



PMI RESEARCH & DEVELOPMENT

Clinical Study Report Corrigendum

ZRHM-REXA-07-JP

Study Title:	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
Short Title:	Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting
Study Number:	ZRHM-REXA-07-JP
Product Name:	Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Initiated (first subject screened):	01 August 2013
Study Completed (last subject last visit):	03 July 2014
Principal Investigator and Affiliation:	Mamoru Oki, MD PhD, Seishukai Clinic 3-18-5, Matsugaya, Taitou-ku, Tokyo 111-0036, Japan Masahiro Endo, MD, Tokyo Heart Center Osaki Hospital 5-4-12, Kita-Shinagawa, Shinagawa-ku, Tokyo 141-0001, Japan
Sponsor:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Sponsor Signatories:	Christelle Haziza, PhD, Manager P1 Clinical Program, Clinical Scientist Nicola Lama, PhD, Biostatistician Andrea Donelli, Clinical Scientist Patrick Picavet, MD, Medical Safety Officer
Version, Date:	Clinical Study Report: v1.0, 24 February 2016 Clinical Study Report Corrigendum 1: v1.0, 23 May 2016

This study was conducted in accordance with Good Clinical Practice.

Confidentiality Statement

This document is confidential. Disclosure of any of its contents to third parties is not permitted except by the prior written consent of Philip Morris Products S.A.



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1. LIST OF IN TEXT FIGURES

Figure 1 Geometric Mean and 95% CI o-tol Concentration Adjusted for Creatinine During the Course of the Study (PP Set)

2. LIST OF IN TEXT TABLES

Table 1 Analysis of o-tol versus mCC and SA on Day 5 (PP Set)

Table 2 Analysis of o-tol versus mCC and SA on Day 90 (PP Set)



3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations used in this document are consistent with those reported in the study report.

4. DEFINITION OF TERMS

Special terms used in this document are consistent with those reported in the study report.

5. RATIONALE

This Clinical Study Report (CSR) Corrigendum provides updated results of Carbon monoxide (CO) biomarker of exposure in exhaled breath and Ames mutagenicity (YG1024+S9) test to the final CSR version 1.0 dated 24 February 2016. Summaries of the CO data were incorrectly calculated for the Full Analysis Set (FAS) due to an error in the tabulation program not correctly accounting for one subject discontinued during confinement. In the summaries of the Ames mutagenicity test, the percent change from baseline results were omitted for the endpoint expressed in REV/24h units.

This CSR Corrigendum also provides updated text for the results of o-toluidine biomarker of exposure because the arithmetic mean values were inappropriately used to describe the central tendency of the percent change from baseline results, because of the highly skewed distribution of this data, especially at Day 90. For interpretation purposes, the median together with the first and third quartiles will be used to describe these results because these descriptive statistics are not sensitive to skewed data.

6. CORRIGENDUM TO THE CLINICAL STUDY REPORT

6.1 Biomarkers of Exposure CO

Descriptive statistics of the exhaled CO during the course of the study for the FAS were provided in Appendix 15, [Table 15.2.4.6.2](#) (v3.0, 03 August 2015). This Corrigendum provides a [new version of this table](#) (v4.0, 27 April 2016).

Compared to the results in Appendix 15, the updated summary statistics are calculated on all 42 subjects, instead of 41 subjects, for the mCC group. Other summary statistics showed negligible differences in the mCC group.

No change to the CSR text is necessary because the results were provided in Appendix only.



6.2 Ames mutagenicity test

Descriptive statistics of the Ames mutagenicity test during the course of the study were provided in Appendix 15, [Table 15.2.4.46.1](#) and [Table 15.2.4.46.1](#) (03 August 2015). This Corrigendum provides a [new version of these tables](#) (27 April 2016) which include the results for the percent change from baseline for REV/24h units.

No change to the CSR text is necessary because these results would be provided in the Appendix only.

6.3 Biomarker of exposure o-toluidine

The following Section of the Corrigendum replaces [Section 11.2.3.7](#) o-toluidine in 24-hour Urine during the study in the final CSR. The text highlighted in bold italics details the changes.

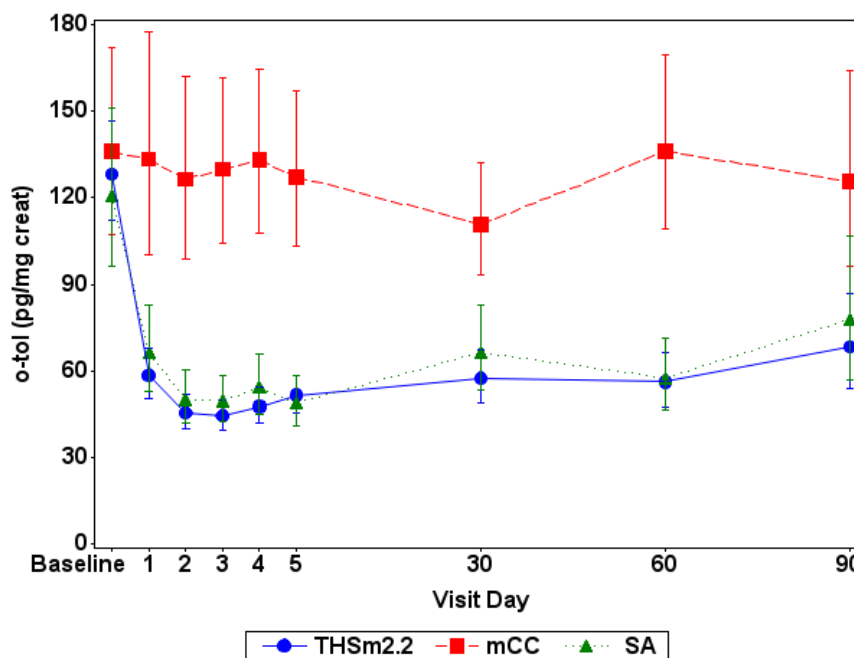
6.3.1 o-toluidine in 24-hour Urine During the Study

Subject listings of o-toluidine data are provided in Appendix 15, [Listing 15.3.3.1](#).

Descriptive statistics of o-toluidine concentration adjusted for creatinine measured in 24-hour urine and urinary quantity excreted over 24 hours during the course of the study are provided together with changes from baseline in Appendix 15, [Table 15.2.4.12.1](#) and [Table 15.2.4.12.2](#) for the PP Set and FAS, respectively. Geometric mean and 95% CIs for o-toluidine urinary concentration adjusted for creatinine are presented graphically in Appendix 15, [Figure 15.1.1.2](#) and [Figure 15.1.1.4](#) for the PP Set and the FAS, respectively. Data for the PP Set are also presented in [Figure 1](#).



Figure 1 Geometric Mean and 95% CI o-tol Concentration Adjusted for Creatinine During the Course of the Study (PP Set)



Abbreviations: CI = confidence interval; mCC = menthol conventional cigarettes; o-tol = o-toluidine; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Baseline is the last assessment prior to first randomized product use in mCC/THS m2.2 arms on Day 1 or last assessment prior to 10:00 AM in SA arm on Day 1.

Baseline is summarized using the baseline data from the PP Set for Period 1.

Data Source: Appendix 15, Figure 15.1.1.2.

