TABLE OF CONTENTS

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LIST OF FIGURES

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LIST OF TABLES

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1. CLINICAL INDIVIDUAL HEALTH

1.1. Additional Studies Completed after Issuance of the MRGO

While the studies are detailed hereafter, study reports and study documentation will be made available to the Agency upon request.

1.1.1. *ZRHR-ERS-09-EXT-US Study*

The 6-month ZRHR-ERS-09-EXT-US study was an extension of the 6-month ZRHR-ERS-09-US study with the goal to evaluate the maintenance of the beneficial effects of switching to *IQOS* when compared to smoking cigarettes on BoExp and BoPH.

1.1.1.1. ZRHR-ERS-09-EXT-US Design Summary

A brief description of the study design is provided in Figure 1, while a summary of the main endpoints and methodology is provided in Table 1.

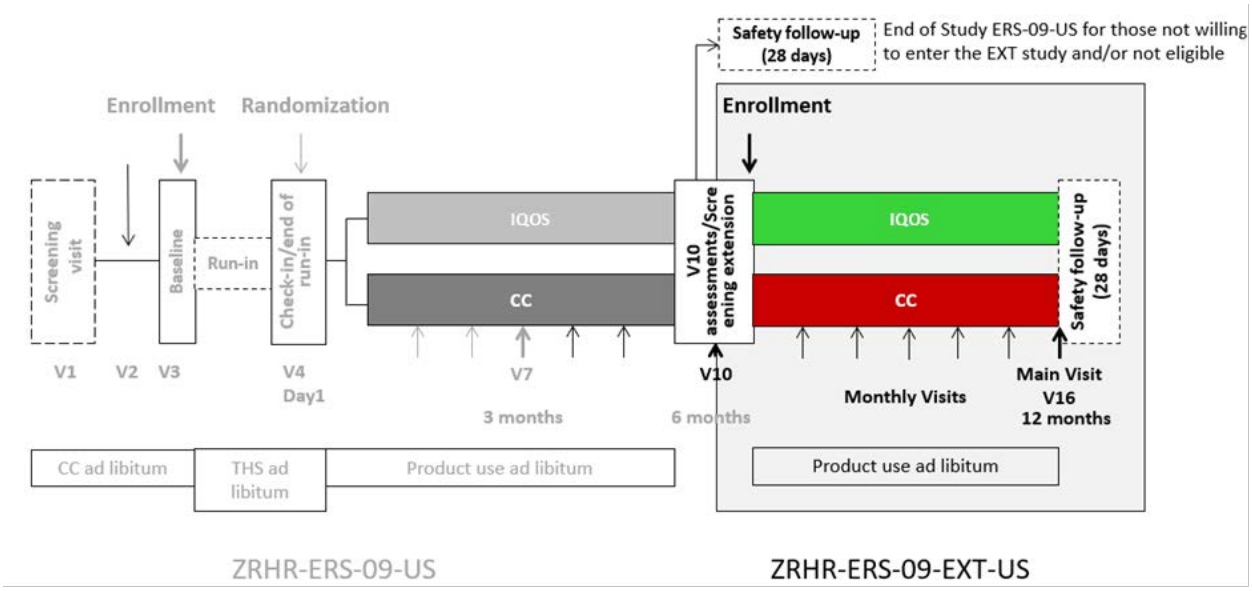

Figure 1 Scheme of the ZRHR-ERS-09-EXT-US Study

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Table 1 Methodology of the ZRHR-ERS-09-EXT-US Study

Study Title:
A 26-week extension study to determine the biological and functional changes in healthy smokers who switched from cigarettes (CC) to Tobacco Heating System 2.2 (THS 2.2) compared to those who continued to smoke CC in the ZRHR-ERS-09-US study.

ClinicalTrials.gov: ID NCT02649556.

Goal of the study: to determine the effect of THS 2.2 compared to CC at Week 52 on the components of the 8 core set BoPH defined in the primary objective of the first 6-months period, and to provide additional information to the results of the original study (ZRHR-ERS-09-US) for a prolonged Exposure Period.

Hypothesis:
This study had no formal pre-specified hypotheses associated with the study objectives.

