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6.1.3.2 Summary of Biomarkers of Exposure Assessments

6.1.3.2.1 Background and Overview

In accordance with the FDA MRTP draft guidance PMI conducted 4 clinical studies to "demonstrate that the level of exposure to harmful substances has been statistically significantly reduced" (FDA (Food and Drug Administration) 2012). Two studies were of 5 days exposure duration in Confinement (i.e. residential setting at the investigational site(s)) and randomly assigned smokers of conventional cigarettes (CC) to switch to either THS, or continue use with their own brand CC or abstain from using tobacco products. Two studies of 3 months duration combined a 5 days Confinement period with a subsequent long term follow up of 3 months in a near real world, Ambulatory setting (Table 1). The selection and justification of the Biomarkers of Exposure (BoExp) assessed in these studies is presented in section 6.1.3.1. The clinical study reports related to each of the individual clinical studies, are included in [Section 7.3.1]. In these studies, smoking abstinence was used as a comparator, to help evaluating to which extent the use of THS approaches smoking cessation (IOM (Institute of Medicine) 2012).

Table 1 Biomarkers of Exposure Assessment Studies

Study Code	Country	Product Variant	Number of subjects	Randomly allocated groups	Exposure Duration
[ZRHR-REXC-03-EU]	Poland	Regular	160	THS, CC, SA	5 day exposure in Confinement
[ZRHR-REXC-04-JP]	Japan	Regular	160	THS, CC, SA	5 day exposure in Confinement
[ZRHM-REXA-07-JP]	Japan	Menthol	160	THS, CC, SA	3 month exposure Ambulatory (including 5 day exposure of Confinement)
[ZRHM-REXA-08-US]	USA	Menthol	160	THS, CC, SA	3 month exposure Ambulatory (including 5 day exposure of Confinement)

Abbreviations: CC = conventional cigarettes; THS = Tobacco Heating System; SA: smoking abstinence

In Confinement, product use was monitored by the study staff at site and subjects in the THS and CC group used the THS without restriction (*ad libitum*) during an extended daily time window (16 hours). Dual use of CC and THS was not permitted. Hence, at the end of the Confinement period it was possible to measure the maximal reduction of the exposure markers after 5 days of exclusive THS use compared to continued CC use. The smoking abstinence (SA) arm provided the other point of reference in addition to CC for evaluating performance of THS.

In order to demonstrate that the reduction in exposure is sustained in an Ambulatory, near real world environment, the 3 month studies extended the evidence obtained from the

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Confinement studies over a prolonged period. While in Confinement, subjects were closely monitored by study staff, in Ambulatory condition, subjects were instructed to use exclusively their allocated product/regimen, however the use of tobacco/nicotine containing product was not a reason for discontinuation from the study. Potential dual use of THS and CC during the Ambulatory phase was recorded based on self-reporting. The 3 month studies could detect changes in exposure markers with longer half-lives, such as total NNAL, and informed on actual use of the products and their acceptance.

BoExp to harmful and potentially harmful constituents (HPHCs) or their metabolites, are used to assess exposure reduction in biological fluids, as they provide direct, quantitative evidence of the presence of HPHCs. They provide an estimate of the accumulated exposure, reflecting both individual puffing behavior and number of conventional cigarettes smoked or alternative tobacco products used (section 6.1.3.1).

The selected harmful and potentially harmful constituents (HPHCs) (Table 2) and their respective BoExp were chosen according to the following criteria:

1) The HPHCs selected are representative of a variety of chemical classes and organ toxicity classes as defined by the FDA (carcinogen (CA), cardiovascular toxicant (CT), respiratory toxicant (RT), reproductive and development toxicant (RDT), or addictive (AD)).
2) The HPHC reflects a specific toxic exposure or is a reliable surrogate of such an exposure.
3) The HPHCs assessed cover a broad range of formation temperatures.
4) The HPHC is specific to the source of exposure with other sources being minor or non-existent.
5) The BoExp to a HPHC is reliably detectable using validated, reproducible, precise analytical methods.

The justification of the selection of HPHCs and their respective BoExp is further described in section 6.1.3.1.

Table 2 List of HPHCs Considered for PMI's Clinical Program, with the Chemical Classes, Presence in Gas/Vapor (GVP) or Particulate Phases (PP) and FDA's Risk Categories

PMI's List of HPHCs Covered in Clinical Studies	None	CA	CT	RT	RDT	AD
Gas:						
carbon monoxide (GVP)	-	-	-	-	●	-
Aliphatic dienes:						
1,3-butadiene (GVP)	-	●	-	●	●	-
Carbonyls:						
acrolein (GVP)	-	-	●	●	-	-
crotonaldehyde (GVP)	-	●	-	-	-	-

(table continues)

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PMI's List of HPHCs Covered in Clinical Studies	None	CA	CT	RT	RDT	AD
Acid derivatives:						
acrylonitrile (GVP)	-	●	-	●	-	-
Epoxides:						
ethylene oxide (GVP)	-	●	-	●	●	-
Inorganic compounds:						
none	-	-	-	-	-	-
Monocyclic aromatic hydrocarbons:						
benzene (GVP)	-	●	●	-	●	-
toluene (GVP/TPM)	-	-	-	●	●	-
Aromatic amines:						
1-NA (TPM)	-	●	-	-	-	-
2-NA (TPM)	-	●	-	-	-	-
4-ABP (TPM)	-	●	-	-	-	-
o-toluidine (TPM)	-	●	-	-	-	-
N-nitrosamines:						
NNK (TPM)	-	●	-	-	-	-
NNN (TPM)	-	●	-	-	-	-
Phenols:						
None	-	-	-	-	-	-
Polycyclic aromatic hydrocarbons (PAH):						
B[a]P (TPM)	-	●	-	-	-	-
Pyrene (TPM) #	●	-	-	-	-	-
Metals and Elements:						
None	-	-	-	-	-	-
Alkaloids:						
nicotine (TPM)	-	-	-	-	●	●

Abbreviations: HPHC = harmful and potentially harmful constituents; CC = conventional cigarettes; GVP = gas/vapor phase; THS = Tobacco Heating System; TPM = Total particulate matter; SA: smoking abstinence; CA = carcinogen; CT = cardiovascular toxicant; RT = respiratory toxicant; RDT = reproductive and development toxicant; AD = addictive

Pyrene is not listed as a HPHC by FDA, but is nevertheless listed here because its metabolite 1-OHP serves as a surrogate for PAH in general.

Exposure to 16 smoke constituents, not including nicotine, was chosen in order to substantiate reduced exposure associated with THS use compared with CC smoking (Table 3). Assessment of markers which are not specific to a particular HPHC, but rather reflecting overall exposure to HPHCs, was additionally performed. This included 1- CYP1A2 activity, an enzyme which can be induced by polycyclic aromatic amines, and 2- urine mutagenicity potential, a measure to assess exposure to various carcinogenic/mutagenic substances. Results on the monitoring of exposure to nicotine and its metabolites in the 4 reduced exposure studies is summarized in [Section 6.2.2 Product Use].

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Table 3 List of PMI's Selected HPHCs with their Corresponding Biomarkers of Exposure

BoExp	HPHCs	Abbreviation (BoExp)
Monohydroxybutenyl-mercapturic acid	1,3 Butadiene	MHBMA
3-Hydroxypropylmercapturic acid	Acrolein	3 HPMA
S-Phenylmercapturic acid	Benzene	S-PMA
Carboxyhemoglobin	Carbon monoxide (CO)	COHb
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	4 (Methylnitrosamino)-1-(3-pyridyl)-1butanone (NNK)	Total NNAL
Total 1-hydroxypyrene	Pyrene #	1-OHP
Total N-nitrosonornicotine	N-nitrosonornicotine	Total NNN
4-Aminobiphenyl	4-Aminobiphenyl	4-ABP
1-Aminonaphthalene	1-Aminonaphthalene	1-NA
2-Aminonaphthalene	2-Aminonaphthalene	2-NA
o-Toluidine	*o*-Toluidine	*o*-Toluidine
2-Cyanoethylmercapturic acid	Acrylonitrile	CEMA
2-Hydroxyethylmercapturic acid	Ethylene oxide	HEMA
Total 3-hydroxybenzo[a]pyrene	Benzo[a]pyrene	3-OH-B[a]P (or B[a]P)
3-Hydroxy-1-methylpropyl-mercapturic acid	Crotonaldehyde	HMPMA
S-Benzylmercapturic acid	Toluene	S-BMA

Pyrene is not listed as a HPHC by the FDA or any other health or regulatory authority, but is nevertheless listed here because its metabolite 1-OHP serves as a surrogate for PAH in general.

In addition to exposure assessment in these 4 studies, subjective effects associated with smoking (craving, withdrawal symptoms, and product evaluation) were assessed systematically and summarized in [Section 6.2.1 PK/PD].

Also, clinical risk markers were examined in the 3 month Ambulatory studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US] and summarized in [Section 6.1.4 Clinical Risk Endpoints].

Exposure to nicotine and its metabolites were monitored; daily product consumption and puffing behavior were recorded. The recorded results are discussed in detail in [Section 6.2.2 Product Use].

Study Synopses are provided in [Section 6.1.3.4 REX Overview of Studies], while the summary of the results on BoExp across studies is presented in section [Section 6.1.3.1 Summary of BoExp Assessment].

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6.1.3.2.2 Summary of Results of Individual Studies

6.1.3.2.2.1 ZRHR-REXC-03-EU

The purpose of the study was to evaluate the reduction in selected BoExp to HPHCs with *ad libitum* use of THS for 5 days by healthy adult smokers. Information was gathered about safety in subjects using the THS product, compared to smokers who continued smoking their own preferred brand of CC. Smoking abstinence (SA) was used as a reference point to THS, to evaluate how similar the reduced exposure in the THS arm was compared to the results observed when subjects stopped smoking for the duration of the study. Smokers who were asked to abstain from smoking were not allowed to use any nicotine/tobacco-containing products.

6.1.3.2.2.1.1 Methodology of the ZRHR-REXC-03-EU

A brief description of study design, endpoints and methodology is given in Table 4.

Table 4 Methodology of the ZRHR-REXC-03-EU Study

Reduced exposure study in smokers using the Tobacco Heating System 2.2 (THS 2.2) for 5 days in a Confinement setting
Title of the study: A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes (CC), for 5 days in Confinement
Study design: This was a randomized, controlled, open-label, 3-arm, parallel group, single-center study to compare the use of THS 2.2 with continuing to smoke CC and smoking abstinence (SA) in Confinement.
Subjects: Randomized: 160; Data set for safety analysis: 169. Completed: 159; Number of subjects in the THS arm (completed): 80 (79). Number of subjects in the CC arm (completed): 41 (41); Number of subjects in the SA arm (completed): 39 (39).
Main criteria for inclusion: • Subject was aged from 21 (minimal legal smoking age + 3 years of smoking history) to 65 years (inclusive) • Subject was of Caucasian origin • Considered as healthy based on good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening • Subject was a current smoker (based on self-reporting) who had smoked for the last 4 weeks at least 10 commercially available non-menthol CC per day (no brand restrictions). The subject had smoked for at least the last 3 consecutive years. Did not plan to quit smoking in the next 3 months. • Body mass index <18.5 or ≥32.0 kg/m^2
Test Product: Tobacco Heating System 2.2 (THS 2.2) Regular. Ad-libitum use
Comparison Product: Commercially available CC with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) as labeled on the cigarette package
Reference: Smoking abstinence. No Nicotine Replacement Therapy

(table continues)

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Reduced exposure study in smokers using the Tobacco Heating System 2.2 (THS 2.2) for 5 days in a Confinement setting

Duration of Use: The exposure period lasted 5 days and was defined as the period after randomization from Day 1, 06:30 AM until Day 5, 11:00 PM, in which the subject could use the assigned product (THS 2.2 or CC), or abstained from smoking.

Analytical Method: All bioanalytical assays and laboratory assessments were carried out using validated methods. The bioanalytical methods used, and the results obtained, are documented in the [Appendix A16.1.9] of the [ZRHR-REXC03-EU] study report. The methods used are summarized in [Section 6.1.3.3 Bioanalytical Methods].

Objectives

Biomarkers of Exposure

- To demonstrate a reduction of 50% or more in 24-hour urine concentration of MHBMA, 3-HPMA, S-PMA and COHb in blood (% saturation of hemoglobin) at Day 5, in smokers switching from CC to THS, compared to smokers continuing to smoke CC.
- To determine the reduction of the other selected BoExp on Day 5 in smokers switching from CC to THS 2.2, as compared to smokers continuing to smoke CC.
- To describe the levels of all selected BoExp over the exposure period in smokers switching from CC to THS 2.2, compared to smokers continuing to smoke CC.

Xenobiotic Metabolism:

To describe the changes in CYP1A2 enzymatic activity at Day 5 in smokers switching from CC to THS, switching from CC to SA, and continuing to smoke CC, as assessed by the molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma.

Mutagenicity:

To describe the urine mutagenicity at Baseline and Day 5 of smokers switching from CC to THS compared to smokers continuing to smoke CC and smokers switching from CC to SA, as assessed with the Ames mutagenicity test (YG1024+S9).

Criteria for Evaluation:

To demonstrate a reduction of 50% or more in 24-hour urine concentration of MHBMA, 3-HPMA, S-PMA and COHb in blood (% saturation of hemoglobin) at Day 5, in smokers switching from CC to THS, compared to smokers continuing to smoke CC. The levels of selected BoExp over the exposure period in smokers switching from CC to THS were compared. The maximal BoExp reduction in smoking abstinence was determined.

6.1.3.2.2.1.2 Results

6.1.3.2.2.1.2.1 Biomarkers of Exposure

The kinetics and the magnitude of decrease of BoExp levels observed in the THS arm were approaching the levels observed in the SA arm (Figure 1). S-BMA levels did not show any difference in levels across all study arms (section 6.1.3.2.3.16).

The study demonstrated that switching from CC smoking to THS use resulted in statistically significant reductions in BoExp levels to 15 out of 16 selected HPHCs ranging from -56% to -96%, while maintaining comparable levels of nicotine after 5 days of exposure (Figure 2).

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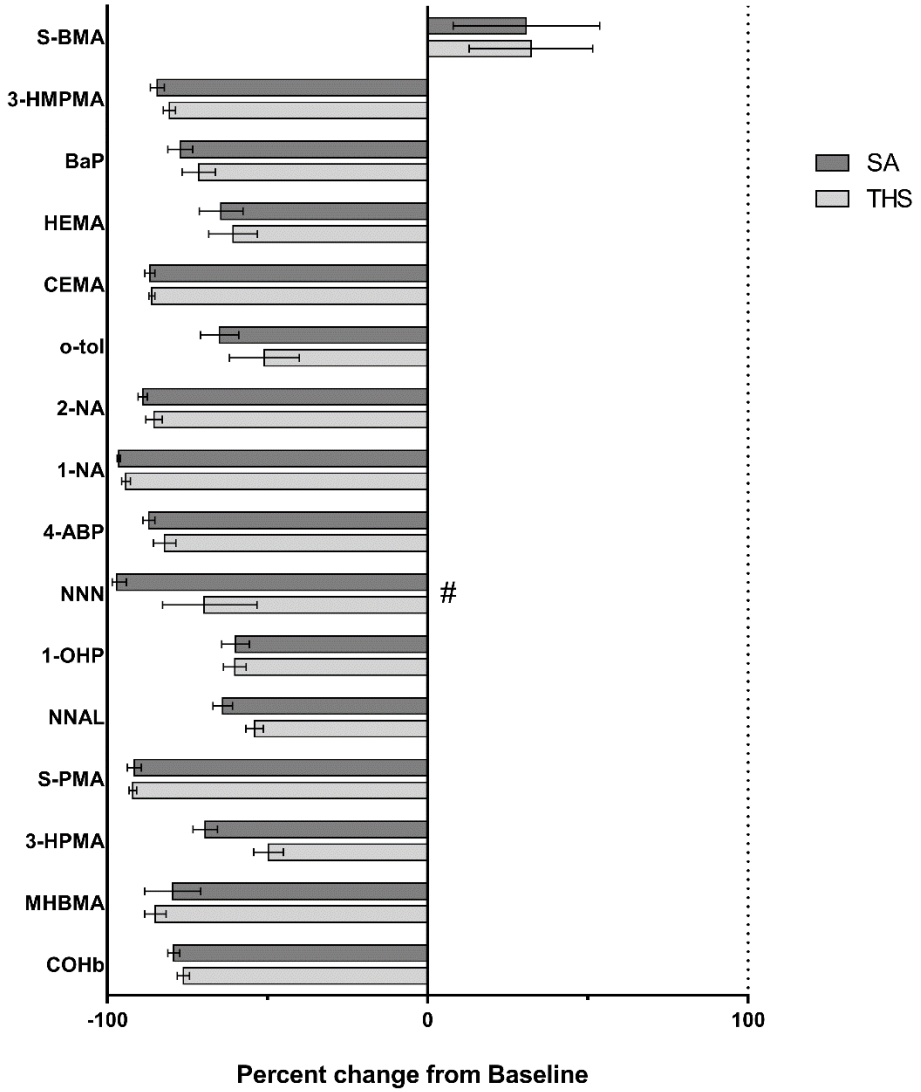


Figure 1 Percent Change from Baseline of Geometric Mean Levels and CIs at Day 5 in ZRHR-REXC-03-EU

Abbreviations: carboxyhemoglobin (COHb), monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), total 1-hydroxypyrene (1-OHP), total N-nitrosonornicotine (NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), *o*-toluidine (*o*-tol), 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy[a]benzopyrene (BaP), 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA), S-benzylmercapturic acid (S-BMA), nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence interval (CI).

Because of one outlier in the THS arm, percent change from Baseline values for total NNN are reported here as median (and Q_1; Q_3), both for the THS and SA arms.

[Data source: Clinical Study Report ZRHR-REXC-03-EU Appendix 15; COHb Table 15.2.3.5; MHBMA Table 15.2.3.5; 3-HPMA Table 15.2.3.5; S-PMA Table 15.2.3.5; NNAL Table 15.2.4.32; 1-OHP Table 15.2.4.10; NNN Table 15.2.4.12; 4-ABP Table 15.2.4.14; 1-NA Table 15.2.4.16; 2-NA Table 15.2.4.18; o-tol Table 15.2.4.20; CEMA Table 15.2.4.22; HEMA Table 15.2.4.24; BaP Table 15.2.4.26; 3-HMPMA Table 15.2.4.28; S-BMA Table 15.2.4.30]

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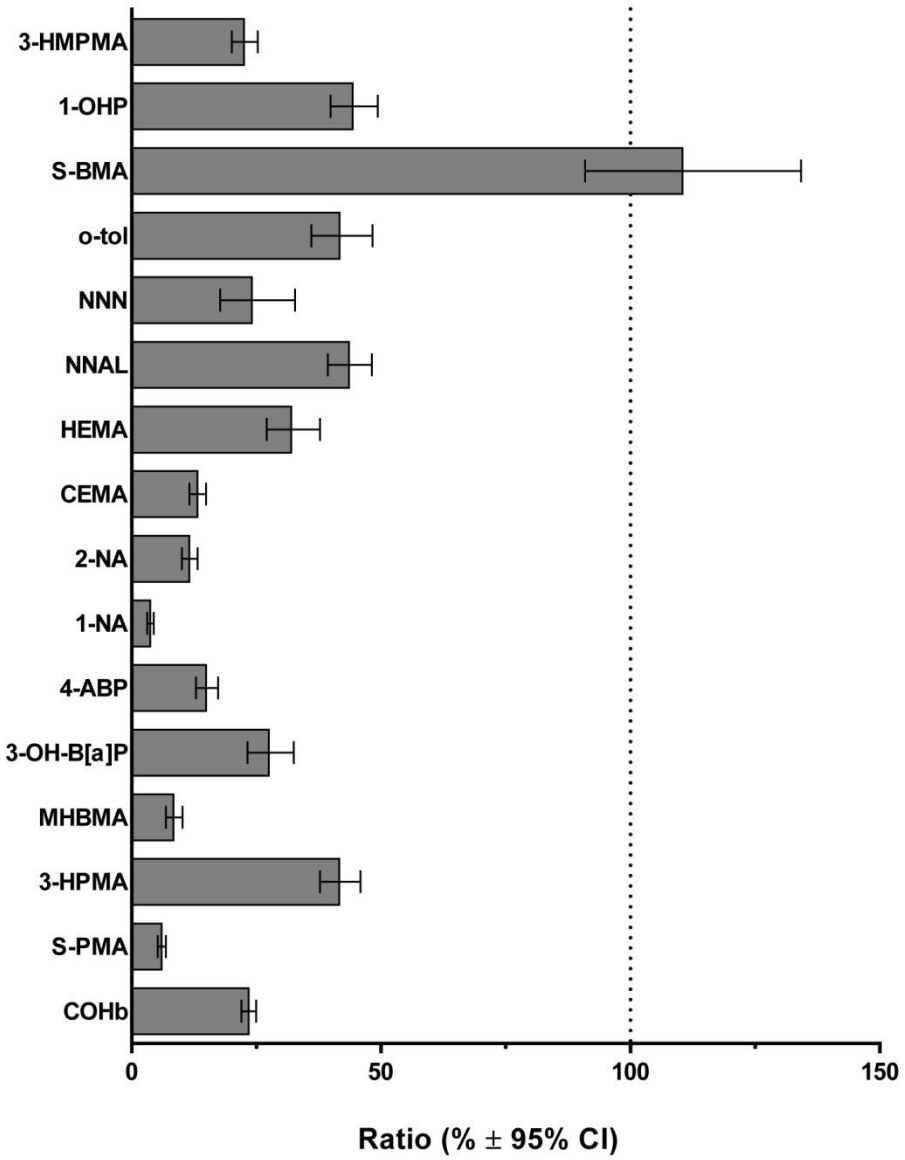


Figure 2 Adjusted Geometric LS Means and CIs from an ANCOVA Model of THS to CC at Day 5 in ZRHR-REXC-03-EU

Abbreviations: carboxyhemoglobin (COHb), S-phenylmercapturic acid (S-PMA), 3-hydroxypropylmercapturic acid (3-HPMA), monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxy(a)benzopyrene (3-OH-B[a]P), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), total N-nitrosonornicotine (NNN), S-benzylmercapturic acid (S-BMA), total 1-hydroxypyrene (1-OHP), 3-hydroxy-1-methylpropylmercapturic acid (3 HMPMA), nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence interval (CI), least squares (LS).

[Data source: Clinical Study Report ZRHR-REXC-03-EU Appendix 15; COHb Table 15.2.4.1; MHBMA Table 15.2.4.1; 3-HPMA Table 15.2.4.1; S-PMA Table 15.2.4.1; 1-OHP Table 15.2.4.9; NNN Table 15.2.4.11; 4-ABP Table 15.2.4.13; 1-NA Table 15.2.4.15; 2-NA Table 15.2.4.17; o-tol Table 15.2.4.19; CEMA Table 15.2.4.21; HEMA Table 15.2.4.23; 3-OH-BaP Table 15.2.4.25; HMPMA Table 15.2.4.27; S-BMA Table 15.2.4.29; NNAL Table 15.2.4.31]

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6.1.3.2.2.1.2.2 Xenobiotic Metabolism

At Baseline, CYP1A2 activity was comparable between the 3 arms (range from 110 % to 113%). CYP1A2 activity decreased from Baseline by -16.5% after switching to THS and by -15% in subjects who abstained from smoking. In the CC arm, CYP1A2 activity increased by approximately 13% during the 5 day study period.

This resulted in differences in absolute CYP1A2 activity at Day 5 of -33.60% (95% CI: -40.59, -26.61) between subjects who switched from CC to THS and subjects who continued smoking. There was no difference in absolute CYP1A2 activity on Day 5 between subjects who switched to THS use and subjects who abstained from smoking.

6.1.3.2.2.1.2.3 Urine Mutagenicity

At Baseline, median Ames mutagenicity test values were 19681 Rev/24h for THS, 22540 Rev/24h for the SA arms, and 15775 Rev/24h for the CC arm. On Day 5, in the THS and SA arms, median Ames mutagenicity test values had decreased from Baseline by approximately -57% and -62%, respectively, while in the CC arm, median values increased from Baseline by approximately 29%.

6.1.3.2.2.1.3 Conclusion

The [ZRHR-REXC-03-EU] study demonstrated that switching from CC smoking to THS use resulted in statistically significant reductions in exposure to 15 BoExp to selected HPHCs. The reductions -by at least 50% in the levels of COHb, MHBMA, 3-HPMA, and S-PMA, tested as endpoints of the primary objective between THS and CC arms, were consistent with the study hypothesis and evaluation criteria.

The kinetics and the magnitude of decrease of BoExp levels observed in the THS arm, were approaching the levels observed in the SA arm. Detoxification activity of xenobiotic metabolism, as shown by CYP1A2 activity, as well as urine mutagenicity, decreased similarly for THS than for SA.

6.1.3.2.2.2 Study ZRHR-REXC-04-JP

The purpose of this study [ZRHR-REXC-04-JP] was to compare THS with conventional cigarettes in terms of exposure to HPHC in healthy adult Japanese smokers. Selected BoExp for HPHCs were measured under *ad libitum* use of THS for 5 days. Information was gathered about safety in subjects using the THS product, compared to smokers who continued smoking their own preferred brand of CC. Smokers who were asked to abstain from smoking were not allowed to use any nicotine/tobacco-containing products. SA was used as a reference point to THS to evaluate how similar the reduced exposure in the THS arm was compared to the results observed when subjects stopped smoking for the duration of the study.

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6.1.3.2.2.2.1 Methodology of the ZRHR-REXC-04-JP Study

A brief description of study design, endpoints and methodology is given in Table 5.

Table 5 Methodology of the ZRHR-REXC-04-JP Study

Reduced exposure study in Japanese smokers using the Tobacco Heating System 2.2 (THS 2.2) for 5 days in a Confinement setting
Title of the study: A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes (CC), for 5 days in Confinement
Study design: This was a randomized, controlled, open-label, 3-arm, parallel group, single-center study to compare the use of THS 2.2 with continuing to smoke CC and smoking abstinence (SA) in Confinement.
Subjects: Randomized: 160; Data set for safety analysis: 166. Completed: 158; Number of subjects in the THS arm (completed): 80 (80). Number of subjects in the CC arm (completed): 40 (40); Number of subjects in the SA arm (completed): 38 (38).
Main criteria for inclusion: • Subject was aged from 23 (minimal legal smoking age + 3 years of smoking history) to 65 years (inclusive) • Subject was of Japanese origin • Considered as healthy based on good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening • Subject was a current smoker (based on self-reporting) who had smoked for the last 4 weeks at least 10 commercially available non-menthol CC per day (no brand restrictions). The subject had smoked for at least the last 3 consecutive years. Did not plan to quit smoking in the next 3 months. • Body mass index <18.5 or ≥32 kg/m^2.
Test Product: Tobacco Heating System 2.2 (THS 2.2) Regular. Ad-libitum use
Comparison Product: Commercially available CC with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) as labeled on the cigarette package
Reference: Smoking abstinence. No Nicotine Replacement Therapy
Duration of Use: The exposure period lasted 5 days and was defined as the period after randomization from Day 1, 06:30 AM until Day 5, 11:00 PM, in which the subject was allowed to use the assigned product (THS 2.2 or CC), or abstained from smoking.
Analytical Method: All bioanalytical assays and laboratory assessments were carried out using validated methods. The bioanalytical methods used, and the results obtained, are documented in the [Appendix A16.1.9] of the [ZRHR-REXC-04-JP] study report. The methods used are summarized in [Section 6.1.3.3 Bioanalytical Methods].

(table continues)

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Reduced exposure study in Japanese smokers using the Tobacco Heating System 2.2 (THS 2.2) for 5 days in a Confinement setting

Objectives

Biomarkers of Exposure

- To demonstrate a reduction of 50% or more in 24-hour urine concentration of MHBMA, 3-HPMA, S-PMA and COHb in blood (% saturation of hemoglobin) at Day 5, in smokers switching from CC to THS compared to smokers continuing to smoke CC.
- To determine the reduction of the other selected BoExp on Day 5 in smokers switching from CC to THS 2.2 compared to smokers continuing to smoke CC.
- To describe the levels of all selected BoExp over the exposure period in smokers switching from CC to THS 2.2 compared to smokers continuing to smoke CC.

Xenobiotic Metabolism:

- To describe the changes in CYP1A2 enzymatic activity at Day 5 in smokers switching from CC to THS, switching from CC to SA, and continuing to smoke CC, as assessed by the molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma.

Mutagenicity:

- To describe the urine mutagenicity at Baseline and Day 5 of smokers switching from CC to THS compared to smokers continuing to smoke CC and smokers switching from CC to SA, as assessed with the Ames mutagenicity test (YG1024+S9).

Criteria for evaluation:

To demonstrate a reduction of 50% or more in 24-hour urine concentration of MHBMA, 3-HPMA, S-PMA and COHb in blood (% saturation of hemoglobin) at Day 5, in smokers switching from CC to THS compared to smokers continuing to smoke CC. The levels of selected BoExp over the exposure period in smokers switching from CC to THS were compared. The maximal BoExp reduction in smoking abstinence was assessed.

6.1.3.2.2.2.2 Results

6.1.3.2.2.2.1 Biomarkers of Exposure

The kinetics and the magnitude of decrease of BoExp levels observed in the THS arm were approaching the levels observed in the SA arm (Figure 3). S-BMA did not show any difference in levels across all study arms. The study demonstrated that switching from CC smoking to THS use resulted in statistically significant reductions in BoExp levels to 15 HPHCs, ranging from -47% to -96%, while maintaining comparable levels of nicotine (Figure 4).

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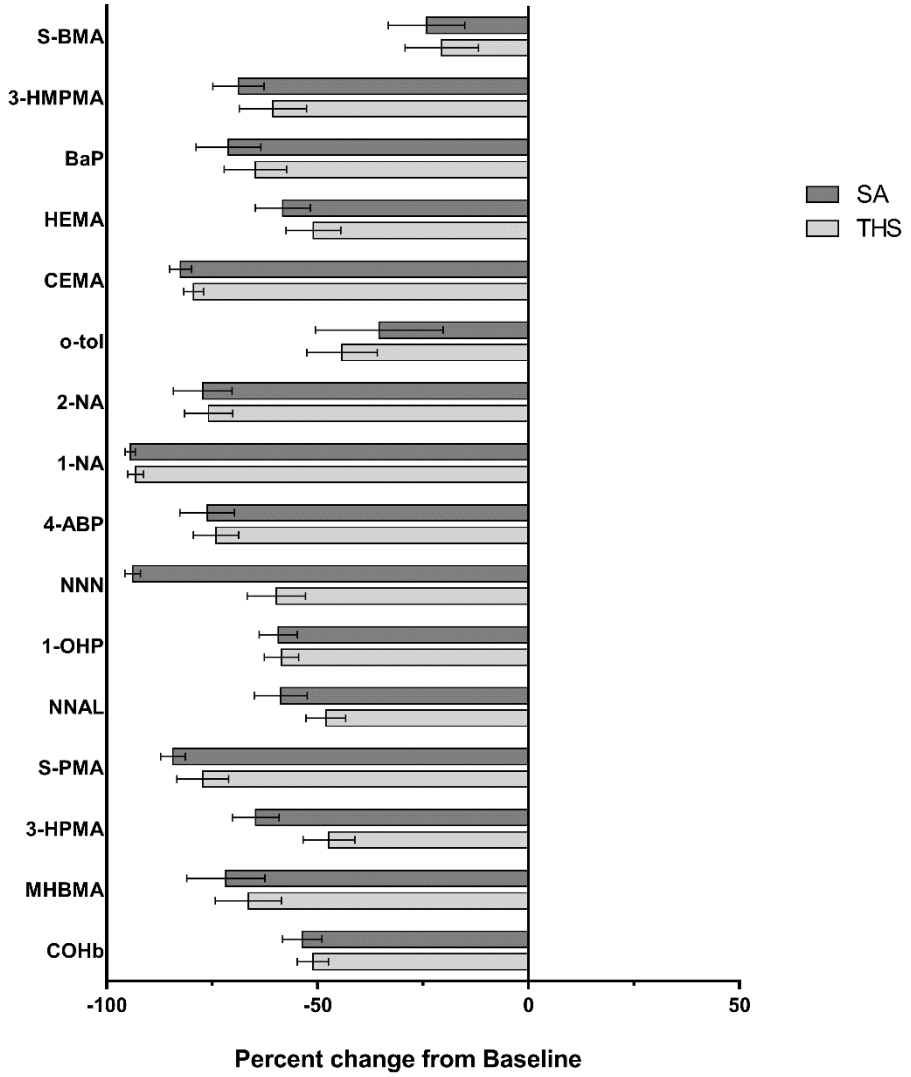


Figure 3 Mean Percent Change from Baseline of Geometric Mean Levels and CIs at Day 5 in ZRHR-REXC-04-JP

Abbreviations: carboxyhemoglobin (COHb), monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), total 1-hydroxypyrene (1-OHP), total N-nitrosonornicotine (NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), *o*-toluidine (*o*-tol), 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy[a]benzopyrene (BaP), 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA), S-benzylmercapturic acid (S-BMA), nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence interval (CI).

[Data source: Clinical Study Report ZRHR-REXC-04-JP Appendix 15; COHb Table 15.2.3.5; MHBMA Table 15.2.3.5; 3-HPMA Table 15.2.3.5; S-PMA Table 15.2.3.5; NNAL Table 15.2.4.32; 1-OHP Table 15.2.4.10; NNN Table 15.2.4.12; 4-ABP Table 15.2.4.14; 1-NA Table 15.2.4.16; 2-NA Table 15.2.4.18; o-tol Table 15.2.4.20; CEMA Table 15.2.4.22; HEMA Table 15.2.4.24; BaP Table 15.2.4.26; 3-HMPMA Table 15.2.4.28; S-BMA Table 15.2.4.30]

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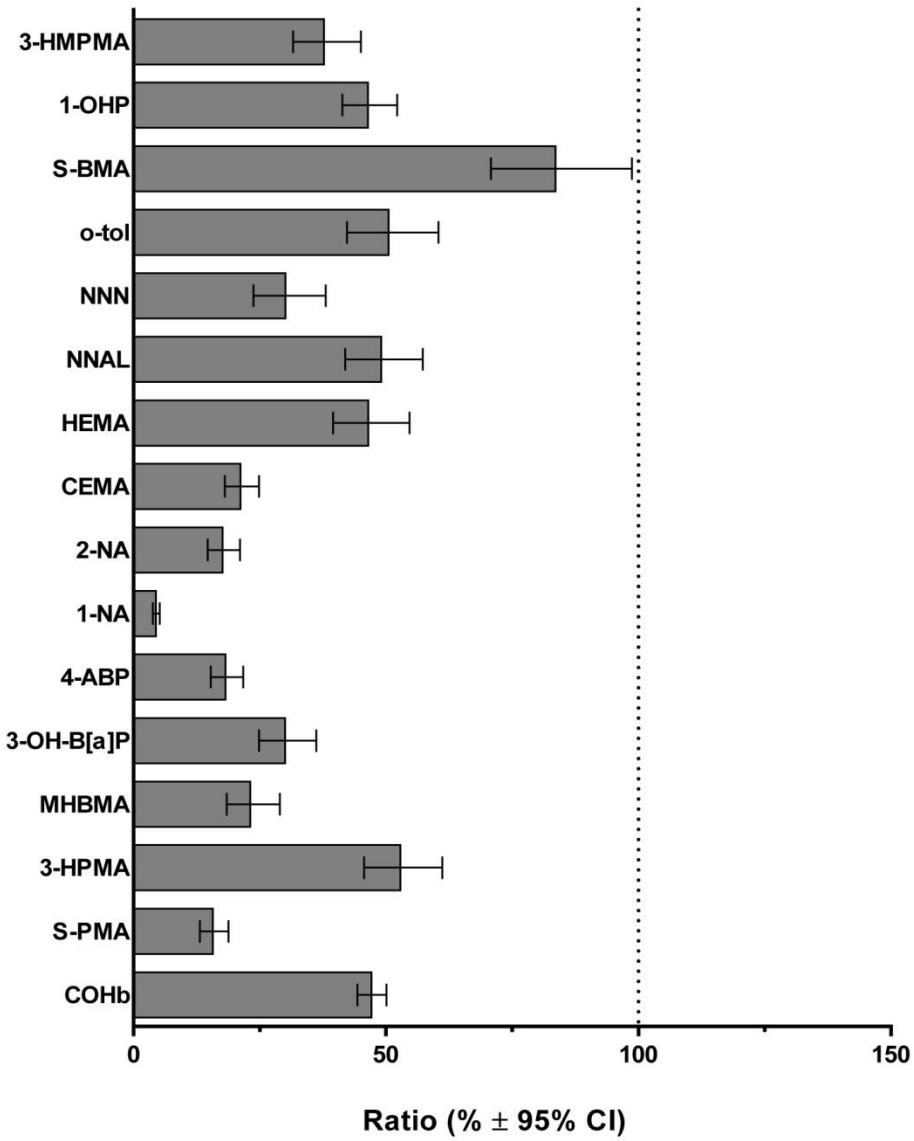


Figure 4 Adjusted Geometric LS Means and CIs from an ANCOVA Model of THS to CC at Day 5 in ZRHR-REXC-04-JP

Abbreviations: carboxyhemoglobin (COHb), S-phenylmercapturic acid (S-PMA), 3-hydroxypropylmercapturic acid (3-HPMA), monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxy(a)benzopyrene (3-OH-B[a]P), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), total N-nitrosonornicotine (NNN), S-benzylmercapturic acid (S-BMA), total 1-hydroxypyrene (1-OHP), 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA), nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence interval (CI), least squares (LS).

[Data source: Clinical Study Report ZRHR-REXC-04-JP Appendix 15; COHb Table 15.2.4.1; MHBMA Table 15.2.4.1; 3-HPMA Table 15.2.4.1; S-PMA Table 15.2.4.1; 1-OHP Table 15.2.4.9; NNN Table 15.2.4.11; 4-ABP Table 15.2.4.13; 1-NA Table 15.2.4.15; 2-NA Table 15.2.4.17; o-tol Table 15.2.4.19; CEMA Table 15.2.4.21; HEMA Table 15.2.4.23; 3-OH-BaP Table 15.2.4.25 (Addendum); HMPMA Table 15.2.4.27; S-BMA Table 15.2.4.29; NNAL Table 15.2.4.31]

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6.1.3.2.2.2.2 Xenobiotic Metabolism

At Baseline, CYP1A2 activity was comparable between study arms (range from 78% to 81%). In the THS and SA arms at Day 5, CYP1A2 activity had decreased from Baseline by approximately -27% and -30%, respectively, while in the CC arm, CYP1A2 activity decreased from Baseline by approximately -1%. This resulted in differences in absolute CYP1A2 activity at Day 5 (THS - CC) of --21.65% (95% CI: -25,49, -17.81). There was no notable difference in absolute CYP1A2 activity on Day 5 in CYP1A2 activity between subjects who switched to THS use and subjects who abstained from smoking.

6.1.3.2.2.2.3 Urine Mutagenicity

At Baseline, median Ames mutagenicity test values were comparable between the THS and SA arms (17221.6 and 15016.5 REV/24h, respectively) and slightly lower in the CC arm (12574.4 REV/24h). On Day 5, in the THS and SA arms, median Ames mutagenicity test values had decreased from Baseline by approximately -43% and -55%, respectively, while in the CC arm, median Ames mutagenicity test values decreased from Baseline by approximately -24%.

6.1.3.2.2.3 Conclusion

The [ZRHR-REXC-04-JP] study demonstrated that switching from CC smoking to THS use resulted in statistically significant reductions in exposure to 15 BoExp to selected HPHCs. The reductions by at least 50% in the levels of COHb, MHBMA, and S-PMA, together with the reduction of 47% in the level of 3-HPMA (with a confidence interval including 50%), tested as endpoints of the primary objective between THS vs CC arms, were consistent with the study hypothesis and evaluation criteria.

The kinetics and the magnitude of decrease of BoExp levels observed in the THS arm, were approaching the levels observed in the SA arm. Detoxification activity of xenobiotic metabolism, as shown by CYP1A2 activity, as well as urine mutagenicity, decreased similarly for THS than for SA.

6.1.3.2.2.3 Study ZRHM-REXA-07-JP

The goal of the 3 month study was to provide information on the reduction in the levels of selected BoExp to HPHCs and to obtain safety information in subjects using THS, compared to smokers continuing to smoke their preferred brand of mCC in a Confinement setting for 5 days followed by an Ambulatory setting for 85 days. Smokers who were asked to abstain from using any nicotine/tobacco-containing products were used as a reference point. The smokers allocated to THS and CC arms were allowed to use the product they were allocated *ad libitum* during the day.

An additional aim of the study was to understand the effect of using THS on selected variables and their potential association to the reduced exposure to HPHCs (e.g. urine mutagenicity and cytochrome P450 1A2 [CYP1A2] activity).

6.1.3.2.2.3.1 Methodology of the ZRHM-REXA-07-JP Study

A brief description of study design, endpoints and methodology is given in Table 6.

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Table 6 Methodology of the ZRHM-REXA-07-JP Study

Reduced exposure study using THS 2.2 Menthol with 5 days in a Confinement setting and 85 days in an Ambulatory setting
Title of the study: A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions 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 (mCC), for 5 days in Confinement and prolonged by 85 days in an Ambulatory setting.
Study design: This was a randomized, controlled, open-label, 3-arm, parallel group, single-center study to compare the use of THS 2.2 with continuing to smoke CC and smoking abstinence (SA). This was an ad libitum smoking study, with 5 days in Confinement followed by 85 days in Ambulatory setting
Subjects: Randomized: 216; Data set for safety analysis: 231. Completed: 160; Number of subjects in the THS arm (completed): 78 (76). Number of subjects in the CC arm (completed): 42 (41); Number of subjects in the SA arm (completed): 40 (38).
Main criteria for inclusion: • Male and female Japanese aged 23 (minimal legal smoking age + 3 years of smoking history) to 45 years • Considered as healthy based on good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening. • Smoking at least 10 mCC per day for the last 4 weeks with a maximum nicotine yield of 1 mg (ISO) • Did not plan to quit smoking in the following 3 months • Body mass index between <18.5 or ≥32 kg/m^2.
Test Product: Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Comparison Product: Commercially available mCC
Reference: Smoking abstinence with support of Nicotine Replacement Therapy during the Ambulatory period if considered necessary by the Principal Investigator or requested by the subject.
Duration of Use: The exposure period lasted 90 days, from Day 1, 06:30 AM until 11:00 PM on Day 90.The exposure period included both the exposure period in Confinement and the exposure period in the Ambulatory setting. Product use periods were subsets of the exposure period and were defined as Confinement period 1 (Day 1 to Day 6 [Confinement]), Ambulatory period 2 (Day 6 to Day 30 Visit), period 3 (Day 30 Visit to Day 60 Visit), and period 4 (Day 60 Visit to Day 90 Visit).
Analytical Method: All bioanalytical assays and laboratory assessments were carried out using validated methods. The bioanalytical methods used, and the results obtained The methods used are summarized in [Section 6.1.3.3 Bioanalytical Methods].

(table continues)

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Reduced exposure study using THS 2.2 Menthol with 5 days in a Confinement setting and 85 days in an Ambulatory setting

Objectives

Biomarkers of Exposure

- To demonstrate a reduction of 50% or more in 24-hour urine concentration of MHBMA, 3-HPMA, S-PMA and COHb in blood (% saturation of hemoglobin) at Day 5 in smokers switching from CC to THS, compared to smokers continuing to smoke CC.
- To demonstrate a reduction of 50% or more in 24-hour urine concentration of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL) at Day 90, in smokers switching from CC to THS, compared to smokers continuing to smoke CC.
- To determine the reduction of all other selected BoExp in smokers switching from mCC to THS 2.2 Menthol, compared to smokers continuing to smoke mCC by testing whether the levels of these BoExp are lower for THS 2.2 Menthol relative to mCC at Day 5, and if significant at Day 90.
- To describe the levels of all selected BoExp over the entire Exposure period (Confinement and Ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol, compared to smokers continuing to smoke mCC and to SA.

Xenobiotic Metabolism:

- To describe the changes in CYP1A2 enzymatic activity at Day 5 and Day 90 in smokers switching from CC to THS, switching from CC to SA, and continuing to smoke CC, as assessed by the molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma.

Mutagenicity:

- To describe the urine mutagenicity at Day 5 and Day 90 of smokers switching from CC to THS compared to smokers continuing to smoke CC and smokers switching from CC to SA, as assessed with the Ames mutagenicity test (YG1024+S9).

Criteria for evaluation:

The hypothesis tested was that the geometric mean level of the BoExp for THS 2.2 Menthol were lower relative to mCC. For BoExp included as endpoints in the primary objective, the hypothesis was tested on Day 5 for MHBMA, 3-HPMA, S-PMA, and COHb, and on Day 90 Visit for Total NNAL.

The secondary objectives tested the BoExp included as endpoints in the primary objective and the remaining BoExp. If the hypothesis test was significant at Day 5 then the endpoint was further tested Day 90.

6.1.3.2.2.3.2 Results

6.1.3.2.2.3.2.1 Biomarkers of Exposure

The kinetics and the magnitude of the decrease observed for the majority of BoExp in the THS arm were close to that observed in the SA arm, in both the timing and magnitude of the reductions throughout both the Confinement and Ambulatory exposure periods (Figure 5). S-BMA levels did not show any difference in levels across all study arms. The study demonstrated that switching from CC to THS use in a Japanese smoking population resulted in statistically significant reductions in the levels of BoExp to 15 HPHCs. The majority of the reduction was achieved after 5 days in Confinement and ranged from 49% to 94%, and was sustained throughout the 85 days of the Ambulatory period of the study.

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The reductions seen at Day 90 ranged from 46% to 93%, while levels of nicotine were maintained (Figure 6).

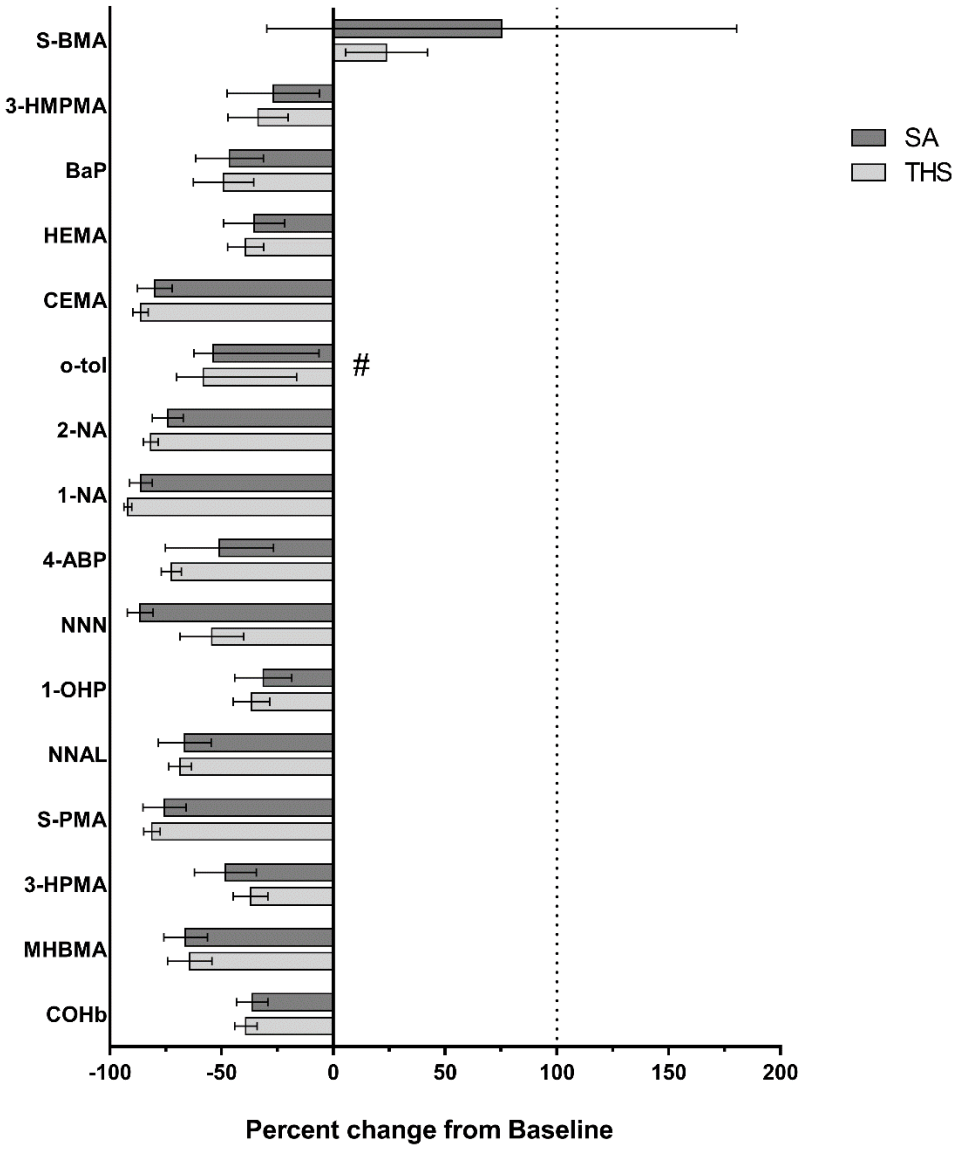


Figure 5 Percent Change from Baseline and 95% CIs at Day 90 in ZRHM-REXA-07-JP

Abbreviations: carboxyhemoglobin (COHb), monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), total 1-hydroxypyrene (1-OHP), total N-nitrosonornicotine (NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), *o*-toluidine (*o*-tol), 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy[a]benzopyrene (BaP), 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA), S-benzylmercapturic acid (S-BMA), nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence interval (CI).

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Because of outliers in the THS and SA arms, values percent change from Baseline values for *o*-toluidine are reported as median (and Q1; Q3) for both arms.