The profile of o-toluidine for the THS 2.2 Menthol arm was comparable to that of the SA arm, with a sharp decline on Day 1 and a further decrease observed on Day 2, before remaining decreased from baseline. *The distribution of % change from baseline was highly skewed and median together with first and third quartiles (Q25,Q75) were considered appropriate descriptive statistics for these results.*

Geometric mean o-toluidine values decreased in the THS 2.2 Menthol arm from baseline (128.19 pg/mg creat) to Day 5 (51.64 pg/mg creat), whereas o-toluidine in the mCC arm had a baseline value of 136.04 pg/mg creat and a Day 5 of 127.28 pg/mg creat. These values corresponded to *median* percent changes from baseline of **-64.25%** (Q25,Q75: **-72.78, -47.11**) and **-2.51%** (Q25,Q75: **-17.88, 15.33**) for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean o-toluidine values decreased from baseline (120.54 pg/mg creat) to Day 5 (48.82 pg/mg creat), as expected, which corresponded to a **-60.29** (Q25,Q75: **-74.46, -37.77**) % change from baseline.



During the Ambulatory Period, geometric mean o-toluidine values in the THS 2.2 Menthol arm remained decreased from baseline on Days 30, 60, and 90 (57.46, 56.15, and 68.35 pg/mg creat, respectively), but were higher than the Day 5 value. o-toluidine in the mCC arm on Days 30, 60, and 90 was 110.84, 136.16, and 125.64 pg/mg creat, respectively). These values corresponded to **median** percent changes from baseline on Day 90 of **-58.22%**(**Q25,Q75: -70.12, -16.48**) and **-8.70%** (**Q25,Q75: -35.74, 13.02**) for the THS 2.2 Menthol and mCC arms, respectively. In the SA arm, geometric mean o-toluidine values remained decreased from baseline, as expected, with a **-53.82** (**Q25,Q75: -62.41, -6.44**) % change from baseline on Day 90 (77.86 pg/mg creat).

Analyses of o-toluidine urinary concentration adjusted for creatinine and urinary quantity of o-toluidine excreted over 24 hours for THS 2.2 Menthol use versus mCC use and SA on Day 5 are tabulated in Appendix 15, [Table 15.2.3.4](#) and [Table 15.2.3.5](#) for the PP Set and FAS, respectively. In addition, sensitivity analyses including analysis of the Compliant Population and use of a mixed model on the PP Set were performed, and are tabulated in Appendix 15, [Table 15.2.3.7](#) and [Table 15.2.3.6](#), respectively. Data for the PP Set are also tabulated in [Table 1](#) and [Table 2](#).

**Table 1 Analysis of o-tol versus mCC and SA on Day 5 (PP Set)**

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)			CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	59.98	41.61	51.21			
	mCC	40	144.15					
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	52.17	43.80	50.51			
	mCC	40	119.11					

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)			CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	76	59.98	98.55	51.21			
	SA	39	60.86					
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	76	52.17	102.80	50.51			
	SA	39	50.75					

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; o-tol = o-toluidine; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric 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.
Data Source: Appendix 15, [Table 15.2.3.4](#).

On Day 5, the LS mean of o-toluidine concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 56.20% lower than that of subjects who continued to smoke mCC (95% CI: 47.17, 63.69; p-value <0.001). The results for the quantity of o-toluidine excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 5, the LS means of both o-toluidine urinary concentrations adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis on the PP Set using a mixed model showed consistent results to those presented.



There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

Table 2 Analysis of o-tol versus mCC and SA on Day 90 (PP Set)

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:mCC) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	77.95	61.96	100.63	44.26, 86.74
	mCC	40	125.80			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	69.75	59.16	102.96	42.02, 83.29
	mCC	40	117.90			

Parameter	Exposure	Number of Subjects	Geometric LS Mean	Geometric LS Mean Ratio (THS m2.2:SA) (%)	CV%	95% CI
Quantity excreted over 24 hours (ng)	THS m2.2	70	77.95	88.35	100.63	63.12, 123.67
	SA	37	88.22			
Concentration adjusted for creatinine (pg/mg creat)	THS m2.2	70	69.75	87.24	102.96	61.98, 122.80
	SA	37	79.95			

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CV = coefficient of variance; LS = least squares; mCC = menthol conventional cigarette; o-tol = o-toluidine; PP = per protocol; SA = smoking abstinence; THS m2.2 = Tobacco Heating System 2.2 Menthol.

Adjusted geometric 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.
Data Source: Appendix 15, Table 15.2.3.4.

On Day 90, the LS mean of o-toluidine concentration adjusted for creatinine in subjects who switched to THS 2.2 Menthol use was 40.84% lower than that of subjects who continued to smoke mCC (95% CI: 16.71, 57.98; p-value = 0.001). The results for the quantity of o-toluidine excreted over 24 hours were consistent with the results of the urinary concentration adjusted for creatinine.

On Day 90, the LS means of both o-toluidine concentration adjusted for creatinine and quantity excreted over 24 hours were comparable between subjects who switched to



THS 2.2 Menthol and subjects who abstained from smoking, with the 95% CIs for both assessments spanning 100%.

Analysis using the FAS, and sensitivity analysis of the PP Set using a mixed model and analysis on the Compliant Population showed consistent results to those presented.

There was no difference between the geometric LS mean ratios of the quantity excreted and the concentration adjusted for creatinine for either the THS 2.2 Menthol : mCC or THS 2.2 Menthol : SA ratios.

6.4 Discussion and Conclusions

The updated results reported in the table do not change the interpretation of the exhaled CO and Ames mutagenicity results. The tables with program run of 27 April 2016 supersede those of 03 August 2015.

The updated text for o-toluidine clarifies and better support the original interpretation of the results.



7. REFERENCE LIST

N.A.



8. PRINCIPAL INVESTIGATOR'S SIGNATURE



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8. PRINCIPAL INVESTIGATOR'S SIGNATURE

PRINCIPAL INVESTIGATORS' SIGNATURE

Study Title: 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

Study Number: ZRHM-REXA-07-JP

I have read the Corrigendum to Clinical Study Report version v1.0, 24 February 2016 referenced above and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed: _____
Mamoru Oki, MD PhD

Date: _____

Signed: Masahiro Endo
Masahiro Endo, MD

Date: 28 MAY 2016



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Study Number: ZRHM-REXA-07-JP

I have read the Corrigendum to Clinical Study Report version v1.0, 24 February 2016 referenced above and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed: Mamoru Oki
Mamoru Oki, MD PhD

Date: 28 May 2016

Signed: _____
Masahiro Endo, MD

Date: _____



9. SIGNATURES OF SPONSORS RESPONSIBLE PERSONNEL



9. SIGNATURES OF SPONSORS RESPONSIBLE PERSONNEL

This Clinical Study Report was subject to critical review and has been approved by the Sponsor.

SPONSOR SIGNATORIES


Study Title:

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

Study Number:

ZRHM-REXA-07-JP

We, the undersigned, confirm that to the best of our knowledge this Corrigendum to Clinical Study Report v1.0, 24 February 2016 accurately describes the experimental methods and results of the study.