Evaluation Criteria:
The study targeted to describe the THS effect as compared to CC at Week 52 on the components of the 8 core set of BoPH defined in the primary objective of the first 6-months period with a precision of ±75% of the anticipated THS effect at Week 52. Two-sided p-values (null hypothesis of no difference between groups) were presented for baseline comparability and for the THS effect on BoPH, on BoExp to HPHCs, and on BoExp to nicotine.

Study Design:
This was a 26-week extension study of the original study (ZRHR-ERS-09-US), a randomized, controlled, open-label, 2-arm, parallel group study design conducted in an ambulatory setting at 19 clinical sites in the US. An additional site had been activated, but terminated during the ZRHR-ERS-09-US study due to non-GCP compliance.

V10 (Week 26) represented both the last visit of the original study as well as the first visit (enrolment) of the extension study. Once all V10 assessments from the original study had been performed, subjects were offered to enter into the extension study. Enrolled subjects were informed to continue to use *ad libitum* the product they were randomized to in the original study as follows:

- THS 2.2 arm: use of THS 2.2 *ad libitum.*
- CC arm: use of their own CC brand *ad libitum.*

Subjects continued to capture the number of each of the products used including THS Tobacco Sticks, CC, and other nicotine/tobacco-containing products on a daily basis in a product use diary until the next visit 26 weeks later (16).

Twenty-four-hour urine collection started the day before V16 and ended on the morning of V16 (week 52 post baseline of the original study). At V16, lung function was measured and BoExp and BoPHs assessed.

<u>The Safety Follow-up Period (from the Check-out of V16 [Week 52] plus 28 days)</u>

The Safety Follow-up Period was defined as 28 days following check-out at V16 or early termination by the subject.

Subjects
Randomized who completed Month 6 of the original study: 803 subjects

Randomized who enrolled into the extension study: 672 subjects

Safety Population:
1012 subjects*

Full Analysis Set – as Exposed (FAS-EX) Population: 857 subjects*

* populations included subjects in the original study that did not enter the extension study for combined analyses.

Main Criteria for Inclusion:

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Male or female smoking adult subjects who met the following main inclusion criteria were planned to be enrolled:

- Subject had completed V10 of the original study (ZRHR-ERS-09-US).
- Subject was willing to comply to study procedures and to continue to use the product he/she was allocated to during the original study (THS 2.2 or CC) for an additional 26 weeks at V10.
- Subject gave written informed consent to enter the 26-week extension study at V10.

Test product: THS 2.2 (tobacco flavor); provided by the sponsor

Reference product: commercially available cigarettes (subjects' own usual brand; regular or menthol); purchased by the subjects

Duration of Study:
The entire extension study duration per subject was up to 26 weeks (6 months) plus 28 days of Safety Follow-up. The end of study (EOS) for a subject was defined as the check-out of V16 or the date of early termination of the subject plus the 28-day Safety Follow-up Period, unless the subject was lost to follow-up.

Objectives and Endpoints:
Primary Objective and Endpoints:
To determine the changes in the core set of 8 BoPH defined in the primary objective of the first 6-months period in smokers who switched from CC to THS 2.2 as compared to those who continued to smoke CC during the extension study

(Note: other biological or functional markers associated with respiratory diseases and cardiovascular diseases (CVD) were tested as well for supportive purposes, however, they are not reported here for simplification purposes):

BoPH measured at V16 (Week 52 = Month 12):

Biomarkers of Potential Harm (BoPH)	Disease pathway	Matrix
High density lipoprotein cholesterol (HDL-C)	Lipid pathway	Serum
White blood cell (WBC) total count	Inflammation	Blood
Soluble intercellular adhesion molecule 1 (sICAM-1)	Endothelial dysfunction	Serum
11-dehydrothromboxane B2 (11-DTX-B_2)	Platelet function	Urine*
8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$)	Oxidative stress	Urine*
Carboxyhemoglobin (COHb)	Cardiovascular effects	Blood
Forced expiratory volume in 1 second (FEV_1) post-bronchodilator,	Lung function	Breath
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL)	Genotoxicity	Urine*

*expressed as a concentration adjusted for creatinine

Main Secondary Objectives and Endpoints:

- To evaluate self-reported product use (CC and THS 2.2) over the duration of the study.
  Endpoint:
  - Number of CC or THS Tobacco Sticks used daily as reported in the self-reported product use electronic diary.

