	0	0	1 (0.6%)
Hemoglobin decreased	0	0	1 (2.5%)	0	1 (0.6%)
Protein urine present	1 (1.3%)	0	0	0	1 (0.6%)
White blood cell count decreased	0	1 (1.25%)	0	0	1 (0.6%)

Abbreviations: AE = adverse event; CC = conventional cigarette; N = number of subjects; SA = smoking abstinence; THS 2.2 = Tobacco Heating System 2.2.
Terms coded using MedDRA® version 16.0.
Percentages were calculated using the N of subjects in the column headers.
Data Source: Study ZRHR-REXC-04-JP Clinical study report Appendix 15, Table 15.2.6.2.1.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

4. Adverse Events Reported in 3-month Clinical Studies – Confinement Period - THS Menthol

Table 11 ZRHM-REXA-07-JP. Summary of Adverse Events by SOC and PT – Confinement Period

System Organ Class	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)		Overall Safety (N=160)	
Preferred Term	**n (%)**	**Events**	**n (%)**	**Events**	**n (%)**	**Events**	**n (%)**	**Events**
Any adverse events	6 (7.7)	9	1 (2.4)	2	8 (20.0)	10	15 (9.4)	21
Investigations	3 (3.8)	4	1 (2.4)	1	2 (5.0)	3	6 (3.8)	8
White blood cell count decreased	1 (1.3)	1	0	0	1 (2.5)	1	2 (1.3)	2
Alanine aminotransferase increased	0	0	0	0	1 (2.5)	1	1 (0.6)	1
Aspartate aminotransferase increased	0	0	0	0	1 (2.5)	1	1 (0.6)	1
Blood bilirubin increased	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Blood triglycerides increased	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Haemoglobin decreased	0	0	1 (2.4)	1	0	0	1 (0.6)	1
Neutrophil count decreased	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Gastrointestinal disorders	2 (2.6)	3	1 (2.4)	1	1 (2.5)	1	4 (2.5)	5
Constipation	1 (1.3)	1	1 (2.4)	1	1 (2.5)	1	3 (1.9)	3
Diarrhoea	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Rectal prolapse	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Infections and infestations	1 (1.3)	1	0	0	2 (5.0)	2	3 (1.9)	3
Hordeolum	1 (1.3)	1			0	0	1 (0.6)	1
Nasopharyngitis	0	0			1 (2.5)	1	1 (0.6)	1
Periodontitis	0	0			1 (2.5)	1	1 (0.6)	1
Ear and labyrinth disorders	0	0	0	0	2 (5.0)	2	2 (1.3)	2
Vertigo					2 (5.0)	2	2 (1.3)	2
General disorders and administration site conditions	0	0	0	0	1 (2.5)	1	1 (0.6)	1
Pyrexia					1 (2.5)	1	1 (0.6)	1
Injury, poisoning and procedural complications	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Scar	1 (1.3)	1					1 (0.6)	1
Psychiatric disorders	0	0	0	0	1 (2.5)	1	1 (0.6)	1
Insomnia					1 (2.5)	1	1 (0.6)	1

Note: The Overall Safety refers to all subjects exposed to THSm2.2. Only subjects randomized are summarized in post-randomization tables.
Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.
Note: Percentages are based on the number of subjects indicated in the column header (N).
Source: Study ZRHM-REXA-07 Clinical study report Appendix: 15.3.6.1.1, Table 15.2.6.3.1

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 12 **ZRHM-REXA-08-US. Summary of Adverse Events by SOC and PT - Confinement Period**