Signed: 
Christelle Haziza, PhD
Manager P1 Clinical Program, Clinical Scientist

Date: 23 May 2016

Signed: 
Nicola Lama, PhD
Biostatistician

Date: 23 MAY 2016

Signed: 
Andrea Donelli
Clinical Scientist

Date: 23 MAY 2016

Signed: 
Patrick Picavet, MD
Medical Safety Officer

Date: 24 MAY 2016



10. ADDITIONAL SUMMARIES NOT INCLUDED IN THE TEXT

10.1 Figures

Not applicable.

10.2 Tables

Table 3 Descriptive statistics of of Exhaled CO (ppm) - FAS

Table 4 Descriptive statistics of Ames mutagenicity Test(YG1024+S9)-PP set

Table 5 Descriptive statistics of Ames mutagenicity Test(YG1024+S9)-FAS

**Table 3 Descriptive statistics of of Exhaled CO (ppm) - FAS****Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
15 Min < T0 - Baseline							
	n	78		42			
	BLOQ, n (%)	0		0			
	Geometric Mean (CV%)	4.85 (92.54)		NC			
	95% CI of Geometric Mean	4.05, 5.79		NC			
	Median	6.00		6.00			
	Q25, Q75	3.00, 9.00		3.00, 9.00			
	Min, Max	1.0, 23.0		0.0, 22.0			
	Mean (SD)	6.26 (4.158)		6.83 (4.591)			
	95% CI of Mean	5.31, 7.20		5.40, 8.27			

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
08:00 - 09:30							
- Baseline							
	n					40	
	BLOQ, n (%)					0	
	Geometric Mean (CV%)					6.11 (61.39)	
	95% CI of Geometric Mean					5.09, 7.32	
	Median					6.00	
	Q25, Q75					5.00, 9.00	
	Min, Max					1.0, 15.0	
	Mean (SD)					6.98 (3.340)	
	95% CI of Mean					5.90, 8.05	

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
12:00 - 13:30							
- Baseline							
	n	78		42		40	
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	10.34 (71.13)		10.47 (90.25)		11.29 (57.86)	
	95% CI of Geometric Mean	8.94, 11.94		8.23, 13.33		9.51, 13.42	
	Median	11.50		11.00		11.50	
	Q25, Q75	8.00, 16.00		7.00, 21.00		8.00, 16.50	
	Min, Max	2.0, 30.0		1.0, 38.0		4.0, 31.0	
	Mean (SD)	12.23 (6.394)		13.40 (8.852)		12.95 (6.947)	
	95% CI of Mean	10.78, 13.68		10.64, 16.17		10.72, 15.18	

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
16:00 - 17:30							
- Baseline							
	n	78		42		40	
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	10.74 (79.01)		NC		11.63 (79.47)	
	95% CI of Geometric Mean	9.18, 12.58		NC		9.29, 14.55	
	Median	11.00		12.00		13.00	
	Q25, Q75	7.00, 19.00		6.00, 19.00		8.00, 18.50	
	Min, Max	2.0, 43.0		0.0, 41.0		1.0, 43.0	
	Mean (SD)	13.33 (8.628)		13.64 (9.181)		14.15 (8.439)	
	95% CI of Mean	11.38, 15.28		10.78, 16.51		11.45, 16.85	

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

Appendix: 15.3.3.2

Study ID:ZRHM-REXA-07-JP

Program: T1502042602_ZRHM_REXA_07_JP_V4.0.sas

Status: Final v4.0/27APR2016

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**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
20:00 - 21:30							
- Baseline							
	n	78		42		40	
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		10.24 (101.31)		10.55 (85.87)	
	95% CI of Geometric Mean	NC		7.88, 13.32		8.31, 13.39	
	Median	14.00		11.50		12.00	
	Q25, Q75	9.00, 19.00		7.00, 18.00		7.50, 16.50	
	Min, Max	0.0, 43.0		1.0, 40.0		1.0, 35.0	
	Mean (SD)	14.74 (8.268)		13.36 (8.633)		13.08 (7.846)	
	95% CI of Mean	12.87, 16.61		10.66, 16.05		10.56, 15.59	

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

Appendix: 15.3.3.2

Study ID:ZRHM-REXA-07-JP

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Status: Final v4.0/27APR2016

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**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 1 - 12:00							
- 13:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	3.64 (74.33)		10.10 (83.76)		4.36 (60.19)	
	95% CI of Geometric Mean	3.13, 4.23		8.04, 12.68		3.65, 5.22	
	Median	4.00	-60.00	11.50	0.00	4.50	-60.36
	Q25, Q75	3.00, 6.00	-71.43, -50.00	7.00, 17.00	-36.36, 33.33	3.50, 6.00	-72.22, -40.00
	Min, Max	1.0, 13.0	-92.9, 50.0	2.0, 28.0	-71.4, 400.0	1.0, 11.0	-93.3, 25.0
	Mean (SD)	4.37 (2.419)	-58.55 (23.615)	12.57 (7.494)	13.73 (79.786)	4.98 (2.402)	-55.42 (23.511)
	95% CI of Mean	3.82, 4.92	-63.88, -53.22	10.23, 14.91	-11.14, 38.59	4.20, 5.75	-62.95, -47.90

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

Appendix: 15.3.3.2

Study ID: ZRHM-REXA-07-JP

Program: T1502042602_ZRHM_REXA_07_JP_V4.0.sas

Status: Final v4.0/27APR2016

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**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 1 - 16:00 - 17:30	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		NC		3.92 (58.77)	
	95% CI of Geometric Mean	NC		NC		3.29, 4.67	
	Median	4.00	-72.05	13.00	0.00	4.50	-67.95
	Q25, Q75	2.00, 5.00	-80.00, -50.00	7.00, 18.00	-27.59, 28.57	3.00, 6.00	-75.60, -53.59
	Min, Max	0.0, 12.0	-100.0, 150.0	0.0, 31.0	-70.0, 250.0	1.0, 8.0	-88.5, 200.0
	Mean (SD)	3.99 (2.195)	-59.23 (37.401)	13.17 (7.967)	11.84 (56.975)	4.45 (2.051)	-57.05 (45.893)
	95% CI of Mean	3.49, 4.49	-67.67, -50.80	10.68, 15.65	-5.92, 29.60	3.79, 5.11	-71.73, -42.37

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 1 - 20:00 - 21:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		11.70 (78.67)		NC	
	95% CI of Geometric Mean	NC		9.42, 14.53		NC	
	Median	3.00	-76.83	12.00	13.39	3.00	-75.00
	Q25, Q75	2.00, 4.00	-82.35, -64.29	9.00, 18.00	-18.18, 50.00	2.00, 4.00	-81.25, -59.17
	Min, Max	0.0, 10.0	-100.0, 200.0	1.0, 36.0	-66.7, 900.0	0.0, 12.0	-100.0, 100.0
	Mean (SD)	3.44 (1.898)	-66.92 (38.546)	14.12 (7.925)	41.12 (146.527)	3.55 (2.100)	-60.89 (39.031)
	95% CI of Mean	3.00, 3.87	-75.62, -58.23	11.64, 16.59	-4.54, 86.79	2.87, 4.23	-73.38, -48.40