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- To determine the reduction in exposure to harmful and potentially harmful constituents (HPHCs) in smokers who switched from CC to THS 2.2 as compared to those who continued to smoke CC.
  Endpoints at V16 (Week 52 = Month 12):
  - Carbon monoxide (CO); parts per million (ppm) CO Exhaled breath
  - Total N nitrosonornicotine (total NNN); concentration adjusted to creatinine N nitrosonornicotine Urine
- To determine the levels of nicotine exposure in smokers who switched from CC to THS 2.2 as compared to those who continued to smoke CC.
  Endpoints (BoExp to nicotine) over the duration of the study:
  - Nicotine equivalent (Neq): molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide in urine (expressed as concentration adjusted for creatinine).
  - Nicotine and cotinine in plasma expressed in ng/mL.
- To evaluate the safety profiles associated with THS 2.2 and CC.
  Endpoints over the duration of the study:
  - Adverse events (AEs), serious adverse events (SAEs) and device events, including THS 2.2 malfunction/ misuse.
  - Vital signs.
  - Electrocardiogram (ECG).
  - Clinical chemistry, hematology and urine analysis safety panel.
  - Physical examination.
  - Concomitant medications.

Type of Blinding:
This was an open-label study; therefore, the subjects and Principal Investigator(s) or designee(s) were unblinded to the subject's study arm after randomization. However, there was a limited degree of blinding during the conduct of the study, including the data review and data analysis process. Analyses included the Full Analysis Set – As Randomized (FAS/AR); the Full Analysis Set – As Exposed (FAS EX); the Per Protocol (PP) Population; and the Safety Population.

Statistical Methods:
Data from ZRHR-ERS-09-EXT-US study were analyzed together with data collected in ZRHR-ERS-09-US study. Results were presented for relevant analysis time points of both studies.

Full Analysis Set population – As Exposed (FAS EX); subjects in FAS-AR who had at least 1 record of reported investigational product use diary post randomization. The exposure assignment was actual product exposure, based on subject's classification as per product use pattern categories. In particular, the analysis on FAS-EX was conducted using time-varying product use categories, where Month 1 – Month 6 was analyzed using product use categories defined for]V4, V10[, and Month 7–Month 12 data were analyzed using the product use categories defined for]V4, V16[.

Safety population - Subjects enrolled with signed informed consent who had at least one valid value for a safety assessment, excluding subjects enrolled at one site terminated due to findings of non-compliance with Good Clinical Practice (GCP) and/or the protocol. In general, safety data was presented by randomization arm or product use pattern categories defined for]V4, V16[.

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Analysis Populations

The analysis of endpoints at Month 12 was based on product use pattern categories derived by combining the product use categories of the two 6-month periods (main study and extension). Overall Month 12 category was in general set to Other-use in case of inconsistency between the product use categories between the original and extension studies, with the exception of cases where subjects were classified as Dual-use during 1 period and THS-use during another period, in which case subjects were classified as Dual-use.

For each 6-month period, product use categories were defined as follows:

- THS-use: ≥1 THS or CC, and ≥70% THS use over the entire analysis period, and ≥70% THS use on >50% of days in the analysis period.
- Dual-use: ≥1 THS or CC, and 1% ≤THS <70% over the entire analysis period, or THS-use and CC-use categories do not apply to 50% of these days.
- CC-use: ≥1 THS or CC, and <1% THS use over entire analysis period and <1% THS use on ≥50% of days in the analysis period).
- Other-use: Subjects with missing product use, using e-cigarettes or other tobacco products, quitters, or subjects who switched across different use patterns between consecutive analysis periods.

For all analysis sets, results were generally presented for the analysis time points: Baseline, Month 3 (V7), Month 6 (V10), and Month 12 (V16)

Primary Analyses

The eight core primary biomarkers of potential harm supporting the primary objective evaluation of the initial 6-month period in the ZRHR-ERS-09-US study were assessed at Baseline, Months 3, 6, and 12 for the comparison between THS 2.2 and CC, and prior to analyses were either log-transformed ($base_e$) (sICAM-1, 11-DTX-B2, 8-epi-$PGF_{2\alpha}$, COHb, and total NNAL) or analyzed in the original scale (HDL-C, WBC, and FEV_1). Concentrations of urinary BoPH were adjusted for creatinine.