[Data source: Clinical Study Report ZRHM-REXA-07-JP Appendix 15; COHb Table 15.2.4.1.1; MHBMA Table 15.2.4.2.1; 3-HPMA Table 15.2.4.3.1; S-PMA Table 15.2.4.4.1; NNAL Table 15.2.4.5.1; 1-OHP Table 15.2.4.7.1; NNN Table 15.2.4.8.1; 4-ABP Table 15.2.4.9.1; 1-NA Table 15.2.4.10.1; 2-NA Table 15.2.4.11.1; o-tol Table 15.2.4.12.1; CEMA Table 15.2.4.13.1; HEMA Table 15.2.4.14.1; BaP Table 15.2.4.15.1; 3-HMPMA Table 15.2.4.16.1; S-BMA Table 15.2.4.17.1]

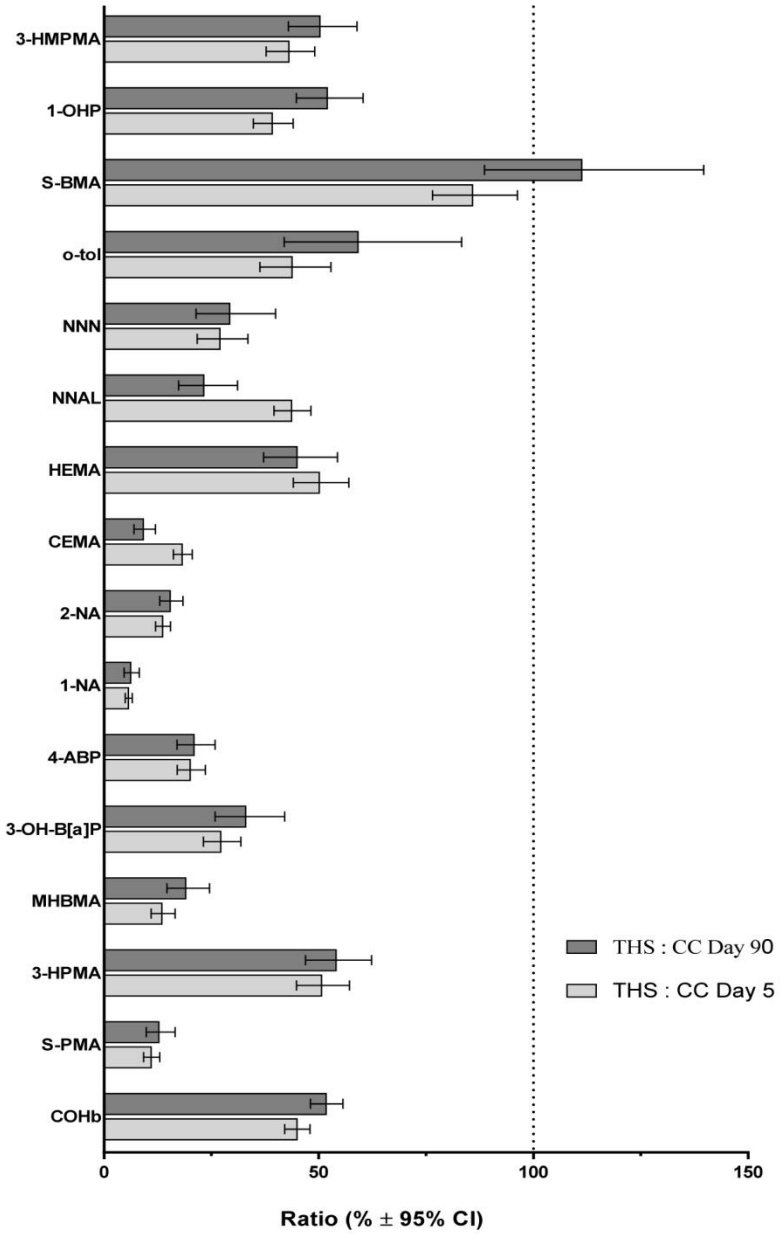


Figure 6 Adjusted Geometric LS Means and 95% CIs from an ANCOVA Model of THS to CC at Day 5 and Day 90 in ZRHM-REXA-07-JP

Abbreviations: carboxyhemoglobin (COHb), S-phenylmercapturic acid (S-PMA), 3-hydroxypropylmercapturic acid (3-HPMA), monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxy(a)benzopyrene (3-OH-B[a]P), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), 2-cyanoethylmercapturic acid

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(CEMA), 2-hydroxyethyl mercapturic acid (HEMA), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), total N-nitrosonornicotine (NNN), S-benzylmercapturic acid (S-BMA), total 1-hydroxypyrene (1-OHP), 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA), nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence interval (CI), least squares (LS).

[Data source: Clinical Study Report ZRHM-REXA-07-JP, Appendix 15; Table 15.2.3.4]

6.1.3.2.2.3.2.2 Xenobiotic Metabolism

At Baseline, CYP1A2 activity was similar between study arms, (ranged from 70% to 74%). On Day 5, CYP1A2 activity had decreased from Baseline by -22% and -24% in the THS and SA arms, respectively; while in the CC arm, CYP1A2 activity had increased from Baseline by 10%. During the Ambulatory period, CYP1A2 activity remained decreased with a -20% and -16% change from Baseline in the THS 1 and SA arms, respectively, and increased from Baseline in the CC arm of 16% on Day 90. The CYP1A2 activity in subjects who switched to THS use was 33% lower than in subjects who continued to smoke CC on Day 5, which was sustained during the Ambulatory period with CYP1A2 activity 32% lower than CC on Day 90.

6.1.3.2.2.3.2.3 Urine Mutagenicity

At Baseline, median Ames mutagenicity test values were comparable between the three arms (range from 13235.99 and 14000.04 REV/24h). On Day 5, in the THS and SA arms, median Ames mutagenicity test values were decreased from Baseline by -57% and -37% respectively; while in the CC arm, no change was observed from Baseline [Clinical study report ZRHM-REXA-07-JP - Table 112].

On Day 90, in the THS and SA arms, median Ames mutagenicity test values were decreased from Baseline, by -61% and -45%, respectively; while in the CC arm, mean urine mutagenicity test values were increased by 16% from Baseline [Clinical study report ZRHM-REXA-07-JP - Table 113].

6.1.3.2.2.3.3 Conclusion

The [ZRHM-REXA-07-JP] study demonstrated that switching from CC smoking to THS use resulted in statistically significant reductions in exposure to 15 BoExp to selected HPHCs in a controlled setting, which was sustained in a more near real-world, Ambulatory setting. Reduction by at least 50% was demonstrated for COHb, S.PMA, and MHBMA after 5 days of exposure and for total NNAL after 90 days of exposure, tested as endpoints of the primary objective. The reduction of 3-HPMA at Day 5 was of 49%, with confidence interval including 50%. These results were consistent with the study hypothesis and evaluation criteria.

The kinetics and the magnitude of decrease of BoExp levels observed in the THS 2.2 arm were approaching the levels observed in the SA arm. Detoxification activity of xenobiotic metabolism, as shown by CYP1A2 activity, as well as urine mutagenicity, decreased similarly for THS and for SA.

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6.1.3.2.2.4 Study ZRHM-REXA-08-US

The goal of this 3 month study was to provide information on the reduction in the levels of selected BoExp to HPHCs and to obtain safety information in subjects using THS compared to smokers continuing to smoke their preferred brand of CC. There was an initial period of 5 days in a Confinement setting followed by an Ambulatory setting of 85 days. Smokers who were asked to abstain from using any nicotine/tobacco-containing products were used as a reference point. The smokers allocated to the THS and CC arms were allowed to use the product they were allocated ad libitum during the day.

An additional aim of the study was to understand the effect of using THS on selected variables and their potential association to the reduced exposure to HPHCs (e.g. urine mutagenicity and cytochrome P450 1A2 [CYP1A2] activity).

6.1.3.2.2.4.1 Methodology of the ZRHM-REXA-08-US Study

A brief description of study design, endpoints and methodology is given in Table 7.

Table 7 Methodology of the ZRHM-REXA-08-US Study

Reduced exposure study using THS 2.2 Menthol with 5 days in a Confinement setting and 86 days in an Ambulatory setting
Title of the study: A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions 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 (mCC), for 5 days in Confinement and prolonged by 86 days in an Ambulatory setting.
Study design: This was a randomized, controlled, open-label, 3-arm, parallel group, single-center study to compare the use of THS 2.2 with continuing to smoke CC and smoking abstinence (SA). This was an ad libitum smoking study with 5 days in Confinement followed by 86 days in an Ambulatory setting.
Subjects: Randomized: 160; Data set for safety analysis: 165. Completed: 139; Number of subjects in the THS arm (completed): 80 (73). Number of subjects in the CC arm (completed): 41 (35); Number of subjects in the SA arm (completed): 39 (31).
Main criteria for inclusion: • Male and female smokers aged at a minimum 22 years (minimal legal smoking age + 3 years of smoking history) • Considered as healthy based on good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening • Smoking at least 10 mCC per day for at least the last 3 consecutive years. The smoking status was verified with a urinary cotinine test (cotinine ≥200 ng/mL). • Did not plan to quit smoking in the following 3 months • Body mass index between <18.5 or ≥35 kg/m2.
Test Product: Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Comparison Product: Commercially available mCC

(table continues)

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Reduced exposure study using THS 2.2 Menthol with 5 days in a Confinement setting and 86 days in an Ambulatory setting

Reference: Smoking abstinence with support of Nicotine Replacement Therapy during the Ambulatory period if considered necessary by the Principal Investigator or requested by the subject.

Duration of Use: The exposure period lasted 91 days, from Day 1, 06:30 AM until 11:00 PM on Day 91.The exposure period included both the exposure period in Confinement and the exposure period in the Ambulatory setting. Product use periods were subsets of the exposure period and were defined as Confinement period 1 (Day 1 to Day 6 [Confinement]), Ambulatory period 2 (Day 6 to Day 30 Visit), period 3 (Day 30 Visit to Day 60 Visit), and period 4 (Day 60 Visit to Day 90 Visit).

Analytical Method: All bioanalytical assays and laboratory assessments were carried out using validated methods. The bioanalytical methods used, and the results obtained by the methods used are summarized in [Section 6.1.3.3 Bioanalytical Methods].

Objectives:

Biomarkers of Exposure

- To demonstrate a reduction of 50% or more in 24-hour urine concentration of MHBMA, 3-HPMA, S-PMA and COHb in blood (% saturation of hemoglobin) at Day 5 in smokers switching from CC to THS, compared to smokers continuing to smoke CC.
- To demonstrate a reduction of 50% or more in 24-hour urine concentration of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL) at Day 90, in smokers switching from CC to THS, compared to smokers continuing to smoke CC.
- To determine the reduction of all other selected BoExp in smokers switching from mCC to THS 2.2 Menthol, compared to smokers continuing to smoke mCC by testing whether the levels of these BoExp are lower for THS 2.2 Menthol relative to mCC at Day 5, and if significant at Day 90.
- To describe the levels of all selected BoExp over the entire Exposure period (confinement and Ambulatory periods) in smokers switching from mCC to THS 2.2 Menthol, compared to smokers continuing to smoke mCC and to SA.

Xenobiotic Metabolism:

To describe the changes in CYP1A2 enzymatic activity at Day 5 and Day 90 in smokers switching from CC to THS, switching from CC to SA, and continuing to smoke CC, as assessed by the molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma.

Mutagenicity:

To describe excretion of mutagenic material in urine: Ames mutagenicity test (YG1024+S9) at Day 5 and Day 90 Visit in 24-hour urine in a Confinement and/or Ambulatory setting in smokers switching from mCC to THS 2.2 Menthol, compared to smokers continuing to smoke mCC and to SA.

Criteria for evaluation:

The hypothesis tested was that the geometric mean level of the BoExp for THS 2.2 Menthol were lower relative to mCC. For BoExp included as endpoints in the primary objective, the hypothesis was tested on Day 5 for MHBMA, 3-HPMA, S-PMA, and COHb, and on Day 90 Visit for Total NNAL.

The secondary objectives tested the BoExp included as endpoints in the primary objective and the remaining BoExp. If the hypothesis test was significant at Day 5 then the endpoint was further tested at Day 90.

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6.1.3.2.2.4.2 Results

6.1.3.2.2.4.2.1 Biomarkers of Exposure

The kinetics and the magnitude of decreases observed for the majority of BoExp levels in the THS arm were approaching those observed in the SA arm, in both the timing and magnitude of the reductions (Figure 7). S-BMA levels did not show any difference in levels across all study arms.

The study demonstrated that switching from CC smoking to THS use resulted in statistically significant reductions in BoExp to 15 HPHCs, with the majority of the reduction achieved after 5 Days in Confinement. This reduction ranged from 51% to 96%, and was sustained throughout the 86 days of the Ambulatory period of the study. Reductions at Day 90 ranged from 48% to 86%, while maintaining comparable levels of nicotine (Figure 8).

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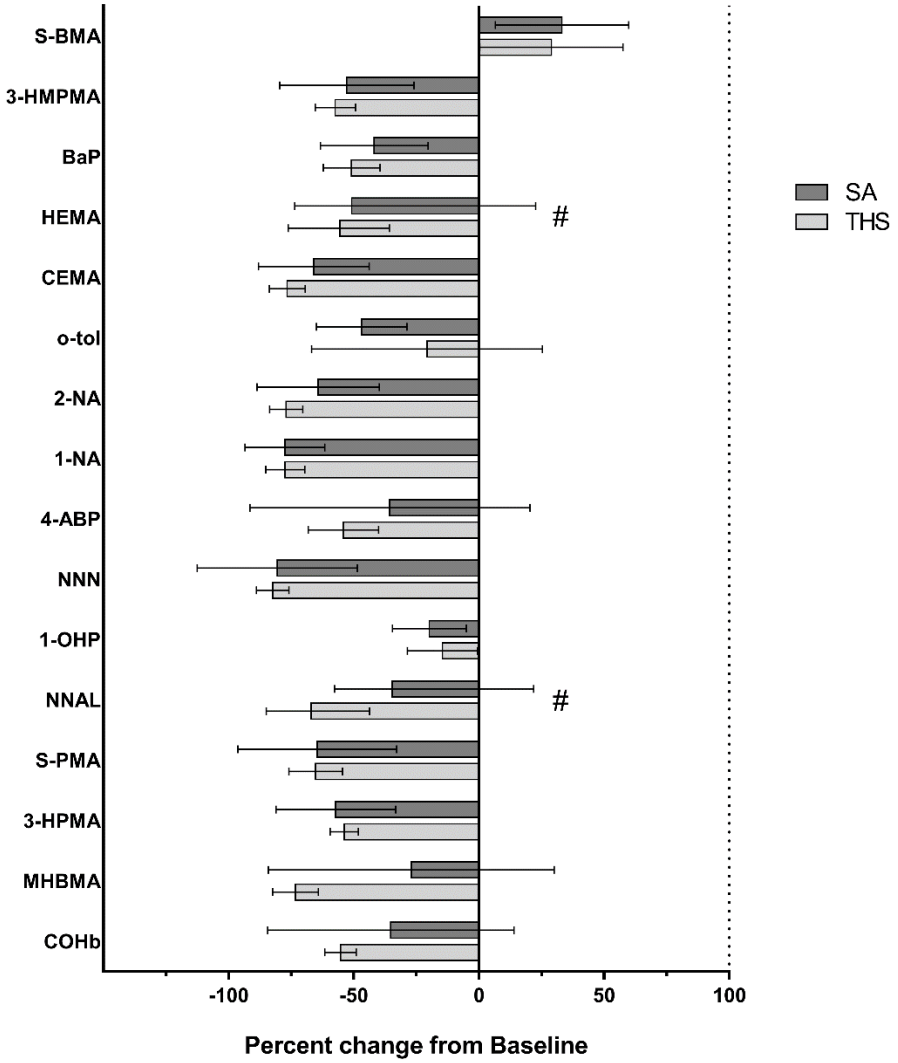


Figure 7 Percent Change from Baseline and 95% CIs at Day 90 in ZRHM-REXA-08-US

Abbreviations: carboxyhemoglobin (COHb), monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), total 1-hydroxypyrene (1-OHP), total N-nitrosonornicotine (NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), *o*-toluidine (*o*-tol), 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy[a]benzopyrene (BaP), 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA), S-benzylmercapturic acid (S-BMA), nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence interval (CI).

Because of limited number of subjects in the SA arm and outliers, percent change from Baseline values for total NNAL and HEMA are reported as median (and Q1; Q3) for both for the THS and SA arms.

[Data source: Clinical Study Report ZRHM-REXA-08-US Appendix 15; COHb Table 15.2.4.1.1; MHBMA Table 15.2.4.2.1; 3-HPMA Table 15.2.4.3.1; S-PMA Table 15.2.4.4.1; NNAL Table 15.2.4.5.1; 1-OHP Table 15.2.4.7.1; NNN Table 15.2.4.8.1; 4-ABP Table 15.2.4.9.1; 1-NA Table 15.2.4.10.1; 2-NA Table 15.2.4.11.1; o-tol Table 15.2.4.12.1; CEMA Table 15.2.4.13.1; HEMA Table 15.2.4.14.1; BaP Table 15.2.4.15.1; 3-HMPMA Table 15.2.4.16.1; S-BMA Table 15.2.4.17.1]

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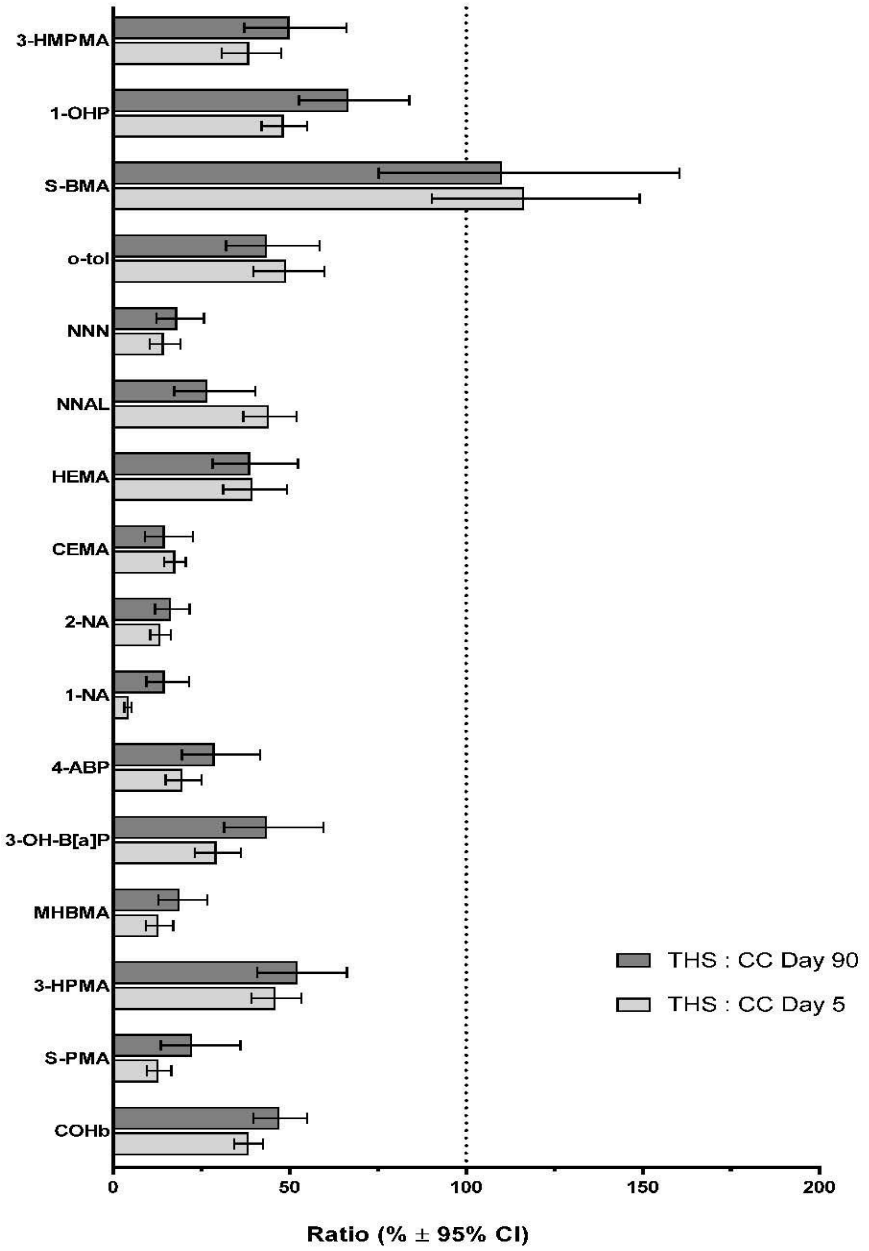


Figure 8 Adjusted Geometric LS Means and 95% CIs from an ANCOVA Model of THS to CC at Day 5 and Day 90 in ZRHM-REXA-08-US

Abbreviations: carboxyhemoglobin (COHb), S-phenylmercapturic acid (S-PMA), 3-hydroxypropylmercapturic acid (3-HPMA), monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxy(a)benzopyrene (3-OH-B[a]P), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), total N-nitrosonornicotine (NNN), S-benzylmercapturic acid (S-BMA), total 1-hydroxypyrene (1-OHP), 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA), nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence interval (CI), least squares (LS).

[Data source: Clinical Study Report ZRHM-REXA-08-US Appendix 15; Table 15.2.3.4]

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6.1.3.2.2.4.2.2 Xenobiotic Metabolism

At Baseline, CYP1A2 activity was similar between study arms, with geometric mean values of 117.6%, 121.6%, and 114.0% for the THS, CC, and SA arms, respectively.

On Day 5, CYP1A2 activity had decreased from Baseline by approximately -33% and -35% in the THS and SA arms, respectively; while in the CC arm, CYP1A2 activity had increased from Baseline by approximately 4%. During the Ambulatory period, CYP1A2 activity remained decreased with a -32% and -35% change from Baseline in the THS and SA arms, respectively, and an increase from Baseline in the CC arm of 17% on Day 90.

The CYP1A2 activity in subjects who switched to THS use was 36% (95% CI: 30.8, 41.7) lower than subjects who continued to smoke CC on Day 5 and 21% lower (95% CI: 7.0, 33.6) at Day 90. There was no notable difference in CYP1A2 activity between subjects who switched to THS 2 use and subjects who abstained from smoking (102%; 95% CI: 92.1, 111.9 on Day 5; 105%; 95% CI: 80.5, 137.9 on Day 90).

6.1.3.2.2.4.2.3 Urine Mutagenicity

At Baseline, median Ames mutagenicity test values were 19463.24, 17384.40, and 25823 REV/24h for the THS 2.2, CC, and SA arms, respectively On Day 5, in the THS and SA arms, median Ames mutagenicity test values had decreased from their respective Baseline values by -72% and -74%, respectively. In the CC arm, Ames mutagenicity test values (REV/24h) showed a median increase from Baseline of approximately 40% (Table 110). [Clinical study report ZRHM-REXA-08-US - Table 110].

On Day 90, in the THS and SA arms, median Ames mutagenicity test values were decreased from Baseline by -62% and -68%, respectively; while in the CC arm, median Ames mutagenicity test values were increased from Baseline by 11% higher than Baseline [Clinical study report ZRHM-REXA-08-US - Table 111].

6.1.3.2.2.4.1 Conclusion

The [ZRHM-REXA-08-US] study demonstrated that switching from CC smoking to THS use resulted in statistically significant reductions in exposure to 15 BoExp to selected HPHCs in a controlled setting, which was sustained in a more near real-world, Ambulatory setting. Reduction by at least 50% was demonstrated for COHb, S-PMA, 3-HPMA, and MHBMA after 5 days of exposure and for total NNAL after 90 days of exposure. These results were consistent with study hypothesis and success criteria.

The kinetics and the magnitude of decrease of BoExp levels observed in the THS arm were approaching the levels observed in the SA arm. Detoxification activity of xenobiotic metabolism, as shown by CYP1A2 activity, as well as urine mutagenicity, decreased similarly for THS than for SA.

6.1.3.2.3 Summary of Analyses Across Studies

The purpose of this section is to provide an overview of results obtained for each BoExp assessed across all reduced exposure clinical studies reported in this application. Results presented here are those of the per protocol (PP) population.

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Descriptive statistics, i.e., profiles of the levels of BoExp throughout the studies, including Baseline values, are presented with the BoExp concentrations adjusted to creatinine (except COHb, which is measured in blood and expressed as percent of saturation of hemoglobin) expressed as geometric means. CYP1A2 activity is presented as arithmetic mean values, and urine mutagenicity, as median values. For urinary BoExp, quantities excreted over 24 hours are occasionally presented in the conclusions, to allow comparison with published data.

Mean percent change from Baseline is the mean of all individual subjects' percent change from Baseline values, which was calculated by subtracting the individual subject's Baseline value from the value at the desired timepoint and then dividing this calculated value by the individual subject's Baseline value and multiplying by 100. When published data were available, percent changes from Baseline obtained in PMI's studies were compared with those published. However, when published data did not report percent changes from Baseline, these were calculated based on the means provided in the publications, which *in stricto sensu* is not exactly comparable, but still allows an overall comparison.

In the subsections "Analyses", the levels of reduction were calculated by geometric least squares (LS) mean ratios of the level in the THS arm over the level in the CC arm (i.e., THS : CC), and were calculated with 95% CI. For CYP1A2 activity, reductions were expressed as differences (i.e., THS – CC). An analysis of covariance (ANCOVA) (Snedecor 1989) model was used with terms for the log-transformed baseline value, sex, average daily CC consumption over the last 4 weeks as reported at Screening (stratification factors) and randomization arm. The LS means and estimate of the difference or the ratio along with two-sided 95% CI were back-transformed before being presented in the tables. Statistical differences were estimated using one-sided test with 2.5% type I error probability. No statistical analysis was performed on the urine mutagenicity assessment.

In this section, comparisons across studies are based on summary statistics of individual studies. The verbal qualifiers "comparable" and "similar" are used to qualitatively describe findings in a comprehensive rather than exclusively statistical manner; although CIs were considered for the assessment of findings, they mainly informed about the precision of parameter estimates, rather than on effects in an inferential manner.

6.1.3.2.3.1 COHb – BoExp for Exposure to Carbon Monoxide

Carbon monoxide exposure and consequently high levels of COHb have been linked to cardiovascular risk through mechanisms of tissue hypoxia, particularly in subjects with already compromised cardiac function (U.S. Department of Health and Human Services 2012b, WHO (World Health Organization) 2010). FDA has classified it as a reproductive or developmental toxicant (U.S. Department of Health and Human Services 2012a).

At Baseline, blood levels of COHb ranged from 4.65% to 6.66% across studies. Japanese subjects exhibited the lowest levels of COHb at Baseline (Table 8).

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Table 8 Geometric Means and 95% CIs of Blood COHb (%) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	34
		Mean	4.68	5.40	5.17	6.16
		95% CI	4.22; 5.18	4.88; 5.97	4.70; 5.70	5.59; 6.80
		Min; Max	2.6; 11.2	2.5; 10.8	2.4; 10.3	2.8; 9.7
	THS	N	80	80	76	74
		Mean	4.65	5.15	5.11	6.66
		95% CI	4.29; 5.04	4.80; 5.52	4.75; 5.49	6.23; 7.13
		Min; Max	1.6; 9.3	2.3; 9.9	2.1; 9.7	2.2; 12.6
	SA	N	39	40	39	23
		Mean	4.96	5.46	5.15	6.54
		95% CI	4.51; 5.46	4.94; 6.04	4.72; 5.62	5.79; 7.38
		Min; Max	2.5; 8.8	2.7; 10.2	3.1; 8.3	3.4; 9.5
Day 5	CC	N	41	40	42	34
		Mean	4.51	5.14	5.55	6.07
		95% CI	4.05; 5.01	4.66; 5.66	5.06; 6.08	5.52; 6.68
		Min; Max	2.7; 10.1	2.6; 9.1	2.7; 9.5	2.8; 9.7
	THS	N	79	80	76	74
		Mean	1.06	2.39	2.48	2.37
		95% CI	1.03; 1.08	2.32; 2.46	2.40; 2.57	2.23; 2.51
		Min; Max	0.9; 1.4	1.7; 3.2	1.4; 3.2	0.8; 5.9
	SA	N	39	38	39	23
		Mean	0.99	2.37	2.50	2.42
		95% CI	0.95; 1.03	2.28; 2.47	2.38; 2.64	2.08; 2.81
		Min; Max	0.7; 1.2	1.9; 3.2	1.7; 3.4	1.6; 8.1
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	5.73	5.62
		95% CI	NA	NA	5.24; 6.25	5.00; 6.32
		Min; Max	NA	NA	3.2; 11.9	2.4; 10.3
	THS	N	NA	NA	70	47
		Mean	NA	NA	2.97	2.66
		95% CI	NA	NA	2.88; 3.06	2.40; 2.94
		Min; Max	NA	NA	2.4; 4.3	1.6; 6.4
	SA	N	NA	NA	37	9
		Mean	NA	NA	3.04	2.84
		95% CI	NA	NA	2.84; 3.26	1.93; 4.16
		Min; Max	NA	NA	2.2; 5.3	1.5; 7.7

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CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:30 AM in SA arm at Day 1.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.6; ZRHR-REXC-04-JP, Table 15.2.3.6; ZRHM-REXA-07-JP, Table 15.2.4.1.1; ZRHM-REXA-08-US, Table 15.2.4.1.1]

COHb decreased rapidly in THS users and in the SA group. Already after Day 1, levels were plateauing until the end of the Confinement period of all 4 exposure assessment studies (Figure 9). Relative changes from Baseline of blood COHb during the Confinement periods ranged from -49% to -76% for the THS arms and from -49% to -79% for the SA arms (Table 9).

In the 2 Ambulatory studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], the decrease from Baseline in COHb ranged at Day 90 from -39% to -55% in the users of THS, and from -35% to -36% in the SA study arms, respectively (Table 9).

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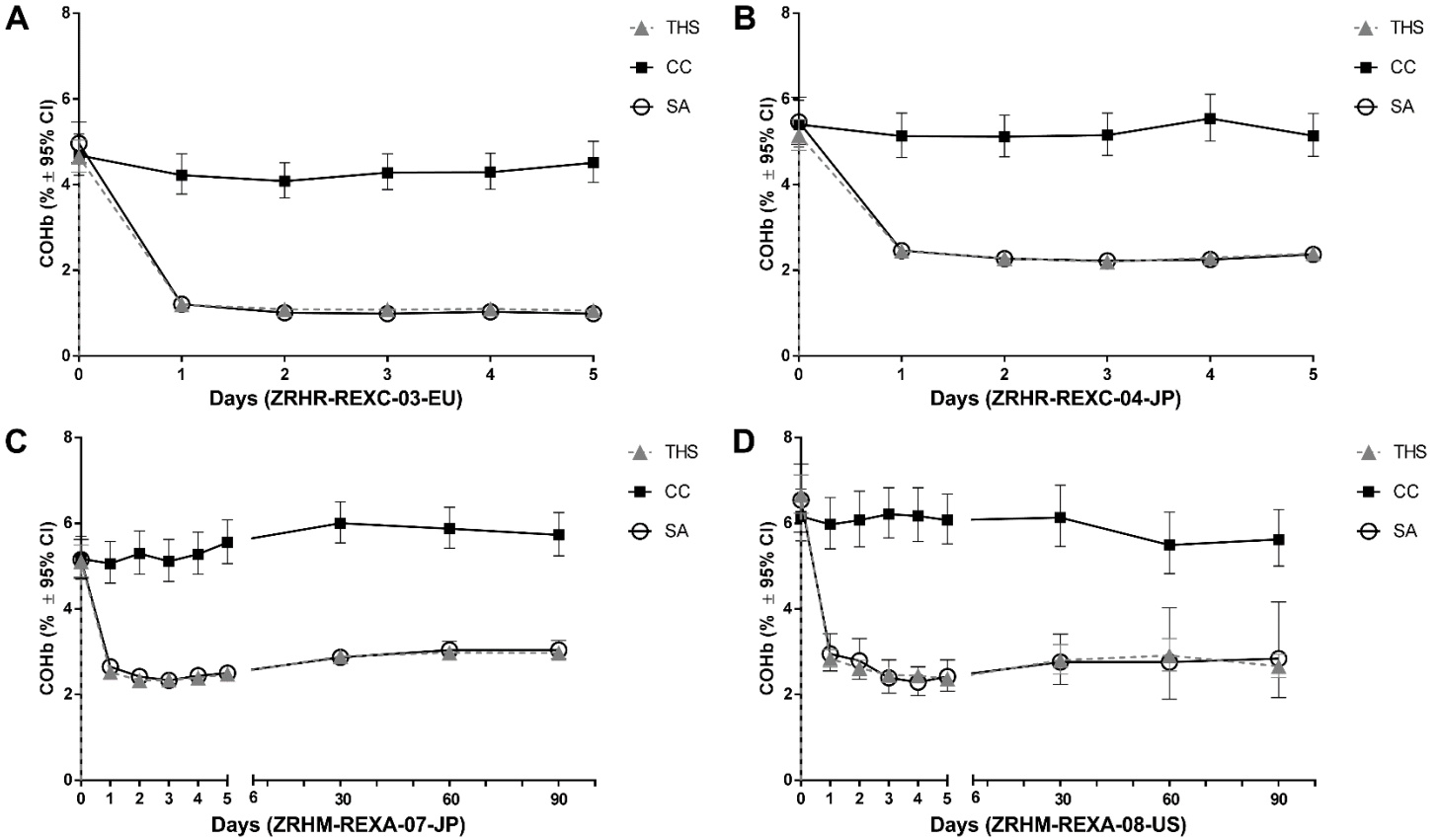


Figure 9 Geometric Mean and 95% CIs of Urinary COHb Concentrations (%), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.6; ZRHR-REXC-04-JP, Table 15.2.3.6; ZRHM-REXA-07-JP, Table 15.2.4.1.1; ZRHM-REXA-08-US, Table 15.2.4.1.1]

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At Day 5, the levels of evening blood COHb were generally comparable between studies, both in the THS and SA arms, with levels ranging from 1.06 to 2.48% and from 0.99% to 2.50%, respectively. At Day 90, the levels of COHb remained comparable in both arms across studies, with levels ranging from 2.66% to 2.97% and from 2.84% to 3.04% in the THS and SA arms, respectively. The levels of COHb in the CC groups remained generally unchanged with levels ranging at Day 5 from 4.51% to 6.07% and from 5.62% to 5.73% at Day 90 (Table 9).

Table 9 Mean Percent Change from Baseline and 95% CIs of Blood COHb (%) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	34
		% Change	-1.16%	-2.98%	8.90%	-0.55%
		95% CI	-8.31; 5.99	-9.37; 3.41	2.98; 14.81	-5.48; 4.39
	THS	N	79	80	76	74
		% Change	-76.20%	-51.13%	-49.24%	-61.67%
		95% CI	-78.11; -74.29	-54.86; -47.41	-52.69; -45.78	-65.51; -57.82
	SA	N	39	38	39	23
		% Change	-79.24%	-53.62%	-49.11%	-60.02%
		95% CI	-81.09; -77.40	-58.28; -48.97	-54.42; -43.80	-68.30; -51.75
Day 90	CC	N	NA	NA	41	32
		% Change	NA	NA	14.17%	-6.88%
		95% CI	NA	NA	5.33; 23.01	-14.87; 1.11
	THS	N	NA	NA	65	47
		% Change	NA	NA	-39.52%	-55.30%
		95% CI	NA	NA	-44.74; -34.29	-61.58; -49.03
	SA	N	NA	NA	37	9
		% Change	NA	NA	-36.34%	-35.24%
		95% CI	NA	NA	-43.33; -29.35	-84.44; 13.96

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; SA = smoking abstinence; THS = Tobacco Heating System.

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.5; ZRHR-REXC-04-JP, Table 15.2.3.5; ZRHM-REXA-07-JP, Table 15.2.4.1.1; ZRHM-REXA-08-US, Table 15.2.4.1.1]

6.1.3.2.3.1.1 Analysis of COHb Levels at Day 5 and Day 90

A significant reduction of exposure to CO was consistently demonstrated. At Day 5, across all 4 studies, switching to THS resulted in at least a 53% reduction of COHb, with a maximum reduction of 77% compared to CC smoking ($p < 0.001$ for each study; Table 10). At Day 90, these results were maintained with 48% in the Japanese THS

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Menthol users [ZRHM-REXA-07-JP] and decrease of 53% COHb in the US study population THS Menthol consumers [ZRHM-REXA-08-US] (Table 10) (p<0.001).

Table 10 Adjusted Geometric LS Means of THS to CC ratios of COHb at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	Mean	23.45%	47.10%	44.94%	38.14%
		95% CI	22.00; 24.99	44.30; 50.08	42.11; 47.97	34.24; 42.47
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	Mean	NA	NA	51.72%	46.76%
		95% CI	NA	NA	48.07; 55.65	39.75; 55.00
		p Value	NA	NA	<0.001	<0.001

CC = conventional cigarette; CI = confidence interval; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.1; ZRHR-REXC-04-JP, Table 15.2.3.1; ZRHM-REXA-07-JP, Table 15.2.3.2; ZRHM-REXA-08-US, Table 15.2.3.2]

6.1.3.2.3.1.2 Conclusion

Blood levels of COHb at Baseline, were overall comparable between studies, with slightly higher levels in the US population, and with the lowest levels found in the European study. For most other selected BoExp assessed, the European subjects had the highest levels at Baseline, as they were on average heavier smokers than the subjects in the other studies. The most likely explanation is that the observed differences in COHb levels are related to inter-laboratory variability and differences in the methods used to measure COHb, even though they were validated. Different laboratories had to be used for this BoExp, as stability of COHb samples is limited and did not allow for shipment of COHb samples to a single central laboratory. The similarity in COHb levels at Baseline for the 2 Japanese studies, analyzed by the same laboratory, supports this hypothesis.

The Japanese preference for cigarettes with charcoal-containing filters in non-menthol cigarettes is reported (Muscat 2005) and 7 out of 10 brands sold in Japan have a charcoal filter (Coggins 2008). However, in contrast to other BoExp, charcoal-containing cigarette filters reduce levels of CO in the aerosol by only a maximum of 10% to 15%, if at all (Polzin 2008), which could add to the explanation why the levels of COHb in the Japanese population at Baseline are not lower than in the European or American populations.

The profiles of reductions observed over the 5 days of Confinement in the THS and SA arms, with a maximum decrease observed after Day 1, plateauing thereafter, are consistent with published half-lives of COHb, i.e, 1 to 4 hours (Benowitz 2009, Scherer 2006a).

Percent changes from Baseline of COHb across studies, at the end of the Confinement periods (Day 5), ranged from -49% to -76% for the THS arms and from -49% to -79% for the SA arms. Several smoking cessation studies conducted over 3 to 8 days showed

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reductions of COHb levels ranging from -83% to -92% from Baseline (Frost-Pineda 2008a, Roethig 2007, Theophilus 2015, Tricker 2012a, Tricker 2012d). A change from Baseline of -42% was found in a study lasting 3 months (Pezzuto 2013), and changes from Baseline ranged from -63% to -71% in 2 studies lasting up to 6 months (Polonia 2009, Ramos 2011). In PMI's studies, changes from Baseline at Day 90 ranged from -39% to -55% in the users of THS, and from -35% to -36%in the SA study arms, thus being in line with those published data.

Means of COHb levels for smokers were reported to be about 4-7%, and those for non-smokers about 1-2% (Scherer 2006a). In smoking cessation studies of various durations, levels of blood COHb at the beginning of the studies showed a large variability with values ranging from 1.5% to 6.8% and decreasing to ranges of 0.45% to 2.1% (Frost-Pineda 2008a, Pezzuto 2013, Polonia 2009, Ramos 2011, Sakaguchi 2014, Theophilus 2015, Tricker 2012a, Tricker 2012b, Tricker 2012d, van Staden 2013). In PMI's studies, COHb levels in the Japanese and US studies after 5 days were slightly above 2% in THS and SA study arms, i.e. higher than the values reported in the literature for non-smokers and quitters and close to values considered as being of potential concern by the Agency for Toxic Substances and Disease Registry report that COHb levels (i.e., values ≥ 2.4% may have adverse cardiovascular effects in subjects with compromised cardiovascular function (U.S. Department of Health and Human Services 2012b). Similar values between the 2 arms, however, indicate THS levels reached the best possible reduction. Inter-laboratory differences in the bioanalytical method to measure COHb might explain why these values were above, but still close to the less than 2% values that should be measured in non-smokers (IOM (Institute of Medicine) 2012). Furthermore, occasional use of CC, which was possible to some extent, in both the THS and SA arms, could also explain higher levels of COHb than those expected.

At the end of the exposure, the COHb levels were similar in the THS and SA arms with values of 2.39% and 2.37% respectively, i.e. close to values considered as being of potential concern by the Agency for Toxic Substances and Disease Registry report that COHb levels (i.e., values ≥ 2.4% may have adverse cardiovascular effects in subjects with compromised cardiovascular function (U.S. Department of Health and Human Services 2012b)..

Clinical studies conducted with products based on the heat-not-burn principle showed reductions of blood COHb levels ranging from -53% to -87% in smokers who switched from CC to the test systems for 5 to 8 days, in Confinement conditions (Frost-Pineda 2008a, Hecht 1999b, Roethig 2007, Tricker 2012a, Tricker 2012c). These studies were conducted in the US, UK, Japan and Korea. On the other hand, a Japanese study using another heat-not-burn test product failed to show reductions of COHb after 6 days of switching from CC to the test cigarette (Sakaguchi 2014). In studies conducted over longer periods of time, i.e. 34 days or 12 weeks of switching, in Poland and in the US, changes from Baseline when switching to heat-not-burn products were of -47% and -23%, respectively (Frost-Pineda 2008b, Martin Leroy 2012).

There was a statistically significant reduction in level of COHb observed in the THS arms compared to the CC arms at Day 5 with reductions ranging from -53% to -77%. The

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slightly smaller reductions during the Ambulatory period, which is less controlled, could be related to environmental sources of CO, such as car traffic, indoor air, with appliances that burn natural gasoline, kerosene or other fuels (U.S. Department of Health and Human Services 2012b), or to the occasional use of CC.

In summary, the levels of COHb observed with THS were statistically significantly lower at Day 5 and Day 90 from values observed in the CC arms and approaching levels observed in the SA arms, as well as to published literature from smoking cessation studies. In addition, the reduction of exposure to carbon monoxide observed with THS aerosol in the *in vivo* non-clinical studies is in support of the levels observed in the clinical assessment.

6.1.3.2.3.2 MHBMA – BoExp for Exposure to 1,3-Butadiene

FDA has classified 1,3-butadiene as a carcinogen, and as a respiratory and reproductive or developmental toxicant (U.S. Department of Health and Human Services 2012a).

At Baseline CC consumption, 24 hour urine concentration of MHBMA varied considerably across studies. Levels ranged from 490 pg/mg$_{creat}$ in study [ZRHR-REXC-04-JP] to a mean level of 2317 pg/mg$_{creat}$ in study [ZRHR-REXC-03-EU] (Table 11).

Table 11 Geometric Means and 95% CIs of MHBMA$_{adjC}$ (pg/mg$_{creat}$) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	2317.31	490.97	737.29	922.66
		95% CI	1861.41; 2884.85	344.01; 700.72	554.67; 980.04	596.93; 1426.12
		Min; Max	311.7; 7533.3	71.5; 3178.4	145.8; 3506.2	96.3; 5519.7
	THS	N	80	80	76	65
		Mean	1888.27	538.46	653.78	1416.94
		95% CI	1542.95; 2310.86	416.79; 695.65	530.04; 806.39	1137.42; 1765.14
		Min; Max	231.9; 7218.5	64.3; 4420.8	80.8; 4067.8	155.7; 10792.9
	SA	N	39	38	39	21
		Mean	1699.39	511.94	614.87	1145.57
		95% CI	1200.16; 2406.29	369.91; 708.50	451.06; 838.16	721.09; 1819.91
		Min; Max	221.7; 6886.5	77.3; 2470.3	139.2; 2896.8	125.0; 5922.7

(table continues)

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			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	33
		Mean	2399.40	450.19	622.58	760.36
		95% CI	1884.60; 3054.83	300.07; 675.42	454.60; 852.64	457.27; 1264.34
		Min; Max	155.8; 7163.6	75.4; 4674.5	109.2; 3901.1	43.5; 4975.4
	THS	N	79	80	76	71
		Mean	192.93	107.39	81.71	113.01
		95% CI	174.90; 212.83	97.24; 118.60	75.52; 88.41	99.03; 128.96
		Min; Max	62.8; 384.6	43.5; 358.7	27.3; 150.6	23.6; 686.5
	SA	N	39	38	39	22
		Mean	163.17	92.18	80.72	93.99
		95% CI	138.41; 192.36	80.18; 105.98	70.92; 91.88	75.54; 116.94
		Min; Max	68.7; 431.1	43.9; 270.3	30.7; 202.4	45.0; 200.0
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	785.27	1040.71
		95% CI	NA	NA	576.82; 1069.04	677.79; 1597.94
		Min; Max	NA	NA	77.9; 3942.3	55.4; 6715.6
	THS	N	NA	NA	70	47
		Mean	NA	NA	141.74	260.98
		95% CI	NA	NA	120.62; 166.57	205.28; 331.79
		Min; Max	NA	NA	30.7; 3645.2	62.3; 1359.2
	SA	N	NA	NA	37	9
		Mean	NA	NA	136.83	243.00
		95% CI	NA	NA	114.40; 163.66	128.12; 460.90
		Min; Max	NA	NA	58.6; 473.8	60.2; 1141.2

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.7; ZRHR-REXC-04-JP, Table 15.2.3.7; ZRHM-REXA-07-JP, Table 15.2.4.2.1; ZRHM-REXA-08-US, Table 15.2.4.2.1]

The maximum decrease of MHBMA was reached within 2 days, in both the THS and SA arms (Figure 10).

In the Confinement period, the exposure marker to 1,3-butadiene was decreased by -66% to -88% for subjects who switched to THS and was lowered by -72% to -82% in subjects in SA arm (Table 12). In the 2 Ambulatory studies, this decrease was maintained with percent change from Baseline at Day 90 ranging from -64% to -73% in the THS arms, and from -27% [ZRHM-REXA-08-US] to -66% [ZRHM-REXA-07-JP] in the SA arms. Subjects who continued with their own CC brand showed variable levels across studies. From a relative decrease compared to Baseline of -12% in study [ZRHM-REXA-07-JP] up to an increase of +36% in the US [ZRHM-REXA-08-US] study (Table 12).

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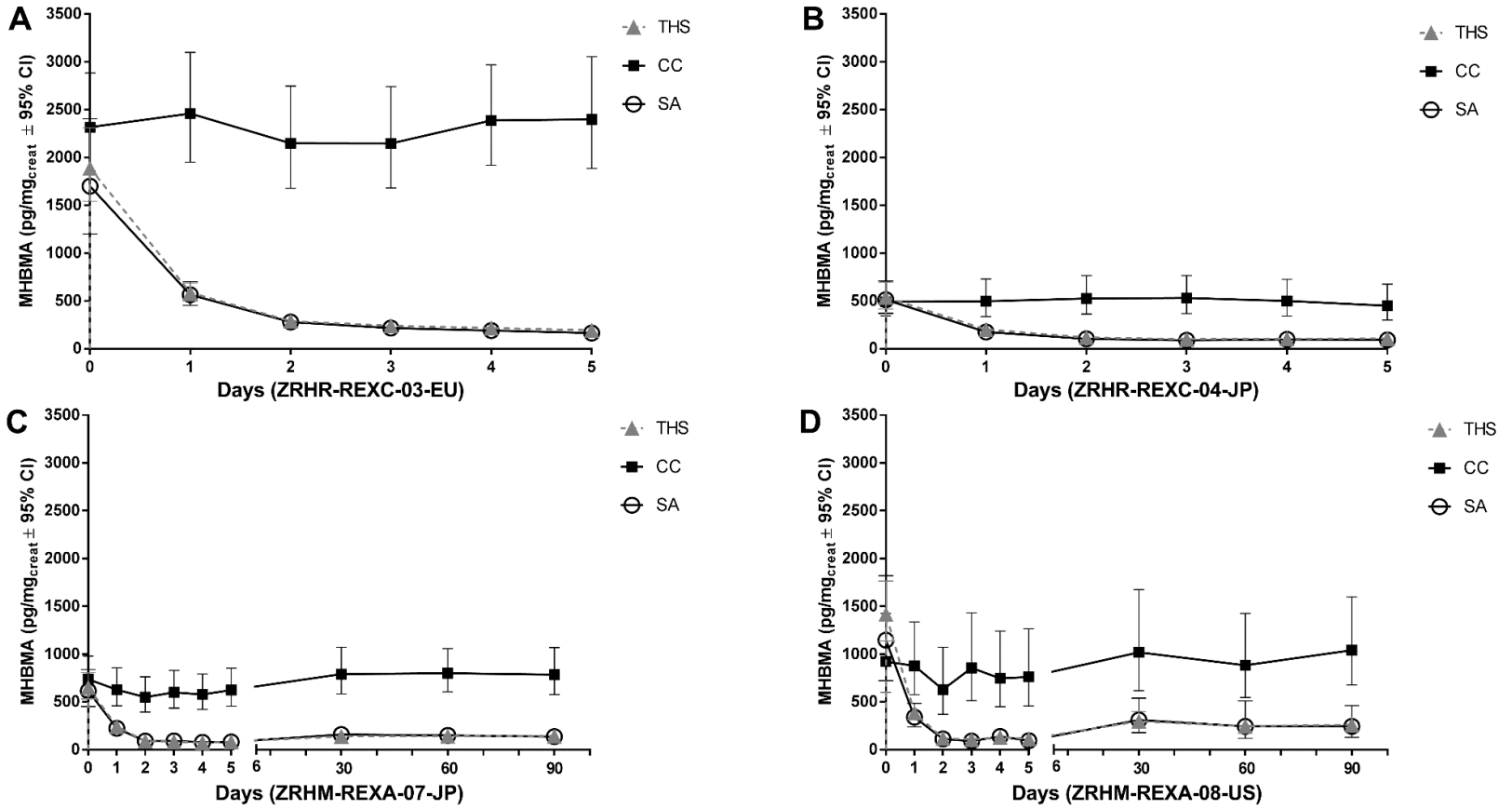


Figure 10 Geometric Mean and 95% CIs of Urinary MHBMA$_{adjC}$ Concentrations (pg/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.7; ZRHR-REXC-04-JP, Table 15.2.3.7; ZRHM-REXA-07-JP, Table 15.2.4.2.1; ZRHM-REXA-08-US, Table 15.2.4.2.1]

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Table 12 Mean Percent Change from Baseline and 95% CIs of Urinary $MHBMA_{adjC}$ (pg/mg_{creat}) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	6.89%	4.90%	-11.98%	2.27%
		95% CI	-1.37; 15.15	-13.60; 23.39	-20.96; -3.01	-26.69; 31.23
	THS	N	79	80	76	65
		% Change	-84.98%	-66.41%	-80.54%	-87.52%
		95% CI	-88.32; -81.63	-74.24; -58.58	-85.31; -75.76	-91.13; -83.91
	SA	N	39	38	39	21
		% Change	-79.56%	-71.76%	-78.67%	-82.14%
		95% CI	-88.33; -70.79	-81.01; -62.51	-84.83; -72.52	-97.05; -67.23
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	15.68%	36.09%
		95% CI	NA	NA	-4.28; 35.64	-1.13; 73.32
	THS	N	NA	NA	70	43
		% Change	NA	NA	-64.30%	-73.29%
		95% CI	NA	NA	-74.18; -54.42	-82.43; -64.15
	SA	N	NA	NA	37	9
		% Change	NA	NA	-66.12%	-27.04%
		95% CI	NA	NA	-75.86; -56.38	-84.07; 29.99

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.7; ZRHR-REXC-04-JP, Table 15.2.3.7; ZRHM-REXA-07-JP, Table 15.2.4.2.1; ZRHM-REXA-08-US, Table 15.2.4.2.1]

6.1.3.2.3.2.1 Analysis of MHBMA Levels at Day 5 and Day 90

Reduced exposure to 1,3-butadiene and measured by MHBMA was clearly demonstrated in 4 studies in different ethnicities, and in controlled, and more near real-world, actual use conditions. At Day 5, switching to THS in Confinement resulted in at least a 77% reduction of MHBMA with a maximum reduction of 91% compared to CC smoking ($p < 0.001$ for each study; Table 13). At Day 90, these levels of reduction were maintained at 81%, in both Ambulatory studies (Table 13) ($p \leq 0.001$).