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 2 -							
Within 15 Min							
Prior To							
Smoking							
	n	78	78	42	42		
	BLOQ, n (%)	0		0			
	Geometric Mean (CV%)	NC		NC			
	95% CI of Geometric Mean	NC		NC			
	Median	2.00	-66.67	6.00	0.00		
	Q25, Q75	1.00, 3.00	-77.78, -33.33	3.00, 9.00	-28.57, 28.57		
	Min, Max	0.0, 9.0	-100.0, 200.0	0.0, 22.0	-66.7, 900.0		
	Mean (SD)	2.32 (1.428)	-44.66 (57.899)	6.98 (4.693)	34.72 (154.455)		
	95% CI of Mean	1.99, 2.65	-57.72, -31.60	5.51, 8.44	-13.42, 82.85		

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 2 - 08:00							
- 09:30							
	n					40	40
	BLOQ, n (%)					0	
	Geometric Mean (CV%)					NC	
	95% CI of Geometric Mean					NC	
	Median					3.00	-64.58
	Q25, Q75					1.00, 3.00	-80.00, -47.22
	Min, Max					0.0, 7.0	-100.0, 100.0
	Mean (SD)					2.60 (1.662)	-57.21 (34.991)
	95% CI of Mean					2.06, 3.14	-68.41, -46.02

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 2 - 12:00							
- 13:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		8.80 (107.55)		2.47 (55.17)	
	95% CI of Geometric Mean	NC		6.69, 11.56		2.09, 2.91	
	Median	2.00	-80.00	11.00	0.00	3.00	-78.17
	Q25, Q75	2.00, 3.00	-88.24, -62.50	7.00, 15.00	-27.27, 20.00	2.00, 3.00	-86.41, -68.63
	Min, Max	0.0, 5.0	-100.0, 0.0	1.0, 37.0	-89.5, 116.7	1.0, 7.0	-93.3, 0.0
	Mean (SD)	2.40 (1.166)	-72.02 (23.933)	11.79 (8.020)	-3.82 (44.200)	2.80 (1.472)	-73.46 (19.024)
	95% CI of Mean	2.13, 2.67	-77.42, -66.62	9.28, 14.29	-17.60, 9.96	2.32, 3.28	-79.55, -67.38

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 2 - 16:00 - 17:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	3.00	-79.47	13.00	1.72	3.00	-75.96
	Q25, Q75	2.00, 4.00	-86.05, -63.64	8.00, 21.00	-22.22, 33.33	2.00, 4.00	-87.94, -67.95
	Min, Max	0.0, 7.0	-100.0, 50.0	0.0, 33.0	-100.0, 500.0	0.0, 6.0	-100.0, 400.0
	Mean (SD)	2.76 (1.514)	-70.23 (27.115)	14.19 (8.940)	24.13 (96.408)	3.05 (1.664)	-62.17 (77.445)
	95% CI of Mean	2.41, 3.10	-76.35, -64.11	11.40, 16.98	-5.92, 54.18	2.51, 3.59	-86.94, -37.40

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 2 - 20:00 - 21:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	3.00	-81.53	13.00	18.00	3.00	-81.53
	Q25, Q75	1.00, 4.00	-88.89, -72.73	9.00, 20.00	0.00, 42.86	1.00, 4.00	-88.56, -67.71
	Min, Max	0.0, 7.0	-100.0, 100.0	0.0, 29.0	-100.0, 700.0	0.0, 9.0	-100.0, 14.3
	Mean (SD)	2.62 (1.523)	-72.94 (31.749)	14.14 (7.956)	34.37 (117.991)	2.83 (1.973)	-69.57 (29.730)
	95% CI of Mean	2.27, 2.96	-80.10, -65.77	11.66, 16.63	-2.40, 71.14	2.19, 3.46	-79.09, -60.06

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 3 -							
Within 15 Min							
Prior To							
Smoking							
	n	78	78	42	42		
	BLOQ, n (%)	0		0			
	Geometric Mean (CV%)	NC		5.15 (79.66)			
	95% CI of Geometric Mean	NC		4.13, 6.41			
	Median	2.00	-66.67	6.00	0.00		
	Q25, Q75	1.00, 3.00	-77.78, -42.86	3.00, 8.00	-28.57, 42.86		
	Min, Max	0.0, 4.0	-100.0, 100.0	1.0, 13.0	-66.7, 200.0		
	Mean (SD)	1.97 (1.057)	-54.92 (39.059)	6.26 (3.444)	16.67 (72.993)		
	95% CI of Mean	1.73, 2.22	-63.73, -46.11	5.18, 7.34	-6.08, 39.42		

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

Appendix: 15.3.3.2

Study ID: ZRHM-REXA-07-JP

Program: T1502042602_ZRHM_REXA_07_JP_V4.0.sas

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**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 3 - 08:00 - 09:30	n					40	40
	BLOQ, n (%)					0	
	Geometric Mean (CV%)					NC	
	95% CI of Geometric Mean					NC	
	Median					2.00	-66.67
	Q25, Q75					1.50, 3.00	-76.39, -50.00
	Min, Max					0.0, 5.0	-100.0, 100.0
	Mean (SD)					2.33 (1.072)	-59.65 (32.843)
	95% CI of Mean					1.98, 2.67	-70.16, -49.14

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 3 - 12:00							
- 13:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		8.91 (91.51)		2.01 (53.70)	
	95% CI of Geometric Mean	NC		6.98, 11.37		1.71, 2.37	
	Median	2.00	-81.82	10.00	-20.76	2.00	-80.91
	Q25, Q75	2.00, 3.00	-87.50, -70.00	5.00, 18.00	-42.86, 22.22	1.00, 3.00	-89.64, -71.36
	Min, Max	0.0, 6.0	-100.0, 0.0	1.0, 34.0	-71.4, 400.0	1.0, 5.0	-95.0, -25.0
	Mean (SD)	2.15 (1.021)	-76.66 (17.981)	11.43 (7.412)	5.47 (85.354)	2.25 (1.007)	-77.56 (15.912)
	95% CI of Mean	1.92, 2.39	-80.72, -72.60	9.11, 13.74	-21.13, 32.07	1.92, 2.58	-82.66, -72.47

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 3 - 16:00 - 17:30	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	2.06 (60.42)		NC		2.30 (56.89)	
	95% CI of Geometric Mean	1.81, 2.34		NC		1.93, 2.73	
	Median	2.00	-81.82	12.00	-9.40	3.00	-81.39
	Q25, Q75	1.00, 3.00	-90.00, -66.67	8.00, 17.00	-31.25, 33.33	2.00, 3.00	-87.50, -69.62
	Min, Max	1.0, 6.0	-95.2, 50.0	0.0, 29.0	-100.0, 900.0	1.0, 5.0	-97.7, 400.0
	Mean (SD)	2.38 (1.282)	-73.34 (25.400)	12.62 (7.458)	29.23 (159.178)	2.60 (1.216)	-64.57 (77.409)
	95% CI of Mean	2.09, 2.68	-79.08, -67.61	10.29, 14.95	-20.37, 78.84	2.21, 2.99	-89.34, -39.81

