TABLE OF CONTENTS

6.1.3.4 REX Overview of Studies 2
6.1.3.4.1 ZRHR-REXC-03-EU 2
6.1.3.4.1.1 Statistical methods 8
6.1.3.4.1.1.1 Primary Analyses 8
6.1.3.4.1.1.2 Secondary Analyses 8
6.1.3.4.1.2 Study Hypotheses and Evaluation Criteria 8
6.1.3.4.1.3 Summary of Selected Results Relevant for BoExp Assessment 9
6.1.3.4.1.3.1 BoExp Assessment 9
6.1.3.4.1.4 Conclusion 23
6.1.3.4.2 ZRHR-REXC-04-JP 24
6.1.3.4.2.1 Statistical methods 29
6.1.3.4.2.1.1 Primary Analyses 29
6.1.3.4.2.1.2 Secondary Analyses 30
6.1.3.4.2.2 Study Hypotheses and Evaluation Criteria 30
6.1.3.4.2.3 Summary of selected results relevant for BoExp Assessment 30
6.1.3.4.2.3.1 BoExp Assessment 30
6.1.3.4.2.4 Conclusion 44
6.1.3.4.3 ZRHM-REXA-07-JP 45
6.1.3.4.3.1 Statistical methods 52
6.1.3.4.3.1.1 Primary Analyses 52
6.1.3.4.3.1.2 Secondary Analyses 52
6.1.3.4.3.2 Study Hypotheses and Evaluation Criteria 53
6.1.3.4.3.3 Summary of selected results relevant for BoExp Assessment 53
6.1.3.4.3.3.1 BoExp Assessment 53
6.1.3.4.3.4 Conclusion 72
6.1.3.4.4 ZRHM-REXA-08-US 74
6.1.3.4.4.1 Statistical methods 81
6.1.3.4.4.1.1 Primary Analyses 81
6.1.3.4.4.1.2 Secondary Analyses 82
6.1.3.4.4.2 Study Hypotheses and Evaluation Criteria 83
6.1.3.4.4.3 Summary of selected results relevant for BoExp Assessment 83
6.1.3.4.4.3.1 BoExp Assessment 83
6.1.3.4.4.4 Conclusion 101

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.

6.1.3.4 REX Overview of Studies

6.1.3.4.1 ZRHR-REXC-03-EU

STUDY ZRHR-REXC-03-EU	**Source: Section 7.3.1, Clinical Study Report ZRHR-REXC-03-EU**

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, for 5 days in Confinement

Protocol-No.: ZRHR-REXC-03-EU		
Date of final report: 08 March 2016		
Investigators:	Principal Investigator: Katarzyna Jarus-Dziedzic, MD, PhD	
Study center:	BioVirtus Research Site Sp. z o.o., Mokra 7, 05-830 Kajetany, Poland	
Time of clinical part:	29 June 2013 – 26 September 2013	**Clinical Phase:** II (Product Performance)

Objective:

The aim of this study was to demonstrate reduction in exposure to selected HPHCs (except nicotine) in smokers switching to the THS 2.2. THS 2.2 was also compared with smoking abstinence, used as a reference point. Furthermore, nicotine exposure, product use, subjective effects and changes in Human Puffing Topography over time in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC were assessed.

Study design:

- Single center
- Ad-libitum use
- Randomized
- Parallel
- Open-label

Confidentiality Statement

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

- 5 Days of Exposure

Subjects:

• Planned:	160 subjects
• Enrolled:	169 subjects
• Randomized:	160 subjects
• Discontinuations:	1 subject
• Completed:	159 subjects
• Safety population	169 subjects
• Full analysis set (FAS) population	160 subjects
• Per-protocol (PP) population:	160 subjects

Main criteria for inclusion:

- Male or female Caucasians from 21 to 65 years of age and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening.
- Spirometry evaluation had to show forced expiratory volume in 1 second {FEV_1}/forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV_1 >80% predicted value, and post-bronchodilator FVC >0.8.
- Subjects were smoking at least 10 commercially available non- menthol CC (CC) per day with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) CC, as labelled on the cigarette package, for the last 4 weeks, and did not plan to quit smoking in the following 3 months. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
- Female subjects of child-bearing potential should had confirmed negative pregnancy test and used effective methods of contraception.
- Provide written informed consent prior to study participation.
- Able to communicate well with the investigator and comply with the requirements of the study.
- The subject was a current smoker who did not plan to quit smoking in the next 3 months.
- The subject was ready to accept using the THS 2.2 product or to accept 5 days of SA.

THS 2.2:	Product:	Cigarette batch number of THS Tobacco Sticks B-05875 Production date: 07 June 2013. Expiry date: 06 January 2014
	ISO nicotine Content:	0.5 mg
	Use:	Ad-libitum use
	Manufacturer:	PMI
Conventional Cigarette:	Product:	Own conventional cigarette brand.
	ISO nicotine Content:	

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.

	Use: Manufacturer:	Maximum yield of 1 mg per CC as per cigarette package label Ad-libitum use Commercially available non-menthol conventional cigarettes

Smoking Abstinence	Smoking abstinence was used as a reference point without support of Nicotine Replacement Therapy or any drug for smoking cessation support.
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, during which the subject was allowed to use the assigned product (THS 2.2 or CC), or abstained from smoking**.**
Analytical Methods:	All analytical methods, with the exception of Carboxyhemoglobin (measured by (b) (4)) were developed at (b) (4) , and validated according to the standard operating procedures (SOPs) in effect during the conduct of the validation. These SOPs were written in accordance with the principles of good laboratory practice (GLP) described in 21 Code of Federal Regulation (CFR) Part 58 and the Guidance for Industry – Bioanalytical Method Validation (CDER, May 2001). (b) (b) (4) t (b) (4) , (b) (4) A detailed summary of the description of the analytical methods by BoExp, the matrix used and the validation are described in section 6.1.3.4.

Primary Objective:

1. To demonstrate the reduction of primary biomarkers of exposure (BoExp) in smokers switching from conventional cigarettes (CC) to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoints:

   - Monohydroxybutenylmercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA) (concentration adjusted for creatinine) in 24-hour urine, and carboxyhemoglobin (COHb) in blood (expressed as % saturation of hemoglobin) as measured on Day 5.

Secondary Objectives:

Confidentiality Statement

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

1. To determine the reduction of secondary BoExp on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoints:

   - Quantity excreted in urine over 24 hours for MHBMA, S-PMA, and 3-HPMA.
   - Carbon monoxide ([CO] expressed as ppm) in exhaled breath
   - Urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

2. To describe the levels of primary and secondary BoExp over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoints:

   - CO (expressed as ppm) in exhaled breath.
   - COHb in blood (expressed as % saturation of hemoglobin).
   - Primary and secondary urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

3. To determine the levels of nicotine on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and to describe their levels over the exposure period from Day 1 to Day 5.

   Endpoints:

   - Nicotine equivalent ([NEQ] expressed in quantity excreted and concentration adjusted to creatinine) in 24-hour urine on Day 5 and from Day 1 to Day 5.
   - Plasma nicotine and cotinine concentrations.

4. To describe the levels of primary, secondary BoExp, and BoExp to nicotine over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers switching from CC to smoking abstinence (SA).

   Endpoints:

   - COHb in blood (expressed as % saturation of hemoglobin).
   - CO (expressed as ppm) in exhaled breath.
   - Primary and secondary urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

5. To describe the pharmacokinetic (PK) profiles of the nicotine and cotinine in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoints:

   - Peak (highest concentration value along the day) on Day 5 in plasma.
   - Time to peak (actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
   - Weighted average concentration over 24 hours on Day 5.

6. To describe the changes in cytochrome P450 1A2 (CYP1A2) enzymatic activity on Day 5 in smokers switching from CC to THS 2.2, switching from CC to SA, and continuing to smoke CC.

   Endpoint:

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.

- Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5.

7. To describe the daily THS Tobacco Stick/CC consumption over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoint:

   - Number of THS Tobacco Sticks and CC used each day for each subject from Day 1 to Day 5.

Confidentiality Statement

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

Exploratory Objectives:

1. To describe the following parameters in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and smokers switching from CC to SA:

   Endpoints:

   - Ames mutagenicity test (YG1024+S9).
   - The total score, Factor 1 (relief) and Factor 2 (reward) from Questionnaire of Smoking Urges (brief version [QSU-brief]).
   - The total scores from Minnesota Nicotine Withdrawal Scale (MNWS).
   - Cytochrome P450 2A6 (CYP2A6 enzymatic activity as a molar ratio of 3-hydroxycotinine and cotinine)
   - Selected risk markers (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine: 8-epi-prostaglandine F2α (8-epi-$PGF_{2\alpha}$) and 11-dehydrothromboxane B2 (11-DTX-B2).

2. To evaluate in smokers switching from CC to THS 2.2, smokers continuing to smoke CC and smokers switching from CC to SA the relationship between:

   Endpoints:

   - Primary and secondary BoExp and NEQ.
   - Selected risk markers (8-epi-$PGF_{2\alpha}$ and 11-DTX-B2) and NEQ.

3. To describe the following parameters over the course of the study in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC:

   Endpoints:

   Product evaluation as measured with the Modified Cigarette Evaluation Questionnaire (MCEQ):

   - Smoking Satisfaction subscale.
   - Enjoyment of Respiratory Tract Sensation subscale.
   - Psychological Reward subscale.
   - Aversion subscale.
   - Craving Reduction subscale.

4. To describe the following parameter over the course of the study in smokers switching from CC to THS 2.2:

   Endpoints:

   Smoking pattern: human smoking topography (HST) parameters and HST questionnaire.

   - Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.
   - Filter analysis: smoke nicotine in filter and UV absorbance at 310 nm.

Safety:

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.

Adverse events, assessments of physical condition, concomitant medications, vital signs and body measurements, spirometry, respiratory symptoms, electrocardiogram, and monitoring of laboratory values. Device events, including THS 2.2 malfunction/misuse.

6.1.3.4.1.1 Statistical methods

6.1.3.4.1.1.1 Primary Analyses

The primary endpoints, assessed on Day 5 for the comparison of THS 2.2 and CC, were MHBMA, 3-HPMA, S-PMA in 24-hour urine (concentration adjusted to creatinine), and COHb in blood (expressed as % saturation of hemoglobin).

The primary endpoints were log-transformed ($base_e$) prior to analysis. An analysis of covariance (ANCOVA) model was used with terms for the log-transformed Baseline value, sex, and average daily CC consumption over the last 4 weeks as reported during Screening, as well as product.

Exposure to HPHCs is known to be highly variable, with cigarette consumption and sex described as strongest factors, therefore these terms were included in the ANCOVA model. There is a dose-response relationship between cigarette consumption and exposure levels to HPHCs, with higher consumption resulting in higher exposure levels. Male smokers tend to have higher levels of exposure to HPHCs than females. Age was also reported to be a potential factor, with higher levels of exposure with increasing age, however, this effect is limited and might be confounded by longer smoking history and higher cigarette consumption with increasing age. Therefore, age was not included in the model.

The least squares (LS) means and estimate of the difference along with its 95% CI were back-transformed before presenting in the tables. The geometric LS means for each product along with the ratio (THS 2.2:CC) and 95% CI were presented in the tables. The primary analysis was performed on the FAS.

6.1.3.4.1.1.2 Secondary Analyses

The BoExp assessed as secondary endpoints (with the exception of exhaled CO) were analyzed as both adjusted for creatinine and quantity excreted over 24 hours using the same methodology as the primary analysis. The BoExp assessed as primary endpoints were also analyzed as quantity excreted over 24 hours in the same manner. Additionally, BoExp assessed as primary and secondary endpoints were examined to compare THS 2.2 to SA in the same way.

Exhaled CO and CYP1A2, CYP2A6, and subjective effects (mCEQ, QSU-brief and MNWS questionnaires) were analyzed using the same ANCOVA model, but on the natural scale. Least squares means for each product along with the difference (THS 2.2 – CC, and THS 2.2 -SA) and 95% CI were presented in the tables.

The changes from Baseline in nicotine and cotinine plasma concentrations were analyzed using an ANCOVA model with terms for Baseline concentration, sex, average daily CC consumption over the last 4 weeks as reported during Screening, and product use. Least squares means for each product along with the difference (THS 2.2 - CC) and 95% CI were presented.

All figures, summaries, and analyses were performed on the FAS only.

For all endpoints, descriptive statistics of the values and percent change from Baseline (where applicable), and supportive listings were provided.

6.1.3.4.1.2 Study Hypotheses and Evaluation Criteria

The hypothesis to be tested for each of the primary and secondary BoExp was that the geometric mean level on Day 5 of the BoExp for THS 2.2 was lower relative to CC.

The study was considered successful if the study demonstrated a 50% or more reduction in MHBMA, 3-HPMA, S-PMA, and COHb in the THS 2.2 arm compared to the CC arm (as measured on Day 5), using a one-sided test with 2.5% type I error probability.

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.

6.1.3.4.1.3 Summary of Selected Results Relevant for BoExp Assessment

Please refer to section 7.3.1 for full results.

6.1.3.4.1.3.1 BoExp Assessment

The study demonstrated that switching from CC smoking to THS 2.2 use resulted in substantial reductions in BoExp levels to 15 selected HPHCs ranging from -56% to -94%, while maintaining comparable levels of nicotine (Figure 1 and Table 1). 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 (Figure 2 and Table 2). S-BMA levels did not show any difference in levels across all study arms.

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.

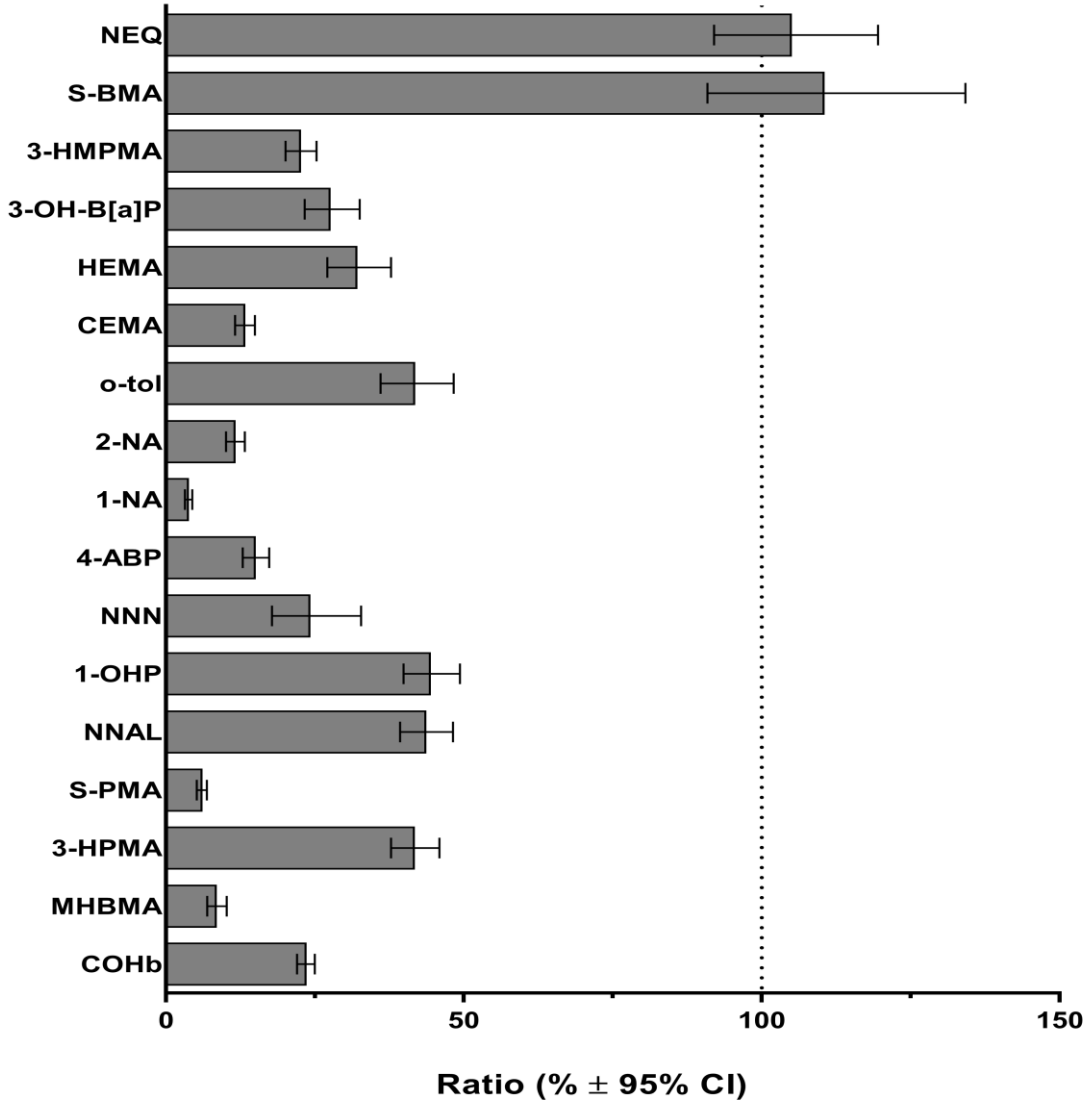


Figure 1 Adjusted Geometric LS Means and CIs from an ANCOVA Model of THS to CC ratios of BoExp Levels at Day 5

Abbreviations: analysis of covariance (ANCOVA), 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, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy(a)benzopyrene (3-OH-B[a]P), 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), least squares (LS).

Confidentiality Statement

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

Table 1 Analysis of BoExp in ZRHR-REXC-03-EU at Day 5

BoExp	HPHCs [aerosol phase]	ZRHR-REXC-03-EU		
COHb	CO [gas]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	23.45% 22.00; 24.99 <0.001
MHBMA	1,3-Butadiene [gas]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	8.38% 6.89; 10.20 <0.001
3-HPMA	Acrolein [gas]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	41.63% 37.75; 45.91 <0.001
S-PMA	Benzene [gas]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	5.99% 5.21; 6.87 <0.001
Total NNAL	NNK [particulate]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	43.54% 39.34; 48.19 <0.001
Total 1-OHP	Pyrene [particulate]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	44.35% 39.88; 49.33 NA
Total NNN	NNN [particulate]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	24.12% 17.76; 32.75 NA
4-ABP	4-Aminobiphenyl [particulate]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	14.94% 12.89; 17.33 NA
1-NA	1-Aminonaphthalene [particulate]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	3.73% 3.15; 4.42 NA
2-NA	2-Aminonaphthalene [particulate]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	11.54% 10.08; 13.21 NA
o-toluidine	*o*-Toluidine [gas]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	41.70% 36.01; 48.29 NA
CEMA	Acrylonitrile [gas]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	13.16% 11.58; 14.95 NA
HEMA	HEMA [particulate]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	32.00% 27.10; 37.79 NA
3-OH-B[a]P	Benzo[a]pyrene [particulate]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	27.50% 23.25; 32.52 NA
3-HMPMA	Crotonaldehyde [gas]	THS:CC Ratio	Geometric LS Mean 95% CI p Value	22.54% 20.10; 25.29 NA

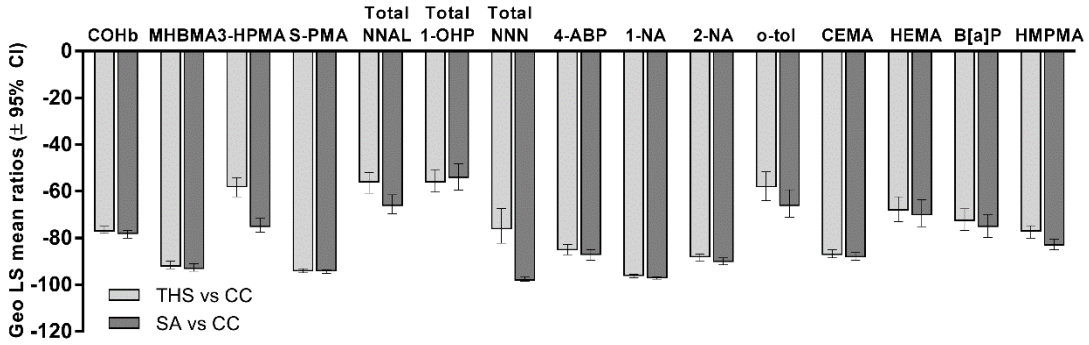
Confidentiality Statement

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.

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 (total 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 (3-OH-B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), Tobacco Heating System (THS), conventional cigarette (CC), not applicable (NA), smoking abstinence (SA), least squares (LS), confidence intervals (CI).

Data Source:
Primary Endpoints: Clinical Study Report section 11.1 and Appendix 15, Table 15.2.3.1 to Table 15.2.3.4
Secondary Endpoints: Clinical Study Report section 11.2 and Appendix 15, Table 15.2.4.6 to Table 15. 2.4.34

Figure 2 Reduction of BoExp in ZRHR-REXC-03-EU at Day 5 (THS:CC and SA:CC in %)



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 (total 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 (B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), seast squares (LS), confidence intervals (CI).

Table 2 Reduction of BoExp in ZRHR-REXC-03-EU at Day 5 [100- (THS:CC) ratio and 100- (SA:CC) ratio in %]

BoExp	HPHCs [aerosol phase]		Reduction at Day 5	95% CI
COHb (%)	CO [gas]	THS:CC	-77%	-78 ; -75
		SA:CC	-78%	-79.9 ; -76.7
MHBMA (pg/mg creat)	1,3-Butadiene [gas]	THS:CC	-92%	-93.1 ; -89.8
		SA:CC	-93%	-94.2 ; -90.9
3-HPMA (ng/mg creat)	Acrolein [gas]	THS:CC	-58%	-62.2 ; -54.1
		SA:CC	-75%	-77.4 ; -71.6

Confidentiality Statement

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

S-PMA (pg/mg creat)	Benzene [gas]	THS:CC	-94%	-94.8 ; -93.1
		SA:CC	-94%	-95.2 ; -93.4
Total NNAL (pg/mg creat)	NNK [particulate]	THS:CC	-56%	-60.7 ; -51.8
		SA:CC	-66%	-69.6 ; -61.5
Total 1-OHP (pg/mg creat)	Pyrene [particulate]	THS:CC	-56%	-60.1 ; -50.7
		SA:CC	-54%	-59.4 ; -48.1
Total NNN (pg/mg creat)	NNN [particulate]	THS:CC	-76%	-82.2 ; -67.3
		SA:CC	-98%	-98.3 ; -96.5
4-ABP (pg/mg creat)	4-Aminobiphenyl [particulate]	THS:CC	-85%	-87.1 ; -82.7
		SA:CC	-87%	-89.4 ; -85
1-NA (pg/mg creat)	1-Aminonaphthalene [particulate]	THS:CC	-96%	-96.8 ; -95.6
		SA:CC	-97%	-97.6 ; -96.5
2-NA (pg/mg creat)	2-Aminonaphthalene [particulate]	THS:CC	-88%	-89.9 ; -86.8
		SA:CC	-90%	-91.5 ; -88.4
o-tol (pg/mg creat)	*o*-Toluidine [gas]	THS:CC	-58%	-64 ; -51.7
		SA:CC	-66%	-71 ; -59.2
CEMA (ng/mg creat)	Acrylonitrile [gas]	THS:CC	-87%	-88.4 ; -85.1
		SA:CC	-88%	-89.6 ; -86
HEMA (pg/mg creat)	HEMA [particulate]	THS:CC	-68%	-72.9 ; -62.2
		SA:CC	-70%	-75.1 ; -63.4
B[a]P (fg/mg creat)	Benzo[a]pyrene [particulate]	THS:CC	-73%	-76.7 ; -67.5
		SA:CC	-75%	-79.7 ; -70.1
HMPMA (ng/mg creat)	Crotonaldehyde [gas]	THS:CC	-77%	-79.9 ; -74.7
		SA:CC	-83%	-85.1 ; -80.6

Abbreviations: monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3 HPMA), S-phenylmercapturic acid (S-PMA), carboxyhemoglobin (COHb), carbon monoxide (CO), Total 1-hydroxypyrene (1-OHP), Total N-nitrosonornicotine (NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), o-toluidine, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy(a)benzopyrene (3-OH-B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (3 HMPMA), S-benzylmercapturic acid (S-BMA), Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), 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).

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.

Xenobiotic Metabolism:

The CYP1A2 enzymes are monooxygenases, which are involved in the activation of carcinogenic heterocyclic and aromatic amines, strong carcinogens associated with colon and bladder cancer. The expression of CYP1A2 itself is induced by polycyclic aromatic hydrocarbons (PAH), which are found in cigarette smoke.

At Baseline, CYP1A2 activity was comparable between study arms (range of 110% to 113%). In the THS 2.2 and SA arms at Day 5, CYP1A2 activity had decreased by approximately 17% and 15%, respectively, while in the CC arm, CYP1A2 activity increased by approximately 13%. This resulted in differences in absolute and change from Baseline CYP1A2 activity (THS 2.2 - CC) of -34% (95% CI: -41, -27). There was no notable difference in absolute CYP1A2 activity on Day 5 or change from Baseline in CYP1A2 activity between subjects who switched to THS 2.2 use and subjects who abstained from smoking. These results are in line with what is reported in the literature and are likely to be linked to the overall reduction of exposure to PAH. Overall, the results are indicative of a reduction of harmful metabolites resulting in reduced CYP1A2 activity after THS 2.2 use and SA.

Data Source:
Clinical Study Report section 11.2.5 Table 67, 68 and Appendix 15, Table 15.2.4.49-52.

Mutagenicity:

At Baseline, median Ames mutagenicity test values were comparable between the THS 2.2 and SA arms (19.68 and 22.54 Rev/24h, respectively) and slightly lower in the CC arm (15.78 Rev/24h). On Day 5, in the THS 2.2 and SA arms, median Ames mutagenicity test values had decreased by approximately 57% and 62%, respectively, while in the CC arm, median Ames mutagenicity test values increased by approximately 29%. This decrease in urinary mutagenicity can be considered as the result of the exposure reduction achieved when switching from CC to THS 2.2 use.

Data Source:
Clinical Study Report section 11.3.1 Table 69 and Appendix 15, Table 15.2.4.42

Nicotine Exposure over Time:

The profiles were comparable for the THS 2.2 and CC arms, with the exception of a decrease in NEQ levels on Days 1 and 2 in the THS 2.2 arm. In the THS 2.2 arm, geometric mean NEQ values increased from Baseline (9.01 mg/g creat) to Day 5 (10.60 mg/g creat) while the results from the CC arm were comparable with those of the THS 2.2 arm, and showed an increase in NEQ from Baseline (8.69 mg/g creat) to Day 5 (9.76 mg/g creat). These values correspond to percent changes from Baseline of 22.95% and 14.78% for the THS 2.2 and CC arms, respectively. In the SA arm, NEQ values decreased from Baseline (9.53 mg/g creat) to Day 5 (0.14 mg/g creat), as expected, which corresponded to a -98.25% change from Baseline (Figure 3).

On Day 5, both the NEQ urinary concentration adjusted for creatinine (mg/g creat) and the quantity excreted over 24 hours (mg) were comparable between subjects who switched to THS 2.2 and subjects who continued to smoke CC (Table 3).

Confidentiality Statement

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

The nicotine plasma concentration profiles were comparable for the THS 2.2 and CC arms, with similar mean nicotine concentrations reported on all days except on Day 1 when the nicotine plasma concentration in the THS 2.2 arm (9.52 ng/mL) was lower than that of the CC arm (12.28 ng/mL). In the SA arm, mean nicotine concentrations were comparable to those of the other study arms at Baseline before decreasing to 0.29 ng/mL at Day 1 and remained low for the remainder of the study.

For cotinine, similar mean plasma cotinine concentrations were reported at Baseline (208.54 and 211.26 ng/mL, in THS and CC respectively) and on Day 5 (224.82 ng/mL and 204.69 ng/mL in THS and CC respectively).

For both nicotine and cotinine exposure on Day 5, peak and weighted average plasma concentrations, there were no notable differences between the THS 2.2 and CC arms. The time to peak concentration on Day 5 was identical for the THS 2.2 and CC arms for both nicotine and cotinine.

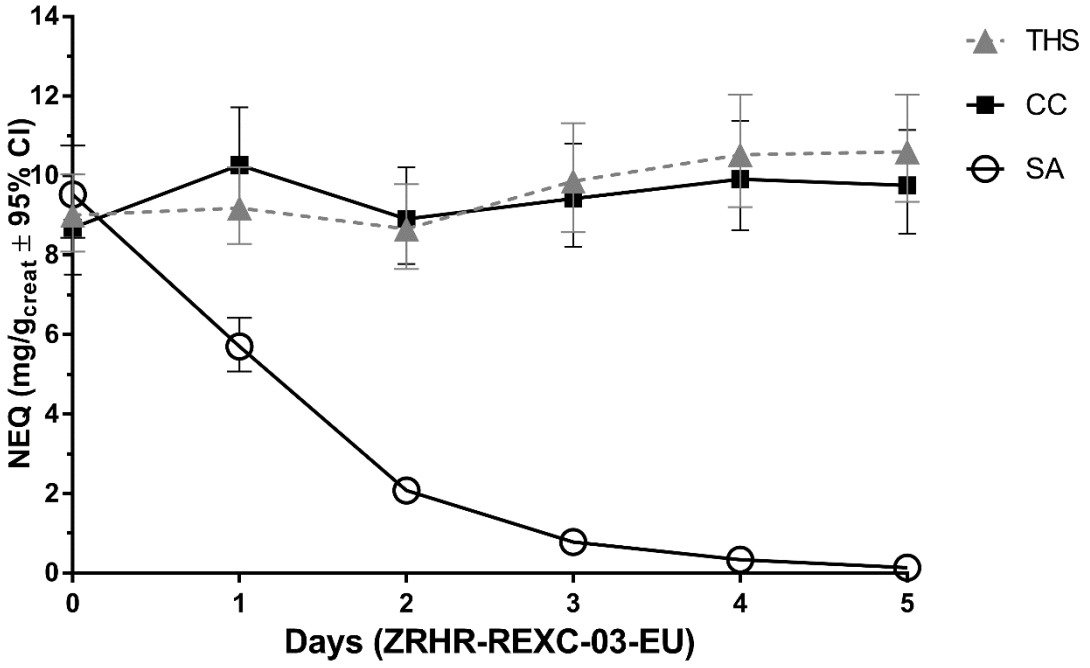


Figure 3 Geometric Mean NEQ Urinary Concentration Adjusted for Creatinine During the Course of the Study (PP Population)

Abbreviations: Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, nicotine equivalents adjusted to creatinine (NEQ_{adjC}), creatinine (creat), per protocol set (PP), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI).