System Organ Class	THSm2.2 (N=80)		mCC (N=41)		SA (N=39)		Overall Safety (N=160)	
Preferred Term	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**
Any adverse events	23 (28.8)	39	11 (26.8)	14	13 (33.3)	27	47 (29.4)	80
Blood and lymphatic system disorders	1 (1.3)	1	0		0		1 (0.6)	1
Anaemia	1 (1.3)	1					1 (0.6)	1
Eye disorders	0		0		1 (2.6)	1	1 (0.6)	1
Scleral haemorrhage					1 (2.6)	1	1 (0.6)	1
Gastrointestinal disorders	9 (11.3)	10	2 (4.9)	2	3 (7.7)	3	14 (8.8)	15
Abdominal pain	0		1 (2.4)	1	0		1 (0.6)	1
Constipation	2 (2.5)	2	0		0		2 (1.3)	2
Dry mouth	1 (1.3)	1	0		1 (2.6)	1	2 (1.3)	2
Flatulence	1 (1.3)	1	0		0		1 (0.6)	1
Lip dry	1 (1.3)	1	1 (2.4)	1	0		2 (1.3)	2
Nausea	2 (2.5)	2	0		1 (2.6)	1	3 (1.9)	3
Paraesthesia oral	1 (1.3)	1	0		0		1 (0.6)	1
Salivary hypersecretion	1 (1.3)	1	0		0		1 (0.6)	1
Toothache	1 (1.3)	1	0		1 (2.6)	1	2 (1.3)	2
General disorders and administration site conditions	0		0		1 (2.6)	1	1 (0.6)	1
Feeling hot					1 (2.6)	1	1 (0.6)	1
Infections and infestations	1 (1.3)	1	2 (4.9)	2	0		3 (1.9)	3
Oral herpes	0		1 (2.4)	1			1 (0.6)	1
Pharyngitis	1 (1.3)	1	0				1 (0.6)	1
Upper respiratory tract infection	0		1 (2.4)	1			1 (0.6)	1
Injury, poisoning and procedural complications	0		3 (7.3)	3	1 (2.6)	1	4 (2.5)	4
Administration related reaction			2 (4.9)	2	0		2 (1.3)	2
Contusion			1 (2.4)	1	0		1 (0.6)	1
Muscle strain			0		1 (2.6)	1	1 (0.6)	1
Investigations	9 (11.3)	10	3 (7.3)	3	4 (10.3)	4	16 (10.0)	17
Blood potassium increased	0		1 (2.4)	1	0		1 (0.6)	1
Blood triglycerides increased	1 (1.3)	1	0		1 (2.6)	1	2 (1.3)	2
Forced expiratory volume decreased	1 (1.3)	1	0		0		1 (0.6)	1
Haemoglobin decreased	3 (3.8)	3	0		2 (5.1)	2	5 (3.1)	5