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

Appendix: 15.3.3.2

Study ID:ZRHM-REXA-07-JP

Program: T1502042602_ZRHM_REXA_07_JP_V4.0.sas

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**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 3 - 20:00 - 21:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		11.18 (93.61)		NC	
	95% CI of Geometric Mean	NC		8.73, 14.33		NC	
	Median	2.00	-82.35	13.00	0.00	2.00	-82.29
	Q25, Q75	2.00, 3.00	-88.89, -71.43	7.00, 19.00	-30.00, 66.67	1.50, 3.00	-87.50, -71.66
	Min, Max	0.0, 7.0	-100.0, 66.7	1.0, 31.0	-85.7, 600.0	0.0, 10.0	-100.0, 14.3
	Mean (SD)	2.49 (1.297)	-74.31 (28.889)	14.02 (8.075)	38.76 (118.464)	2.65 (1.875)	-69.68 (30.361)
	95% CI of Mean	2.19, 2.78	-80.83, -67.80	11.50, 16.54	1.84, 75.68	2.05, 3.25	-79.39, -59.96

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 4 -							
Within 15 Min							
Prior To							
Smoking							
	n	78	78	42	42		
	BLOQ, n (%)	0		0			
	Geometric Mean (CV%)	NC		NC			
	95% CI of Geometric Mean	NC		NC			
	Median	2.00	-66.67	6.00	0.00		
	Q25, Q75	1.00, 3.00	-77.78, -50.00	4.00, 8.00	-28.57, 25.00		
	Min, Max	0.0, 4.0	-100.0, 200.0	0.0, 23.0	-80.0, 250.0		
	Mean (SD)	2.06 (0.959)	-48.91 (50.480)	6.50 (4.044)	13.37 (65.815)		
	95% CI of Mean	1.84, 2.29	-60.29, -37.52	5.23, 7.77	-7.14, 33.88		

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 4 - 08:00							
- 09:30							
	n					40	40
	BLOQ, n (%)					0	
	Geometric Mean (CV%)					NC	
	95% CI of Geometric Mean					NC	
	Median					2.00	-66.67
	Q25, Q75					1.00, 3.00	-80.00, -52.78
	Min, Max					0.0, 4.0	-100.0, 0.0
	Mean (SD)					2.15 (1.167)	-66.11 (20.383)
	95% CI of Mean					1.77, 2.53	-72.64, -59.59

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 4 - 12:00 - 13:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	2.00	-80.63	11.50	0.00	2.00	-81.82
	Q25, Q75	1.00, 3.00	-90.00, -66.67	6.00, 16.00	-44.83, 50.00	1.00, 3.00	-91.67, -69.62
	Min, Max	0.0, 6.0	-100.0, 0.0	0.0, 30.0	-100.0, 333.3	0.0, 6.0	-100.0, -25.0
	Mean (SD)	2.19 (1.152)	-74.59 (22.647)	11.93 (6.912)	14.33 (85.839)	2.15 (1.189)	-77.64 (17.437)
	95% CI of Mean	1.93, 2.46	-79.71, -69.48	9.77, 14.09	-12.42, 41.08	1.76, 2.54	-83.22, -72.06

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 4 - 16:00							
- 17:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		10.23 (82.70)		NC	
	95% CI of Geometric Mean	NC		8.17, 12.82		NC	
	Median	2.00	-80.63	11.00	-18.47	2.50	-83.48
	Q25, Q75	1.00, 4.00	-87.10, -69.23	8.00, 17.00	-38.46, 50.00	1.00, 3.00	-90.69, -70.71
	Min, Max	0.0, 7.0	-100.0, 100.0	1.0, 35.0	-69.2, 750.0	0.0, 5.0	-100.0, 300.0
	Mean (SD)	2.55 (1.448)	-70.68 (32.504)	12.57 (7.409)	40.10 (163.240)	2.35 (1.232)	-69.68 (61.837)
	95% CI of Mean	2.22, 2.88	-78.01, -63.34	10.26, 14.89	-10.78, 90.97	1.95, 2.75	-89.46, -49.90

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 4 - 20:00							
- 21:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	1.98 (59.27)		11.73 (87.51)		2.33 (66.70)	
	95% CI of Geometric Mean	1.74, 2.25		9.27, 14.85		1.92, 2.84	
	Median	2.00	-83.33	14.00	6.70	2.00	-80.00
	Q25, Q75	1.00, 3.00	-90.91, -75.00	10.00, 19.00	-22.22, 64.00	2.00, 3.50	-87.50, -62.58
	Min, Max	1.0, 7.0	-97.3, 100.0	1.0, 41.0	-66.7, 500.0	1.0, 9.0	-96.3, 50.0
	Mean (SD)	2.29 (1.291)	-75.04 (30.262)	14.31 (7.605)	36.22 (99.229)	2.80 (1.843)	-67.84 (32.738)
	95% CI of Mean	2.00, 2.59	-81.87, -68.21	11.93, 16.68	5.29, 67.14	2.21, 3.39	-78.31, -57.36

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 5 -							
Within 15 Min							
Prior To							
Smoking							
	n	78	78	42	42		
	BLOQ, n (%)	0		0			
	Geometric Mean (CV%)	NC		NC			
	95% CI of Geometric Mean	NC		NC			
	Median	2.00	-66.67	6.00	-3.85		
	Q25, Q75	1.00, 3.00	-77.78, -50.00	3.00, 8.00	-35.71, 14.29		
	Min, Max	0.0, 4.0	-100.0, 200.0	0.0, 14.0	-85.7, 300.0		
	Mean (SD)	2.04 (0.890)	-45.66 (57.147)	6.02 (3.558)	11.60 (84.200)		
	95% CI of Mean	1.83, 2.24	-58.55, -32.77	4.91, 7.14	-14.64, 37.84		

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

Appendix: 15.3.3.2

Study ID: ZRHM-REXA-07-JP

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**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 5 - 08:00							
- 09:30							
	n					40	40
	BLOQ, n (%)					0	
	Geometric Mean (CV%)					NC	
	95% CI of Geometric Mean					NC	
	Median					2.00	-66.67
	Q25, Q75					2.00, 3.00	-80.00, -60.00
	Min, Max					0.0, 5.0	-100.0, 100.0
	Mean (SD)					2.05 (1.061)	-62.10 (35.314)
	95% CI of Mean					1.71, 2.39	-73.40, -50.80

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 5 - 12:00							
- 13:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	2.05 (47.57)		NC		NC	
	95% CI of Geometric Mean	1.85, 2.27		NC		NC	
	Median	2.00	-80.00	11.00	0.00	2.00	-80.63
	Q25, Q75	2.00, 3.00	-88.46, -70.00	9.00, 18.00	-25.00, 37.50	1.50, 3.00	-91.07, -72.73
	Min, Max	1.0, 6.0	-95.7, 50.0	0.0, 34.0	-100.0, 800.0	0.0, 5.0	-100.0, -40.0
	Mean (SD)	2.26 (0.987)	-73.15 (24.896)	12.93 (7.882)	27.93 (136.219)	2.13 (1.018)	-79.35 (14.251)
	95% CI of Mean	2.03, 2.48	-78.77, -67.53	10.47, 15.39	-14.52, 70.38	1.79, 2.46	-83.91, -74.79