Confidentiality Statement

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

Table 3 Analysis of NEQ versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	N	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours (mg)	THS 2.2	79	15.30	102.80	0.082	87.50, 120.78
	CC	41	14.89			
Concentration adjusted for creatinine (mg/g creat)	THS 2.2	79	10.61	104.89	0.067	92.03, 119.55
	CC	41	10.12			

Abbreviations: Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, conventional cigarette (CC), CI = confidence interval (CI), standard error (SE), LS = least squares (LS), number of subjects (N), Tobacco Heating System 2.2 (THS 2.2) full analysis set (FAS).

Data Source:
NEQ: Clinical Study Report section 11.2.4.2, Table 56 and Appendix 15, Table 15.2.4.33 and Appendix 15, Table 15.2.4.34
Nicotine: Clinical Study Report section 11.2.4.2.1, Table 57 and Appendix 15, Table 15.2.4.41 and Appendix 15, Table 15.2.4.39
Cotinine: Clinical Study Report section 11.2.4.2.2, Table 60 and Appendix 15, Table 15.2.4.41 and Appendix 15, Table 15.2.4.40

Product Use:

In the THS 2.2 arm, the mean number of THS Tobacco Sticks consumed daily initially decreased from the number of CC smoked at Baseline (16 cigarettes/day) to Day 1 before starting to increase over Day 2 to Day 5 (21 THS Tobacco Sticks/day). In the CC arm, the mean number of CC consumed daily initially decreased from Baseline (16 cigarettes/day) to Day 1, before increasing over Day 2 to Day 5, and was comparable to the Baseline value at Day 5 (17 cigarettes/day). On Day 1 to Day 5, subjects in the THS 2.2 arm consumed more THS Tobacco Sticks than the number of CC smoked in the CC arm and the average daily product use between Baseline and the end of the exposure period increased by approximately 30% in the THS 2.2 arm, and remained in the same range in the CC arm (Figure 4 and Table 4). Despite differences in product use, the exposure to nicotine was similar between the THS 2.2 and CC arms throughout the exposure period. These results suggest a transitional adaptation after switching to a new product with different characteristics in terms of nicotine yield, taste, sensory and ritual, compared to the subjects own brand of CC, to achieve the levels of nicotine desired by the THS 2.2 user. More importantly, the increase in product use in the THS 2.2 did not affect the reduction in exposure to HPHCs.

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.

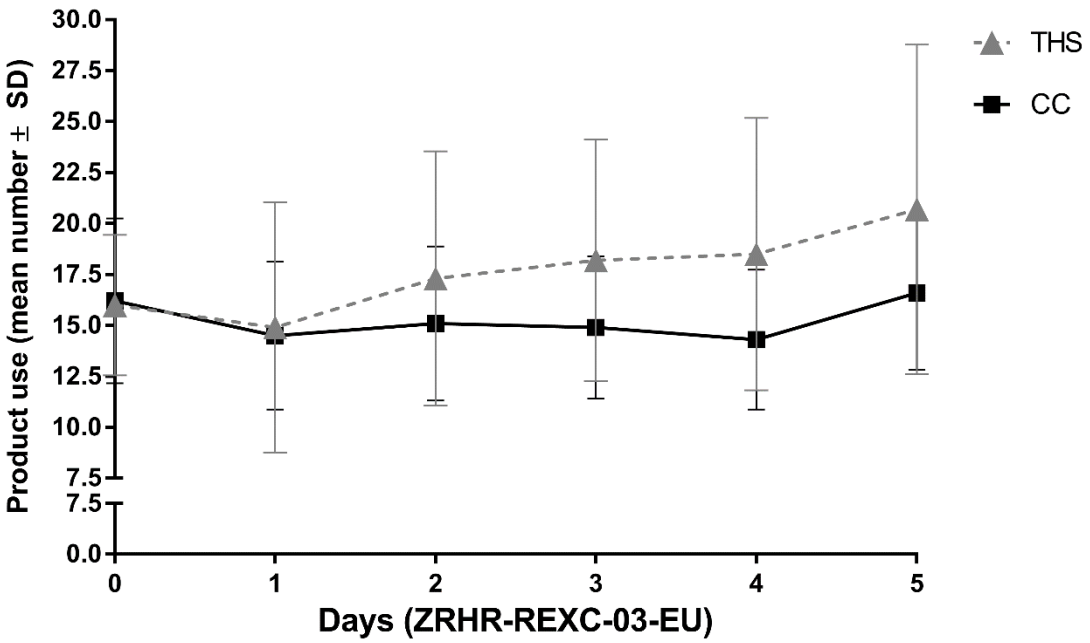


Figure 4 Product Consumption (Number of products used) from Baseline to Day 5

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC); standard deviation (SD)

Confidentiality Statement

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

Table 4 Number of THS Tobacco Sticks and Conventional Cigarettes Consumed Daily (Safety Population)

Study Arm	Visit	N	Mean (SD)	Min	Median	Max
THS 2.2	Day 0 (Baseline, CC use)	80	16.0 (3.45)	9	16.0	33
	Day 1	80	14.9 (6.14)	5	14.0	50
	Day 2	80	17.3 (6.25)	6	17.0	40
	Day 3	80	18.2 (5.94)	6	17.0	38
	Day 4	79	18.5 (6.69)	9	17.0	50
	Day 5	79	20.7 (8.09)	9	20.0	60
CC	Day 0 (Baseline)	41	16.2 (4.05)	10	16.0	32
	Day 1	41	14.5 (3.63)	6	14.0	22
	Day 2	41	15.1 (3.79)	8	15.0	24
	Day 3	41	14.9 (3.49)	8	15.0	22
	Day 4	41	14.3 (3.43)	8	14.0	21
	Day 5	41	16.6 (3.79)	10	16.0	26

Abbreviations: conventional cigarette (CC), maximum (Max), minimum (Min), number of subjects (N), standard deviation (SD), Tobacco Heating System 2.2 (THS 2.2)

Data Source:
Clinical Study Report section 10.5, Table 24 and Appendix 15, Table 15.2.2.1

Human Puffing Topography (HPT):

Baseline values for each assessed HPT parameter were comparable between the THS 2.2 and the CC arms while subjects were using their usual brand of CC. In the CC arm, the values for all parameters were stable between Baseline and Day 1, and between Day 1 and Day 4.

In the THS 2.2 arm, values for total number of puffs, total puff volume and average puff volume were stable from Baseline (CC use) to Day 4. Average puff duration, total puff duration, and puff frequency increased from Baseline to Day 1, while average inter puff interval and total smoking duration decreased from Baseline to Day 1.

For each study arm, the majority of mean values for each smoking parameter were comparable on Day 1 and Day 4, with no apparent differences between THS 2.2 and CC use in the total number of puffs, total puff volume, and average puff volume on both Day 1 and Day 4 (Table 5). Average puff duration, total puff duration and puff frequency were all greater for THS 2.2 use compared to CC use on both Day 1 and Day 4. Average inter puff interval and total smoking duration were all lower for THS 2.2 use compared to CC use.

In summary, the HPT parameters assessed indicated that THS 2.2 users were taking a similar number of puffs and puff volume compared to CC, but adapted to the product by taking longer puffs, thus shortening the interpuff interval, and increasing the puffing time index. Similar to the change in product use, this change in puffing topography is part of an adaptation process to THS 2.2 use.

Confidentiality Statement

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

Table 5 Analysis of HPT Parameters (Averaged over All Cigarettes per Day) (FAS Population)

Variable (units)	Time Point	Product Exposure	N	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	CV (%)	95% CI
Total number of puffs	Day 1	THS 2.2	55	16.53	103.06	18.49	94.26, 112.70
		CC	27	16.04			
	Day 4	THS 2.2	55	16.06	97.14	17.08	89.42, 105.53
		CC	27	16.53			
Total puff volume (mL)	Day 1	THS 2.2	55	766.65	109.53	30.67	94.73, 126.64
		CC	27	699.95			
	Day 4	THS 2.2	55	791.70	105.26	27.10	92.59, 119.65
		CC	27	752.16			
Average puff volume (mL)	Day 1	THS 2.2	55	46.29	101.55	24.54	90.61, 113.80
		CC	27	45.59			
	Day 4	THS 2.2	55	49.44	105.50	21.22	95.55, 116.48
		CC	27	46.87			
Average puff duration (s)	Day 1	THS 2.2	55	1.89	126.07	19.04	115.33, 137.81
		CC	27	1.50			
	Day 4	THS 2.2	55	1.98	132.25	20.38	120.24, 145.46
		CC	27	1.49			
Total puff duration (s)	Day 1	THS 2.2	55	31.55	136.09	26.96	119.89, 154.47
		CC	27	23.19			
	Day 4	THS 2.2	55	32.21	137.33	29.94	119.35, 158.03
		CC	27	23.45			
Average inter puff interval (s)	Day 1	THS 2.2	55	10.26	68.24	29.37	59.20, 78.68
		CC	27	15.03			
	Day 4	THS 2.2	55	9.85	67.83	26.88	59.51, 77.31
		CC	27	14.52			
Total smoking duration (s)	Day 1	THS 2.2	55	205.27	80.39	21.10	72.80, 88.77
		CC	27	255.35			
	Day 4	THS 2.2	55	194.84	77.64	22.79	69.77, 86.41
		CC	27	250.94			
Puff frequency (puffs/min)	Day 1	THS 2.2	55	5.08	131.32	23.76	116.97, 147.43
		CC	27	3.87			
	Day 4	THS 2.2	55	5.29	132.33	23.0	118.25,

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.

	CC	27	4.00		4	148.09

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed Baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

Abbreviations: analysis of covariance (ANCOVA), full analysis set (FAS), conventional cigarette (CC); confidence interval (CI); coefficient of variation (CV); least squares (LS), number of subjects (N), Tobacco Heating System 2.2 (THS 2.2).

Data Source
Clinical Study Report section 11.3.5, Table 16 and Appendix 15, Table 15.2.4.59

Subjective Effects:

The present study included endpoints to assess the overall satisfaction, to evaluate if THS 2.2 could be an acceptable substitute to CC. The results of the QSU-brief showed a similar reduction in urge-to smoke for THS 2.2 compared to CC and clearly different results from what was observed during SA, where the urge-to-smoke increased from Baseline to Day 1 before decreasing slowly from Day 1 to Day 5 (Figure 5).

Similar results were observed for withdrawal symptoms in the different study arms as assessed by the MNWS, where no apparent differences between subjects who switched to THS 2.2 and smokers who continued to smoke CC were observed. The MCEQ scale evaluated the overall satisfaction of THS 2.2 users compared to CC smokers, and showed that craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction were all lower; while aversion was higher for subjects who switched to THS 2.2 compared to subjects who continued to smoke CC (Figure 6).

The change in taste, sensorial experience, ritual, and differences in the ISO nicotine yield of THS 2.2, are likely additional reasons for the observed differences in overall satisfaction.

Nevertheless, overall subjective appreciation measures illustrate that THS 2.2 offered a close experience to what was observed in CC smokers. Different patterns observed for the corresponding domains in the SA arm tend to substantiate these observations. Further studies will determine if a longer time for adapting to THS 2.2 will further close the gap in perceived subjective effects.

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.

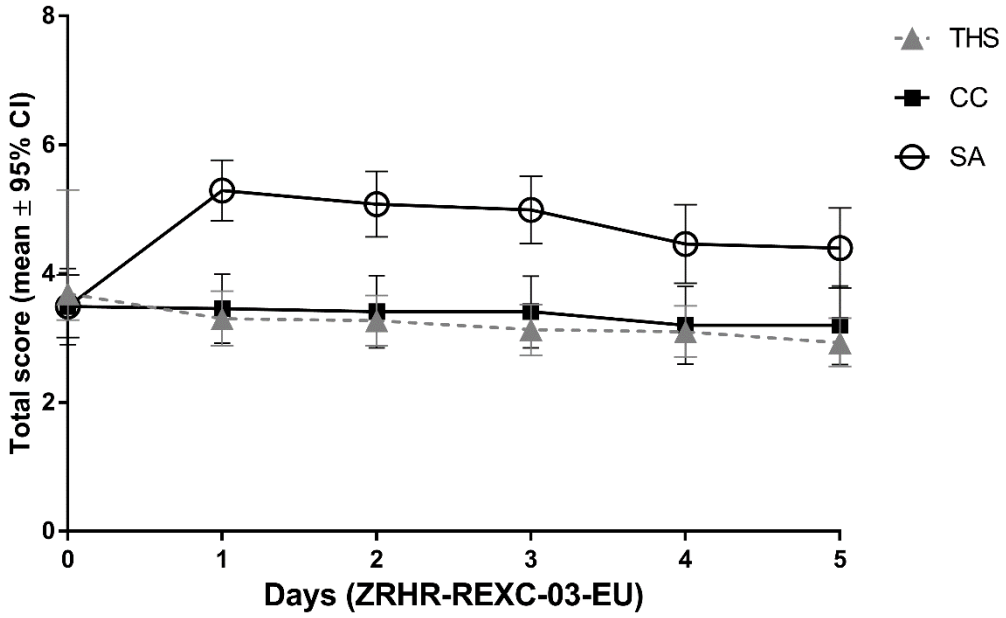


Figure 5 Total Score – Questionnaire of Smoking Urges from Baseline to Day 5

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI)

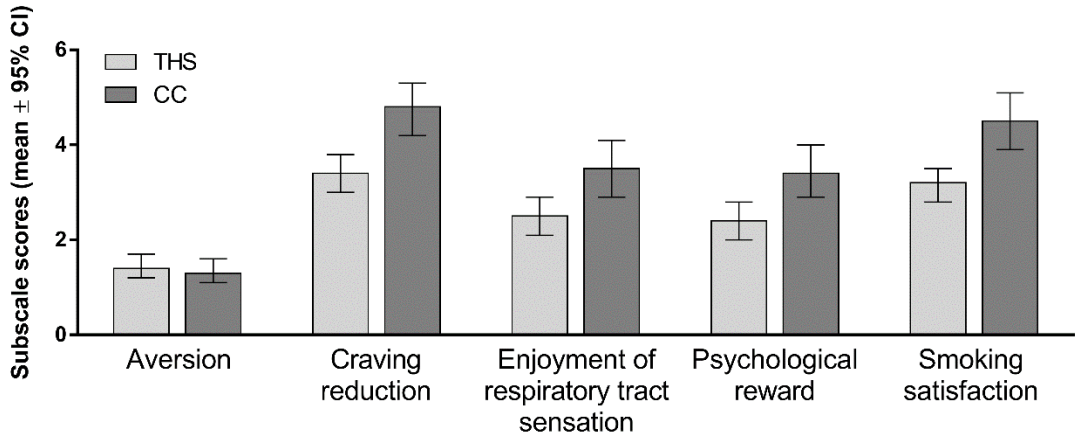


Figure 6 MCEQ Subscales on Day 5

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), confidence intervals (CI)

Data Source:
QSU: Clinical Study Report section 11.3.4.1, Table 76 and Appendix 15, Table 15.2.4.43
MNWS: Clinical Study Report section 11.3.4.2, Table 77 and Appendix 15, Table 15.2.4.46

MCEQ: Clinical Study Report section 11.3.4.3, Table 78 and Appendix 15, Table 15.2.4.48

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.

Clinical Risk Endpoints:

At Baseline, the concentration of 8-epi-PGF2α adjusted for creatinine was comparable between study arms (geometric mean range of 189.93 to 209.01 pg/mg creat). At Day 5, the levels of 8-epi-PGF2α concentration adjusted for creatinine were 236.11, 232.76, and 241.95 pg/mg creat (an increase from Baseline of approximately 15%, 25%, and 28%) in the THS 2.2, CC, and SA arms, respectively and no notable differences observed in both the urinary concentration of 8-epi-PGF2α adjusted for creatinine and the quantity excreted over 24 hours between all study groups.

The concentration of 11-DTX-B2 adjusted for creatinine was comparable in the CC and SA arms (geometric mean values of 467.88 and 468.61 pg/mg creat, respectively) and was higher in the THS 2.2 arm (536.12 pg/mg creat) at Baseline. At Day 5, the 11-DTX-B2 adjusted for creatinine was comparable to the Baseline value in the THS 2.2 and SA arms (approximately a 1% increase and 3% decrease, respectively), and had increased to 565.18 pg/mg creat (an increase from Baseline of approximately 30%) in the CC arm.

For both markers, results for the quantity excreted over 24 hours showed a comparable trend.

On Day 5, the LS mean level of the concentration of 11-DTX-B2 adjusted for creatinine in subjects who switched to THS 2.2 use was 16.37% lower than that of subjects who continued to smoke CC (95% CI: 9.54, 22.69) and 10.07% higher than that of subjects who abstained from smoking (95% CI: 101.22, 119.70). The results for the quantity of 11-DTX-B2 excreted over 24 hours were consistent with the results of the concentration adjusted for creatinine, with an 18.74% decrease in subjects who switched to THS 2.2 compared to subjects who continued to smoke CC (95% CI: 9.34, 27.17). There was no notable difference observed in the quantity of 11-DTX-B2 excreted over 24 hours between subjects who switched to THS 2.2 and subjects who abstained from smoking, with the 95% CIs spanning 100%.

Data Source:
11-DTX-B2: Clinical Study Report section 11.3.3.1, Table 73 and Appendix 15, Table 15.2.4.55
8-epi-$PGF_{2\alpha}$: Clinical Study Report section 11.3.3.2, Table 72 and Appendix 15, Table 15.2.4.54

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.

Safety:

There were no SAEs reported in this study and no randomized subjects discontinued from the study due to an AE. Overall, there were 227 AEs reported by 112 of the 169 subjects (66.3%) in the Safety population, most of which were mild or moderate in severity. Only 1 severe AE was reported which occurred in the CC arm, and was not considered to be related to investigational product (IP) or study procedures. The incidence and frequency of AEs were comparable in the THS 2.2 (98 AEs in 50/80 subjects [62.5%]), the CC (63 AEs reported by 29/41 [70.7%] subjects), and the SA arms (49 AEs in 24/39 [61.5%] subjects). The most frequent AEs after THS 2.2 or CC exposure were headache, oropharyngeal pain, syncope, polyuria, and spirometry abnormal. The most frequent AEs after SA were headache, back pain, influenza-like illness, spirometry abnormal, abdominal distension, hypertriglyceridemia, polyuria, hypertension, and vertigo. Only 26 of the 227 reported AEs were assessed as being related to THS 2.2 or CC use and were reported by 23 of the 130 subjects in the THS 2.2 and CC arms and by subjects enrolled but not randomized (17.7%). The incidence of AEs assessed as related to IP use was comparable for the THS 2.2 (14/80 subjects [17.5%]) and CC arms (7/41 subjects [17.1%]). The most frequent AEs assessed as related to IP use were spirometry abnormal, syncope, COHb increased, cough, and vertigo. All other AEs assessed as related to IP use were reported by single subjects in the THS 2.2 arm only.

During THS 2.2 use, 12 subjects experienced a total of 19 device events or malfunctions which led to the replacement of the THS Tobacco Stick Holder or Charger. None of these events led to an AE.

Data Source:
Summary of AEs: Clinical Study Report section 12.1.1, Table 81 and Appendix 15, Table 15.2.6.1 and Table 15.2.6.5
AEs by study arm, SOC and PT: Clinical Study Report section 12.1.2 by study arm in Table 82 and in Appendix 15, Table 15.2.6.2.1, by SOC in Appendix 15, Table 15.2.6.2.2, and by PT in Appendix 15, Table 15.2.6.2.3

6.1.3.4.1.4 Conclusion

- The study demonstrated that switching from CC smoking to THS 2.2 use resulted in substantial reductions in exposure to 15 selected HPHCs. 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.
- Exposure to nicotine was similar between the THS 2.2 and CC arms, and patterns of product use behavior (number of products used and HPT) indicating that users adapt quickly to the new product and achieve their individual nicotine levels.
- The combination of the results of nicotine-exposure, and subjective effects measures indicated that THS 2.2 offers comparable satisfaction to what was observed in CC smokers.
- No SAEs and 1 severe AE (occurring in the CC arm) were reported during this study, with the total number of AEs being evenly balanced across study arms.

In summary, this study demonstrated that THS 2.2 reduced exposure to HPHCs close to levels observed when abstaining from smoking, and was acceptable to users with regards to taste, ritual, sensorial experience, and nicotine delivery, which could make it a suitable CC substitute for adult smokers that users could easily adapt to.

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.

6.1.3.4.2 ZRHR-REXC-04-JP

STUDY ZRHR-REXC-04-JP	**Source: Section 7.3.1, Clinical Study Report ZRHR-REXC-04-JP**

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 from conventional cigarettes to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to smokers continuing to use conventional cigarettes for 5 days in Confinement.

Protocol-No.: ZRHR-REXC-04-JP		
Date of final report: 22 July 2015		
Investigators:	Principal Investigator: H Miura, MD	
Study center:	Higashi Shinjuku Clinic, Daito Building 1-11-3 Okubo, Shinjuku-ku, Tokyo, Japan	
Time of clinical part:	23 July 2013 – 09 December 2013	**Clinical Phase:** II (Product Performance)

Objective:

The aim of this study was to demonstrate reduction in exposure to selected HPHCs (except nicotine) in smokers switching to the THS 2.2. THS 2.2 was also compared with smoking abstinence, used as a reference point. Furthermore, exposure to nicotine, product use, subjective effects and changes in Human Puffing Topography over time, in smokers switching from CC to THS 2.2, as compared to smokers continuing to smoke CC were assessed.

Study design:

- Single center
- Ad-libitum use
- Randomized
- Parallel
- Open-label

Confidentiality Statement

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

- 5 Days of Exposure

Subjects:

• Planned:	160 subjects
• Enrolled:	166 subjects
• Randomized:	160 subjects
• Discontinuations:	2 subjects
• Completed:	158 subjects
• Safety population	166 subjects
• Full analysis set (FAS) population	160 subjects
• Per-protocol (PP) population:	160 subjects

Main criteria for inclusion:

- Male or female Japanese from 23 to 65 years of age and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening.
- Spirometry evaluation had to show forced expiratory volume in 1 second {FEV_1}/forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV_1 >80% predicted value, and post-bronchodilator FVC >0.8.
- Subjects were smoking at least 10 commercially available non- menthol CC (CC) per day with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) CC, as labeled on the cigarette package, for the last 4 weeks, and did not plan to quit smoking in the following 3 months. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
- Female subjects of child-bearing potential should have had a confirmed negative pregnancy test and used effective methods of contraception
- Provide written informed consent prior to study participation.
- Able to communicate well with the investigator and comply with the requirements of the study.
- The subject was a current smoker who did not plan to quit smoking in the next 3 months.
- The subject was ready to accept using the THS 2.2 product or to accept 5 days of SA.

THS 2.2:	Product:	Cigarette batch number of THS Tobacco Sticks B-05772 Production date: 11 June 2013. Expiry date: 10 January 2014.
	ISO nicotine Content:	0.5 mg
	Use:	Ad-libitum use
	Manufacturer:	PMI
Conventional Cigarette:	Product:	Own conventional cigarette brand
	ISO nicotine Content:	Maximum yield of 1 mg per CC as per cigarette package label

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.

	Use: Manufacturer:	Ad-libitum use Commercially available non-menthol conventional cigarettes

Smoking Abstinence	Smoking abstinence was used as a reference point without support of Nicotine Replacement Therapy or any drug for smoking cessation support.
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 Methods:	All analytical methods, with the exception of Carboxyhemoglobin (measured by (b) (4)) were developed at (b) (4) , and validated according to the standard operating procedures (SOPs) in effect during the conduct of the validation. These SOPs were written in accordance with the principles of good laboratory practice (GLP) described in 21 Code of Federal Regulation (CFR) Part 58 and the Guidance for Industry – Bioanalytical Method Validation (CDER, May 2001). (b) (b) (4) (b) (4) , (b) (4) . A detailed summary of the description of the analytical methods by BoExp, the matrix used and the validation are described in section 6.1.3.4.

Primary Objective:

1. To demonstrate the reduction of primary biomarkers of exposure (BoExp) in smokers switching from conventional cigarettes (CC) to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoints:

   - Monohydroxybutenylmercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA) (concentration adjusted for creatinine) in 24-hour urine, and carboxyhemoglobin (COHb) in blood (expressed as % saturation of hemoglobin) as measured on Day 5.

Secondary Objectives:

1. To determine the reduction of secondary BoExp on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoints:

   - Quantity excreted in urine over 24 hours for MHBMA, S-PMA, and 3-HPMA.
   - Carbon monoxide ([CO] expressed as ppm) in exhaled breath

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.

- Urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

2. To describe the levels of primary and secondary BoExp over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoints:

   - CO (expressed as ppm) in exhaled breath.
   - COHb in blood (expressed as % saturation of hemoglobin).
   - Primary and secondary urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

3. To determine the levels of nicotine on Day 5 in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC, and to describe their levels over the exposure period from Day 1 to Day 5.

   Endpoints:

   - Nicotine equivalent ([NEQ] expressed in quantity excreted and concentration adjusted to creatinine) in 24-hour urine on Day 5 and from Day 1 to Day 5.
   - Plasma nicotine and cotinine concentrations.

4. To describe the levels of primary, secondary BoExp, and BoExp to nicotine over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers switching from CC to smoking abstinence (SA).

   Endpoints:

   - COHb in blood (expressed as % saturation of hemoglobin).
   - CO (expressed as ppm) in exhaled breath.
   - Primary and secondary urinary BoExp (expressed as quantity excreted and concentration adjusted to creatinine) in 24-hour urine.

5. To describe the pharmacokinetic (PK) profiles of the nicotine and cotinine in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoints:

   - Peak (highest concentration value along the day) on Day 5 in plasma.
   - Time to peak (actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
   - Weighted average concentration over 24 hours on Day 5.

6. To describe the changes in cytochrome P450 1A2 (CYP1A2) enzymatic activity on Day 5 in smokers switching from CC to THS 2.2, switching from CC to SA, and continuing to smoke CC.

   Endpoint:

   - Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5.

Confidentiality Statement

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

7. To describe the daily THS Tobacco Stick/CC consumption over the exposure period in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC.

   Endpoint:

   - Number of THS Tobacco Sticks and CC used each day for each subject from Day 1 to Day 5.

Exploratory Objectives:

1. To describe the following parameters in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC and smokers switching from CC to SA:

   Endpoints:

   - Ames mutagenicity test (YG1024+S9).
   - The total score, Factor 1 (relief) and Factor 2 (reward) from Questionnaire of Smoking Urges (brief version [QSU-brief]).
   - The total scores from Minnesota Nicotine Withdrawal Scale (MNWS).
   - Cytochrome P450 2A6 (CYP2A6 enzymatic activity as a molar ratio of 3-hydroxycotinine and cotinine
   - Selected risk markers (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine: 8-epi-prostaglandine F2α (8-epi-$PGF_{2\alpha}$) and 11-dehydrothromboxane B2 (11-DTX-B2).

2. To evaluate in smokers switching from CC to THS 2.2, smokers continuing to smoke CC and smokers switching from CC to SA the relationship between:

   Endpoints:

   - Primary and secondary BoExp and NEQ.
   - Selected risk markers (8-epi-$PGF_{2\alpha}$ and 11-DTX-B2) and NEQ.

3. To describe the following parameters over the course of the study in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC:

   Endpoints:

   Product evaluation as measured with the Modified Cigarette Evaluation Questionnaire (MCEQ):

   - Smoking Satisfaction subscale.
   - Enjoyment of Respiratory Tract Sensation subscale.
   - Psychological Reward subscale.
   - Aversion subscale.
   - Craving Reduction subscale.

Confidentiality Statement

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

4. To describe the following parameter over the course of the study in smokers switching from CC to THS 2.2:

   Endpoints:

   Smoking pattern: human smoking topography (HST) parameters and HST questionnaire.

   - Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.

Safety:

Adverse events, assessments of physical condition, concomitant medications, vital signs and body measurements, spirometry, respiratory symptoms, electrocardiogram, and monitoring of laboratory values. Device events, including THS 2.2 malfunction/misuse.

6.1.3.4.2.1 Statistical methods

6.1.3.4.2.1.1 Primary Analyses

The primary endpoints, assessed on Day 5 for the comparison of THS 2.2 and CC, were MHBMA, 3-HPMA, S-PMA in 24-hour urine (concentration adjusted to creatinine), and COHb in blood (expressed as % saturation of hemoglobin).

The primary endpoints were log-transformed ($base_e$) prior to analysis. An analysis of covariance (ANCOVA) model was used with terms for the log-transformed Baseline value, sex, and average daily CC consumption over the last 4 weeks as reported during Screening, as well as product.

Exposure to HPHCs is known to be highly variable with cigarette consumption and sex described as strongest factors, therefore these terms were included in the ANCOVA model. There is a dose-response relationship between cigarette consumption and exposure levels to HPHCs, with higher consumption resulting in higher exposure levels. Male smokers tend to have higher levels of exposure to HPHCs than females. Age was also reported to be a potential factor, with higher levels of exposure with increasing age, however this effect is limited and might be confounded by longer smoking history and higher cigarette consumption with increasing age. Therefore age was not included in the model.

The least squares (LS) means and estimate of the difference along with its 95% CI were back-transformed before presenting in the tables. The geometric LS means for each product along with the ratio (THS 2.2:CC) and 95% CI were presented in the tables. The primary analysis was performed on the FAS.

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.

6.1.3.4.2.1.2 Secondary Analyses

The BoExp assessed as secondary endpoints (with the exception of exhaled CO) were analyzed as both adjusted for creatinine and quantity excreted over 24 hours using the same methodology as the primary analysis. The BoExp assessed as primary endpoints were also analyzed as quantity excreted over 24 hours in the same manner. Additionally, BoExp assessed as primary and secondary endpoints were examined to compare THS 2.2 to SA in the same way.

Exhaled CO, CYP1A2, CYP2A6 and subjective effects (mCEQ, QSU-brief and MNWS questionnaires) were analyzed using the same ANCOVA model, but on the natural scale. Least squares means for each product along with the difference (THS 2.2 – CC, and THS 2.2 -SA) and 95% CI were presented in the tables.

The changes from Baseline in nicotine and cotinine plasma concentrations were analyzed using an ANCOVA model with terms for Baseline concentration, sex, average daily CC consumption over the last 4 weeks as reported during Screening, and product. Least squares means for each product along with the difference (THS 2.2 - CC) and 95% CI were presented.

All figures, summaries, and analyses were performed on the FAS only.

For all endpoints, descriptive statistics of the values and percent change from Baseline (where applicable), and supportive listings were provided.

6.1.3.4.2.2 Study Hypotheses and Evaluation Criteria

The hypothesis to be tested for each of the primary and secondary BoExp is that the geometric mean level on Day 5 of the BoExp for THS 2.2 was lower relative to CC.

The study was considered successful if the study demonstrated a 50% or more reduction in MHBMA, 3-HPMA, S-PMA, and COHb in the THS 2.2 arm compared to the CC arm (as measured on Day 5), using a one-sided test with 2.5% type I error probability.