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Table 13 Adjusted Geometric LS Means of THS to CC ratios of MHBMA at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	8.38%	23.09%	13.49%	12.58%
		95% CI	6.89; 10.20	18.41; 28.95	10.96; 16.60	9.27; 17.05
		p Value	<0.001	<0.001	<0.001	<0.001
		95% CI	94.78; 140.76	92.02; 145.78	80.56; 123.06	83.12; 164.24
Day 90	THS:CC Ratio	LS Mean	NA	NA	19.01%	18.52%
		95% CI	NA	NA	14.68; 24.61	12.85; 26.67
		p Value	NA	NA	<0.001	0.001

CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.2; ZRHR-REXC-04-JP, Table 15.2.3.2; ZRHM-REXA-07-JP, Table 15.2.3.2; ZRHM-REXA-08-US, Table 15.2.3.2]

6.1.3.2.3.2.2 Conclusion

At Baseline, $MHBMA_{adjC}$ were different between studies, with differences of up to 5-fold. The levels were lower in the Japanese populations, while the highest levels were observed in the European study. As the same method was used to measure $MHBMA_{adjC}$ levels across studies, this likely indicates a difference in smoking behavior between population including differences in cigarette brands.

According to literature, Japanese are reported to have preference for cigarettes with charcoal-containing filters, which can retain, to a certain extent, a number of gas smoke constituents found in main stream smoke, and 70% of the brands sold in Japan have a charcoal filter, whereas they are much less popular outside Japan (Coggins 2008, Muscat 2005). Levels of urinary MHBMA in smokers of cigarettes with charcoal-containing filters have been shown to be from 36% to more than 90% lower than those who smoke cigarettes with cellulose acetate filters, while nicotine uptake is similar (Sarkar 2008, Scherer 2006b). On the other hand, Polish population has been shown to have a high prevalence of heavy smokers (with high CC consumption) (Jassem 2014), which could further explain why levels of MHBMA levels at Baseline were the highest in the European study, which was conducted in Poland. MHBMA levels have indeed been shown to be correlated with the number of cigarettes per day (Theophilus 2015). This hypothesis is reinforced by the results of PMI studies where the Baseline daily CC consumption levels were higher in Poland (mean: of around 16 CC per day) compared to US and Japan (between 10 to 13 CC per day) at Baseline [Section 6.2.2 Product Use]. Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g_{creat} [Section 6.2.2 Product Use], which can be also indicative of different smoking behaviors. A study comparing levels of urinary MHBMA levels in different ethnicities in the US found that nicotine equivalents were the strongest predictors of MHBMA levels (Park 2014).

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The profiles of reductions over the 5 days of Confinement were similar in the THS and SA arms, with a maximum decrease observed within the first 2 days, and a plateau appearing from around Day 3, thus being consistent with published half-lives of $MHBMA_{adjC}$, i.e. around 9 hours (Sarkar 2005). The profiles of reductions during the Ambulatory periods were also similar for the THS and SA arms, with an increase of MHBMA levels in both the THS and SA arms from Day 30 to Day 90 compared to Day 5. This increase could be related to exposure to environmental sources of 1,3-butadiene, such as release from carpet backings, butadiene-based food packaging materials (European Chemical Agency (ECHA) 2002), car exhaust fumes in traffic, forest fires or other combustion (U.S. Environmental Protection Agency (EPA) 2009), or to the occasional use of CC. This small increase was, however, also apparent in the CC arms, thus suggesting environmental exposure rather than use of CC.

Percent changes from Baseline of $MHBMA_{adjC}$ during the Confinement periods ranged from -66% to -88% for the THS arms and from -72% to -82% for the SA arms. During the Ambulatory periods, these percent changes were overall maintained in the THS arms, ranging from -64% to -73%, as well as in the SA arms, ranging from -73% to -88%. Several smoking cessation studies conducted over 3 to 8 days showed reductions of $MHBMA_{adjC}$ levels ranging from -82% to -92% from Baseline (Carmella 2012, Carmella 2009, Theophilus 2015, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). A change from Baseline of more than -90% was still observed in a smoking cessation study lasting up to 56 days (Carmella 2012, Carmella 2009). Levels of urinary MHBMA concentrations at the beginning of those published studies ranged from 1630 to 7710 ng/24h, decreasing to ranges of 270 to 632 ng/24h at the end of the studies. Values obtained in PMI's studies at Baseline in the SA arm (range from 525 ng/24h in ZRHR-REXC-04-JP to 2685 ng/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), and at Day 5 (range from 97 ng/24h in ZRHR-REXC-04-JP to 256 ng/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), are thus in line with those published studies, except for the Japanese studies, with lower values in PMI's studies. A former publication assessing decrease of MHBMA in a smoking abstinent group of Japanese subjects after 8 days, also showed concentrations in line with the other studies (Tricker 2012b). Because the method used to measure MHBMA was the same for all studies, it is difficult to explain why Japanese Baseline levels were so low, other than by suggesting a different smoking behavior. The percent changes from Baseline of MHBMA in PMI's studies are nevertheless consistent with published smoking cessation studies of 3 to 8 days.

Clinical studies conducted products based on the heat-not-burn principle, showed reductions of urinary MHBMA levels ranging from -18% to -72% in smokers who switched from CC to the test systems for 5 to 8 days, in Confinement conditions (Frost-Pineda 2008a, Sakaguchi 2014, Tricker 2012a, Tricker 2012b, Tricker 2012d). These studies were conducted in the US, UK, Japan or Korea. In a study conducted over 34 days in Poland, change form Baseline when switching to a heat-not-burn product was of -53% (Martin Leroy 2012).

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Statistically significant reductions were observed in the levels of $MHBMA_{adjC}$ assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 77% to 92%, while there was no overall difference between the THS and SA arms. The reductions in MHBMA observed at Day 5 during the Confinement periods for the THS arms compared to CC arms were overall sustained during the Ambulatory periods of both studies, with reductions of 81% at Day 90.

In summary, the levels of MHBMA observed with THS use were statistically significantly lower from values observed in the CC arms at Day 5 and Day 90 and approaching levels observed in the SA arms as well as to published literature from smoking cessation studies.

6.1.3.2.3.3 3-HPMA – BoExp for Exposure to Acrolein

Acrolein has been classified by the FDA as a respiratory and cardiovascular toxicant (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of 3-HPMA adjusted for creatinine were overall comparable between studies and across arms, with values ranging from 630 to 861 $ng/mg_{creat,}$ and were generally lower in the Japanese populations (Table 14).

Table 14 Geometric Means and 95% CIs of $3\text{-}HPMA_{adjC}$ (ng/mg_{creat}) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	799.37	685.45	642.20	777.25
		95% CI	693.71; 921.13	602.02; 780.44	552.68; 746.21	655.30; 921.88
		Min; Max	287.9; 2246.7	326.8; 1484.9	253.0; 2075.8	286.3; 1838.1
	THS	N	80	80	76	67
		Mean	841.84	661.25	667.53	721.15
		95% CI	745.88; 950.14	582.13; 751.13	599.28; 743.54	645.68; 805.44
		Min; Max	94.6; 2495.7	80.4; 2134.0	264.9; 2669.4	181.0; 2004.9
	SA	N	39	38	39	21
		Mean	861.88	630.87	691.14	711.68
		95% CI	744.98; 997.12	532.70; 747.14	587.29; 813.34	555.64; 911.52
		Min; Max	352.7; 2530.7	209.5; 1474.9	273.3; 1873.9	166.9; 1942.1

(table continues)

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			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	34
		Mean	931.01	599.67	591.33	655.19
		95% CI	825.73; 1049.72	511.70; 702.76	507.72; 688.69	530.57; 809.08
		Min; Max	451.6; 1896.6	182.5; 1421.5	261.3; 1548.8	105.6; 1838.1
	THS	N	79	80	76	73
		Mean	402.26	311.08	304.68	283.88
		95% CI	366.55; 441.45	279.59; 346.12	284.63; 326.14	259.80; 310.20
		Min; Max	36.8; 1261.8	86.8; 814.5	163.3; 631.0	95.1; 730.2
	SA	N	39	38	39	22
		Mean	245.69	199.04	186.71	151.43
		95% CI	226.15; 266.91	173.02; 228.97	163.39; 213.36	126.56; 181.19
		Min; Max	126.9; 436.5	80.8; 740.5	48.9; 366.7	56.7; 295.2
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	695.58	606.10
		95% CI	NA	NA	602.43; 803.13	468.27; 784.48
		Min; Max	NA	NA	271.5; 1945.2	73.4; 1652.8
	THS	N	NA	NA	70	47
		Mean	NA	NA	386.37	314.05
		95% CI	NA	NA	356.30; 418.97	281.51; 350.34
		Min; Max	NA	NA	225.1; 945.4	115.6; 744.4
	SA	N	NA	NA	37	9
		Mean	NA	NA	276.13	177.90
		95% CI	NA	NA	242.11; 314.93	90.83; 348.41
		Min; Max	NA	NA	121.9; 678.1	22.1; 383.1

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.8; ZRHR-REXC-04-JP, Table 15.2.3.8; ZRHM-REXA-07-JP, Table 15.2.4.3.1; ZRHM-REXA-08-US, Table 15.2.4.3.1]

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In subjects who switched to THS or who were abstinent from smoking, a swift reduction compared to CC use at Baseline of 24-hour urinary 3-HPMA$_{adjC}$ was found across the 4 studies. By Day 2 of the study, the amount of excreted 3-HPMA did not drop further in the SA arm. A similar decrease was recorded in the THS group although not entirely at the level of abstainers (Figure 11). Percent changes from Baseline of urinary 3-HPMA$_{adjC}$ levels during the Confinement periods in all 4 studies at Day 5 ranged from -47% to -59% for the THS arms and from -65% to -76% for the SA arms.

In the Ambulatory studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], these changes were maintained at a lesser magnitude, with percent change from Baseline at Day 90 ranging from -37% to -54% in the THS arms, and from -48% to -57% in the SA arms (Table 15).

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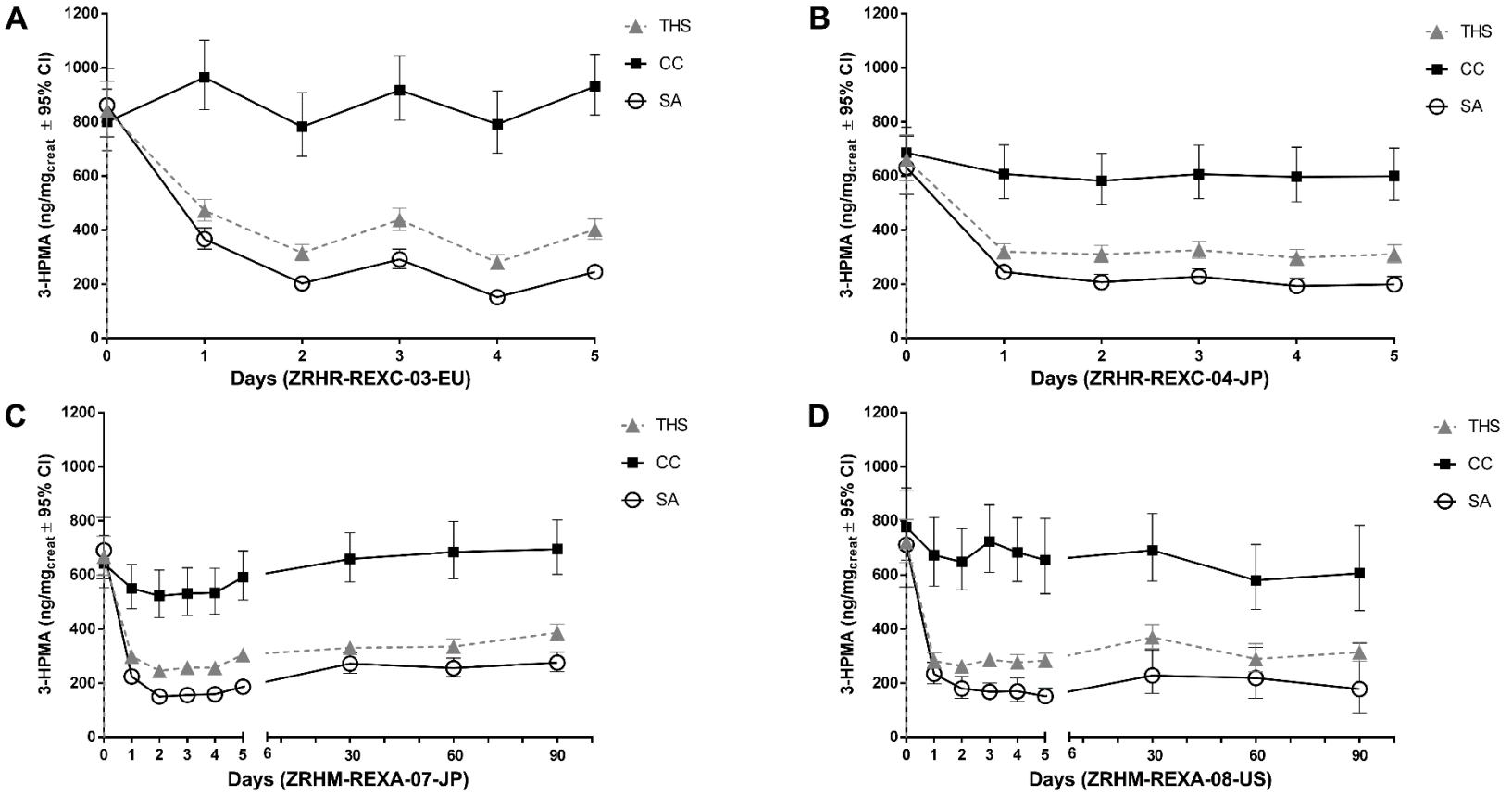


Figure 11 Geometric Mean Urinary and 95% CIs of 3-HPMA$_{adjC}$ Concentrations (ng/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.8; ZRHR-REXC-04-JP, Table 15.2.3.8; ZRHM-REXA-07-JP, Table 15.2.4.3.1; ZRHM-REXA-08-US, Table 15.2.4.3.1]

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Table 15 Mean Percent Change from Baseline and 95% CIs of Urinary 3-HPMA$_{adjC}$ (ng/mg$_{creat}$) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	20.28%	-7.24%	-5.48%	-12.91%
		95% CI	10.41; 30.14	-17.50; 3.02	-12.15; 1.19	-25.18; -0.64
	THS	N	79	80	76	67
		% Change	-49.68%	-47.33%	-50.90%	-58.76%
		95% CI	-54.32; -45.04	-53.47; -41.18	-55.27; -46.54	-62.60; -54.91
	SA	N	39	38	39	21
		% Change	-69.45%	-64.68%	-68.42%	-75.51%
		95% CI	-73.27; -65.63	-70.24; -59.11	-74.39; -62.44	-81.94; -69.07
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	18.63%	-5.54%
		95% CI	NA	NA	3.16; 34.10	-23.91; 12.84
	THS	N	NA	NA	70	43
		% Change	NA	NA	-37.09%	-53.82%
		95% CI	NA	NA	-44.88; -29.30	-59.50; -48.15
	SA	N	NA	NA	37	9
		% Change	NA	NA	-48.38%	-57.21%
		95% CI	NA	NA	-62.21; -34.55	-81.14; -33.28

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.8; ZRHR-REXC-04-JP, Table 15.2.3.8; ZRHM-REXA-07-JP, Table 15.2.4.3.1; ZRHM-REXA-08-US, Table 15.2.4.3.1]

6.1.3.2.3.3.1 Analysis of 3-HPMA$_{adjC}$ at Day 5 and Day 90

At Day 5 switching to THS resulted in at least a 47% reduction of 3-HPMA, with a maximum reduction of 58% compared to CC smoking ($p<0.001$ for each study; Table 16). At Day 90, these effects of switching levels were maintained, with 46% reduction in [ZRHM-REXA-07-JP] and 48% in [ZRHM-REXA-08-US]. A significant reduction of exposure to acrolein was achieved in Menthol and Regular THS, in Caucasian and Asian ethnicities (Table 16) ($p<0.001$).

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Table 16 Adjusted Geometric LS Means of THS to CC ratios of 3-HPMA at Day 5 and Day 90

		ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5 THS:CC Ratio	LS Mean	41.63%	52.86%	50.67%	45.77%
	95% CI	37.75; 45.91	45.67; 61.17	44.88; 57.20	39.22; 53.41
	p Value	<0.001	<0.001	<0.001	<0.001
Day 90 THS:CC Ratio	LS Mean	NA	NA	54.08%	52.02%
	95% CI	NA	NA	46.94; 62.32	40.80; 66.33
	p Value	NA	NA	<0.001	<0.001

CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.3; ZRHR-REXC-04-JP, Table 15.2.3.3; ZRHM-REXA-07-JP, Table 15.2.3.2; ZRHM-REXA-08-US, Table 15.2.3.2]

6.1.3.2.3.3.2 Conclusion

At Baseline, urinary concentrations of 3-HPMA$_{adjC}$ were higher in the European subjects than the Japanese or American (up to 1.6-fold). As the same laboratory and analytical method was used to measure 3-HPMA across studies, this likely indicates a difference in smoking behavior, but also possibly an influence of a difference in diet, as food is a major source of exposure to acrolein (IARC (International Agency for Research on Cancer) 1995).

Polish population has been shown to have a high prevalence of heavy smokers (Jassem 2014), which could explain why levels of 3-HPMA$_{adjC}$ levels at Baseline were the highest in the European study conducted in Poland. 3-HPMA$_{adjC}$ levels were indeed found to be correlated with nicotine equivalent levels (Park 2015, Roethig 2009), and with the number of cigarettes per day (Theophilus 2015). This hypothesis is further reinforced by the results of PMI studies where the Baseline daily CC consumption levels were higher in Poland (mean of around 16 CC per day) compared to US and Japan (between 10 to 13 CC per day) at Baseline [Section 6.2.2 Product Use]. Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g$_{creat}$ [Section 6.2.2 Product Use], which can be also indicative of different smoking behaviors.

The profiles of reductions over the 5 days of Confinement were overall similar in the THS and SA arms both during Confinement and Ambulatory settings. During the Confinement period, the maximum decrease was observed by Day 1, thus being consistent with published half-lives of 3-HPMA, i.e. around 5-9hrs (Gregg 2013). The 3-HPMA$_{adjC}$ levels at which the THS arm plateaued were, however, consistently higher than those of the SA arms, throughout the Confinement and the Ambulatory periods. Slight increases of 3-HPMA$_{adjC}$ after the Confinement periods were observed in in the SA and THS arms of both the ZRHM-REXA-07-JP and ZRHM-REXA-08-US studies, which is likely due to environmental sources of acrolein, or to the occasional use of CC. Small

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amounts of acrolein are produced endogenously during the normal intermediary catabolism of various amino acids and polyamines, as well as during the peroxidation of membrane lipids (International Programme on Chemical Safety (IPCS) 2002, Stevens 2008). Cooked or grilled food derived from cooking oils is also known as a major source of acrolein (IARC (International Agency for Research on Cancer) 1995). The meals provided during the Confinement periods did not include any grilled or pan-fried meat, smoked pre-cooked meats, smoked bacon and sausages, but this was not the case during the Ambulatory period, which can likely explain parts of the increase of 3-HPMA observed in both THS and SA arms after the Confinement periods. As for the differences in levels of 3-HPMA$_{adjC}$ being consistently higher in the THS than in the SA arms, it rather indicates a residual generation of acrolein in THS, which can be produced at relatively low temperature ranges, i.e., between 200-400°C (Torikai 2004). Acrolein is naturally present in tobacco (Rodgman 2013) and is further produced by combustion. In non-combusted tobacco, it may also be formed through heating of glycerin, a constituent which is 2-3 times higher in THS Tobacco Sticks compared to the reference cigarette, 3R4F (see Investigator's Brochures (Philip Morris Products S.A. 2015a, Philip Morris Products S.A. 2015b). Pyrolysis of glycerin has been studied in steam, below 300ºC, or above 600ºC, with acrolein and acetaldehyde observed as the major products at higher temperatures (> 600ºC) (Antal Jr 1985, Stein 1983). Acrolein, however, is already produced from glycerin at temperatures of 200-400ºC (Qadariyah 2011).

Percent changes from Baseline of 3-HPMA$_{adjC}$ during the Confinement periods ranged from -47% to -59% for the THS arms and from -65% to -76% for the SA arms. During the Ambulatory periods, these percent changes were overall maintained in the THS arms, when considering the variability, ranging from -37% to -54%, as well as in the SA arms, ranging from -48% to -57%. Several smoking cessation studies conducted over 3 to 8 days showed reductions of 3-HPMA levels ranging from -35% to -86% from Baseline, with the majority of the studies showing reductions of more than 70% (Carmella 2009, Frost-Pineda 2008a, Sarkar 2008, Theophilus 2015, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). A change from Baseline of -85% was still observed in a smoking cessation study lasting up to 56 days (Carmella 2009). Levels of urinary 3-HPMA concentrations at the beginning of those studies ranged from 434 to 2610 µg/24h, decreasing to ranges of 58 to 1680 µg/24h at the end of the studies. Values obtained in PMI's studies at Baseline in the SA arm (645 µg/24h in ZRHR-REXC-04-JP and 1362 µg/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), and at Day 5 (210 µg/24h in ZRHR-REXC-04-JP and 385 µg/24h ZRHR-REXC-03-EU; data available in the clinical study reports), as well as the percent changes from Baseline, are thus consistent with published smoking cessation studies of 3 to 8 days.

Clinical studies conducted with products based on the heat-not-burn principle showed reductions of urinary 3-HPMA levels ranging from -1% to -57% in smokers who switched from CC to the test systems for 5 to 8 days, in confined conditions (Frost-Pineda 2008a, Roethig 2007, Sakaguchi 2014, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). These studies were conducted in the US, UK, Japan, Poland or Korea. In studies conducted over longer periods of time in Ambulatory conditions, i.e. 34 days or 12 weeks of switching, changes from Baseline when switching to heat-not-burn

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products were only of -21% and -25%, respectively (Frost-Pineda 2008b, Martin Leroy 2012).

Statistically significant reductions were observed in the levels of 3-HPMA$_{adjC}$ assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 47% (with a confidence interval including 50%) to 58%. The magnitude of decrease observed in the SA arms was higher than that observed in the THS arm. The reductions in 3-HPMA$_{adjC}$ observed at Day 5 during the Confinement periods for the THS arms compared to CC arms were overall sustained during the Ambulatory periods, with reductions of 46% and 48% at Day 90.

In summary, the levels of 3-HPMA observed with THS use were statistically significantly lower from values observed in the CC arms at Day 5 and Day 90 and approaching levels observed in the SA arms as well as to published literature from smoking cessation studies. In addition, the reduction of exposure to acrolein observed with THS aerosol in the *in vivo* non-clinical studies is in support of the levels observed in the clinical assessment.

6.1.3.2.3.4 S-PMA – BoExp for Exposure to Benzene

Benzene has been classified by FDA as a carcinogen, and as a cardiovascular and reproductive or developmental toxicant (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of S-PMA concentration adjusted to creatinine (S-PMA$_{adjC}$) ranged from 784 to 2765 pg/mg$_{creat}$, with the highest levels observed in the European population, and the lowest levels seen in the Japanese study populations (Table 17).

Table 17 Geometric Means of S-PMA$_{adjC}$ (pg/mg$_{creat}$) by Study Arm in All Studies, at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	2765.20	784.67	1096.79	1433.17
		95% CI	2227.38; 3432.88	570.61; 1079.02	823.05; 1461.57	1032.20; 1989.89
		Min; Max	357.1; 8830.3	119.1; 6524.2	206.8; 6078.8	160.80; 4946.24
	THS	N	80	80	76	65
		Mean	2394.03	911.15	1058.84	1510.14
		95% CI	1982.83; 2890.50	715.17; 1160.83	857.94; 1306.79	1213.34; 1879.53
		Min; Max	395.9; 11111.1	34.2; 7085.6	167.6; 6057.5	93.03; 9243.90
	SA	N	39	38	39	21
		Mean	2153.82	941.25	1027.37	1488.78
		95% CI	1595.57; 2907.38	724.18; 1223.38	751.76; 1404.03	1012.87; 2188.30
		Min; Max	336.7; 9539.9	200.0; 4073.6	190.4; 5315.9	213.48; 8015.02

(table continues)

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			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	33
		Mean	2922.81	850.02	1096.47	1062.05
		95% CI	2362.80; 3615.54	620.40; 1164.63	805.13; 1493.22	685.84; 1644.62
		Min; Max	352.0; 9345.5	173.8; 8385.4	174.4; 7234.4	118.66; 6677.63
	THS	N	79	80	76	71
		Mean	164.45	143.77	118.36	133.64
		95% CI	144.45; 187.22	126.08; 163.93	107.37; 130.48	111.94; 159.55
		Min; Max	43.9; 873.8	29.4; 597.6	51.5; 280.7	18.74; 1269.23
	SA	N	39	38	39	22
		Mean	143.70	126.34	102.51	133.11
		95% CI	122.15; 169.04	105.51; 151.28	85.19; 123.34	92.18; 192.21
		Min; Max	67.2; 509.0	38.8; 495.9	21.4; 279.9	20.90; 1008.61
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	1157.25	1218.56
		95% CI	NA	NA	848.59; 1578.17	822.54; 1805.25
		Min; Max	NA	NA	168.7; 8096.2	127.1; 7266.2
	THS	N	NA	NA	70	47
		Mean	NA	NA	145.58	314.02
		95% CI	NA	NA	121.67; 174.18	219.66; 448.93
		Min; Max	NA	NA	19.8; 1165.8	25.7; 4007.9
	SA	N	NA	NA	37	9
		Mean	NA	NA	144.07	181.62
		95% CI	NA	NA	109.87; 188.92	72.23; 456.60
		Min; Max	NA	NA	19.3; 1378.4	27.7; 1960.5

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.9; ZRHR-REXC-04-JP, Table 15.2.3.9; ZRHM-REXA-07-JP, Table 15.2.4.4.1; ZRHM-REXA-08-US, Table 15.2.4.4.1]

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A significant reduction of exposure to benzene can be obtained in CC smokers who switch to THS or stop smoking. Following a rapid decrease, at Day 3 the S-PMA levels did not decline any further (Figure 12). At Day 5 of the Confinement, S-PMA lessened from -77% to -92% for THS, and from -84% to -92% for the SA arms across studies. In the 3-month studies, benzene exposure in the THS arm was reduced from Baseline by -81% compared to Baseline levels in the [ZRHM-REXA-07-JP] study and by -65% in the US [ZRHM-REXA-08-US] study (Table 18).

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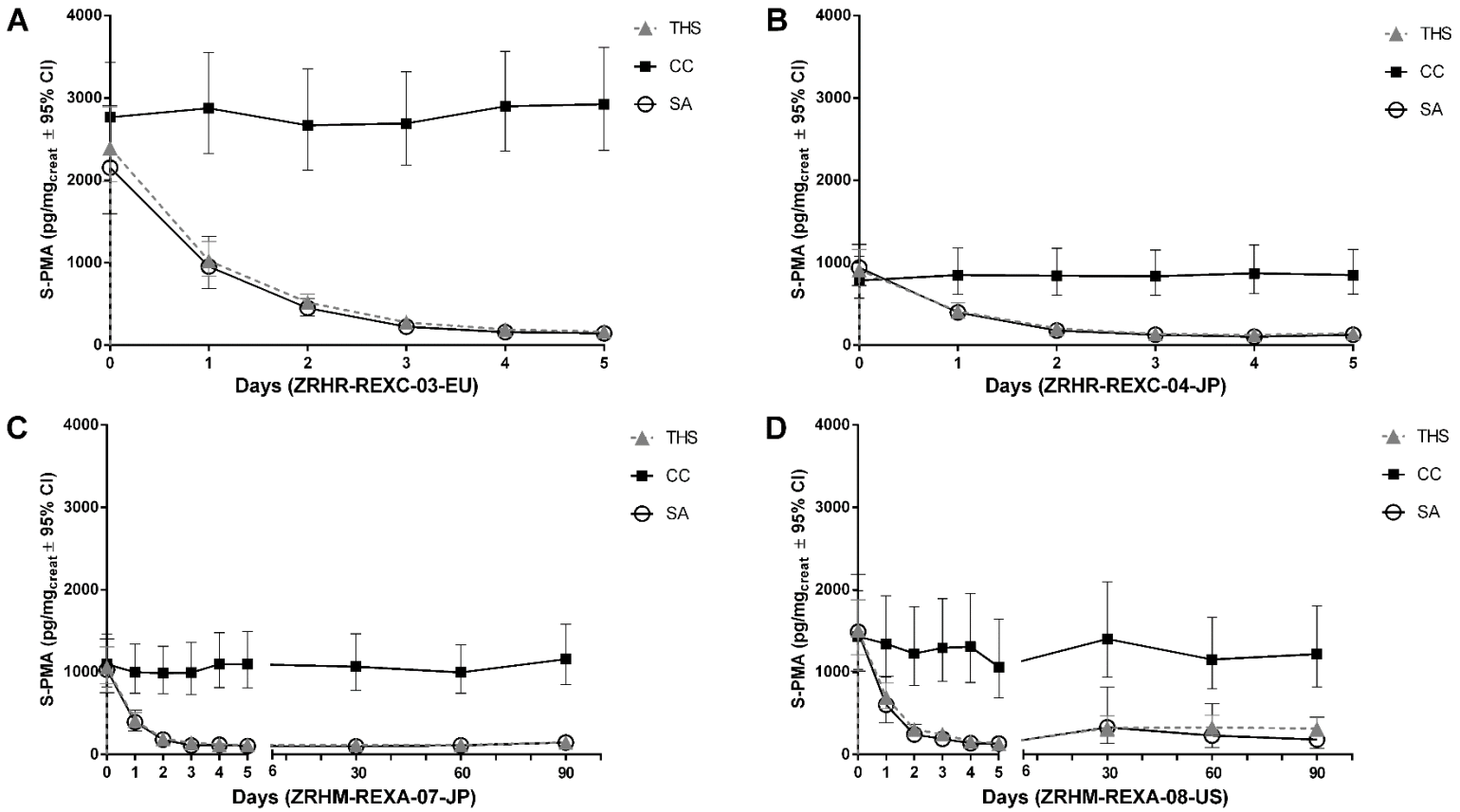


Figure 12 Geometric Mean Urinary and 95% CIs of S-PMA$_{adjC}$ Concentrations (pg/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.9; ZRHR-REXC-04-JP, Table 15.2.3.9; ZRHM-REXA-07-JP, Table 15.2.4.4.1; ZRHM-REXA-08-US, Table 15.2.4.4.1]

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Table 18 Mean Percent Change from Baseline and 95% CIs of Urinary S-PMA$_{adjC}$ (pg/mg$_{creat}$) by Study at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	9.48%	21.22%	5.44%	-12.55%
		95% CI	-0.48; 19.45	2.70; 39.75	-5.72; 16.60	-28.52; 3.41
	THS	N	79	80	76	65
		% Change	-92.03%	-77.24%	-85.88%	-88.81%
		95% CI	-93.20; -90.85	-83.40; -71.08	-88.31; -83.45	-90.98; -86.64
	SA	N	39	38	39	21
		% Change	-91.52%	-84.32%	-86.80%	-89.87%
		95% CI	-93.72; -89.33	-87.25; -81.39	-90.31; -83.29	-92.73; -87.01
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	14.28%	5.54%
		95% CI	NA	NA	-3.83; 32.40	-18.43; 29.52
	THS	N	NA	NA	70	43
		% Change	NA	NA	-81.21%	-65.24%
		95% CI	NA	NA	-84.91; -77.50	-75.98; -54.50
	SA	N	NA	NA	37	9
		% Change	NA	NA	-75.57%	-64.63%
		95% CI	NA	NA	-85.26; -65.88	-96.32; -32.93

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.3.5; ZRHR-REXC-04-JP, Table 15.2.3.5; ZRHM-REXA-07-JP, Table 15.2.4.4.1; ZRHM-REXA-08-US, Table 15.2.4.4.1]

6.1.3.2.3.4.1 Analysis of S-PMA$_{adjC}$ Levels in All Studies at Day 5 and Day 90

A statistically significant reduction of S-PMA$_{adjC}$ in subjects who switched to THS use was demonstrated. At Day 5, across all 4 studies, switching to THS resulted in at least a 84% reduction of S-PMA$_{adjC}$, with a maximum reduction of 94% compared to CC smoking ($p < 0.001$ for each study; Table 19). At Day 90, these observations were maintained, with 87% reduction in ZRHM-REXA-07-JP and 78% reduction in ZRHM-REXA-08-US ($p < 0.001$ for each study).

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Table 19 Adjusted Geometric LS Means of THS to CC ratios of S-PMA at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	5.99%	15.68%	10.97%	12.58%
		95% CI	5.21; 6.87	13.09; 18.78	9.26; 12.99	9.54; 16.58
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	12.80%	22.08%
		95% CI	NA	NA	9.88; 16.58	13.52; 36.06
		p Value	NA	NA	<0.001	0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Tables 15.2.3.4 and 15.2.4.1; ZRHR-REXC-04-JP, Tables 15.2.3.4 and 15.2.4.1; ZRHM-REXA-07-JP, Table 15.2.3.2; ZRHM-REXA-08-US, Table 15.2.3.2]

6.1.3.2.3.4.2 Conclusion

At Baseline, S-PMA$_{adjC}$ levels were different between studies, with differences of up to 2.6 fold in the mean values. The levels were lowest in the Japanese populations, while the highest levels were observed in the European study. As the same laboratory and analytical method was used to measure S-PMA levels across studies, this likely indicates a difference in smoking behavior between populations, including differences in cigarette brands.

Japanese are reported to have preference for non-menthol cigarettes with charcoal-containing filters, which can retain, to a certain extent, a number of gas smoke constituents found in mainstream smoke, and 70% of the brands sold in Japan have a charcoal filter, whereas they are much less popular outside Japan (Coggins 2008, Muscat 2005). Levels of urinary S-PMA in smokers of cigarettes with charcoal-containing filters have been shown to be from 36% up to more than 90% lower than those who smoke cigarettes with cellulose acetate filters, while nicotine uptake is similar (Sarkar 2008, Scherer 2006b). On the other hand, the Polish smoker population has been shown to have a high prevalence of heavy smokers (Jassem 2014), which could further explain why levels of S-PMA levels at Baseline were the highest in the European study (conducted in Poland) as S-PMA levels have indeed been shown to be correlated with the number of cigarettes per day (Theophilus 2015). This hypothesis is reinforced by the results observed in the PMI studies reported here where the Baseline daily CC consumption levels were higher in Poland (mean of around 16 CC per day) compared to US and Japan (between 10 to 13 CC per day) at Baseline [Section 6.2.2 – Product Use]. Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g$_{creat}$ [Section 6.2.2 – Product Use], which can be also indicative of different smoking behaviors.

The profiles of reductions were similar in the THS and SA arms both in Confinement and Ambulatory settings. During the Confinement periods of all 4 studies, a maximum decrease was observed within the first 2 days, with a plateau appearing from around Day 3, thus being consistent with published half-lives of S-PMA, i.e. around 9 hours (Benowitz 2009, Boogaard 1996, van Sittert 1993), while there were slightly higher S-PMA$_{adjC}$ levels in the THS arm compared to the SA arm from Day 30 to Day 90 in the US study.

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Percent changes from Baseline of S-PMA$_{adjC}$ across studies throughout both Confinement and Ambulatory periods ranged from -77% to -92% for the THS arms and from -84% to -92% for the SA arms. Several published smoking cessation studies conducted over 3 to 8 days showed similar reductions of S-PMA levels ranging from -56% to -95% from Baseline, with the majority of the studies showing reductions of more than 70% (Carmella 2009, Feng 2006, Sarkar 2008, Theophilus 2015, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). A change from Baseline of more than -90% was still observed in a smoking cessation study lasting up to 56 days (Carmella 2009). In PMI's studies, percent change from Baseline at the end of the Ambulatory phases, i.e., Day 90, were still of -65% to -81% for the THS arms, and of -64% and -76% for the SA arms. Levels of S-PMA$_{adjC}$ at the beginning of those published studies ranged from 766 to 4980 ng/24h, decreasing to ranges of 95 to 1370 ng/24h at the end of the studies. Values obtained in PMI's studies at Baseline in the SA arm (range from 963 ng/24h in ZRHR-REXC-04-JP to 3404 ng/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), and at Day 5 (range from 125 ng/24h in ZRHM-REXA-07-JP to 225 ng/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), as well as the percent changes from Baseline, are thus consistent with published smoking cessation studies of 3 to 8 days.

Clinical studies conducted with products based on the heat-not-burn principle, showed reductions of urinary S-PMA$_{adjC}$ levels ranging from -40% to -86% in smokers who switched from CC to the test systems for 5 to 8 days, in Confinement conditions (Frost-Pineda 2008a, Roethig 2007, Sakaguchi 2014, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). These studies were conducted in the US, UK, Japan or Korea. In studies conducted over longer periods of time in Ambulatory conditions, , i.e. 34 days or 12 weeks of switching, in Poland and in the US, changes from Baseline when switching to heat-not-burn products were of -64% and -48%, respectively (Frost-Pineda 2008b, Martin Leroy 2012).

Significant reductions were observed in the levels of S-PMA$_{adjC}$ assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 84% to 94%, while there was overall no difference between the THS and SA arms. These reductions were sustained during the Ambulatory periods, with decreases of 78% to 87% at Day 90. The smaller reductions at the end of the Ambulatory periods could be related to exposure to environmental sources of benzene, such as car exhaust fumes in traffic or fumes from gasoil stations (U.S. Department of Health and Human Services 2007), or to the occasional use of CC, or any other confounding factors.

In summary, the levels of S-PMA observed with THS use were statistically significantly lower from values observed in the CC arms, at Day 5 and Day 90, and approaching levels observed in the SA arms as well as to published literature from smoking cessation studies. In addition, the reduction of exposure to benzene observed with THS aerosol in the *in vivo* non-clinical studies is in support of the levels observed in the clinical assessment.

6.1.3.2.3.5 Total NNAL – BoExp for Exposure to NNK

NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) has been classified by FDA as a carcinogen (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of Total NNAL concentration adjusted to creatinine (NNAL$_{adjC}$) differed between studies and across arms, with values ranging form 77.0 to 150.01 pg /mg$_{creat}$,

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with the highest levels observed in the US population, while the lowest levels were found in the Japanese populations (Table 20).

Table 20 Geometric Means and 95% CIs of Total $NNAL_{adjC}$ (pg/mg_{creat}) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	105.05	77.29	84.77	147.90
		95% CI	84.10; 131.21	58.68; 101.81	68.88; 104.33	104.97; 208.39
		Min; Max	24.2; 323.9	10.1; 407.8	17.0; 318.8	15.3; 1154.7
	THS	N	80	80	76	67
		Mean	111.01	77.86	85.64	150.01
		95% CI	95.44; 129.13	64.20; 94.42	72.96; 100.51	119.80; 187.83
		Min; Max	7.7; 302.7	5.0; 612.6	11.9; 342.9	5.0; 643.9
	SA	N	39	38	39	21
		Mean	119.40	77.00	79.54	142.18
		95% CI	94.97; 150.10	60.85; 97.42	61.76; 102.42	94.14; 214.73
		Min; Max	25.0; 387.1	23.4; 278.1	11.0; 376.4	35.3; 979.6
Day 5	CC	N	41	40	42	34
		Mean	107.04	76.55	85.94	120.29
		95% CI	85.90; 133.37	59.76; 98.04	70.93; 104.13	82.09; 176.26
		Min; Max	20.5; 402.5	20.7; 433.4	15.1; 273.8	6.1; 1154.7
	THS	N	79	80	76	73
		Mean	49.65	37.77	37.90	57.04
		95% CI	42.47; 58.05	31.43; 45.38	32.29; 44.48	46.17; 70.48
		Min; Max	5.5; 164.7	4.6; 355.8	5.0; 123.8	1.2; 240.5
	SA	N	39	38	39	22
		Mean	41.51	28.63	29.58	54.74
		95% CI	31.76; 54.26	21.02; 39.00	22.24; 39.35	36.17; 82.83
		Min; Max	4.5; 183.7	4.4; 153.4	3.3; 139.7	11.9; 392.4

(table continues)

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			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	95.03	152.11
		95% CI	NA	NA	77.31; 116.82	108.38; 213.47
		Min; Max	NA	NA	22.4; 284.5	20.8; 542.9
	THS	N	NA	NA	70	47
		Mean	NA	NA	23.23	47.53
		95% CI	NA	NA	19.34; 27.91	34.80; 64.91
		Min; Max	NA	NA	3.5; 158.0	2.3; 474.7
	SA	N	NA	NA	37	9
		Mean	NA	NA	13.95	48.63
		95% CI	NA	NA	9.00; 21.60	17.69; 133.71
		Min; Max	NA	NA	1.0; 166.1	2.9; 235.3

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.32; ZRHR-REXC-04-JP, Table 15.2.4.32; ZRHM-REXA-07-JP, Table 15.2.4.5.1; ZRHM-REXA-08-US, Table 15.2.4.5.1]

The profile of Total $NNAL_{adjC}$ decrease was found similar between THS and SA. The decline was gradual from Baseline to Day 5, without having yet reached a plateau. In the ZRHM-REXA-07-JP, the levels of Total $NNAL_{adjC}$ reached the maximum reduction at Day 90 with a gradual and continuous reduction throughout the Ambulatory period (Figure 13).

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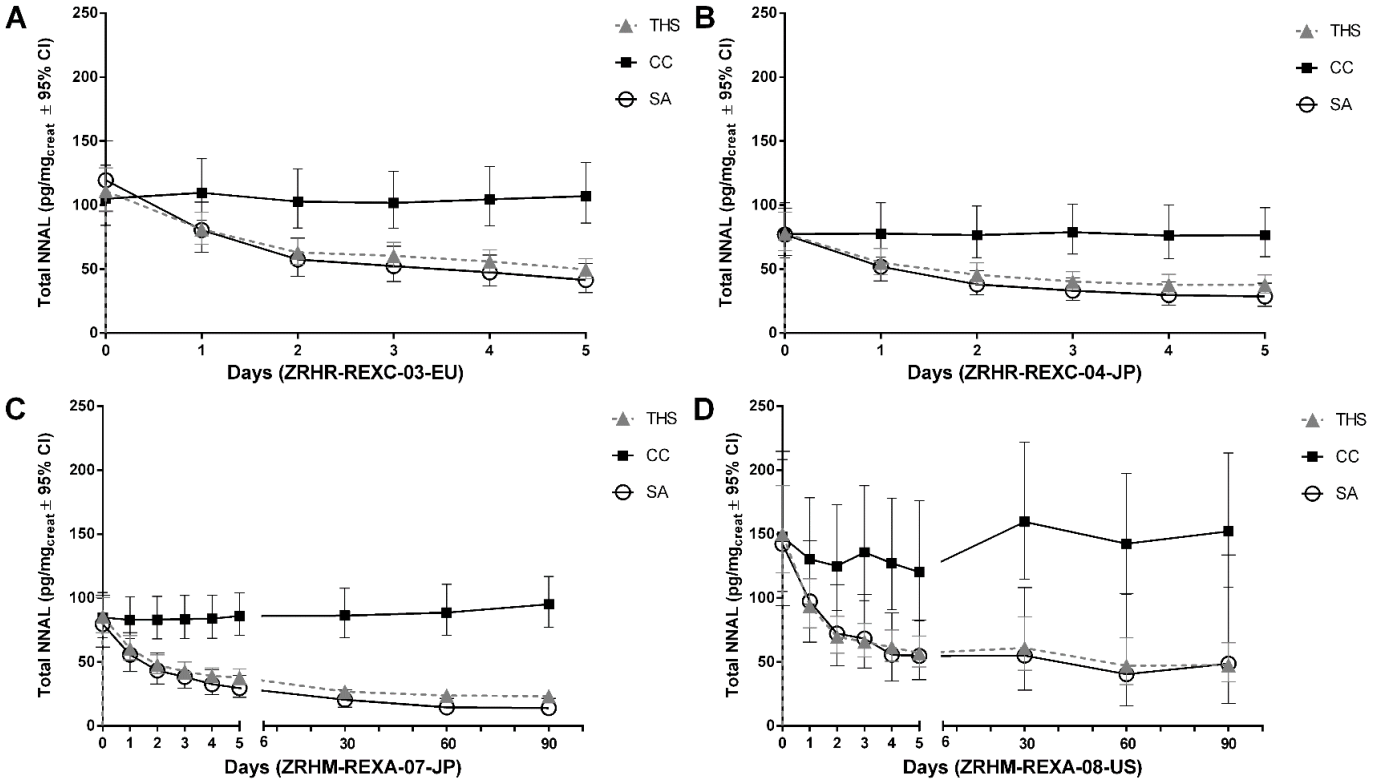


Figure 13 Geometric Mean and 95% CIs of Urinary Total NNAL$_{adjC}$ Concentrations (pg/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.32; ZRHR-REXC-04-JP, Table 15.2.4.32; ZRHM-REXA-07-JP, Table 15.2.4.5.1; ZRHM-REXA-08-US, Table 15.2.4.5.1]

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At Day 5, the levels of urinary Total NNAL were comparable between studies, with levels ranging from 33 to 57 pg/mg_{creat} in the THS arms and from 28 to 54 pg/mg_{creat} in the SA arm. The lowest levels were observed in the Japanese populations and the highest in the US population. At Day 90, the levels of Total NNAL were higher for the US population, with 23 and 47 pg/mg_{creat} in the THS arms in ZRHM-REXA-07-JP and ZRHM-REXA-08-US, respectively, and 13 and 48 pg/mg_{creat} in the SA arms (Table 20).

Percent changes from Baseline of urinary Total NNAL levels during the Confinement periods in all 4 studies at Day 5 ranged from -48% to -61% for the THS arms and from -59% to -64% for the SA arms. In the 2 Ambulatory studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], these changes were retained or further increased, with percent change from Baseline at Day 90 of -69% and -67% (median value) respectively in the THS study arms (Table 21).

In the SA group of the [ZRHM-REXA-07-JP] study, percent change from Baseline at Day 90 was of -67%. In the SA arm of the [ZRHM-REXA-08-US] study, the distribution was skewed by outliers and by the limited number of subjects in the the SA group at Day 90 (N=9). The median values at Day 90are thus reported instead of the mean, for all arms.

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Table 21 Percent Change from Baseline and 95% CIs of Urinary Total $NNAL_{adjC}$ (pg/mg_{creat}) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	3.85%	8.82%	3.91%	-5.58%
		95% CI	-2.84; 10.54	-6.42; 24.07	-3.83; 11.65	-20.09; 8.93
	THS	N	79	80	76	67
		% Change	-53.98%	-48.04%	-54.39%	-60.23%
		95% CI	-56.69; -51.27	-52.73; -43.36	-57.01; -51.78	-63.66; -56.81
	SA	N	39	38	39	21
		% Change	-63.95%	-58.75%	-61.03%	-58.86%
		95% CI	-66.98; -60.92	-65.04; -52.47	-64.46; -57.59	-66.99; -50.74
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	18.79%	24.87% #
		95% CI (or Q1, Q3 #)	NA	NA	5.57; 32.01	-9.32; 51.26 #
	THS	N	NA	NA	70	43
		% Change	NA	NA	-68.58%	-67.08% #
		95% CI (or Q1, Q3 #)	NA	NA	-73.66; -63.50	-84.97; -43.71 #
	SA	N	NA	NA	37	9
		% Change	NA	NA	-66.54%	-34.62% #
		95% CI (or Q1, Q3 #)	NA	NA	-78.36; -54.73	-57.72; 21.82 #

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Because of limited number of subjects in the SA arm and outliers, percent change from Baseline values for ZRHM-REXA-08-US are reported as median at Day 90 (Q1; Q3).

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.32; ZRHR-REXC-04-JP, Table 15.2.4.32; ZRHM-REXA-07-JP, Table 15.2.4.5.1; ZRHM-REXA-08-US, Table 15.2.4.5.1]

6.1.3.2.3.5.1 Analysis of Total NNAL at Day 5 and Day 90

At Day 5, a reduction upon switching to THS of at least 50% was already observed in all 4 studies. A statistically significant reduction at Day 90 of urinary Total $NNAL_{adjC}$ in subjects who switched to THS use, was demonstrated ($p < 0.001$ for each study; Table 22). At Day 90, across the 2 Ambulatory studies, switching to THS resulted in at least a 74% reduction of Total $NNAL_{adjC}$, with a maximum reduction of 77% compared to CC smoking (Table 22) ($p < 0.001$).

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Table 22 Adjusted Geometric LS Means of THS to CC to SA ratios of NNAL at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	43.54%	49.03%	43.69%	43.81%
		95% CI	39.34; 48.19	41.95; 57.30	39.62; 48.17	36.92; 51.97
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	23.25%	26.41%
		95% CI	NA	NA	17.38; 31.11	17.31; 40.26
		p Value	NA	NA	<0.001	<0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.31; ZRHR-REXC-04-JP, Table 15.2.4.31; ZRHM-REXA-07-JP, Table 15.2.3.2; ZRHM-REXA-08-US, Table 15.2.3.2]

6.1.3.2.3.5.2 Conclusion

At Baseline, urinary concentrations of Total $NNAL_{adjC}$ were different between studies, with differences being almost 2-fold. The levels were the lowest in the Japanese populations, while the highest levels were observed in the US study. As the same laboratory and analytical method were used to measure Total NNAL levels across studies, this likely indicates a difference in smoking behavior between population including differences in cigarette brands.