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 5 - 16:00 - 17:30	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		11.20 (94.46)		2.32 (63.45)	
	95% CI of Geometric Mean	NC		8.72, 14.36		1.92, 2.80	
	Median	2.00	-80.00	13.50	6.25	2.00	-79.47
	Q25, Q75	2.00, 3.00	-87.50, -60.00	8.00, 20.00	-25.00, 54.55	2.00, 3.50	-87.98, -70.71
	Min, Max	0.0, 6.0	-100.0, 100.0	1.0, 34.0	-90.0, 650.0	1.0, 7.0	-95.3, 400.0
	Mean (SD)	2.53 (1.256)	-70.98 (29.987)	14.05 (7.862)	43.90 (133.086)	2.73 (1.602)	-65.06 (77.213)
	95% CI of Mean	2.24, 2.81	-77.75, -64.22	11.59, 16.50	2.42, 85.37	2.21, 3.24	-89.76, -40.36

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 5 - 20:00							
- 21:30							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		12.63 (78.31)		2.47 (68.42)	
	95% CI of Geometric Mean	NC		10.17, 15.67		2.02, 3.02	
	Median	2.00	-81.82	13.00	28.29	2.00	-80.00
	Q25, Q75	2.00, 3.00	-90.00, -68.75	9.00, 22.00	-13.64, 66.67	2.00, 4.00	-86.19, -64.58
	Min, Max	0.0, 8.0	-100.0, 50.0	2.0, 32.0	-66.7, 500.0	1.0, 8.0	-95.5, 33.3
	Mean (SD)	2.55 (1.492)	-74.16 (27.669)	15.31 (8.435)	42.71 (94.035)	2.98 (1.902)	-66.86 (30.926)
	95% CI of Mean	2.21, 2.89	-80.40, -67.92	12.68, 17.94	13.40, 72.02	2.36, 3.59	-76.75, -56.96

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 6/Discharge Confinement	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	2.12 (44.86)		8.41 (76.09)		NC	
	95% CI of Geometric Mean	1.92, 2.34		6.81, 10.39		NC	
	Median	2.00	-80.00	10.00	-14.29	2.00	-83.33
	Q25, Q75	2.00, 3.00	-86.96, -66.67	5.00, 13.00	-50.00, 30.00	1.00, 2.00	-91.67, -76.39
	Min, Max	1.0, 5.0	-95.7, 100.0	1.0, 27.0	-75.0, 300.0	0.0, 5.0	-100.0, 25.0
	Mean (SD)	2.31 (0.917)	-72.42 (27.520)	10.17 (5.922)	-3.44 (66.014)	1.88 (0.853)	-80.03 (20.257)
	95% CI of Mean	2.10, 2.52	-78.63, -66.21	8.32, 12.02	-24.02, 17.14	1.60, 2.15	-86.52, -73.55

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

Appendix: 15.3.3.2

Study ID: ZRHM-REXA-07-JP

Program: T1502042602_ZRHM_REXA_07_JP_V4.0.sas

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**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 30	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	2.00	-80.48	13.00	11.81	2.00	-82.58
	Q25, Q75	2.00, 3.00	-86.96, -75.00	9.00, 20.00	-46.88, 128.57	1.00, 2.50	-91.99, -70.29
	Min, Max	0.0, 7.0	-100.0, 150.0	0.0, 34.0	-100.0, 600.0	0.0, 8.0	-100.0, -25.0
	Mean (SD)	2.41 (1.324)	-72.87 (32.209)	14.02 (7.621)	49.32 (137.897)	2.35 (1.875)	-78.07 (17.560)
	95% CI of Mean	2.11, 2.71	-80.13, -65.60	11.64, 16.40	6.34, 92.29	1.75, 2.95	-83.69, -72.45

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 60							
	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	NC		9.65 (86.34)		NC	
	95% CI of Geometric Mean	NC		7.65, 12.19		NC	
	Median	2.00	-84.62	12.50	0.00	2.00	-81.18
	Q25, Q75	1.00, 3.00	-90.91, -72.73	7.00, 16.00	-27.27, 40.00	2.00, 3.00	-89.88, -67.71
	Min, Max	0.0, 10.0	-100.0, 400.0	1.0, 30.0	-85.7, 600.0	0.0, 7.0	-100.0, 25.0
	Mean (SD)	2.21 (1.724)	-70.05 (61.204)	11.95 (6.739)	27.53 (122.013)	2.53 (1.649)	-73.25 (25.203)
	95% CI of Mean	1.81, 2.60	-83.85, -56.24	9.85, 14.06	-10.49, 65.56	1.99, 3.06	-81.32, -65.19

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated

**Table 15.2.4.6.2 Descriptive Statistics of Exhaled CO (ppm) - FAS****Parameter (units): Exhaled CO (ppm)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 90	n	78	78	42	42	40	40
	BLOQ, n (%)	0		0		0	
	Geometric Mean (CV%)	2.07 (55.28)		9.46 (88.51)		NC	
	95% CI of Geometric Mean	1.84, 2.33		7.46, 12.00		NC	
	Median	2.00	-83.33	11.00	0.00	2.00	-83.97
	Q25, Q75	2.00, 3.00	-88.89, -66.67	7.00, 16.00	-43.48, 66.67	1.00, 3.00	-90.69, -70.83
	Min, Max	1.0, 7.0	-96.2, 50.0	1.0, 29.0	-95.8, 400.0	0.0, 9.0	-100.0, -10.0
	Mean (SD)	2.37 (1.369)	-71.56 (27.552)	11.81 (6.869)	23.95 (99.347)	2.48 (1.975)	-75.44 (23.391)
	95% CI of Mean	2.06, 2.69	-77.77, -65.34	9.66, 13.96	-7.01, 54.92	1.84, 3.11	-82.93, -67.95

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: NC=Not calculated



Table 4 Descriptive statistics of Ames mutagenicity Test(YG1024+S9)-PP set

**Table 15.2.4.46.1 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - PP Set****Parameter (units): Ames Mutagenicity (REV/mL)**
Product Use Time Period: Period 1

Timepoint	Statistic	THSm2.2 (N=76)		mCC (N=42)		SA (N=39)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Baseline	n	65		38		35	
	Missing, n (%)	11 (14.5)		4 (9.5)		4 (10.3)	
	Geometric Mean (CV%)	NC		7.76 (70.591)		NC	
	95% CI of Geometric Mean	NC		6.29, 9.56		NC	
	Median	7.66		8.10		6.85	
	Q25, Q75	5.12, 11.70		5.36, 12.00		4.92, 10.40	
	Min, Max	0.0, 32.2		2.1, 28.5		0.0, 21.7	
	Mean (SD)	9.07 (5.798)		9.41 (6.176)		7.93 (5.243)	
	95% CI of Mean	7.63, 10.52		7.38, 11.45		6.12, 9.74	

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

Appendix: 15.3.5.1

Study ID: ZRHM-REXA-07-JP

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**Table 15.2.4.46.1 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - PP Set****Parameter (units): Ames Mutagenicity (REV/mL)**
Product Use Time Period: Period 1