6.1.3.4.2.3 Summary of selected results relevant for BoExp Assessment

Please refer to section 7.3.1 for full results.

6.1.3.4.2.3.1 BoExp Assessment

The study demonstrated that switching from CC smoking to THS 2.2 use resulted in substantial reductions in BoExp levels to 15 selected HPHCs, ranging from -47% to -96%, while maintaining comparable levels of nicotine (Figure 7 and Table 6). 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. S-BMA levels did not show any difference in levels across all study arms (Figure 8 and Table 7).

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.

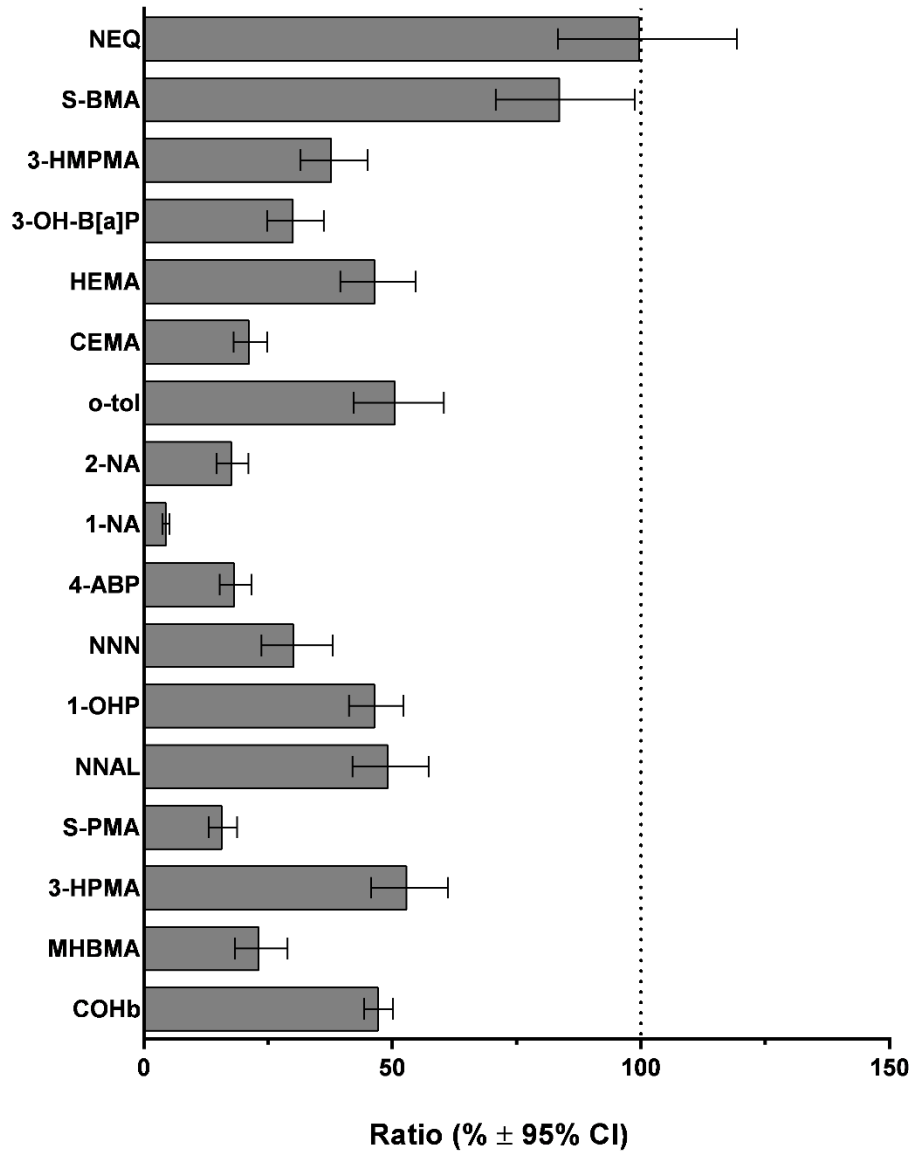


Figure 7 Adjusted Geometric LS Means and CIs from an ANCOVA Model of THS to CC ratios of BoExp Levels at Day 5

Abbreviations: analysis of covariance (ANCOVA), 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, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy(a)benzopyrene (3-OH-B[a]P), 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), least squares (LS).

Table 6 Analysis of BoExp in ZRHR-REXC-04-JP at Day 5

Confidentiality Statement

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

BoExp	HPHCs [aerosol phase]	ZRHR-REXC-04-JP		
COHb	CO [gas]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	47.10% 44.30; 50.08 <0.001
MHBMA	1,3-Butadiene [gas]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	23.09% 18.41; 28.95 <0.001
3-HPMA	Acrolein [gas]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	52.86% 45.67; 61.17 <0.001
S-PMA	Benzene [gas]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	15.68% 13.09; 18.78 <0.001
Total NNAL	NNK [particulate]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	49.03% 41.95; 57.30 <0.001
Total 1-OHP	Pyrene [particulate]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	46.44% 41.32; 52.19 NA
Total NNN	NNN [particulate]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	30.06% 23.74; 38.06 NA
4-ABP	4-Aminobiphenyl [particulate]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	18.21% 15.29; 21.69 NA
1-NA	1-Aminonaphthalene [particulate]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	4.44% 3.80; 5.18 NA
2-NA	2-Aminonaphthalene [particulate]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	17.62% 14.72; 21.08 NA
o-Toluidine	o-Toluidine [gas]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	50.52% 42.28; 60.38 NA
CEMA	Acrylonitrile [gas]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	21.21% 18.10; 24.86 NA
HEMA	HEMA [particulate]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	46.50% 39.53; 54.69 NA
3-OH-B[a]P	Benzo[a]pyrene [particulate]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	29.99% 24.84; 36.20 NA
3-HMPMA	Crotonaldehyde [gas]	THS:C C Ratio	Geometric LS Mean 95% CI p Value	37.71% 31.57; 45.05 NA

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 (total NNAL), total 1-hydroxypyrene (1-OHP), total N-nitrosonornicotine (NNN), 4-aminobiphenyl

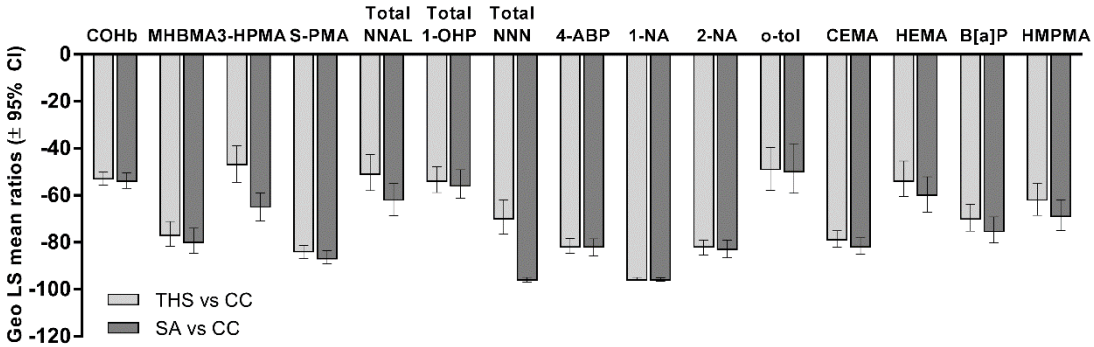
Confidentiality Statement

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

(4-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 (3-OH-B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), seast squares (LS), confidence intervals (CI).

Data Source:
Primary Endpoints: Clinical Study Report section 11.1 and Appendix 15, Table 15.2.3.1 to Table 15.2.3.9.2
Secondary Endpoints: Clinical Study Report section 11.2 and Appendix 15, Table 15.2.4.2 to Table 15.2.4.34

Figure 8 Reduction of BoExp in ZRHR-REXC-04-JP at Day 5 (THS:CC and SA:CC in %)



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 (total 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 (B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), seast squares (LS), confidence intervals (CI).

Table 7 Reduction of BoExp in ZRHR-REXC-04-JP at Day 5 (THS:CC and SA:CC in %)

BoExp	HPHCs [aerosol phase]		Reduction at Day 5	95% CI
COHb (%)	CO [gas]	THS:CC	-53%	-55.7 ; -49.9
		SA:CC	-54%	-57 ; -50.4
MHBMA (pg/mg creat)	1,3-Butadiene [gas]	THS:CC	-77%	-81.6 ; -71.1
		SA:CC	-80%	-84.7 ; -74
3-HPMA (ng/mg creat)	Acrolein [gas]	THS:CC	-47%	-54.3 ; -38.8
		SA:CC	-65%	-70.8 ; -58.9
S-PMA (pg/mg creat)	Benzene [gas]	THS:CC	-84%	-86.9 ; -81.2
		SA:CC	-87%	-89.1 ; -83.4
	NNK [particulate]	THS:CC	-51%	-58 ; -42.7

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.

Total NNAL (pg/mg creat)		SA:CC	-62%	-68.7 ; -55
Total 1-OHP (pg/mg creat)	Pyrene [particulate]	THS:CC	-54%	-58.7 ; -47.8
		SA:CC	-56%	-61.3 ; -49.1
NNN (pg/mg creat)	NNN [particulate]	THS:CC	-70%	-76.3 ; -61.9
		SA:CC	-96%	-97 ; -94.8
4-ABP (pg/mg creat)	4-Aminobiphenyl [particulate]	THS:CC	-82%	-84.7 ; -78.3
		SA:CC	-82%	-85.7 ; -78.5
1-NA (pg/mg creat)	1-Aminonaphthalene [particulate]	THS:CC	-96%	-96.2 ; -94.8
		SA:CC	-96%	-96.4 ; -94.9
2-NA (pg/mg creat)	2-Aminonaphthalene [particulate]	THS:CC	-82%	-85.3 ; -78.9
		SA:CC	-83%	-86.3 ; -79.1
o-tol (pg/mg creat)	*o*-Toluidine [gas]	THS:CC	-49%	-57.7 ; -39.6
		SA:CC	-50%	-59.1 ; -37.9
CEMA (ng/mg creat)	Acrylonitrile [gas]	THS:CC	-79%	-81.9 ; -75.1
		SA:CC	-82%	-84.9 ; -78.1
HEMA (pg/mg creat)	HEMA [particulate]	THS:CC	-54%	-60.5 ; -45.3
		SA:CC	-60%	-67.2 ; -52.1
B[a]P (fg/mg creat)	Benzo[a]pyrene [particulate]	THS:CC	-70%	-75.2 ; -63.8
		SA:CC	-75%	-80.2 ; -69.2
HMPMA (ng/mg creat)	Crotonaldehyde [gas]	THS:CC	-62%	-68.4 ; -55.0
		SA:CC	-69%	-74.9 ; -61.9

Abbreviations: monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3 HPMA), S-phenylmercapturic acid (S-PMA), carboxyhemoglobin (COHb), carbon monoxide (CO), Total 1-hydroxypyrene (1-OHP), Total N-nitrosonornicotine (NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), o-toluidine, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy(a)benzopyrene (3-OH-B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (3 HMPMA), S-benzylmercapturic acid (S-BMA), Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), 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).

Xenobiotic Metabolism:

The CYP1A2 enzymes are monooxygenases, which are involved in the activation of carcinogenic heterocyclic and aromatic amines, strong carcinogens associated with colon and bladder cancer.

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.

The expression of CYP1A2 itself is induced by polycyclic aromatic hydrocarbons (PAH) which are found in cigarette smoke.

At Baseline, CYP1A2 activity was comparable between study arms (range of approximately 78% to 81%). In the THS 2.2 and SA arms at Day 5, CYP1A2 activity had decreased by approximately 27% and 31%, respectively, while in the CC arm, CYP1A2 activity decreased by approximately 1%. This resulted in differences in absolute and change from Baseline CYP1A2 activity (THS 2.2 - CC) of -22% (95% CI: -25, -18 for both absolute and changes from Baseline values). There was no notable difference in absolute CYP1A2 activity on Day 5 or change from Baseline in CYP1A2 activity between subjects who switched to THS 2.2 use and subjects who abstained from smoking. These results are in line with what is reported in the literature and are likely to be linked to the overall reduction of exposure to PAH. Overall, the results are indicative of a reduction of harmful metabolites resulting in reduced CYP1A2 activity after THS 2.2 use and SA.

Data Source
Clinical Study Report section 11.2.5, Table 63 and 64 and Appendix 15, Table 15.3.6.15 and Table 15.2.4.50

Mutagenicity:

At Baseline, median Ames mutagenicity test values were comparable between the THS 2.2 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 2.2 and SA arms, median Ames mutagenicity test values had decreased by approximately 43% and 55%, respectively, while in the CC arm, median Ames mutagenicity test values decreased by approximately 24%. This decrease in urinary mutagenicity can be considered the result of the exposure reduction achieved when switching from CC to THS 2.2 use.

Data Source:
Clinical Study Report section 11.3.1, Table 65 and Appendix 15, Table 15.2.4.42

Nicotine Exposure over Time:

The profiles from the THS 2.2 and CC arms were generally comparable from Baseline throughout the entire exposure period, although the THS 2.2 arm had a slightly lower level of NEQ from Days 2 to 4 compared to the CC arm. In the THS 2.2 arm, geometric mean NEQ values increased from Baseline (5.21 mg/g creat) to Day 5 (5.44 mg/g creat), which was comparable to the results from the CC arm where an increase from Baseline (5.30 mg/g creat) to Day 5 (5.52 mg/g creat) was also observed. These values correspond to percent changes from Baseline of 16.94% and 9.49% for the THS 2.2 and CC arms, respectively. In the SA arm, NEQ values decreased from Baseline (5.00 mg/g creat) to Day 5 (0.15 mg/g creat), as expected, which corresponded to a -96.25% change from Baseline.

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.

The profiles for mean NEQ quantity excreted over 24 hours were similar to those of the concentrations adjusted for creatinine for the THS 2.2, CC, and SA arms.

On Day 5, both the NEQ urinary concentration adjusted for creatinine (mg/g creat) and the quantity excreted over 24 hours (mg) were comparable between subjects who switched to THS 2.2 and subjects who continued to smoke CC. Mean levels of NEQ urinary concentration adjusted for creatinine and quantity of NEQ excreted over 24 hours in subjects who switched to THS 2.2 use were higher (approximately 35-fold and 36-fold higher, respectively) than those of subjects who abstained from smoking (Figure 9 and Table 8).

Mean plasma nicotine concentrations increased from Day 0 to Day 5 for both the THS 2.2 and CC arms. There was no notable difference in the changes from Day 0 plasma nicotine concentrations to Day 5 between subjects who switched to THS 2.2 and subjects who continued to smoke CC. For cotinine, mean plasma concentrations increased from Day 0 to Day 5 in the THS 2.2 and CC arms, with no notable difference in the LS means.

For both nicotine and cotinine exposure on Day 5, peak and weighted average plasma concentrations, there were no notable differences between the THS 2.2 and CC arms. The time to peak concentration on Day 5 was identical for the THS 2.2 and CC arms for both nicotine and cotinine.

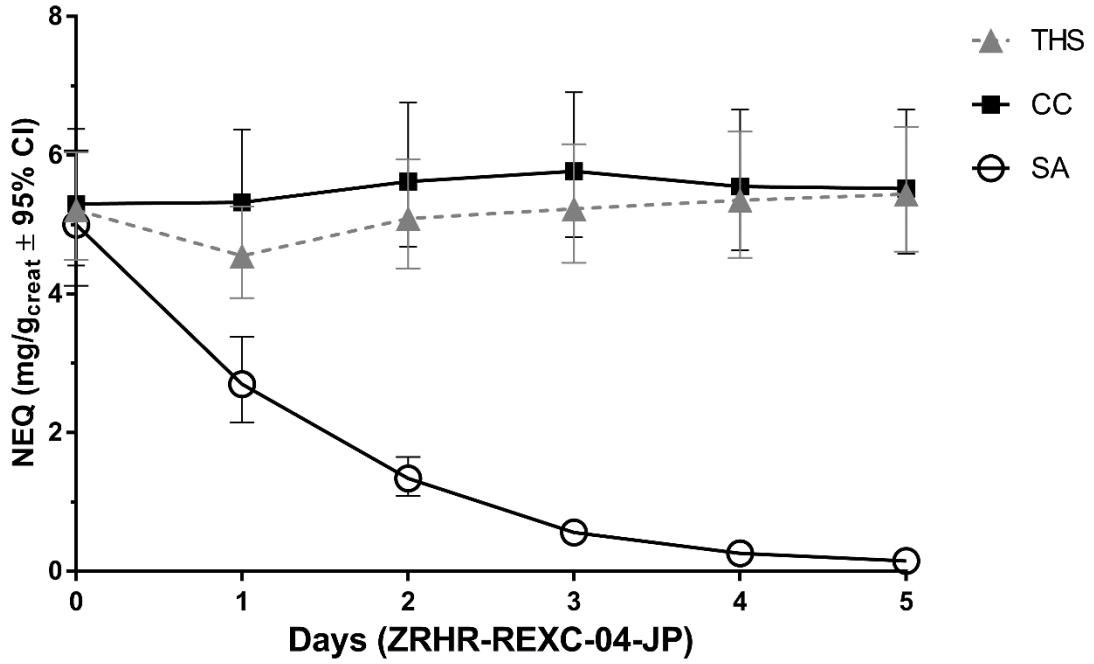


Figure 9 Geometric Mean NEQ Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population)

Abbreviations: Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, nicotine equivalents adjusted to creatinine (NEQ_{adjC}), creatinine (creat), full analysis set (FAS), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI).

Confidentiality Statement

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

Table 8 Analysis of NEQ versus CC and SA on Day 5 (FAS Population)

Parameter	Exposure	N	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	SE	95% CI
Quantity excreted over 24 hours (mg)	THS 2.2	80	5.89	97.98	0.097	80.98, 118.54
	CC	40	6.02			
Concentration adjusted for creatinine (mg/g creat)	THS 2.2	80	5.44	99.72	0.091	83.33, 119.33
	CC	40	5.45			

Abbreviations: Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, conventional cigarette (CC), CI = confidence interval (CI), standard error (SE), LS = least squares (LS), number of subjects (N), Tobacco Heating System 2.2 (THS 2.2) full analysis set (FAS).

Data Source:
NEQ: Clinical Study Report section 11.2.4.2, Table 56 and Appendix 15, Table 15.2.4.33 and Appendix 15, Table 15.2.4.34
Nicotine: Clinical Study Report section 11.2.4.2.1, Table 57 and Appendix 15, Table 15.2.4.41 and Appendix 15, Table 15.2.4.39
Cotinine: Clinical Study Report section 11.2.4.2.2, Table 60 and Appendix 15, Table 15.2.4.41 and Appendix 15, Table 15.2.4.40

Product Use:

In the THS 2.2 arm, the mean number of THS Tobacco Sticks consumed daily was similar from Days 1 to 5 with the mean number of THS Tobacco Sticks consumed on each of these study days being comparable to the number of CC smoked by subjects in the THS 2.2 arm at Baseline (10.3 cigarettes/day). In the CC arm, there was an increase in the mean number of CC consumed daily from Baseline (10.5 cigarettes/day) to Day 5 (12.5 cigarettes/day). In addition, the mean number of CC smoked by subjects in the CC arm was slightly higher than the number of THS Tobacco Sticks consumed by subjects in the THS 2.2 arm on all days from Day 1 to Day 5 (Figure 10 and Table 9).

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.

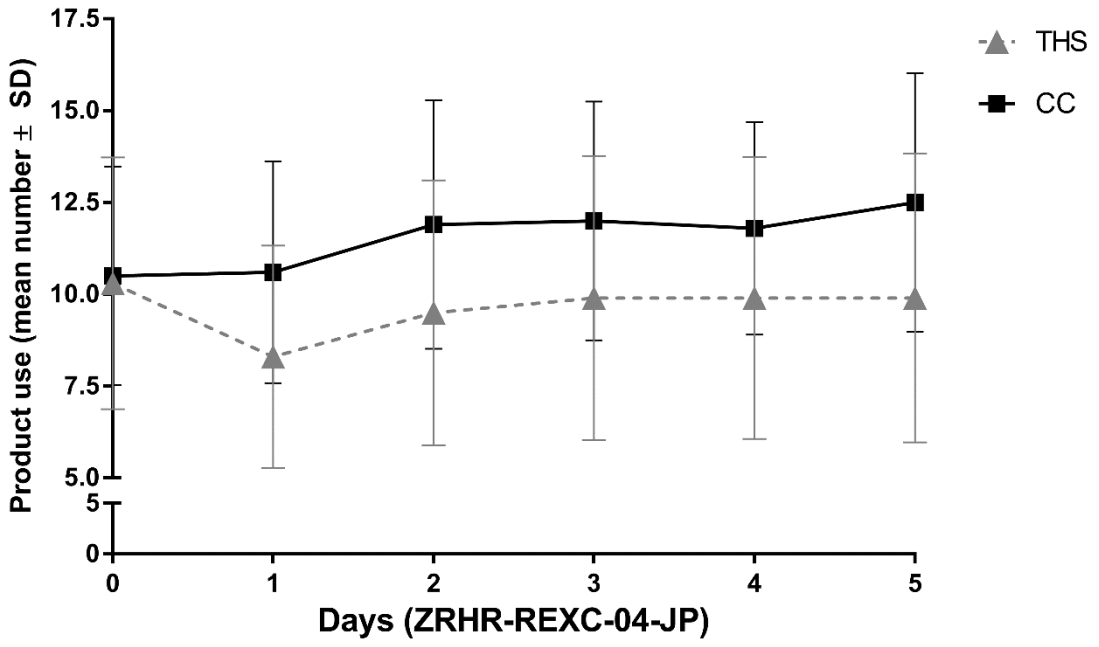


Figure 10 Product Consumption (Number of products used) from Baseline to Day 5

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), standard deviation (SD)

Table 9 Number of THS Tobacco Sticks and Conventional Cigarettes Consumed Daily (Safety Population)

Study Arm	Visit	N	Mean (SD)	Min	Median	Max
THS 2.2	Day 0 (Baseline, CC use)	80	10.3 (3.43)	2	10.0	19
	Day 1	80	8.3 (3.03)	1	8.0	15
	Day 2	80	9.5 (3.61)	1	10.0	18
	Day 3	80	9.9 (3.87)	1	10.0	20
	Day 4	80	9.9 (3.84)	1	10.0	19
	Day 5	80	9.9 (3.93)	1	10.0	19
CC	Day 0 (Baseline)	40	10.5 (2.97)	4	10.0	19
	Day 1	40	10.6 (3.02)	3	11.0	19
	Day 2	40	11.9 (3.38)	6	11.0	19
	Day 3	40	12.0 (3.25)	5	12.0	18
	Day 4	40	11.8 (2.90)	6	12.0	17
	Day 5	40	12.5 (3.52)	6	11.5	20

Abbreviations: CC = conventional cigarette (CC); maximum (max), minimum (min), number of subjects (N), standard deviation (SD); Tobacco Heating System 2.2 (THS 2.2).

Data Source: Clinical Study Report section 10.5, Table 21 and Appendix 15, Table 15.2.2.1

Confidentiality Statement

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

Human Puffing Topography (HPT):

Values for HPT parameters assessed were comparable at Baseline between the THS 2.2 and the CC arms for each assessed parameter while subjects were using their usual brand of CC (Table 10).

In the THS 2.2 arm, decreases from Baseline to Day 1 were observed in average inter puff interval, total puff volume and average puff volume; whereas there was an increase from Baseline to Day 1 in total number of puffs and puffing frequency.

Total number of puffs, puff frequency and total puff duration were increased in subjects who switched to THS 2.2 use compared to subjects who continued to smoke CC on Days 1 and 4. In addition, average puff volume and average inter puff interval were decreased in subjects who switched to THS 2.2 use compared to subjects who continued to smoke CC on Days 1 and 4. Total puff volume was decreased on Day 1 in subjects who switched to THS 2.2 use compared to subjects who continued to smoke CC, but there was no difference observable on Day 4.

In the CC arm, the values for all parameters were generally stable between Baseline and Day 4 compared to the THS 2.2 arm, with the exception of total number of puffs and total puff volume which decreased slightly in CC arm on Day 1, and average inter puff interval which increased from Baseline to Day 4.

No notable differences were observed in average puff duration and total smoking duration on both Days 1 and 4 between subjects who switched to THS 2.2 use and subjects who continued to smoke CC.

Table 10 Analysis of HPT Parameters (Averaged over All Cigarettes per Day) (FAS Population)

Variable (units)	Time Point	Product Exposure	N	Geometric LS Mean	Geometric LS Mean Ratio (THS 2.2:CC) (%)	CV (%)	95% CI
Total number of puffs	Day 1	THS 2.2	74	15.74	111.04	24.60	100.84, 122.27
		CC	38	14.18			
	Day 4	THS 2.2	74	17.22	118.57	20.59	109.35, 128.57
		CC	38	14.52			
Total puff volume (mL)	Day 1	THS 2.2	74	545.68	81.58	44.22	68.90, 96.58
		CC	38	668.82			
	Day 4	THS 2.2	74	648.37	99.24	37.34	85.90, 114.64
		CC	38	653.36			
Average puff volume (mL)	Day 1	THS 2.2	74	34.92	74.78	30.57	66.42, 84.20
		CC	38	46.69			
	Day 4	THS 2.2	74	38.10	85.45	30.43	75.93, 96.16
		CC	38	44.58			
Average puff duration (s)	Day 1	THS 2.2	74	1.82	99.14	20.72	91.36, 107.60
		CC	38	1.84			

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.

	Day 4	THS 2.2	74	1.85	102.64	23.94	93.42, 112.78
		CC	38	1.81			
Total puff duration (s)	Day 1	THS 2.2	74	28.65	110.91	35.70	96.69, 127.22
		CC	38	25.83			
	Day 4	THS 2.2	74	32.07	123.45	34.39	108.14, 140.93
		CC	38	25.97			
Average inter puff interval (s)	Day 1	THS 2.2	74	13.13	81.17	26.56	73.16, 90.07
		CC	38	16.17			
	Day 4	THS 2.2	74	11.93	72.64	32.15	64.12, 82.30
		CC	38	16.43			
Total smoking duration (s)	Day 1	THS 2.2	74	238.15	95.12	22.35	87.14, 103.82
		CC	38	250.38			
	Day 4	THS 2.2	74	242.07	92.91	22.04	85.22, 101.29
		CC	38	260.55			
Puff frequency (puffs/min)	Day 1	THS 2.2	74	4.12	117.76	22.55	107.74, 128.72
		CC	38	3.50			
	Day 4	THS 2.2	74	4.39	126.61	25.05	114.73, 139.72
		CC	38	3.47			

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed Baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

Abbreviations: analysis of covariance (ANCOVA), full analysis set (FAS), conventional cigarette (CC); confidence interval (CI); coefficient of variation (CV); least squares (LS); Tobacco Heating System 2.2 (THS 2.2).

Data Source: Clinical Study Report section 11.3.5, Table 75 and Appendix 15, Table 15.2.4.59

Subjective Effects:

The present study included endpoints to assess the overall satisfaction, to evaluate if THS 2.2 could be an acceptable substitute to CC.

The results of the QSU-brief showed that for the THS 2.2 and CC arms, the average urge-to-smoke total scores remained stable over the 5 days and were comparable throughout the study (ranges of individual scores 1.0 to 6.7 and 1.0 to 5.8, respectively). In the SA arm, the urge-to-smoke total score increased from Baseline to Day 1 (score of 4.64, corresponding to an increase of 0.66 points), then decreased from 4.64 at Day 1 to 4.12 at Day 5 (Figure 11).

Similar results were observed for withdrawal symptoms as assessed by the MNWS in the different study arms, where the MNWS total scores were comparable for the THS 2.2 and CC arms at Baseline, and remained comparable throughout the study (Total Score 1: mean range of 5.7 to 6.4 and 5.7 to 6.9, respectively). In the SA arm, the MNWS Total Scores 1 and 2 increased from Baseline to Day 2, then decreased moderately from Day 2 to Day 6, and were approaching the Baseline values and the scores of the THS 2.2 and CC arms by Day 6.

The MCEQ scale evaluated the overall satisfaction of THS 2.2 users compared to CC smokers, and showed that psychological reward and smoking satisfaction were lower for subjects who switched to THS 2.2 use compared to subjects who continued to smoke CC on Day 5. Aversion, craving

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.

reduction, and enjoyment of respiratory tract sensation were comparable in the THS 2.2 and CC arms overall and on all individual study days, with the exception of craving reduction on Day 2 which was decreased for THS 2.2 compared to CC (Figure 12).

The change in taste, sensorial experience, ritual, and differences in the ISO tar and nicotine yield of THS 2.2, are additional likely reasons for the observed differences in overall satisfaction. Nevertheless, subjective appreciation measures illustrate that THS 2.2 offered a close experience to what was observed in CC smokers. Different patterns observed for the corresponding domains in the SA arm tend to substantiate these observations. Further studies will determine if a longer time for adaptating to THS 2.2 will further close the gap in perceived smoking effects.

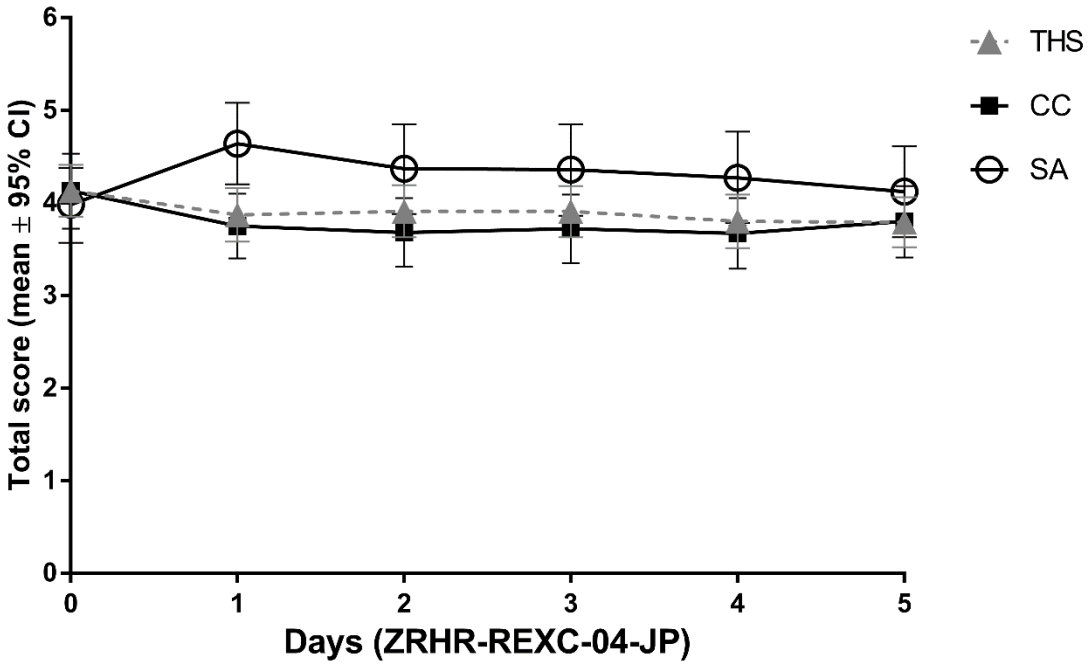


Figure 11 Total Score – Questionnaire of Smoking Urges from Baseline to Day 5

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI)

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.