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

System Organ Class	THSm2.2 (N=80)		mCC (N=41)		SA (N=39)		Overall Safety (N=160)	
Preferred Term	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**
Lymphocyte count increased	2 (2.5)	2	1 (2.4)	1	0		3 (1.9)	3
Neutrophil count decreased	1 (1.3)	1	0		0		1 (0.6)	1
Protein urine	0		0		1 (2.6)	1	1 (0.6)	1
Vital capacity decreased	1 (1.3)	1	0		0		1 (0.6)	1
Carbon monoxide diffusing capacity decreased	1 (1.3)	1	1 (2.4)	1	0		2 (1.3)	2
Metabolism and nutrition disorders	0		0		1 (2.6)	1	1 (0.6)	1
Increased appetite					1 (2.6)	1	1 (0.6)	1
Musculoskeletal and connective tissue disorders	2 (2.5)	3	0		1 (2.6)	1	3 (1.9)	4
Back pain	1 (1.3)	1			1 (2.6)	1	2 (1.3)	2
Muscle spasms	1 (1.3)	1			0		1 (0.6)	1
Pain in extremity	1 (1.3)	1			0		1 (0.6)	1
Nervous system disorders	6 (7.5)	6	0		3 (7.7)	5	9 (5.6)	11
Dizziness	1 (1.3)	1			2 (5.1)	2	3 (1.9)	3
Headache	3 (3.8)	3			2 (5.1)	3	5 (3.1)	6
Paraesthesia	1 (1.3)	1			0		1 (0.6)	1
Presyncope	1 (1.3)	1			0		1 (0.6)	1
Psychiatric disorders	1 (1.3)	1	1 (2.4)	1	3 (7.7)	5	5 (3.1)	7
Abnormal dreams	1 (1.3)	1	0		0		1 (0.6)	1
Anxiety	0		0		1 (2.6)	1	1 (0.6)	1
Depressed mood	0		0		1 (2.6)	1	1 (0.6)	1
Insomnia	0		0		1 (2.6)	1	1 (0.6)	1
Nightmare	0		1 (2.4)	1	0		1 (0.6)	1
Restlessness	0		0		1 (2.6)	1	1 (0.6)	1
Tension	0		0		1 (2.6)	1	1 (0.6)	1
Respiratory, thoracic and mediastinal disorders	4 (5.0)	6	1 (2.4)	1	3 (7.7)	3	8 (5.0)	10
Cough	1 (1.3)	1	0		0		1 (0.6)	1
Dyspnoea	1 (1.3)	1	0		0		1 (0.6)	1
Nasal congestion	1 (1.3)	1	1 (2.4)	1	0		2 (1.3)	2
Nasal discomfort	0		0		1 (2.6)	1	1 (0.6)	1
Oropharyngeal pain	1 (1.3)	1	0		1 (2.6)	1	2 (1.3)	2
Sinus congestion	0		0		1 (2.6)	1	1 (0.6)	1
Sneezing	1 (1.3)	1	0		0		1 (0.6)	1
Upper-airway cough syndrome	1 (1.3)	1	0		0		1 (0.6)	1
Skin and subcutaneous tissue disorders	1 (1.3)	1	1 (2.4)	2	2 (5.1)	2	4 (2.5)	5
Acne	1 (1.3)	1	0		0		1 (0.6)	1

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

System Organ Class	THSm2.2 (N=80)		mCC (N=41)		SA (N=39)		Overall Safety (N=160)	
Preferred Term	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**
Cold sweat	0		0		1 (2.6)	1	1 (0.6)	1
Erythema	0		0		1 (2.6)	1	1 (0.6)	1
Pruritus	0		1 (2.4)	1	0		1 (0.6)	1
Rash	0		1 (2.4)	1	0		1 (0.6)	1

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol
Note: Percentages are based on the number of subjects indicated in the column header (N).
Source: Study ZRHM-REXA-08-US Clinical study report Appendix 15.3.6.1, Table 15.2.6.3

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

5. Adverse Events Reported in 3-month Clinical Studies – Ambulatory Period - THS Menthol

Table 13 ZRHM-REXA-07-JP. Summary of Adverse Events by SOC and PT – Ambulatory Period

