



PMI RESEARCH & DEVELOPMENT

Safety Update Report

Tobacco Heating System / iQOS

Appendix 3 Description of Clinical Studies and estimated exposure to THS products

Report Number: PMI_SURV_2016_SUR01

International Birth Date: 04 Nov 2014

Interval Covered: 01 May 2015 to 31 Dec 2015

Products Covered: Tobacco Heating System 2.2 and 2.4 / All variants

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Appendix 3.1: Description of Completed and Ongoing Clinical Studies

Study ID	Country	Study Title	Study Type	Study Population	FSI ¹	Safety Population	Actual Exposure to THS products ²	CC/NRT/SA ³	Status at DLP
ZRHR-PK-01-EU	UK	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 (THS 2.2) following single use in smoking, healthy subjects compared to conventional cigarettes and nicotine nasal spray	PK/PD Randomized Controlled Open-label Crossover Single-center	Adult smoking, healthy subjects, aged from 21 to 65 years (inclusive)	01 Nov 2013	62	62 Regular	44 CC 18 NRT	Completed
ZRHR-PK-02-JP	Japan	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmaco-	PK/PD Randomized	Smoking, healthy subjects, Japanese, aged from 23 to 65	31 Jul 2013	65	65 Regular	44 CC 18 NRT	Completed

¹ FSI = First Subject In; DLP = Data Lock Point (31 Dec 2015); THS = Tobacco Heating System; CC = Conventional Cigarettes; NRT = Nicotine Replacement Therapy; NNS = Nicotine Nasal Spray; SA = Smoking Abstinence (except for PK/PD studies).

² Actual Exposure to THS (Tobacco Heating System) products = Total number of subjects who have been randomized to receive THS products according to the study protocol

³ CC = Conventional Cigarettes ; NRT = Nicotine Replacement Therapy (NRT gum or NRT nasal spray) ; SA = Smoking Abstinence

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Study ID	Country	Study Title	Study Type	Study Population	FSI ¹	Safety Population	Actual Exposure to THS products ²	CC/NRT/SA ³	Status at DLP
		kinetic profile and safety of Tobacco Heating System 2.2 (THS 2.2) following single use in smoking, healthy subjects compared to conventional cigarettes and nicotine gum	Controlled Open-label Crossover Single-center	years (inclusive)					
ZRHR-REXC-03-EU	Poland	A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement.	Reduced exposure study Randomized Controlled Open-label 3-arm parallel group	Smoking, healthy adults, Caucasian, aged from 21 to 65 years (inclusive)	29 June 2013	169	80 Regular	41 CC 39 SA	Completed

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Study ID	Country	Study Title	Study Type	Study Population	FSI ¹	Safety Population	Actual Exposure to THS products ²	CC/NRT/SA ³	Status at DLP
ZRHR-REXC-04-JP	Japan	A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching from conventional cigarettes to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to smokers continuing to use conventional cigarettes for 5 days in confinement	Randomized Controlled Open-label 3-arm parallel group Single-center	Smoking, healthy adults, Japanese subjects, aged from 23 to 65 years (inclusive)	28 Jul 2013	166	80 Regular	40 CC 40 SA	Completed
ZRHM-PK-05-JP	Japan	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2	PK/PD Open-label Randomized Controlled Crossover Single-center	Smoking, healthy adults, Japanese subjects, aged from 23 to 65 years (inclusive)	01 Aug 2013	73	73 Menthol	43 CC 18 NRT	Completed

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Study ID	Country	Study Title	Study Type	Study Population	FSI ¹	Safety Population	Actual Exposure to THS products ²	CC/NRT/SA ³	Status at DLP
		Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine gum							
ZRHM-PK-06-US	US	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine nasal spray	PK/PD Open-label Randomized Controlled Crossover Single-center	Smoking, healthy adults, subjects without any restriction to races and ethnicities, aged from 22 to 65 years (inclusive)	03 Oct 2013	64	62	41 CC 17 NRT	Completed
ZRHM-REXA-07-JP	Japan	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions	Open-label Randomized Controlled 3-arm parallel group Multi-center	Smoking, healthy adults, Japanese, aged from 23 to 65	23 Aug 2013	231	78 Menthol	42 CC 40 SA	Completed

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Study ID	Country	Study Title	Study Type	Study Population	FSI ¹	Safety Population	Actual Exposure to THS products ²	CC/NRT/SA ³	Status at DLP
		in exposure to selected smoke constituents in 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 five days in confinement and prolonged by 85 days in an ambulatory setting		years (inclusive)					
ZRHM-REXA-08-US	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	Open-label Randomized Controlled 3-arm parallel group Multi-center	Smoking, apparently healthy adult subjects without any restriction to races and ethnicities, age minimum of 22 years	17 Dec 2013	165	80 Menthol	41 CC 39 SA	Ongoing

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Study ID	Country	Study Title	Study Type	Study Population	FSI ¹	Safety Population	Actual Exposure to THS products ²	CC/NRT/SA ³	Status at DLP
		observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for five days in confinement and prolonged by 86 days in an ambulatory setting							
ZRHR-ERS-09-US	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	Randomized Controlled 2-arm parallel group Multi-center	Smoking, healthy adult subjects, age minimum of 30 years	12 Mar 2015	929	430 Regular	426 CC	Ongoing