Japanese preference for cigarettes with charcoal-containing filters has been reported (Muscat 2005), and 7 out of 10 brands sold in Japan have a charcoal filter (Coggins 2008, IARC (International Agency for Research on Cancer) 2004). Levels of NNK in the aerosol of cigarettes with charcoal-containing filters have been shown to be up to 58% lower than in cigarettes with cellulose acetate filters (Muscat 2005). Furthermore, reduction of urinary concentrations levels of Total NNAL was shown to be from 11% to 37% lower in smokers of cigarettes with charcoal-containing filters (Sarkar 2008). Also, tobacco blends differ in Japan, containing Oriental and Virginia types of tobacco, which have been shown to have the lowest concentrations of pre-formed NNK (IARC (International Agency for Research on Cancer) 2004). On the other hand, Polish population has been shown to have a high prevalence of heavy smokers (Jassem 2014), which could explain why levels of Total $NNAL_{adjC}$ levels at Baseline were higher in the European study, which was conducted in Poland, than in the Japanese studies. This hypothesis is reinforced by the results of PMI studies where the Baseline daily CC consumption levels were higher in Poland (mean of around 16 CC per day) compared to Japan (between 10 to 13 CC per day) at Baseline [Section 6.2.2 – Product Use]. Total NNAL levels have indeed been shown to be correlated with the number of cigarettes per day (Theophilus 2015). Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g_{creat} [Section 6.2.2 – Product Use], which can also be indicative of different smoking behaviors. Total NNAL levels have been shown to be well correlated with nicotine. As for why Baseline

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levels were the highest in the US, one plausible explanation is the blends used in different countries, as subjects were free to use their regular brands of cigarettes throughout the studies, when enrolled in a study. There is indeed a wide variation in the amount of TSNAs in marketed cigarettes, being the highest in cigarettes made of dark tobacco, and the lowest in Virginia and American blend cigarettes (IARC (International Agency for Research on Cancer) 2004). Burley tobacco contains the highest levels of TSNAs. American blends, in which a significant portion of the Virginia tobacco is replaced by air-cured tobaccos (usually Burley) (Roemer 2012) thus generally contain more NNK than cigarettes sold in Japan or in Europe, which likely explains why Baseline levels in PMI's studies were the highest in the US population (IARC (International Agency for Research on Cancer) 2004). On the other hand, the Japanese market offers more choices of non-American blends, with cigarettes that often contain more Virginia tobacco, which can thus further explain the lowest Baseline levels in PMI's Japanese studies.

The profiles of reductions over the 5 days of Confinement were similar in the THS and SA arms, with a gradual decrease throughout the whole period, without reaching a plateau, thus being consistent with published half-lives of Total NNAL as up to 40-45 days (Hecht 1999a). Published half-lives of total NNAL are, however, quite variable, ranging from 4 to 45 days. A more recent study suggests a terminal half-life of 10 to 18 days, (Goniewicz 2009). The profiles of reductions during the Ambulatory periods further confirm this long half-life, as the levels continued to steadily decrease, with profiles similar for the THS and SA arms.

NNK is present in non-combusted tobacco (Rodgman 2013) and can be released to an aerosol by evaporation (Forster 2015). Tobacco specific nitrosamines are indeed largely formed during tobacco curing and can thus be transferred even without pyrolysis (Brown 2003). In a recent paper by Forster et al. (Forster 2015), NNK was shown to be quantifiable in smoke chemistry at 140°C and 160°C. Its release did not follow a consistent linear trend throughout the temperature ranges, which is probably because it is transferred by evaporation from the tobacco blend. Release of NNK (and NNN) from tobacco into the aerosol was low (<10%) compared to the available amounts in the used tobacco rod (Forster 2015). Direct transfer of TSNAs from tobacco to smoke accounts for about 30% of the NNK (and 40% of the NNN), with the remainder being formed during smoking (Rodgman 2013). At low temperatures, NNK could thus be released (despite the 90% or more decrease in smoke chemistry compared to a 3R4F reference cigarette (Philip Morris Products S.A. 2015a, Philip Morris Products S.A. 2015b), at somewhat lower levels than NNN, which seems to be the case for THS, as the differences of NNN levels in the THS compared to the SA arms were more marked than those with Total NNAL (section 6.1.3.2.3.7).

Percent changes from Baseline of Total $NNAL_{adjC}$ during the Confinement periods ranged from -48% to -60% for the THS arms and from -59% to -64%, for the SA arms. During the Ambulatory periods, these percent changes were overall maintained in the THS arms, ranging from -56% to -69%. In the SA arm of the ZRHM-REXA-07-JP study, percent change from Baseline at Day 90 was of -67%, while the interpretation of this assessment in the ZRHM-REXA-08-US was limited, because of an extremely high variability, certainly linked to the low number of subjects in this group at the end of the

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study (n=9). The median value in this case is probably a more reliable measure, showing a percent change from Baseline of -34%.

Several smoking cessation studies conducted over 3 to 8 days showed reductions of Total NNAL levels ranging from 60% to 78% from Baseline (Carmella 2009, Roethig 2007, Stepanov 2009a, Theophilus 2015, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). Smoking cessation studies of 2 weeks, with the use of nicotine replacement therapies, showed decreases of Total NNAL of 78% to 86% (Stepanov 2009a, Stepanov 2009b). Levels of urinary Total NNAL quantity excreted over 24 hours at the beginning of those published studies ranged from 146 to 731 ng/24h, decreasing to ranges of 45 to 311 ng/24h at the end of the studies. Values obtained in PMI's studies at Baseline in the SA arm (range from 78 ng/24h in ZRHR-REXC-04-JP to 228 ng/24h in ZRHM-REXA-08-US; data available in the clinical study reports), and at Day 5 (range from 36 ng/24h in ZRHM-REXA-07-JP to 91 ng/24h in ZRHM-REXA-08-US; data available in the clinical study reports), as well as the percent changes from Baseline, are thus consistent with those published smoking cessation studies of 3 to 8 days. Absolute values obtained in PMI's studies, both in the THS and SA arms, appeared to be slightly lower than those published, including those published for smokers not undergoing smoking cessation (ranges provided by the Institute of Medicine are 230-606 ng/24h (IOM (Institute of Medicine) 2012). One plausible explanation would be the effectiveness of measures taken on curing and agricultural practices designed to minimize TSNA formation in tobacco, as shown by a significant reduction of NNN and NNK in cigarette brands between 2000 and 2014 (Gunduz 2016). Smokers today are thus likely to be less exposed to TSNAs than those assessed even a few years ago. Differences in bioanalytical methods could also contribute to this difference. Percent changes from Baseline are, however, consistent with published smoking cessation studies of 3 to 8 days.

Clinical studies conducted with products based on the heat-not-burn principle showed reductions of urinary total NNAL levels ranging from -39% to -87% in smokers who switched from CC to the test systems for 5 to 8 days, in Confinement conditions (Frost-Pineda 2008a, Roethig 2007, Sakaguchi 2014, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). These studies were conducted in the US, UK, Japan or Korea. In studies conducted over longer periods of time, i.e. 34 days or 12 weeks of switching, in Poland and in the US, reductions from Baseline when switching to heat-not-burn products were of 47% and 62%, respectively (Frost-Pineda 2008b, Martin Leroy 2012).

Statistically significant reductions were observed in the levels of Total $NNAL_{adjC}$ assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 51% to 56% in the 4 studies, with levels overall comparable, with only slight differences, to those who were abstinent from smoking. Further reductions in Total $NNAL_{adjC}$ to those measured at Day 5 during the Confinement periods for the THS arms compared to CC arms were observed during the Ambulatory periods, with reductions of 74% to 77% at Day 90, in ZRHM-REXA-08-US and ZRHM-REXA-07-JP, respectively. Total NNAL being tobacco specific, there is no risk of environmental exposure during the Ambulatory periods, other than second-hand or third-hand smoke or occasional use of CC (IARC (International Agency for Research on Cancer) 2007).

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In summary, the levels of Total NNAL observed with THS use were statistically significantly lower from values observed in the CC arms at Day 90, but also at Day 5 and approaching levels observed in the SA arms as well as to published literature from smoking cessation studies. In addition, the reduction of exposure to NNK observed with THS aerosol in the *in vivo* non-clinical studies is in support of the levels observed in the clinical assessment.

6.1.3.2.3.6 1-OHP – BoExp for Exposure to Pyrene

Pyrene exposure has often been used as a surrogate for exposure to polycyclic aromatic hydrocarbons (PAH), despite the lack of demonstrated toxicity of this specific PAH.

At Baseline, urinary levels of total 1-OHP adjusted to creatinine (1-OHP_{adjC}) differed between studies and across arms, with values ranging from 107.62 to 223.95 pg/mg_{creat}. The highest levels were observed in the European population and the lowest levels in the US population (Table 23).

Table 23 Geometric Means and 95% CIs of Total 1-OHP_{adjC} (pg/mg_{creat}) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	218.41	177.51	164.33	139.92
		95% CI	196.28; 243.03	158.88; 198.33	143.20; 188.58	111.20; 176.05
		Min; Max	106.3; 476.8	98.1; 381.2	76.4; 517.8	29.8; 386.7
	THS	N	80	80	76	65
		Mean	217.69	189.90	153.98	146.56
		95% CI	197.88; 239.48	171.66; 210.07	138.85; 170.75	127.08; 169.03
		Min; Max	81.2; 524.1	46.3; 542.5	60.1; 409.2	27.7; 841.5
	SA	N	39	38	39	22
		Mean	223.95	163.51	148.01	107.62
		95% CI	198.89; 252.17	139.51; 191.63	127.26; 172.14	85.31; 135.76
		Min; Max	101.7; 473.8	52.3; 351.8	56.8; 416.0	47.1; 284.2
Day 5	CC	N	41	40	42	33
		Mean	182.85	149.62	122.90	135.14
		95% CI	161.24; 207.37	132.68; 168.72	104.71; 144.26	111.12; 164.35
		Min; Max	79.2; 400.0	62.9; 328.9	50.9; 386.0	47.9; 327.8
	THS	N	79	80	76	71
		Mean	81.22	73.02	46.36	64.87
		95% CI	74.82; 88.16	65.19; 81.79	41.68; 51.55	57.55; 73.12
		Min; Max	38.5; 239.9	21.5; 407.3	17.4; 196.7	10.0; 220.1

(table continues)

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			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 90	SA	N	39	38	39	22
		Mean	85.13	62.99	41.14	47.80
		95% CI	75.37; 96.15	53.07; 74.75	35.42; 47.78	35.48; 64.40
		Min; Max	41.2; 293.3	19.5; 256.8	16.1; 111.8	11.9; 182.9
	CC	N	NA	NA	41	32
		Mean	NA	NA	167.38	163.80
		95% CI	NA	NA	146.23; 191.58	132.71; 202.16
		Min; Max	NA	NA	64.8; 478.5	50.7; 386.3
	THS	N	NA	NA	70	47
		Mean	NA	NA	85.47	117.77
		95% CI	NA	NA	76.64; 95.33	98.44; 140.89
		Min; Max	NA	NA	31.6; 293.9	33.9; 387.6
	SA	N	NA	NA	37	9
		Mean	NA	NA	88.21	70.19
		95% CI	NA	NA	75.53; 103.01	50.22; 98.11
		Min; Max	NA	NA	30.0; 267.9	40.3; 139.2

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.10; ZRHR-REXC-04-JP, Table 15.2.4.10; ZRHM-REXA-07-JP, Table 15.2.4.7.1; ZRHM-REXA-08-US, Table 15.2.4.7.1]

In both, the THS and SA study groups, the majority of the reduction of total 1-OHP levels was reached within the first 2 days after switching to THS, or smoking abstinence, followed by a more gradual decrease to Day 5. Total 1-OHP levels moved up slightly during the beginning of the Ambulatory period of the [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US] studies, but again plateaued from Day 30 onwards (Figure 14).

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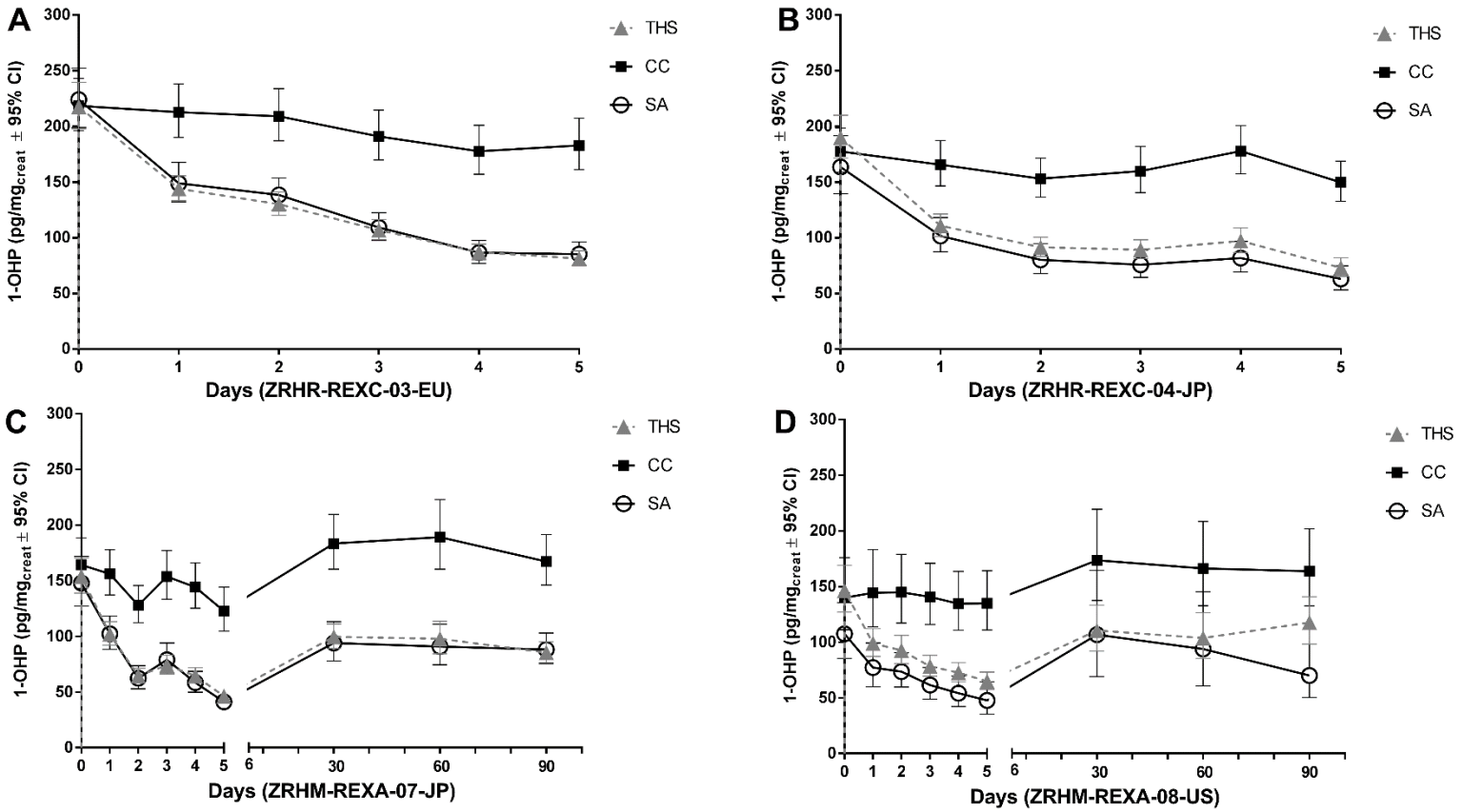


Figure 14 Geometric Mean Urinary and 95% CIs of Total 1-OHP$_{adjC}$ Concentrations (pg/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.10; ZRHR-REXC-04-JP, Table 15.2.4.10; ZRHM-REXA-07-JP, Table 15.2.4.7.1 and ZRHM-REXA-08-US, Table 15.2.4.7.1]

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Percent changes from Baseline of urinary total 1-OHP levels during the Confinement periods in all 4 studies at Day 5 ranged from -53% to -68% or the THS arms and from -53% to -70% for the SA arms. In both 3 month studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], these changes were smaller than during the Confinement periods, with percent change from Baseline at Day 90 ranging from -15% to -37% in the THS arms, and from -20% to -31% in the SA arms (Table 24).

Table 24 Mean Percent Change from Baseline and 95% CIs of Urinary Total 1-OHP$_{adjC}$ (pg/mg$_{creat}$) by Study at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	-13.52%	-14.31%	-23.00%	-4.82%
		95% CI	-21.11; -5.92	-19.42; -9.21	-29.55; -16.44	-13.43; 3.79
	THS	N	79	80	76	65
		% Change	-60.17%	-58.57%	-68.08%	-53.41%
		95% CI	-63.70; -56.65	-62.65; -54.49	-70.54; -65.62	-57.59; -49.23
	SA	N	39	38	39	22
		% Change	-59.94%	-59.32%	-70.04%	-53.14%
		95% CI	-64.26; -55.62	-63.86; -54.78	-73.62; -66.47	-59.96; -46.32
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	7.87%	26.54%
		95% CI	NA	NA	-1.84; 17.57	10.95; 42.13
	THS	N	NA	NA	70	43
		% Change	NA	NA	-36.75%	-14.61%
		95% CI	NA	NA	-44.94; -28.56	-28.64; -0.58
	SA	N	NA	NA	37	9
		% Change	NA	NA	-31.39%	-19.83%
		95% CI	NA	NA	-44.18; -18.59	-34.58; -5.07

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.10; ZRHR-REXC-04-JP, Table 15.2.4.10; ZRHM-REXA-07-JP, Table 15.2.4.7.1; ZRHM-REXA-08-US, Table 15.2.4.7.1]

6.1.3.2.3.6.1 Analysis of Total 1-OHP at Day 5 Day 90

At Day 5, across all 4 studies, switching to THS resulted in at least a 52% reduction of total 1-OHP$_{adjC}$, with a maximum reduction of 61% compared to CC smoking ($p < 0.001$ fro each study; Table 25). At Day 90, these levels of reduction were maintained, at slightly lower levels, with reductions of 48% in [ZRHM-REXA-07-JP] and 34% in [ZRHM-REXA-08-US] ($p < 0.001$) (Table 25).

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Table 25 Adjusted Geometric LS Means of THS to CC ratios of Total 1-OHP at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	44.35%	46.44%	39.18%	48.11%
		95% CI	39.88; 49.33	41.32; 52.19	34.82; 44.07	42.11; 54.96
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	52.02%	66.46%
		95% CI	NA	NA	44.83; 60.38	52.67; 83.84
		p Value	NA	NA	<0.001	<0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.9; ZRHR-REXC-04-JP, Table 15.2.4.9; ZRHM-REXA-07-JP, Table 15.2.3.4; ZRHM-REXA-08-US, Table 15.2.3.4]

6.1.3.2.3.6.2 Conclusion

At Baseline, urinary concentrations of total 1-OHP were quite comparable between studies, with levels that were slightly higher in the European study (about 1.5 fold maximum). As the same method was used to measure total 1-OHP levels across studies, this likely indicates a difference in smoking behavior between population including differences in cigarette brands with likely no influence of the charcoal filters. Indeed, the influence of cigarettes with charcoal-containing filters on the release of the least volatile compounds of tobacco smoke, including PAHs, has been shown to be minimal (Polzin 2008).

The Polish population has been shown to have a high prevalence of heavy smokers (Jassem 2014), which could explain why levels of total 1-OHP levels at Baseline were slightly higher in the European study, conducted in Poland. Total 1-OHP levels have indeed been shown to be correlated with the number of cigarettes per day (Theophilus 2015). This hypothesis is reinforced by the results of PMI studies where the Baseline daily CC consumption levels were higher in Poland (mean of around 16 CC per day) compared to US and Japan (between 10 to 13 CC per day) at Baseline [Section 6.2.2 – Product Use]. Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g_{creat} [Section 6.2.2 – Product Use], which can also be indicative of different smoking behaviors.

The profiles of reductions over the 5 days of Confinement were overall similar in the THS and SA arms, with the majority of the reduction of total 1-OHP levels occurring within the first 2 days, followed by a more gradual decrease to Day 5, thus being consistent with published half-lives of total 1-OHP, i.e. between 12 and 20 hours (Becher 1983, Brandt 2003, Viau 1995a, Viau 1995b). In the ZRHM-REXC-04-JP and the ZRHM-REXA-08-US studies, the levels of total 1-OHP were slightly, but consistently, higher than in the SA arms. The profiles of reductions during the Ambulatory periods were also overall similar for the THS and SA arms, with an increase of total 1-OHP in all

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arms after the Confinement periods, including the CC arm, thus being indicative of environmental exposure in Ambulatory conditions (U.S. Department of Health and Human Services 2009, U.S. Department of Health and Human Services 1995).

Percent changes from Baseline of urinary total 1-OHP concentrations adjusted to creatinine during the Confinement periods ranged from -53% to -68% for the THS arms and from -53% to -70% for the SA arms. During the Ambulatory periods, these percent changes were not maintained to the same levels, in either arm, ranging at Day 90 from -15% to -37% for THS and from -20% to -31% for the SA arm. The variability within this assessment was, however, high. Several smoking cessation studies conducted over 3 to 8 days showed reductions of total 1-OHP levels ranging from -39% to -76% from Baseline (Carmella 2009, Feng 2006, Theophilus 2015, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). In a smoking cessation study lasting up to 56 days, percent change from Baseline was of -49% after 7 days and of around -20% after 56 days (Carmella 2009). Levels of urinary total 1-OHP concentrations at the beginning of those published studies ranged from 136 to 313 ng/24h, decreasing to ranges of 37 to 127 ng/24h at the end of the studies. Values obtained in the SA arms of PMI's studies ranged from 168.49 to 353.89 ng/24h at Baseline and from 52.34 to 133.54 ng/24h at Day 5 (data available in the clinical study reports). Excreted amounts of total 1-OHP over 24h, as well as the percent changes from Baseline obtained in PMI's studies are thus consistent with published smoking cessation studies of 3 to 8 days.

Clinical studies conducted with products based on the heat-not-burn principle, showed reductions of urinary 1-OHP levels ranging from -38% to -86% in smokers who switched from conventional cigarettes to the test systems for 5 to 8 days, in Confinement conditions (Frost-Pineda 2008a, Roethig 2007, Sakaguchi 2014, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). These studies were conducted in the US, UK, Japan, or Korea. In studies conducted over longer periods of time, i.e. 34 days or 12 weeks of switching, in Poland and in the US, changes from Baseline when switching to heat-not-burn products were of -17% and +17%, respectively (Frost-Pineda 2008b, Martin Leroy 2012).

Statistically significant reductions were observed in the levels of total 1-OHP assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 52% to 61%. The reductions in total 1-OHP observed at Day 5 during the Confinement periods for the THS arms compared to CC arms were overall sustained during the Ambulatory periods, with reductions of 34% to 48% at Day 90. The slightly smaller reductions at the end of the ambulatory periods could be related to exposure to environmental sources of pyrene, such as car exhaust fumes in traffic or fumes from gasoil stations (Jongeneelen 1988), or to the occasional use of conventional cigarettes. Broiled and smoked foods are also sources of pyrene (Strickland 1999).

In summary, the levels of total 1-OHP observed with THS use were statistically significantly lower from values observed in the CC arms, at Day 5 and Day 90, and approaching levels observed in the SA arms, as well as to published literature from smoking cessation studies.

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6.1.3.2.3.7 Total NNN – BoExp for Exposure to NNN

FDA has classified NNN as a carcinogen (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of total NNN concentration adjusted to creatinine (Total NNN_{adjC}) were from 3.97 pg/mg_{creat} to 5.14 pg/mg_{creat} across studies. The highest Baseline levels were observed in the [ZRHM-REXA-08-US] study, ranging from 5.32 to 6.87 pg/mg_{creat}, with large variability (Table 26).

Table 26 Geometric Means and 95% CIs of Total NNN_{adjC} (pg/mg_{creat}) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	4.34	4.57	3.97	6.70
		95% CI	3.56; 5.28	3.42; 6.11	2.87; 5.47	4.78; 9.38
		Min; Max	1.4; 14.8	1.0; 49.8	0.5; 93.8	0.9; 73.4
	THS	N	80	80	76	67
		Mean	4.81	4.08	4.45	6.87
		95% CI	3.99; 5.78	3.26; 5.10	3.38; 5.86	5.48; 8.62
		Min; Max	0.5; 49.9	0.2; 87.5	0.1; 86.2	0.2; 55.6
	SA	N	39	38	39	21
		Mean	5.14	4.67	4.13	5.32
		95% CI	3.93; 6.70	3.49; 6.25	2.84; 6.00	3.42; 8.28
		Min; Max	0.9; 25.6	0.8; 35.1	0.4; 132.3	1.3; 51.8
Day 5	CC	N	41	40	42	34
		Mean	5.99	4.64	4.10	6.14
		95% CI	4.94; 7.26	3.51; 6.12	2.94; 5.73	4.42; 8.53
		Min; Max	1.9; 26.8	1.1; 25.4	0.5; 91.5	0.8; 73.4
	THS	N	79	79	76	73
		Mean	1.55	1.31	1.20	0.90
		95% CI	1.17; 2.05	1.06; 1.61	0.97; 1.49	0.71; 1.13
		Min; Max	0.1; 5125.3	0.1; 16.5	0.1; 16.4	0.0; 6.6
	SA	N	39	38	39	22
		Mean	0.16	0.18	0.15	0.12
		95% CI	0.14; 0.19	0.15; 0.22	0.12; 0.18	0.09; 0.15
		Min; Max	0.1; 0.4	0.1; 0.5	0.1; 0.5	0.0; 0.4

(table continues)

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			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	4.28	4.47
		95% CI	NA	NA	3.03; 6.05	3.24; 6.17
		Min; Max	NA	NA	0.5; 138.8	0.8; 19.9
	THS	N	NA	NA	70	47
		Mean	NA	NA	1.40	0.94
		95% CI	NA	NA	1.13; 1.73	0.72; 1.23
		Min; Max	NA	NA	0.2; 25.2	0.1; 11.1
	SA	N	NA	NA	37	9
		Mean	NA	NA	0.26	0.26
		95% CI	NA	NA	0.17; 0.40	0.11; 0.63
		Min; Max	NA	NA	0.0; 16.7	0.1; 3.0

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.12; ZRHR-REXC-04-JP, Table 15.2.4.12; ZRHM-REXA-07-JP, Table 15.2.4.8.1; ZRHM-REXA-08-US, Table 15.2.4.8.1]

In all 4 exposure assessment studies, the levels of urinary Total NNN decreased substantially in the THS and SA arms compared to Baseline CC use, with lower levels of total NNN in the SA arm compared to the THS arm throughout studies and assessment days (Figure 15).

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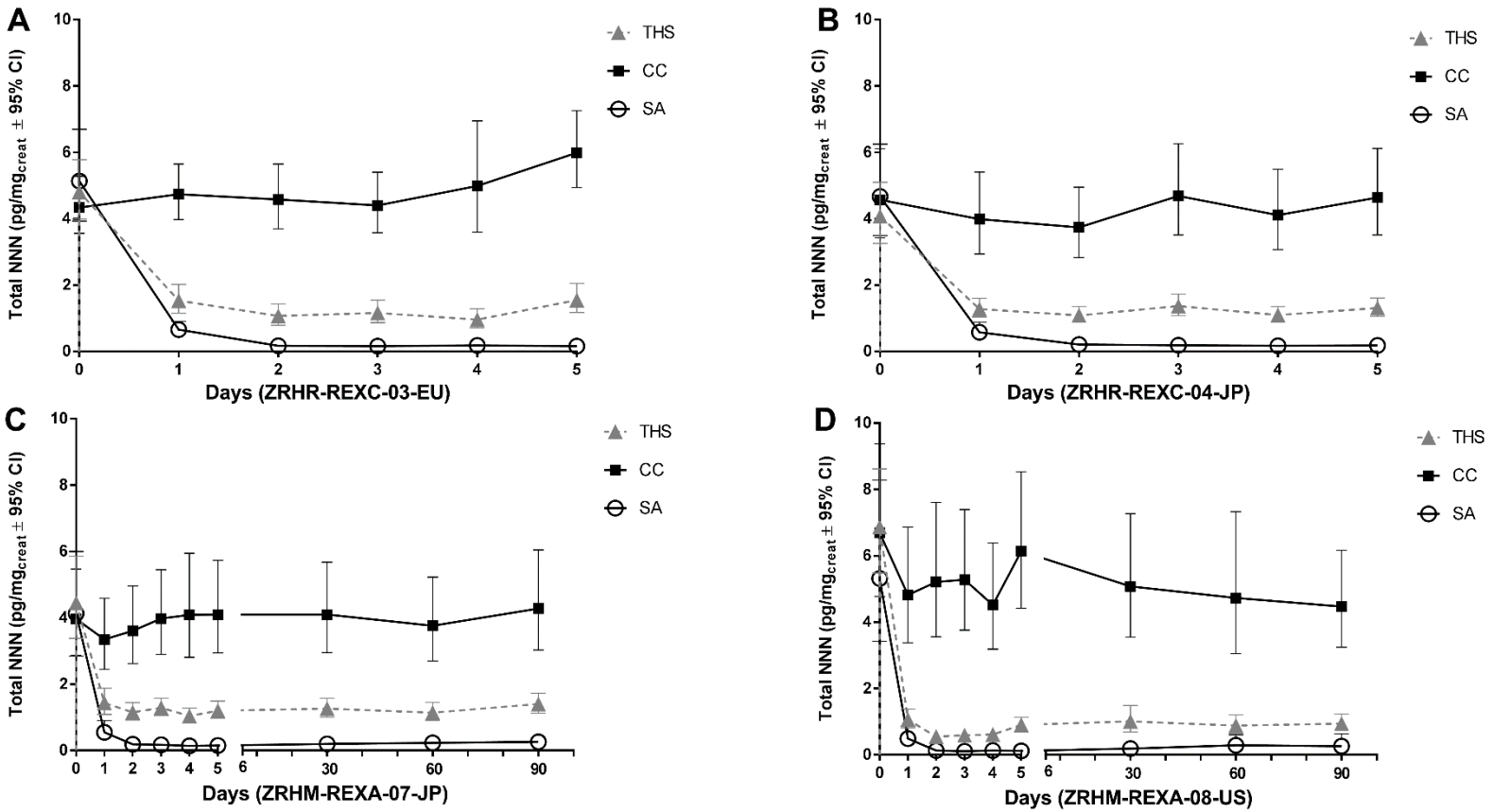


Figure 15 Geometric Mean Urinary and 95% CIs of Total NNN_{adjC} Concentrations (pg/mg_{creat}), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.12; ZRHR-REXC-04-JP, Table 15.2.4.12; ZRHM-REXA-07-JP, Table 15.2.4.8.1; ZRHM-REXA-08-US, Table 15.2.4.8.1]

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Percent changes from Baseline of urinary total NNN levels during the Confinement periods in all 4 studies at Day 5 ranged from -59% to -80% for the THS arms and from -94% to -97% for the SA arms. In the THS arm of the [ZRHR-REXC-03-EU] study at Day, the distribution was skewed by outliers. The median values are thus reported instead of the mean, for all arms. In the 2 Ambulatory studies, these changes were largely conserved, with percent change from Baseline at Day 90 ranging from -54% to -82% in the THS arms and from -81% to -86% in the SA arms (Table 27).

Table 27 Percent Change from Baseline and 95% CIs of Urinary Total NNN_{adjC} (pg/mg_{creat}) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU [#]	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	29.93% [#]	18.35%	20.30%	8.94%
		95% CI (or Q1; Q3 [#])	12.84; 74.96 [#]	-4.02; 40.73	-10.11; 50.72	-9.39; 27.27
	THS	N	79	79	76	67
		% Change	-69.75% [#]	-59.81%	-65.80%	-79.62%
		95% CI (or Q1; Q3 [#])	-82.75, -53.26 [#]	-66.73; -52.89	-72.27; -59.33	-85.34; -73.90
	SA	N	39	38	39	21
		% Change	-97.04% [#]	-93.86%	-93.89%	-96.64%
		95% CI (or Q1; Q3 [#])	-98.46; -94.06 [#]	-95.70; -92.02	-96.28; -91.50	-98.40; -94.89
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	34.37%	-1.49%
		95% CI	NA	NA	-7.53; 76.26	-24.39; 21.40
	THS	N	NA	NA	70	43
		% Change	NA	NA	-54.33%	-82.37%
		95% CI	NA	NA	-68.60; -40.06	-88.85; -75.90
	SA	N	NA	NA	37	9
		% Change	NA	NA	-86.48%	-80.54%
		95% CI	NA	NA	-92.28; -80.69	-112.54; -48.53

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Because of one outlier in the THS arm, percent change from Baseline values for total NNN are reported for ZRHR-REXC-03-EU as median at Day 5 (and Q1; Q3).

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.12; ZRHR-REXC-04-JP, Table 15.2.4.12; ZRHM-REXA-07-JP, Table 15.2.4.8.1; ZRHM-REXA-08-US, Table 15.2.4.8.1]

6.1.3.2.3.7.1 Analysis of Total NNN at Day 5 and Day 90

At Day 5, across all 4 studies, switching to THS resulted in at leat a 70% reduction of total NNN, with a maximum reduction of 86%, compared to CC smoking ($p < 0.001$ for

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each study; Table 28). At Day 90, these levels of reduction were maintained at 71% in ZRHM-REXA-07-JP and 82% in ZRHM-REXA-08-US (Table 28) ($p < 0.001$).

Table 28 Adjusted Geometric LS Means of THS to CC ratios of Total NNN at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	24.12%	30.06%	27.02%	14.06%
		95% CI	17.76; 32.75	23.74; 38.06	21.75; 33.55	10.38; 19.06
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	29.31%	17.80%
		95% CI	NA	NA	21.48; 39.98	12.31; 25.75
		p Value	NA	NA	<0.001	<0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.11; ZRHR-REXC-04-JP, Table 15.2.4.11; ZRHM-REXA-07-JP, Table 15.2.3.4; ZRHM-REXA-08-US Table 15.2.3.4]

6.1.3.2.3.7.2 Conclusion

At Baseline, total NNN_{adjC} were similar between the European and the Japanese studies, while they were slightly higher in the US study (up to 1.7 fold difference).

The profiles of reductions over the 5 days of Confinement were comparable in the THS and SA arms, with a maximum decrease observed already after Day 1, and a plateau appearing from around Day 3, thus being consistent with a rapid disappearance of total NNN over a period of 24 hours (Stepanov 2009a), and with the half-life of 45 min estimated in patas monkeys (Upadhyaya 2002). The levels of total NNN in the THS arm remained close, but were consistently higher than in the SA arm, considering the absolute levels observed. The profiles of reductions during the Ambulatory periods were also similar for the THS and SA arms, with plateaus largely maintained throughout the whole studies.

The levels of total NNN_{adjC} were higher in the THS than SA arms throughout the 4 studies. However, considering the low concentrations found in both arms, the relevance of this difference is difficult to interpret. These differences between the 2 arms are likely due to the fact that there is still some NNN transferred into the aerosol of THS, despite a reduction of more than 90% in the aerosol compared to the smoke of the 3R4F reference cigarette (Chepiga 2000), while subjects in the SA arms are free of exposure to NNN in a confined environment. Because total NNN is exclusively tobacco specific, there is also a minimal risk of environmental exposure during the ambulatory phases of the studies, other than second-hand or third-hand smoke, or occasional use of CC (Toxicology Data Network 2010). NNN is present in non-combusted tobacco (Rodgman 2013) and can be released to an aerosol by evaporation (Forster 2015). Tobacco specific nitrosamines are indeed largely formed during tobacco curing and can thus be transferred even without

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pyrolysis (Brown 2003). In a recent paper by Forster et al. (Forster 2015), NNN was shown to be quantifiable at 140°C and 160°C. Its release did not follow a consistent linear trend throughout the temperature ranges, which is probably because it is transferred by evaporation from the tobacco blend. Release of NNN (and NNK) from tobacco into the aerosol is low (<10%) compared to the available amounts in the tobacco rod. Direct transfer of TSNAs from tobacco to smoke accounts for about 40% of the NNN (and 30% of the NNK), with the remainder being formed during smoking (Rodgman 2013). At low temperatures, NNN could thus be released at somewhat higher levels than NNK, which seems to be the case for THS, as the differences of NNN levels in the THS compared to the SA arms were more marked than those with total NNAL (section 6.1.3.2.3.5). Finally, it has been reported in one publication that endogenous formation of total NNN can occur through the nitrosation of nicotine or its metabolites in subjects using nicotine replacement therapy (Stepanov 2009b), thus the higher levels of total NNN_{adjC} observed between THS and SA could also be derived from the nicotine intake with THS that is absent in the SA arms.

Percent changes from Baseline of total NNN_{adjC} during the Confinement periods across studies ranged from -60% to -80% for THS arms for from -94% to -97% for the SA arms. Because of an outlier in the THS arm of ZRHR-REXC-03-EU, the median value is probably a more reliable measure in this case, showing a percent change from Baseline of -69%. These reductions were overall maintained during the Ambulatory periods of both sudies, with changes ranging from -54% to -82% and from -81% to -86% for the THS and SA arms, respectively. Two studies conducted over 5 days showed percent changes from Baseline of more than -35% and of -77% in quitters at the end of the studies (Theophilus 2015, Urban 2009). In another study, conducted over 56 days, changes from Baseline were of -42% at the end of the study (Stepanov 2009a). Levels of urinary total NNN concentrations at the beginning of those published studies were around 24 pg/mg_{creat} (Stepanov 2009a) or 24 ng/24h (Theophilus 2015), decreasing to around 14 pg/mg_{creat} or 4 ng/24h at the end of the studies. Values for quantities of total NNN excreted over 24h obtained in PMI's studies at Baseline in the SA arm ranged from 4.82 ng/24h in ZRHR-REXC-04-JP to 8.53 ng/24h in ZRHM-REXA-08-US (data available in clinical study reports), and at Day 5, from 0.18 ng/24h in ZRHM-REXA-07-JP to 0.26 ng/24h in ZRHR-REXC-03-EU (data available in clinical study reports). Values of total NNN_{adjC} in the SA arms ranged from 4.13 to 5.32 pg/mg_{creat} at Baseline and from 0.12 to 0.18 pg/mg_{creat} at Day 5. Urinary total NNN levels obtained in PMI's studies, both in the THS and SA arms, thus appear to be slightly lower than those published, including those published for smokers not undergoing smoking cessation (Kavvadias 2009, Shepperd 2013, Stepanov 2005, Yuan 2011, Zhu 2013). One plausible explanation would be the effectiveness of measures taken on curing and agricultural practices designed to minimize TSNA formation in tobacco, as shown by a significant reduction of NNN and NNK in cigarette brands between 2000 and 2014 (Gunduz 2016). Smokers today are thus likely to be less exposed to TSNAs than those assessed even a few years ago. Percent changes from Baseline are, however, consistent with published smoking cessation studies of 5 days. A difference in analytical method could also partially explain this difference.

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Statistically significant reductions were observed in the levels of total NNN_{adjC} as assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 70% to 86%. Reductions of total NNN_{ajdC} were overall maintained during the ambulatory periods of both sudies, with decreases ranging from 71% to 82%.

In summary, the levels of total NNN observed with THS use were statistically significantly lower from values observed in the CC arms at Day 5 and Day 90, and slightly higher than levels observed in the SA arms. Percent changes from Baseline were consistent with published literature from smoking cessation studies.

6.1.3.2.3.8 4-ABP – BoExp for Exposure to 4-ABP

The FDA has classified 4-aminobiphenyl (4-ABP) as a carcinogen (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of 4-ABP concentration adjusted to creatinine ($4\text{-}ABP_{adjC}$) varied between studies, with differences ranging from 7.72 pg/mg_{creat} to 13.53 pg/mg_{creat} across all arms. The Baseline levels were lower in the Japanese populations, with the highest levels observed in the European subjects. In the US population, the levels were slighly higher than those of the Japanese, but lower than the subjects in Europe (Table 29).

Table 29 Geometric Means and 95% CIs of $4\text{-}ABP_{adjC}$ (pg/mg_{creat}) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	13.11	8.40	8.75	11.59
		95% CI	11.33; 15.16	7.14; 9.87	7.44; 10.29	9.42; 14.26
		Min; Max	5.8; 34.7	2.5; 20.1	2.3; 19.9	4.3; 47.8
	THS	N	80	80	76	67
		Mean	13.25	7.72	9.33	10.76
		95% CI	11.85; 14.81	6.75; 8.83	8.44; 10.32	9.01; 12.86
		Min; Max	2.8; 39.9	1.5; 27.8	2.5; 26.1	0.4; 58.8
	SA	N	39	38	39	21
		Mean	13.53	7.80	7.99	9.78
		95% CI	11.71; 15.63	6.45; 9.43	6.57; 9.71	7.14; 13.38
		Min; Max	4.9; 37.6	1.9; 20.4	1.1; 23.1	2.6; 42.4
Day 5	CC	N	41	40	42	34
		Mean	12.58	8.57	9.50	9.63
		95% CI	11.03; 14.34	7.11; 10.34	8.15; 11.07	7.76; 11.95
		Min; Max	5.3; 34.2	1.9; 24.2	3.3; 22.5	1.8; 47.8
	THS	N	79	80	76	73
		Mean	1.90	1.53	1.97	1.76
		95% CI	1.70; 2.12	1.37; 1.70	1.76; 2.21	1.50; 2.08
		Min; Max	0.8; 9.2	0.5; 5.0	0.6; 6.8	0.6; 17.3

(table continues)

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			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 90	SA	N	39	38	39	22
		Mean	1.60	1.49	2.16	1.44
		95% CI	1.40; 1.83	1.29; 1.72	1.87; 2.50	1.06; 1.97
		Min; Max	0.8; 3.5	0.7; 4.1	0.5; 4.1	0.5; 5.4
	CC	N	NA	NA	41	32
		Mean	NA	NA	9.62	11.31
		95% CI	NA	NA	8.12; 11.39	8.75; 14.61
		Min; Max	NA	NA	3.3; 22.9	1.7; 35.5
	THS	N	NA	NA	70	47
		Mean	NA	NA	2.07	3.77
		95% CI	NA	NA	1.82; 2.36	2.88; 4.93
		Min; Max	NA	NA	0.6; 10.0	0.6; 30.6
	SA	N	NA	NA	37	9
		Mean	NA	NA	2.35	2.98
		95% CI	NA	NA	1.90; 2.89	1.39; 6.37
		Min; Max	NA	NA	0.7; 8.1	0.9; 11.0

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.14; ZRHR-REXC-04-JP, Table 15.2.4.14; ZRHM-REXA-07-JP, Table 15.2.4.9.1; ZRHM-REXA-08-US, Table 15.2.4.9.1]

In all the studies, the levels of urinary 4-ABP had similar profiles of decrease from Baseline in the THS and SA arms, with curves overlapping throughout the 5 days of the Confinement periods in each study. Most of the reduction in 4-ABP was achieved by Day 3, with values plateauing thereafter. In the [ZRHM-REXA-07-JP] study, the 4-ABP levels in the THS and SA arms remained at a low level during the whole Ambulatory period, while in [ZRHM-REXA-08-US], there was a slight increase of 4-ABP levels during the transition from Confinement to Ambulatory condition in both arms (Figure 16).

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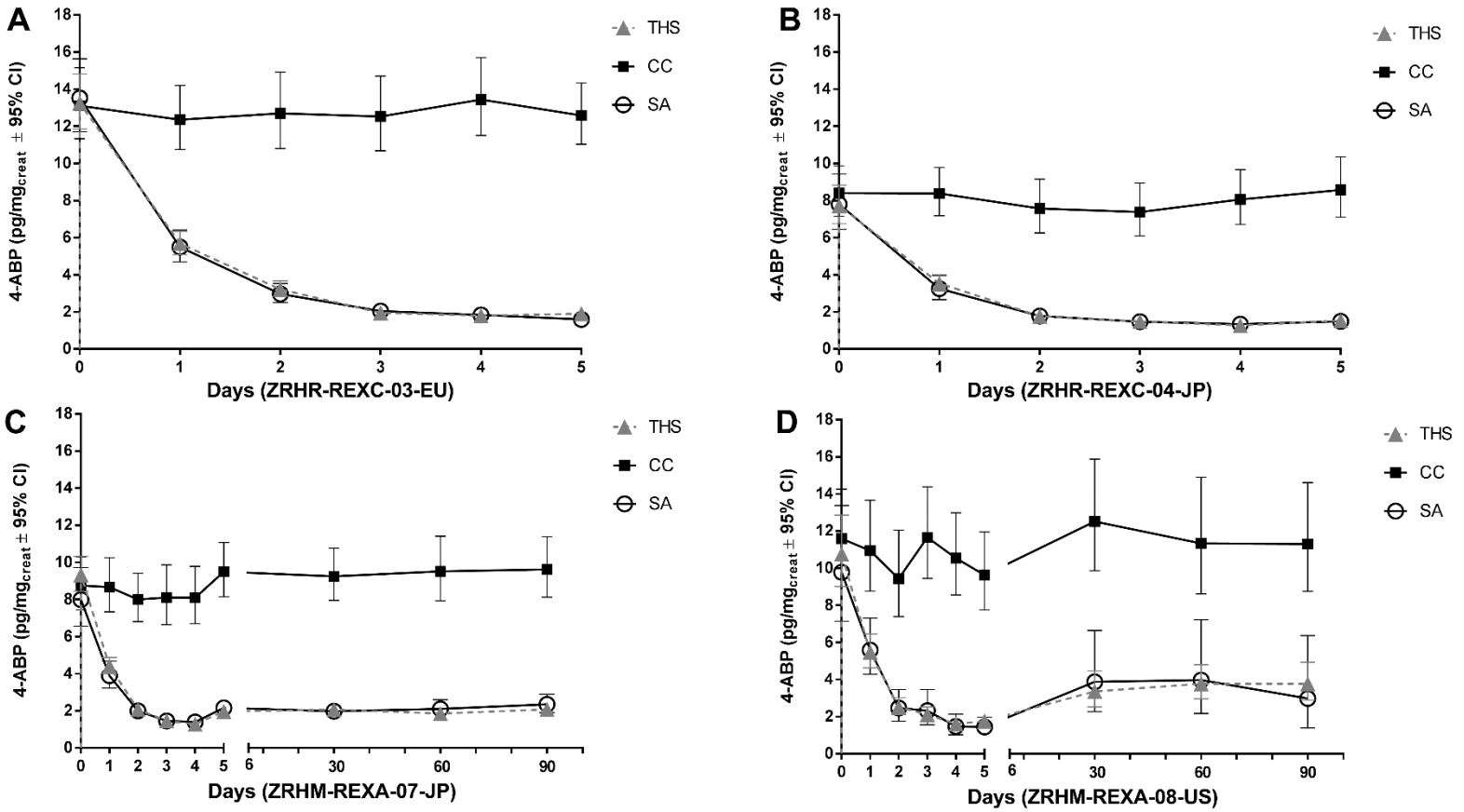


Figure 16 Geometric Mean and 95% CIs of Urinary 4-ABP$_{adjC}$ Concentrations (pg/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.14; ZRHR-REXC-04-JP, Table 15.2.4.14; ZRHM-REXA-07-JP, Table 15.2.4.9.1; ZRHM-REXA-08-US, Table 15.2.4.9.1]

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At Day 5 the percent changes from Baseline of urinary 4-ABP$_{adjC}$ levels during the Confinement periods in all 4 studies ranged from -74% to -82% for the THS arms and from -64% to -87% for the SA arms (Table 30). At Day 90, the percent change from Baseline of 4-ABPranged from -54% to -73% and from -36% to -51%, in the THS and SA arms, respectively (Table 29).

Table 30 Mean Percent Change from Baseline and 95% CIs of Urinary 4-ABP$_{adjC}$ (pg/mg$_{creat}$) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	-1.66%	13.50%	10.87%	-7.13%
		95% CI	-8.59; 5.26	-3.30; 30.30	3.46; 18.28	-21.06; 6.80
	THS	N	79	80	76	67
		% Change	-82.12%	-74.08%	-74.36%	-73.78%
		95% CI	-85.59; -78.64	-79.46; -68.69	-79.27; -69.45	-83.84; -63.72
	SA	N	39	38	39	21
		% Change	-86.99%	-76.20%	-64.19%	-80.83%
		95% CI	-88.87; -85.12	-82.70; -69.70	-78.36; -50.01	-87.41; -74.25
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	24.84%	22.21%
		95% CI	NA	NA	-0.80; 50.48	3.87; 40.54
	THS	N	NA	NA	70	43
		% Change	NA	NA	-72.57%	-54.19%
		95% CI	NA	NA	-77.07; -68.08	-68.26; -40.13
	SA	N	NA	NA	37	9
		% Change	NA	NA	-50.96%	-35.58%
		95% CI	NA	NA	-75.12; -26.80	-91.54; 20.39

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.14; ZRHR-REXC-04-JP, Table 15.2.4.14; ZRHM-REXA-07-JP, Table 15.2.4.9.1; ZRHM-REXA-08-US, Table 15.2.4.9.1]

6.1.3.2.3.8.1 Analysis of 4-ABP at Day 5 and Day 90

At Day 5, across all 4 studies, switching to THS resulted in at least a 80% reduction of 4-ABP with a maximum reduction of 85% compared to CC smoking ($p<0.001$ for each study; Table 31). At Day 90, these levels of reduction were maintained, with reductions of 79% in [ZRHM-REXA-07-JP] and 72% in [ZRHM-REXA-08-US] (Table 31) ($p<0.001$).

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Table 31 Adjusted Geometric LS Means of THS to CC ratios of 4-ABP at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	14.94%	18.21%	20.10%	19.31%
		95% CI	12.89; 17.33	15.29; 21.69	17.08; 23.64	14.90; 25.01
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	21.00%	28.48%
		95% CI	NA	NA	17.02; 25.89	19.51; 41.58
		p Value	NA	NA	<0.001	<0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.13; ZRHR-REXC-04-JP, Table 15.2.4.13; ZRHM-REXA-07-JP, Table 15.2.3.4; ZRHM-REXA-08-US, Table 15.2.3.4]

6.1.3.2.3.8.2 Conclusion

At Baseline, urinary concentrations of 4-ABP$_{adjC}$ varied between studies, with differences of up to 1.7 fold. The levels were lower in the Japanese populations, while the highest levels were observed in the European study. As the same method was used to measure 4-ABP levels across studies, this likely indicates a difference in smoking behavior, but also of cigarette brands: Japanese preference for cigarettes with charcoal-containing filters has indeed been reported (Muscat 2005), and 7 out of 10 brands sold in Japan have a charcoal filter (Coggins 2008). The ability of charcoal containing filters to retain HPHCs within the particulate phase (as opposed to gas constituents) has however not been demonstrated (Coggins 2008), thus pointing rather at a difference in smoking behaviors. Polish population has been shown to have a high prevalence of heavy smokers (Jassem 2014), which could explain why levels of 4-ABP$_{adjC}$ levels at Baseline were the highest in the European study, which was conducted in Poland. 4-ABP levels have been shown to be correlated with the number of cigarettes per day (Theophilus 2015). This hypothesis is further reinforced by the results of PMI studies where the Baseline daily CC consumption levels were higher in Poland (mean of around 16 CC per day) compared to US and Japan (between 10 to 13 CC per day) at Baseline [Section 6.2.2 Product Use]. Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g$_{creat}$ [Section 6.2.2 Product Use], which can be also indicative of different smoking behaviors.