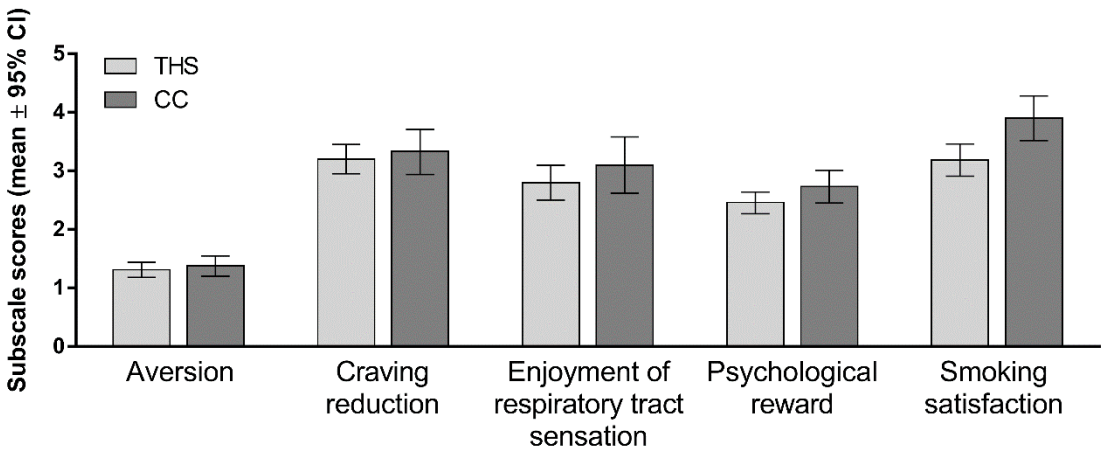


Figure 12 MCEQ Subscales on Day 5

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), confidence intervals (CI)

Data Source:
QSU: Clinical Study Report section 11.3.4.1, Table 72 and Appendix 15, Table 15.2.4.43
MNWS: Clinical Study Report section 11.3.4.2, Table 73 and Appendix 15, Table 15.2.4.45
MCEQ: Clinical Study Report section 11.3.4.3, Table 74 and Appendix 15, Table 15.2.4.47

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.

Clinical Risk Endpoints:

At Baseline, the concentration of 8-epi-PGF2α adjusted for creatinine was comparable between THS 2.2, CC, and SA study arms (geometric means of 219.16, 210.20, and 230.13 pg/mg creat, respectively). At Day 5, the 8-epi-PGF2α adjusted for creatinine were 212.70, 233.20, and 217.67 pg/mg creat (changes from Baseline of approximately -0.25%, 13.27%, and -2.64%) in the THS 2.2, CC, and SA arms, respectively. Results for the quantity of 8-epi-$PGF_{2\alpha}$ excreted over 24 hours showed a comparable trend.

On Day 5, the LS mean of 8-epi-PGF2α adjusted for creatinine in subjects who switched to THS 2.2 use was 11.53% lower than that of subjects who continued to smoke CC (95% CI: 4.39, 18.13) with no notable differences observed between subjects who switched to THS 2.2 and subjects who abstained from smoking. The results for 8-epi-PGF2α excreted over 24 hours, were similar to the concentrations adjusted for creatinine.

At Baseline, the concentration of 11-DTX-B2 adjusted for creatinine was comparable in the CC and SA arms (geometric mean values of 515.52 and 455.46 pg/mg creat, respectively) and was higher in the THS 2.2 arm (546.15 pg/mg creat). At Day 5, the 11-DTX-B2 adjusted for creatinine was comparable to the Baseline value in the THS 2.2 and SA arms (approximate 10% decrease and 16% increase, respectively), and had increased to 538.98 pg/mg creat (an increase from Baseline of approximately 8%) in the CC arm. However, the data were highly variable, and when the medians are compared they showed both THS 2.2 and SA to be similar to Baseline at Day 5, with median changes from Baseline of approximately -12% and -4%, respectively. In the CC arm, there was a median increase from Baseline of 8.84%. Results for the quantity of 11-DTX-B2 excreted over 24 hours showed a comparable trend.

On Day 5, the LS mean of the quantity of 11-DTX-B2 adjusted for creatinine in subjects who switched to THS 2.2 use was 15.45% lower than that of subjects who continued to smoke CC (95% CI: 5.16, 24.63) and with no notable difference between subjects who switched to THS 2.2 and subjects who abstained from smoking. Results for the quantity of 11-DTX-B2 excreted over 24 hours showed a comparable trend.

Data Source:
8-epi-$PGF_{2\alpha}$: Clinical Study Report section 11.3.3.1, Table 68 and Appendix 15, Table 15.2.4.53
11-DTX-B2: Clinical Study Report section 11.3.3.2, Table 69 and Appendix 15, Table 15.2.4.55

Safety:

There were no SAEs reported in this study and no randomized subjects discontinued from the study due to an AE.

Overall, there were 11 AEs reported by 10 of the 166 subjects (6.0%) in the safety population, all of which were mild in intensity. The incidence and frequency of AEs were comparable in the THS 2.2 (6 AEs in 6/80 subjects [7.5%]), the CC (4 AEs in 3/40 subjects [7.5%]), and the SA arms (1 AE in 1/40 subjects [2.5%]).

The most frequent AEs after THS 2.2 or CC exposure were blood triglycerides increased, neutrophil count decreased, blood potassium decreased, protein urine present, and white blood cell count decreased. The only AE reported after SA was hemoglobin decreased.

None of AEs reported were assessed as being related to THS 2.2 or CC use.

During THS 2.2 use, 4 subjects experienced a total of 5 device events or malfunctions, which led to the replacement of the THS Tobacco Stick Holder or Charger. None of these events led to an AE.

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.

Data Source:
Summary of AEs: Clinical Study Report section 12.1.1, Table 77 and Appendix 15, Table 15.2.6.1 and Table 15.2.6.5
AEs by study arm, SOC and PT: Clinical Study Report section 12.1.2 by study arm in Table 78 and in Appendix 15, Table 15.2.6.2.1, by SOC in Appendix 15, Table 15.2.6.2.2, and by PT in Appendix 15, Table 15.2.6.2.3

6.1.3.4.2.4 Conclusion

- The study demonstrated that switching from CC smoking to THS 2.2 use resulted in substantial reductions in exposure to 15 selected HPHCs. 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.
- The exposure to nicotine was similar between the THS 2.2 and CC arms indicating that users adapted gradually to the new product and achieved their desired nicotine levels.
- The combination of the results of nicotine exposure and subjective effects measures indicated that THS 2.2 offered comparable satisfaction to what was observed in CC smokers. Different patterns observed for the corresponding domains in the SA arm tended to substantiate these observations.
- No SAEs or severe AEs were reported during this study, with the total number of AEs being evenly balanced across study arms.

In summary, this study demonstrated that THS 2.2 reduced exposure to HPHCs close to what was observed when abstaining from smoking, and was acceptable with regards to taste, ritual, sensorial experience, and nicotine delivery to the users and therefore might be a suitable substitute for CC for adult smokers which users can easily adapt to.

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.

6.1.3.4.3 ZRHM-REXA-07-JP

STUDY ZRHM-REXA-07-JP	**Source: Section 7.3.1, Clinical Study Report ZRHM-REXA-07-JP**

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, for 5 days in Confinement and prolonged by 85 days in an Ambulatory setting.

Protocol-No.: ZRHM-REXA-07-JP		
Date of final report: 24 February 2016		
Publication (reference):	ClinicalTrials.gov ID: NCT01970995. Reduced Exposure Study Using the Tobacco Heating System 2.2 (THS 2.2) Menthol for 90 Days in Confinement and Ambulatory	
Investigators:	Principal Investigator: 1) Masahiro Endo, MD 2) Mamoru Oki, MD PhD	
Study center:	1) Tokyo Heart Center Osaki Hospital, 5-4-12, Kita Shinagawa, Shinagawa-ku, Tokyo 141-0001, Japan 2) Seishukai Clinic, 3-18-5, Matsugaya, Taitou-ku, Tokyo 111-0036, Japan	
Time of clinical part:	01 August 2013 - 03 July 2014	**Clinical Phase:** II (Product Performance)

Objective:

The aim of this study was to demonstrate reduction in exposure to selected HPHCs (except nicotine) in smokers switching to the THS 2.2 Menthol first in a confined and controlled, then followed by a more "real-world" Ambulatory setting. THS 2.2 Menthol was also compared with smoking abstinence, which was used as a reference point. Furthermore exposure to nicotine exposure, product use, subjective effects and changes in Human Puffing Topography over time in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC were assessed.

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.

Study design:

- Multi-center
- Ad-libitum use
- Randomized
- Parallel
- Open-label
- 90 Days of Exposure

Subjects:

• Planned:	160 subjects
• Enrolled:	231 subjects
• Randomized (Tokyo Heart Center):	160 subjects
• Discontinuations:	61 subjects
• Completed:	155 subjects
• Safety population (Tokyo Heart Center)	175 subjects
• Full analysis set (FAS) population	160 subjects
• Per-protocol (PP) population (Day 90):	148 subjects

Main criteria for inclusion:

- Male or female Japanese from 23 to 65 years of age and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening.
- Spirometry evaluation had to show forced expiratory volume in 1 second {FEV_1}/forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV_1 >80% predicted value, and post-bronchodilator FVC >0.8.
- Subjects were smoking at least 10 commercially available menthol CC (mCC) per day with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) mCC, as labeled on the cigarette package, for the last 4 weeks, and did not plan to quit smoking in the following 3 months. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
- Female subjects of child-bearing potential should had confirmed negative pregnancy test and used effective methods of contraception
- Provide written informed consent prior to study participation.
- Able to communicate well with the investigator and comply with the requirements of the study.
- The subject was a current smoker who did not plan to quit smoking in the next 3 months.
- The subject was ready to accept using the THS 2.2 Menthol product or to accept 90 days of SA.

mTHS 2.2:	Product:	Batch number of THS Tobacco Sticks: B-05775 Production date: 12-Jun-2013, Expiry date: 11-Mar-2014;

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.

	ISO nicotine Content: Use: Manufacturer:	Batch number of THS Tobacco Sticks: B-08544, Production date: 25-Oct-2013, Expiry date: 24-Jul-2014. 0.5 mg Ad-libitum use PMI
Menthol Conventional Cigarette:	Product: ISO nicotine Content: Use: Manufacturer:	Own conventional menthol cigarette brand. Maximum yield of 1 mg per mCC as per cigarette package label Ad-libitum use Commercially available non-menthol conventional cigarettes
Smoking Abstinence	Smoking abstinence was used as a reference point without support of Nicotine Replacement Therapy (NRT) or any drug for smoking cessation support during the Confinement period. NRT use during the Ambulatory period was allowed if considered necessary by the Investigator or if required by the subject.	
Duration of use:	The Exposure Period was approximately 90 days and lasted from Day 1, 06:30 AM, until 11:00 PM on Day 90. Day of Discharge was defined as Day 90, 11:00 PM, until Discharge 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 Period 1, Period 2, Period 3, and Period 4.	
Analytical Method:	All analytical methods, with the exception of Carboxyhemoglobin (measured by (b) (4)) were developed at (b) (4) , (b) (4) , and validated according to the standard operating procedures (SOPs) in effect during the conduct of the validation. These SOPs were written in accordance with the principles of good laboratory practice (GLP) described in 21 Code of Federal Regulation (CFR) Part 58 and the Guidance for Industry – Bioanalytical Method Validation (CDER, May 2001). (b) (b) (4) t (b) (4) a. A detailed summary of the description of the analytical methods by BoExp, the matrix used and the validation are described in section 6.1.3.4.	

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.

Primary Objectives:

1. To demonstrate the reduction of primary biomarkers of exposure (BoExp) to harmful and potentially harmful constituents (HPHCs) (except Total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol [NNAL]) in a Confinement setting in smokers switching from menthol conventional cigarette (mCC) to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoints:

   - Monohydroxybutenylmercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA) (concentration adjusted for creatinine) in 24-hour urine, and carboxyhemoglobin (COHb) in blood (expressed as % saturation of hemoglobin) as measured on Day 5.

2. To demonstrate the reduction of Total NNAL in an Ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoint:

   - Total NNAL level (concentration adjusted for creatinine) in 24-hour urine fraction as measured on Day 90 Visit

Secondary Objectives:

1. To evaluate self-reported nicotine/tobacco product use including dual-use in an Ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to smoking abstinence (SA).

   Endpoint:

   - Number of mCC or THS Menthol Tobacco Sticks smoked daily as reported on the log during the Confinement Period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary.

2. To determine the reduction of secondary BoExp in a Confinement setting and in an Ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoint:

   - BoExp listed as secondary (expressed as quantity excreted or concentration adjusted for creatinine) as measured in 24-hour urine on Day 5 and Day 90 Visit.

3. To describe the levels of primary and secondary BoExp over the entire Exposure Period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

   Endpoints:

   - BoExp listed as primary and secondary from Day 1 to Day 5 and Day 30 Visit, Day 60 Visit, and Day 90 Visit as follows:
     - Carbon monoxide ([CO] expressed as ppm) in exhaled breath.
     - Carboxyhemoglobin in blood (expressed as % saturation of hemoglobin).

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.

- Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine.

4. To determine the levels of nicotine over the entire Exposure Period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire Exposure Period.

   Endpoints:

   - Nicotine equivalents (NEQ; expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine from Day 1 to Day 5 and on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Nicotine and cotinine in plasma from Day 1 to Day 5, and on Day 30 Visit, Day 60 Visit, and Day 90 Visit.

5. To describe the pharmacokinetic (PK) profiles of the nicotine and cotinine in a Confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoints:

   - Peak (highest concentration along the day) on Day 5.
   - Time to peak (t_{peak}; actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
   - Weighted average concentration over 24 hours (C_{avg}) on Day 5.

6. To describe the change in cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, and to SA.

   Endpoint:

   - Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5 and Day 90 Visit.

7. To monitor the safety profiles during the study.

   Endpoints:

   - Adverse events (AEs)/serious adverse events (SAEs), and device events including THS 2.2 Menthol malfunction/misuse.
   - Respiratory symptoms: cough assessment by visual analogue scale (VAS) and Likert scales and one open question.
   - Vital signs.
   - Spirometry.
   - Electrocardiogram (ECG).
   - Clinical chemistry, hematology, and urine analysis safety panel.
   - Physical examination.
   - Concomitant medications.

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.

8. To monitor selected risk markers (CREs) in a Confinement and Ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

   Endpoints:

   - Systolic and diastolic blood pressure on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - High sensitive C-reactive protein (hs-CRP), homocysteine, blood glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TGs), total cholesterol (TC) in serum on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Fibrinogen in plasma on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Hemoglobin A1c (HbA1c) in blood on Day 90 Visit.
   - Soluble intercellular adhesion molecule-1 (sICAM-1) in serum on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - White blood cell (WBC) and platelet count in blood on Day 6, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - 8-epi-prostaglandin F2 alpha (8-epi-$PGF_{2\alpha}$) and 11-dehydro-thromboxane B2 (11 DTX-B2) in 24-hour urine on Day 5, Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine).
   - Body weight and waist circumference on Day 90 Visit.

Exploratory Objectives:

1. To describe the following parameters in a Confinement and/or Ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA:

   Endpoints:

   - Excretion of mutagenic material in urine: Ames mutagenicity test (YG1024+S9) on Day 5 and Day 90 Visit in 24-hour urine.
   - Subjective effect of smoking: Questionnaire of Smoking Urges (brief version) (QSU-brief); questionnaire Minnesota Nicotine Withdrawal Scale (MNWS) − Revised on Day 5, and the Day 90 Visit.
   - Cytochrome P450 2A6 (CYP2A6) activity: in plasma on Day 6, and the Day 90 Visit using the molar metabolic ratio of trans-3'-hydroxycotinine/cotinine.
   - Nicotine dependence as assessed by the Fagerström Test for Nicotine Dependence (FTND) questionnaire: score from FTND questionnaire on the Day 90 Visit.

2. To evaluate in smokers switching from mCC to THS 2.2 Menthol and smokers continuing smoking mCC the relationship between NEQ and:

   Endpoints:

   - BoExp for the primary and secondary objectives on Day 5 and on Day 90 Visit in 24-hour urine.

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.

- Selected risk markers (CREs; hs-CRP, homocysteine, blood glucose, LDL cholesterol, HDL cholesterol, TG, TC, fibrinogen, HbA1c, sICAM-1, WBC, platelet count, 8-epi-$PGF_{2\alpha}$, 11-DTX-B2) in respective body matrix when available on Day 5 and Day 90 Visit.

3. To describe the following parameters over the course of the study in smokers switching from mCC to the THS 2.2 Menthol as compared to smokers continuing smoking mCC:

   Endpoints:

   - Product evaluation: Modified Cigarette Evaluation Questionnaire (MCEQ).
   - Smoking pattern: human smoking topography (HST) parameters and HST questionnaire.

4. To describe the following parameters over the course of the study in smokers switching from mCC to THS 2.2 Menthol:

   Endpoints:

   - Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.
   - Filter analysis: smoke nicotine in filter and UV absorbance at 310 nm (during a Confinement setting only).

5. To describe the product use over the course of the study according to the product preference of the subject:

   Endpoint:

   - Number of mCC or THS Menthol Tobacco Sticks smoked daily as reported on the log during the Confinement Period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the electronic diary.

Safety:

Adverse events, assessments of physical condition, concomitant medications, vital signs and body measurements, spirometry, respiratory symptoms, electrocardiogram, and monitoring of laboratory values. Device events, including THS 2.2 malfunction/misuse.

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.

6.1.3.4.3.1 Statistical methods

6.1.3.4.3.1.1 Primary Analyses

The endpoints included in the primary objectives were log-transformed ($base_e$) prior to analysis. An analysis of covariance (ANCOVA) model was used with terms for the log-transformed Baseline value, stratification factors (sex, average daily mCC consumption over the last 4 weeks as reported during Screening), and randomization arm. The least squares (LS) means and estimate of the difference were back-transformed. The geometric LS means for each randomization arm along with the ratio (THS 2.2 Menthol : mCC), two-sided 95% confidence interval (CI) and one-sided p-value were tabulated. These analyses were performed on the PP Set, the FAS, and the Compliant Population. A sensitivity analysis was also performed on the PP Set using a mixed model approach (conducted with Baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors).

Exposure to HPHCs is known to be highly variable with cigarette consumption and sex described as strongest factors, therefore these terms were included in the ANCOVA model. There is a dose-response relationship between cigarette consumption and exposure levels to HPHCs, with higher consumption resulting in higher exposure levels. Male smokers tend to have higher levels of exposure to HPHCs than females. Age was also reported to be a potential factor, with higher levels of exposure with increasing age, however this effect is limited and might be confounded by longer smoking history and higher cigarette consumption with increasing age. Therefore age was not included in the model.

The least squares (LS) means and estimate of the difference along with its 95% CI were back-transformed before presenting in the tables. The geometric LS means for each product along with the ratio (THS 2.2 Menthol: mCC) and 95% CI were presented in the tables.

The PP Set was the primary analysis data set for BoExp, CREs, and questionnaire assessments. The FAS was the primary analysis data set for compliance to randomization arm. The Per-Protocol (PP) population was defined as:

- Subjects that were correctly randomized and assigned study product.
- Subjects with at least one post-randomization product use (for mCC and THS 2.2 Menthol).
- Subjects with at least one valid post-randomization BoExp measurement.
- Subjects that were adherent with their assigned study product.
- Subjects without major protocol deviations that impacted the validity of the evaluation of the study results.

The PP Population was selected as the primary analysis to assess the maximum exposure reduction achievable (optimal effect) in subjects who were using THS 2.2 Menthol ad-libitum and exclusively or at least predominantly, rather than the effect in the full population representing a heterogeneous exposure (e.g., as mixed product use, or non-use of the assigned product).

The optimal effect may be a somewhat ideal scenario, which differs from the real-world effect (effect under actual use setting) mainly by reducing the impact of non-compliance on the estimate.

6.1.3.4.3.1.2 Secondary Analyses

The BoExp included as endpoints in the primary objectives were analyzed in the secondary objectives at Day 5 for Total NNAL and Day 90 for COHb, MHBMA, 3-HPMA, and S-PMA, for the PP Set and FAS using the same methodology as for the primary analysis, including the sensitivity analysis. The BoExp were also examined to compare the reductions in THS 2.2 Menthol versus SA using the same methodology as for the primary analysis for the PP Set.

The BoExp included as endpoints in the secondary objectives were exhaled CO and Total 1-hydroxypyrene (1-OHP), Total N-nitrosonornicotine (NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), o-toluidine, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxybenzo(a)pyrene (B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), S-benzylmercapturic acid (S-BMA), and NEQ (all analyzed from a 24-hour urine collection) on Day 5 and

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.

Day 90 to compare reductions in THS 2.2 Menthol versus mCC and versus SA.

Biomarkers of exposure were analyzed using the same model described for the primary analysis. Exhaled CO was analyzed on the linear scale and arithmetic means and differences were calculated; whereas other BoExp were analyzed on the logarithmic scale to calculate geometric means and ratios. For all BoExp, if the results from the Day 5 analysis were significant (one-sided p-value ≤ 0.025) then the statistical significance was evaluated for the results of the Day 90 analysis. Least squares means for each product along with the difference or ratio, and 95% CI were tabulated.

Nicotine and cotinine concentrations at each post-Baseline time point were also analyzed in the log space using the same ANCOVA model as the primary analysis.

Log-transformed C_{peak} and C_{avg} on Day 5 were compared using analysis of variance (ANOVA) model with terms for stratification factors, and randomization arm. Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were generated. The t_{peak} on Day 5 was compared using the Wilcoxon Rank Sum test. All PK concentrations and parameter summaries and analyses were performed using the PP Set and FAS as defined above.

Product compliance and extent of exposure was assessed by summarizing daily product use during the Confinement Period and the Ambulatory period by randomization arm, and by product use category during the Ambulatory period. In addition, in the SA arm, the levels of CO in exhaled breath were summarized.

CYP1A2 and CYP2A6 were analyzed with the log-transformed Day 5 (Day 6 for CYP2A6) values using an ANOVA model. If the results from the Day 5 analyses were significant (one-sided p-value ≤ 0.025) then the analyses were repeated for the Day 90 values. Geometric LS means for each product along with the ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated. All CYP1A2 and CYP2A6 summaries and analyses were performed using the PP Set and FAS.

For analysis of CREs, the results on Days 5, 30, 60, and 90 Visits, as applicable, between the THS 2.2 Menthol and mCC arms, and between the THS 2.2 Menthol and SA arms using the same ANCOVA model as the primary analysis. If applicable and there was evidence of non-normality, the results were log-transformed prior to analysis. Least squares means for each product along with the difference (THS 2.2 Menthol - mCC) or ratio (THS 2.2 Menthol : mCC) and 95% CI were tabulated along with a forest plot of the results. Additionally, an additional analysis was performed for the FEV_1 parameter following the same approach as for other CREs.

For the MCEQ scores, QSU-Brief and the HST parameters, Least squares means for each product along with the difference (THS 2.2 Menthol - mCC) with 95% CI were presented.

For all endpoints, descriptive statistics of the values and percent change from Baseline (where applicable), and supportive listings were provided.

6.1.3.4.3.2 Study Hypotheses and Evaluation Criteria

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 objectives, 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.

The study was considered successful if a 50% or more reduction in MHBMA, 3-HPMA, S-PMA, and COHb on Day 5 and in Total NNAL on Day 90 was demonstrated in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, using a one-sided test with 2.5% type I error probability.

6.1.3.4.3.3 Summary of selected results relevant for BoExp Assessment

Please refer to section 7.3.1 for full results.

6.1.3.4.3.3.1 BoExp Assessment

The study demonstrated that switching from mCC smoking to THS 2.2 Menthol use resulted in substantial

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.

and rapid reductions in BoExp levels to 15 selected HPHCs from Baseline to Day 5 ranging from -49% to -94%. These reductions were sustained through the Ambulatory period ranging from -41% to -94% at Day 90, while maintaining comparable levels of nicotine (Figure 13 and Table 11). The kinetics and the magnitude of decrease of BoExp levels observed in the THS 2.2 Menthol arm were approaching the levels observed in the SA arm (Figure 14 and Table 12). S-BMA levels did not show any difference in levels across all study arms.

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.

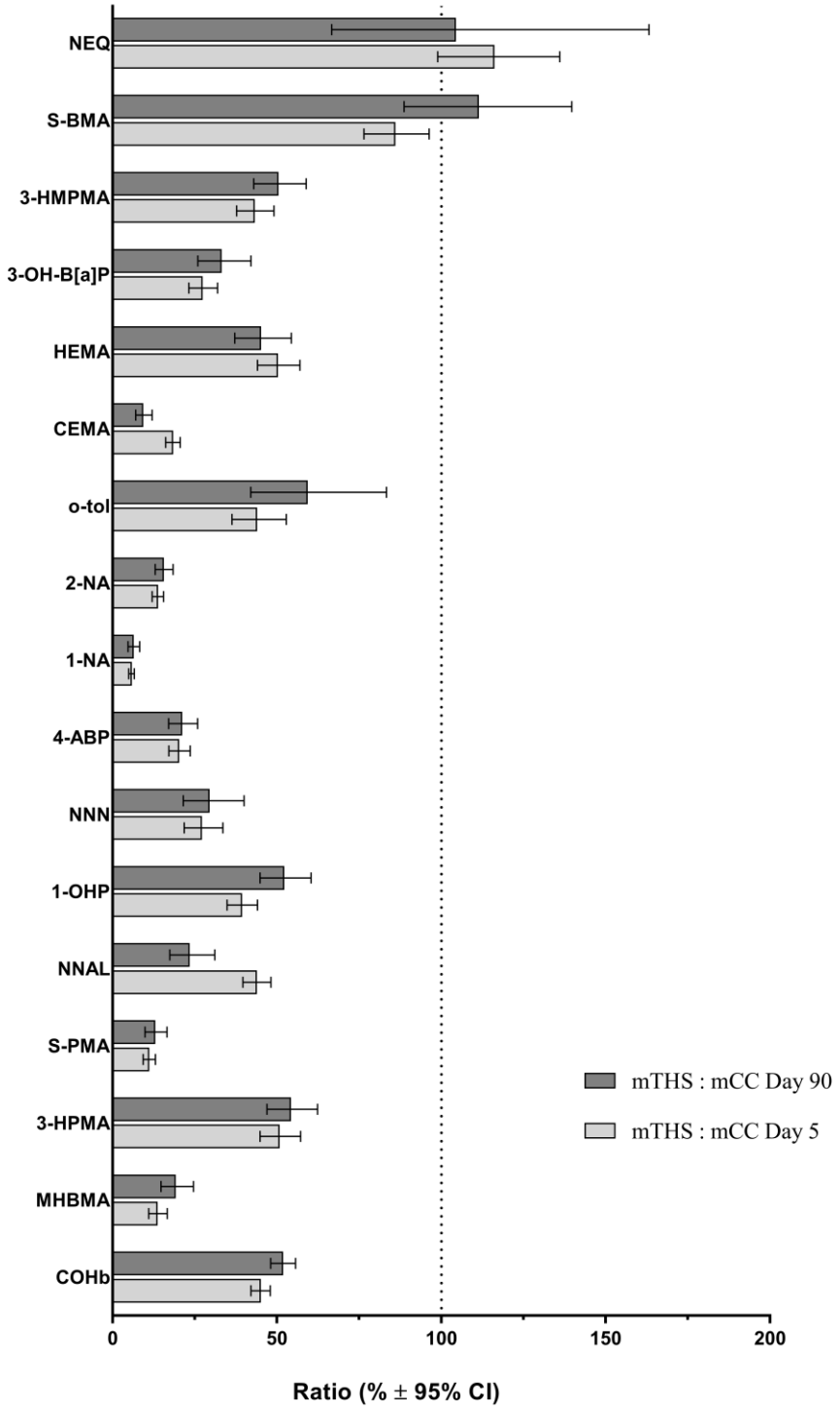


Figure 13 Adjusted Geometric LS Means and CIs from an ANCOVA Model of THS Menthol or mCC ratios of BoExp Levels at Day 5 and Day 90

Abbreviations: analysis of covariance (ANCOVA), 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, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA),

Confidentiality Statement

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

3-hydroxy(a)benzopyrene (3-OH-B[a]P), 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 Menthol (mTHS), menthol Conventional Cigarette (mCC), Smoking Abstinence (SA), confidence interval (CI), least squares (LS).

Table 11 Analysis of BoExp in ZRHM-REXA-07-JP at Day 5 and Day 90

				ZRHR-REXA-07-JP	
BoExp	**HPHCs [aerosol phase]**			**Day 5**	**Day 90**
COHb	CO [gas]	mTHS:mCC Ratio	Geometric LS Mean	44.94%	51.72%
			95% CI	42.11; 47.97	48.07; 55.65
			p Value	<0.001	<0.001
MHBMA	1,3-Butadiene [gas]	mTHS:mCC Ratio	Geometric LS Mean	13.49%	19.01%
			95% CI	10.96; 16.60	14.68; 24.61
			p Value	<0.001	<0.001
3-HPMA	Acrolein [gas]	mTHS:mCC Ratio	Geometric LS Mean	50.67%	54.08%
			95% CI	44.88; 57.20	46.94; 62.32
			p Value	<0.001	<0.001
S-PMA	Benzene [gas]	mTHS:mCC Ratio	Geometric LS Mean	10.97%	12.80%
			95% CI	9.26; 12.99	9.88; 16.58
			p Value	<0.001	<0.001
Total NNAL	NNK [particulate]	mTHS:mCC Ratio	Geometric LS Mean	43.69%	23.25%
			95% CI	39.62; 48.17	17.38; 31.11
			p Value		<0.001
Total 1-OHP	Pyrene [particulate]	mTHS:mCC Ratio	Geometric LS Mean	39.18%	52.02%
			95% CI	34.82; 44.07	44.83; 60.38
			p Value	<0.001	<0.001
Total NNN	NNN [particulate]	mTHS:mCC Ratio	Geometric LS Mean	27.02%	29.31%
			95% CI	21.75; 33.55	21.48; 39.98
			p Value	<0.001	<0.001
4-ABP	4-Aminobiphenyl [particulate]	mTHS:mCC Ratio	Geometric LS Mean	20.10%	21.00%

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.