System Organ Class	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)		Overall Safety (N=160)	
Preferred Term	**n (%)**	**Events**	**n (%)**	**Events**	**n (%)**	**Events**	**n (%)**	**Events**
Any adverse events	29 (37.2)	40	14 (33.3)	20	9 (22.5)	12	52 (32.5)	72
Investigations	23 (29.5)	29	8 (19.0)	11	8 (20.0)	10	39 (24.4)	50
Haemoglobin decreased	11 (14.1)	13	3 (7.1)	4	3 (7.5)	4	17 (10.6)	21
Neutrophil count decreased	4 (5.1)	4	1 (2.4)	1	2 (5.0)	2	7 (4.4)	7
Blood triglycerides increased	3 (3.8)	3	1 (2.4)	1	2 (5.0)	2	6 (3.8)	6
Gamma-glutamyltransferase increased	2 (2.6)	2	0	0	0	0	2 (1.3)	2
Protein urine present	0	0	1 (2.4)	1	1 (2.5)	1	2 (1.3)	2
Alanine aminotransferase increased	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Blood cholesterol increased	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Blood creatinine increased	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Blood glucose increased	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Eosinophil count increased	0	0	0	0	1 (2.5)	1	1 (0.6)	1
Glucose urine present	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Lymphocyte count decreased	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Lymphocyte count increased	0	0	1 (2.4)	1	0	0	1 (0.6)	1
Neutrophil count increased	0	0	1 (2.4)	1	0	0	1 (0.6)	1
Protein total decreased	0	0	1 (2.4)	1	0	0	1 (0.6)	1
White blood cell count decreased	1 (1.3)	1	0	0	0	0	1 (0.6)	1
White blood cell count increased	0	0	1 (2.4)	1	0	0	1 (0.6)	1
Infections and infestations	5 (6.4)	6	3 (7.1)	3	1 (2.5)	1	9 (5.6)	10
Nasopharyngitis	3 (3.8)	3	1 (2.4)	1	1 (2.5)	1	5 (3.1)	5
Pharyngitis	1 (1.3)	2	1 (2.4)	1	0	0	2 (1.3)	3
Hordeolum	0	0	1 (2.4)	1	0	0	1 (0.6)	1
Rhinitis	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Gastrointestinal disorders	2 (2.6)	2	1 (2.4)	1	0	0	3 (1.9)	3
Constipation	1 (1.3)	1	0	0			1 (0.6)	1
Dental caries	1 (1.3)	1	0	0			1 (0.6)	1
Toothache	0	0	1 (2.4)	1			1 (0.6)	1
Injury, poisoning and procedural complications	1 (1.3)	1	0	0	1 (2.5)	1	2 (1.3)	2
Hand fracture	0	0			1 (2.5)	1	1 (0.6)	1
Tooth fracture	1 (1.3)	1			0	0	1 (0.6)	1
Blood and lymphatic system disorders	0	0	1 (2.4)	1	0	0	1 (0.6)	1
Anaemia			1 (2.4)	1			1 (0.6)	1

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

System Organ Class	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)		Overall Safety (N=160)	
Preferred Term	**n (%)**	**Events**	**n (%)**	**Events**	**n (%)**	**Events**	**n (%)**	**Events**
Musculoskeletal and connective tissue disorders	0	0	1 (2.4)	1	0	0	1 (0.6)	1
Intervertebral disc protrusion			1 (2.4)	1			1 (0.6)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (2.4)	1	0	0	1 (0.6)	1
Uterine leiomyoma			1 (2.4)	1			1 (0.6)	1
Nervous system disorders	0	0	1 (2.4)	1	0	0	1 (0.6)	1
Headache			1 (2.4)	1			1 (0.6)	1
Psychiatric disorders	0	0	1 (2.4)	1	0	0	1 (0.6)	1
Insomnia			1 (2.4)	1			1 (0.6)	1
Respiratory, thoracic and mediastinal disorders	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Oropharyngeal pain	1 (1.3)	1					1 (0.6)	1
Skin and subcutaneous tissue disorders	1 (1.3)	1	0	0	0	0	1 (0.6)	1
Eczema	1 (1.3)	1					1 (0.6)	1

Note: The Overall Safety refers to all subjects exposed to THSm2.2. Only subjects randomized are summarized in post-randomization tables.
Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.
Note: Percentages are based on the number of subjects indicated in the column header (N).
Source: Study ZRHM-REXA-07 Clinical study report Appendix: 15.3.6.1.1, Table 15.2.6.3.1

Table 14 ZRHM-REXA-07-JP. Summary of Adverse Events by SOC and PT - Safety Follow-up Period

System Organ Class	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)		Overall Safety (N=160)	
Preferred Term	**n (%)**	**Events**	**n (%)**	**Events**	**n (%)**	**Events**	**n (%)**	**Events**
Any adverse events	0	0	0	0	0	0	0	0

Note: The Overall Safety refers to all subjects exposed to THSm2.2. Only subjects randomized are summarized in post-randomization tables.
Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.
Note: Percentages are based on the number of subjects indicated in the column header (N).
Source: Study ZRHM-REXA-07 Clinical study report Appendix: 15.3.6.1.1, Table 15.2.6.3.1