Timepoint	Statistic	THSm2.2 (N=76)		mCC (N=42)		SA (N=39)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 5	n	73	65	40	38	37	35
	Missing, n (%)	3 (3.9)	11 (14.5)	2 (4.8)	4 (9.5)	2 (5.1)	4 (10.3)
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	2.71	-52.31	8.01	-4.00	3.39	-28.63
	Q25, Q75	1.74, 4.74	-82.23, 0.00	4.11, 10.70	-39.59, 0.00	2.09, 5.40	-74.60, 0.00
	Min, Max	0.0, 18.1	-100.0, 64.7	0.0, 25.1	-100.0, 162.1	0.0, 21.2	-100.0, 22.5
	Mean (SD)	3.76 (3.731)	-47.40 (41.960)	8.08 (5.017)	-5.37 (50.510)	4.66 (4.754)	-33.78 (38.716)
	95% CI of Mean	2.89, 4.64	-57.81, -37.00	6.47, 9.69	-21.98, 11.24	3.07, 6.25	-47.08, -20.47

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

**Table 15.2.4.46.1 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - PP Set**

Parameter (units): Ames Mutagenicity (REV/mL)
Product Use Time Period: Period 4

Timepoint	Statistic	THSm2.2 (N=70)		mCC (N=41)		SA (N=37)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Baseline	n	60		37		33	
	Missing, n (%)	10 (14.3)		4 (9.8)		4 (10.8)	
	Geometric Mean (CV%)	NC		7.68 (71.353)		NC	
	95% CI of Geometric Mean	NC		6.19, 9.51		NC	
	Median	7.73		8.02		6.73	
	Q25, Q75	5.07, 11.95		5.36, 12.00		4.92, 8.94	
	Min, Max	0.0, 32.2		2.1, 28.5		0.0, 21.7	
	Mean (SD)	9.27 (5.986)		9.36 (6.253)		7.80 (5.329)	
	95% CI of Mean	7.71, 10.82		7.27, 11.45		5.91, 9.70	

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

Appendix: 15.3.5.1

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**Table 15.2.4.46.1 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - PP Set****Parameter (units): Ames Mutagenicity (REV/mL)**
Product Use Time Period: Period 4

Timepoint	Statistic	THSm2.2 (N=70)		mCC (N=41)		SA (N=37)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 90	n	70	60	40	37	37	33
	Missing, n (%)	0	10 (14.3)	1 (2.4)	4 (9.8)	0	4 (10.8)
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	3.22	-56.20	8.73	22.60	3.18	-34.54
	Q25, Q75	2.21, 4.97	-74.69, -12.43	4.91, 14.20	-11.03, 51.59	2.47, 6.19	-76.71, 0.00
	Min, Max	0.0, 17.0	-100.0, 60.9	0.0, 26.4	-100.0, 129.6	0.0, 15.5	-100.0, 308.0
	Mean (SD)	3.67 (2.798)	-45.61 (42.248)	9.80 (6.294)	19.19 (53.837)	4.25 (3.587)	-24.97 (81.789)
	95% CI of Mean	3.00, 4.34	-56.53, -34.69	7.78, 11.82	1.24, 37.15	3.05, 5.45	-53.98, 4.04

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

**Table 15.2.4.46.1 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - PP Set****Parameter (units): Ames Mutagenicity (REV/24h)****Product Use Time Period: Period 1**

Timepoint	Statistic	THSm2.2 (N=76)		mCC (N=42)		SA (N=39)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Baseline	n	65		38		35	
	Missing, n (%)	11 (14.5)		4 (9.5)		4 (10.3)	
	Geometric Mean (CV%)	NC		11858.12 (86.039)		NC	
	95% CI of Geometric Mean	NC		9284.59, 15145.00		NC	
	Median	13943.72		13235.99		14000.04	
	Q25, Q75	8398.26, 21406.00		8050.44, 20372.80		6876.90, 20698.62	
	Min, Max	0.0, 51505.1		2331.6, 51400.0		0.0, 44541.2	
	Mean (SD)	17293.80 (12542.526)		15132.36 (10702.139)		14508.13 (10211.609)	
	95% CI of Mean	14185.90, 20401.69		11614.65, 18650.07		11000.31, 18015.94	

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

**Table 15.2.4.46.1 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - PP Set****Parameter (units): Ames Mutagenicity (REV/24h)****Product Use Time Period: Period 1**

Timepoint	Statistic	THSm2.2 (N=76)		mCC (N=42)		SA (N=39)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 5	n	73	65	40	38	37	35
	Missing, n (%)	3 (3.9)	11 (14.5)	2 (4.8)	4 (9.5)	2 (5.1)	4 (10.3)
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	4856.25	-56.55	13578.55	0.00	6385.80	-37.21
		2920.94,		8265.04,		3388.44,	
	Q25, Q75	9683.10	-81.86, 0.00	17876.00	-40.63, 30.33	10009.78	-69.54, 0.00
	Min, Max	0.0, 47872.0	-100.0, 23.6	0.0, 39632.9	-100.0, 349.2	0.0, 44541.2	-100.0, 149.4
		7500.05		13476.64		9237.10	
	Mean (SD)	(8886.202)	-47.31 (40.190)	(7826.055)	12.40 (82.315)	(10000.878)	-25.29 (54.808)
		5426.74,		10973.74,		5902.64,	
	95% CI of Mean	9573.36	-57.27, -37.34	15979.54	-14.66, 39.46	12571.57	-44.12, -6.45

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

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**Table 15.2.4.46.1 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - PP Set****Parameter (units): Ames Mutagenicity (REV/24h)****Product Use Time Period: Period 4**

Timepoint	Statistic	THSm2.2 (N=70)		mCC (N=41)		SA (N=37)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Baseline	n	60		37		33	
	Missing, n (%)	10 (14.3)		4 (9.8)		4 (10.8)	
				11801.17			
	Geometric Mean (CV%)	NC		(87.502)		NC	
				9177.93,			
	95% CI of Geometric Mean	NC		15174.19		NC	
	Median	13949.74		12743.78		13085.26	
		7599.80,		8050.44,		6876.90,	
	Q25, Q75	23110.55		20372.80		17037.00	
	Min, Max	0.0, 51505.1		2331.6, 51400.0		0.0, 44541.2	
		17642.22		15158.37		13810.64	
	Mean (SD)	(12947.588)		(10848.545)		(10036.883)	
		14297.50,		11541.28,		10251.71,	
	95% CI of Mean	20986.94		18775.46		17369.57	

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

**Table 15.2.4.46.1 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - PP Set****Parameter (units): Ames Mutagenicity (REV/24h)****Product Use Time Period: Period 4**

Timepoint	Statistic	THSm2.2 (N=70)		mCC (N=41)		SA (N=37)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 90	n	70	60	40	37	37	33
	Missing, n (%)	0	10 (14.3)	1 (2.4)	4 (9.8)	0	4 (10.8)
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	5399.62	-61.35	13192.79	16.20	4977.36	-45.18
		2920.94,		8337.02,		2744.36,	
	Q25, Q75	9437.22	-77.45, -20.48	23117.80	-7.81, 57.01	11718.27	-87.39, 0.83
	Min, Max	0.0, 47872.0	-100.0, 196.0	0.0, 47824.0	-100.0, 263.3	0.0, 35588.0	-100.0, 444444.0
		6761.03		17204.22		8136.60	13437.81
	Mean (SD)	(6689.370)	-43.38 (57.595)	(12257.969)	31.33 (78.755)	(8523.113)	(77373.220)
		5166.00,		13283.93,		5294.85,	-13997.54,
	95% CI of Mean	8356.06	-58.26, -28.50	21124.52	5.07, 57.60	10978.36	40873.17