			95% CI	17.08; 23.64	17.02; 25.89
			p Value	<0.001	<0.001
1-NA	1-Aminonaphthalene [particulate]	mTHS:mCC Ratio	Geometric LS Mean	5.70%	6.22%
			95% CI	4.93; 6.59	4.70; 8.22
			p Value	<0.001	<0.001
2-NA	2-Aminonaphthalene [particulate]	mTHS:mCC Ratio	Geometric LS Mean	13.66%	15.45%
			95% CI	12.04; 15.49	12.98; 18.39
			p Value	<0.001	<0.001
o-Toluidine	*o*-Toluidine [gas]	mTHS:mCC Ratio	Geometric LS Mean	43.80%	59.16%
			95% CI	36.31; 52.83	42.02; 83.29
			p Value	<0.001	0.001
CEMA	Acrylonitrile [gas]	mTHS:mCC Ratio	Geometric LS Mean	18.23%	9.17%
			95% CI	16.16; 20.56	7.01; 12.00
			p Value	<0.001	<0.001
HEMA	HEMA [particulate]	mTHS:mCC Ratio	Geometric LS Mean	50.14%	44.96%
			95% CI	44.09; 57.02	37.17; 54.37
			p Value	<0.001	<0.001
3-OH - B[a]P	Benzo[a]pyrene [particulate]	mTHS:mCC Ratio	Geometric LS Mean	27.19%	33.02%
			95% CI	23.17; 31.91	25.92; 42.08
			p Value	<0.001	<0.001
3-HMPMA	Crotonaldehyde [gas]	mTHS:mCC Ratio	Geometric LS Mean	43.06%	50.31%
			95% CI	37.75; 49.10	42.96; 58.91
			p Value	<0.001	<0.001

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 (total 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 (3-OH-B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), Tobacco Heating System Menthol (mTHS), Menthol Conventional Cigarette (mCC), Smoking Abstinence (SA), least squares (LS), confidence intervals (CI).

Data Source:
Primary Endpoints: Clinical Study Report section 11.1 and Appendix 15, Table 15.2.3.1.1 to Table 15.2.3.7
Secondary Endpoints: Clinical Study Report section 11.2 and Appendix 15, Table 15.2.4.1.1 to Table 15.2.4.50

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.

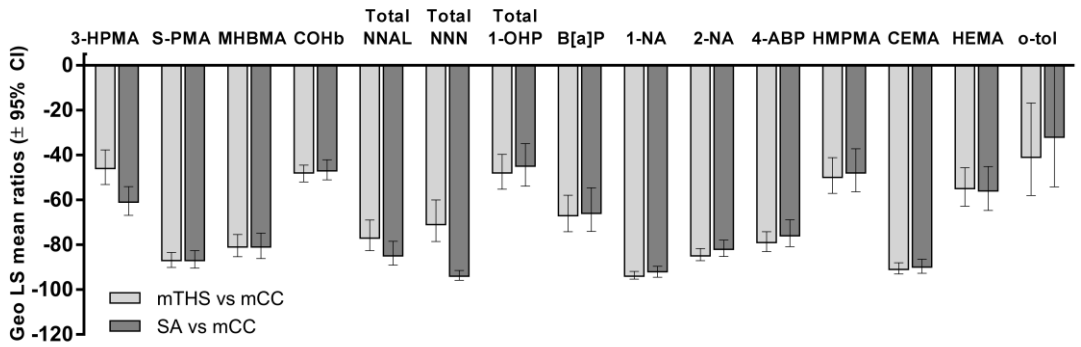


Figure 14 Reduction of BoExp in ZRHR-REXC-07-EU at Day 90 (mTHS:mCC and SA:mCC in %)

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 (total 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 (B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), Tobacco Heating System Menthol (mTHS), menthol Conventional Cigarette (mCC), Smoking Abstinence (SA), seast squares (LS), confidence intervals (CI).

Confidentiality Statement

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

Table 12 Reduction of BoExp Levels at Day 90 (mTHS:mCC and SA:mCC in %)

BoExp	HPHCs [aerosol phase]	ZRHM-REXA-07-JP		
			Reduction	95% CI
COHb (%)	CO [gas]	mTHS:mCC	-48%	-51.9 ; -44.4
		SA:mCC	-47%	-51 ; -42
MHBMA (pg/mg creat)	1,3-Butadiene [gas]	mTHS:mCC	-81%	-85.3 ; -75.4
		SA:mCC	-81%	-86.1 ; -74.7
3-HPMA (ng/mg creat)	Acrolein [gas]	mTHS:mCC	-46%	-53.1 ; -37.7
		SA:mCC	-61%	-66.8 ; -54
S-PMA (pg/mg creat)	Benzene [gas]	mTHS:mCC	-87%	-90.1 ; -83.4
		SA:mCC	-87%	-90.4 ; -82.6
Total NNAL (pg/mg creat)	NNK [particulate]	mTHS:mCC	-77%	-82.6 ; -68.9
		SA:mCC	-85%	-89 ; -78.4
Total 1-OHP (pg/mg creat)	Pyrene [particulate]	mTHS:mCC	-48%	-55.2 ; -39.6
		SA:mCC	-45%	-53.8 ; -34.8
Total NNN (pg/mg creat)	NNN [particulate]	mTHS:mCC	-71%	-78.5 ; -60
		SA:mCC	-94%	-95.8 ; -91.4
4-ABP (pg/mg creat)	4-Aminobiphenyl [particulate]	mTHS:mCC	-79%	-83 ; -74.1
		SA:mCC	-76%	-80.8 ; -68.8
1-NA (pg/mg creat)	1-Aminonaphthalene [particulate]	mTHS:mCC	-94%	-95.3 ; -91.8
		SA:mCC	-92%	-94.4 ; -89.5
2-NA (pg/mg creat)	2-Aminonaphthalene [particulate]	mTHS:mCC	-85%	-87 ; -81.6
		SA:mCC	-82%	-85.2 ; -77.9
o-toluidine (pg/mg creat)	*o*-Toluidine [gas]	mTHS:mCC	-41%	-58 ; -16.7
		SA:mCC	-32%	-54.1 ; 0.3
HMPMA (ng/mg creat)	Crotonaldehyde [gas]	mTHS:mCC	-50%	-57 ; -41.1
		SA:mCC	-48%	-56.3 ; -37.1
	Acrylonitrile [gas]	mTHS:mCC	-91%	-93 ; -88

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.

CEMA (ng/mg creat)		SA:mCC	-90%	-92.7 ; -86.4
HEMA (pg/mg creat)	HEMA [particulate]	mTHS:mCC	-55%	-62.8 ; -45.6
		SA:mCC	-56%	-64.6 ; -45.1
B[a]P (fg/mg creat)	Benzo[a]pyrene [particulate]	mTHS:mCC	-67%	-74.1 ; -57.9
		SA:mCC	-66%	-74 ; -54.5
3-HMPMA (ng/mg creat)	Crotonaldehyde [gas]	mTHS:mCC	-50%	-57 ; -41.1
		SA:mCC	-48%	-56.3 ; -37.1

Abbreviations: monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3 HPMA), S-phenylmercapturic acid (S-PMA), carboxyhemoglobin (COHb), carbon monoxide (CO), Total 1-hydroxypyrene (1-OHP), Total N-nitrosonornicotine (NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), o-toluidine, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy(a)benzopyrene (3-OH-B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (3 HMPMA), S-benzylmercapturic acid (S-BMA), Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, Tobacco Heating System Menthol (mTHS), menthol Conventional Cigarette (mCC)

Xenobiotic Metabolism:

The CYP1A2 enzymes are monooxygenases, which are involved in the activation of carcinogenic heterocyclic and aromatic amines, strong carcinogens associated with colon and bladder cancer. The expression of CYP1A2 itself is induced by polycyclic aromatic hydrocarbons (PAH) which are found in cigarette smoke.

At Baseline, CYP1A2 activity was comparable between study arms (range of approximately 70.45% to 74.18%). In the THS 2.2 Menthol and SA arms at Day 5, CYP1A2 activity had decreased by approximately 21.75% and 23.81%, respectively, while in the mCC arm, CYP1A2 activity increased by 9.65%. Baseline values for the PP Set for period 4 remained in a similar range and CYP1A2 activity decreased by 20.22% and 15.82% by Day 90 in the THS 2.2 Menthol and SA arms, respectively while in the mCC arm, CYP1A2 activity had increased by 15.77%.

The CYP1A2 activity in subjects who switched to THS 2.2 Menthol use was 28% (95% CI: 22.8, 32.9) lower than in subjects who continued to smoke mCC on Day 5, which was sustained during the Ambulatory Period with CYP1A2 activity 31% (95% CI: 22.3, 38.6) lower than mCC on Day 90. There was no notable difference in CYP1A2 activity between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (102%; 95% CI: 95.4, 110.0 on Day 5; 93%; 95% CI: 82.0, 104.4 on Day 90).

These results are in line with what is reported in the literature and are likely to be linked to the overall reduction of exposure to PAH. Overall, the results are indicative of a reduction of harmful metabolites resulting in reduced CYP1A2 activity after THS 2.2 Menthol use and SA.

Data Source:
Clinical Study Report section 11.2.4.3, Table 100-103 and Appendix 15, Table 15.2.4.24.1 and Table 15.2.4.24.2

Mutagenicity:

At Baseline, mean Ames mutagenicity test values were consistent between the THS 2.2 Menthol and mCC arms (17293.80 and 15132.36 REV/24h, respectively) and lower in the SA arm (14508.13 REV/24h). On

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.

Day 5, in the THS 2.2 Menthol and SA arms, mean Ames mutagenicity test values were approximately 2.3-fold and 1.6-fold lower than Baseline; while in the mCC arm, mean Ames mutagenicity test values were approximately 1.1-fold lower than Baseline. The results for THS 2.2 Menthol and SA were confirmed at Day 90 with mean Ames mutagenicity test values approximately 2.6- and 1.8-fold lower than at Baseline for THS 2.2 Menthol and SA, respectively; while in the mCC arm, mean Ames mutagenicity test values were approximately 1.1-fold higher than Baseline.

This decrease in urinary mutagenicity can be considered the result of the exposure reduction achieved when switching from mCC to THS Menthol 2.2 use.

Data Source:
Clinical Study Report section 11.3.1, Table 112, 113 and Appendix 15, Table 15.2.4.46.1

Nicotine Exposure over Time:

The NEQ urinary concentration adjusted for creatinine were comparable at Baseline across study arms.

In the mCC arm, mean NEQ values remained similar to Baseline throughout the Confinement Period, whereas NEQ values in the THS 2.2 Menthol arm decreased from Baseline to Day 1 before increasing gradually for the remainder of the Confinement Period (Figure 15). In the SA arm, NEQ levels steadily decreased from Day 1 to Day 5. Geometric mean NEQ values at Baseline and Day 5 were 5.71 and 6.16 mg/g creat, respectively, for the THS 2.2 Menthol arm, and 5.56 and 5.22 mg/g creat, respectively, for the mCC arm. These values corresponded to percent changes from Baseline at Day 5 of 16.00% % and -3.30%, for the THS 2.2 Menthol and mCC respectively. In the SA arm, geometric mean NEQ values decreased from Baseline (5.40 mg/g creat) to Day 5 (0.16 mg/g creat), as expected, corresponding to a -96.21% % change from Baseline.

During the Ambulatory Period, the profile of mean NEQ in the THS 2.2 Menthol arm was comparable to that of the mCC arm with percent changes from Baseline on Day 90 of 36.47% and 25.83% for the THS 2.2 Menthol and mCC arms, respectively. Geometric mean NEQ values in the THS 2.2 Menthol arm on Days 90 were 6.85 mg/g creat and 6.33 mg/g creat in the mCC arm, respectively. In the SA arm, NEQ values remained decreased from Baseline, as expected, with a -58.18% change from Baseline on Day 90 (0.37 mg/g creat).

In comparison to mCC, NEQ urinary concentration adjusted for creatinine both NEQ urinary concentration adjusted for creatinine and quantity excreted over 24 hours was approximately 16% (95% CI; 98.91, 136.04) and 9% (95% CI; 92.33, 129.10) higher, respectively, in the THS 2.2 Menthol arm compared to subjects who continued to smoke mCC on Day 5 (Table 13). On Day 90, no notable differences in LS means were observed for either NEQ urinary concentration adjusted for creatinine and quantity excreted over 24 hours between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC (Table 14).

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.

A similar trend was observed for nicotine and cotinine concentrations in plasma. On Day 5, the levels of nicotine and cotinine were 10% and 12% higher, respectively, in the THS 2.2 Menthol arm compared to the mCC arm (95% CI: -7.9, 32.3 for nicotine; and 95% CI: -0.13, 24.8 for cotinine). These differences decreased over time, starting from Day 60. There were no notable differences in evening plasma nicotine or cotinine levels in the THS 2.2 Menthol arm compared to the mCC arm on Day 90 (nicotine: 103%; 95% CI: 82.7, 129.3; cotinine: 106%; 95% CI: 89.9, 124.8).

For the nicotine PK profile on Day 5, peak plasma concentrations were 31% (95% CI: 6.9, 59.6; 20.70 ng/mL for THS 2.2 Menthol arm and 15.67 ng/mL for mCC arm) higher in the THS 2.2 Menthol arm compared to mCC arm, and weighted average concentrations were 27% (95% CI: 1.3, 59.2; 11.20 ng/mL for THS 2.2 Menthol arm and 8.72 ng/mL for the mCC arm) higher in the THS 2.2 Menthol arm compared to mCC arm.

For cotinine PK profile on Day 5, peak and weighted average plasma concentrations were 17% (95% CI: -5.1, 44.2; 192.10 ng/mL for the THS 2.2 Menthol arm and 163.42 ng/mL for the mCC arm) and 16% (95% CI: -6.3, 42.4; 171.25 ng/mL for the THS 2.2 Menthol arm and 147.39 ng/mL for the mCC arm) higher, respectively, for the THS 2.2 Menthol arm compared to the mCC arm.

The median time to peak concentration on Day 5 was identical for the THS 2.2 Menthol and mCC arms for both nicotine (12 hours) and cotinine (16 hours).

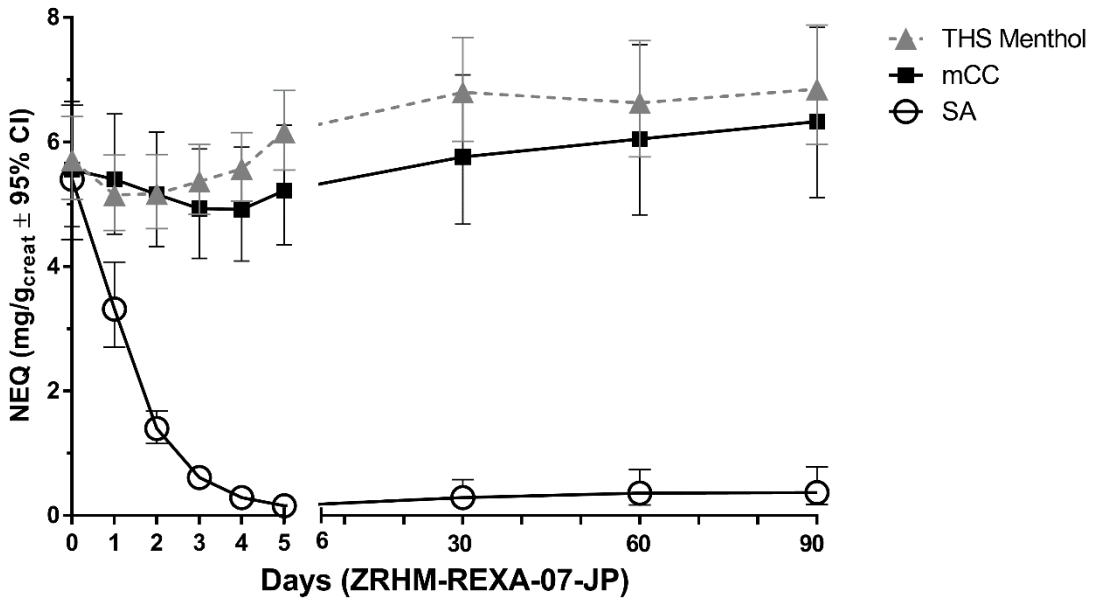


Figure 15 Geometric Mean NEQ Urinary Concentration Adjusted for Creatinine During the Course of the Study (PP Population)

Abbreviations: Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, nicotine equivalents adjusted to creatinine (NEQ_{adjC}), creatinine (creat), full analysis set (FAS), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI).

Confidentiality Statement

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

Table 13 Analysis of NEQ versus mCC on Day 5 (PP Set)

Parameter	Exposure	N	Geometric LS Mean	Geometric LS Mean Ratio (mTHS 2.2:mCC) (%)	CV%	95% CI
Concentration adjusted for creatinine (mg/g creat)	mTHS 2.2	76	6.06	116.00	43.83	98.91, 136.04
	mCC	42	5.23			

Adjusted geometric LS means and CIs from an ANCOVA model conducted with Baseline values, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Abbreviations: analysis of covariance (ANCOVA), full analysis set (FAS), menthol Conventional Cigarette (mCC); confidence interval (CI); coefficient of variation (CV); least squares (LS); nicotine equivalents (NEQ), number of subjects (N), per protocol (PP), Tobacco Heating System 2.2 Menthol (mTHS 2.2).

Table 14 Analysis of NEQ versus mCC on Day 90 (PP Set)

Parameter	Exposure	N	Geometric LS Mean	Geometric LS Mean Ratio (mTHS 2.2 : mCC) (%)	CV%	95% CI
Concentration adjusted for creatinine (mg/g creat)	mTHS 2.2	70	6.75	104.30	165.93	66.65, 163.20
	mCC	41	6.47			

Adjusted geometric LS means and CIs from an ANCOVA model conducted with Baseline values, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Abbreviations: analysis of covariance (ANCOVA), menthol Conventional Cigarette (mCC); confidence interval (CI); coefficient of variation (CV); least squares (LS); nicotine equivalents (NEQ), per protocol (PP), Tobacco Heating System 2.2 Menthol (mTHS 2.2), N = Number of Subjects

Data Source:
NEQ: Clinical Study Report section 11.2.4.2, Table 90, 91 and Appendix 15, Table 15.2.4.18.1, Appendix 15, Table 15.2.4.18.2, Appendix 15, Table 15.2.2.1.2 and Appendix 15, Table 15.2.2.3.2
Nicotine: Clinical Study Report section 11.2.4.2.1 Table 92, 93 and Appendix 15, Table 15.2.4.20.1 and Appendix 15, Table 15.2.4.20.2

Cotinine: Clinical Study Report section 11.2.4.2.2, Table 96, 97 and Appendix 15, Table 15.2.4.20.1 and Appendix 15, Table 15.2.4.20.2

Product Use:

At Baseline, the mean number of mCC consumed daily in the THS 2.2 Menthol and mCC arms was 13.1 (95% CI: 12, 14) and 12.5 (95% CI: 11, 14) mCC/day, respectively (Table 15). The number of THS Tobacco Sticks consumed daily in the THS 2.2 Menthol arm initially decreased from Baseline to Day 1 (11.4 [95% CI: 11, 12] THS Tobacco sticks/day) and subsequently increased to Day 5 (14.0 [95% CI: 13, 15] THS Tobacco sticks/day) (Figure 16). Similarly, the daily consumption of mCC in the mCC arm decreased compared to Baseline, with a mean of 11.0 (95% CI: 10, 12) mCC/day on Day 1, and then increased to

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.

13.6 (95% CIs: 12, 15) mCC/day on Day 5.

During the Ambulatory Period, the mean number of THS Tobacco Sticks consumed daily in the THS 2.2 Menthol arm returned to similar levels as Baseline, with a mean 11.7 (95% CI: 10.2, 13.1), 12.7 (95% CI: 11.1, 14.2), and 12.7 (95% CI: 11.2, 14.3) THS Tobacco sticks/day reported on Day 30, 60 and 90, respectively. In the mCC arm, the mean number of mCC consumed daily during the Ambulatory Period remained higher, compared to Baseline, with a mean 15.2 mCC/day (95% CI: 13.5, 16.8) reported on Day 90. For each product use period in the Ambulatory Period, the mean reported daily number of THS Tobacco Sticks was lower than the daily product use in the mCC arm (Figure 16 and Table 15).

Compliance to Product Use (FAS Population):

During the Confinement Period, as product use/regimen was fully controlled, 100% of subjects in each study arm (i.e., THS 2.2 Menthol, mCC, and SA) were compliant with their product regimen.

During the Ambulatory Period, in the THS 2.2 Menthol study arm at least 82.1% of subjects in each period exclusively used the assigned THS 2.2 Menthol product (100%). More than 85.9% of subjects in each period were classified as primarily THS 2.2 Menthol users (>95% of THS 2.2 Menthol arm). In the mCC arm all 41 subjects who completed the study, used the assigned product exclusively in each period, and in the SA study arm at least 92.5% remained abstinent in each period.

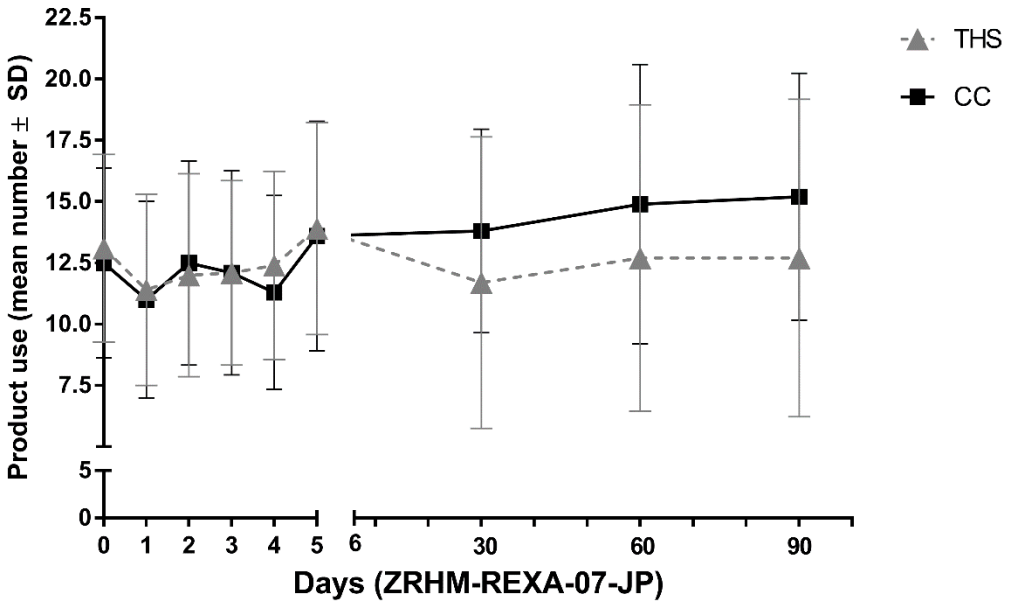


Figure 16 Product Consumption (Number of products used) from Baseline to Day 90

Abbreviations: Tobacco Heating System (THS), Conventional Cigarette (CC), standard deviation (SD)

Table 15 Number of THS Menthol Tobacco Sticks and menthol Conventional Cigarettes Consumed Daily in the Confinement Period – PP Set Period 1

Study Arm	Visit	N	Arithmetic Mean (SD)	Min	Median	Max

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.

mTHS 2.2	Day 0 (Baseline, mCC use)	76	13.1 (3.83)	4	13.0	22
	Day 1	76	11.4 (3.91)	4	11.0	24
	Day 2	76	12.0 (4.14)	3	11.0	28
	Day 3	76	12.1 (3.76)	5	11.0	21
	Day 4	76	12.4 (3.84)	5	11.5	21
	Day 5	76	13.9 (4.33)	6	13.0	22
	Day 30	74	11.7 (5.95)	0	11.0	26
	Day 60	71	12.7 (6.25)	0	11.9	27
	Day 90	70	12.7 (6.48)	0	12.0	29
mCC	Day 0 (Baseline)	42	12.5 (3.87)	5	12.0	24
	Day 1	42	11.0 (4.01)	5	10.0	25
	Day 2	41	12.5 (4.16)	7	11.0	25
	Day 3	41	12.1 (4.17)	7	11.0	23
	Day 4	41	11.3 (3.96)	6	10.0	25
	Day 5	41	13.6 (4.68)	6	12.0	24
	Day 30	41	13.8 (4.16)	8	12.9	24
	Day 60	41	14.9 (5.70)	7	14.2	39
	Day 90	41	15.2 (5.04)	9	14.1	35

Abbreviations: menthol Conventional Cigarette (mCC), maximum (Max), minimum (Min), number of subjects (N), standard deviation (SD), Tobacco Heating System 2.2 Menthol (mTHS 2.2)

Data Source: Clinical Study Report section 10.5, Table 33, 127 and Appendix 15, Tables 15.2.2.1.2

Human Puffing Topograhy (HPT):

Values were comparable at Baseline between the THS 2.2 Menthol and the mCC arms for each assessed parameter while subjects were using their usual brand of mCC (Table 16). On Day 1, total puff volume, average puff volume, average inter puff interval, and total smoking duration decreased from Baseline in the THS 2.2 Menthol arm. By Day 4, total puff volume, and average puff volume had increased from Day 1 and remained at approximately the Day 4 level through the rest of the study to Day 90, although, total puff volume did fluctuate between Days 30, 60 and 90. Average inter puff interval, and total smoking duration had continued to decrease from Day 1 and to Day 30. Total smoking duration gradually increased afterwards from Day 30 to Day 90, whereas average inter puff interval continued to decrease from Baseline from Day 30 to Day 90.

In contrast, total number of puffs, average puff duration, total puff duration, and puff frequency of the THS 2.2 Menthol arm increased from Baseline to Day 1 and either continued to increase or remained stable on Day 4. Total number of puffs increased slightly from Baseline to Day 1 and then decreased to approximately Baseline levels by Day 4, fluctuated over the exposure period to reach levels above Baseline on Day 90. A similar fluctuation was observed for average puff duration with levels at Day 90 comparable to what was observed on Day 1. Puff frequency, which had increased from Baseline on Days 1 and 4 in the Confinement Period, continued to increase through to Day 90.

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.

In the mCC arm most HPT parameters remained at approximate Baseline levels through the Confinement Period. Total puff volume decreased from Baseline and total number of puffs and total puff duration had a similar mCC profile during the Confinement Period as in the THS 2.2 Menthol arm, with an initial increase and then decrease to Day 4. In the case of total puff duration, the magnitude of the change was lower than for the THS 2.2 Menthol arm. Overall, the total number of puffs and total puff duration had a similar profile to the THS 2.2 Menthol arm, but at a lower overall magnitude (including Baseline). Average puff volume, average puff duration and puffing frequency remained at approximate Baseline levels throughout the study.

On Day 90, the total puff volume showed little difference between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (-23.5 mL difference (95% CI: -141.54, 94.61). This was achieved through an adaptation process for subjects using THS 2.2 Menthol who, compared to subjects in the mCC arm, increased the total number of puffs (3.19 puffs difference; 95% CI: 0.49, 5.89) and the puff frequency (+1.03 puffs/min [95% CI: 0.11, 1.94]) to compensate for a 9.67 mL (95% CI: 3.48, 15.87) lower average puff volume. Average puff duration was also 0.26 s (95% CI: -0.02, 0.54) longer in the THS 2.2 Menthol vs. mCC arm.

The total smoking duration was approximately 3.4 minutes for both arms (1.84 s difference; 95% CI: 35.93, 32.24).

Confidentiality Statement

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

Table 16 Analysis of HPT Parameters per-Cigarette During the Confinement and Ambulatory Period (Averaged over Visit) (PP Set)

Variable (units)	Time Point	Product Exposure	N	LS Mean	mTHS 2.2 – mCC Difference	95% CI
Total puff volume (mL)	Day 1	mTHS 2.2	50	723.39	-115.87	-233.83, 2.09
		mCC	28	839.26		
	Day 4	mTHS 2.2	49	758.25	-35.82	-170.54, 98.90
		mCC	25	794.07		
	Day 90	mTHS 2.2	43	729.85	-23.47	-141.54, 94.61
		mCC	25	753.32		
Average puff volume (mL)	Day 1	mTHS 2.2	50	41.27	-8.32	-13.84, -2.79
		mCC	28	49.58		
	Day 4	mTHS 2.2	49	45.42	-3.05	-9.45, 3.35
		mCC	25	48.47		
	Day 90	mTHS 2.2	43	41.49	-9.67	-15.87,-3.48
		mCC	25	51.17		
Average puff duration (s)	Day 1	mTHS 2.2	50	1.89	0.19	0.01, 0.38
		mCC	28	1.69		
	Day 4	mTHS 2.2	49	1.94	0.30	0.13, 0.47
		mCC	25	1.64		
	Day 90	mTHS 2.2	43	1.90	0.26	-0.02, 0.54
		mCC	25	1.64		
Total puff duration (s)	Day 1	mTHS 2.2	50	33.40	4.06	-0.71, 8.82
		mCC	28	29.34		
	Day 4	mTHS 2.2	49	32.45	4.92	0.29, 9.55
		mCC	25	27.53		
	Day 90	mTHS 2.2	43	34.06	10.12	3.31, 16.92
		mCC	25	23.94		
Puff frequency (puffs/min)	Day 1	mTHS 2.2	50	5.32	0.32	-0.08, 0.72
		mCC	28	5.00		
	Day 4	mTHS 2.2	49	5.37	0.22	-0.28, 0.73
		mCC	25	5.14		
	Day 90	mTHS 2.2	43	6.20	1.03	0.11, 1.94
		mCC	25	15.37		
Total number of puffs	Day 1	mTHS 2.2	50	19.05	0.87	-1.52, 3.26
		mCC	28	18.17		
	Day 4	mTHS 2.2	49	17.61	0.43	-1.70, 2.57
		mCC	25	17.17		
	Day 90	mTHS 2.2	43	18.57	3.19	0.49, 5.89
		mCC	25	15.37		
Average inter puff interval (s)	Day 1	mTHS 2.2	50	11.58	-1.07	-2.49, 0.36
		mCC	28	12.64		
	Day 4	mTHS 2.2	49	10.82	-1.91	-3.51, -0.31
		mCC	25	12.73		

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.

Total smoking duration (s)	Day 90	mTHS 2.2	43	9.75	-3.00	-5.25, -0.74
		mCC	25	12.74		
	Day 1	mTHS 2.2	50	235.24	-2.47	-27.44, 22.51
		mCC	28	237.70		
	Day 4	mTHS 2.2	49	214.85	-19.63	-51.28, 12.03
		mCC	25	234.48		
	Day 90	mTHS 2.2	43	202.93	-1.84	-35.93, 32.24
		mCC	25	204.77		

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed Baseline value, study arm, sex, and CC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

Abbreviations: analysis of covariance (ANCOVA), Menthol conventional cigarette (mCC); confidence interval (CI); coefficient of variation (CV); least squares (LS); nicotine equivalents (NEQ), , number of subjects (N), per protocol (PP), Tobacco Heating System 2.2 Menthol (mTHS 2.2).