Each BoPH was analyzed in the FAS-EX for the subgroup comparing THS-use with CC-use categories, using a mixed-effect model for repeated measurements (MMRM) adjusting for sex, Caucasian origin, time point, value of the endpoint at Baseline and its interaction with time point, product use pattern category and its interaction with time point, and other Baseline covariates relevant for each specific BoPH. Site was included as a random effect.

The least squares (LS) means and estimate of the difference along with its 95% CI and 2-sided p-value were presented in tables for HDL-C, WBC, and FEV_1. For other BoPH results were presented back transformed in the original scale as a ratio, as well as percent reduction relative to CC-use (i.e., 1 – THS-use: CC-use ratio).

Additional sensitivity analyses were conducted.

Descriptive statistics were computed to summarize data, including change from Baseline (for BoPH analyzed in original scale) or percent change and percent relative change from Baseline (for BoPH analyzed in log-normal scale).

Secondary Analyses

Product Use

The number of CC smoked or THS Tobacco Sticks used daily (as reported on the self-reported product use electronic diary) were described on the FAS-EX and PP Population, and on the Safety Population. Summaries included product use of other nicotine/tobacco-containing products and overall tobacco product grouping CC, THS Tobacco Sticks, and other tobacco products. Summaries were also presented by sex and average daily CC consumption at V1 for the 12-month product use categories for the FAS-EX. The number and percent of subjects in each product use pattern category was summarized for the first 6-month interval and for the entire 12-month interval.

Reduction of Exposure to Harmful and Potentially Harmful Constituents (HPHCs)

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The level of the BoExp (CO, total NNN) and their change from Baseline (for CO) or percent change from Baseline (for total NNN) were summarized at Months 3, 6, and 12. Total NNN data were adjusted for creatinine and log-transformed. The estimates of the difference or ratio/percent reduction were derived using an MMRM and presented together with 95% CI for THS-use versus CC-use, Dual-use versus CC-use for the FAS-EX, and THS 2.2 versus CC arms for the FAS-AR and PP.

Nicotine Exposure

The level of Neq in 24-hour urine adjusted for creatinine, nicotine and cotinine in plasma and their percent change from Baseline were summarized at Months 3, 6, and 12 for the different analysis populations. The estimates of the ratio were derived using a MMRM and presented together with 95% CI for THS-use versus CC-use, Dual-use versus CC-use (FAS-EX) and THS 2.2 versus CC arms (FAS-AR and PP).

Cough Symptoms

Cough symptoms were assessed by means of the cough questionnaire. Descriptive analyses for change from Baseline were presented for the visual analog scale (VAS) score evaluating the level of cough bother at Months 3, 6, and 12.

In addition, a logistic MMRM was used to compare the percentages of subjects reporting the need to cough between THS-use and CC-use and between Dual-use and CC-use at Month 3, Month 6 and Month 12.

Modified Cigarette Evaluation Questionnaire

Descriptive analysis and summaries for change from Baseline were presented for the 5 domain scores at Months 3, 6, and 12. The estimates of the mean difference were derived using an MMRM and presented together with 95% CI for THS-use versus CC-use, Dual-use versus CC-use (FAS-EX), and THS 2.2 versus CC arms (FAS-AR and PP).

Safety Analyses

All summaries for safety parameters were conducted on the Safety Population. In general, summaries were produced overall by randomization arm and product use pattern categories. All AEs were categorized by system organ class (SOC) and preferred term (PT) and coded according to the Medical Dictionary for Regulatory Activities (MedDRA; version 18.0). Body weight, vital signs (systolic and diastolic blood pressure, pulse rate, and respiratory rate), respiratory symptoms (cough assessment VAS and Likert scales), spirometry (chronic obstructive pulmonary disease [COPD] categorization (GOLD guideline 2013 [1]), ECG data, concomitant medications, clinical laboratory safety parameters (clinical chemistry, hematology, and urine analysis), body mass index (BMI), and physical examination were summarized.

1.1.1.2. ZRHR-ERS-09-EXT-US Results Summary

In this section, only the results of the FAS-EX population are presented, which was the primary analysis set for BoPH, BoExp, and questionnaires, except for the safety findings, which are presented for the Safety population.