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 15 ZRHM-REXA-08-US. Summary of Adverse Events by SOC and PT - Ambulatory Period

System Organ Class	THSm2.2 (N=80)		mCC (N=41)		SA (N=39)		Overall Safety (N=160)	
Preferred Term	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**
Any adverse events	41 (51.3)	74	14 (34.2)	18	14 (35.9)	22	69 (43.1)	114
Blood and lymphatic system disorders	0		0		1 (2.6)	1	1 (0.6)	1
Leukocytosis					1 (2.6)	1	1 (0.6)	1
Ear and labyrinth disorders	0		0		1 (2.6)	1	1 (0.6)	1
Ear pain					1 (2.6)	1	1 (0.6)	1
Eye disorders	2 (2.5)	2	0		0		2 (1.3)	2
Conjunctivitis	1 (1.3)	1					1 (0.6)	1
Eye pruritus	1 (1.3)	1					1 (0.6)	1
Gastrointestinal disorders	7 (8.8)	10	0		0		7 (4.4)	10
Abdominal pain	1 (1.3)	1					1 (0.6)	1
Constipation	1 (1.3)	1					1 (0.6)	1
Diarrhoea	1 (1.3)	1					1 (0.6)	1
Dry mouth	1 (1.3)	1					1 (0.6)	1
Gingival bleeding	1 (1.3)	1					1 (0.6)	1
Gingival pain	1 (1.3)	1					1 (0.6)	1
Nausea	1 (1.3)	1					1 (0.6)	1
Toothache	1 (1.3)	2					1 (0.6)	2
Vomiting	1 (1.3)	1					1 (0.6)	1
General disorders and administration site conditions	2 (2.5)	2	0		1 (2.6)	1	3 (1.9)	3
Chest discomfort	1 (1.3)	1			0		1 (0.6)	1
Non-cardiac chest pain	1 (1.3)	1			0		1 (0.6)	1
Pyrexia	0				1 (2.6)	1	1 (0.6)	1
Infections and infestations	4 (5.0)	4	3 (7.3)	3	1 (2.6)	1	8 (5.0)	8
Upper respiratory tract infection	3 (3.8)	3	3 (7.3)	3	1 (2.6)	1	7 (4.4)	7
Urinary tract infection	1 (1.3)	1	0		0		1 (0.6)	1
Injury, poisoning and procedural complications	5 (6.3)	6	1 (2.4)	1	2 (5.1)	2	8 (5.0)	9
Arthropod bite	0		0		1 (2.6)	1	1 (0.6)	1
Excoriation	1 (1.3)	1	0		0		1 (0.6)	1
Laceration	1 (1.3)	1	0		0		1 (0.6)	1
Ligament sprain	3 (3.8)	3	0		0		3 (1.9)	3
Muscle strain	0		0		1 (2.6)	1	1 (0.6)	1
Thermal burn	1 (1.3)	1	0		0		1 (0.6)	1
Wound	0		1 (2.4)	1	0		1 (0.6)	1