Data Source: Clinical Study Report section 11.3.5, Table 126, 127 Appendix 15, Tables 15.2.4.43

Subjective Effects:

The present study included endpoints to assess the overall satisfaction, to evaluate if THS 2.2 could be an acceptable substitute to mCC.

The mean urge-to-smoke total scores were comparable across study arms at Baseline with mean urge-to-smoke total scores of 3.60 for the THS 2.2 Menthol arm, 3.22 for the mCC arm and 3.65 for the SA arm. For the THS 2.2 Menthol and mCC arms, the mean urge-to-smoke total scores remained stable over the 5 days of the Confinement Period (ranges of individual scores of 1.0 to 6.6 and 1.0 to 5.9, respectively). In the SA arm, the mean urge-to-smoke total score increased from Baseline to 5.01 on Day 1 (corresponding to a mean increase of 52.19%). From Day 2 to 5, total score values continously further decreased, with a value of 4.47 on Day 5. During the Ambulatory Period, the mean urge-to-smoke total scores remained stable compared to Baseline for THS 2.2 Menthol and mCC arms, with Day 90 values of 3.25 and 2.83, respectively and further decreased in the SA arm (Day 90 value: 2.19) (Figure 17).

Similar results were observed for withdrawal symptoms as assessed by the MNWS in the different study arms, where the MNWS total scores were comparable for the THS 2.2 Menthol, mCC and SA arms at Baseline with values of 0.89, 0.77 and 0.93 for the SA arm, respectively. For the THS 2.2 Menthol and mCC arms, the mean MNWS-R withdrawal score values remained stable over the 5 days of the Confinement Period (ranges of individual scores of 0.0 to 3.0 and 0.0 to 2.4, respectively). In the SA arm, the mean MNWS-R withdrawal score values increased from Baseline to 1.56 on Day 1 (corresponding to a mean increase of 138.91%). The mean MNWS-R withdrawal score value was 1.25 on Day 5. During the Ambulatory Period, the mean MNWS-R withdrawal scores remained stable compared to Baseline for the THS 2.2 Menthol and mCC arms, with Day 90 values of 0.77 and 0.60, respectively. In the SA arm, the MNWS-R withdrawal score was 0.47 at Day 90, corresponding to a decrease from Baseline of -39.20%.

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.

The MCEQ scale evaluated the overall satisfaction of THS 2.2 Menthol users compared to mCC smokers, and showed that on Day 1, the mean scores for the craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales were lower in subjects who switched to THS 2.2 Menthol use compared to those observed in subjects who continued to smoke mCC. Between Day 1 and the end of the Exposure Period the differences between the THS 2.2 Menthol and mCC arm became less and less pronounced for all subscales, with differences on Day 5 of -0.02, -0.13, -0.21, and -0.39 for the craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction subscales, respectively, and were negligible on Day 90 with differences of -0.15, 0.30, 0.00, and 0.01, respectively (Figure 18).

The change in taste, sensorial experience, ritual, and differences in the ISO tar and nicotine yield of THS 2.2 Menthol, are additional likely reasons for the observed differences in overall satisfaction. Nevertheless, overall subjective appreciation measures illustrate that TH2 2.2 Menthol offered a close experience to what was observed in mCC smokers. Different patterns observed for the corresponding domains in the SA arm tend to substantiate these observations. Further studies will determine if a longer time for adaptating to THS 2.2 Menthol will further close the gap in perceived smoking effects

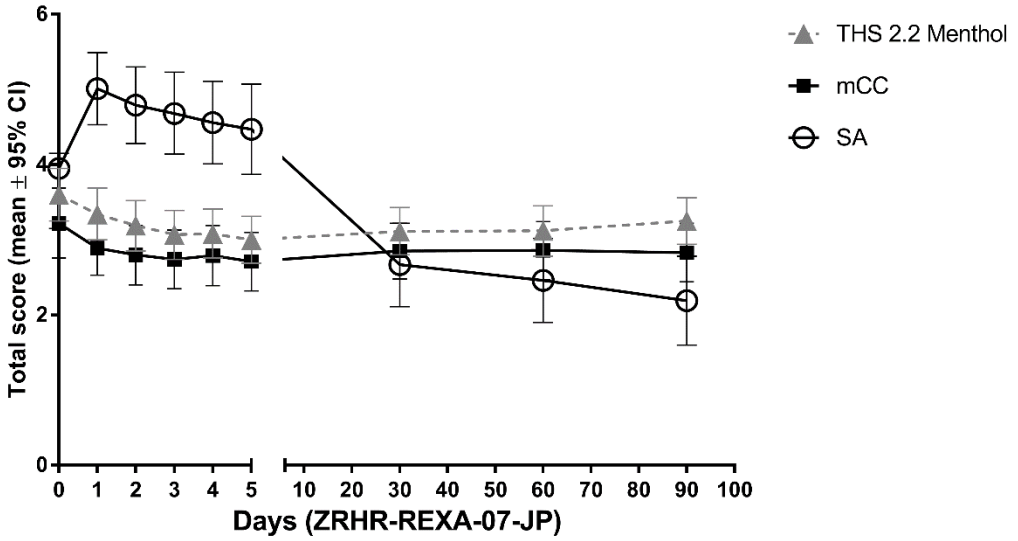


Figure 17 Total Score – Questionnaire of Smoking Urges from Baseline to Day 90

Abbreviations: Tobacco Heating System (THS), menthol Conventional Cigarette (mCC), Smoking Abstinence (SA), confidence intervals (CI)

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.

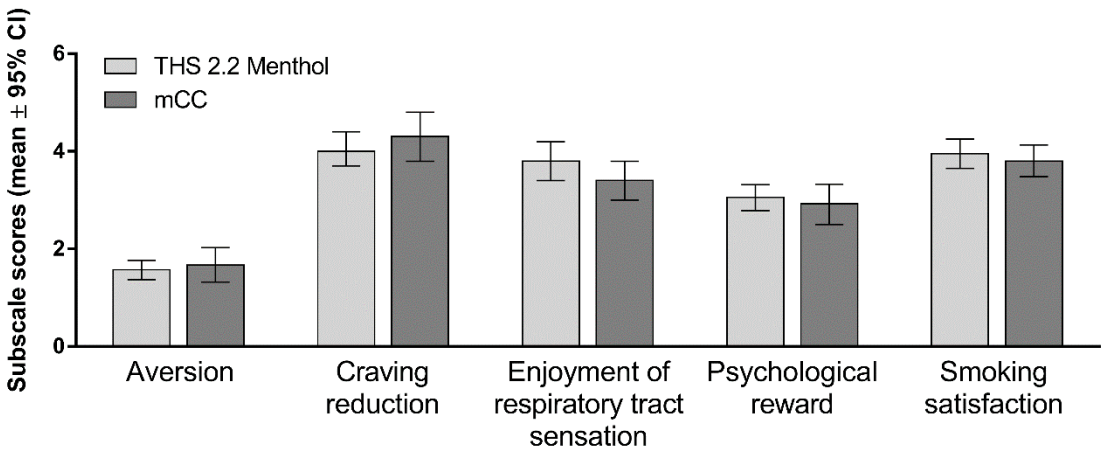


Figure 18 MCEQ Subscales on Day 90

Abbreviations: Tobacco Heating System (THS), menthol Conventional Cigarette (mCC), confidence intervals (CI)

Data Source:
QSU: Clinical Study Report section 11.3.4.1, Table 119, 120 and Appendix 15, Table 15.2.4.35.1 and Table 15.2.4.36.2
MNWS: Clinical Study Report section 11.3.4.2, Table 121, 122 and Appendix 15, Table 15.2.4.40.1 and Table 15.2.4.40.2
MCEQ: Clinical Study Report section 11.3.4.3, Table 123, 124, Appendix 15, Table 15.2.4.37.1 and Appendix 15, Table 15.2.4.38.1

Clinical Risk Endpoints:

Risk Marker of Oxidative Stress: 8-epi-PGF$_{2\alpha}$ (Concentration Adjusted for Creatinine) (Day 90 visit)

The levels of 8-epi-PGF$_{2\alpha}$ in subjects who switched to THS 2.2 Menthol were 12.7% (95% CI: 2.55, 21.81) lower than that observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (92.8% ratio; 95% CI: 82.80, 103.96) (Table 17).

Risk Marker of Platelet Activation: 11-DTX-B2 (Concentration Adjusted for Creatinine) (Day 90 visit)

The levels of 11-DTX-B2 in subjects who switched to THS 2.2 Menthol were 9.0% (95% CI: -2.94, 19.52) lower than that observed in subjects who continued to smoke mCC. The levels of 11-DTX-B2 in subjects who switched to THS 2.2 Menthol were 13% (95% CI: -0.53, 28.12) higher than that observed in subjects who abstained from smoking (Table 17).

Risk Marker of Endothelial Dysfunction: sICAM-1 (Day 90 visit)

The levels of sICAM-1 in subjects who switched to THS 2.2 Menthol use were 8.7% (95% CI: 2.05, 14.94) lower than that observed in subjects who continued to smoke mCC. There was no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (102.4% ratio; 95% CI: 95.24, 110.12) (Table 17).

Risk Markers of Lipid Metabolism: HDL Cholesterol, (Day 90 visit)

The HDL cholesterol levels were increased by approximately 4.5 mg/dL (95% CI: 1.17, 7.88) in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC. There was no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-1.8 difference; 95% CI: -5.28, 1.61) (Table 17).

Risk Markers of Inflammation: White Blood Cell Differential Counts (Day 90 visit)

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.

Total WBC (leukocytes) counts in subjects who switched to THS 2.2 Menthol use were 0.6 GI/L (95% CI: 0.10, 1.04) lower than that observed in subjects who continued to smoke mCC. There were no notable differences observed in the leukocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-0.2 difference; 95% CI: -0.65, 0.33) (Table 17).

Risk Markers Associated with Respiratory Diseases (Day 90 visit)

The value of FEV_1 (without bronchodilator) in subjects who switched to THS 2.2 Menthol use were 1.92 %pred (95% CI: -0.14, 3.97) higher than that observed in subjects who continued to smoke mCC. There were no notable differences observed in FEV_1 between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-0.02 difference; 95% CI: -2.15, 2.11) (Table 17).

Table 17 Analysis of Clinical Risk Endpoints at Day 90 (PP Population)

Disease Pathway	Marker	Expected SA Effect at 6m(*)	SA Effect vs mCC Day 90 (95% CI)	mTHS Effect vs mCC Day 90 (95% CI)
Lipid Metabolism	HDL-C	4.13 mg/dL	6.4 mg/dL	4.5 mg/dL (1.2, 7.6)
Inflammation	Total WBC count	-0.81 10^9/L	-0.41 10^9/L	-0.57 10^9/L (-1.0, -0.1)
Airway Impairment	FEV_1	2.18 %pred	1.93 % pred	1.91 % pred (-0.1, 4.0)
Endothelial Dysfunction	sICAM-1	20.0 %reduction	10.9 % reduction	8.7 % reduction (2.0, 14.9)
Oxidative Stress	8-epi-$PGF_{2\alpha}$	32.0 %reduction	6.0 % reduction	12.7 % reduction (2.5, 21.8)
Clotting	11-DTX-B_2	22.0 %reduction	19.4 % reduction	9.0 % reduction

Confidentiality Statement

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

	(-2.9, 19.5)

(*) Expected SA effect from literature data

Abbreviations: High density lipoprotein – Cholesterol (HDL-C); white blood cell count (WBC); forced expiratory volume in 1 second (FEV_1),; Soluble intercellular adhesion molecule-1 (sICAM-1); 8-epi-prostaglandin F2 alpha (8-epi-PGF2α); 11-dehydro-thromboxane B2 (11 DTX-B2); Menthol Tobacco Heating System (mTHS); menthol Conventional Ciagrette (mCC)

Data Source:
8-epi-$PGF_{2\alpha}$: Clinical Study Report section 11.2.6, Table 104, 105 and Appendix 15, Table 15.2.4.32.1-2.
11-DTX-B2: Clinical Study Report section 11.2.6, Table 106, 107 and Appendix 15, Table 15.2.4.32.1.1-Table 15.2.4.32.2.1

Safety:

There were no SAEs or severe AEs reported in this study and no randomized subjects were discontinued due to an AE.

Overall, there were 93 AEs reported post-randomization by 60 of the 160 subjects (37.5%) in the Safety Population, most of which were mild in severity. Only 2 AEs were considered moderate, with 1 moderate AE reported in the Confinement Period for the SA arm and 1 moderate AE reported in the Ambulatory Period for the mCC arm. The number of subjects reporting AEs in each study arm were 32/78 (41.0%) for the THS 2.2 Menthol arm, 14/42 (33.3%) for the mCC arm, and 14/40 (35.0%) for the SA arm.

Only 1 AE reported was considered to be related to the investigational product. This was diarrhea reported in the THS 2.2 Menthol arm during the Confinement Period and was considered not expected.

Overall, the most frequent AEs reported post-randomization were decreased hemoglobin, decreased neutrophils, increased blood TGs, and nasopharyngitis, with the majority of incidences occurring for these PTs during the Ambulatory Period. Throughout the study, 11/78 subjects (14.1%) in the THS 2.2 Menthol arm, 3/42 subjects (7.1%) in the mCC arm, and 3/40 subjects (7.5%) in the SA arm experienced decreased hemoglobin. Overall the proportion of subjects who experienced neutrophil count decreased, blood TG increased, and nasopharyngitis was ≤5.0% and the proportions of subjects in each study arm were similar.

Overall, 53 subjects in the THS 2.2 Menthol arm (67.9%) reported a total of 144 major device events or malfunctions; 26 subjects (33.3%) during the Confinement Period and 44 subjects (56.5%) during the Ambulatory Period. None of these events led to an AE.

Data Source:
Summary of AEs: Clinical Study Report section 12.1.1, Table 130-131 and Appendix 15, Table 15.2.6.1.1 and Table 15.2.6.5
AEs by study arm, SOC and PT: Clinical Study Report section 12.1.2 by study arm in Table 132-133 and in Appendix 15, Table 15.2.6.2.1, by SOC in Appendix 15, Table 15.2.6.3.1, and by PT in Appendix 15, Table 15.2.6.3.1.1

6.1.3.4.3.4 Conclusion

- The study demonstrated that switching from mCC smoking to THS Menthol 2.2 use resulted in substantial reductions in exposure to 15 selected HPHCs in a controlled settting which was sustained in a more "real-world", Ambulatory setting. The kinetics and the magnitude of decrease of BoExp levels observed in the THS 2.2 Menthol arm were approaching the levels observed in the SA arm.
- The exposure to nicotine,was similar between the THS 2.2 Menthol and mCC arms at Day 90 indicating that users adapted to the new product and achieved their desired nicotine levels.

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.

- The combination of the results of nicotine exposure and subjective effects measures showed that THS 2.2 Menthol offered comparable satisfaction to what was observed in mCC smokers after an initial adaptation phase.
- The directional shift of CREs in the THS 2.2 Menthol arm towards SA adds to the clinical relevance of the observed exposure reduction, and may indicate that the exposure reduction attained by switching to THS 2.2 Menthol may translate into biological and functional changes, potentially reducing the risk of smoking-related diseases with a prolonged use of THS 2.2 Menthol instead of mCC over time
- No SAEs or severe AEs were reported during this study, with the total number of AEs being evenly balanced across study arms.

In summary, the study demonstrated a sustained exposure reduction to HPHCs after switching to THS 2.2 Menthol in both confined and Ambulatory settings, close to levels observed after SA, transforming into favourable changes in CREs, while providing an acceptable alternative to users with regards to taste, ritual, sensorial experience, and nicotine delivery. Therefore, THS 2.2 Menthol might be a suitable substitute for mCC for adult smokers with the potential to reduce the risk of smoking-related diseases with a prolonged use of THS 2.2 Menthol instead of mCC over time.

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.

6.1.3.4.4 ZRHM-REXA-08-US

STUDY ZRHM-REXA-08-US	**Source: Section 7.3.1, Clinical Study Report ZRHM-REXA-08-US**

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 apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in Confinement and prolonged by 86 days in an Ambulatory setting.

Protocol-No.: ZRHM-REXA-08-US		
Date of final report: 29 April 2016		
Publication (reference):	ClinicalTrials.gov ID: NCT01989156. Reduced exposure study using THS 2.2 Menthol with 5 days in a Confinement setting followed by 86 days in an Ambulatory setting.	
Investigators:	Principal Investigator: 1) Dr. William Lewis, MD 2) Dr. Frank Farmer, MD	
Study center:	1) Covance Dallas Site, 1341 W. Mockingbird Ln., Suite 400E, Dallas, TX 75247. 2) Covance Daytona Beach Site, 1900 Mason Ave., Suite 140, Daytona Beach, FL 32117.	
Time of clinical part:	17 December 2013 - 12 October 2014	**Clinical Phase:** II (Product Performance)

Objective:

The aim of this study was to demonstrate reduction in exposure to selected HPHCs (except nicotine) in smokers switching to the THS 2.2 Menthol first in a confined and controlled setting, then followed by a more "real-worl" Ambulatory setting. THS 2.2 Menthol was also compared with smoking abstinence, used as a reference point. Furthermore, nicotine exposure, product use, subjective effects and changes in Human Puffing Topography over time in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC were assessed.

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.

Study design:

- Multi-center
- Ad-libitum use
- Randomized
- Parallel
- Open-label
- 90 Days of Exposure

Subjects:

• Planned:	160 subjects
• Enrolled:	164 subjects
• Randomized:	160 subjects
• Discontinuations:	21 subjects
• Completed:	139 subjects
• Safety population	165 subjects
• Full analysis set (FAS) population	160 subjects
• Per-protocol (PP) population (Day 90):	88 subjects

Main criteria for inclusion:

- Male or female subjects, minimum 22 years of age and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, spirometry, chest X-ray and laboratory tests at screening.
- Spirometry evaluation had to show forced expiratory volume in 1 second {FEV1}/forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV1 >80% predicted value, and post-bronchodilator FVC >0.8.
- Subjects were smoking at least 10 commercially available menthol CC (mCC) per day with a maximum yield of 1 mg nicotine International Organization for Standardization (ISO) mCC, as labeled on the cigarette package, for the last 4 weeks, and did not plan to quit smoking in the following 3 months. The smoking status was verified based on a urinary cotinine test (cotinine ≥200 ng/mL).
- Female subjects of child-bearing potential should have had a confirmed negative pregnancy test and used effective methods of contraception
- Provide written informed consent prior to study participation.
- Able to communicate well with the investigator and comply with the requirements of the study
- The subject was a current smoker who did not plan to quit smoking in the next 3 months.
- The subject was ready to accept using the THS 2.2 Menthol product or to accept 90 days of SA.

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.

mTHS 2.2:	Product: ISO nicotine Content: Use: Manufacturer:	Batch number of THS Tobacco Sticks: B-08545. Production date: 28 October 2013, Expiry date: 27 November 2014. 0.5 mg Ad-libitum use PMI
Conventional Cigarette:	Product: ISO nicotine Content: Use: Manufacturer:	Own menthol conventional cigarette brand. N/A Ad-libitum use Commercially available non-menthol conventional cigarettes

Smoking Abstinence	Smoking abstinence was used as a reference point without support of Nicotine Replacement Therapy (NRT) or any drug for smoking cessation support during the Confinement period. NRT use during the Ambulatory period was allowed if considered necessary by the Investigator or if required by the subject.
Duration of use:	The exposure period was approximately 91 days and was from Day 1, 06:30 AM until Discharge on Day 91. The exposure period included both exposure during the Confinement and the Ambulatory Setting. Product use periods were subsets of the exposure period and were defined as Period 1, Period 2, Period 3, and Period 4.
Analytical Method:	The analytical methods were developed at (b) (4) , and validated according to the standard operating procedures (SOPs) in effect during the conduct of the validation. These SOPs were written in accordance with the principles of good laboratory practice (GLP) described in 21 Code of Federal Regulation (CFR) Part 58 and the Guidance for Industry – Bioanalytical Method Validation (CDER, May 2001). (b) (4) (b) (4) (b) (4) , (b) (4) A detailed summary of the description of the analytical methods by BoExp, the matrix used and the validation are described in section 6.1.3.4.

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.

Primary Objectives:

1. To demonstrate the reduction of primary biomarkers of exposure (BoExp) to harmful and potentially harmful constituents (HPHCs) (except Total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol [NNAL]) in a Confinement setting in smokers switching from menthol conventional cigarette (mCC) to THS 2.2 Menthol, compared to smokers continuing to smoke mCC.

   Endpoints:

   - Monohydroxybutenylmercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA) (concentration adjusted for creatinine) in 24-hour urine, and carboxyhemoglobin (COHb) in blood (expressed as % saturation of hemoglobin) as measured on Day 5.

2. To demonstrate the reduction of Total NNAL in an Ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoint:

   - Total NNAL level (concentration adjusted for creatinine) in 24-hour urine fraction as measured on Day 90 Visit

Secondary Objectives:

1. To evaluate self-reported nicotine/tobacco product use including dual-use in an Ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to smoking abstinence (SA).

   Endpoints

   - Number of mCC or THS Menthol Tobacco Sticks smoked daily as reported on the usage log during the Confinement Period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary.

2. To determine the reduction of secondary BoExp in a Confinement setting and in an Ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoints

   - BoExp listed as secondary (expressed as quantity excreted or concentration adjusted for creatinine) as measured in 24-hour urine on Day 5 and on Day 90 Visit.

3. To describe the levels of primary and secondary BoExp over the entire exposure period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

   Endpoints

   - BoExp listed as primary and secondary from Day 1 to Day 5 and Day 30 Visit, Day 60 Visit and Day 90 Visit as follows:
     - Carbon monoxide (CO) (expressed as ppm) in exhaled breath.
     - COHb in blood (expressed as % saturation of hemoglobin).
     - Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine.

Confidentiality Statement

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

4. To determine the levels of nicotine over the entire exposure period (Confinement and Ambulatory Periods) in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to describe their levels over the entire exposure period.

   Endpoints

   - Nicotine equivalents (NEQ) (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine from Day 1 to Day 5 and on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Nicotine and cotinine in plasma from Day 1 to Day 5, and on Day 30 Visit, Day 60 Visit, and Day 90 Visit.

5. To describe the pharmacokinetic (PK) profiles of the nicotine and cotinine in a Confinement setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoints

   - Peak (highest concentration along the day) on Day 5.
   - Time to peak (t_{peak}, actual time when the peak was observed compared to the time of the first cigarette) on Day 5.
   - Weighted average concentration over 24 hours (C_{avg}) on Day 5.

6. To describe the change in cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

   Endpoints

   - Molar metabolic ratio of paraxanthine (PX)/caffeine (CAF) in plasma on Day 5 and Day 90 Visit.

7. To determine the changes in lung functions in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC.

   Endpoints

   - Full lung functions: Diffusion capacity for lung CO (DLCO), rate constant of CO (KCO), forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), vital capacity (VC) expressed as liters (L), total lung capacity (TLC), forced residual volume (FRV), inspiratory capacity (IC), mid expiratory flow (MEF 25-75).

8. To monitor the safety profiles during the study.

   Endpoints

   - Adverse events (AEs)/serious adverse events (SAEs), and device events including THS 2.2 Menthol malfunction/misuse.
   - Respiratory symptoms: cough assessment by visual analogue scale (VAS) and Likert scales and one open question.
   - Vital signs.
   - Electrocardiogram (ECG).
   - Clinical chemistry, hematology, and urine analysis safety panel.
   - Physical examination.
   - Concomitant medications.

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.

9. To monitor selected risk markers (CREs) in a Confinement and Ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

   Endpoints

   - Systolic and diastolic blood pressure on Day 6/Discharge Confinement, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Highly sensitive C-reactive protein (hs-CRP), homocysteine, blood glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC) in serum on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Fibrinogen in plasma on Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - Hemoglobin A1c (HbA1c) in blood on Day 90 Visit.
   - Apolipoprotein A1 (Apo A1) and Apolipoprotein B (Apo B) in serum on Day 90 Visit.
   - Soluble inter-cellular adhesion molecule-1 (sICAM-1) in serum on Day 6/Discharge Confinement, on Day 30 Visit, Day 60 Visit and Day 90 Visit.
   - White blood cell (WBC) and platelet count in blood on Day 6/Discharge Confinement, Day 30 Visit, Day 60 Visit, and Day 90 Visit.
   - 8-epi-prostaglandin F2α (8-epi-PGF2α) and 11-dehydro-thromboxane B2 (11-DTX-B2) in 24-hour urine on Day 5 and on Day 30 Visit, Day 60 Visit, and Day 90 Visit (expressed as concentration adjusted for creatinine).
   - Body weight and waist circumference on Day 90 Visit.

Exploratory Objectives:

1. To describe the following parameters in a Confinement and/or Ambulatory setting in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA:

   Endpoints

   - Excretion of mutagenic material in urine: Ames Mutagenicity test (YG1024+S9) on Day 5 and Day 90 Visit in 24-hour urine.
   - Subjective effect of smoking: Questionnaire of Smoking Urges-brief (QSU-brief); Minnesota Nicotine Withdrawal Scale (MNWS) - Revised on Day 5 and Day 90 Visit, and nicotine dependence as assessed by the Fagerström Test for Nicotine Dependence (FTND) questionnaire score on Day 90 Visit.
   - CYP2A6 activity: in plasma on Day 6/Discharge Confinement, and on Day 90 Visit using the molar metabolic ratio of *trans*-3'-hydroxycotinine/cotinine.

2. To describe the following parameters over the course of the study in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC:

   Endpoints

   - Product evaluation: Modified Cigarette Evaluation Questionnaire (MCEQ).
   - Smoking puffing behavior: HPT parameters and HPT questionnaire.
   - HPT parameters as measured per cigarette from the HPT device.

Confidentiality Statement

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

3. To describe the following parameter over the course of the study in smokers switching from mCC to THS 2.2 Menthol:

   Endpoints

   - Potential combustion occurrences in tobacco plugs: visual inspection of the tobacco plugs.

4. To describe the changes in levels of oxysterols on Day 6/Discharge Confinement and Day 90 Visit in smokers switching from mCC to THS 2.2 Menthol, and in smokers switching from mCC to SA.

   Endpoints

   - Plasma concentrations of 6α-hydroxy-5α-cholestane. 24(R)-hydroxycholesterol, 7α-hydroxycholesterol, 25-hydroxycholesterol, 5α,6α-epoxycholestanol, 27-hydroxycholesterol, 7-ketocholesterol, Total cholesterol (TC), 7β-hydroxycholesterol, 22(R)-hydroxycholesterol, 5β,6β-epoxycholestanol, 4ß-hydroxycholesterol.

5. To describe the product use over the course of the study according to the product preference of the subject.

   Endpoint

   - Number of mCC or THS Menthol Tobacco Sticks smoked daily as reported on the usage log during the Confinement Period and self-reported number of any nicotine/tobacco product use on a daily basis as reported on the product use electronic diary by product preference.

6. To describe the smokers' mental state for the intention to quit at Screening, on Day -2, Day 30 Visit, Day 60 Visit, and Day 90 Visit.

   Endpoint

   - By the means of the Prochaska 'Stage of Change' questionnaire.

7. To describe the changes and reductions in the levels of urinary BoExp and CREs measured in 4-hour urine fraction on Day 90 Visit in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC and to SA.

   Endpoints

   - Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 4-hour urine fraction:
   - Urinary CREs 8-epi-PGF2α and 11-DTX-B2 (expressed as quantity excreted and concentration adjusted for creatinine) in 4-hour urine fraction.

8. To evaluate in smokers switching from mCC to THS 2.2 Menthol, and smokers continuing smoking mCC the relationship between*:

   Endpoints

   - Primary and secondary BoExp and NEQ on Day 5 in 24-hour urine and on Day 90 Visit.

   *The reporting of the objective was the subject of a separate report.

9. To determine the concordance between the results for BoExp and CREs in 24-hour urine and in 4-hour urine fraction

   Endpoints

   - MHBMA, 3-HPMA, S-PMA, total NNAL, Total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, CEMA, HEMA, B[a]P, HMPMA, S-BMA, NEQ (expressed as quantity excreted and

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.

concentration adjusted for creatinine in 24-hour urine collection and concentration adjusted for creatinine in 4-hour urine fraction) at Baseline and at Day 90 Visit.

- 8-epi-PGF2α and 11-DTX-B2 (expressed as quantity excreted and concentration adjusted for creatinine in 24-hour urine collection and concentration adjusted for creatinine in 4-hour urine fraction) at Baseline and at Day 90 Visit.
- MHBMA, 3-HPMA, S-PMA, total NNAL, Total 1-OHP, Total NNN, 4-ABP, 1-NA, 2-NA, o-toluidine, CEMA, HEMA, B[a]P, HMPMA, S-BMA, NEQ (expressed as change in quantity excreted and concentration adjusted for creatinine in 24-hour urine collection and change in concentration adjusted for creatinine in 4-hour urine fraction from Baseline to Day 90 Visit).
- 8-epi-PGF2α and 11-DTX-B2 (expressed as change in quantity excreted and concentration adjusted for creatinine in 24-hour urine collection and change in concentration adjusted for creatinine in 4-hour urine fraction from Baseline to Day 90 Visit).

10. To monitor the BoExp in subjects quitting smoking according to the time since they quit.

Endpoints

- Carbon monoxide (expressed as ppm) in exhaled breath.
- COHb in blood (expressed as % saturation of hemoglobin).
- Urinary BoExp (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine collection and 4-hour urine fraction.
- NEQ (expressed as quantity excreted and concentration adjusted for creatinine) in 24-hour urine collection and 4-hour urine collection.
- Selected CREs (hs-CRP, homocysteine, blood glucose, LDL, HDL, TG, TC, fibrinogen, HbA1c, Apo A1, Apo B, sICAM-1, WBC count, platelet count, 8-epi-PGF2α, 11-DTX-B2) in respective body matrix when available.

Safety:

Adverse events, assessments of physical condition, concomitant medications, vital signs and body measurements, spirometry, respiratory symptoms, electrocardiogram, and monitoring of laboratory values. Device events, including THS 2.2 malfunction/misuse.

6.1.3.4.4.1 Statistical methods

6.1.3.4.4.1.1 Primary Analyses

The BoExp included as endpoints in the primary objectives and assessed on Day 5 for the comparison of THS 2.2 Menthol and mCC in a Confinement setting were MHBMA, 3-HPMA, S-PMA (concentration adjusted for creatinine) in 24-hour urine, and COHb in blood (expressed as % saturation of hemoglobin). The BoExp included as endpoints in the primary objective and assessed for the comparison of THS 2.2 Menthol and mCC in an Ambulatory setting was Total NNAL (adjusted for creatinine) in 24-hour urine as measured at the Day 90 Visit.