The profiles of reductions over the 5 days of Confinement were similar in the THS and SA arms, with most of the reduction achieved by Day 3, and a plateau appearing thereafter, thus being consistent with published half-lives of 4-ABP, i.e. between 15 and 48 hours (Karreth 1991). The profiles of reductions during the Ambulatory periods were also similar for the THS and SA arms, with a slight increase of 4-ABP in the THS and SA arms in the US study, after the Confinement period, which then plateaued until Day 90.

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Percent changes from Baseline of 4-ABP urinary concentrations adjusted to creatinine during the Confinement periods ranged from -74% to -82% for the THS arms and from -64% to -87% for the SA arms. During the Ambulatory periods, these percent changes were slightly lower, particularly in the US study, ranging from -54% to -73% in the THS arms, and from -36% to -51% in the SA arms, but with a relatively high variability of this assessment, particularly in the SA arms. Several published smoking cessation studies conducted over 5 to 8 days showed reductions of 4-ABP levels ranging from -54% to -88% from Baseline (Frost-Pineda 2008a, Sarkar 2010, Theophilus 2015, Tricker 2012a, Tricker 2012b, Tricker 2012c). Levels of urinary 4-ABP concentrations at the beginning of those published studies ranged from 10.4 to 27.8 ng/24h, decreasing to ranges of 2.0 to 5.5 ng/24h at the end of the studies. Values obtained in PMI's studies at Baseline in the SA arm (range from 8.0 ng/24h in ZRHR-REXC-04-JP to 21.4 ng/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), and at Day 5 (range from 1.6 ng/24h to 2.5 ng/24h in ZRHR-REXC-04-JP and ZRHR-REXC-03-EU, respectively; data available in the clinical study reports), as well as the percent changes from Baseline, are thus consistent with published smoking cessation studies of 3 to 8 days despite levels in the Japanese studies at Baseline being slightly lower than those published.

Clinical studies conducted with products based on the heat-not-burn principle, showed reductions of urinary 4-ABP levels ranging from -33% to -84% in smokers who switched from CC to the test systems for 5 to 8 days, in Confinement conditions (Frost-Pineda 2008a, Sakaguchi 2014, Tricker 2012a, Tricker 2012b, Tricker 2012c). These studies were conducted in the US, Japan, or Korea. In a study conducted over longer periods, i.e. 34 days of switching, in ambulatory condition, in Poland, changes from Baseline when switching to a heat-not-burn product were of –51% at the end of the study (Frost-Pineda 2008b, Martin Leroy 2012).

Statistically significant reductions were observed in the levels of 4-ABP_{ajdC} assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 80% to 85%, while there was overall small or no difference between the THS and SA arms. The reductions in 4-ABP_{ajdC} observed at Day 5 during the Confinement periods for the THS arms compared to CC arms were overall sustained during the ambulatory periods, with decreases of 72% to 79% at Day 90. The slightly smaller reductions at the end of the ambulatory periods could be related to exposure to environmental sources of 4-ABP, such as hair dyes, food colorant, fungicide used on apples, fumes from cooking oils (IARC (International Agency for Research on Cancer) 2012, National Center for Biotechnology Information (NCBI) 2014a), or to the occasional use of CC.

In summary, the levels of 4-ABP_{adjC} observed with THS use were statistically significantly lower from values observed in the CC arms, at Day 5 and Day 90, and approaching levels observed in the SA arms as well as to published literature from smoking cessation studies.

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6.1.3.2.3.9 1-NA – BoExp for Exposure to 1-NA

The FDA has classified 1-aminonaphthalene (1-NA) as a carcinogen (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of 1-NA concentration adjusted to creatinine (1-NA_{adjC}) differed relatively little between studies and across arms, with values ranging from 48 pg/mg_{creat} to 77 pg/mg_{creat}.

Table 32 Geometric Means and 95% CIs of 1-NA_{adjC} (pg/mg_{creat}) by Study Arm in All Studies, at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	77.84	55.41	57.24	62.93
		95% CI	66.32; 91.36	47.36; 64.83	49.04; 66.80	51.07; 77.54
		Min; Max	30.0; 316.7	15.6; 152.0	14.3; 144.7	20.3; 220.5
	THS	N	80	80	76	67
		Mean	73.83	48.61	61.45	61.36
		95% CI	66.48; 81.99	42.45; 55.66	55.12; 68.52	52.78; 71.33
		Min; Max	14.4; 171.7	6.1; 189.0	13.7; 151.1	6.1; 409.8
	SA	N	39	38	39	21
		Mean	77.31	51.74	53.48	56.16
		95% CI	67.76; 88.21	43.68; 61.29	44.92; 63.68	41.01; 76.91
		Min; Max	32.4; 222.4	15.8; 128.7	18.5; 140.4	10.7; 156.7
Day 5	CC	N	41	40	42	34
		Mean	89.37	57.08	53.27	63.05
		95% CI	77.81; 102.64	48.55; 67.11	45.86; 61.89	51.83; 76.71
		Min; Max	31.9; 287.1	14.3; 134.1	15.4; 124.4	14.7; 220.5
	THS	N	79	80	76	73
		Mean	3.30	2.47	3.14	2.51
		95% CI	2.89; 3.78	2.23; 2.72	2.85; 3.46	2.18; 2.89
		Min; Max	1.0; 29.2	0.9; 7.3	1.3; 10.6	0.6; 17.6
	SA	N	39	38	39	22
		Mean	2.56	2.45	2.85	2.17
		95% CI	2.25; 2.90	2.12; 2.82	2.50; 3.26	1.58; 2.97
		Min; Max	1.1; 5.8	1.1; 6.8	1.4; 6.6	0.8; 12.6
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	55.34	59.69
		95% CI	NA	NA	46.21; 66.26	47.34; 75.24
		Min; Max	NA	NA	14.5; 147.8	9.1; 147.5
	THS	N	NA	NA	70	47
		Mean	NA	NA	3.55	9.64
		95% CI	NA	NA	2.96; 4.26	7.31; 12.72
		Min; Max	NA	NA	1.1; 31.7	1.0; 71.0
	SA	N	NA	NA	37	9
		Mean	NA	NA	4.22	5.90
		95% CI	NA	NA	3.20; 5.55	2.27; 15.30
		Min; Max	NA	NA	1.3; 24.2	1.3; 20.7

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Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.16; ZRHR-REXC-04-JP, Table 15.2.4.16; ZRHM-REXA-07-JP, Table 15.2.4.10.1; ZRHM-REXA-08-US, Table 15.2.4.10.1]

There was a swift reduction of 1-NA once smokers switched to the THS or abstained from smoking compared to users of CC (Figure 17).

Percent changes from Baseline of urinary 1-NA_{adjC} levels during the Confinement periods in all 4 studies at Day 5 ranged from -93% to -94% for the THS arms and from -93% to -96% for the SA arms (Table 33). At Day 90, the changes from Baseline ranged from -77% to 92% and from -78% to -86%, in the THS and SA arms, respectively (Table 32).

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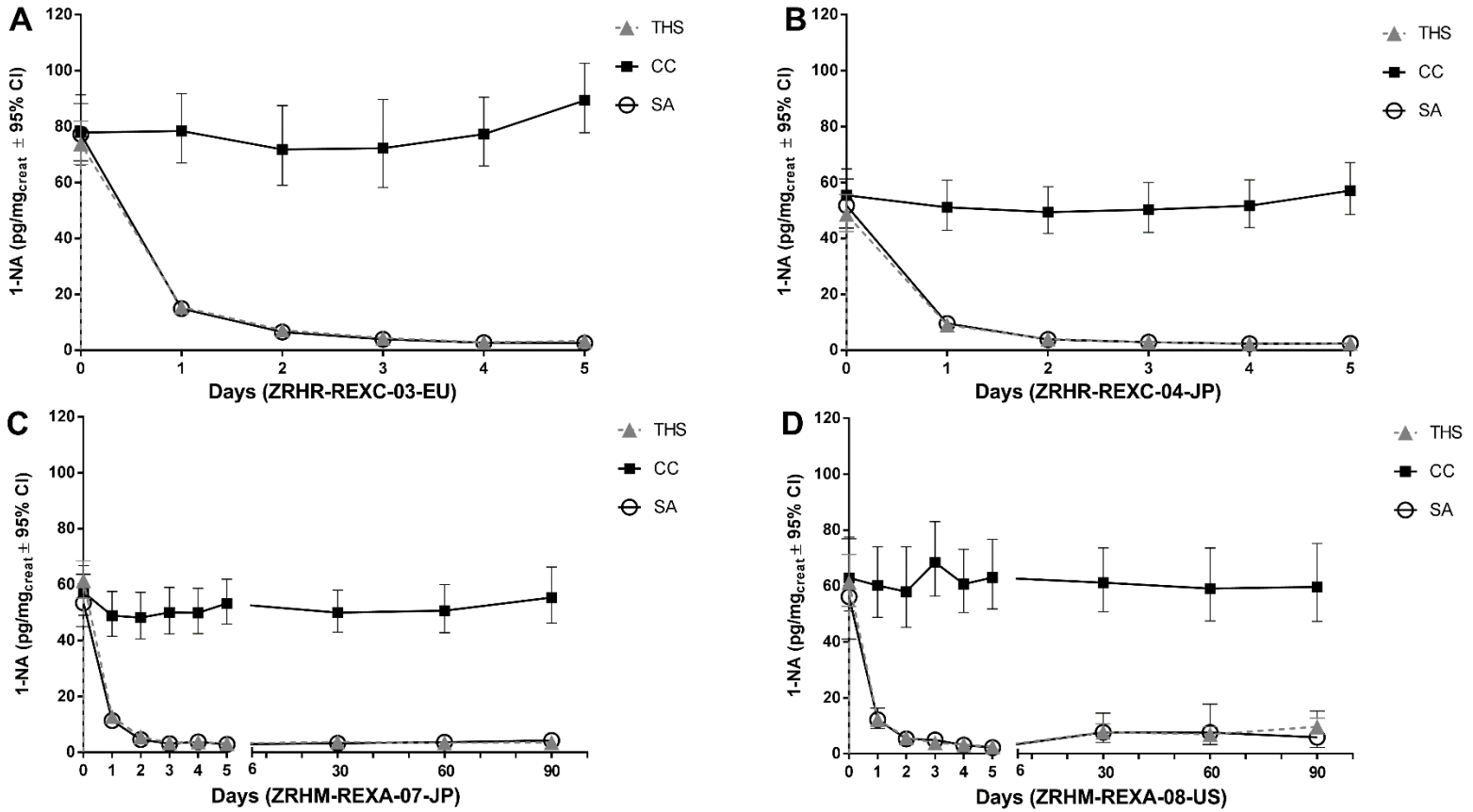


Figure 17 Geometric Mean and 95% CIs of Urinary 1-NA$_{adjC}$ Concentrations (pg/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.16; ZRHR-REXC-04-JP, Table 15.2.4.16; ZRHM-REXA-07-JP, Table 15.2.4.10.1; ZRHM-REXA-08-US, Table 15.2.4.10.1]

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Table 33 Mean Percent Change from Baseline and 95% CIs of Urinary 1-NA_{adjC} (pg/mg_{creat}) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	19.17%	11.23%	-3.64%	13.02%
		95% CI	9.08; 29.26	-3.21; 25.67	-11.27; 4.00	-7.41; 33.45
	THS	N	79	80	76	67
		% Change	-94.16%	-93.12%	-94.13%	-94.30%
		95% CI	-95.49; -92.82	-94.98; -91.26	-94.95; -93.31	-95.75; -92.85
	SA	N	39	38	39	21
		% Change	-96.41%	-94.44%	-93.49%	-94.00%
		95% CI	-96.89; -95.93	-95.62; -93.27	-95.27; -91.70	-96.95; -91.05
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	7.68%	14.16%
		95% CI	NA	NA	-9.92; 25.28	-6.69; 35.01
	THS	N	NA	NA	70	43
		% Change	NA	NA	-92.01%	-77.41%
		95% CI	NA	NA	-93.76; -90.26	-85.19; -69.62
	SA	N	NA	NA	37	9
		% Change	NA	NA	-86.11%	-77.53%
		95% CI	NA	NA	-91.19; -81.03	-93.46; -61.61

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.16; ZRHR-REXC-04-JP, Table 15.2.4.16; ZRHM-REXA-07-JP, Table 15.2.4.10.1; ZRHM-REXA-08-US, Table 15.2.4.10.1]

6.1.3.2.3.9.1 Analysis of 1-NA at Day 5 and Day 90

The unbiased estimates across all 4 studies of 1-NA reduction in subjects who switched to THS use resulted in at least a 94% reduction at Day 5 ($p<0.001$ for each study; Table 34). At Day 90 the results corroborated the large reduction of exposure to 1-NA (Table 34) ($p<0.001$).

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Table 34 Adjusted Geometric LS Means of THS to CC ratios of 1-NA at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	3.73%	4.44%	5.70%	4.15%
		95% CI	3.15; 4.42	3.80; 5.18	4.93; 6.59	3.28; 5.25
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	6.22%	14.29%
		95% CI	NA	NA	4.70; 8.22	9.47; 21.56
		p Value	NA	NA	<0.001	<0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.15; ZRHR-REXC-04-JP, Table 15.2.4.15; ZRHM-REXA-07-JP, Table 15.2.3.4; ZRHM-REXA-08-US, Table 15.2.3.4]

6.1.3.2.3.9.2 Conclusion

At Baseline, urinary concentrations of 1-NA_{adjC} were comparable between studies, with the lowest levels observed in the Japanese studies, and the highest in the European study. This likely indicates a difference in smoking behavior, including preference for cigarette brands. This hypothesis is reinforced by the results of PMI studies where the Baseline daily CC consumption levels were higher in Poland (mean of around 16 CC per day) compared to US and Japan (between 10 to 13 CC per day) at Baseline [Section 6.2.2 Product Use]. Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g_{creat} [Section 6.2.2 Product Use], which can be also indicative of different smoking behaviors.

The profiles of reductions were similar in the THS and SA arms during both the Confinement and Ambulatory settings. During the Confinement period, a maximum decrease was observed within the first 2 days, plateauing thereafter. No published half-lives of 1-NA could be found, but it is likely to be short, i.e. a few hours, as most of the 1-NA urinary levels had reached a plateau already after one day. The profiles of reductions during the Ambulatory periods were also similar for the THS and SA arms, with a slight increase of 1-NA_{adjC} levels in the THS and SA arms after the Confinement period in the US study, likely due to the occasional use of CC.

Percent changes from Baseline of 1-NA_{adjC} during the Confinement periods ranged from -93% to -94% for the THS arms and from -93% to -96% for the SA arms. During the Ambulatory periods, these percent changes were overall maintained in the THS arms, ranging from -78% to -92%, as well as in the SA arms, ranging from -78% to -86%, despite a slight decrease of reduction in both arms observed mainly in the US study.

No published smoking cessation study could be found where levels of 1-NA were assessed. In fact, few data are available on 1-NA in smokers, but 2 studies showed levels of 1-NA ranging from 12 to 68 ng/24h in non-smokers and 67 to 506 ng/24h in smokers (Grimmer 2000, Yu 2014). Values obtained in PMI's studies, both in the continuing and

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smoking abstinence arms, are consistent with those published data with levels ranging at Day 5 from 62 to 134 and from 2 to 4 ng/24h, in the CC and SA arms, respectively (data available in clinical study reports), and indicate that levels in the THS arms reached the levels of non-smokers already within 5 days.

Statistically significant reductions were observed in the levels of 1-NA_{adjC} assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 94% to 96%, while there was overall no or small difference between the THS and SA. These reductions were overall sustained during the ambulatory periods, with decreases from 86% to 94% at Day 90. Because 1-NA does not occur naturally, except through occupational or smoke exposures (National Center for Biotechnology Information (NCBI) 2014b, Toxicology Data Network), any change in the reductions of 1-NA during the ambulatory periods likely has to be explained by the occasional use of CC.

In summary, the levels of 1-NA_{adjC} observed with THS use were statistically significantly lower from values observed in the CC arms at Day 5 and Day 90 and approaching levels observed in the SA arms, as well as to published literature on non-smokers.

6.1.3.2.3.10 2-NA – BoExp for Exposure to 2-NA

The FDA has classified 2-aminonaphthalene (2-NA) as a carcinogen (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of 2-NA concentration adjusted to creatinine (2-NA_{adjC}) differed ranged from 13.22 to 24.59 pg/mg_{creat} (Table 35).

Table 35 Geometric Means and 95% CIs of 2-NA_{adjC} (pg/mg_{creat}) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	24.14	13.88	15.32	18.65
		95% CI	21.18; 27.51	11.66; 16.52	13.13; 17.87	14.82; 23.47
		Min; Max	10.7; 55.1	3.6; 31.3	3.8; 37.6	4.2; 68.3
	THS	N	80	80	76	67
		Mean	24.54	13.22	15.49	17.45
		95% CI	22.12; 27.22	11.52; 15.16	13.82; 17.37	14.75; 20.64
		Min; Max	5.7; 52.1	2.5; 45.0	4.0; 52.4	1.5; 98.8
	SA	N	39	38	39	21
		Mean	24.59	13.41	13.64	15.97
		95% CI	21.52; 28.10	10.94; 16.44	11.43; 16.28	11.56; 22.06
		Min; Max	9.5; 67.8	2.4; 40.5	3.8; 37.0	2.0; 52.1

(table continues)

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			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	34
		Mean	25.32	13.38	14.23	16.28
		95% CI	22.27; 28.79	10.93; 16.37	12.18; 16.62	13.08; 20.26
		Min; Max	11.5; 58.4	3.0; 35.0	3.6; 31.7	3.0; 68.3
	THS	N	79	80	76	73
		Mean	2.96	2.33	1.97	2.10
		95% CI	2.67; 3.28	2.10; 2.59	1.80; 2.15	1.85; 2.39
		Min; Max	1.4; 9.6	0.9; 7.3	0.7; 4.1	0.6; 6.8
	SA	N	39	38	39	22
		Mean	2.52	2.27	2.04	1.98
		95% CI	2.23; 2.84	1.96; 2.63	1.82; 2.28	1.52; 2.58
		Min; Max	1.3; 5.9	1.1; 6.8	0.9; 5.1	0.8; 10.2
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	14.84	17.29
		95% CI	NA	NA	12.63; 17.44	13.62; 21.95
		Min; Max	NA	NA	4.6; 41.4	2.9; 53.2
	THS	N	NA	NA	70	47
		Mean	NA	NA	2.34	3.21
		95% CI	NA	NA	2.11; 2.59	2.57; 4.00
		Min; Max	NA	NA	0.9; 6.6	1.0; 19.8
	SA	N	NA	NA	37	9
		Mean	NA	NA	2.63	3.03
		95% CI	NA	NA	2.20; 3.15	1.80; 5.11
		Min; Max	NA	NA	1.09; 8.53	1.33; 10.51

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.18; ZRHR-REXC-04-JP, Table 15.2.4.18; ZRHM-REXA-07-JP, Table 15.2.4.11.1; ZRHM-REXA-08-US, Table 15.2.4.11.1]

Similar to the results of 1-aminonaphthalene exposure, a substantial decrease of 24 hour urinary levels of the aromatic amine was achieved by switching to THS. The maximum decrease of 2-NA levels was attained by Day 2 (Figure 18).

Percent changes from Baseline of urinary 2-NA during the Confinement periods in all 4 studies at Day 5 ranged from -76% to -85% for the THS arms and from -77% to -89% for the SA arms.

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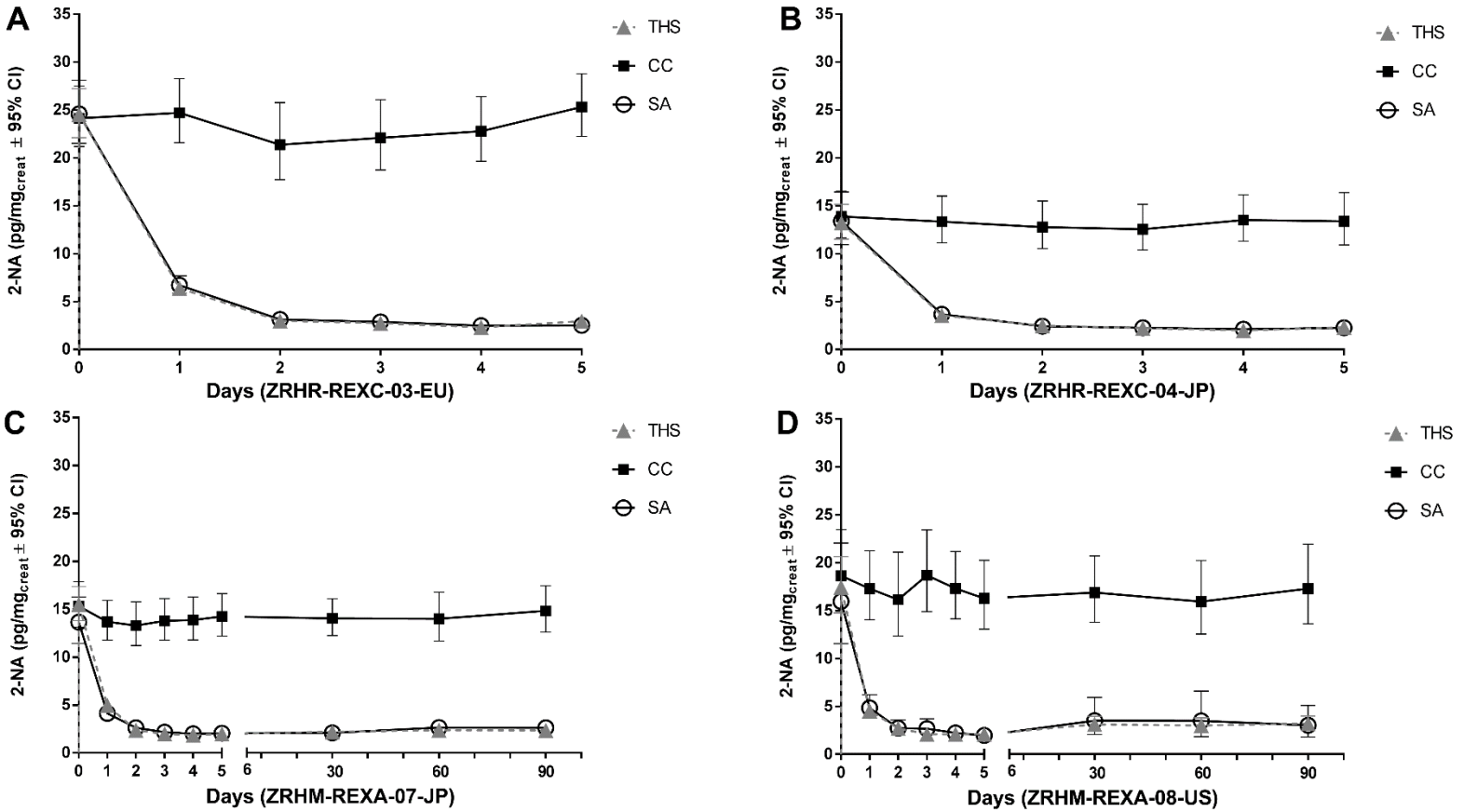


Figure 18 Geometric Mean and 95% CIs of Urinary 2-NA$_{adjC}$ Concentrations (pg/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.18; ZRHR-REXC-04-JP, Table 15.2.4.18; ZRHM-REXA-07-JP, Table 15.2.4.11.1; ZRHM-REXA-08-US, Table 15.2.4.11.1]

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In the 2 ambulatory studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], the change from Baseline at Day 90 ranged from -77% to -82% in the THS arms, and from -64% to -74% in the SA arm (Table 36).

Table 36 Mean Percent Change from Baseline and 95% CIs of Urinary 2-NA_{adjC} (pg/mg_{creat}) by Study at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	7.19%	6.31%	-4.74%	0.23%
		95% CI	0.41; 13.97	-8.86; 21.48	-11.44; 1.96	-16.54; 16.99
	THS	N	79	80	76	67
		% Change	-85.39%	-75.84%	-85.26%	-80.97%
		95% CI	-87.95; -82.82	-81.56; -70.13	-87.36; -83.16	-87.52; -74.41
	SA	N	39	38	39	21
		% Change	-88.93%	-77.24%	-83.02%	-82.14%
		95% CI	-90.38; -87.47	-84.22; -70.26	-86.12; -79.91	-92.23; -72.04
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	6.31%	11.04%
		95% CI	NA	NA	-10.43; 23.05	-5.78; 27.86
	THS	N	NA	NA	70	43
		% Change	NA	NA	-81.75%	-77.01%
		95% CI	NA	NA	-85.04; -78.46	-83.63; -70.39
	SA	N	NA	NA	37	9
		% Change	NA	NA	-74.09%	-64.26%
		95% CI	NA	NA	-80.97; -67.21	-88.69; -39.84

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.18; ZRHR-REXC-04-JP, Table 15.2.4.18; ZRHM-REXA-07-JP, Table 15.2.4.11.1; ZRHM-REXA-08-US, Table 15.2.4.11.1]

6.1.3.2.3.10.1 Analysis of 2-NA at Day 5 and Day 90

The reduction of 2-NA was more than 80% across studies and assessment time points ($p<0.001$ for each study; Table 35). The largest difference was seen in the study population with the highest Baseline values of 2-aminonaphthalene exposure due to CC consumption at study entry [ZRHR-REXC-03-EU] (Table 35) ($p<0.001$).

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Table 37 Adjusted Geometric LS Means of THS to CC ratios of 2-NA at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	11.54%	17.62%	13.66%	13.12%
		95% CI	10.08; 13.21	14.72; 21.08	12.04; 15.49	10.49; 16.40
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	15.45%	16.04%
		95% CI	NA	NA	12.98; 18.39	11.87; 21.67
		p Value	NA	NA	<0.001	<0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.17; ZRHR-REXC-04-JP, Table 15.2.4.17; ZRHM-REXA-07-JP, Table 15.2.3.4; ZRHM-REXA-08-US, Table 15.2.3.4]

6.1.3.2.3.10.2 Conclusion

At Baseline, urinary concentrations of 2-NA_{adjC} differed between studies, with the lowest levels observed in the Japanese studies, and the highest in the European study. As the same method was used to measure 2-NA levels across studies, this likely indicates a difference in smoking behavior between population including differences in cigarette brands.

It has been shown that increased concentrations of sodium nitrate in the tobacco may be associated with higher 2-NA values in mainstream cigarette smoke, thus different tobacco blends can affect 2-NA intake (Smith 1997). Burley tobaccos frequently have higher nitrate concentrations than flue-cured tobaccos, thus American blend cigarettes, which contain some Burley (Roemer 2012), are generally expected to yield higher 2-NA concentrations than cigarettes containing only flue-cured tobacco (Smith 1997), such as those more frequent in Japan, that contain Oriental and Virginia tobacco (IARC (International Agency for Research on Cancer) 2004). On the other hand, Polish population has been shown to have a high prevalence of heavy smokers (Jassem 2014), which could explain why levels of 2-NA levels at Baseline were the highest in the European study, which was conducted in Poland. 2-NA levels have been shown to be correlated with the number of cigarettes per day (Theophilus 2015). This hypothesis is reinforced by the results of PMI studies where the Baseline daily CC consumption levels was slightly higher in Poland (mean of around 16 CC per day) compared to US and Japan (between 10 to 13 CC per day) at Baseline [Section 6.2.2 Product Use]. Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g_{creat} [Section 6.2.2 Product Use], which can be also indicative of different smoking behaviors.

The profiles of reductions over the 5 days of Confinement were similar in the THS and SA arms, with a maximum decrease observed within the first 2 days, plateauing thereafter. No published half-lives of 2-NA could be found, but it is likely to be short, i.e.

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a few hours, as the majority of the 2-NA urinary levels had reached a plateau already after one day. The profiles of reductions during the Ambulatory periods were also similar for the THS and SA arms, with a slight increase of 2-NA_{adjC} levels in the THS and SA arms after the Confinement period in the US study, but plateauing from Day 30 onward. Because 2-NA is no longer produced at large scales by industries, any change in the reductions of 2-NA has to be explained by the occasional use of CC or environmental smoke exposures (IARC (International Agency for Research on Cancer) 2012, National Center for Biotechnology Information (NCBI) 2014a).

Percent changes from Baseline of 2-NA_{adjC} during the Confinement periods ranged from -76% to -85% for the THS arms and from -77% to -89% for the SA arms. During the Ambulatory periods, these percent changes were overall maintained in the THS arms, ranging from -77% to -82%, as well as in the SA arms, ranging from -64% to -74%, despite a slight decrease of reduction in both arms observed mainly in the US study. Several smoking cessation studies conducted over 3 to 8 days showed reductions of 2-NA levels ranging from -38% to 90% from Baseline, with the majority of the studies showing reductions of more than -80% (Frost-Pineda 2008a, Theophilus 2015, Tricker 2012a, Tricker 2012b, Tricker 2012c). Levels of urinary 2-NA concentrations at the beginning of those published studies ranged from 7 to 40 ng/24h, decreasing to ranges of 2 to 5 ng/24h at the end of the studies. Values obtained in PMI's studies at Baseline in the SA arm (range from 14 ng/24h in ZRHR-REXC-04-JP to 39 ng/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), and at Day 5 (range from 2 ng/24h in ZRHR-REXC-04-JP and ZRHM-REXA-07-JP to 4 ng/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), thus the values of 2-NA quantity excreted as well as the percent changes from Baseline, are consistent with published smoking cessation studies of 3 to 8 days.

Clinical studies conducted with products based on the heat-not-burn principle, showed reductions of urinary 2-NA_{ajdC} levels ranging from -9% to -82% in smokers who switched from CC to the test systems for 5 to 8 days, in Confinement conditions (Frost-Pineda 2008a, Tricker 2012a, Tricker 2012b, Tricker 2012c). These studies were conducted in the US, Japan, or Korea. In a study conducted over 34 days of switching, in Poland, change from Baseline when switching to a heat-not-burn product was of -51% (Martin Leroy 2012).

Statistically significant reductions were observed in the levels of 2-NA_{ajdC} assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 82% to 88%, while there was overall small or no difference between the THS and SA arms. The reductions in 2-NA_{ajdC} observed at Day 5 during the Confinement periods for the THS arms compared to CC arms were sustained during the Ambulatory periods, with decreases of 84% and 85% at Day 90.

In summary, the levels of 2-NA_{adjC} observed with THS use were statistically significantly lower from values observed in the CC arms at Day 5 and Day 90 and approaching levels observed in the SA arms as well as to published literature on non-smokers.

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6.1.3.2.3.11 o-Toluidine – BoExp for Exposure to o-Toluidine

The FDA has classified o-toluidine as a respiratory and reproductive or developmental toxicant (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of *o*-toluidine concentration adjusted to creatinine (o-toluidine$_{adjC}$) varied between 94.65 to 135.20 pg/mg$_{creat}$ across studies (Table 38).

Table 38 Geometric Means and 95% CIs of o-Toluidine$_{adjC}$ (pg/mg$_{creat}$) by Study Arm in All Studies, at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	38	30
		Mean	131.32	106.51	136.04	114.59
		95% CI	115.72; 149.01	87.32; 129.91	107.42; 172.27	92.45; 142.04
		Min; Max	48.1; 382.0	35.8; 477.9	33.1; 1037. 7	26.3; 299.3
	THS	N	80	80	76	67
		Mean	135.20	111.82	128.19	98.12
		95% CI	122.75; 148.90	95.48; 130.96	112.28; 146.36	84.75; 113.59
		Min; Max	35.5; 291.8	25.1; 1578.1	26.9; 1407.1	12.4; 685.4
	SA	N	39	38	39	21
		Mean	132.49	98.68	120.54	94.65
		95% CI	114.75; 152.97	81.25; 119.86	96.23; 150.98	73.46; 121.95
		Min; Max	41.1; 362.0	38.5; 371.9	36.3; 1014.9	38.4; 267.2
Day 5	CC	N	41	40	40	34
		Mean	121.16	98.18	127.28	92.68
		95% CI	105.07; 139.71	82.69; 116.57	103.27; 156.88	77.80; 110.39
		Min; Max	45.5; 265.9	24.8; 298.3	35.7; 493.3	39.0; 277.0
	THS	N	79	80	76	73
		Mean	51.15	50.40	51.64	42.20
		95% CI	46.10; 56.75	44.64; 56.91	45.52; 58.59	37.79; 47.13
		Min; Max	20.3; 192.3	16.9; 244.8	22.1; 288.7	12.4; 136.6
	SA	N	39	38	39	22
		Mean	41.64	48.91	48.82	34.05
		95% CI	36.74; 47.18	40.56; 58.97	40.94; 58.21	26.55; 43.68
		Min; Max	16.2; 100.8	21.9; 453.0	17.5; 198.5	9.3; 101.9
Day 90	CC	N	NA	NA	40	32
		Mean	NA	NA	125.64	107.39
		95% CI	NA	NA	96.13; 164.20	84.14; 137.07
		Min; Max	NA	NA	34.4; 1525.2	30.2; 686.7
	THS	N	NA	NA	70	47
		Mean	NA	NA	68.35	47.53
		95% CI	NA	NA	53.91; 86.67	39.00; 57.92

(table continues)

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		ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
	Min; Max	NA	NA	15.3; 2348.0	19.4; 961.5
SA	N	NA	NA	37	9
	Mean	NA	NA	77.86	37.30
	95% CI	NA	NA	56.72; 106.88	28.60; 48.66
	Min; Max	NA	NA	21.7; 1519.5	26.6; 65.3

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.20; ZRHR-REXC-04-JP Table 15.2.4.20; ZRHM-REXA-07-JP, Table 15.2.4.12.1; ZRHM-REXA-08-US, Table 15.2.4.12.1]

o-Toluidine$_{adjC}$ decreased similarly from Baseline in the THS and SA arms with time course curves superimposed of THS and SA at Day 5 (Figure 19). In the sequenced Ambulatory period after the Confinement phase in study [ZRHR-REXC-04-JP] and [ZRHM-REXA-08-US], *o*-toluidine moved slightly up maintaining a large difference to the excreted *o*-toluidine levels in continued CC users.

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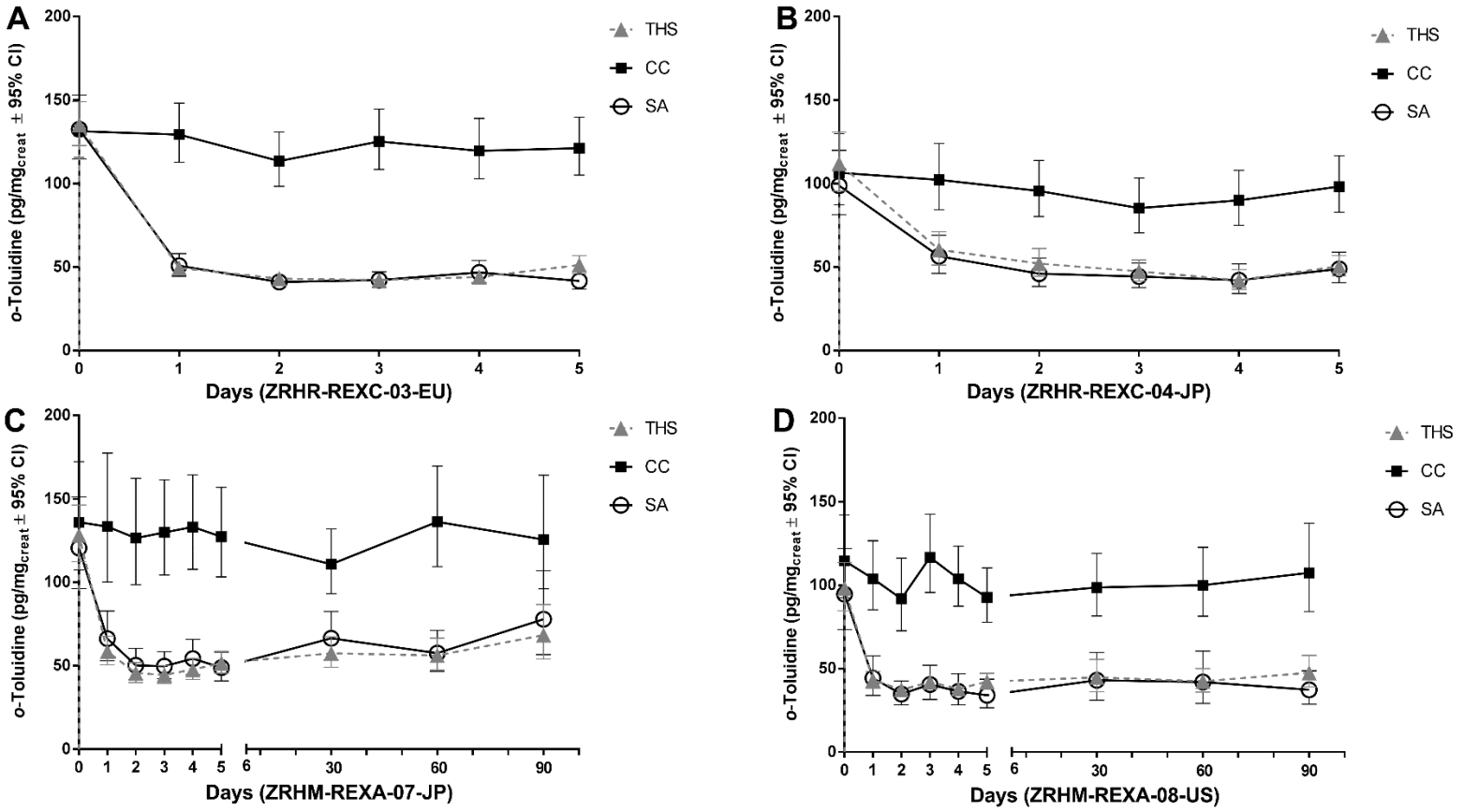


Figure 19 Geometric Mean and 95% CIs of Urinary *o*-Toluidine$_{adjC}$ Concentrations (pg/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.20; ZRHR-REXC-04-JP, Table 15.2.4.20; ZRHM-REXA-07-JP, Table 15.2.4.12.1; ZRHM-REXA-08-US, Table 15.2.4.12.1]

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At Day 5, the levels of urinary *o*-toluidine$_{adjC}$ were generally comparable between studies, both in the THS and SA arms, with levels ranging from 42 to 51 and from 34 to 48 pg/mg$_{creat}$, respectively. At Day 90, the levels of *o*-toluidine were comparable, with levels ranging from 47 to 68 in the THS group and from 37 to 77 pg/mg$_{creat}$ in the SA arms (Table 38).

Percent changes from Baseline of urinary *o*-toluidine$_{adjC}$ levels during the Confinement periods in all 4 studies at Day 5 ranged from -41% to -51% for the THS arms and from -35% to -65% for the SA arms. In the 2 ambulatory studies, these changes ranged at Day 90 from -21% to -58% in the THS arms, and from -47% to -54% in the SA arms, in [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], respectively. In the THS and SA arms of the [ZRHM-REXA-07-JP] study at Day 90, the distribution was skewed by outliers. The median values are thus reported instead of the mean, for all arms.

Table 39 Percent Change from Baseline and 95% CIs of Urinary *o*-Toluidine$_{adjC}$ (pg/mg$_{creat}$) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP #	ZRHM-REXA-08-US
Day 5	CC	N	41	40	38	30
		% Change	-3.08%	4.66%	-3.37%	-10.68%
		95% CI	-12.17; 6.01	-12.50; 21.83	-14.12; 7.38	-24.74; 3.37
	THS	N	79	80	76	67
		% Change	-50.96%	-44.23%	-46.70%	-40.73%
		95% CI	-61.87; -40.05	-52.58; -35.89	-61.72; -31.69	-54.28; -27.17
	SA	N	39	38	39	21
		% Change	-64.96%	-35.41%	-52.53%	-54.59%
		95% CI	-70.90; -59.01	-50.55; -20.28	-61.81; -43.24	-71.40; -37.78
Day 90	CC	N	NA	NA	37	29
		% Change	NA	NA	-8.70% #	10.33%
		95% CI (or Q1; Q3 #)	NA	NA	-35.74; 13.02 #	-12.50; 33.15
	THS	N	NA	NA	70	43
		% Change	NA	NA	-58.22% #	-20.76%
		95% CI (or Q1; Q3 #)	NA	NA	-70.12, -16.4 #	-66.83; 25.31
	SA	N	NA	NA	37	9
		% Change	NA	NA	-53.82% #	-46.88%
		95% CI (or Q1; Q3 #)	NA	NA	-62.41; -6.44 #	-64.92; -28.84

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Because of outliers in the THS and SA arm, values percent change from Baseline values for *o*-toluidine in ZRHM-REXA-07-JP are reported as median at Day 90 (Q1; Q3), for all arms.

[Datasource: Clinical Study Reports; ZRHR-REXC-03-EU, Table 15.2.4.20; ZRHR-REXC-04-JP Table 15.2.4.20; ZRHM-REXA-07-JP, Table 15.2.4.12.1; ZRHM-REXA-08-US, Table 15.2.4.12.1]

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6.1.3.2.3.11.1 Analysis of o-Toluidine at Day 5 and Day 90

At Day 5, across all 4 studies, switching to THS resulted in at leat a 49% reduction of *o*-toluidine$_{adjC}$, with a maximum reduction of 58% compared to CC smoking ($p<0.001$ for each study; Table 40). At Day 90, these levels of reduction were overall maintained, with reductions of 41% in [ZRHM-REXA-07-JP] and 57% in [ZRHM-REXA-08-US] (Table 40) ($p\leq0.001$).

Table 40 Adjusted Geometric LS Means of THS to CC to SA ratios of o-Toluidine at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	41.70%	50.52%	43.80%	48.72%
		95% CI	36.01; 48.29	42.28; 60.38	36.31; 52.83	39.70; 59.79
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	59.16%	43.29%
		95% CI	NA	NA	42.02; 83.29	32.00; 58.55
		p Value	NA	NA	0.001	<0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.19; ZRHR-REXC-04-JP, Table 15.2.4.19; ZRHM-REXA-07-JP, Table 15.2.3.4; ZRHM-REXA-08-US, Table 15.2.3.4]

6.1.3.2.3.11.2 Conclusion

At Baseline, *o*-toluidine$_{adjC}$ showed relatively small differences between studies, which was not the case for many other BoExp. The highest levels were observed in the European population.

The profiles of reductions over the 5 days of Confinement were similar in the THS and SA arms, with a maximum decrease observed after Day 1, and a plateau appearing thereafter, except in the ZRHR-REXC-04-JP study, where levels decreased gradually up to Day 4. These data are thus overall consistent with the estimated half-life of *o*-toluidine, i.e. around 4 hours (Herdevall 2003). The profiles of reductions during the Ambulatory periods were also similar for the THS and SA arms, with a slight increase of *o*-toluidine$_{adjC}$ in both the THS and SA arms throughout the whole Ambulatory period in the ZRHM-REXA-07-JP study, while levels plateaued throughout in the ZRHM-REXA-08-US study.

Percent changes from Baseline of *o*-toluidine$_{adjC}$ during the Confinement periods ranged from -41% to -51% for the THS arms and from -35% to -65% for the SA arms. Because of outliers in the THS and SA arms of ZRHR-REXC-03-EU, the median values are probably in this case a more reliable measure. Percent changes from Baseline at the end of the Ambulatory periods ranged from -21% to -58% in the THS arms, and from -47% to -54% in the SA arms. In contrast to [ZRHM-REXA-07-JP], it appeared that the levels of reduction were not as sustained during the Ambulatory periods when compared with

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the Confinement periods in [ZRHM-REXA-08-US], even though the profiles of reductions clearly show a sustained reduction compared to CC. This is probably due to the presence of outliers . Several smoking cessation studies conducted over 5 to 8 days showed reductions of *o*-toluidine levels ranging from -50% to -72% from Baseline (Frost-Pineda 2008a, Sarkar 2010, Theophilus 2015, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). Levels of urinary *o*-toluidine at the beginning of those published studies ranged from 70 to 210 ng/24h, decreasing to ranges of 30 to 96 ng/24h at the end of the studies. Values obtained in PMI's studies at Baseline in the SA arm (range from 101 ng/24h in ZRHR-REXC-04-JP to 209 ng/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), and at Day 5 (range from 51 ng/24h in ZRHR-REXC-04-JP to 65 ng/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), as well as the percent changes from Baseline, are thus consistent with published smoking cessation studies of 5 to 8 days.

Clinical studies conducted with products based on the heat-not-burn principle showed reductions of urinary *o*-toluidine levels ranging from -48% to -73% in smokers who switched from CC to the test systems for 5 to 8 days, in Confinement conditions (Frost-Pineda 2008a, Roethig 2007, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). These studies were conducted in the US, UK, Japan or Korea. In a study conducted over 34 days in Poland, changes from Baseline when switching to the heat-not-burn product were of -39% (Martin Leroy 2012).

Statistically significant reductions were observed in the levels of *o*-toluidine$_{adjC}$ assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 49% to 58%, while there was overall no difference between the THS and SA arms. The reductions in *o*-toluidine$_{adjC}$ observed at Day 5 during the Confinement periods for the THS arms compared to CC arms were overall sustained during the ambulatory periods, with decreases of 41% to 57% at Day 90. A slightly smaller reduction at the end of the Ambulatory periods is likely to be related to exposure to environmental sources of *o*-toluidine, as it is found ubiquitously, including in a large variety of food and beverages, and also in dyes (IARC (International Agency for Research on Cancer) 2010, Richter 2015, WHO (World Health Organization) 1998). Road dust is another source of *o*-toluidine exposure, as *o*-toluidine is used in the manufacturing of rubber, used for tires (OECD (Organization for Economic Co-operation and Development) 2004).

In summary, the levels of *o*-toluidine$_{adjC}$ observed with THS use were statistically significantly lower from values observed in the CC arms at Day 5 and Day 90 and approaching levels observed in the SA arms as well as to published literature from smoking cessation studies.

6.1.3.2.3.12 CEMA – BoExp for Exposure to Acrylonitrile

Acrylonitrile has been classified by the FDA as a carcinogen and a respiratory toxicant (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of CEMA concentration adjusted to creatinine (CEMA$_{adjC}$) varied between studies, with differences ranging from 56.35 ng/mg$_{creat}$ to 103.51

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ng/mg_{creat} (Table 41). The Baseline levels were the lowest in the Japanese populations, with the highest levels observed in the European subjects.

Table 41 Geometric Means and 95% CIs of $CEMA_{adjC}$ (pg/mg_{creat}) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	98.46	63.19	75.19	99.50
		95% CI	83.81; 115.67	52.60; 75.90	62.27; 90.80	80.67; 122.71
		Min; Max	24.6; 260.0	19.6; 189.9	16.0; 219.3	19.6; 322.7
	THS	N	80	80	76	67
		Mean	98.03	57.12	75.32	90.62
		95% CI	85.10; 112.92	48.28; 67.59	66.47; 85.36	78.59; 104.48
		Min; Max	5.5; 246.1	2.9; 228.5	19.7; 312.1	14.5; 317.1
	SA	N	39	38	39	21
		Mean	103.51	56.35	76.74	91.97
		95% CI	89.35; 119.91	46.59; 68.16	63.97; 92.05	69.22; 122.18
		Min; Max	39.8; 237.7	15.3; 151.9	18.3; 261.9	13.1; 205.8
Day 5	CC	N	41	40	42	34
		Mean	99.48	54.19	68.17	88.40
		95% CI	85.79; 115.35	43.47; 67.55	56.39; 82.40	71.73; 108.94
		Min; Max	31.7; 207.7	13.3; 198.6	16.3; 206.1	11.2; 322.7
	THS	N	79	80	76	73
		Mean	13.18	10.61	12.43	14.39
		95% CI	11.37; 15.27	9.17; 12.29	11.12; 13.90	12.30; 16.83
		Min; Max	1.2; 45.4	1.9; 35.5	3.7; 44.2	2.1; 52.3
	SA	N	39	38	39	22
		Mean	12.60	9.04	11.78	13.40
		95% CI	10.12; 15.70	7.05; 11.60	9.84; 14.10	10.06; 17.86
		Min; Max	1.3; 44.4	1.0; 51.3	2.5; 27.8	4.4; 70.2

(table continues)

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			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	83.98	87.35
		95% CI	NA	NA	69.17; 101.95	66.11; 115.41
		Min; Max	NA	NA	18.2; 262.4	4.4; 249.5
	THS	N	NA	NA	70	47
		Mean	NA	NA	7.91	14.12
		95% CI	NA	NA	6.74; 9.29	10.16; 19.61
		Min; Max	NA	NA	2.2; 68.4	1.1; 121.9
	SA	N	NA	NA	37	9
		Mean	NA	NA	8.41	13.81
		95% CI	NA	NA	5.99; 11.81	4.70; 40.57
		Min; Max	NA	NA	1.6; 50.2	1.4; 100.6

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.22; ZRHR-REXC-04-JP, Table 15.2.4.22; ZRHM-REXA-07-JP, Table 15.2.4.13.1; ZRHM-REXA-08-US, Table 15.2.4.13.1]

A substantial reduction in CEMA was achieved by Day 2 and plateaued thereafter. During the Ambulatory phase, CEMA levels in the THS and SA arms remained low in the [ZRHM-REXA-07-JP] study. In the [ZRHM-REXA-08-US] study the CEMA reduction achieved at Day 5 in Confinement was not different to the one noted in the Ambulatory phase at Day 90 (Figure 20; Table 41).