1.1.1.2.1. Demographics and Baseline Characteristics

Of the 984 subjects enrolled and randomized into the original study ZRHR-ERS-09-US, 672 subjects were enrolled into the extension study: 309 subjects continued in the *IQOS* arm and 363 subjects continued in the CC arm. Overall, 614 subjects completed the Month 12 visit; 285 subjects in the *IQOS* arm and 329 subjects in the CC arm. They were then categorized as per their product use group (i.e., *IQOS*-use, Dual-use, CC-use or Other use), based on their self-reported product consumption. “Other use” data are not shown here for simplification purposes. At month 12, overall, subjects’ characteristics were well balanced between the different groups, with a

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comparable sex ratio, as summarized in Figure 2. No strong differential post-randomization attrition was observed in subjects enrolling into the extension study based on randomization.

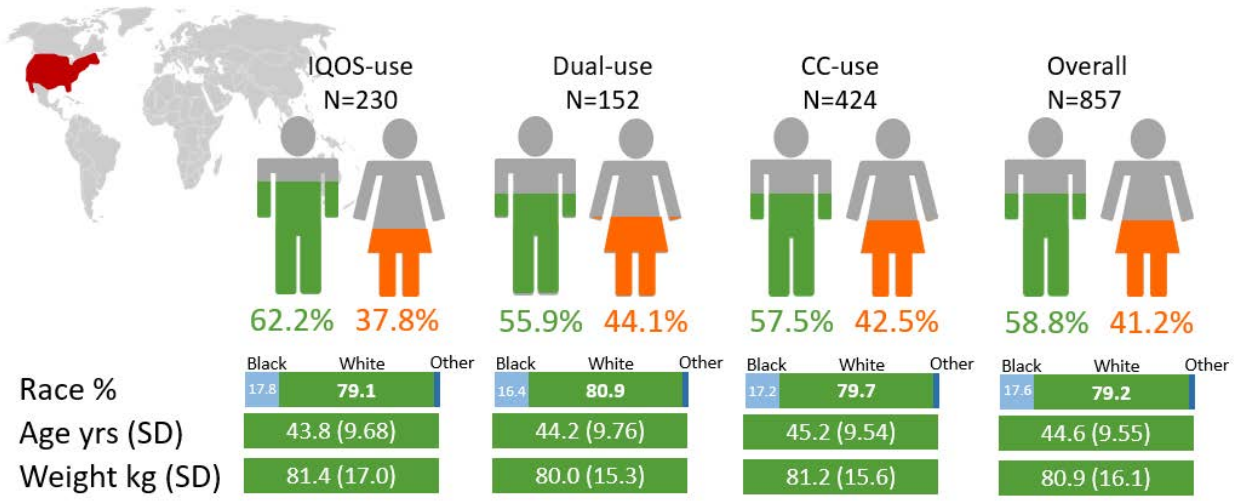

Figure 2 Summary of Demographic Data by 12 Month Product Use Category (FAS-EX: Other use not shown)

1.1.1.2.2. Primary Objective and Associated Endpoints (BoPH)-Analyses Between Predominant *IQOS* Users, Dual Users and Smokers

Compared with the cigarette-use category (smokers who continued with their own cigarettes), all eight core primary BoPH shifted in the same direction as they would upon smoking cessation (as reported in the literature and in PMP's smoking cessation study, section 1.1.2) in the THS-use category at Month 12. Marked changes occurred for WBC count, sICAM-1, COHb, and total NNAL (Table 2).

Table 2 Primary Analysis of BoPH Endpoints Between THS-use and CC-use Categories at Month 12 (FAS-EX)

BoPH	Expected Direction of Change upon Smoking Cessation	Change From CC-use	LS Mean Difference / Relative Reduction (95% CI)	2-sided p-value
HDL-C	↗	Difference	1.75 (-0.160, 3.65)	0.072

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BoPH	Expected Direction of Change upon Smoking Cessation	Change From CC-use	LS Mean Difference / Relative Reduction (95% CI)	2-sided p-value
WBC Count	↘	Difference	-0.413 (-0.694, -0.131)	0.004*
sICAM-1	↘	% Reduction	3.11 (0.0231, 6.10)	0.048*
11-DTX-B_2	↘	% Reduction	3.44 (-8.74, 14.3)	0.563
8-epi-$PGF_{2\alpha}$	↘	% Reduction	7.15 (-1.03, 14.7)	0.085
COHb	↘	% Reduction	31.7 (23.3, 39.1)	<0.001*
FEV_1 %pred post-bronchodilator	↗	Difference	0.914 (-0.339, 2.17)	0.152
Total NNAL	↘	% Reduction	46.3 (36.2, 54.8)	<0.001*

*denotes a significant p-value at the 5% level using exploratory hypothesis testing, as there were no formal pre-specified hypotheses.