The endpoints included in the primary objectives were log-transformed ($base_e$) prior to analysis. An analysis of covariance (ANCOVA) model was used with terms for the log-transformed Baseline value, stratification factors (sex, average daily mCC consumption over the last 4 weeks as reported during Screening), and randomization arm. The least squares (LS) means and estimate of the difference were back-transformed. The geometric LS means for each randomization arm along with the ratio (THS 2.2 Menthol : mCC), two-sided 95% confidence interval (CI) and one-sided p-value were tabulated. These analyses were performed on the PP Set, the FAS, and the Compliant Population. A sensitivity analysis was also performed on the PP Set using a mixed model approach (conducted with Baseline value, study arm, sex, and mCC consumption

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.

reported at Screening as fixed effect factors).

The stratification and fixed effect factors considered in the ANCOVA model were chosen as exposure to HPHCs is known to be highly variable with cigarette consumption and sex described as the strongest factors. A dose-response relationship exists between cigarette consumption and exposure levels to HPHCs, with higher consumption resulting in higher exposure levels. Male smokers tend to have higher levels of exposure to HPHCs than females. Age was reported to be a potential factor, with higher levels of exposure with increasing age. However this effect is limited and might be confounded by longer smoking history and higher cigarette consumption with increasing age. Therefore age was not adjusted for in the model.

The least squares (LS) means and estimate of the difference along with its 95% CI were back-transformed before presenting in the tables. The geometric LS means for each product along with the ratio (mTHS 2.2 mCC) and 95% CI were presented in the tables.

The PP Set was the primary analysis data set for BoExp, CREs, and questionnaire assessments. The FAS was the primary analysis data set for compliance to randomization arm. The Per-Protocol (PP) population was defined as:

- Subjects that were correctly randomized and assigned study product.
- Subjects with at least one post-randomization product use (form mCC and mTHS).
- Subjects with at least one valid post-randomization BoExp measurement.
- Subjects that were adherent with their assigned study product.
- Subjects without major protocol deviations that impacted the validity of the evaluation of the study results.

The PP Population was selected as the primary analysis to assess the maximum exposure reduction achievable (optimal effect) in subjects who were using THS 2.2 Menthol ad-libitum and exclusively or at least predominantly, rather than the effect in the full population representing a heterogeneous exposure (e.g., as mixed product use, or non-use of the assigned product).

The optimal effect may be a somewhat ideal scenario, which differs from the real-world effect (effect under actual use setting) mainly by reducing the impact of non-compliance on the estimate.

6.1.3.4.4.1.2 Secondary Analyses

The BoExp included as endpoints in the primary objectives were analyzed in the secondary objectives at Day 5 for Total NNAL and Day 90 for COHb, MHBMA, 3-HPMA, and S-PMA for the PP Set and FAS using the same methodology as for the primary analysis, including the sensitivity analysis. The BoExp were also examined to compare the reductions in THS 2.2 Menthol versus SA using the same methodology as for the primary analysis for the PP Set.

The BoExp included as secondary endpoints were exhaled CO and Total 1-hydroxypyrene (1-OHP), Total N-nitrosonornicotine (Total NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), o-toluidine, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxybenzo(a)pyrene (B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), S-benzylmercapturic acid (S-BMA), and NEQ (all analyzed from a 24-hour urine collection) on Day 5 and Day 90 to compare reductions in THS 2.2 Menthol versus mCC and versus SA.

Biomarkers of exposure were analyzed using the same model described for the primary analysis. Exhaled CO was analyzed on the linear scale and arithmetic means and differences were calculated; whereas other BoExp were analyzed to calculate geometric means and ratios from the logarithmic scale. For all BoExp, if the results from the Day 5 analysis were significant (one-sided p-value ≤ 0.025) then the statistical significance was evaluated for the results of the Day 90 analysis. Least squares means for each product along with the difference or ratio, and 95% CI were presented.

Plasma Nicotine and cotinine concentrations at each post-Baseline time point were also analyzed in the log space using the same ANCOVA model as the primary analysis. Log-transformed C_{peak} and C_{avg} on Day 5 were compared using an analysis of variance (ANOVA) model with terms for stratification factors, and

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.

randomization arm. Geometric LS means for each product along with the ratio (mTHS 2.2 : mCC) and 95% CI were generated. t_{peak} on Day 5 was compared using the Wilcoxon Rank Sum test.

All PK concentrations and parameter summaries and analyses were performed on the PP Set and FAS as defined above.

Product compliance and extent of exposure was assessed by summarizing daily product use during the Confinement Period and the Ambulatory period by randomization arm, and product use category during the Ambulatory period. In addition, in the SA arm, the levels of CO in exhaled breath were summarized.

CYP1A2 and CYP2A6 were analyzed with the log-transformed Day 5 (Day 6 for CYP2A6) values using an ANOVA model. If the results from the Day 5 analyses were significant (one-sided p-value ≤0.025) then the analyses were repeated for the Day 90 values. Geometric LS means for each product along with the ratio (mTHS 2.2 : mCC) and 95% CI were presented in the tables. All CYP1A2 summaries and analyses were performed on the FAS and PP Set as above.

For analysis of CREs, the results on Days 5, 30, 60 and 90 Visits, as applicable, between the THS 2.2 Menthol and mCC arms, and between the THS 2.2 Menthol and SA arms using the same ANCOVA model as the primary analysis. If applicable and there was evidence of non-normality, the results were log-transformed prior to analysis. Least squares means for each product along with the difference (mTHS 2.2 - mCC) or ratio (mTHS 2.2 : mCC) and 95% CI were tabulated along with a forest plot of the results. All CRE summaries and analyses were performed on the PP Set and the FAS.

Product preference was summarized by randomization arm using the product which the subject preferred to be randomized to (THS 2.2 Menthol, mCC, SA or No preference).

For the MCEQ scores; QSU-Brief, MNWS and the HST parameters, Least squares means for each product along with the difference (mTHS 2.2 - mCC) with 95% CI were presented.

For all endpoints, descriptive statistics of the values and percent change from Baseline (where applicable), and supportive listings were provided.

6.1.3.4.4.2 Study Hypotheses and Evaluation Criteria

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 objectives, 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 objectives and the remaining BoExp. If the hypothesis test was significant at Day 5 then the endpoint was further tested Day 90.

The study was considered successful if a 50% or more reduction in MHBMA, 3-HPMA, S-PMA, and COHb on Day 5 and in Total NNAL on Day 90 was demonstrated in smokers switching from mCC to THS 2.2 Menthol as compared to smokers continuing to smoke mCC, using a one-sided test with 2.5% type I error probability.

6.1.3.4.4.3 Summary of selected results relevant for BoExp Assessment

Please refer to section 7.3.1 for full results.

6.1.3.4.4.3.1 BoExp Assessment

The study demonstrated that switching from mCC smoking to THS 2.2 Menthol use resulted in substantial and rapid reductions in BoExp levels to 15 selected HPHCs from Baseline to Day 5 ranging from -51% to -96%. These reductions were sustained through the Ambulatory period ranging from -34% to -86% at Day 90, while maintaining comparable levels of nicotine (Figure 19 and Table 18). The kinetics and the magnitude of decrease of BoExp levels observed in the THS 2.2 Menthol arm were approaching the levels observed in the SA arm (Figure 20 and Table 19). S-BMA levels did not show any difference in levels across all study arms.

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.

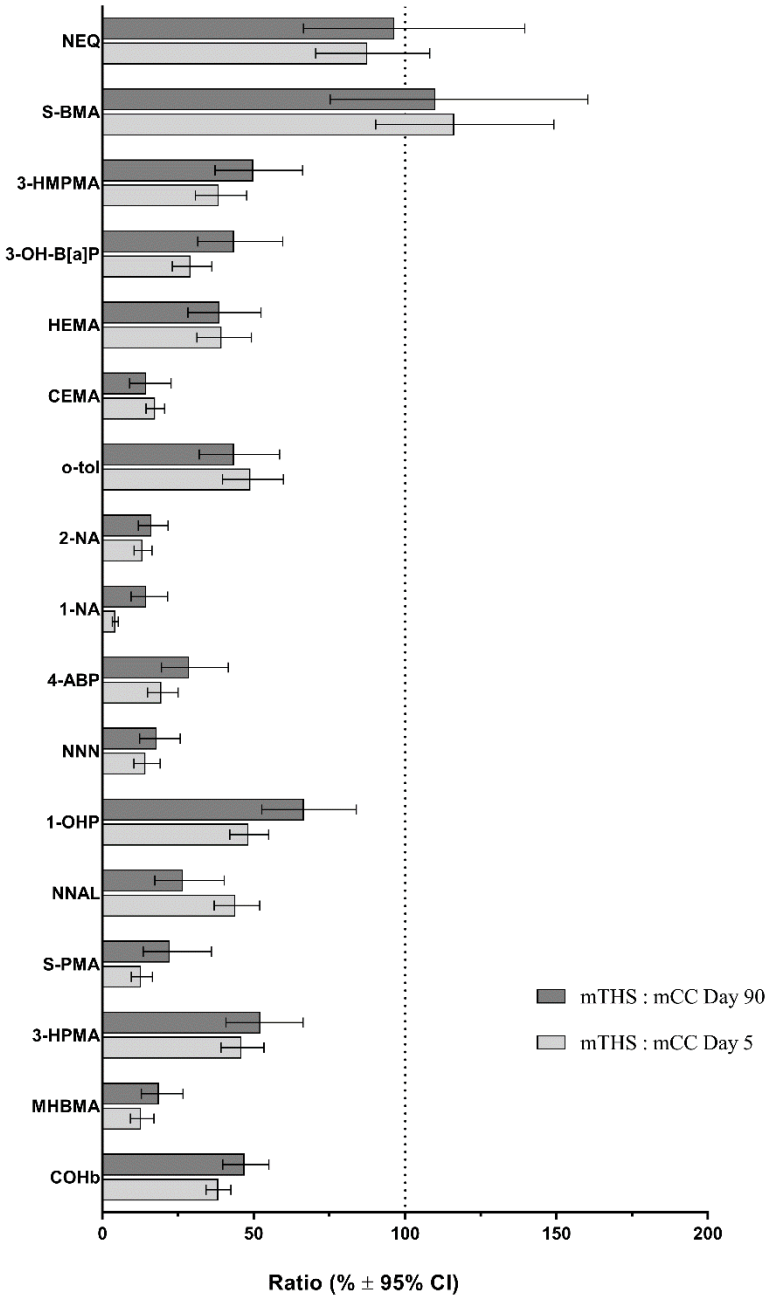


Figure 19 Adjusted Geometric LS Means and CIs from an ANCOVA Model of mTHS to mCC ratios of BoExp Levels at Day 5 and Day 90

Abbreviations: analysis of covariance (ANCOVA), 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, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy(a)benzopyrene (3-OH-B[a]P), 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 Menthol (mTHS), menthol Conventional Cigarette (mCC), Smoking Abstinence (SA), confidence interval (CI), least squares (LS).

Confidentiality Statement

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

Table 18 Analysis of BoExp in ZRHM-REXA-08-US at Day 5 and Day 90

BoExp	HPHCs [aerosol phase]			ZRHR-REXA-08-US Day 5	ZRHR-REXA-08-US Day 90
COHb	CO [gas]	mTHS:mCC Ratio	Geometric LS Mean	38.14%	46.76%
			95% CI	34.24; 42.47	39.75; 55.00
			p Value	<0.001	<0.001
MHBMA	1,3-Butadiene [gas]	mTHS:mCC Ratio	Geometric LS Mean	12.58%	18.52%
			95% CI	9.27; 17.05	12.85; 26.67
			p Value	<0.001	<0.001
3-HPMA	Acrolein [gas]	mTHS:mCC Ratio	Geometric LS Mean	45.77%	52.02%
			95% CI	39.22; 53.41	40.80; 66.33
			p Value	<0.001	<0.001
S-PMA	Benzene [gas]	mTHS:mCC Ratio	Geometric LS Mean	12.58%	22.08%
			95% CI	9.54; 16.58	13.52; 36.06
			p Value	<0.001	<0.001
Total NNAL	NNK [particulate]	mTHS:mCC Ratio	Geometric LS Mean	43.81%	26.41%
			95% CI	36.92; 51.97	17.31; 40.26
			p Value	<0.001	<0.001
Total 1-OHP	Pyrene [particulate]	mTHS:mCC Ratio	Geometric LS Mean	48.11%	66.46%
			95% CI	42.11; 54.96	52.67; 83.84
			p Value	<0.001	<0.001
Total NNN	NNN [particulate]	mTHS:mCC Ratio	Geometric LS Mean	14.06%	17.80%
			95% CI	10.38; 19.06	12.31; 25.75
			p Value	<0.001	<0.001
4-ABP	4-Aminobiphenyl [particulate]	mTHS:mCC Ratio	Geometric LS Mean	19.31%	28.48%
			95% CI	14.90; 25.01	19.51; 41.58
			p Value	<0.001	<0.001
1-NA		mTHS:mCC Ratio	Geometric LS Mean	4.15%	14.29%

Confidentiality Statement

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

	1-Aminonaphthalene [particulate]		**95% CI**	3.28; 5.25	9.47; 21.56
			p Value	<0.001	<0.001
2-NA	2-Aminonaphthalene [particulate]	**mTHS:mCC Ratio**	**Geometric LS Mean**	13.12%	16.04%
			95% CI	10.49; 16.40	11.87; 21.67
			p Value	<0.001	<0.001
o-toluidine	*o*-Toluidine [gas]	**mTHS:mCC Ratio**	**Geometric LS Mean**	48.72%	43.29%
			95% CI	39.70; 59.79	32.00; 58.55
			p Value	<0.001	<0.001
CEMA	Acrylonitrile [gas]	**mTHS:mCC Ratio**	**Geometric LS Mean**	17.23%	14.29%
			95% CI	14.44; 20.55	9.01; 22.67
			p Value	<0.001	<0.001
HEMA	HEMA [particulate]	**mTHS:mCC Ratio**	**Geometric LS Mean**	39.19%	38.49%
			95% CI	31.22; 49.20	28.28; 52.38
			p Value	<0.001	<0.001
3-OH-B[a]P	Benzo[a]pyrene [particulate]	**mTHS:mCC Ratio**	**Geometric LS Mean**	28.94%	43.33%
			95% CI	23.14; 36.20	31.52; 59.57
			p Value	<0.001	<0.001
3-HMPMA	Crotonaldehyde [gas]	**mTHS:mCC Ratio**	**Geometric LS Mean**	38.26%	49.63%
			95% CI	30.73; 47.64	37.25; 66.13
			p Value	<0.001	<0.001

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 (total 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 (3-OH-B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), Tobacco Heating System Menthol (mTHS), menthol Conventional Cigarette (mCC), Smoking Abstinence (SA), seast squares (LS), confidence intervals (CI).

Data Source: Primary Endpoints: Clinical Study Report section 11.1 and Appendix 15, Table 15.2.3.1.1 to Table 15.2.3.7
Secondary Endpoints: Clinical Study Report section 11.2 and Appendix 15, Table 15.2.4.1.1 to Table 15.2.4.68

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.

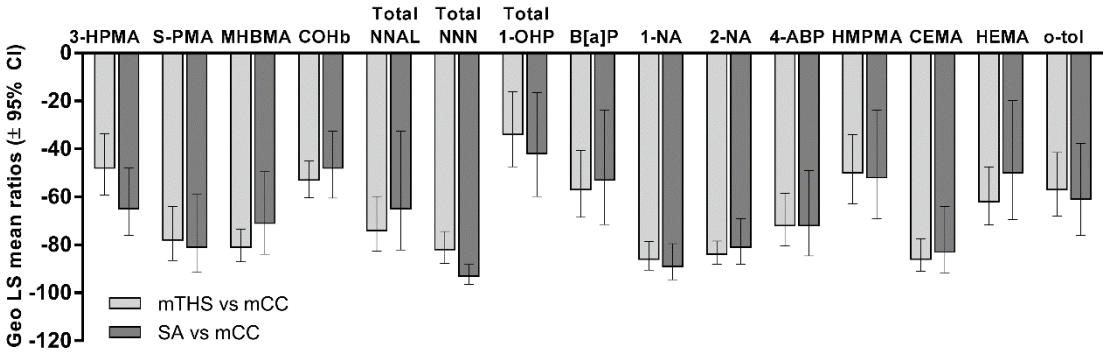


Figure 20 Reduction of BoExp Levels at Day 90 (mTHS:mCC and SA:mCC in %)

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 (total 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 (B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), Tobacco Heating System Menthol (mTHS), menthol Conventional Cigarette (mCC), Smoking Abstinence (SA), seast squares (LS), confidence intervals (CI).

Table 19 Reduction of BoExp Levels at Day 90 (mTHS:mCC and SA:mCC in %)

BoExp	HPHCs [aerosol phase]	ZRHM-REXA-08-US		
			Ratio	95% CI
COHb (%)	CO [gas]	mTHS:mCC	-53%	-60.2 ; -45
		SA:mCC	-48%	-60.4 ; -32.6
MHBMA (pg/mg creat)	1,3-Butadiene [gas]	mTHS:mCC	-81%	-87.1 ; -73.3
		SA:mCC	-71%	-83.8 ; -49.4
3-HPMA (ng/mg creat)	Acrolein [gas]	mTHS:mCC	-48%	-59.2 ; -33.7
		SA:mCC	-65%	-76.1 ; -47.9
S-PMA (pg/mg creat)	Benzene [gas]	mTHS:mCC	-78%	-86.5 ; -63.9
		SA:mCC	-81%	-91.4 ; -59
Total NNAL (pg/mg creat)	NNK [particulate]	mTHS:mCC	-74%	-82.7 ; -59.7
		SA:mCC	-65%	-82.1 ; -32.5
Total 1-OHP (pg/mg creat)	Pyrene [particulate]	mTHS:mCC	-34%	-47.3 ; -16.2
		SA:mCC	-42%	-59.8 ; -16.5
NNN (pg/mg creat)	NNN [particulate]	mTHS:mCC	-82%	-87.7 ; -74.3
		SA:mCC	-93%	-96.3 ; -88.2

Confidentiality Statement

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

4-ABP (pg/mg creat)	4-Aminobiphenyl [particulate]	mTHS:mCC	-72%	-80.5 ; -58.4
		SA:mCC	-72%	-84.6 ; -48.9
1-NA (pg/mg creat)	1-Aminonaphthalene [particulate]	mTHS:mCC	-86%	-90.5 ; -78.4
		SA:mCC	-89%	-94.5 ; -79.5
2-NA (pg/mg creat)	2-Aminonaphthalene [particulate]	mTHS:mCC	-84%	-88.1 ; -78.3
		SA:mCC	-81%	-88.1 ; -69
o-tol (pg/mg creat)	*o*-Toluidine [gas]	mTHS:mCC	-57%	-68 ; -41.5
		SA:mCC	-61%	-76.1 ; -37.6
CEMA (ng/mg creat)	Acrylonitrile [gas]	mTHS:mCC	-86%	-91 ; -77.3
		SA:mCC	-83%	-91.6 ; -63.9
HEMA (pg/mg creat)	HEMA [particulate]	mTHS:mCC	-62%	-71.7 ; -47.6
		SA:mCC	-50%	-69.5 ; -19.7
B[a]P (fg/mg creat)	Benzo[a]pyrene [particulate]	mTHS:mCC	-57%	-68.5 ; -40.4
		SA:mCC	-53%	-71.5 ; -23.7
HMPMA (ng/mg creat)	Crotonaldehyde [gas]	mTHS:mCC	-50%	-62.7 ; -33.9
		SA:mCC	-52%	-69.2 ; -23.8

Abbreviations: monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3 HPMA), S-phenylmercapturic acid (S-PMA), carboxyhemoglobin (COHb), carbon monoxide (CO), Total 1-hydroxypyrene (1-OHP), Total N-nitrosonornicotine (NNN), 4-aminobiphenyl (4-ABP), 1-aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), o-toluidine, 2-cyanoethylmercapturic acid (CEMA), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy(a)benzopyrene (3-OH-B[a]P), 3-hydroxy-1-methylpropylmercapturic acid (3 HMPMA), S-benzylmercapturic acid (S-BMA), Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, Tobacco Heating System Menthol (mTHS), menthol Conventional Cigarette (mCC), Smoking Abstinence (SA).

Xenobiotic Metabolism:

The CYP1A2 enzymes are monooxygenases, which are involved in the activation of carcinogenic heterocyclic and aromatic amines, strong carcinogens associated with colon and bladder cancer. The expression of CYP1A2 itself is induced by polycyclic aromatic hydrocarbons (PAH) which are found in cigarette smoke.

At Baseline, CYP1A2 activity was comparable between study arms (range of approximately 114.03% to 121.60%). In the THS 2.2 Menthol and SA arms at Day 5, CYP1A2 activity had decreased by approximately 32.81% and 34.53% respectively, while in the mCC arm, CYP1A2 activity increased by 3.56%.

Baseline values for the PP Set for period 4 remained in a similar range and CYP1A2 activity was decreased by 31.96% and 35.36% by Day 90 in the THS 2.2 Menthol and SA arms, respectively while in the mCC arm, CYP1A2 activity increased by 16.71%.

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.

The CYP1A2 activity in subjects who switched to THS 2.2 Menthol use was 36.48% (95% CI: 30.83, 41.66) lower than in subjects who continued to smoke mCC on Day 5, which was sustained during the Ambulatory Period with CYP1A2 activity 21.43% (95% CI: 6.98, 33.64) lower than mCC on Day 90. There was no notable difference in CYP1A2 activity between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (102%; 95% CI: 92.14, 111.89 on Day 5; 105%; 95% CI: 80.49, 137.86on Day 90).

These results are in line with what is reported in the literature and are likely to be linked to the overall reduction of exposure to PAH. Overall, the results are indicative of a reduction of harmful metabolites resulting in reduced CYP1A2 activity after THS 2.2 Menthol use and SA.

Data Source:
Clinical Study Report section 11.2.4.3, Table 107, 109 and Appendix 15, Table 15.2.4.24.1

Mutagenicity:

At Baseline, mean Ames mutagenicity test values were comparable between the THS 2.2 Menthol and SA arms (30251.24 and 28259.41 REV/24h, respectively) and lower in the mCC arm (14508.13 REV/24h).

On Day 5, in the THS 2.2 Menthol and SA arms, mean Ames mutagenicity values had decreased by approximately 72% and 62%, respectively. In the mCC arm, Ames mutagenicity test values (REV/24h) showed a mean increase from Baseline of approximately 47%. Consistent results were also observed in median values, with values on Day 5 70% and 85% lower than Baseline in the THS 2.2 Menthol and SA arms, respectively, and 76% higher than Baseline in the mCC arm.

Data Source:
Clinical Study Report section 11.3.1, Table 110 and Appendix 15, Table 15.2.4.64.1

Nicotine Exposure over Time:

The NEQ urinary concentrations adjusted for creatinine were comparable across study arms at Baseline.

In the mCC arm, mean NEQ values remained similar to Baseline throughout the Confinement Period, whereas NEQ values in the THS 2.2 Menthol arm decreased from Baseline to Day 2 before increasing gradually for the remainder of the Confinement Period (Figure 21). In the SA arm, NEQ levels steadily decreased from Day 1 to Day 5. Geometric mean NEQ values at Baseline and Day 5 were 7.52 and 6.74 mg/g creat, respectively, for the THS 2.2 Menthol arm, and 8.30 and 8.55 mg/g creat, respectively, for the mCC arm. These values corresponded to percent changes from Baseline of -1.77% and 6.02%, for the THS 2.2 Menthol and mCC respectively. In the SA arm, geometric mean NEQ values decreased from Baseline (7.68 mg/g creat) to Day 5 (0.23 mg/g creat), as expected, corresponding to a 92.74% change from Baseline. During the Ambulatory Period, mean NEQ values reached levels comparable to Baseline at Day 30 for the THS 2.2 Menthol and mCC arm before decreasing again moderately at Days 60 and 90 with percent changes from Baseline at Day 90 of -3.86% for the THS 2.2 Menthol arm, and -4.24% for the mCC arm, respectively. In the SA arm, NEQ values remained decreased from Baseline, but not to the same extent as during the Confinement period (-63.38% change from Baseline) which may reflect incomplete abstinence.

In comparison to mCC NEQ urinary concentration adjusted for creatinine was 13% lower in the THS 2.2 Menthol arm compared to subjects who continued to smoke mCC (95% CI: -8.2, 29.5) on Day 5. This difference progressively reduced over time and on Day 90, where NEQ levels were comparable between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC (96%; 95% CI: 66.4, 139.6) (Table 21 and Figure 21).

A similar trend was observed for nicotine and cotinine concentrations in plasma. On Day 5, the levels of nicotine and cotinine were 20% and 16% lower, respectively, in the THS 2.2 Menthol arm compared to the mCC arm (95% CI: 3.4, 34.3 for nicotine; and 95% CI: 1.8, 28.0 for cotinine). These differences decreased over time, starting from Day 30. On Days 30, 60, and 90, plasma nicotine concentrations were approximately 8%, 14%, and 28% lower in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC. Plasma cotinine concentrations were approximately 13%, 6%, and 3% higher on Days 30, 60, and 90 in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC.

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.

For the nicotine PK profile on Day 5, peak plasma concentrations and weighted average concentrations were 11% (95% CI: -8.5, 26.3; 20.96 ng/mL for THS 2.2 Menthol arm and 23.43 ng/mL for the mCC arm) lower and 15% (95% CI: -5.6, 31.3; 11.05 ng/mL for THS 2.2 Menthol arm and 12.97 ng/mL for the mCC arm) lower, respectively in the THS 2.2 Menthol arm compared to mCC arm. For cotinine PK profile on Day 5, peak and weighted average plasma concentrations were 15% (95% CI: -2.7, 29.1; 217.64 ng/mL for THS 2.2 Menthol arm and 254.96 ng/mL for the mCC arm) and 18% (95% CI: -0.9, 34.1; 189.00 ng/mL for THS 2.2 Menthol arm and 231.72 ng/mL for the mCC arm) lower, respectively, for the THS 2.2 Menthol arm compared to the mCC arm.

The median time to peak concentration on Day 5 was similar for the THS 2.2 Menthol and mCC arms for both nicotine (15.9 versus 14 hours, respectively) and cotinine (16 hours for both arms).

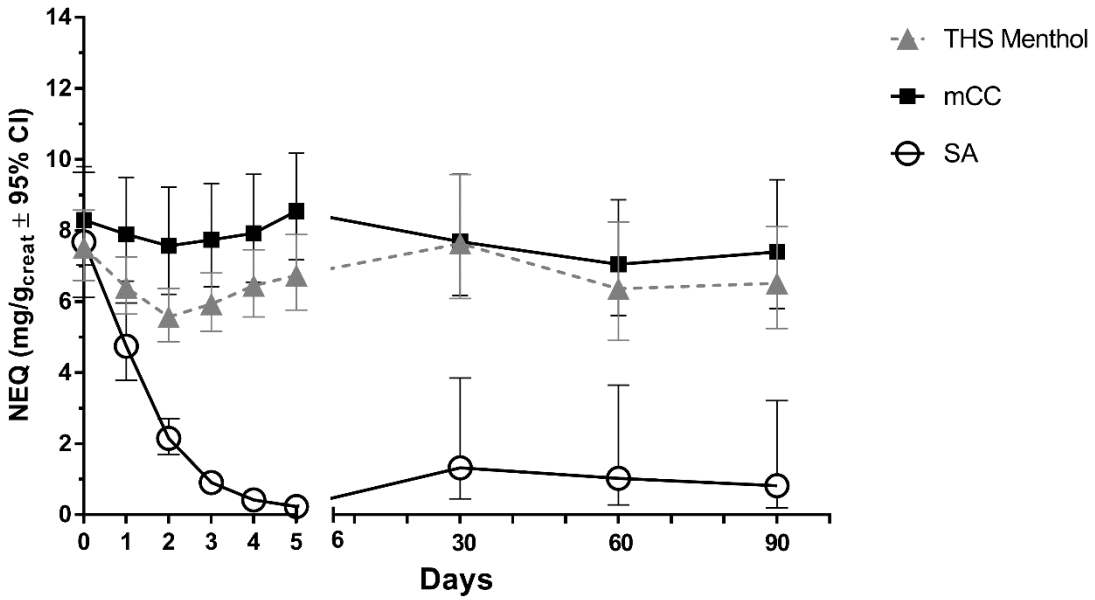


Figure 21 Geometric Mean NEQ Urinary Concentration Adjusted for Creatinine During the Course of the Study (FAS Population

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed Baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

Abbreviations: analysis of covariance (ANCOVA); Nicotine equivalents (NEQ) comprised of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide, nicotine equivalents adjusted to creatinine (NEQ_{adjC}), least squares (LS), creatinine (creat), full analysis set (FAS), Tobacco Heating System (THS), menthol Conventional Cigarette (mCC), Smoking Abstinence (SA), confidence intervals (CI).

Data Source: Appendix 15, Table 15.2.3.4 and Appendix 15, Table 15.2.4.18.1

Confidentiality Statement

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

Table 20 Analysis of NEQ versus mCC on Day 5 (PP Set)

Parameter	Exposure	N	Geometric LS Mean	Geometric LS Mean Ratio (mTHS 2.2:mCC) (%)	CV%	95% CI
Concentration adjusted for creatinine (mg/g creat)	THSm2.2	67	7.06	87.33	52.06	70.49, 108.18
	mCC	30	8.08			

Abbreviations: analysis of covariance (ANCOVA); confidence interval (CI); coefficient of variation (CV); least squares; menthol Conventional Cigarette (mCC); number of subjects (N); nicotine equivalents (NEQ); per protocol (PP); Tobacco Heating System 2.2 Menthol (mTHS 2.2).

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

Data Source: Appendix 15, Table 15.2.3.4

Table 21 Analysis of NEQ versus mCC on Day 90 (PP Set)

Parameter	Exposure	N	Geometric LS Mean	Geometric LS Mean Ratio (mTHS 2.2:mCC) (%)	CV%	95% CI
Concentration adjusted for creatinine (mg/g creat)	THSm2.2	43	6.59	96.30	89.23	66.43, 139.59
	mCC	29	6.84			

Adjusted geometric LS means and CIs from an ANCOVA model conducted on log-transformed values with log-transformed Baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors. Geometrical CV% of the ratio is estimated from the residual mean squares.

Abbreviations: analysis of covariance (ANCOVA); confidence interval (CI); coefficient of variation (CV); least squares; menthol Conventional Cigarette (mCC); number of subjects (N); nicotine equivalents (NEQ); per protocol (PP); Tobacco Heating System 2.2 Menthol (mTHS 2.2).