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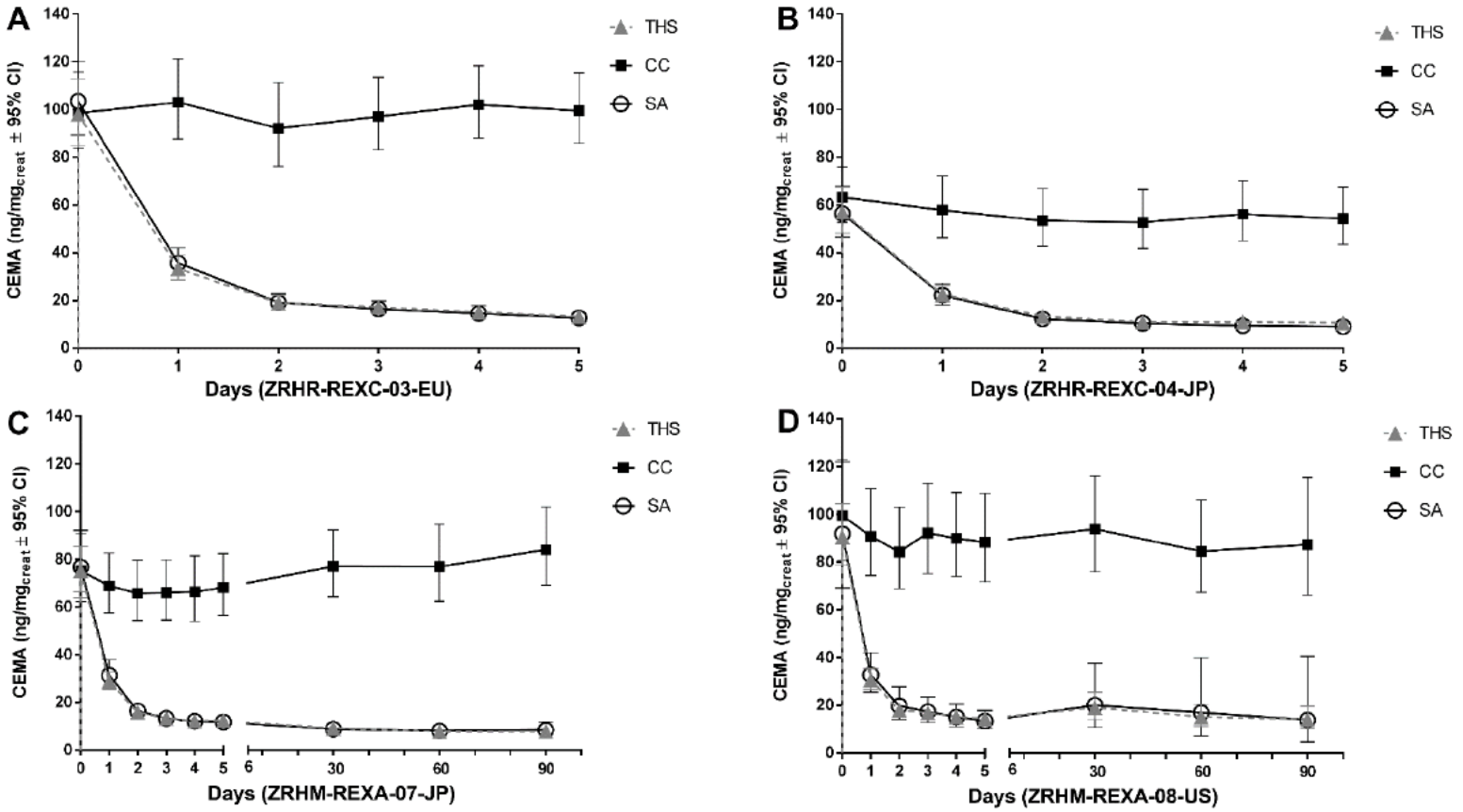


Figure 20 Geometric Mean and 95% CIs of Urinary CEMA$_{adjC}$ Concentrations (pg/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.22; ZRHR-REXC-04-JP, Table 15.2.4.22; ZRHM-REXA-07-JP, Table 15.2.4.13.1; ZRHM-REXA-08-US, Table 15.2.4.13.1]

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At Day 5, the percent changes from Baseline of urinary $CEMA_{adjC}$ levels during the Confinement periods in all 4 studies ranged from -79% to -86% in the THS arms and from -82% to -87% in the SA arms (Table 42). At Day 90, the changes from Baseline ranged from -77% to -86% and from -66% to -80%, in the THS and SA arms, respectively (Table 42).

Table 42 Mean Percent Change from Baseline and 95% CIs of Urinary $CEMA_{adjC}$ (pg/mg_{creat}) by Study at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	4.21%	-7.83%	-6.18%	-9.05%
		95% CI	-4.18; 12.61	-18.77; 3.11	-14.03; 1.67	-19.71; 1.60
	THS	N	79	80	76	67
		% Change	-86.10%	-79.42%	-82.39%	-83.00%
		95% CI	-87.04; -85.17	-81.75; -77.08	-83.84; -80.93	-85.04; -80.96
	SA	N	39	38	39	21
		% Change	-86.74%	-82.49%	-83.70%	-83.83%
		95% CI	-88.30; -85.17	-85.12; -79.86	-85.56; -81.84	-88.02; -79.64
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	21.70%	2.56%
		95% CI	NA	NA	5.38; 38.02	-14.27; 19.40
	THS	N	NA	NA	70	43
		% Change	NA	NA	-86.31%	-76.58%
		95% CI	NA	NA	-89.75; -82.88	-83.76; -69.40
	SA	N	NA	NA	37	9
		% Change	NA	NA	-79.89%	-65.96%
		95% CI	NA	NA	-87.68; -72.10	-88.08; -43.85

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.22; ZRHR-REXC-04-JP, Table 15.2.4.22; ZRHM-REXA-07-JP, Table 15.2.4.13.1; ZRHM-REXA-08-US, Table 15.2.4.13.1]

6.1.3.2.3.12.1 Analysis of CEMA Levels at Day 5 and Day 90

Across all 4 studies, a substantial reduction of CEMA in subjects who switched to THS was shown. Reductions of CEMA levels of more than 80% were found with THS use at Day 5 ambulatory and at Day 90 compared with CC use ($p<0.001$ for each study; Table 43).

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Table 43 Adjusted Geometric LS Means of THS to CC ratios of CEMA at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	13.16%	21.21%	18.23%	17.23%
		95% CI	11.58; 14.95	18.10; 24.86	16.16; 20.56	14.44; 20.55
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	9.17%	14.29%
		95% CI	NA	NA	7.01; 12.00	9.01; 22.67
		p Value	NA	NA	<0.001	<0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.21; ZRHR-REXC-04-JP, Table 15.2.4.21; ZRHM-REXA-07-JP, Table 15.2.3.4; ZRHM-REXA-08-US, Table 15.2.3.4]

6.1.3.2.3.12.2 Conclusion

At Baseline, urinary concentrations of $CEMA_{ajdC}$ were quite different between studies, with differences of up to 1.7 fold. The levels were the lowest in the Japanese populations, while the highest levels were observed in the European study. This likely indicates a difference in smoking behavior, but also of cigarette brands: Japanese are reported to have preference for cigarettes with charcoal-containing filters, which can retain, to a certain extent, a number of gas smoke constituents found in main stream smoke, and 70% of the brands sold in Japan have a charcoal filter, whereas they are much less popular outside Japan (Coggins 2008, Muscat 2005). Levels of urinary acrylonitrile in cigarette smoke have been reported to be decreased by charcoal filters (Coggins 2008). On the other hand, Polish population has been shown to have a high prevalence of heavy smokers (Jassem 2014), which could explain why levels of $CEMA_{ajdC}$ levels at Baseline were the highest in the European study, which was conducted in Poland. CEMA levels have indeed been shown to be correlated with the number of cigarettes per day (Theophilus 2015). This hypothesis is further reinforced by the results of PMI studies where the Baseline daily CC consumption levels were higher in Poland (mean of around 16 CC per day) compared to US and Japan (between 10 to 13 CC per day) at Baseline [Section 6.2.2 Product Use]. Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g_{creat} [Section 6.2.2 Product Use], which can be also indicative of different smoking behaviors.

The profiles of reductions over the 5 days of Confinement were similar in the THS and SA arms, with the majority of the reduction achieved by Day 2, plateauing thereafter, thus being consistent with published half-lives of CEMA, i.e. 7 to 9 hours (Jakubowski 1987). The profiles of reductions during the Ambulatory periods were also similar for the THS and SA arms, with a small but consistent decrease in both arms in the Japanese study during the Ambulatory period, while it appeared to be steadier in the US study. The kinetics of excretion of CEMA has been shown to not be uniform (Gregg 2013), and because its half-life has been estimated only in short-term studies, the excretion of

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CEMA may actually follow a 2-phase type of elimination, and its half-life may have been underestimated (Gregg 2013).

Percent changes from Baseline of CEMA urinary concentrations adjusted to creatinine during the Confinement periods ranged from -79% to -86% for the THS arms and from -82% to -87% for the SA arms. During the Ambulatory periods, these percent changes were overall maintained in the THS arms, ranging from -77% to -86%, as well as in the SA arms, ranging from -80% to -66%, despite a slight decrease of reduction in the SA arm of the US study. Two smoking cessation studies conducted over 5 to 8 days showed reductions of CEMA levels ranging from -85% to -90% from Baseline (Scherer 2010, Theophilus 2015). Levels of urinary CEMA concentrations at the beginning of those published studies ranged from 259 to 263 µg/24h, decreasing to ranges of 25 to 38 µg/24h at the end of the studies. Values obtained in PMI's studies at Baseline in the SA arm (range from 58 µg/24h in ZRHR-REXC-04-JP to 164 µg/24h in ZRHR-REXC-03-EU; data available in clinical study reports), and at Day 5 (range from 9 µg/24h in ZRHM-REXA-07-JP to 22 µg/24h in ZRHR-REXA-08-US; data available in clinical study reports) are slightly lower than those measured in published smoking cessation studies of 5 to 8 days. Percent changes from Baseline are, however, consistent with published smoking cessation studies of 3 to 8 days.

Significant reductions were observed in the levels of $CEMA_{adjC}$ assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 79% to 87%, while there was overall small or no difference between the THS and SA arms. The reductions in $CEMA_{adjC}$ observed at Day 5 during the Confinement periods for the THS arms compared to CC arms were overall sustained during the Ambulatory periods, with decreases of 86% to 91% at Day 90. For most BoExp, reductions were slightly lower at Day 90 than Day 5, which was not the case for $CEMA_{adjC}$. In the Japanese study, the levels of CEMA in the CC group appeared to increase slightly during the Ambulatory period, which could contribute to this observation, but this was, however, not the case in the US study. Unlike many other HPHCs, exposure to environmental acrylonitrile, besides cigarette smoke, is fairly restricted, as it occurs only in the vicinity of industrial sources (WHO (World Health Organization) 2002).

In summary, the levels of $CEMA_{ajdC}$ observed with THS use were statistically significantly lower from values observed in the CC arms at Day 5 and Day 90 and approaching levels observed in the SA arms as well as to published literature from smoking cessation studies. In addition, the reduction of exposure to acrylonitrile observed with THS aerosol in the *in vivo* non-clinical studies is in support of the levels observed in the clinical assessment.

6.1.3.2.3.13 HEMA – BoExp for Exposure to Ethylene Oxide

The FDA has classified ethylene oxide as a carcinogen, respiratory, and reproductive or developmental toxicant (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of HEMA concentration adjusted to creatinine ($HEMA_{adjC}$) were about half in the [ZRHR-REXC-04-JP] study compared to the [ZRHR-REXC-03-EU] study conducted in Poland (Table 44).

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Table 44 Geometric Means and 95% CIs of $HEMA_{adjC}$ (pg/mg_{creat}) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	4718.48	2299.17	3148.47	3520.78
		95% CI	3582.18;	1776.20;	2465.16; 4021.17	2596.02; 4774.95
		Min; Max	990.3; 30887.4	231.8; 9624.1	184.8; 14128.6	778.4; 18109.2
	THS	N	80	80	76	67
		Mean	4161.66	2391.21	3203.95	3702.58
		95% CI	3409.70;	1984.68;	2699.53; 3802.62	2998.48; 4572.00
		Min; Max	68.8; 25495.8	317.2; 24903.5	572.7; 18905.5	736.9; 21768.7
	SA	N	39	38	39	21
		Mean	4114.78	2140.49	3201.31	3289.73
		95% CI	3127.42;	1658.04;	2477.20; 4137.07	2300.10; 4705.13
		Min; Max	797.6; 25494.1	452.6; 8941.5	625.4; 18930.0	409.3; 13621.7
Day 5	CC	N	41	40	42	34
		Mean	4504.00	2099.41	2235.37	2903.31
		95% CI	3506.73;	1614.33;	1742.88; 2867.03	2163.19; 3896.66
		Min; Max	1092.3; 23853.2	497.7; 16063.0	126.5; 11088.4	489.6; 17316.7
	THS	N	79	80	76	73
		Mean	1342.40	997.76	1137.96	1145.34
		95% CI	1140.44;	866.57; 1148.82	995.50; 1300.81	951.15; 1379.18
		Min; Max	183.8; 6280.2	252.9; 6655.6	390.7; 5784.0	200.0; 6806.3
	SA	N	39	38	39	22
		Mean	1248.27	806.29	1113.73	1075.28
		95% CI	980.62; 1588.98	666.35; 975.61	923.72; 1342.83	762.54; 1516.30
		Min; Max	219. 7; 6494.8	254.4; 2475.7	308.2; 6801.6	249.2; 4087.6
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	3739.46	3265.62
		95% CI	NA	NA	2858.39; 4892.12	2275.30; 4686.97
		Min; Max	NA	NA	185.8; 19069.8	154.9; 20141.3
	THS	N	NA	NA	70	47
		Mean	NA	NA	1741.53	1481.32
		95% CI	NA	NA	1510.19; 2008.30	1193.81; 1838.07
		Min; Max	NA	NA	541.7; 7396.3	400.0; 13759.5
	SA	N	NA	NA	37	9
		Mean	NA	NA	1633.12	1565.88
		95% CI	NA	NA	1286.77; 2072.69	892.46; 2747.43
		Min; Max	NA	NA	477.8; 7776.7	360.2; 4259. 9

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-

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REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.24; ZRHR-REXC-04-JP, Table 15.2.4.24; ZRHM-REXA-07-JP, Table 15.2.4.14.1; ZRHM-REXA-08-US, Table 15.2.4.14.1]

The decrease in $CEMA_{ajdC}$ levels over time was not different between THS and SA. The majority of the reduction in CEMA was achieved by Day 2 and plateaued thereafter. During the Ambulatory phase, $CEMA_{ajdC}$ levels in the THS and SA arms remained decreased from Baseline in the ZRHM-REXA-07-JP, with levels that continued to slightly but gradually decrease. In the ZRHM-REXA-08-US study, after a marginal increase during the transition phase from Confinement to Ambulatory settings, $CEMA_{ajdC}$ levels in the THS and SA arms also gradually decreased until the end of the study (Figure 21).

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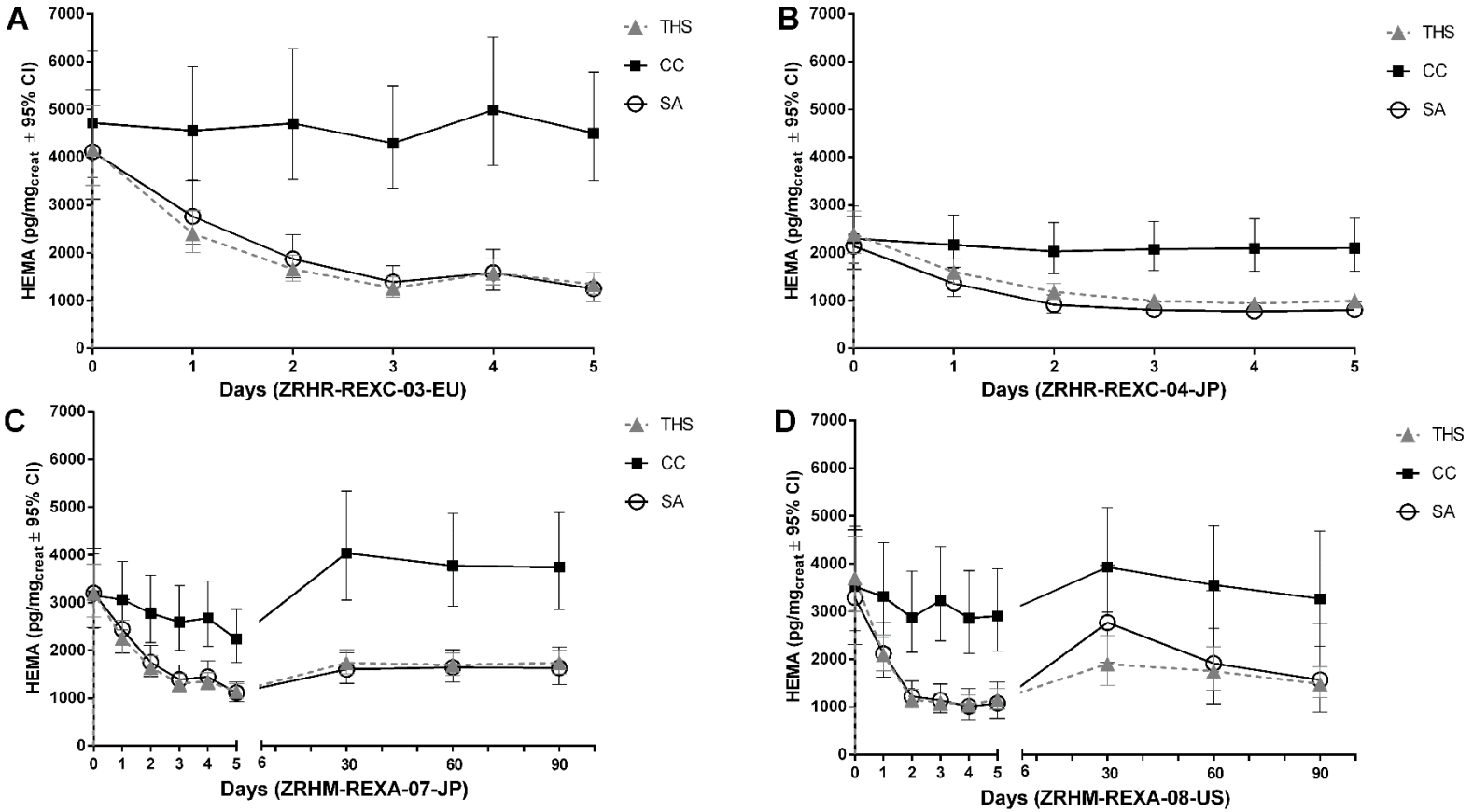


Figure 21 Geometric Mean and 95% CIs of Urinary $HEMA_{adjC}$ Concentrations (pg/mg_{creat}), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.24; ZRHR-REXC-04-JP, Table 15.2.4.24; ZRHM-REXA-07-JP, Table 15.2.4.14.1; ZRHM-REXA-08-US, Table 15.2.4.14.1]

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At Day 5, a reduction of HEMA ranging from -50% to -65% compared to Baseline was achieved in both study groups. In the ambulatory studies, the HEMA levels of THS compared to CC remained clearly distinct, although not at the same low level as at Day 5 during Confinement, with changes from Baseline ranging from to -39% to -55%, and from -35% to -51%, in the THS and SA arms, respectively. In subjects who continued consuming their own brand of CC in the Ambulatory studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], the HEMA levels in urine were found to be higher than during Confinement (Figure 21; Table 44). In the SA arm of the [ZRHM-REXA-08-US] study at Day 90, the distribution was skewed by outliers. The median values are thus reported instead of the mean, for all arms.

Table 45 Mean Percent Change from Baseline and 95% CIs of Urinary $HEMA_{adjC}$ (pg/mg_{creat}) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US [#]
Day 5	CC	N	41	40	42	30
		% Change	0.74%	3.26%	-26.60%	-7.74%
		95% CI	-9.86; 11.34	-15.67; 22.18	-32.48; -20.71	-22.66; 7.19
	THS	N	79	80	76	67
		% Change	-60.71%	-50.99%	-61.14%	-62.69%
		95% CI	-68.31; -53.11	-57.47; -44.51	-64.94; -57.33	-67.78; -57.60
	SA	N	39	38	39	21
		% Change	-64.48%	-58.25%	-61.24%	-62.03%
		95% CI	-71.29; -57.66	-64.77; -51.73	-67.03; -55.46	-72.63; -51.43
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	33.12%	8.19% [#]
		95% CI (or Q1; Q3 [#])	NA	NA	10.72; 55.53	17.62, 23.04 [#]
	THS	N	NA	NA	70	43
		% Change	NA	NA	-39.29%	-55.49% [#]
		95% CI (or Q1; Q3 [#])	NA	NA	-47.39; -31.19	-76.24; -35.80 [#]
	SA	N	NA	NA	37	9
		% Change	NA	NA	-35.41%	-50.76% [#]
		95% CI (or Q1; Q3 [#])	NA	NA	-49.07; -21.75	-73.55; 22.61 [#]

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Because of limited number of subjects in the SA arm and outliers, percent change from Baseline values for ZRHM-REXA-08-US are reported as median at Day 90 (Q1; Q3).

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.24; ZRHR-REXC-04-JP, Table 15.2.4.24; ZRHM-REXA-07-JP, Table 15.2.4.14.1; ZRHM-REXA-08-US, Table 15.2.4.14.1]

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6.1.3.2.3.13.1 Analysis of HEMA at Day 5 and Day 90

At Day 5, switching to THS resulted in at least a 50% reduction of HEMA with a maximum reduction of 68% compared to CC smoking ($p<0.001$ for each study; Table 46). At Day 90, these levels of reduction were overall maintained, with reductions of 55% in [ZRHM-REXA-07-JP] and 62% in [ZRHM-REXA-08-US] (Table 46) ($p<0.001$).

Table 46 Adjusted Geometric LS Means of THS to CC ratios of HEMA at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	32.00%	46.50%	50.14%	39.19%
		95% CI	27.10; 37.79	39.53; 54.69	44.09; 57.02	31.22; 49.20
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	44.96%	38.49%
		95% CI	NA	NA	37.17; 54.37	28.28; 52.38
		p Value	NA	NA	<0.001	<0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.23; ZRHR-REXC-04-JP, Table 15.2.4.23; ZRHM-REXA-07-JP, Table 15.2.3.4; ZRHM-REXA-08-US, Table 15.2.3.4]

6.1.3.2.3.13.2 Conclusion

At Baseline, $HEMA_{adjC}$ were notably different between studies, with differences of up to 1.7 fold. The levels were the lowest in the Japanese populations, while the highest levels were observed in the European study. As the same method was used to measure HEMA levels across studies, this likely indicates a difference in smoking behavior between population including differences in cigarette brands: Japanese are reported to have preference for cigarettes with charcoal-containing filters, which can retain, to a certain extent, a number of gas smoke constituents found in main stream smoke, and 70% of the brands sold in Japan have a charcoal filter, whereas they are much less popular outside Japan (Coggins 2008, Muscat 2005). Commercial charcoal filters were shown to efficiently decrease ethylene oxide from cigarette smoke. On the other hand, Polish population has been shown to have a high prevalence of heavy smokers (Jassem 2014), which could further explain why levels of HEMA levels at Baseline were the highest in the European study, which was conducted in Poland. HEMA levels have indeed been shown to be correlated with the number of cigarettes per day (Theophilus 2015). This hypothesis is reinforced by the results of PMI studies where the Baseline daily CC consumption levels were higher in Poland (mean of around 16 CC per day) compared to US and Japan (between 10 to 13 CC per day) at Baseline [Section 6.2.2 – Product Use]. Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g_{creat} [Section 6.2.2 – Product Use], which can be also indicative of different smoking behaviors.

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The profiles of reductions over the 5 days of Confinement were similar in the THS and SA arms, with a maximum decrease observed within the first 2 days, plateauing thereafter, thus being consistent with the published half-life of HEMA, ie. around 5 hours (Haufroid 2007). The profiles of reductions during the Ambulatory periods were also similar for the THS and SA arms, with a slight increase of $HEMA_{adjC}$ in all arms, including CC, after the Confinement periods. Because the environmental exposure to ethylene oxide is fairly negligible (IARC (International Agency for Research on Cancer) 2008a, IARC (International Agency for Research on Cancer) 2008b) (potential sources being release of occupational ethylene oxide into the atmosphere, mainly by its use as sterilizing agent), the increase during the Ambulatory periods could be related to the occasional use of CC.

Percent changes from Baseline of $HEMA_{adjC}$ during the Confinement periods ranged from -51% to -63% for the THS arms and from -58% to -64% for the SA arms. During the Ambulatory periods, these percent changes decreased slightly in the THS arms, ranging from -39% to -53%. Because of outliers and low number of subjects in the SA arm of ZRHM-REXA-08-US at the end of the study, the median value is probably in this case a more reliable measure. In the SA arms, the percent change from Baseline thus ranged from -35% to -56% at Day 90.

Two smoking cessation studies conducted over 3 or 5 days showed reductions of HEMA levels ranging from -59% to -76% from Baseline (Carmella 2012, Carmella 2009, Theophilus 2015). A change from Baseline of -81% was still observed in a study lasting up to 56 days (Carmella 2009). Levels of urinary HEMA concentrations at the beginning of those published studies ranged from 10570 to 14400 ng/24h, decreasing to ranges of 2487 to 4800 ng/24h at the end of the studies. Values obtained in PMI's studies at Baseline in the SA arm (range from 2183 ng/24h in ZRHR-REXC-04-JP to 6502 ng/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), and at Day 5 (range from 850 ng/24h in ZRHR-REXC-04-JP to 1958 ng/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), are lower than those published, however, the percent changes from Baseline were overall consistent with published smoking cessation studies.

Statistically significant reductions were observed in the levels of HEMA assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 50% to 68%, while there was overall no difference between the THS and SA arms. The reductions in $HEMA_{adjC}$ observed at Day 5 during the Confinement periods for the THS arms compared to CC arms were overall sustained during the ambulatory periods, with decreases of 55% to 61% at Day 90.

In summary, the levels of $HEMA_{adjC}$ observed with THS use were statistically significantly lower from values observed in the CC arms at Day 5 and Day 90 and overall comparable to levels observed in the SA arms as well as to published literature from smoking cessation studies.

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6.1.3.2.3.14 3-OH-B[a]P – BoExp for Exposure to B[a]P

The FDA has classified benzo[a]pyrene (B[a]P) as a carcinogen (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of 3-OH-B[a]P concentration adjusted to creatinine (3-OH-B[a]P_{adjC}) varied from 71.96 fg/mg_{creat} to 169.58 fg/mg_{creat} across studies,and were found to be at lowest level in the Japanese study populations (Table 47).

Table 47 Geometric Means and 95% CIs of 3-OH-B[a]P_{adjC} (fg/mg_{creat}) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	149.47	106.17	82.00	132.19
		95% CI	128.96; 173.23	89.08; 126.54	67.42; 99.71	103.81; 168.33
		Min; Max	50.2; 477.8	25.4; 289.0	16.5; 318.4	29.6; 454.8
	THS	N	80	80	76	67
		Mean	161.17	115.78	83.73	135.23
		95% CI	142.28; 182.57	98.47; 136.14	70.69; 99.18	113.24; 161.49
		Min; Max	18.6; 602.6	10.2; 469.1	13.6; 365.7	17.7; 778.0
	SA	N	39	38	39	21
		Mean	169.58	113.18	71.96	86.69
		95% CI	147.04; 195.57	91.05; 140.69	59.20; 87.47	66.36; 113.24
		Min; Max	63.2; 451.5	19.3; 331.4	18.4; 220.3	27.0; 225.8
Day 5	CC	N	41	40	42	34
		Mean	130.29	96.42	75.10	107.09
		95% CI	110.17; 154.07	80.55; 115.41	62.60; 90.08	82.19; 139.54
		Min; Max	36.2; 520.5	29.7; 286.1	17.8; 177.6	30.5; 338. 9
	THS	N	79	80	76	73
		Mean	37.07	29.52	20.72	33.44
		95% CI	33.25; 41.32	26.01; 33.50	18.61; 23.07	29.29; 38.16
		Min; Max	12.5; 96.2	8.9; 109.5	4.8; 79.6	9.8; 110.0
	SA	N	39	38	39	22
		Mean	33.64	24.47	17.84	18.34
		95% CI	28.84; 39.24	20.70; 28.91	15.45; 20.58	13.51; 24.88
		Min; Max	15.5; 90.3	10.8; 71.8	7.4; 50.6	4.6; 64.2
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	86.92	116.04
		95% CI	NA	NA	71.78; 105.27	88.25; 152.58
		Min; Max	NA	NA	19.4; 236.6	28.9; 359.3
	THS	N	NA	NA	70	47
		Mean	NA	NA	30.02	61.27
		95% CI	NA	NA	25.29; 35.65	48.60; 77.25
		Min; Max	NA	NA	7.7; 188.8	12.4; 426.3
	SA	N	NA	NA	37	9
		Mean	NA	NA	28.88	46.50

(table continues)

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	ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
95% CI	NA	NA	22.56; 36.98	34.32; 63.01
Min; Max	NA	NA	5.2; 164.0	27.7; 89.5

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.26; ZRHR-REXC-04-JP, Table 15.2.4.26; ZRHM-REXA-07-JP, Table 15.2.4.15.1; ZRHM-REXA-08-US, Table 15.2.4.15.1]

The 3-OH-B[a]P_{adjC} time course after switching to THS or smoking abstinence exhibited the same profile and extent of lowered exposure to benzo[a]pyrene compared to CC, and was not found to be different between Japanese, European and US smokers (Figure 22).

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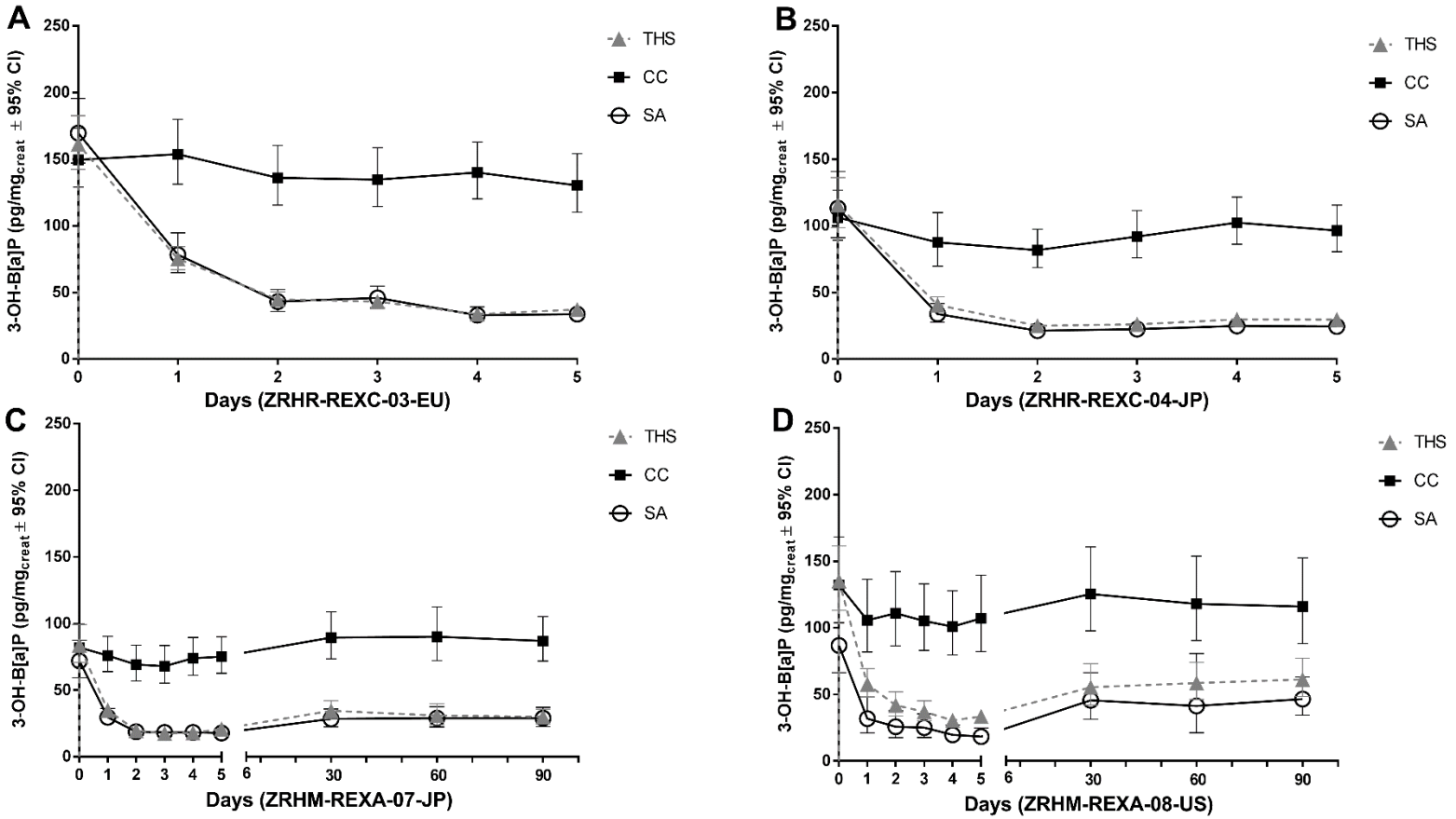


Figure 22 Geometric Mean and 95% CIs of Urinary 3-OH-B[a]P$_{adjC}$ Concentrations (fg/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.26; ZRHR-REXC-04-JP, Table 15.2.4.26; ZRHM-REXA-07-JP, Table 15.2.4.15.1; ZRHM-REXA-08-US, Table 15.2.4.15.1]

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Percent changes from Baseline of urinary 3-OH-B[a]P_{adjC} levels during the Confinement periods in all 4 studies at Day 5 ranged from -65% to -71% for the THS arms and from -67% to -77% for the SA arms. In the 2 Ambulatory studies (ZRHM-REXA-07-JP and ZRHM-REXA-08-US), these changes were generally preserved but to a lesser extent, with percent change from Baseline at Day 90 ranging from -49% to -51% in the THS arms, and from -42% to -47% in the SA arms (Table 48).

Table 48 Mean Percent Change from Baseline and 95% CIs of Urinary 3-OH-B[a]P_{adjC} (fg/mg_{creat}) by Study at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	-8.92%	-2.75%	-3.79%	-8.68%
		95% CI	-17.00; -0.84	-13.51; 8.02	-13.70; 6.11	-18.44; 1.08
	THS	N	79	80	76	67
		% Change	-71.43%	-64.76%	-68.42%	-68.31%
		95% CI	-76.65; -66.21	-72.17; -57.35	-74.27; -62.56	-74.94; -61.67
	SA	N	39	38	39	21
		% Change	-77.24%	-71.15%	-67.04%	-75.41%
		95% CI	-81.14; -73.34	-78.84; -63.46	-76.32; -57.76	-83.48; -67.34
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	21.49%	18.37%
		95% CI	NA	NA	-1.00; 43.99	-13.68; 50.41
	THS	N	NA	NA	70	43
		% Change	NA	NA	-49.20%	-50.86%
		95% CI	NA	NA	-62.68; -35.71	-62.25; -39.47
	SA	N	NA	NA	37	9
		% Change	NA	NA	-46.51%	-41.82%
		95% CI	NA	NA	-61.64; -31.37	-63.36; -20.29

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.26; ZRHR-REXC-04-JP, Table 15.2.4.26; ZRHM-REXA-07-JP, Table 15.2.4.15.1; ZRHM-REXA-08-US, Table 15.2.4.15.1]

6.1.3.2.3.14.1 Analysis of 3-OH-B[a]P at Day 5 and Day 90

At Day 5, across all 4 studies, switching to THS resulted in at least a 70% reduction of 3-OH-B[a]P_{adjC}, with a maximum reduction of 73% compared to CC smoking ($p<0.001$ for each study; Table 49). At Day 90, these reductions were of 67% in [ZRHM-REXA-07-JP] study and 57% in [ZRHM-REXA-08-US] study (<0.001) (Table 49).

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Table 49 Adjusted Geometric LS Means of THS to CC ratios of 3-OH-B[a]P at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	27.50%	29.99%	27.19%	28.94%
		95% CI	23.25; 32.52	24.84; 36.20	23.17; 31.91	23.14; 36.20
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	33.02%	43.33%
		95% CI	NA	NA	25.92; 42.08	31.52; 59.57
		p Value	NA	NA	<0.001	<0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.25; ZRHR-REXC-04-JP, Table 15.2.4.25 (Addendum); ZRHM-REXA-07-JP, Table 15.2.3.4; ZRHM-REXA-08-US, Table 15.2.3.4]

6.1.3.2.3.14.2 Conclusion

At Baseline, 3-OH-B[a]P$_{ajdC}$ levels were markedly different between studies, with differences of up to 2-fold. They were the lowest in the Japanese populations, while the highest levels were observed in the European study. As the same method was used to measure 3-OH-B[a]P, this likely indicates a difference in smoking behavior, including in cigarette brands: Japanese preference for cigarettes with charcoal-containing filters has indeed been postulated (Muscat 2005), and 7 out of 10 brands sold in Japan have a charcoal filter (Coggins 2008). A study has, however, shown no or small reductions of B[a]P in the smoke of cigarettes with charcoal-containing filters (Hearn 2010), which thus rather points at a difference in smoking behavior, or ethnic differences in CYP1A2 activity. Polish population has been shown to have a high prevalence of heavy smokers (Jassem 2014), which could explain why levels of 3-OH-B[a]P levels at Baseline were the highest in the European study, which was conducted in Poland. 3-OH-B[a]P levels have indeed been shown to be correlated with the number of cigarettes per day (Theophilus 2015). Smoking behavior most likely differed between the populations enrolled in PMI's studies, as indicated by a lower Baseline daily CC consumption levels in Japan (between 10 to 13 CC per day) than in Poland (mean of around 16 CC per day). Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g$_{creat}$ [Section 6.2.2 – Product Use], which can be also indicative of different smoking behaviors. Finally, a difference in CYP1A2 activity (MacLeod 1997), which is involved in the metabolism of polycyclic aromatic hydrocarbons, such as B[a]P, could also partly explain the difference in levels of 3-OH-B[a]P across populations. Asian populations seem to have generally lower CYP1A2 activity compared to Caucasians (McGraw 2012). This hypothesis is further emphasized by data in PMI's studies, showing that Japanese subjects indeed had lower CYP1A2 activities at Baseline (section 6.1.3.2.3.17).

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The profiles of reductions over the 5 days of Confinement were similar in the THS and SA arms, with a maximum decrease observed within the first 2 days, and a plateau appearing from around Day 3, thus being consistent with published half-lives of 3-OH-B[a]P, i.e. around 3-4 h (Chien 2012). In the ZRHM-REXA-08-US study, levels were consistently slightly higher in the THS than the SA arm, including at Baseline. The profiles of reductions during the Ambulatory periods were also similar for the THS and SA arms, with a slight increase of 3-OH-B[a]P in all arms after the Confinement periods. Similarly to the Confinement period, 3-OH-B[a]P levels in the THS arm were consistently higher than in the SA arm in the ZRHM-REXA-08-US study. The reason for this difference is unclear, as it was observed from Baseline, and it was not seen in any of the other studies, making it unlikely to be due to residual levels of B[a]P in the aerosol of THS.

Percent changes from Baseline of 3-OH-B[a]P_{adjC} during the Confinement periods ranged from -65% to -71% for the THS arms and from -67% to -77% for the SA arms. During the Ambulatory periods, these percent changes decreased slightly in the THS arms, ranging from -49% to -51%, and in the SA arms, ranging from -42% to -47%. Two smoking cessation studies conducted over 5 and 8 days showed reductions of 3-OH-B[a]P levels ranging from -63% to -65% from Baseline (Sarkar 2010, Theophilus 2015). Levels of urinary 3-OH-B[a]P concentrations at the beginning of those published studies ranged from 162 to 242 fg/24h, decreasing to ranges of 55 to 67 fg/24h at the end of the studies. Values obtained in PMI's studies at Baseline in the SA arm (range from 86 fg/24h in ZRHR-REXA-07-JP to 268 fg/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), and at Day 5 (range from 22 fg/24h in ZRHM-REXA-07-JP to 53 fg/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), as well as the percent changes from Baseline, are thus consistent with published smoking cessation studies of 5 to 8 days, with the lowest levels being slightly lower than those published. This may well be specific to Japanese populations, because of the genetic polymorphism of CYP1A2.

Statistically significant reductions were observed in the levels of 3-OH-B[a]P assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 70% to 73%. The reductions in 3-OH-B[a]P observed at Day 5 during the confinement periods for the THS arms compared to CC arms were overall sustained during the ambulatory periods, with decreases of 57% to 67% at Day 90. The slightly smaller reductions at the end of the ambulatory periods could be related to exposure to environmental sources of B[a]P, such as industrial emissions, environmental pollution due to heating with wood or coal, for example, car exhaust fumes in traffic (WHO Study Group 2008), or to the occasional use of CC.

In summary, the levels of 3-OH-B[a]P observed with THS use were statistically significantly lower from values observed in the CC arms at Day 5 and Day 90 and approaching to levels observed in the SA arms as well as to published literature from smoking cessation studies.

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6.1.3.2.3.15 3-HMPMA – BoExp for Exposure to Crotonaldehyde

The FDA has classified crotonaldehyde as a carcinogen (U.S. Department of Health and Human Services 2012a).

At Baseline, urinary levels of 3-HMPMA concentration adjusted to creatinine (3-HMPMA$_{adjC}$) were markedly different between studies, with differences ranging from 180.62 ng/mg$_{creat}$ to 479.34 ng/mg$_{creat}$ across arms. The highest levels were observed in the European study [ZRHR-REXC-03-EU] (Table 50).

Table 50 Geometric Means and 95% CIs of 3-HMPMA$_{adjC}$ (ng/mg$_{creat}$) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	460.52	195.10	298.73	312.55
		95% CI	407.39; 520.59	163.02; 233.49	256.46; 347.96	257.11; 379.94
		Min; Max	197.9; 1326.7	68.5; 618.2	118.3; 715.8	69.6; 960.4
	THS	N	80	80	76	67
		Mean	479.34	194.95	300.07	297.82
		95% CI	435.40; 527.72	168.47; 225.59	266.94; 337.32	262.69; 337.64
		Min; Max	147.2; 1364.1	27.2; 709.2	91.9; 1098.6	89.4; 1173.2
	SA	N	39	38	39	21
		Mean	443.71	180.62	298.08	304.27
		95% CI	382.03; 515.35	149.23; 218.62	258.32; 343.96	235.97; 392.34
		Min; Max	161.7; 1266.9	41.6; 464.8	138.5; 692.6	67.3; 785.5
Day 5	CC	N	41	40	42	34
		Mean	376.78	157.83	286.80	270.99
		95% CI	329.54; 430.80	128.07; 194.51	251.37; 327.21	216.76; 338.79
		Min; Max	158.5; 712.1	27.8; 689.9	143.0; 710.5	24.4; 960.4
	THS	N	78	80	76	73
		Mean	86.65	59.51	124.47	95.35
		95% CI	80.31; 93.49	53.40; 66.30	115.36; 134.30	82.67; 109.98
		Min; Max	36.8; 164.4	13.6; 192.5	63.3; 226.6	16.1; 334.6
	SA	N	39	38	39	22
		Mean	63.25	47.84	113.48	84.11
		95% CI	57.79; 69.22	40.62; 56.34	99.38; 129.59	61.73; 114.60
		Min; Max	30.3; 108.7	16.2; 187.6	41.8; 268.4	28.8; 316.7
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	299.41	215.20
		95% CI	NA	NA	260.62; 343.97	167.61; 276.30
		Min; Max	NA	NA	92.6; 691.7	23.1; 620.8

(table continues)

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		ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
THS	N	NA	NA	70	47
	Mean	NA	NA	154.30	105.12
	95% CI	NA	NA	137.07; 173.70	86.68; 127.47
	Min; Max	NA	NA	59.3; 383.5	23.5; 379.3
SA	N	NA	NA	37	9
	Mean	NA	NA	158.57	93.92
	95% CI	NA	NA	132.95; 189.14	49.42; 178.49
	Min; Max	NA	NA	57.0; 538.0	22.1; 325.7

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System.

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.28; ZRHR-REXC-04-JP, Table 15.2.4.28; ZRHM-REXA-07-JP, Table 15.2.4.16.1; ZRHM-REXA-08-US, Table 15.2.4.16.1]

A similar decrease of crotonaldehyde exposure, in terms of urinary 3-HMPMA excretion, took place in subjects who switched to THS and those who were smoking abstinent. In the [ZRHM-REXA-07-JP] study, there was an overall sustained reduction throughout the Ambulatory period. In the [ZRHM-REXA-08-US] study, both, SA and THS showed a slight increase in the levels of 3-HMPMA during the transition from Confinement to Ambulatory setting, but again decreasing thereafter, until the end of the study (Figure 23).

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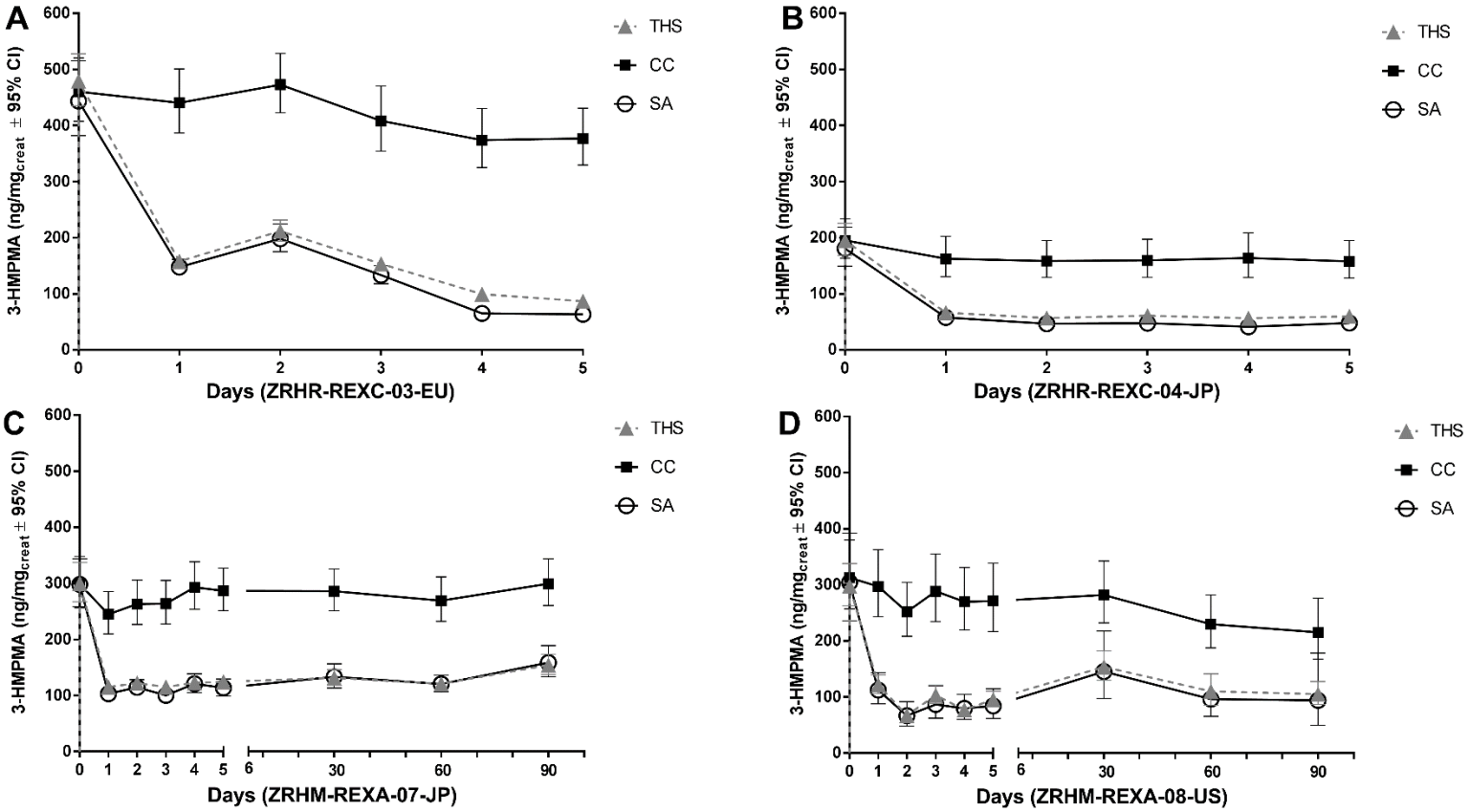


Figure 23 Geometric Mean and 95% CIs of Urinary 3-HMPMA$_{adjC}$ Concentrations (ng/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.28; ZRHR-REXC-04-JP, Table 15.2.4.28; ZRHM-REXA-07-JP, Table 15.2.4.16.1; ZRHM-REXA-08-US, Table 15.2.4.16.1]

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During Confinement, the largest percentage of change from Baseline for 3-HMPMA in the SA arms was observed in the [ZRHR-REXC-03-EU] study, with changes of -80%, while the lowest was observed in the [ZRHM-REXA-07-JP] study, with changes of -50%. This is in line with the fact that the levels in the Japan study were only about half of the European values at Baseline, and that some endogenous or background level of crotonaldehyde other than smoke exposure exists. At Day 5, the reduction from Baseline achieved with THS ranged from -51% to -81% (Table 51). At Day 90, these changes were preserved but to a lesser extent, with percent change from Baseline at Day 90 ranging from -34% to -57% and from -27% to -53% in the THS and SA arms, respectively (Table 51).

Table 51 Mean Percent Change from Baseline and 95% CIs of Urinary 3-HMPMA$_{adjC}$ (ng/mg$_{creat}$) by Study at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	30
		% Change	-14.53%	-12.85%	0.27%	-12.69%
		95% CI	-22.49; -6.57	-23.15; -2.55	-8.68; 9.23	-24.49; -0.89
	THS	N	78	80	76	67
		% Change	-80.58%	-60.61%	-50.77%	-63.03%
		95% CI	-82.48; -78.68	-68.59; -52.64	-58.03; -43.50	-68.71; -57.35
	SA	N	39	38	39	21
		% Change	-84.39%	-68.77%	-54.44%	-68.67%
		95% CI	-86.58; -82.20	-74.83; -62.70	-64.26; -44.62	-78.34; -59.01
Day 90	CC	N	NA	NA	41	29
		% Change	NA	NA	15.67%	-18.97%
		95% CI	NA	NA	-6.67; 38.01	-32.85; -5.08
	THS	N	NA	NA	70	43
		% Change	NA	NA	-33.72%	-57.41%
		95% CI	NA	NA	-47.25; -20.19	-65.44; -49.37
	SA	N	NA	NA	37	9
		% Change	NA	NA	-26.90%	-52.81%
		95% CI	NA	NA	-47.56; -6.24	-79.64; -25.98

CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.28; ZRHR-REXC-04-JP, Table 15.2.4.28; ZRHM-REXA-07-JP, Table 15.2.4.16.1; ZRHM-REXA-08-US, Table 15.2.4.16.1]

6.1.3.2.3.15.1 Analysis of 3-HMPMA Levels at Day 5 and Day 90

A significant reduction of 3-HMPMA in subjects who switched to THS use was demonstrated. At Day 5, across all 4 studies, switching to THS resulted in at least a 57% reduction of 3-HMPMA$_{adjC}$, with a maximum reduction compared to CC smoking ($p<0.001$ for each study; Table 52). At Day 90, the levels of reductions were overall maintained, with reductions of 50% in both studies (Table 52) ($p<0.001$).