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Study ID	Country	Study Title	Study Type	Study Population	FSI ¹	Safety Population	Actual Exposure to THS products ²	CC/NRT/SA ³	Status at DLP
ZRHR-ERS-09-US EXT	US	A 26 week extension study to ZRHR-ERS-09-US, a 26 week, randomized, controlled, 2-arm parallel group, multi-center study, to determine biological and functional changes in healthy smokers who have switched from conventional cigarettes to THS 2.2 or who have continued to smoke conventional cigarettes.	Randomized Controlled 2-arm parallel group Multi-center	Smoking, healthy adult subjects, age minimum of 30 years	30 Sep 2015	359	172 Regular (From the 430 subjects randomized in the main study)	187 CC (From the 426 subjects randomized in the main study)	Ongoing

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Appendix 3.2: Estimated cumulative subject exposure for completed and ongoing Clinical Studies since DIBD

Study ID	Study Arm	Number of Subjects at DLP	
		Safety Population	Actual Exposure to Products ⁴
ZRHR-PK-01-EU	THS 2.2 Regular		62
	Conventional cigarettes		44
	NRT		18
	TOTAL	62	
ZRHR-PK-02-JP	THS 2.2 Regular		65
	Conventional cigarettes		44
	NRT		18
	TOTAL	65	
ZRH-REXC-03-EU	THS 2.2 Regular		80
	Conventional cigarettes		41
	Smoking abstinence		39
	TOTAL	169	
ZRHR-REXC-04-JP	THS 2.2 Regular		80
	Conventional cigarettes		40

⁴ THS 2.2 = Tobacco Heating System 2.2; CC = Conventional Cigarettes; NRT = Nicotine Replacement Therapy; SA = Smoking Abstinence

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Study ID	Study Arm	Number of Subjects at DLP	
		Safety Population	Actual Exposure to Products ⁴
	Smoking abstinence		40
	TOTAL	166	
ZRHM-PK-05-JP	THS 2.2 Menthol		73
	Conventional cigarettes		43
	NRT		18
	TOTAL	73	
ZRHM-PK-06-US	THS 2.2 Menthol		64
	Menthol conventional cigarettes		41
	NRT		17
	TOTAL	64	
ZRHM-REXA-07-JP	THS 2.2 Menthol		78
	Menthol conventional cigarettes		42
	Smoking abstinence		40
	TOTAL	231	
ZRHM-REXA-08-US	THS 2.2 Menthol		80
	Menthol conventional cigarettes		41
	Smoking abstinence		39
	TOTAL	165	

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Study ID	Study Arm	Number of Subjects at DLP	
		Safety Population	Actual Exposure to Products ⁴
ZRHR-ERS-09-US	THS 2.2 Regular		430
	Conventional cigarettes		426
	TOTAL	929	
ZRHR-ERS-09-US EXT ⁵	THS 2.2 Regular		172
	Conventional cigarettes		187
	TOTAL	359	
TOTAL BY STUDY ARM	THS 2.2 Regular		717
	THS 2.2 Menthol		295
	THS PRODUCTS		1'012
	Comparator (CC, NRT)		798
	Smoking abstinence		158
TOTAL		1'924	

⁵ As of SUR DLP (31 Dec 2015): from the 430 subjects randomized to the THS arm of the main study ZRHR-ERS-09-US, 172 subjects were continuing in the THS arm of the EXT study. Subjects in ZRHR-ERS-09-US EXT are counted in ZRHR-ERS-09-US number of subjects.

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Appendix 3.3: Estimated cumulative subject exposure by Demographics for completed and ongoing Clinical Studies

Study ID	Study arm	Sex		Race						Age	Safety Population
		Male	Female	Asian (Japanese)	Black or African American	White	Hispanic or Latino	Other ⁶	Unk		
ZRHR-PK-01-EU	THS 2.2 Regular	35	27	-	-	62	-	-	-	21 - 65	62
ZRHR-PK-02-JP	THS 2.2 Regular	34	31	65	-	-	-	-	-	23 - 65	65
ZRH-REXC-03-EU	THS 2.2 Regular	85	84	-	-	169	-	-	-	21 - 65	169
ZRHR-REXC-04-JP	THS 2.2 Regular	84	82	166	-	-	-	-	-	23 - 65	166
ZRHM-PK-05-JP	THS 2.2 Menthol	37	36	73	-	-	-	-	-	23 - 65	73
ZRHM-PK-06-US	THS 2.2 Menthol	35	29	1	35	27	-	1	-	22 - 65	64
ZRHM-REXA-07-JP	THS 2.2 Menthol	92	68	160	-	-	-	-	-	23 - 65	160 ⁷
ZRHM-REXA-08-US	THS 2.2 Menthol	98	67	-	51	104	-	9	1	Min 22	165

⁶ Other = Not Hispanic or Latino⁷ Full safety population included 231 subjects (exposed to THS/comparators). Demographics figures were available for Post randomization data i.e., for 160 subjects.**Confidentiality Statement**

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Study ID	Study arm	Sex		Race						Age	Safety Population
		Male	Female	Asian (Japanese)	Black or African American	White	Hispanic or Latino	Other ⁶	Unk		
ZRHR-ERS-09-US and ZRHR-ERS-09-US EXT ⁸	THS 2.2 Regular	553	376	-	-	-	58	8713	-	Min 30	929
TOTAL		1'053	800	464	86	362	58	881	1	NA	1'853
⁸ Subjects are counted in the ZRHR-ERS-09-US clinical study											

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