Data Source:
NEQ: Clinical Study Report section 11.2.4.2, Table 98, 99 and Appendix 15, Table 15.2.3.4
Nicotine: Clinical Study Report section 11.2.4.2.1, Table 100, 101 and Appendix 15, Table 15.2.4.20.1 and Table 15.2.4.21.1
Cotinine: Clinical Study Report section 11.2.4.2.2, Table 103, 105 and Appendix 15, Table 15.2.4.20.1 Table 15.2.4.22.1 and Table 15.2.4.22.1

Confidentiality Statement

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

Product Use:

At Baseline, the mean number of mCC consumed daily in the THS 2.2 Menthol and mCC arms was 12.2 (95% CI: 11, 13) and 12.2 (95% CI: 11.3, 13.1) cigarettes/day, respectively (Table 22). During the Confinement Period (Period 1), the number of THS Tobacco Sticks consumed daily in the THS 2.2 Menthol arm increased from a mean of 12.5 (95% CI: 11.4, 13.6) THS Tobacco sticks/day on Day 1 to 16.5 (95% CI: 15.1, 17.9) THS Tobacco sticks/day on Day 5 (Figure 22). The mean number of mCC consumed daily also slightly increased throughout the Confinement Period from 11.3 (95% CI: 10.1; 12.5) to 13.7 (95% CI: 12.2; 15.1) mCC/day at Day 1 and Day 5, respectively.

During the Ambulatory Period the mean number of THS Tobacco Sticks consumed daily in the THS 2.2 Menthol arm was lower than Day 5 but higher than the number of cigarettes consumed at Baseline, with a mean 14.7 (95% CI: 12.8, 16.7), 15.2 (95% CI: 12.9, 17.4), and 14.2 (95% CI: 12.1, 16.3) THS Tobacco sticks/day reported during Periods 2, 3, and 4. In the mCC arm, the mean number of mCC consumed daily during the Ambulatory Period remained higher than consumed at Baseline, with a mean 15.5 mCC/day (95% CI: 13.4, 17.7) reported during Period 4. For each product use period in the Ambulatory Period, the mean reported daily number of THS Tobacco Sticks was slightly lower than the daily product use in the mCC arm.

Compliance to Investigational Product and Product Use (PP population)

During Confinement, full compliance was examined for the THS 2.2 Menthol and mCC arms based on the product distribution log. Out of the 75 subjects in the THS 2.2 Menthol arm and 35 subjects in the mCC arm in the PP Set Population, all were exclusively using their allocated product during Confinement. For subjects in the SA arm, the abstinence during Confinement was verified daily using an exhaled CO breath test: Of 39 subjects in the SA arm, 6 subjects had CO breath test above 10 ppm, the cut-off point used to assess SA; all but 1 value above 10 ppm occurred on Day 6 and were excluded from the PP Set Population; 24 subjects had no CO breath test value above 10 ppm after Day 1 during Confinement.

During the Ambulatory period, full compliance was examined for THS 2.2 Menthol and mCC arms based on product consumption as recorded in the e-diary. Thirty-two, 36 and 41 subjects in periods 2, 3 and 4, respectively, for THS 2.2 Menthol arm were exclusively using THS 2.2 Menthol. One subject in the mCC arm was using another product in addition to mCC during periods 3 and 4. All other subjects were exclusively using mCC during the Ambulatory period. For subjects in the SA arm, 8, 7 and 7 subjects in periods 2, 3 and 4 were categorized as fully abstinent.

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.

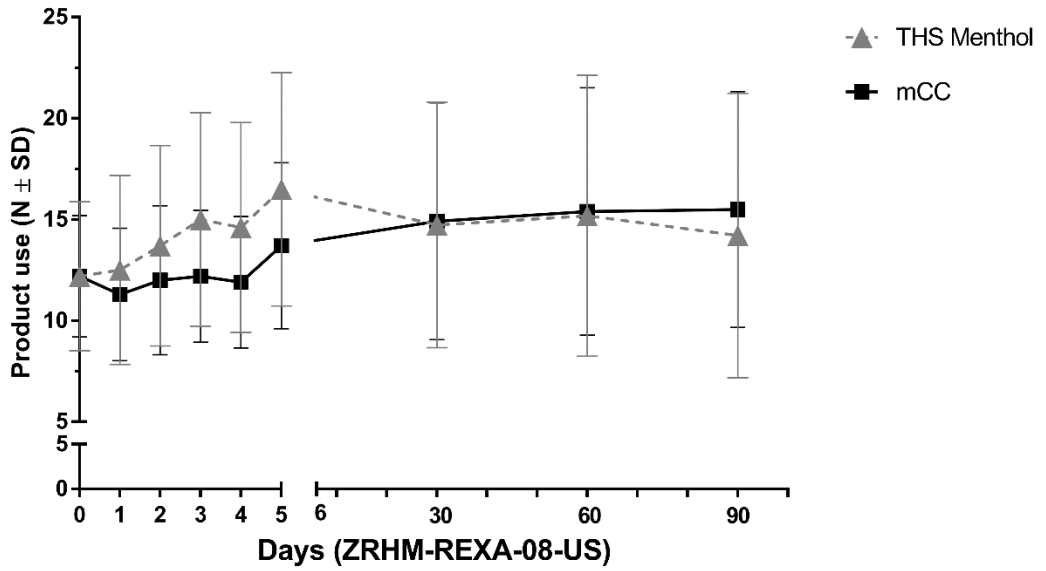


Figure 22 Product Consumption (Number of products used) from Baseline to Day 90

Abbreviations: Tobacco Heating System (THS), menthol Conventional Cigarette (mCC), standard deviation (SD)

Table 22 Number of THS Menthol Tobacco Sticks and Menthol Conventional Cigarettes Consumed Daily in the Confinement Period – PP Set Period 1

Study Arm	Visit	N	Mean (SD)	Min	Median	Max
mTHS 2.2	Day 0 (Baseline, mCC use)	75	12.2 (3.68)	6	11.0	20
	Day 1	75	12.5 (4.68)	3	12.0	23
	Day 2	75	13.7 (4.96)	3	12.0	26
	Day 3	75	15.0 (5.27)	3	14.0	28
	Day 4	75	14.6 (5.19)	1	14.0	26
	Day 5	75	16.5 (5.77)	2	16.0	31
	Day 30	39	14.73 (6.068)	3.1	14.42	35.5
	Day 60	39	15.18 (6.950)	0.0	15.59	33.5
	Day 90	47	14.21 (7.027)	0.0	14.38	30.2
mCC	Day 0 (Baseline)	35	12.2 (3.01)	6	12.0	19
	Day 1	35	11.5 (3.28)	4	11.0	19
	Day 2	34	12.0 (3.68)	6	11.5	21
	Day 3	34	12.2 (3.27)	7	12.0	20
	Day 4	34	11.9 (3.25)	7	11.5	18
	Day 5	34	13.7 (4.11)	7	14.0	23

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.

	Day 30	34	14.91 (5.854)	2.9	14.94	31.0
	Day 60	32	15.36 (6.124)	2.7	14.32	29.6
	Day 90	31	15.50 (5.840)	8.6	14.34	32.4

Abbreviations: menthol Conventional Cigarette (mCC), maximum (Max), minimum (Min), number of subjects (N), standard deviation (SD), Tobacco Heating System 2.2 Menthol (mTHS 2.2)

Data Source: Clinical Study Report section 10.5, Table 38 and Appendix 15, Tables 15.2.2.1.2 and 15.2.2.3.2.

Human Puffing Topography (HPT):

Values were comparable at Baseline between the THS 2.2 Menthol and the mCC arms for each assessed parameter while subjects were using their usual brand of mCC (Table 23).

On Day 1, total puff volume, average puff volume, total number of puffs, average puff duration, and puff frequency all increased from Baseline to Day 1 and continued to increase at Day 4 for subjects who switched to the THS 2.2 Menthol use compared to subjects who continued to smoke mCC. Total number of puffs and puff frequency remained comparable to the Day 4 value for the Ambulatory Period, whereas total puff volume, average puff volume, average puff duration, and total puff duration decreased from Day 4 to Day 30 and then stabilized for the remainder of the Ambulatory Period. In contrast, average inter puff interval and total smoking duration decreased from Baseline to Day 4 in the THS 2.2 Menthol arm for and continued to decrease through Day 4 and Day 30 before stabilizing for the remainder of the Ambulatory Period.

In the mCC arm HPT parameters remained generally stable during the entire study period, with values similar to those of Baseline.

On Day 90 the total puff volume of THS 2.2 Menthol versus mCC was 792.98 mL and 623.15 mL respectively in subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (169.84 mL difference; 95% CI: -69.94, 409.61). This difference was driven by an increase of the total number of puffs (3.34 puffs difference; 95% CI: 0.13, 6.81) and an increase in puff frequency of 2.22 puffs/min (95% CI: 0.55, 3.90) which was observed in subjects using THS 2.2 Menthol use in comparison with subjects who continued to smoke mCC. Average puff volume and average puff duration remained comparable between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC, with a 0.12 mL (95% CI: -11.29, 11.05) and 0.32 s (95% CI: -0.08, 0.71) difference, respectively.

The total smoking duration was approximately 1.5 minutes lower for subjects who switched to smoking THS 2.2 Menthol compared to subjects who continued to smoke mCC (-88.62 s difference; 95% CI: -146.88, -30.36).

The differences observed describe an adaptation process to a product with different characteristics and in particular with a significantly lower nicotine yield of THS 2.2 Menthol compared to subjects own brand. This would explain in particular the higher total puff volume and the longer product use time to achieve comparable levels of nicotine uptake with THS 2.2 Menthol compared to subjects own brand. It is to note, that these changes in HPT parameters had no effect on the reduction of exposure to HPHCs.

Confidentiality Statement

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

Table 23 Analysis of HPT Parameters per-Cigarette During the Confinement and Ambulatory Period (Averaged over Visit) (PP Set)

Variable (units)	Time Point	Product Exposure	N	LS Mean	mTHS 2.2 – mCC Difference	95% CI
Total puff volume (mL)	Day 1	mTHS 2.2	47	779.95	126.30	-32.72, 285.31
		mCC	23	653.65		
	Day 4	mTHS 2.2	46	868.42	187.51	28.11, 346.91
		mCC	21	680.90		
	Day 90	mTHS 2.2	26	792.98	169.84	-69.94, 409.61
		mCC	13	623.15		
Average puff volume (mL)	Day 1	mTHS 2.2	47	55.93	7.37	-1.57, 16.31
		mCC	23	48.56		
	Day 4	mTHS 2.2	46	60.19	8.35	-2.74, 19.44
		mCC	21	51.85		
	Day 90	mTHS 2.2	26	51.27	-0.12	-11.29, 11.05
		mCC	13	51.39		
Average puff duration (s)	Day 1	mTHS 2.2	47	2.09	0.35	0.09, 0.61
		mCC	23	1.75		
	Day 4	mTHS 2.2	46	2.19	0.49	0.22, 0.75
		mCC	21	1.70		
	Day 90	mTHS 2.2	26	1.98	0.32	-0.08, 0.71
		mCC	13	1.67		
Total puff duration (s)	Day 1	mTHS 2.2	47	30.11	7.88	2.78, 12.98
		mCC	23	22.23		
	Day 4	mTHS 2.2	46	32.29	11.12	5.55, 16.69
		mCC	21	21.17		
	Day 90	mTHS 2.2	26	31.92	12.79	2.94, 22.64
		mCC	13	19.13		
Puff frequency (puffs/min)	Day 1	mTHS 2.2	47	3.53	0.73	0.20, 1.26
		mCC	23	2.79		
	Day 4	mTHS 2.2	46	3.89	1.04	0.39, 1.69
		mCC	21	2.84		
	Day 90	mTHS 2.2	26	4.56	2.22	0.55, 3.90
		mCC	13	2.33		
Total number of puffs	Day 1	mTHS 2.2	47	14.74	1.22	-0.30, 2.75
		mCC	23	13.52		
	Day 4	mTHS 2.2	46	15.22	1.88	0.45, 3.30
		mCC	21	13.35		
	Day 90	mTHS 2.2	26	15.73	3.34	-0.13, 6.81
		mCC	13	12.40		
	Day 1	mTHS 2.2	47	17.44	-6.32	-9.29, -3.35
		mCC	23	23.76		

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.

Average inter puff interval (s)	Day 4	mTHS 2.2	46	15.62	-8.72	-12.34, -5.11
		mCC	21	24.34		
	Day 90	mTHS 2.2	26	15.80	-13.27	-21.02, -5.52
		mCC	13	29.07		
Total smoking duration (s)	Day 1	mTHS 2.2	47	267.86	-55.52	-85.03, -26.02
		mCC	23	323.38		
	Day 4	mTHS 2.2	46	257.38	-65.54	-100.43, -30.65
		mCC	21	322.92		
	Day 90	mTHS 2.2	26	243.31	-88.62	-146.88, -30.36
		mCC	13	331.93		

Adjusted LS means and CIs from an ANCOVA model conducted with Baseline value, study arm, sex, and mCC consumption reported at Screening as fixed effect factors.

Abbreviations: analysis of covariance (ANCOVA), Menthol conventional cigarette (mCC); confidence interval (CI); coefficient of variation (CV); least squares (LS); number of subjects (N); nicotine equivalents (NEQ), per protocol (PP), Tobacco Heating System 2.2 Menthol (mTHS 2.2).

Data Source: Clinical Study Report section 11.3.6, Table 122-124 and Appendix 15, Table 15.2.4.61.

Subjective Effects:

The present study included endpoints to assess overall satisfaction, to evaluate if THS 2.2 Menthol could be an acceptable substitute to mCC.

The average urge-to-smoke total scores were 4.19 for the THS 2.2 Menthol arm, 4.17 for the mCC arm, and 3.99 for the SA arm at Baseline (Figure 23). For the THS 2.2 Menthol and mCC arms, the average urge-to-smoke total scores remained stable over the 5 days of the Confinement Period (3.78 to 3.93 for the THS 2.2 Menthol arm and 3.86 to 4.13 for the mCC arm; ranges of individual scores were 1.0 to 7.0 for both arms). In the SA arm, the urge-to-smoke total score increased from Baseline to Day 1 (score of 5.16, corresponding to an increase of 52.64%). Total score value then slowly decreased and was comparable to the THS 2.2 Menthol and mCC arms at Day 5 (score of 3.95). During the Ambulatory Period, the mean urge-to-smoke total scores remained stable and comparable to Baseline over the 90 days of the Ambulatory Period for the THS 2.2 Menthol and mCC arms, with Day 90 values of 3.84 and 3.93, respectively. In the SA arm, following increases from Baseline in the urge-to-smoke scores during the Confinement Period, the urge-to-smoke total score was decreased from Baseline at Day 30 (-41.37%), with a -40.13% decrease at Day 90.

The average MNWS-R withdrawal score values were 0.87 for the THS 2.2 Menthol arm, 0.77 for the mCC arm, and 0.95 for the SA arm at Baseline. For the THS 2.2 Menthol and mCC arms, the average MNWS-R withdrawal score values remained comparable to Baseline through the Confinement Period (0.67 to 0.73 for the THS 2.2 Menthol arm and 0.69 to 0.76 for the mCC arm; ranges of individual scores were 0.0 to 3.1 for the THS 2.2 Menthol arm and 0.0 to 3.2 for the mCC arm). In the SA arm, the MNWS-R withdrawal score increased from Baseline to Day 2 (1.33, corresponding to an increase of 86.72%). The MNWS-R withdrawal score value then decreased slowly for the remainder of the Confinement Period and was 0.86 at Discharge. During the Ambulatory Period, the mean MNWS-R withdrawal score values decreased modestly for the THS 2.2 Menthol and mCC arms, with Day 90 values of 0.51 and 0.57, respectively, corresponding to changes from Baseline of -16.04% and -16.98%, respectively. In the SA arm, the MNWS-R withdrawal score also decreased from the end of the Confinement Period and was 0.38 at Day 90, which corresponded to a change from Baseline of -53.24%.

The MCEQ scale evaluated the overall satisfaction of THS 2.2 Menthol users compared to mCC smokers (Figure 24), and showed that Craving reduction (mTHS 2.2 – mCC difference: -1.1; 95% CI: -1.8, -0.4), enjoyment of respiratory tract sensation (difference: -0.6; 95% CI: -1.3, 0.1), and smoking satisfaction (difference: -1.0; 95% CI: -1.5, -0.4) were all lower for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC. Over the course of the study, these differences between the THS 2.2 Menthol and mCC arms for the craving reduction,

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.

enjoyment of respiratory tract sensation, and smoking satisfaction subscales reduced so that there were no notable differences observed for subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC (difference of 0.1 [95% CI: -0.2, 0.3] for aversion; difference of -0.2 [95% CI: -0.8, 0.5] for enjoyment of respiratory tract sensation; and difference of -0.4 [95% CI: -0.9, 0.1] for smoking satisfaction mCEQ subscales). Craving reduction was still notably lower on Day 90 but less of a difference than on Day 5 (mTHS 2.2 – mCC difference: -0.7; 95% CI: -1.4, 0.0).

The change in taste, sensorial experience, ritual, and differences in the ISO tar and nicotine yield of THS 2.2 Menthol, are additional likely reasons for the observed differences in overall satisfaction. Nevertheless, overall subjective appreciation measures illustrate that THS 2.2 Menthol offered a close experience to what was observed in mCC smokers. Different patterns observed for the corresponding domains in the SA arm tend to substantiate these observations. Further studies will determine if a longer time for adapting to THS 2.2 will further close the gap in perceived smoking effects.

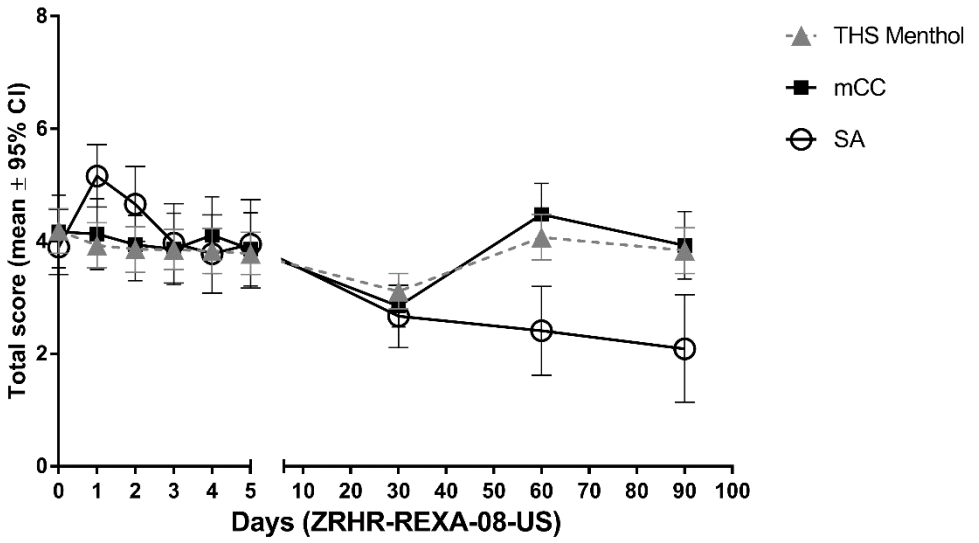


Figure 23 Total Score – Questionnaire of Smoking Urges from Baseline to Day 90

Abbreviations: Tobacco Heating System (THS), menthol Conventional Cigarette (mCC), Smoking Abstinence (SA), confidence intervals (CI)

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.

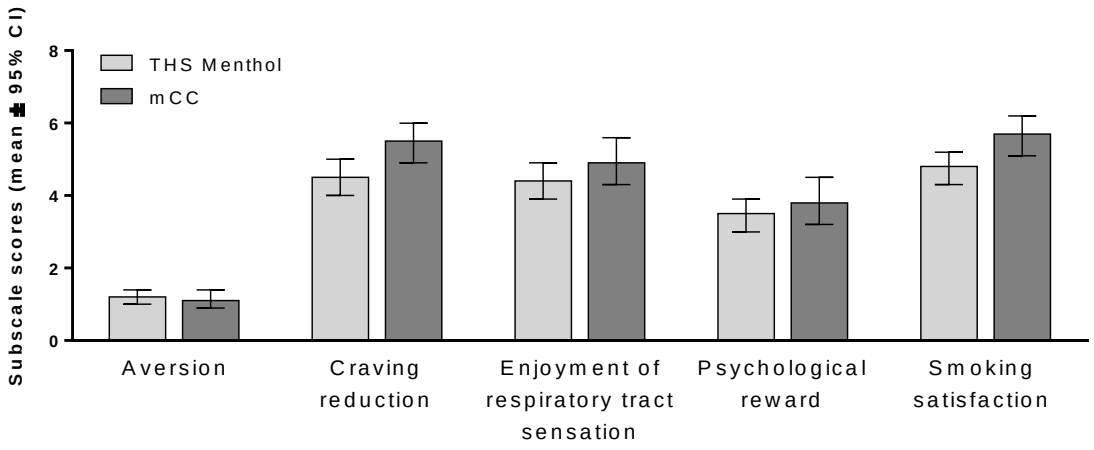


Figure 24 MCEQ Subscales on Day 90

Abbreviations: Tobacco Heating System (THS), menthol Conventional Cigarette (mCC), confidence intervals (CI)

Data Source:
QSU: Clinical Study Report section 11.3.4.1, Table 117, 118 and Appendix 15, Table 15.2.4.52.1
MNWS: Clinical Study Report section 11.3.4.2, Table 119, 120 and Appendix 15, Table 15.2.4.57.1
MCEQ: Clinical Study Report section 11.3.4.3, Table 121, 122 and Appendix 15, Table 15.2.4.55.1

Clinical Risk Endpoints:

Risk Marker of Oxidative Stress: 8-epi-PGF$_{2\alpha}$ (Concentration Adjusted for Creatinine) (Day 90 visit)

The levels of 8-epi-PGF$_{2\alpha}$ in subjects who switched to THS 2.2 Menthol were 14% (95% CI: 2.0, 23.6) lower than that observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (95% ratio; 95% CI: 77.7, 115.1) (Table 24).

Risk Marker of Platelet Activation: 11-DTX-B2 (Concentration Adjusted for Creatinine) (Day 90 visit)

There were no notable differences in levels of 11-DTX-B2 between subjects who switched to THS 2.2 Menthol and those who continued to smoke mCC (96% ratio; 95% CI: 75.4, 123.3) and no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking (104% ratio; 95% CI: 70.4, 153.2) (Table 24).

Risk Marker of Endothelial Dysfunction: sICAM-1 (Day 90 visit)

The levels of sICAM-1 in subjects who switched to THS 2.2 Menthol was 11% (95% CI: 4.0, 16.7) lower than that observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (99% ratio; 95% CI: 88.7, 111.1) (Table 24).

Risk Markers of Lipid Metabolism: HDL Cholesterol, (Day 90 visit)

There were no notable differences observed in the levels HDL-C (1.37 difference, 95%CI: -2.26; 5.00), LDL-C, total cholesterol, Apo A1 and Apo B as well as triglycerides between subjects who switched to THS 2.2 Menthol use, subjects who continued to smoke mCC, and to subjects who abstained from smoking (Table 24).

Risk Markers of Inflammation: White Blood Cell (WBC) Differential Counts (Day 90 visit)

There were no notable differences observed in the WBC counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (0.2 GI/L difference between mTHS and mCC;

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.

95% CI: -0.5, 0.8). Leukocyte count was higher by 1.1 GI/L for subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking (95% CI: 0.1, 2.2) (Table 24).

Risk Markers for Respiratory Diseases: Lung Functions

There were no notable differences at Day 90 in gas transfer parameter (DLCO and KCO), lung volume parameters (FRC, TLC, and IC), or spirometry parameters (FEV_1, FVC, FEV_1/FVC, and MEF_{25-75}) between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC. Vital capacity was 0.10 L higher in subjects who switched to THS 2.2 Menthol compared to subjects who continued to smoke mCC (95% CI: 0.00, 0.21).

Based on 7 to 9 subjects available for analyses in the SA arm, there were no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking at both Day 6 and Day 90 in all lung function parameters except for FRV and IC which were 0.46 L (95% CI: 0.07, 0.76) lower and 0.88L (95% CI: 0.43, 1.33) higher at Day 91/Discharge/Ambulatory in subjects who switched to THS 2.2 Menthol compared to subjects who abstain from smoking.

Confidentiality Statement

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

Table 24 Analysis of Clinical Risk Endpoints at Day 90 (PP Population)

Disease Pathway	Marker	Expected SA Effect at 6m(*)	SA Effect vs mCC Day 90 (95% CI)	mTHS Effect vs mCC Day 90 (95% CI)
Lipid Metabolism	HDL-C	4.13 mg/dL	0.03 mg/dL (-5.77; 5.84)	1.37 mg/dL (-2.26;5.00)
Inflammation	WBC	-0.81 10^9/L	-0.94 10^9/L (-2.00; 0.13)	0.17 10^9/L (-0.46; 0.81)
Airway Impairment	FEV_1	2.18 %pred	1.95 % pred (-3.35; 7.26)	0.49 % pred (-2.77; 3.76)
Endothelial Dysfunction	sICAM-1	20.0 %reduction	9.90 % reduction (-1.07; 19.69)	10.6 % reduction (4.03; 16.7)
Oxidative Stress	8-epi-$PGF_{2\alpha}$	32.0 %reduction	8.51 % reduction (-11.8;25.13)	13.46 % reduction (1.96; 23.6)
Clotting	11-DTX-B_2	22.0 %reduction	7.15 % reduction (-38.3; 37.67)	3.56 % reduction (-23.3; 24.6)

(*) Expected SA effect from literature data

Abbreviations: High density lipoprotein – Cholesterol (HDL-C); white blood cell count (WBC); forced expiratory volume in 1 second (FEV_1), Soluble intercellular adhesion molecule-1 (sICAM-1); 8-epi-prostaglandin F2 alpha (8-epi-PGF2α); 11-dehydro-thromboxane B2 (11 DTX-B2)

Data Source:
8-epi-$PGF_{2\alpha}$: Clinical Study Report section 11.3.3.1, Figure 24 and Appendix 15, Table 15.2.4.32.1
11-DTX-B2: Clinical Study Report section 11.3.3.2, Figure 26 and Appendix 15, Table 15.2.4.32.1

Safety:

There were no SAEs reported by any randomized subject in this study and no randomized subjects were discontinued due to an AE. Prior to randomization, 4 subjects were discontinued from the study, of which 2 subjects were discontinued due to an AE. One subject reported 2 SAEs which were not related to the IP or study procedures and led to the discontinuation of the subject from the study.

Overall, there were 195 AEs reported post-randomization by 95 of the 160 subjects (59.4%) in the randomized Safety Population, most of which were mild or moderate in severity. Twelve severe AEs were reported during the Ambulatory phase, all of which were due to abnormal clinical laboratory findings and were unrelated to IP or study procedures.

The incidence of post-randomization AEs was comparable in the THS 2.2 Menthol arm (52 of 80 subjects [65.0%]) and the SA arm (23 of 39 subjects [59.0%]), and slightly lower in the mCC arm (20 of 41 subjects [48.8%]). Similarly, the frequency of AEs was comparable in the THS 2.2 Menthol arm (114 AEs from 80 subjects and the SA arm (49 AEs from 39 subjects), and slightly lower in the mCC arm (32 AEs from 41 subjects).

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.

There were 6 AEs reported which were considered to be related to the IP during the Confinement Period, and 2 AEs which were considered to be related in the Ambulatory Period. Seven AEs were considered as related to study procedures, with 6 occurring during the Confinement Period and 1 during the Ambulatory Period.

The most frequent AEs by PT reported were decreased hemoglobin, increased lymphocyte count, upper respiratory tract infection, and headache with the majority of incidences occurring for these PTs during the Ambulatory Period. Throughout the study, 11/80 subjects (13.8%) in the THS 2.2 Menthol arm, 4/41 subjects (9.8%) in the mCC arm, and 6/39 subjects (15.4%) in the SA arm experienced decreased hemoglobin (hemoglobin decreased). The proportion of subjects who experienced increased lymphocyte count, upper respiratory tract infection, and headache was <10% of the subjects in each study arm.

There were no clinically relevant abnormalities in vital signs or ECG findings.

Data Source:
Summary of AEs: Clinical Study Report section 12.1.1, Table 130 and Appendix 15, Table 15.2.6.1 and 15.2.6.7. AEs by study arm, SOC and PT: Clinical Study Report section 12.1.2 by study arm in Table 131, 133, 134, 135 and in Appendix 15, Table 15.2.6.1 and Table 15.2.6.2., by SOC in Appendix 15, Table 15.2.6.3, and by PT in Appendix 15, Table 15.2.6.3

6.1.3.4.4.4 Conclusion

- The study demonstrated that switching from mCC smoking to THS 2.2 Menthol use resulted in substantial reductions in exposure to assessed HPHCs, with the majority of the reduction achieved after 5 Days in Confinement and sustained throughout the 86 days of the Ambulatory Period of the study. The kinetics of the reductions observed for the majority of BoExp levels in the THS 2.2 Menthol arm were similar to those observed in the SA arm, in both the timing and magnitude of the reductions.
- After an initial decrease in nicotine uptake from Baseline to Day 2, the exposure to nicotine was comparable from Day 30 onwards between the THS 2.2 Menthol and mCC arms indicating that users adapted gradually to the new product and achieved their desired nicotine levels.
- The observed changes over time in product use, HPT and nicotine exposure were most likely the result of an adaptation process engaged by users to achieve the levels of nicotine desired when switching to a new product, with different characteristics and a lower nicotine yield to that of the own preferred mCC.
- Subjective effects measures indicated that THS 2.2 Menthol offered comparable satisfaction to what was observed in mCC smokers after an initial adaptation phase early on in the study. Different patterns observed for the corresponding domains in the SA arm tended to substantiate these observations.
- Initial changes in some of the CREs assessed and relevant to disease pathways of smoking-related diseases, shifting towards the direction of smoking abstinence, indicate that the exposure reduction achieved with switching to THS 2.2 Menthol may translate into reduced risk of smoking-related diseases with switching from mCC to THS 2.2 Menthol over time.
- There were no SAEs reported by any randomized subject. The majority of AEs were mild in severity, although 12 severe AEs were reported during the Ambulatory phase, all of which were due to abnormal clinical laboratory findings and were unrelated to IP use. The incidence of subjects experiencing AEs during the study was comparable between study arms;

In summary, the study demonstrated a sustained exposure reduction to HPHCs after switching to THS 2.2 Menthol in both confined and ambulatory settings, close to levels observed after SA, transforming into favourable changes in some CREs, while providing an acceptable alternative to users with regards to taste, ritual, sensorial experience, and nicotine delivery. Therefore, THS 2.2 Menthol might be a suitable substitute for mCC for adult smokers with the potential to reduce the risk of smoking-related diseases with a prolonged use of THS 2.2 Menthol instead of mCC over time.

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.

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.