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Table 52 Adjusted Geometric LS Means of THS to CC ratios of 3-HMPMA at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS:CC Ratio	LS Mean	22.54%	37.71%	43.06%	38.26%
		95% CI	20.10; 25.29	31.57; 45.05	37.75; 49.10	30.73; 47.64
		p Value	<0.001	<0.001	<0.001	<0.001
Day 90	THS:CC Ratio	LS Mean	NA	NA	50.31%	49.63%
		95% CI	NA	NA	42.96; 58.91	37.25; 66.13
		p Value	NA	NA	<0.001	<0.001

Abbreviations: CC = conventional cigarette; CI = confidence interval; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.27; ZRHR-REXC-04-JP, Table 15.2.4.27; ZRHM-REXA-07-JP, Table 15.2.3.4; ZRHM-REXA-08-US, Table 15.2.3.4]

6.1.3.2.3.15.2 Conclusion

At Baseline, levels of 3-HMPMA$_{ajdC}$ were different between studies, with differences of up to 2.3 fold. The levels were the lowest in the Japanese populations, while the highest levels were observed in the European study. As the same method was used to measure 3-HMPMA levels across studies, this likely indicates a difference in smoking behavior between population including differences in cigarette brands: Japanese are reported to have preference for cigarettes with charcoal-containing filters, which can retain, to a certain extent, a number of gas smoke constituents found in main stream smoke (Coggins 2008, Muscat 2005), and 70% of the brands sold in Japan have a charcoal filter, whereas they are much less popular outside Japan. Levels of urinary 3-HMPMA of smokers of cigarettes with charcoal-containing filters have been shown to be 17% lower than those who smoke cigarettes with cellulose acetate filters, while nicotine uptake is similar (Scherer 2006b). On the other hand, Polish population has been shown to have a high prevalence of heavy smokers (Jassem 2014), which could explain why levels of 3-HMPMA levels at Baseline were the highest in the European study, which was conducted in Poland. 3-HMPMA levels have indeed been shown to be correlated with the number of cigarettes per day (Theophilus 2015). This hypothesis is reinforced by the results of PMI studies where the Baseline daily CC consumption levels was higher in Poland (mean of around 16 CC per day) compared to US and Japan (between 10 to 13 CC per day) at Baseline [Section 6.2.2 – Product Use]. Furthermore, levels of nicotine equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g$_{creat}$ [Section 6.2.2 – Product Use], which can be also indicative of different smoking behaviors. Finally, a recent study by Park et al. (Park 2015) has shown that 3-HMPMA urinary levels differed significantly between 5 ethnic groups, after adjusting for age, sex, creatinine, and total nicotine equivalents (i.e., African Americans, native Hawaiians, whites, Latinos and Japanese Americans), which could be indicative of either genetic, metabolic or lifestyle differences.

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The profiles of reductions over the 5 days of Confinement were similar in the THS and SA arms, both during the Confinement and Ambulatory setting. During the Confinement period, a maximum decrease was observed within the first 2 days. Altogether, the profiles are, however, consistent with published half-lives of 3-HMPMA, i.e. 5-9h (Gregg 2013, Scherer 2006b, van Welie 1992). The profiles of reductions during the Ambulatory periods were also comparable for the THS and SA arms, with a slight increase of 3-HMPMA in the THS and SA arms after the Confinement period in the American study that was not observed in the Japanese study.

Percent changes from Baseline of 3-HMPMA$_{ajdC}$ urinary concentrations adjusted to creatinine during the Confinement periods ranged from -51% to -81% for the THS arms and from -54% to -84% for the SA arms at Day 5. During the Ambulatory periods, when considering the relatively high variability, these percent changes were slightly smaller in the THS arms, ranging from -34% to -57%, as well as in the SA arms, ranging from -27% to -53%. Several smoking cessation studies conducted over 3 to 8 days showed reductions of 3-HMPMA levels ranging from -69% to -86% from Baseline (Carmella 2012, Carmella 2009, Feng 2006, Frost-Pineda 2008a, Sarkar 2008, Scherer 2007, Theophilus 2015, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). A change from Baseline of more than -86% was still observed in a study lasting up to 56 days (Carmella 2012, Carmella 2009). Levels of urinary 3-HMPMA concentrations at the beginning of those published studies ranged from 715 to 2695 µg/24h, decreasing to ranges of 213 to 1325 µg/24h at the end of the studies. Values obtained in PMI's studies at Baseline in the SA arm (range from 185 µg/24h in ZRHR-REXC-04-JP to 701 µg/24h in ZRHR-REXC-03-EU; data available in the clinical study reports), and at Day 5 (range from 50 µg/24h in ZRHR-REXC-04-JP to 144 µg/24h in ZRHM-REXA-08-US; data available in the clinical study reports) are slightly lower than those measured in those published smoking cessation studies of 3 to 8 days. Percent changes form Baseline were, however, consistent with published data, despite changes in the ZRHM-REXA-07-JP that were low compared to the other PMI studies (i.e. -51% ZRHM-REXA-07-JP vs.-69% to -84% in ZRHR-REXC-03-EU, ZRHR-REXC-04-JP and ZRHM-REXA-08-US).

Clinical studies conducted with products based on the heat-not-burn principle showed reductions of urinary 3-HMPMA$_{adjC}$ levels ranging from -28% to -70% in smokers who switched from CC to the test systems for 5 to 8 days, in Confinement conditions (Frost-Pineda 2008a, Sakaguchi 2014, Tricker 2012a, Tricker 2012c, Tricker 2012d). These studies were conducted in the US, UK, Japan, or Korea.

Statistically significant reductions were observed in the levels of 3-HMPMA$_{ajdC}$ assessed for the THS arms compared to the CC arms at Day 5, with reductions ranging from 57% to 77%, while there was overall no or little difference between the THS and SA arms. The reductions in 3-HMPMA$_{ajdC}$ observed at Day 5 during the confinement periods for the THS arms compared to CC arms were overall sustained during the ambulatory periods, with values of 50% at Day 90, in both studies. The slightly smaller reductions at the end of the ambulatory periods could be related to exposure to environmental sources of crotonaldehyde, such as car exhaust fumes in traffic or exposure to smoke resulting from wood combustion (National Center for Biotechnology Information (NCBI)), or to the occasional use of CC.

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In summary, the levels of 3-HMPMA$_{adjC}$ observed with THS use were statistically significantly lower from values observed in the CC arms at Day 5 and Day 90 and approaching levels observed in the SA arms, as well as to published literature from smoking cessation studies.

6.1.3.2.3.16 S-BMA – BoExp for Exposure to Toluene

The FDA has classified toluene as a respiratory and reproductive or developmental toxicant (U.S. Department of Health and Human Services 2012a).

The levels of urinary S-BMA excretion had similar levels across the studies and throughout the different study vists. Moreover, the time course profiles in the THS, SA, but also CC were not different. Thus, the assay to analyze S-BMA could not discriminate smoking from non-smoking (Table 53, Figure 24).

Table 53 Geometric Means and 95% CIs of S-BMA$_{adjC}$ (pg/mg$_{creat}$) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	41	40	42	30
		Mean	7011.99	2703.81	3383.70	3549.66
		95% CI	6141.12; 8006.37	2268.89; 3222.09	2858.58; 4005.28	3044.85; 4138.16
		Min; Max	2531.2; 15887.4	703.5; 10269.7	964.3; 14637.1	1688.4; 8363.6
	THS	N	80	80	76	65
		Mean	7416.70	2957.22	3026.36	3855.95
		95% CI	6674.19; 8241.82	2599.76; 3363.83	2710.62; 3378.88	3313.41; 4487.33
		Min; Max	2467.4; 25420.9	813.4; 13071.9	1021.3; 12119.9	906.4; 16562.5
	SA	N	39	38	39	21
		Mean	7254.96	3097.91	2718.95	3944.45
		95% CI	6038.57; 8716.38	2616.31; 3668.16	2352.81; 3142.07	2915.56; 5336.43
		Min; Max	3049.2; 29339.5	1384.6; 11292.9	1239.6; 7274.3	1422.2; 15343.3

(table continues)

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			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	41	40	42	33
		Mean	7248.99	2354.17	3108.11	3120.82
		95% CI	6032.10; 8711.37	1968.07; 2816.02	2623.98; 3681.57	2441.42; 3989.27
		Min; Max	2096.8; 23409.1	812.5; 7761.7	969.0; 13564.8	513.7; 15369.5
	THS	N	79	80	76	71
		Mean	8394.71	2098.09	2503.48	3683.79
		95% CI	7238.83; 9735.15	1833.19; 2401.26	2245.48; 2791.11	3144.33; 4315.80
		Min; Max	1598.7; 27536.2	444.9; 8425.0	617.3; 13199.5	653.6; 15631.1
	SA	N	39	38	39	22
		Mean	8397.62	2192.86	2471.21	4769.75
		95% CI	6883.93; 10244.14	1795.91; 2677.54	2154.22; 2834.84	3124.33; 7281.73
		Min; Max	2974.5; 47425.5	826.2; 15347.3	1073.6; 5222.9	1433.1; 57142.9
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	3221.80	3441.11
		95% CI	NA	NA	2450.54; 4235.78	2410.57; 4912.19
		Min; Max	NA	NA	939.1; 73008.1	266.8; 59729.7
	THS	N	NA	NA	70	47
		Mean	NA	NA	3314.09	3688.05
		95% CI	NA	NA	2840.00; 3867.33	3002.09; 4530.74
		Min; Max	NA	NA	656.4; 17728.1	937.5; 29511.4
	SA	N	NA	NA	37	9
		Mean	NA	NA	3249.02	3833.64
		95% CI	NA	NA	2525.28; 4180.17	2123.44; 6921.21
		Min; Max	NA	NA	924.4; 38179.1	1333.3; 17806.8

Abbreviations: CC = conventional cigarette; CI = confidence interval; Max = maximum; Min = minimum; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.30; ZRHR-REXC-04-JP, Table 15.2.4.30; ZRHM-REXA-07-JP, Table 15.2.4.17.1; ZRHM-REXA-08-US, Table 15.2.4.17.1]

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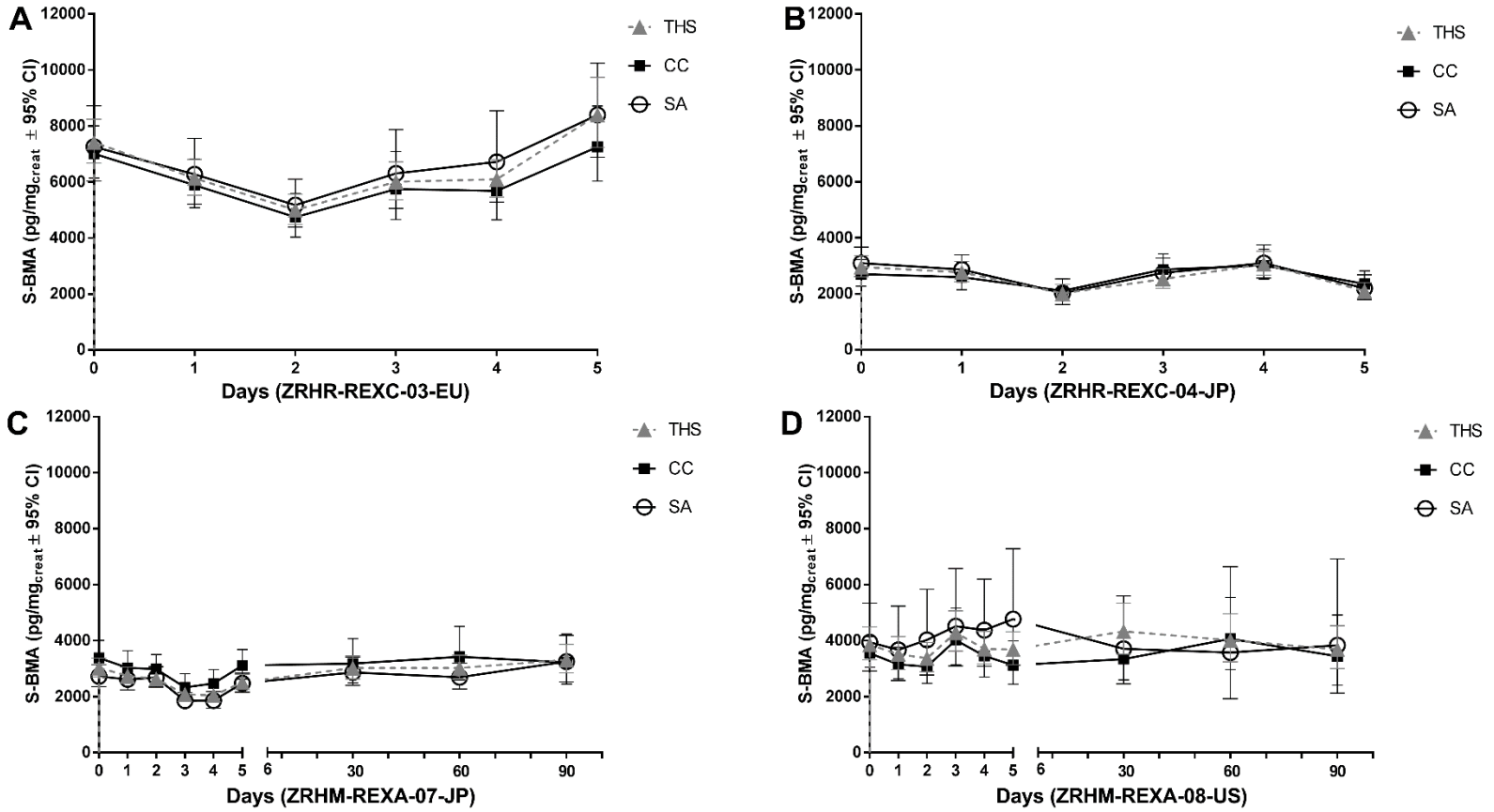


Figure 24 Geometric Mean and 95% CIs of Urinary S-BMA$_{adjC}$ Concentrations (pg/mg$_{creat}$), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.30; ZRHR-REXC-04-JP, Table 15.2.4.30; ZRHM-REXA-07-JP, Table 15.2.4.17.1; ZRHM-REXA-08-US, Table 15.2.4.17.1]

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6.1.3.2.3.16.1 Conclusion

In fact, relatively few data are available on S-BMA in smokers, but published studies showed that there is no significant difference of S-BMA urinary levels between smokers and non-smokers with levels often overlapping (Alwis 2012, B'Hymer 2011, Imbriani 1999, Lovreglio 2010, Maestri 1997, Pluym 2015, Schettgen 2008). No published smoking cessation study could be found where levels of S-BMA were assessed. Levels in smokers and non-smokers ranged from less than 500 to 29'900 and from less than 500 to 32'700 pg/mg_{creat}, respectively, with an average of around 5600 pg/mg_{creat} in both groups (Imbriani 1999, Lovreglio 2010, Maestri 1997, Pluym 2015). Values obtained in PMI's studies in all arms, ranging at Baseline from 2703 to 7055 pg/mg_{creat}, are thus consistent with published data.

From these data, it would appear that although S-BMA has been described as being a valuable BoExp to measure occupational exposure to toluene (Inoue 2004, Lovreglio 2010), this BoExp is not a "fit-for-purpose" BoExp to measure exposure to toluene when the goal is to discriminate smokers from non-smokers. This is further supported by a study by Pluym et al. where no significant difference in S-BMA excretion between smokers and non-smokers, as well as no dose-response-relationship to the smoking dose was found using a high-throughput multiplex LC-MS/MS method (Pluym 2015).

The conclusion drawn by Schettgen et al. (Schettgen 2008) are either 1) that other environmental sources of toluene are contributing in such a way to the individual exposure that smoking is only a minor factor or 2) that the specificity of S-BMA excretion as a biomarker of toluene exposure is insufficient for the determination of environmental exposures and possibly other metabolic routes might in part also lead to the formation (and excretion) of S-BMA. Benzyl alcohol, which is a widespread constituent of cosmetic products like shampoo, creams, after-shave lotions or fragrances, could largely influence the excretion of S-BMA, as it is part of the same metabolic pathway as toluene (Imbriani 1999, Lovreglio 2010). The presence of substantial background levels of S-BMA in the general population with no occupational exposure to toluene has been described in the absence of cigarette smoking (Munaka 2009, Pluym 2015).

In summary, the levels of $S\text{-}BMA_{adjC}$ observed with THS use were not different from values observed in the SA and CC arms at Day 5 and Day 90. S-BMA, was not found to be a suitable BoExp to toluene in the context of smoking.

6.1.3.2.3.17 CYP1A2

The P450 1A2 cytochrome (CYP1A2) is a key factor in the activation metabolism of various constituents, including carcinogens, such as heterocyclic amines, mycotoxins, TSNAs, and aryl amines, found in tobacco smoke, and can thus be indicative of exposure to tobacco smoke (Eaton 1995). In addition, CYP1A2 is induced by polycyclic aromatic hydrocarbons (PAH), which are among HPHCs generated in the smoke of CCs.

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The Baseline levels of CYP1A2 activity, calculated as the molar ratio of caffeine to paraxanthine and expressed as percentage, were markedly different between studies, with levels ranging from 70.45% to 121.60% across all arms and studies (Table 54). The Baseline activities were particularly low in the Japanese populations, with the highest activities in the US population, which were, however quite comparable to those observed in the European population.

Table 54 Mean and 95% CIs of CYP1A2 Activity (%) by Study Arm in All Studies, at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP [1]	ZRHM-REXA-08-US [1]
Baseline	CC	N	40	40	42	34
		Mean	110.260	78.207	70.45	121.602
		95% CI	100.686;	69.815; 86.599	64.48; 76.97	109.158; 135.464
		Min; Max	49.54; 177.59	43.61; 145.93	35.8; 137.5	61.58; 202.77
	THS	N	80	80	76	74
		Mean	112.426	81.321	72.43	117.595
		95% CI	104.414;	73.878; 88.764	67.46; 77.77	109.208; 126.626
		Min; Max	32.10; 204.80	29.48; 172.85	36.3; 142.1	55.68; 237.58
	SA	N	38	38	39	23
		Mean	113.141	77.594	74.18	114.031
		95% CI	98.398; 127.884	69.568; 85.620	66.13; 83.21	96.682; 134.494
		Min; Max	40.02; 204.40	36.14; 133.87	28.4; 142.3	43.37; 260.48
Day 5	CC	N	41	40	42	35
		Mean	123.009	76.496	75.84	123.555
		95% CI	112.067;	68.681; 84.311	68.41; 84.07	112.661; 135.503
		Min; Max	49.98; 186.55	33.99; 126.85	34.1; 144.7	70.24; 202.77
	THS	N	79	80	76	74
		Mean	91.710	56.558	55.62	76.699
		95% CI	85.177; 98.243	52.340; 60.775	52.02; 59.47	70.333; 83.641
		Min; Max	29.37; 186.18	23.08; 113.11	20.8; 112.5	27.39; 175.20
	SA	N	39	38	39	23
		Mean	94.450	52.254	55.34	73.436
		95% CI	82.589; 106.311	47.404; 57.105	49.35; 62.05	60.321; 89.403
		Min; Max	30.63; 190.61	26.13; 97.83	19.9; 94.6	21.37; 181.73
Day 90	CC	N	NA	NA	41	32
		Mean	NA	NA	77.67	95.139
		95% CI	NA	NA	68.27; 88.37	81.904; 110.512
		Min; Max	NA	NA	32.6; 179.8	44.14; 207.15
	THS	N	NA	NA	70	47
		Mean	NA	NA	54.57	71.824
		95% CI	NA	NA	50.23; 59.28	63.161; 81.675
		Min; Max	NA	NA	20.5; 123.1	30.75; 210.87
	SA	N	NA	NA	37	9
		Mean	NA	NA	59.51	85.015

(table continues)

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	ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP [1]	ZRHM-REXA-08-US [1]
95% CI	NA	NA	52.28; 67.74	54.414; 132.825
Min; Max	NA	NA	24.5; 136.4	32.71; 267.34

[1] In the ZRHM-REXA-07-JP and ZRHM-REXA-08-US studies, geometric means and 95% CI of the geometric means were calculated based on an assumption of lognormal distribution

CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System.

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.49; ZRHR-REXC-04-JP, Table 15.2.4.49; ZRHM-REXA-07-JP, Table 15.2.4.23; ZRHM-REXA-08-US, Table 15.2.4.23]

Across studies, the CYP1A2 activity decreased over time, in a comparable manner, in both the THS and the SA arms (Figure 25).

Percentage of changes from Baseline of CYP1A2 activity during the Confinement periods in all 4 studies at Day 5 ranged from -17% to -33% in the users of THS and from -15% to -35% for the SA arms (Table 55). In the 2 ambulatory studies [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], these changes at Day 90 ranged from -20% to -32% in the THS arms, and from -16% to -35% in the SA arms (Table 55).

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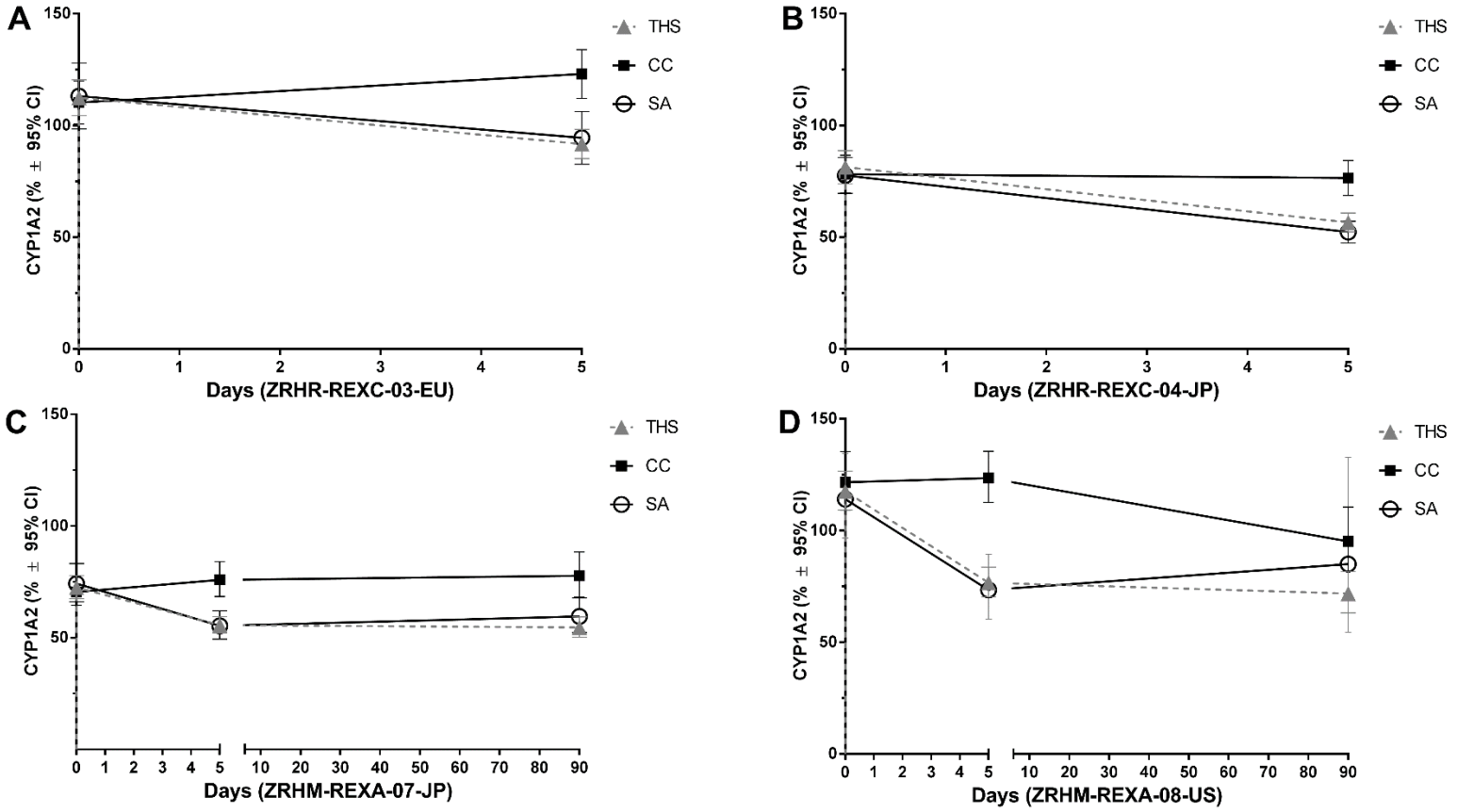


Figure 25 Mean or Geometric Mean CYP1A2 activity (%) with 95% CI, During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.49; ZRHR-REXC-04-JP, Table 15.2.4.49; ZRHM-REXA-07-JP, Table 15.2.4.23; ZRHM-REXA-08-US, Table 15.2.4.23]

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Table 55 Mean Percent Change from Baseline and 95% CIs of CYP1A2 Activity (%) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	40	40	42	34
		% Change	12.714%	-0.990%	9.65%	3.556%
		95% CI	7.705; 17.724	-5.964; 3.985	2.43, 16.86	-1.121; 8.233
	THS	N	79	80	76	74
		% Change	-16.509%	-27.361%	-21.75%	-32.813%
		95% CI	-20.536; -12.481	-30.507; -24.216	-25.24, -18.26	-36.702; -28.923
	SA	N	38	38	39	23
		% Change	-14.860%	-30.461%	-23.81%	-34.532%
		95% CI	-20.053; -9.667	-35.314, -25.609	-29.21, -18.41	-39.631, -29.433
Day 90	CC	N	NA	NA	41	31
		% Change	NA	NA	15.77%	-16.706%
		95% CI	NA	NA	3.24, -28.30	-23.868, -9.545
	THS	N	NA	NA	70	47
		% Change	NA	NA	-20.22%	-31.955%
		95% CI	NA	NA	-26.66, -13.78	-40.407, -23.503
	SA	N	NA	NA	37	9
		% Change	NA	NA	-15.82%	-35.359%
		95% CI	NA	NA	-23.19; -8.46	-53.476; -17.243

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM in SA arm at Day 1.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.49; ZRHR-REXC-04-JP, Table 15.2.4.49; ZRHM-REXA-07-JP, Table 15.2.4.23; ZRHM-REXA-08-US, Table 15.2.4.23]

6.1.3.2.3.17.1 Analysis of CYP1A2 Activities at Day 5 and Day 90

A significant reduction of CYP1A2 activity in subjects who switched to THS use was observed, as assessed by calculating either the differences between THS and CC arms (in [ZRHR-REXC-03-EU] and [ZRHR-REXC-04-JP]) or the ratios of THS to CC (in [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US]). In [ZRHR-REXC-03-EU] and [ZRHR-REXC-04-JP], THS use resulted in at least a 22% difference of activity versus CC at Day 5, with a maximum of 34% difference (Table 56). In [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], CYP1A2 activity was -28% and -36% higher in THS than CC arms, respectively, at Day 5 ($p < 0.001$ in both studies), and -31% and -21% higher at Day 90, respectively.

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Table 56 Analysis of CYP1A2 (%) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	THS – CC (difference)	Geometric LS Mean	-33.60	-21.65	NC	NC
		95% CI	-40.59; -26.61	-25.49; -17.81	NC	NC
Day 5	THS:CC Ratio	Mean	NC	NC	71.96%	63.52%
		95% CI			67.12; 77.16	58.34; 69.17
		p Value			<0.001	<0.001
Day 90	THS:CC Ratio	Mean	NC	NC	69.09%	78.57%
		95% CI			61.45; 77.68	66.36; 93.02
		p Value			<0.001	0.003

CC = conventional cigarette; CI = confidence interval; NC = not calculated; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1. ANCOVA model with log-transformed Baseline values, study arm, sex, and CC consumption reported at screening as fixed effect factors.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.50; ZRHR-REXC-04-JP, Table 15.2.4.50; ZRHM-REXA-07-JP, Table 15.2.4.24.1; ZRHM-REXA-08-US, Table 15.2.4.24.1]

6.1.3.2.3.17.2 Conclusion

At Baseline, the CYP1A2 activities were different between studies, with differences of up to 1.7 fold. The levels were the lowest in the Japanese populations, while the highest activities were observed in the US study. Wide variations in human CYP1A2 have been reported in different populations, with activities ranging from 40- to 130-fold (McGraw 2012). This could be related to a difference in cigarette brands smoked between the 2 countries and the levels of polycyclic aromatic hydrocarbons (PAH), as some smoke constituents generated in the smoke of conventional cigarettes, 1) differ between brands (Ding 2008), and 2) are known to induce CYP1A2 activity (Matsuda 2015). Tobacco blends in Japan often contain Oriental tobacco (IARC (International Agency for Research on Cancer) 2004), which actually produces high yields of (PAH) in smoke, compared to Burley tobacco (Ding 2008), for example, which is more common in American blends of tobacco, and one could have expected higher CYP1A2 activity in the Japanese. However, the Japanese populations in PMI's studies still have the lowest levels of CYP1A2 activity, thus indicating that there is more than "just" the involvement of PAH in the activity of CYP1A2 such as concomitant medications. Whereas the activities of CYP1A2 exhibit polymorphic distributions in human populations, the role of the polymorphisms observed so far is still being discussed (Cosma 1993, Crofts 1994, Faber 2005, Ghotbi 2007, Gunes 2008, MacLeod 1997, Nakajima 1994, Zhou 2010). Slow vs fast metabolizers have, however, been identified, based on their activity levels of CYP1A2 (Butler 1992), and Asian and African populations seem to have generally lower CYP1A2 activity compared with Caucasians (McGraw 2012), which could in part explain the lower levels of CYP1A2 activity in Japanese subjects of PMP's studies. Finally, smoking behavior most likely differed between the populations enrolled in PMP's studies, as indicated by a lower Baseline daily CC consumption level in Japan (between 10 to 13 CC per day) than in Poland (mean of around 16 CC per day). Furthermore, levels of nicotine

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equivalent at Baseline were found to be higher in Poland compared to Japan (around 9 vs 5.2 to 5.7 mg/g_{creat} [Section 6.2.2 – Product Use], which can be also indicative of different smoking behaviors.

confinementambulatoryThe profiles of reductions over the 5 days of Confinement were similar in the THS and SA arms, thus being consistent with the published half-life of CYP1A2 of 38.6 hours (Faber 2004), the half-life in this case being the time it takes for the activity of CYP1A2 to reduce to a half of the original activity. The profiles of reductions during the Ambulatory periods were also similar for the THS and SA arms. In the CC arm of the US study, the activity of CYP1A2 slightly decreased from Day 5 to Day 90. The reason why the CYP1A2 activity is decreased in CC at Day 90 compared to the Confinement period is difficult to explain but could be related to the decrease in nicotine exposure observed between Day 5 (8.55 mg/g_{creat}; data available in clinical study reports) and Day 90 (6.36 mg/g_{creat}; data available in clinical study reports) in this study, thereby suggesting a potential change in smoking behavior despite the fact that no change in the daily CC consumption was observed during this period. Even though some concomitant medications such as ciprofloxacin, fluvoxamine, oral contraceptives are known to influence CYP1A2 activity (inhibition or activation), there is no reason to believe that these influencing factors were specific to the CC arm.

The percentage of change from Baseline in CYP1A2 activity was comparable between THS and SA arms ranging from -17% to 33%, and from -17% to 16% at Day 5, respectively.

Several studies indicate a higher CYP1A2 activity in smokers than in non-smokers (Dobrinas 2011, Ghotbi 2007, Gregg 2013). A smoking cessation study following CYP1A2 activity over 13 days showed a decrease of CYP1A2 activity already after 2 days with around 30% change from Baseline in the activity following 5 days of smoking abstinence (Faber 2004). Such change was similar to the change observed in both SA and THS arms following 5 days of smoking abstinence.

CPY1A2 activity was statistically significantly lower in THS vs CC arms, ranging from 55.62% to 91.710% and from 75.84% to 123.009%, respectively, at Day 5. The activity found in the THS arms were comparable to SA arms (from 52.254% to 94.450%) at Day 5. So meaningful changes in activities in the 3 arms were observed between Confinement and Ambulatory periods, suggesting that confounding factors associated with a non-residential setting have minor influence in PMI's studies.

In summary, the levels of CYP1A2 activity observed with THS use were statistically significantly lower than values observed in the CC arms at Day 5 and Day 90 and overall comparable to levels observed in the SA arms, and are within the expected range found in the published literature from smoking cessation studies. These results are also supported by the observation that in the 8-months inhalation study conducted in Apoe$^{-/-}$ mice (Phillips 2016) (see section 6.1.4.1.1), cigarette smoke induced both mRNA and protein expression of CYP1A2 in the liver (the main site of CYP1A2 expression in mice), while exposure to THS aerosol did not. Furthermore, switching to THS aerosol following 2 months of cigarette smoke exposure led to a reduction in CYP1A2 mRNA and protein expression to levels approaching those of cessation (section 6.1.3.1.2.6) (Lo Sasso 2016).

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6.1.3.2.3.18 Urine Mutagenicity Assay

The urine mutagenicity assay developed by Ames (Ames 1975) provides a relative assessment of the mutagenicity of urine samples from subjects exposed or not to tobacco smoke (Gregg 2013). In PMI's studies, mutagenicity was assessed using the bacterial strain *Salmonella typhimurium* YG1024, a derivative of the original T98 strain used by Ames, which was shown to be more sensitive to mutagenicity of tobacco smoke (Einisto 1990), in presence of the metabolic activator S9. The assay was run in accordance with the "OECD guideline for testing of chemicals: bacterial reverse mutation test" (OECD (Organization for Economic Co-operation and Development) 1997).

At Baseline, when considering the median values, urinary levels of mutagenicity expressed in number of revertants per 24h (rev/24h) values were overall comparable between studies and across arms, with values ranging from 12574.40 to 25823.00 rev/24h (Table 57). The lowest levels were observed in the Japanese populationsand the highest values observed in the American subjects. Variability was, however, extremely high, as evidenced by the minimal and maximal values, ranging from 0 to 148367.2, which is also why results are reported as median values. Mean values are available in the clinical study reports.

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Table 57 Median Values (with Min and Max) of Urine Mutagenicity (Rev/24h) by Study at Baseline, Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Baseline	CC	N	28	35	38	29
		Median	15775.00	12574.40	13235.99	17384.40
		Min; max	0.0; 72216.0	0.0; 45827.7	2331.6; 51400.0	0.0; 81244.2
	THS	N	64	68	65	63
		Median	19681.50	17221.63	13943.72	19463.24
		Min; max	0.0; 107250.0	0.0; 67238.4	0.0; 51505.1	2416.2; 148367.2
	SA	N	23	37	35	21
		Median	22540.00	15016.50	14000.04	25823.00
		Min; max	3060.0; 113620.0	0.0; 82831.1	0.0; 44541.2	5611.2; 80368.2
Day 5	CC	N	28	35	38	34
		Median	21689.00	9656.40	13578.55	30608.70
		Min; max	0.0; 63840	0.0; 55644.3	0.0; 39632.9	0.0; 129114.4
	THS	N	52	62	73	73
		Median	8822.75	8535.39	4856.25	5800.74
		Min; max	0.0; 39600	0.0; 72672.6	0.0; 47872	0.0; 43350.4
	SA	N	26	33	37	23
		Median	7437.00	7567.42	6385.80	3920.18
		Min; max	0.0; 65400.0	0.0; 30496.2	0.0; 44541.2	0.0; 80368.2
Day 90	CC	N	NA	NA	40	32
		Median	NA	NA	13192.79	22047.46
		Min; max	NA	NA	0.0; 47824.0	5968.1 87139.8
	THS	N	NA	NA	70	47
		Median	NA	NA	5399.62	7439.08
		Min; max	NA	NA	0.0; 47872.0	0.0; 53250.4
	SA	N	NA	NA	37	9
		Median	NA	NA	4977.36	6178.08
		Min; max	NA	NA	0.0; 35588.0	0.0; 13607.2

CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; SA = smoking abstinence; THS = Tobacco Heating System.

Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM [ZRHR-REXC-03-EU], 08:00 AM [ZRHR-REXC-04-JP] or 10:00 AM [ZRHM-REXA-07-JP; ZRHM-REXA-08-US] in SA arm at Day 1. In ZRHM-REXA-07-JP and ZRHM-REXA-08-US, Baseline values in the Per Protocol population were assessed for both the Confinement and the Ambulatory periods. Values reported in this table are those of the Confinement period.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.42; ZRHR-REXC-04-JP, Table 15.2.4.42; ZRHM-REXA-07-JP, Table 15.2.4.46.1 (Corrigendum); ZRHM-REXA-08-US, Table 15.2.4.64.1]

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Despite the high variability (not shown on figures but visible from the minimum and maximum values presented in Table 57), there was a clear trend in the decrease of urine mutagenicity values in THS or SA arms, in all studies, already at Day 5 (Figure 26). This decrease was maintained throughout the ambulatory periods of [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US]. By contrast, in the CC arms, the trend showed a mixed profile, with an increase of urine mutagenicity in the [ZRHR-REXC-03-EU] and [ZRHR-REXA-08-US] studies, while it decreased in the [ZRHR-REXC-04-JP] study, to a similar extent than the THS and SA arms, but remaining stable in [ZRHM-REXA-07-JP]. At the end of the ambulatory period of [ZRHR-REXA-08-US], mutagenicity levels in the CC arm were comparable to Baseline. Overall, urine mutagenicity profiles reamained comparable across the studies, with a time course and extent of mutagenicity lowering that was not different between Japanese, EU and US smokers.

At Day 5, the median levels of urine mutagenicity were generally comparable between studies, both in the THS and SA arms, with levels ranging from 4856.25 to 8822.75 and from 3920.18 to 7567.42 rev/24h, respectively (Table 57). At Day 90, the median levels of urine mutagenicity remained overall comparable in both arms, with levels ranging from 5399.62 to 7439.08 and from 4977.36 to 6178.08 rev/24h in the THS and SA arms, respectively, with the lowest levels observed in the Japanese study as observed at Baseline.

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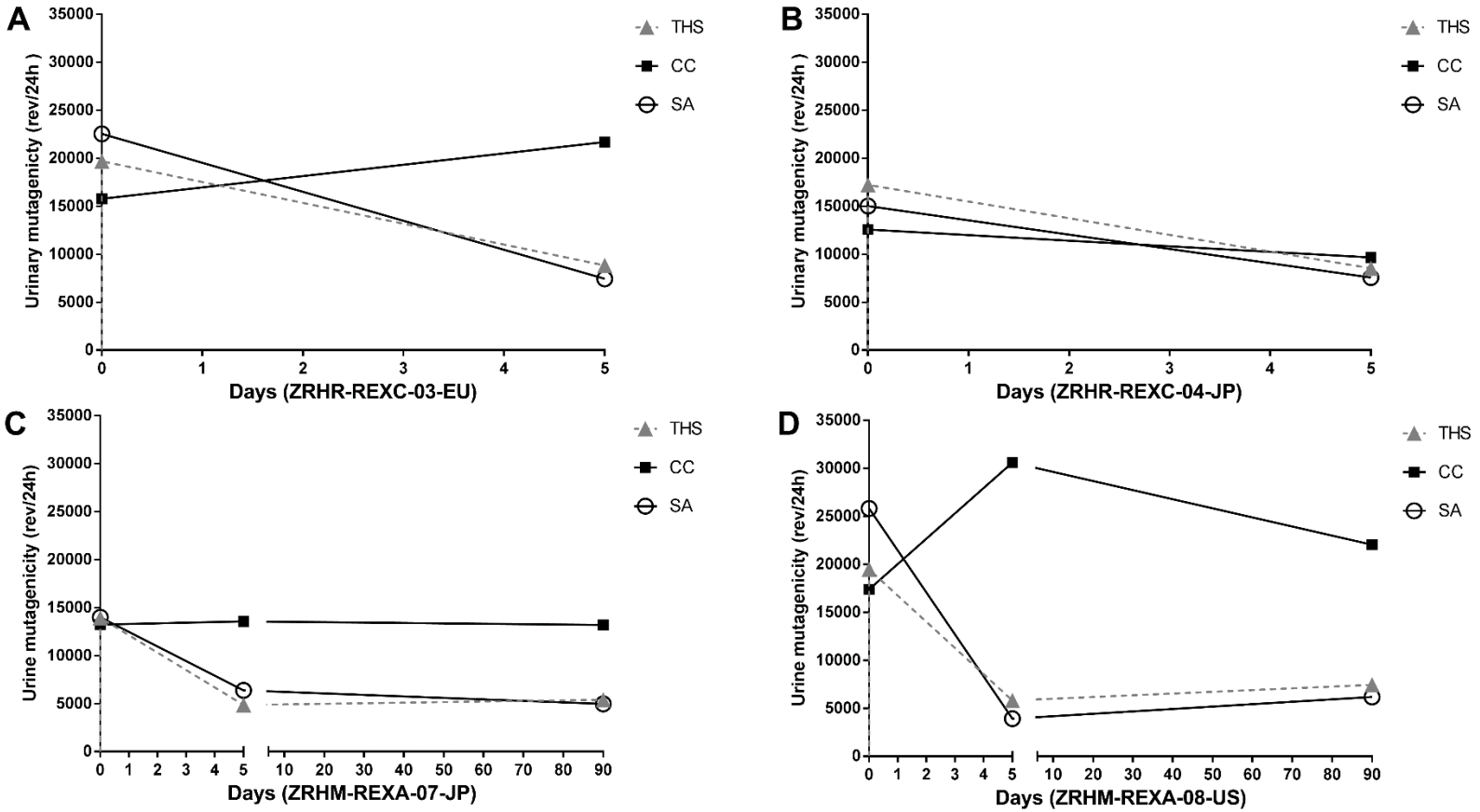


Figure 26 Median Urine Mutagenicity (Rev/24h) During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbreviations: CC = conventional cigarette; CI = confidence interval; SA = smoking abstinence; THS = Tobacco Heating System
[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.42; ZRHR-REXC-04-JP, Table 15.2.4.42; ZRHM-REXA-07-JP, Table 15.2.4.46.1 (Corrigendum); ZRHM-REXA-08-US, Table 15.2.4.64.1]

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Percent changes from Baseline of urine mutagenicity median levels during the Confinement periods in all 4 studies at Day 5 ranged from -43% to -72% for the THS arms and from -29% to -74% for the SA arms (Table 58). In the 2 Ambulatory studies (ZRHM-REXA-07-JP and ZRHM-REXA-08-US), these changes at Day 90 ranged from -56% to -62% in the THS arms, and from -35% to -68% in the SA arms.

Table 58 Median Percent Change from Baseline of Urine Mutagenicity (Rev/24h) by Study Arm in All Studies, at Day 5 and Day 90

			ZRHR-REXC-03-EU	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP	ZRHM-REXA-08-US
Day 5	CC	N	23	30	38	35
		% Change	29.29%	-24.39%	0.0%	40.44%
		Q_1, Q_3	-11.60, 98.60	59.02, 49.18	-40.63, 30.33	-12.32, 138.11
	THS	N	42	54	65	67
		% Change	-56.93%	-42.79%	-56.55%	-72.04%
		Q_1, Q_3	-74.50, -7.25	-76.21, -0.12	-81.86, 0.00	-90.11, -46.97
	SA	N	17	32	35	34
		% Change	-62.44%	-55.25%	-37.21%	-74.00%
		Q_1, Q_3	-87.07, -11.93	-70.72, 2.01	-69.54, 0.00	-89.12, -50.14
Day 90	CC	N	NA	NA	37	28
		% Change	NA	NA	16.20%	10.88%
		Q_1, Q_3	NA	NA	-7.81, 57.01	-34.57, 106.34
	THS	N	NA	NA	60	41
		% Change	NA	NA	-61.35%	-61.58%
		Q_1, Q_3	NA	NA	-77.45, -20.48	-81.19, 0.00
	SA	N	NA	NA	33	9
		% Change	NA	NA	-45.18%	-67.89%
		Q_1, Q_3	NA	NA	-87.39, 0.83	-90.46, -54.37

Abbreviations: CC = conventional cigarette; CI = confidence interval; N = number of subjects; NA = not assessed; Q1, Q3 = first and third quartile; SA = smoking abstinence; THS = Tobacco Heating System. Baseline was defined as the last assessment prior to first product use in CC/THS arms at Day 1 or last assessment prior to 06:29 AM in SA arm at Day 1.

[Data source: Clinical Study Reports Appendix 15; ZRHR-REXC-03-EU, Table 15.2.4.42; ZRHR-REXC-04-JP, Table 15.2.4.42; ZRHM-REXA-07-JP, Table 15.2.4.46.1 (Corrigendum); ZRHM-REXA-08-US, Table 15.2.4.64.2]

6.1.3.2.3.18.1 Conclusion

At Baseline, urine mutagenicity median levels were overall comparable between studies, with the lowest levels observed in the Japanese population, which could be partially explained by a lower exposure to a number of HPHCs, as Japanese population has a preference for cigarettes with charcoal-containing filters that were demonstrated to retain a number of gas smoke constituents found in main stream smoke (Muscat 2005). However, considering the high variability of the Ames results, these median values might be somewhat misleading.

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The Ames mutagenicity assay has been shown to be quite variable, hence, published data often report median values without their variability (e.g. (Miura 2015, Roethig 2008, Sakaguchi 2014, Sarkar 2010)). PMI's data are no exception and the minimum or maximum values for each time point cover a large range. There are several potential causes to this variability: 1) the output of urine mutagenicity testing is a combination between the exposure dose to different mutagenic compounds, including those from sources other than tobacco smoke, such as environmental pollutants or food, which clearly differ between subjects, and those compounds are likely to have different half-lives; 2) the metabolism of those compounds within the exposed subject may be highly variable depending on the environment, diet, ethnicity, exercise, etc…; 3) Ames is a complex cellular assay; 4) the methods to calculate the number of revertants per 24hrs differ between laboratories. Diet was strictly controlled during the Confinement periods of the studies, and similar between subjects, however, this was not the case during the Ambulatory phases of the ZRHM-REXA-07-JP 1 and ZRHM-REXA-08-US studies. The urine mutagenicity test has been shown to be sensitive to the diet, and can thus vary a lot between individuals that are not under a controlled diet (Doolittle 1989, National Research Council (US) Committee on Diet 1982).

The profiles of reductions over the 5 days of Confinement were similar in the THS and SA arms. The profiles of reductions during the Ambulatory periods were also similar for the THS and SA arms. The half-life of the smoking-related urine mutagenic activity is reported to be approximately 7–23h (Kado 1985), and it has been described that the urine mutagenic activity should have disappeared after 8 days of smoking abstinence (Miura 2015). Data in the CC arms do not follow a consistent profile throughout both the Confinement and Ambulatory exposure periods across studies with, as an example, an unexpected decrease in mutagenic activity in the ZRHR-REXC-04-JP, similarly to what was observed in the THS and SA arms. Because of the high variability of this assay and its high sensitivity to confounding factors, the interpretation of data needs to be considered with caution, also considering that mutagenicity levels were already lower at Baseline than the other 2 arms. Despite this variability, an indisputable trend of decrease in urine mutagenicity, was observed in the THS arms, both at Day 5 and Day 90, similar to what was observed in the SA arm.

Percent changes from Baseline of median levels of urine mutagenicity during the Confinement periods ranged from -43% to -72% for the THS arms and from -29% to -74% for the SA arms. During the Ambulatory periods, these percent changes remained overall stable, ranging from -56% to -62% and from -35% to -68%, respectively. Several smoking cessation studies conducted over 5 to 8 days showed reductions of urine mutagenicity levels ranging from -45% to -97% from Baseline, with the majority of the studies showing reductions of more than 70% (Sarkar 2010, Tricker 2012b, Tricker 2012c, Tricker 2012d). Mean absolute values at the beginning of those published smoking cessation studies ranged from 17139 to 85882 rev/24h, decreasing to ranges of 1249 to 9913 rev/24h at the end of the studies (Miura 2015, Roethig 2008, Sarkar 2010). Median values were, however, not reported. In PMI's studies, mean values ranged from 14508.13 to 30251.24 and from 7500.05 to 11506.70 rev/24h at Baseline and Day 5, respectively (data available in clinical study reports). In a study by Miura et al., median

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values in smokers and non-smokers were reported to be of 34459 and 10479 rev/24h, respectively, at the beginning at their studies (Miura 2015). Sakaguchi et al. measured median values ranging from 21371 to 26734 rev/24h in smokers (Sakaguchi 2014). Sarkar et al. found median values of 32118 and 1249 rev/24h at the beginning and the end of an 8-day smoking cessation study (Sarkar 2010). Median values obtained in PMI's studies in the SA arms (median range from 14000.04 to 22540.00 rev/24h at Baseline and from 3920.18 to 7567.42 rev/24h at Day 5) are thus overall consistent with published smoking cessation studies of 5 to 8 days, when considering the high variability of this assay.

In a study where mutagenicity levels were assessed using the bacterial strain TA98, which is less sensitive than the strain YG1024 that is used in PMI's studies (Einisto 1990, Kuenemann-Migeot 1997, Nikoyan 2007), no difference was found between individuals who switched to a product based on the heat-not-burn tobacco technology to that of non-smokers, after 4 weeks of switching (deBethizy 1990). However, other clinical studies conducted with other products based on the heat-not-burn technology showed reductions of urine mutagenicity levels with the YG1024 strain, ranging from -31% to -90% in smokers who switched from conventional cigarettes to the test products for 5 to 8 days, in Confinement conditions (Frost-Pineda 2008a, Sakaguchi 2014, Smith 1996, Tricker 2012a, Tricker 2012b, Tricker 2012c, Tricker 2012d). These studies were conducted in the US, UK, Japan or Korea. In a study conducted over 12 months, the reduction was of -81% (Roethig 2008).

In summary, except for the ZRHR-REXC-04-JP study, where the levels in the CC arm decreased to a similar extent as in the THS and SA arms, the levels of urine mutagenicity observed with THS use were lower than values observed in the CC arms at Day 5 and Day 90, and overall comparable to levels observed in the SA arms, as well as to published literature from smoking cessation studies. Furthermore, these results also show that the overall absence of measureable mutagenicity observed in the pre-clinical *in vitro* Ames test conducted with the total particulate matter of the THS aerosol (in presence and absence of S9) leads to a reduction in urine mutagenicity levels.