1.1.1.2.3. Changes in BoPH Over Time

Predominant *IQOS* users: favorable changes were overall maintained in the THS vs CC users at Month 12, compared to Month 3 and 6, as illustrated in Figure 3. Directional changes observed were in line with those reported for smoking cessation (see Smoking cessation study, section 1.1.2).

Dual users: overall, BoPH for subjects in the Dual-use category showed a slight shift in a favorable direction at Month 12. However, with the exception of HDL-C (increase of 2.80 mg/dL [95% CI: 0.570, 5.03, compared to CC use) and %predicted FEV_1 (increase of 1.25% [-0.221, 2.73], compared to CC use) for which a slightly higher favorable effect was observed compared to the THS use category, the observed magnitude of effects for all other BoPH were lower in the Dual-use category as compared to THS-use category.

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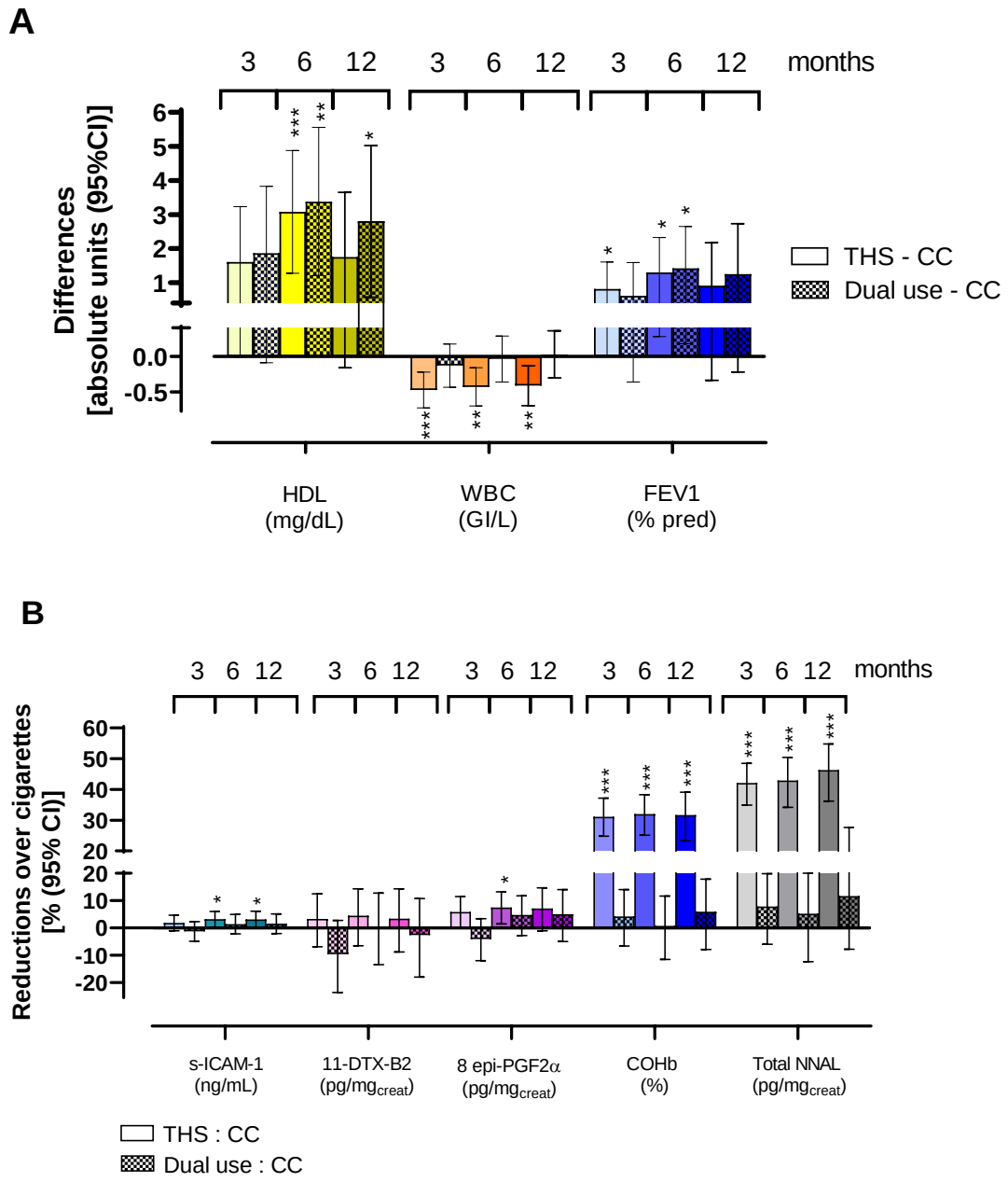