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

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Table 5 Descriptive statistics of Ames mutagenicity Test(YG1024+S9)-FAS

**Table 15.2.4.46.2 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - FAS****Parameter (units): Ames Mutagenicity (REV/mL)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Baseline	n	67		38		36	
	Missing, n (%)	11 (14.1)		4 (9.5)		4 (10.0)	
	Geometric Mean (CV%)	NC		7.76 (70.591)		NC	
	95% CI of Geometric Mean	NC		6.29, 9.56		NC	
	Median	7.66		8.10		6.91	
	Q25, Q75	5.02, 11.90		5.36, 12.00		4.96, 10.90	
	Min, Max	0.0, 32.2		2.1, 28.5		0.0, 21.7	
	Mean (SD)	9.13 (5.840)		9.41 (6.176)		8.11 (5.276)	
	95% CI of Mean	7.70, 10.56		7.38, 11.45		6.32, 9.90	

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

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**Table 15.2.4.46.2 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - FAS****Parameter (units): Ames Mutagenicity (REV/mL)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 5	n	75	67	40	38	38	36
	Missing, n (%)	3 (3.8)	11 (14.1)	2 (4.8)	4 (9.5)	2 (5.0)	4 (10.0)
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	2.80	-51.73	8.01	-4.00	3.43	-25.41
	Q25, Q75	1.74, 5.08	-82.23, 0.00	4.11, 10.70	-39.59, 0.00	2.09, 6.01	-72.97, 0.00
	Min, Max	0.0, 18.1	-100.0, 64.7	0.0, 25.1	-100.0, 162.1	0.0, 21.2	-100.0, 22.5
	Mean (SD)	3.95 (4.016)	-45.99 (42.111)	8.08 (5.017)	-5.37 (50.510)	4.92 (4.943)	-32.84 (38.572)
	95% CI of Mean	3.02, 4.88	-56.27, -35.71	6.47, 9.69	-21.98, 11.24	3.29, 6.55	-45.90, -19.78

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

**Table 15.2.4.46.2 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - FAS****Parameter (units): Ames Mutagenicity (REV/mL)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 90	n	78	67	41	38	40	36
	Missing, n (%)	0	11 (14.1)	1 (2.4)	4 (9.5)	0	4 (10.0)
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	3.23	-54.05	9.28	22.26	3.26	-34.13
	Q25, Q75	2.21, 4.98	-75.44, -8.00	4.93, 13.50	-11.03, 51.59	2.48, 6.34	-77.17, 0.00
	Min, Max	0.0, 17.7	-100.0, 64.7	0.0, 26.4	-100.0, 129.6	0.0, 15.5	-100.0, 308.0
	Mean (SD)	3.84 (3.162)	-43.88 (43.776)	9.84 (6.220)	18.69 (53.196)	4.51 (3.821)	-25.44 (78.919)
	95% CI of Mean	3.12, 4.55	-54.56, -33.19	7.87, 11.80	1.20, 36.18	3.29, 5.74	-52.15, 1.27

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

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**Table 15.2.4.46.2 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - FAS****Parameter (units): Ames Mutagenicity (REV/24h)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Baseline	n	67		38		36	
	Missing, n (%)	11 (14.1)		4 (9.5)		4 (10.0)	
				11858.12			
	Geometric Mean (CV%)	NC		(86.039)		NC	
				9284.59,			
	95% CI of Geometric Mean	NC		15145.00		NC	
	Median	13943.72		13235.99		14042.52	
		7618.40,		8050.44,		7165.53,	
	Q25, Q75	22665.10		20372.80		20843.01	
	Min, Max	0.0, 51505.1		2331.6, 51400.0		0.0, 44541.2	
		17216.05		15132.36		14909.90	
	Mean (SD)	(12533.936)		(10702.139)		(10349.331)	
		14158.78,		11614.65,		11408.18,	
	95% CI of Mean	20273.33		18650.07		18411.61	

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

**Table 15.2.4.46.2 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - FAS****Parameter (units): Ames Mutagenicity (REV/24h)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 5	n	75	67	40	38	38	36
	Missing, n (%)	3 (3.8)	11 (14.1)	2 (4.8)	4 (9.5)	2 (5.0)	4 (10.0)
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	4856.25	-56.00	13578.55	0.00	6494.00	-18.61
		2905.76,		8265.04,		3388.44,	
	Q25, Q75	9706.04	-81.86, 0.00	17876.00	-40.63, 30.33	11382.94	-68.62, 0.00
	Min, Max	0.0, 47872.0	-100.0, 23.6	0.0, 39632.9	-100.0, 349.2	0.0, 44541.2	-100.0, 149.4
		7691.77		13476.64		9756.44	
	Mean (SD)	(9059.355)	-45.90 (40.399)	(7826.055)	12.40 (82.315)	(10371.272)	-24.58 (54.184)
		5607.39,		10973.74,		6347.48,	
	95% CI of Mean	9776.14	-55.75, -36.04	15979.54	-14.66, 39.46	13165.39	-42.92, -6.25

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

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**Table 15.2.4.46.2 Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) - FAS****Parameter (units): Ames Mutagenicity (REV/24h)**

Timepoint	Statistic	THSm2.2 (N=78)		mCC (N=42)		SA (N=40)	
		Value	% Change(*)	Value	% Change(*)	Value	% Change(*)
Day 90	n	78	67	41	38	40	36
	Missing, n (%)	0	11 (14.1)	1 (2.4)	4 (9.5)	0	4 (10.0)
	Geometric Mean (CV%)	NC		NC		NC	
	95% CI of Geometric Mean	NC		NC		NC	
	Median	5399.62	-60.94	13428.90	15.03	5022.00	-46.77
		2704.06,		8498.88,		2762.80,	
	Q25, Q75	9502.92	-78.42, -12.87	22743.00	-7.81, 57.01	12439.29	-86.83, 0.41
	Min, Max	0.0, 47872.0	-100.0, 196.0	0.0, 47824.0	-100.0, 263.3	0.0, 35588.0	-100.0, 444444.0
		6901.56		17130.22		8603.01	12314.10
	Mean (SD)	(6859.626)	-42.65 (56.385)	(12113.046)	30.51 (77.850)	(8856.734)	(74079.442)
		5354.94,		13306.87,		5770.49,	-12750.78,
	95% CI of Mean	8448.17	-56.41, -28.89	20953.58	4.92, 56.10	11435.54	37378.98

Note: mCC = Menthol conventional cigarettes; SA = Smoking abstinence; THSm2.2 = Tobacco Heating System 2.2 Menthol.

Note: * % change from baseline, where baseline is defined as the last assessment prior to first randomized product use in mCC / THS 2.2 Menthol arms or the last assessment prior to 10 AM on Day 1 in the SA arm.

Note: Periods defined as Period 1 ([Day 1 – Day 6 confinement]), Period 2 ([Day 6 ambulatory – Day 30 Visit]), Period 3 ([Day 30 Visit – Day 60 Visit]) and Period 4 ([Day 60 Visit – Day 90 Visit]).

Note: NC = Not calculated

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10.3 Subject Data

Not applicable.

10.4 Statistical Output

Not applicable.

11. CORRIGENDUM APPENDICES

Not applicable.