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

System Organ Class	THSm2.2 (N=80)		mCC (N=41)		SA (N=39)		Overall Safety (N=160)	
Preferred Term	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**
Investigations	20 (25.0)	31	8 (19.5)	10	9 (23.1)	11	37 (23.1)	52
Alanine aminotransferase increased	1 (1.3)	1	0		0		1 (0.6)	1
Aspartate aminotransferase increased	1 (1.3)	1	1 (2.4)	1	0		2 (1.3)	2
Blood bilirubin increased	1 (1.3)	3	0		1 (2.6)	1	2 (1.3)	4
Blood cholesterol increased	0		0		1 (2.6)	1	1 (0.6)	1
Blood potassium increased	2 (2.5)	2	0		0		2 (1.3)	2
Blood triglycerides increased	1 (1.3)	1	2 (4.9)	3	1 (2.6)	1	4 (2.5)	5
Forced expiratory volume decreased	1 (1.3)	1	0		0		1 (0.6)	1
Gamma-glutamyltransferase increased	1 (1.3)	1	0		0		1 (0.6)	1
Haemoglobin decreased	8 (10.0)	11	4 (9.8)	5	5 (12.8)	6	17 (10.6)	22
Lymphocyte count increased	5 (6.3)	5	1 (2.4)	1	1 (2.6)	1	7 (4.4)	7
Neutrophil count decreased	3 (3.8)	4	0		0		3 (1.9)	4
Vital capacity decreased	1 (1.3)	1	0		0		1 (0.6)	1
Carbon monoxide diffusing capacity decreased	0		0		1 (2.6)	1	1 (0.6)	1
Metabolism and nutrition disorders	2 (2.5)	3	0		1 (2.6)	1	3 (1.9)	4
Hyperglycaemia	0				1 (2.6)	1	1 (0.6)	1
Hypertriglyceridaemia	2 (2.5)	3			0		2 (1.3)	3
Nervous system disorders	1 (1.3)	1	1 (2.4)	1	1 (2.6)	1	3 (1.9)	3
Headache	1 (1.3)	1	1 (2.4)	1	1 (2.6)	1	3 (1.9)	3
Renal and urinary disorders	1 (1.3)	1	0		3 (7.7)	3	4 (2.5)	4
Dysuria	0				1 (2.6)	1	1 (0.6)	1
Proteinuria	0				1 (2.6)	1	1 (0.6)	1
Glycosuria	1 (1.3)	1			1 (2.6)	1	2 (1.3)	2
Reproductive system and breast disorders	1 (1.3)	1	0		0		1 (0.6)	1
Erectile dysfunction	1 (1.3)	1					1 (0.6)	1
Respiratory, thoracic and mediastinal disorders	5 (6.3)	9	3 (7.3)	3	0		8 (5.0)	12
Cough	2 (2.5)	2	1 (2.4)	1			3 (1.9)	3
Nasal congestion	2 (2.5)	2	1 (2.4)	1			3 (1.9)	3

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

System Organ Class	THSm2.2 (N=80)		mCC (N=41)		SA (N=39)		Overall Safety (N=160)	
Preferred Term	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**	**n(%)**	**Events**
Oropharyngeal pain	1 (1.3)	1	0				1 (0.6)	1
Pulmonary congestion	1 (1.3)	1	0				1 (0.6)	1
Respiratory disorder	1 (1.3)	1	0				1 (0.6)	1
Rhinitis allergic	0		1 (2.4)	1			1 (0.6)	1
Rhinorrhoea	1 (1.3)	1	0				1 (0.6)	1
Sinus congestion	1 (1.3)	1	0				1 (0.6)	1
Skin and subcutaneous tissue disorders	2 (2.5)	4	0		0		2 (1.3)	4
Acne	1 (1.3)	1					1 (0.6)	1
Pruritus	1 (1.3)	1					1 (0.6)	1
Rash	2 (2.5)	2					2 (1.3)	2

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol
Note: Percentages are based on the number of subjects indicated in the column header (N)
Source: Study ZRHM-REXA-08-US Clinical study report Appendix 15.3.6.1, Table 15.2.6.3.

Table 16 ZRHM-REXA-08-US. Summary of Adverse Events by SOC and PT - Safety Follow-Up Period

System Organ Class	THSm2.2 (N=80)		mCC (N=41)	SA (N=39)	Overall Safety (N=160)	
Preferred Term	**n(%)**	**Events**	**n(%) Events**	**n(%) Events**	**n(%)**	**Events**
Any adverse events	1 (1.3)	1	0	0	1 (0.6)	1
Investigations	1 (1.3)	1	0	0	1 (0.6)	1
Aspartate aminotransferase increased	1 (1.3)	1			1 (0.6)	1

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol
Note: Percentages are based on the number of subjects indicated in the column header (N).
Source: Study ZRHM-REXA-08-US Clinical study report Appendix 15.3.6.1, Table 15.2.6.3

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.