6.1.3.2.3.19 Overall Conclusion on BoExp Assessments in Clinical Studies

Cigarette smoke is a complex mixture containing more than 6000 chemical compounds (Rodgman 2013). It is recognized that full characterization of the aerosol along with the resulting exposure in human is not possible. The selected BoExp measured in these studies correspond to HPHCs present in CC smoke and endorsed by public health advocates as a priority for reduction, monitoring and/or reporting. These HPHCs are also considered by the Institute of Medicine to provide a realistic assessment of human uptake of a variety of toxicants and carcinogens in tobacco-product, and were selected based on a "fit-for-purpose" approach (IOM (Institute of Medicine) 2012). Thus, with respect to the numerous chemical compounds found in cigarette smoke, the criteria applied for their selection (i.e., representativeness of a variety of chemical classes and organ toxicity classes, specificity to HPHCs, dose response to cigarette consumption, reduction upon smoking cessation and different temperatures of formation), this fit-for-purpose approach

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has allowed to obtain a comprehensive understanding of the exposure to those HPHCs of subject using THS.

All 4 reduced exposure studies have demonstrated statistically significant reduction of exposure to the selected HPHCs after switching from CC to THS, with the exception of toluene, for which S-BMA was unable to show a difference between all study arms, including smoking abstinence. The results for S-BMA were similar across all 3 study arms, of the 4 studies, throughout the whole exposure time. Despite the fact that S-BMA is a suitable BoExp to toluene in environmental and occupational studies (Lovreglio 2010), its suitability to discriminate between smokers and non-smokers seems therefore questionable and needs further evaluation. Various studies reported overlapping ranges in S-BMA levels with only subtle increase levels between smokers and non-smokers (Imbriani 1999, Lovreglio 2010, Schettgen 2008), which are in agreement with the findings of this study.

The kinetics and the magnitude of decrease of the other BoExp levels observed in the THS arm were approaching the levels observed in the SA arm. 3-HPMA and total NNN were the only BoExp remaining slightly higher in the THS than the SA arms throughout the whole exposure period, but nevertheless remained much lower than the CC arms. The presence of acrolein in non-combusted tobacco (Rodgman 2013) and its production at low temperature ranges (Torikai 2004), including as a byproduct of glycerin (Qadariyah 2011), as well as distillation of NNN even in the absence of combustion (Fischer 1990, Moldoveanu 2008), likely prevent the complete elimination of these 2 HPHCs from THS aerosol, even in the absence of combustion. Overall, the magnitudes of exposure reduction in [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US] were comparable between the Confinement and Ambulatory periods, although, and as expected, slightly less pronounced in the Ambulatory period, particularly in the US study. With the exception of S-BMA, the results were consistent with the study hypotheses in that the geometric mean levels of each of the other BoExp were lower for the THS arm relative to the CC arm on Day 5.

Reductions of at least 50% were seen in the levels of each BoExp assessed as a primary endpoint for smokers switching to THS compared to smokers continuing to use CC, thus being consistent with the study hypotheses and evaluation criteria. In the two Japanese studies, [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP], reductions in 3-HPMA of 47% and 49%, respectively, were observed in users of THS compared to smokers continuing to smoke CC, with a confidence interval spanning 50%. Lower levels of 3-HPMA at Baseline in the Japanese studies, likely due to the Japanese preference for cigarettes containing charcoal filters, can explain, at least partly, a lower extent of reduction in the levels of this BoExp to acrolein. However, the profiles of 3-HPMA throughout the studies also indicate that despite a very significant reduction of acrolein in THS aerosol, reductions of 3-HPMA levels in THS users do not reach those of smoking abstinence. Acrolein is present in non-combusted tobacco (Rodgman 2013) and is further formed at relatively low temperatures (200-400°C) (Torikai 2004), thus its complete elimination in a tobacco product without combustion is not possible. Acrolein can furthermore be produced from glycerin at temperatures of 200-400ºC (Qadariyah 2011), a constituent which is found at levels 2-3 times higher in THS Tobacco Sticks compared with the

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reference cigarette, 3R4F (see Investigator's Brochures (Philip Morris Products S.A. 2015a, Philip Morris Products S.A. 2015b). In [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US], reductions of 77% and 74%, respectively, of total NNAL were observed at Day 90, thus also being consistent with the study hypotheses.

The two Japanese studies, [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP], generally showed lower levels of BoExp at Baseline, likely due to the daily product consumption, but also, because of the preference of Japanese for cigarettes containing a charcoal filter, which can reduce the emission of some of the volatile gas phase smoke constituents.

Regarding the two studies with an Ambulatory phase, there was a particularly high compliance to product/regimen allocation in the 3 study arms of [ZRHM-REXA-07-JP] during the Ambulatory period, thus providing robust scientific evidence of optimal exposure reduction when smokers predominantly used THS as an alternative to CC in comparison to when smokers quit smoking. In addition, the multiple assessments including measurement of nicotine exposure, reporting of daily product use, product satisfaction evaluation together with the human smoking topography, provided a comprehensive understanding of product adaptation and acceptance over the course of the study. On the other hand, in the [ZRHM-REXA-08-US] study, there was a good compliance of the subjects in the THS arm but poor compliance to abstinence from smoking during the Ambulatory period, with only 7 to 9 out of 41 subjects meeting the criteria for inclusion in the PP Set. The challenge for participants to keep abstinent from smoking for 3 months, together with the incorrect randomization of 5 subjects resulted in a limited number of subjects in the PP Set at Day 90. This had the effect of increasing the ratios variability between THS 2 users with those who abstained from smoking, resulting in broad ranges of 95% CI values for each assessed BoExp. In light of the limited number of subjects in the SA arm and the increased variability, the results obtained using the SA arm should be interpreted with caution

A strength of the 4 reduced exposure studies was that all the urinary BoExp were measured in 24-hour urine collection using validated methods. Compared to partial urine fraction or spot urine, 24-hour collection is considered the most accurate method to assess BoExp. The reduction of each BoExp expressed as quantity excreted showed similar magnitude of reduction as when expressed as concentration adjusted to creatinine (results available in the clinical study reports [section 7.3]. These results showed that differences between subjects in their urinary flow play a minor role in the excretion of the selected BoExp measured in this study.

In conclusion, the observed results are a consequence of the heat-not-burn product design by which combustion is eliminated, and provide reasonable confidence that THS reduces the exposure to HPHCs beyond the toxicants measured in this study, particularly as the levels of BoExp after THS use are approaching those observed upon SA.

6.1.3.2.4 Summary of Results of Non-Clinical Studies

The results obtained in the clinical studies are also supported by the reduced exposure to HPHCs of the animals involved in PMI non-clinical inhalation studies. Although the main purpose of determining BoExp in non-clinical studies was to demonstrate proper

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exposure of the animals to cigarette smoke or THS aerosol, showing the exposure results of the non-clinical studies in the context of the clinical results adds to the evidence demonstrating exposure reduction, as described below. More details on the choice of the selected BoExp can be found in [Section 6.1.3.1 – Justification of Selection of Biomarkers of Exposure].

6.1.3.2.4.1 Overview of BoExp to selected HPHCs

In the non-clinical studies used to assess standard and systems toxicology endpoints, BoExp to selected HPHCs were measured to monitor the exposure of the rodents to the HPHCs to enable a correlation with the endpoints and downstream effects of the aerosols. COHb (in blood) and nicotine metabolites (in urine) have been selected as standard exposure monitoring parameters for many years in inhalation studies, and provide a good indication of the exposure to the gas vapor and particulate phase of the aerosol respectively. In the non-clinical studies in which the effects of aerosols from THS in comparison with smoke from reference cigarettes were assessed, the BoExp selected as primary BoExp in the clinical studies were added to the standard BoExp.

BoExp to these selected HPHCs were assessed in 2 non-clinical safety toxicology studies conducted in rats according to the Organization for Economic Co-operation and Development (OECD) Testing Guideline 413 (OECD (Organization for Economic Co-operation and Development) 2009), as well as in 2 longer-term study conducted in mice. The first mouse study was designed to assess the harm reduction potential of THS in an animal model of both cardiovascular disease and COPD using Apoe-/- mice. The second study was conducted in an animal model of lung cancer and COPD using A/J mice. The studies are listed in Table 59.

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Table 59 Overview of Non-Clinical Studies Performed

Study	Study Number	Type	Design	Study report
Rat OECD THS2.2	15006	*In vivo*	TG413 (air (sham), 3R4F [a], THS2.2)	15006
Rat OECD THS2.2M	15025	*In vivo*	TG413 (air (sham), 3R4F, MRCL[b] and MRCH[b], THS2.2M)	15025
ApoE THS2.2	15015	*In vivo*	Parallel-group, switching (air (sham), 3R4F[a], THS2.2, cessation, switching)	15015_CVD_Resp_ApoE_SW_SR
A/J THS2.2	15020	*In vivo*	TG453 (air (sham), 3R4F, THS2.2)	15020

[a] 3R4F reference cigarette serves as an international standard for research purposes and provides a basis for comparing data collected in various laboratories (Chepiga 2000). It is the third production run and is considered to be representative of the US market cigarettes.

[b] Mentholated reference CCs produced by PMI, with the non-mentholated 3R4F reference cigarette specifications. MRC L was designed to yield 1.2 mg menthol/stick and MRC H to yield 2.4 mg menthol/stick (under ISO smoking regimen).

The subset of BoExp used in the non-clinical studies were selected from the list used in the clinical studies. As availability of toxicokinetic data in rodent models is very limited and the availability of sufficient samples quantity is limited, 18-h or 24-h urine was used for the analysis of (water soluble) metabolites of the following smoke constituents:

- 3-HPMA for acrolein
- S-PMA for benzene
- CEMA for acrylonitrile
- Total NNAL for NNK

Details on sample collection duration, modalities, timing and detailed listing of the results can be found in the [Appendix A6.1.3.26]; the study reports can be consulted in [Section 7.2].

As shown in these documents, rats exposed to 3R4F showed a concentration-response to the BoExp in line with the HPHC concentrations in smoke, while rats exposed to aerosol of THS at similar test atmosphere nicotine concentrations as those exposed to 3R4F, showed a much reduced exposure of the BoExp across all exposure concentrations. Similarly, mice exposed to smoke or aerosol from THS at comparable concentrations of nicotine in the test atmospheres as for 3R4F, and with similar amounts of nicotine metabolites in their urine, showed a large reduction in BoExp. A summary of these results is shown in Table 60: ratios (in %) of concentrations of BoExp of THS-exposed to 3R4F-exposed animals show marked reductions of exposure to the selected HPHCs. Reductions of more than 90% were observed for all BoExp measured, except for 3-HPMA, for which reductions ranged from 34% to 87%. This is in line with the clinical studies for which 3-HPMA also showed lower reduction levels than the other BoExp.

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Table 60 Reduction of BoExp to selected HPHCs in Non-Clinical Studies

	COHb	3-HPMA	S-PMA	CEMA	Total NNAL
Rats studies *	0.2 – 2.2	13 – 25	0.5 – 0.7	0.8 – 0.9	2.2 – 4.8
Apoe$^{-/-}$ mouse study	2.1 – 3.9	47 - 66	2.8 – 4.9	1.2 – 3.2	2.2 – 8.6
A/J mouse study	1.6 – 2.7	31 - 39	1.8 – 2.2	1.0 – 1.4	3.0 – 4.0

Values represent the ranges of ratios of THS:3R4F (%) for BoExp at equal test atmosphere nicotine concentrations.

* For the calculation of the ratios from the rat studies, sham (air exposure) values have been subtracted. Results of the 2 rat studies (studies 15006 and 15025) have been pooled.

Ranges include data from different sample collection time points. Details can be found in section [Appendix A6.1.3.26.1.1]

These BoExp were furthermore used to monitor the effects of smoking cessation and switching from exposure to 3R4F to exposure to THS in the Apoe$^{-/-}$ study. Both cessation and switching reduced the exposure in the Apoe$^{-/-}$ mice in a very similar manner, with comparable kinetics and magnitude of decrease of the levels of BoExp, in line with the clinical study results. For detailed results see [Appendix A6.1.3.26].

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6.1.3.2.4.2 Analysis of BoExp not related to a Specific Chemical Entity

One of the very first effects of exposure to HPHCs in any organism is the activation of the xenobiotic metabolism network. This early response to exposure has been described for example by Eaton et al. (Eaton 1995) and provides a basis to assess the exposure of an organism to at least certain classes of chemicals. For instance, CYP1A2 has been shown to be inducible in mouse liver by PAHs (Shimada 2006, Ma 2007) and cigarettes smoke. The regulation of several CYP1A/1B genes is an indicator of the exposure to PAHs. As CYP1A2 was selected as a blood-based BoExp in humans (section 6.1.3.1.4.11.1), the protein expression of Cyp1a2 was measured in the livers (Lo Sasso 2016) and the lungs (Phillips 2016) of the mice involved in the Apoe$^{-/-}$ inhalation study described in section 6.1.4.1.1. Results are summarized in Table 61, and clearly indicate a much lower expression of Cyp1a/1b in mice exposed to THS than those exposed to 3R4F.

A complete analysis of the xenobiotic metabolism network perturbation in non-clinical studies is available in DOC_Xenobiotic_Metabolism.

Table 61 Expression of Cyp1a/1b in *in vivo* – Mouse Apoe$^{-/-}$ Study (15015)

Tissue	Cyp	Month	Treatment vs sham			
			THS	3R4F	Cessation	Switching
Liver	Cyp1a2 (protein)	2	-0.07	0.52 **	NA	NA
		8	0.01	0.82 **	-0.01	0.04
Lung	Cyp1a1 (mRNA)	2	0.46	1.44 *	NA	NA
		8	0.41	2.01 **	0.05	0.58
	Cyp1b1 (mRNA)	2	0.14	0.74 **	NA	NA
		8	0.01	1.08 **	0.3	0.31
	Cyp1a1 (protein)	2	0.01	0.89 **	NA	NA
		8	-0.07	1.21 **	-0.09	-0.02

Exposure to air (sham, cessation) or 29.9 µg nicotine / L test atmosphere (THS, 3R4F, switch), female mice.

**: fdr < 0.01, *: fdr < 0.05. Positive numbers represent increases of expression versus sham, while negative numbers represent decreased expression levels.

Furthermore, CYP1A1 and CYP1B1 mRNA expression, as well as their combined enzymatic activity, were measured in the systems toxicology-based studies conducted in organotypic tissue cultures of human airway epithelia grown at the air liquid interface and exposed with whole cigarette smoke of THS aerosol or 3R4F smoke (709_Organotypic_Bronch_SR, 1722_Organotypic_Nasal_SR, 1743_Organotypic_Buccal_SR). Results are summarized in Table 62, and clearly

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indicate here as well a much lower expression of CYP1A1/1B1 in cultures exposed to THS aerosol than those exposed to 3R4F smoke.

Table 62 Expression of CYP1A1/1B1 mRNA in *in vitro* Human Organotypic Studies, after Exposure to Air, THS, or 3R4F.

Tissue	Nicotine dose (µg/L) THS/3R4F	CYP	Post - exposure	Treatment vs air-exposed control	
				THS	3R4F
Bronchial	0.13/0.14	CYP1A1 (mRNA)	48h	-0.03	6.29 **
		CYP1B1 (mRNA)	48h	0.16	3.14 **
		CYP1A/1B (activity %)	48h	-0.02	1.3
Nasal	0.15/0.15	CYP1A1 (mRNA)	48h	0.03	5.59 **
		CYP1B1 (mRNA)	48h	0.26	4.32 **
		CYP1A/1B (activity %)	48h	0.02*	0.1*
Buccal	0.31/0.32	CYP1A1 (mRNA)	48h	0.17	4.77 **
		CYP1B1 (mRNA)	48h	0.4	3.76 **
		CYP1A/1B (activity %)	48h	0.02	0.03
	0.46/0.51	CYP1A1 (mRNA)	48h	0.27	3.91 **
		CYP1B1 (mRNA)	48h	0.38	3.19 **
		CYP1A/1B (activity %)	48h	0.05	-0.04

**: fdr < 0.01, *: fdr < 0.05, : fdr <0.1. Positive numbers represent increases of expression versus sham, while negative numbers represent decreased expression levels.

Altogether, the results obtained in non-clinical studies, assessing 1) BoExp levels in the urine of mice exposed to THS or CC smoke, and 2) expression of genes or proteins of the xenobiotic metabolism pathways in the lungs or livers of exposed mice or in human organotypic cultures, are all in line with findings in the clinical studies, and add to the compelling evidence of reduced exposure when using THS instead of CC.

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6.1.3.2.5 References

Alwis KU, Blount BC, Britt AS, Patel D, Ashley DL. Simultaneous analysis of 28 urinary VOC metabolites using ultra high performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (UPLC-ESI/MSMS). Anal Chim Acta. 2012; 750:152-60.

Ames BN, McCann J, Yamasaki E. Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat Res. 1975; 31(6):347-64.

Antal Jr MJ, Mok WSL, Roy JC, Raissi AT, Anderson DGM. Pyrolytic sources of hydrocarbons from biomass. Journal of Analytical and Applied Pyrolysis. 1985; 8:291-303.

B'Hymer C. Validation of an HPLC-MS-MS method for the determination of urinary S-benzylmercapturic acid and S-phenylmercapturic acid. J Chromatogr Sci. 2011; 49(7):547-53.

Becher G, Bjorseth A. Determination of exposure to polycyclic aromatic hydrocarbons by analysis of human urine. Cancer Lett. 1983; 17(3):301-11.

Benowitz NL, Hukkanen J, Jacob P, 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol. 2009; (192):29-60.

Boogaard PJ, van Sittert NJ. Suitability of S-phenyl mercapturic acid and trans-trans-muconic acid as biomarkers for exposure to low concentrations of benzene. Environ Health Perspect. 1996; 104 Suppl 6:1151-7.

Brandt HC, Watson WP. Monitoring human occupational and environmental exposures to polycyclic aromatic compounds. Ann Occup Hyg. 2003; 47(5):349-78.

Brown BG, Borschke AJ, Doolittle DJ. An analysis of the role of tobacco-specific nitrosamines in the carcinogenicity of tobacco smoke. Nonlinearity Biol Toxicol Med. 2003; 1(2):179-98.

Butler MA, Lang NP, Young JF, Caporaso NE, Vineis P, Hayes RB, Teitel CH, Massengill JP, Lawsen MF, Kadlubar FF. Determination of CYP1A2 and NAT2 phenotypes in human populations by analysis of caffeine urinary metabolites. Pharmacogenetics. 1992; 2(3):116-27.

Carmella SG, Chen M, Han S, Briggs A, Jensen J, Hatsukami DK, Hecht SS. Correction to effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers. Chem Res Toxicol. 2012; 25(3):763.

Carmella SG, Chen M, Han S, Briggs A, Jensen J, Hatsukami DK, Hecht SS. Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers Chem Res Toxicol. 2009; 22(4):734-41. Erratum in Chem Res Toxicol. 2012 Mar 19;25(3):763.

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.

Chepiga TA, Morton MJ, Murphy PA, Avalos JT, Bombick BR, Doolittle DJ, Borgerding MF, Swauger JE. A comparison of the mainstream smoke chemistry and mutagenicity of a representative sample of the US cigarette market with two Kentucky reference cigarettes (K1R4F and K1R5F). Food Chem Toxicol. 2000; 38(10):949-62.

Chien YC, Yeh CT. Excretion kinetics of urinary 3-hydroxybenzo[a]pyrene following dietary exposure to benzo[a]pyrene in humans. Arch Toxicol. 2012; 86(1):45-53.

Coggins CR, Gaworski CL. Could charcoal filtration of cigarette smoke reduce smoking-induced disease? A review of the literature. Regul Toxicol Pharmacol. 2008; 50(3):359-65.

Cosma G, Crofts F, Taioli E, Toniolo P, Garte S. Relationship between genotype and function of the human CYP1A1 gene. J Toxicol Environ Health. 1993; 40(2-3):309-16.

Crofts F, Taioli E, Trachman J, Cosma GN, Currie D, Toniolo P, Garte SJ. Functional significance of different human CYP1A1 genotypes. Carcinogenesis. 1994; 15(12):2961-3.

deBethizy JD, Borgerding MF, Doolittle DJ, Robinson JH, McManus KT, Rahn CA, Davis RA, Burger GT, Hayes JR, Reynolds JHt, et al. Chemical and biological studies of a cigarette that heats rather than burns tobacco. J Clin Pharmacol. 1990; 30(8):755-63.

Ding YS, Zhang L, Jain RB, Jain N, Wang RY, Ashley DL, Watson CH. Levels of tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons in mainstream smoke from different tobacco varieties. Cancer Epidemiol Biomarkers Prev. 2008; 17(12):3366-71.

Dobrinas M, Cornuz J, Oneda B, Kohler Serra M, Puhl M, Eap CB. Impact of smoking, smoking cessation, and genetic polymorphisms on CYP1A2 activity and inducibility. Clin Pharmacol Ther. 2011; 90(1):117-25.

Doolittle DJ, Rahn CA, Burger GT, Lee CK, Reed B, Riccio E, Howard G, Passananti GT, Vesell ES, Hayes AW. Effect of cooking methods on the mutagenicity of food and on urinary mutagenicity of human consumers. Food Chem Toxicol. 1989; 27(10):657-66.

Eaton DL, Gallagher EP, Bammler TK, Kunze KL. Role of cytochrome P4501A2 in chemical carcinogenesis: implications for human variability in expression and enzyme activity. Pharmacogenetics. 1995; 5(5):259-74.

Einisto P, Nohmi T, Watanabe M, Ishidate M, Jr. Sensitivity of Salmonella typhimurium YG1024 to urine mutagenicity caused by cigarette smoking. Mutat Res. 1990; 245(2):87-92.

European Chemical Agency (ECHA). Summary risk assessment report: 1,3-butadiene. 2002.

Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. Clin Pharmacol Ther. 2004; 76(2):178-84.

Faber MS, Jetter A, Fuhr U. Assessment of CYP1A2 activity in clinical practice: why, how, and when? Basic Clin Pharmacol Toxicol. 2005; 97(3):125-34.

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FDA (Food and Drug Administration). Guidance for industry - Modified risk tobacco product applications - Draft Guidance. 2012.

Feng S, Roethig HJ, Liang Q, Kinser R, Jin Y, Scherer G, Urban M, Engl J, Riedel K. Evaluation of urinary 1-hydroxypyrene, S-phenylmercapturic acid, trans,trans-muconic acid, 3-methyladenine, 3-ethyladenine, 8-hydroxy-2'-deoxyguanosine and thioethers as biomarkers of exposure to cigarette smoke. Biomarkers. 2006; 11(1):28-52.

Fischer S, Spiegelhalder B, Eisenbarth J, Preussmann R. Investigations on the origin of tobacco-specific nitrosamines in mainstream smoke of cigarettes. Carcinogenesis. 1990; 11(5):723-30.

Forster M, Liu C, Duke MG, McAdam KG, Proctor CJ. An experimental method to study emissions from heated tobacco between 100-200 degrees C. Chem Cent J. 2015; 9:20.

Frost-Pineda K, Zedler BK, Oliveri D, Feng S, Liang Q, Roethig HJ. Short-term clinical exposure evaluation of a third-generation Electrically Heated Cigarette Smoking System (EHCSS) in adult smokers. Regul Toxicol Pharmacol. 2008a; 52:104-10.

Frost-Pineda K, Zedler BK, Oliveri D, Liang Q, Feng S, Roethig HJ. 12-week clinical exposure evaluation of a third-generation Electrically Heated Cigarette Smoking System (EHCSS) in adult smokers. Regul Toxicol Pharmacol. 2008b; 52(2):111-7.

Ghotbi R, Christensen M, Roh HK, Ingelman-Sundberg M, Aklillu E, Bertilsson L. Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype-phenotype relationship in Swedes and Koreans. Eur J Clin Pharmacol. 2007; 63(6):537-46.

Goniewicz ML, Havel CM, Peng MW, Jacob P, 3rd, Dempsey D, Yu L, Zielinska-Danch W, Koszowski B, Czogala J, Sobczak A, Benowitz NL. Elimination kinetics of the tobacco-specific biomarker and lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. Cancer Epidemiol Biomarkers Prev. 2009; 18(12):3421-5.

Gregg EO, Minet E, McEwan M. Urinary biomarkers of smokers' exposure to tobacco smoke constituents in tobacco products assessment: a fit for purpose approach. Biomarkers. 2013.

Grimmer G, Dettbarn G, Seidel A, Jacob J. Detection of carcinogenic aromatic amines in the urine of non-smokers. Sci Total Environ. 2000; 247(1):81-90.

Gunduz I, Kondylis A, Jaccard G, Renaud JM, Hofer R, Ruffieux L, Gadani F. Tobacco-specific N-nitrosamines NNN and NNK levels in cigarette brands between 2000 and 2014. Regul Toxicol Pharmacol. 2016; 76:113-20.

Gunes A, Dahl ML. Variation in CYP1A2 activity and its clinical implications: influence of environmental factors and genetic polymorphisms. Pharmacogenomics. 2008; 9(5):625-37.

Haufroid V, Merz B, Hofmann A, Tschopp A, Lison D, Hotz P. Exposure to ethylene oxide in hospitals: biological monitoring and influence of glutathione S-transferase and epoxide hydrolase polymorphisms. Cancer Epidemiol Biomarkers Prev. 2007; 16(4):796-802.

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Hearn BA, Ding YS, Vaughan C, Zhang L, Polzin G, Caudill SP, Watson CH, Ashley DL. Semi-volatiles in mainstream smoke delivery from select charcoal-filtered cigarette brand variants. Tob Control. 2010; 19(3):223-30.

Hecht SS, Carmella SG, Chen M, Dor Koch JF, Miller AT, Murphy SE, Jensen JA, Zimmerman CL, Hatsukami DK. Quantitation of urinary metabolites of a tobacco-specific lung carcinogen after smoking cessation. Cancer Res. 1999a; 59(3):590-6.

Hecht SS, Tricker AR. Gorrod JW, P. Jacob r, editors. Chapter 11. ed.: Elsevier; 1999b. Nitrosamine derived from nicotine and other tobacco alkaloids. In: Analytical Determination of Nicotine and Related Compounds and their Metabolites. p. 421-88.

Herdevall BM, Klinge B, Persson L, Huledal G, Abdel-Rehim M. Plasma levels of lidocaine, o-toluidine, and prilocaine after application of 8.5 g Oraqix in patients with generalized periodontitis: effect on blood methemoglobin and tolerability. Acta Odontol Scand. 2003; 61(4):230-4.

IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: 1,3-butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). 2008a; Vol. 97.

IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: chemical agents and related occupations. 2012; Vol. 100F.

IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: chemical agents and related occupations - Ethylene oxide. 2008b; Available from: http://monographs.iarc.fr/ENG/Monographs/vol100F/mono100F-28.pdf (Accessed on 5 August 2014).

IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: dry cleaning, some chlorinated solvents and other industrial chemicals. 1995; Vol. 63.

IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: smokeless tobacco and some tobacco-specific N-nitrosamines. 2007; Vol. 89.

IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: some aromatic amines, organic dyes, and related exposures. 2010; Vol. 99.

IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: tobacco smoke and involuntary smoking. 2004; Vol. 83.

Imbriani M, Ghittori S, Cavalleri A. [Significance of urinary concentrations of S-benzyl-N-acetylcysteine (S-BMA) in subjects exposed to toluene] Italian. G Ital Med Lav Ergon. 1999; 21(4):329-33.

Inoue O, Kanno E, Kasai K, Ukai H, Okamoto S, Ikeda M. Benzylmercapturic acid is superior to hippuric acid and o-cresol as a urinary marker of occupational exposure to toluene. Toxicol Lett. 2004; 147(2):177-86.

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International Programme on Chemical Safety (IPCS). Acrolein. Concise International Chemical Assessment Document 43. 2002; Available from: http://www.inchem.org/documents/cicads/cicads/cicad43.htm (Accessed on 27 November 2014).

IOM (Institute of Medicine). Scientific standards for studies on modified risk tobacco products. Washington, DC: The National Academies Press. 2012.

Jakubowski M, Linhart I, Pielas G, Kopecky J. 2-Cyanoethylmercapturic acid (CEMA) in the urine as a possible indicator of exposure to acrylonitrile. Br J Ind Med. 1987; 44(12):834-40.

Jassem J, Przewozniak K, Zatonski W. Tobacco control in Poland-successes and challenges. Transl Lung Cancer Res. 2014; 3(5):280-5.

Jongeneelen FJ, vd Akker W, Bos RP, Anzion RB, Theuws JL, Roelofs HM, Henderson PT. 1-Hydroxypyrene as an indicator of the mutagenicity of coal tar after activation with human liver preparations. Mutat Res. 1988; 204(2):195-201.

Kado NY, Manson C, Eisenstadt E, Hsieh DP. The kinetics of mutagen excretion in the urine of cigarette smokers. Mutat Res. 1985; 157(2-3):227-33.

Karreth S, Lenk W. The metabolism of 4-aminobiphenyl in rat. I. Reaction of N-hydroxy-4-aminobiphenyl with rat blood in vivo. Xenobiotica. 1991; 21(3):417-28.

Kavvadias D, Scherer G, Cheung F, Errington G, Shepperd J, McEwan M. Determination of tobacco-specific N-nitrosamines in urine of smokers and non-smokers. Biomarkers. 2009; 14(8):547-53.

Kuenemann-Migeot C, Callais F, Momas I, Festy B. Use of Salmonella typhimurium TA 98, YG 1024 and YG 1021 and deconjugating enzymes for evaluating the mutagenicity from smokers' urine. Mutat Res. 1997; 390(3):283-91.

Lo Sasso G, Titz B, Nury C, Boue S, Phillips B, Belcastro V, Schneider T, Dijon S, Baumer K, Peric D, Dulize R, Elamin A, Guedj E, Buettner A, Leroy P, Kleinhans S, Vuillaume G, Veljkovic E, Ivanov NV, Martin F, Vanscheeuwijck P, Peitsch MC, Hoeng J. Effects of cigarette smoke, cessation and switching to a candidate modified risk tobacco product on the liver in Apoe(-/-) mice - a systems toxicology analysis. Inhal Toxicol. 2016; 28(5):226-40.

Lovreglio P, Barbieri A, Carrieri M, Sabatini L, Fracasso ME, Doria D, Drago I, Basso A, D'Errico MN, Bartolucci GB, Violante FS, Soleo L. Validity of new biomarkers of internal dose for use in the biological monitoring of occupational and environmental exposure to low concentrations of benzene and toluene. Int Arch Occup Environ Health. 2010; 83(3):341-56.

MacLeod S, Sinha R, Kadlubar FF, Lang NP. Polymorphisms of CYP1A1 and GSTM1 influence the in vivo function of CYP1A2. Mutat Res. 1997; 376(1-2):135-42.

Maestri L, Ghittori S, Imbriani M. Determination of specific mercapturic acids as an index of exposure to environmental benzene, toluene, and styrene. Ind Health. 1997; 35(4):489-501.

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Martin Leroy C, Jarus-Dziedzic K, Ancerewicz J, Lindner D, Kulesza A, Magnette J. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 7: a one-month, randomized, ambulatory, controlled clinical study in Poland. Regul Toxicol Pharmacol. 2012; 64; (2 Suppl):S74-84.

Matsuda K, Takahashi A, Middlebrooks CD, Obara W, Nasu Y, Inoue K, Tamura K, Yamasaki I, Naya Y, Tanikawa C, Cui R, Figueroa JD, Silverman DT, Rothman N, Namiki M, Tomita Y, Nishiyama H, Kohri K, Deguchi T, Nakagawa M, Yokoyama M, Miki T, Kumon H, Fujioka T, Prokunina-Olsson L, Kubo M, Nakamura Y, Shuin T. Genome-wide association study identified SNP on 15q24 associated with bladder cancer risk in Japanese population. Hum Mol Genet. 2015; 24(4):1177-84.

McGraw J, Waller D. Cytochrome P450 variations in different ethnic populations. Expert Opin Drug Metab Toxicol. 2012; 8(3):371-82.

Miura N, Yuki D, Minami N, Kakehi A, Futamura Y. A study to investigate changes in the levels of biomarkers of exposure to selected cigarette smoke constituents in Japanese adult male smokers who switched to a non-combustion inhaler type of tobacco product. Regul Toxicol Pharmacol. 2015.

Moldoveanu SC, Borgerding M. Formation of tobacco specific nitrosamines in mainstream cigarette smoke; Part 1, FTC smoking. Beitrage zur Tabakforschung International/ Contributions to Tobacco Research. 2008; 23(1):19-31.

Munaka M, Katoh T, Kohshi K, Sasaki S. Influence of tea and coffee on biomonitoring of toluene exposure. Occup Med (Lond). 2009; 59(6):397-401.

Muscat JE, Takezaki T, Tajima K, Stellman SD. Charcoal cigarette filters and lung cancer risk in Aichi Prefecture, Japan. Cancer Sci. 2005; 96(5):283-7.

Nakajima M, Yokoi T, Mizutani M, Shin S, Kadlubar FF, Kamataki T. Phenotyping of CYP1A2 in Japanese population by analysis of caffeine urinary metabolites: absence of mutation prescribing the phenotype in the CYP1A2 gene. Cancer Epidemiol Biomarkers Prev. 1994; 3(5):413-21.

National Center for Biotechnology Information (NCBI). Compound summary for CID 7102: 4-biphenylamine. 2014a; Available from: http://pubchem.ncbi.nlm.nih.gov/compound/7102#section=Top (Accessed on 11 December 2014).

National Center for Biotechnology Information (NCBI). Compound summary for CID 8640: 1-naphthylamine. 2014b; Available from: http://pubchem.ncbi.nlm.nih.gov/compound/1-naphthylamine#section=Information-Sources (Accessed on 02 December 2014).

National Center for Biotechnology Information (NCBI). Compound Summary for CID 447466: crotonaldehyde. Available from: http://pubchem.ncbi.nlm.nih.gov/compound/447466#section=Ecological-Information (Accessed on 15 January 2015).

Confidentiality Statement

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National Research Council (US) Committee on Diet, Nutrition, and Cancer. Diet, nutrition, and cancer Available from: http://wwwncbinlmnihgov/books/NBK216630/ (Accessed on 25 April 2016). 13. ed. Washington DC, US: National Academies Press; 1982. Mutagens in food. p. 277-303.

Nikoyan A, De Meo M, Sari-Minodier I, Chaspoul F, Gallice P, Botta A. Evaluation of a battery of Salmonella typhimurium tester strains for biomonitoring of mutagenic polycyclic aromatic hydrocarbons, nitroarenes and aromatic amines. Mutat Res. 2007; 626(1-2):88-101.

OECD (Organization for Economic Co-operation and Development). Guidelines for the testing of chemicals: bacterial reverse mutation test [test 471]. 1997; Avialble from: http://www.oecd.org/chemicalsafety/risk-assessment/1948418.pdf (Accessed on 13 January 2016).

OECD (Organization for Economic Co-operation and Development). Guidelines for the testing of chemicals: subchronic inhalation toxicity: 90-day study [test 413]. 2009; Revised version available from: http://www.oecd-ilibrary.org/docserver/download/9741301e.pdf?expires=1405584197&id=id&accname=guest&checksum=CEBC65DF6EC6726D2F404DED131DC3B9 (Accessed on 17 July 2014).

OECD (Organization for Economic Co-operation and Development). SIDS Initial assessment report for SIAM 19: o-toluidine. 2004; Available from: http://www.inchem.org/documents/sids/sids/95534.pdf (Accessed on 28 January 2015).

Park SL, Carmella SG, Chen M, Patel Y, Stram DO, Haiman CA, Le Marchand L, Hecht SS. Mercapturic acids derived from the toxicants acrolein and crotonaldehyde in the urine of cigarette smokers from five ethnic groups with differing risks for lung cancer. PLoS ONE. 2015; 10(6):e0124841.

Park SL, Kotapati S, Wilkens LR, Tiirikainen M, Murphy SE, Tretyakova N, Le Marchand L. 1,3-butadiene exposure and metabolism among Japanese American, native Hawaiian, and white smokers. Cancer Epidemiol Biomarkers Prev. 2014; 23(11):2240-9.

Pezzuto A, Spoto C, Vincenzi B, Tonini G. Short-term effectiveness of smoking-cessation treatment on respiratory function and CEA level. J Comp Eff Res. 2013; 2(3):335-43.

Philip Morris Products S.A. *Unpublished on file data:* Investigator's Brochure for Tobacco Heating System 2.2 Regular. Edition 5. 2015a.

Philip Morris Products S.A. *Unpublished on file data:* Investigator's Brochure for Tobacco Heating System 2.2 Menthol. Edition 3. 2015b.

Phillips B, Veljkovic E, Boue S, Schlage WK, Vuillaume G, Martin F, Titz B, Leroy P, Buettner A, Elamin A, Oviedo A, Cabanski M, De Leon H, Guedj E, Schneider T, Talikka M, Ivanov NV, Vanscheeuwijck P, Peitsch MC, Hoeng J. An 8-Month Systems Toxicology Inhalation/Cessation Study in Apoe-/- Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared With Conventional Cigarettes. Toxicol Sci. 2016; 149(2):411-32.

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.

Pluym N, Gilch G, Scherer G, Scherer M. Analysis of 18 urinary mercapturic acids by two high-throughput multiplex-LC-MS/MS methods. Anal Bioanal Chem. 2015; 407(18):5463-76.

Polonia J, Barbosa L, Silva JA, Rosas M. Improvement of aortic reflection wave responses 6 months after stopping smoking: a prospective study. Blood Press Monit. 2009; 14(2):69-75.

Polzin GM, Zhang L, Hearn BA, Tavakoli AD, Vaughan C, Ding YS, Ashley DL, Watson CH. Effect of charcoal-containing cigarette filters on gas phase volatile organic compounds in mainstream cigarette smoke. Tob Control. 2008; 17 Suppl 1:i10-6.

Qadariyah L, Mahfud, Sumarno, Machmudah S, Wahyudiono, Sasaki M, Goto M. Degradation of glycerol using hydrothermal process. Bioresour Technol. 2011; 102(19):9267-71.

Ramos EM, De Toledo AC, Xavier RF, Fosco LC, Vieira RP, Ramos D, Jardim JR. Reversibility of impaired nasal mucociliary clearance in smokers following a smoking cessation programme. Respirology. 2011; 16(5):849-55.

Richter E. Biomonitoring of human exposure to arylamines. Front Biosci (Elite Ed). 2015; 7:222-38.

Rodgman A, Perfetti TA. The chemical components of tobacco and tobacco smoke 2nd ed: CRC Press, Taylor & Francis Inc (United States); 2013.

Roemer E, Schorp MK, Piade JJ, Seeman JI, Leyden DE, Haussmann HJ. Scientific assessment of the use of sugars as cigarette tobacco ingredients: a review of published and other publicly available studies. Crit Rev Toxicol. 2012; 42(3):244-78.

Roethig HJ, Feng S, Liang Q, Liu J, Rees WA, Zedler BK. A 12-month, randomized, controlled study to evaluate exposure and cardiovascular risk factors in adult smokers switching from conventional cigarettes to a second-generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol. 2008; 48(5):580-91.

Roethig HJ, Munjal S, Feng S, Liang Q, Sarkar M, Walk RA, Mendes PE. Population estimates for biomarkers of exposure to cigarette smoke in adult U.S. cigarette smokers. Nicotine Tob Res. 2009; 11(10):1216-25.

Roethig HJ, Zedler BK, Kinser RD, Feng S, Nelson BL, Liang Q. Short-term clinical exposure evaluation of a second-generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol. 2007; 47:518.

Sakaguchi C, Kakehi A, Minami N, Kikuchi A, Futamura Y. Exposure evaluation of adult male Japanese smokers switched to a heated cigarette in a controlled clinical setting. Regul Toxicol Pharmacol. 2014.

Sarkar M, Kapur S, Frost-Pineda K, Feng S, Wang J, Liang Q, Roethig H. Evaluation of biomarkers of exposure to selected cigarette smoke constituents in adult smokers switched to carbon-filtered cigarettes in short-term and long-term clinical studies. Nicotine Tob Res. 2008; 10(12):1761-72.

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.

Sarkar M, Liu J, Koval T, Wang J, Feng S, Serafin R, Jin Y, Xie Y, Newland K, Roethig HJ. Evaluation of biomarkers of exposure in adult cigarette smokers using Marlboro snus. Nicotine Tob Res. 2010; 12(2):105-16.

Sarkar MA, Feng S, Kenser R, Roethig H-J. Evaluation of urinary monohydroxybutenyl and dihydroxybutyl mercapturic acid as biomarkers of 1,3-butadiene exposure from cigarette smoke. Poster presented at the American Association for Cancer Research, Anaheim, CA, USA. AACR Meeting Abstracts. 2005; (1):524.

Scherer G. Carboxyhemoglobin and thiocyanate as biomarkers of exposure to carbon monoxide and hydrogen cyanide in tobacco smoke. Exp Toxicol Pathol. 2006a; 58(2-3):101-24.

Scherer G, Urban M, Engl J, Hagedorn HW, Riedel K. Influence of smoking charcoal filter tipped cigarettes on various biomarkers of exposure. Inhal Toxicol. 2006b; 18(10):821-9.

Scherer G, Urban M, Hagedorn HW, Feng S, Kinser RD, Sarkar M, Liang Q, Roethig HJ. Determination of two mercapturic acids related to crotonaldehyde in human urine: influence of smoking. Hum Exp Toxicol. 2007; 26(1):37-47.

Scherer G, Urban M, Hagedorn HW, Serafin R, Feng S, Kapur S, Muhammad R, Jin Y, Sarkar M, Roethig HJ. Determination of methyl-, 2-hydroxyethyl- and 2-cyanoethylmercapturic acids as biomarkers of exposure to alkylating agents in cigarette smoke. J Chromatogr B Analyt Technol Biomed Life Sci. 2010; (878):2520-8.

Schettgen T, Musiol A, Alt A, Kraus T. Fast determination of urinary S-phenylmercapturic acid (S-PMA) and S-benzylmercapturic acid (S-BMA) by column-switching liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2008; 863(2):283-92.

Shepperd CJ, Eldridge A, Camacho OM, McAdam K, Proctor CJ, Meyer I. Changes in levels of biomarkers of exposure observed in a controlled study of smokers switched from conventional to reduced toxicant prototype cigarettes. Regul Toxicol Pharmacol. 2013; 66(1):147-62. Erratum in Regul Toxicol Pharmacol. 2013;67(3):536.

Smith CJ, Livingston SD, Doolittle DJ. An international literature survey of "IARC Group I carcinogens" reported in mainstream cigarette smoke. Food Chem Toxicol. 1997; 35(10-11):1107-30.

Smith CJ, McKarns SC, Davis RA, Livingston SD, Bombick BR, Avalos JT, Morgan WT, Doolittle DJ. Human urine mutagenicity study comparing cigarettes which burn or primarily heat tobacco. Mutat Res. 1996; 361(1):1-9.

Snedecor GW, Cochran WG. Statistical Methods. Chap. 12. 8th ed.: Iowa: Iowa State Univ Press; 1989. One-way classifications: analysis of variance. p. 217-36.

Stein YS, Antal Jr MJ, Jones M. A study of the gas-phase pyrolysis of glycerol. Journal of Analytical and Applied Pyrolysis. 1983; 4(4):283-96.

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.

Stepanov I, Carmella SG, Briggs A, Hertsgaard L, Lindgren B, Hatsukami D, Hecht SS. Presence of the carcinogen N'-nitrosonornicotine in the urine of some users of oral nicotine replacement therapy products. Cancer Res. 2009a; 69(21):8236-40.

Stepanov I, Carmella SG, Han S, Pinto A, Strasser AA, Lerman C, Hecht SS. Evidence for endogenous formation of N'-nitrosonornicotine in some long-term nicotine patch users. Nicotine Tob Res. 2009b; 11(1):99-105.

Stepanov I, Hecht SS. Tobacco-specific nitrosamines and their pyridine-N-glucuronides in the urine of smokers and smokeless tobacco users. Cancer Epidemiol Biomarkers Prev. 2005; 14(4):885-91.

Stevens JF, Maier CS. Acrolein: sources, metabolism, and biomolecular interactions relevant to human health and disease. Mol Nutr Food Res. 2008; 52(1):7-25.

Strickland P, Kang D. Urinary 1-hydroxypyrene and other PAH metabolites as biomarkers of exposure to environmental PAH in air particulate matter. Toxicol Lett. 1999; 108(2-3):191-9.

Theophilus EH, Coggins CRE, Chen P, Schmidt ER, Borgerding MF. Magnitudes of biomarker reductions in response to controlled reductions in cigarettes smoked per day: a one-week clinical confinement study. Regul Toxicol Pharmacol. 2015; 71(2):225-34.

Torikai K, Yoshida S, Takahashi H. Effects of temperature, atmosphere and pH on the generation of smoke compounds during tobacco pyrolysis. Food Chem Toxicol. 2004; 42(9):1409-17.

Toxicology Data Network. 1-naphthylamine (CAS: 134-32-7). [Internet] Bethesda (MD): National Library of Medicine (US); Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+1080 (Accessed on 17 July 2014).

Toxicology Data Network. 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (CASRN: 64091-91-4). 2010; Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~bLaWqY:3 (Accessed on 20 August 2014).

Tricker AR, Jang IJ, Martin Leroy C, Lindner D, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 4: eight-day randomized clinical trial in Korea. Regul Toxicol Pharmacol. 2012a; 64(2 Suppl):S45-53.

Tricker AR, Kanada S, Takada K, Leroy CM, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 5: 8-Day randomized clinical trial in Japan. Regul Toxicol Pharmacol. 2012b; 64(2):S54-S63.

Tricker AR, Kanada S, Takada K, Martin Leroy C, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 6: 6-day randomized clinical trial of a menthol cigarette in Japan. Regul Toxicol Pharmacol. 2012c; 64:S64-S73.

Tricker AR, Stewart AJ, Leroy CM, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 3: eight-day randomized clinical trial in the UK. Regul Toxicol Pharmacol. 2012d; 64:S35-S44.

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.

U.S. Department of Health and Human Services, FDA (Food and Drug Administration). [Docket No. FDA-2012-N-0143]: harmful and potentially harmful constituents in tobacco products and tobacco smoke; established list. Fed Regist. 2012a; 77(64):20034-7.

U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Toxicity of polycyclic aromatic hydrocarbons (PAHs). 2009; Available from: http://www.atsdr.cdc.gov/csem/pah/docs/pah.pdf (Accessed on 12 March 2015).

U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Toxicological profile for benzene. 2007; Available from: http://www.atsdr.cdc.gov/toxprofiles/tp3.pdf (Accessed on 07 July 2014).

U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Toxicological profile for carbon monoxide. 2012b; Available from: http://www.atsdr.cdc.gov/toxprofiles/tp201.pdf (Accessed on 23 November 2014).

U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Toxicological profile for polycyclic aromatic hydrocarbons. 1995; Available from: http://www.atsdr.cdc.gov/toxprofiles/tp69.pdf (Accessed on 04 December 2014).

U.S. Environmental Protection Agency (EPA). 1,3-Butadiene - Hazard summary - Created in April 1992; revised in January 2000, March 2009. 2009; Available from: http://www.epa.gov/ttn/atw/hlthef/butadien.html (Accessed on 03 July 2014).

Upadhyaya P, Zimmerman CL, Hecht SS. Metabolism and pharmacokinetics of N′-nitrosonornicotine in the patas monkey. Drug Metab Dispos. 2002; 30(10):1115-22.

Urban M, Scherer G, Kavvadias D, Hagedorn HW, Feng S, Serafin R, Kapur S, Muhammad R, Jin Y, Mendes P, Roethig H. Quantitation of N'-nitrosonornicotine (NNN) in smokers' urine by liquid chromatography-tandem mass spectrometry. J Anal Toxicol. 2009; 33(5):260-5.

van Sittert NJ, Boogaard PJ, Beulink GD. Application of the urinary S-phenylmercapturic acid test as a biomarker for low levels of exposure to benzene in industry. Br J Ind Med. 1993; 50(5):460-9.

van Staden SR, Groenewald M, Engelbrecht R, Becker PJ, Hazelhurst LT. Carboxyhaemoglobin levels, health and lifestyle perceptions in smokers converting from tobacco cigarettes to electronic cigarettes. S Afr Med J. 2013; 103(11):865-8.

van Welie RT, van Dijck RG, Vermeulen NP, van Sittert NJ. Mercapturic acids, protein adducts, and DNA adducts as biomarkers of electrophilic chemicals. Crit Rev Toxicol. 1992; 22(5-6):271-306.

Viau C, Carrier G, Vyskocil A, Dodd C. Urinary excretion kinetics of 1-hydroxypyrene in volunteers exposed to pyrene by the oral and dermal route. Sci Total Environ. 1995a; 163(1-3):179-86.

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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.

Viau C, Vyskocil A. Patterns of 1-hydroxypyrene excretion in volunteers exposed to pyrene by the dermal route. Sci Total Environ. 1995b; 163(1-3):187-90.

WHO (World Health Organization). Acrylonitrile. Concise International Chemical Assessment Document 39. 2002; Available from: http://www.inchem.org/documents/cicads/cicads/cicad39.htm (Accessed on 02 September 2014).

WHO (World Health Organization). O-toluidine. Concise International Chemical Assessment Document 7. 1998.

WHO (World Health Organization). WHO guidelines for indoor air quality: selected pollutants. 2010.

WHO Study Group, Ashley DL, Burns D, Djordjevic M, Dybing E, Gray N, Hammond SK, Henningfield J, Jarvis M, Reddy KS, Robertson C, Zaatari G. The scientific basis of tobacco product regulation: second report of a WHO study group. World Health Organ Tech Rep Ser. 2008; (951):1-277, 1 p following

Yu J, Wang S, Zhao G, Wang B, Ding L, Zhang X, Xie J, Xie F. Determination of urinary aromatic amines in smokers and nonsmokers using a MIPs-SPE coupled with LC-MS/MS method. J Chromatogr B Analyt Technol Biomed Life Sci. 2014; 958:130-5.

Yuan JM, Knezevich AD, Wang R, Gao YT, Hecht SS, Stepanov I. Urinary levels of the tobacco-specific carcinogen N'-nitrosonornicotine and its glucuronide are strongly associated with esophageal cancer risk in smokers. Carcinogenesis. 2011; 32(9):1366-71.

Zhou SF, Wang B, Yang LP, Liu JP. Structure, function, regulation and polymorphism and the clinical significance of human cytochrome P450 1A2. Drug Metab Rev. 2010; 42(2):268-354.

Zhu AZ, Binnington MJ, Renner CC, Lanier AP, Hatsukami DK, Stepanov I, Watson CH, Sosnoff CS, Benowitz NL, Tyndale RF. Alaska Native smokers and smokeless tobacco users with slower CYP2A6 activity have lower tobacco consumption, lower tobacco-specific nitrosamine exposure and lower tobacco-specific nitrosamine bioactivation. Carcinogenesis. 2013; 34(1):93-101.

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