Figure 3 Differences (A) and Reductions (B) Between THS-Use vs Cigarette-Use, and Dual-Use vs Cigarette-Use for the Eight Core Endpoints at Months 3, 6 and 12 (FAS-EX)

Legend: *: p<0.05; **: p<0.01; ***: p<0.001

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A number of additional BoPH were assessed to support the 8 core BoPH (not shown here). The majority of BoPH measured shifted in the same direction as expected upon smoking cessation (section 1.1.2.2.3), and the changes were generally maintained at Month 12, further supporting the changes observed when switching to THS 2.2 from CC. Only a few BoPH did not change over the course of the study at either time point.

1.1.1.2.4. Need to Cough

Adjusted proportions and adjusted odds ratios were calculated. The observed proportions were adjusted across groups by sex, age, smoking intensity at enrollment, ethnicity, need to cough at the time of enrollment and timepoints of assessment, the main covariates that could influence the outcome. Values are presented in Table 3, with graphical presentations in Figure 4 and Figure 5.

Table 3 Proportion and Odds Ratio of Subjects Reporting Need to Cough Over Study

	Adjusted proportion (95% CI)			**Adjusted Odds Ratio (OR)**		
Timepoint	THS users	CC users	Dual users	OR THS:CC (95% CI)	p-value	OR Dual use:CC
Month 3	23.2% (16.9, 30.9)	31.5% (25.6, 38.1)	26.9% (19.0, 36.6)	65.5% (42.5, 101)	0.056	79.8% (48.7, 131)
Month 6	20.4% (14.5, 27.9)	30.4% (24.6, 36.9)	28.7% (20.4, 38.7)	58.6% (37.3, 92.1)	0.021	92.2% (56.3, 151)
Month 12	19.3% (13.0, 27.5)	28.4% (22.4, 35.2)	32.0% (22.8, 42.9)	60.3% (36.1, 101)	0.053	119% (70.6, 200)

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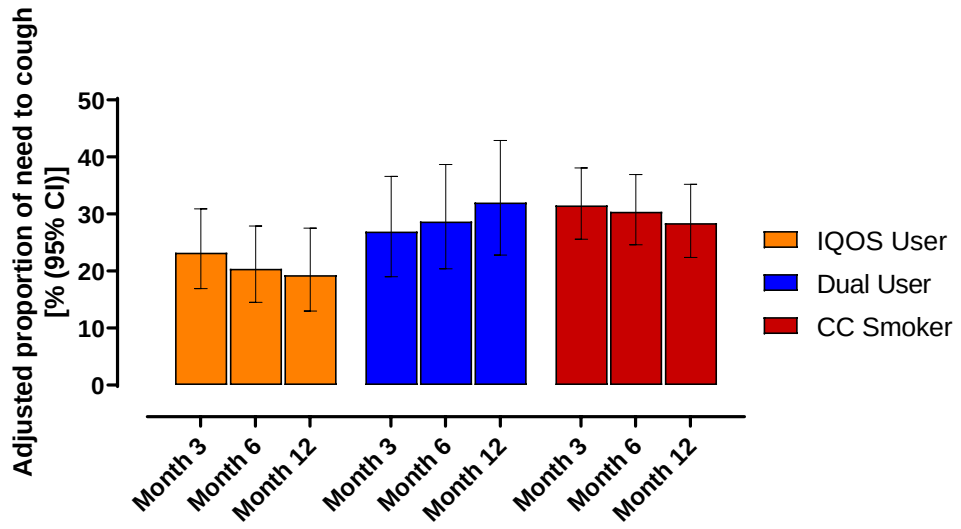

Figure 4Adjusted Proportion of Need to Cough (FAS-EX) According to Actual Product Use (FAS-EX)

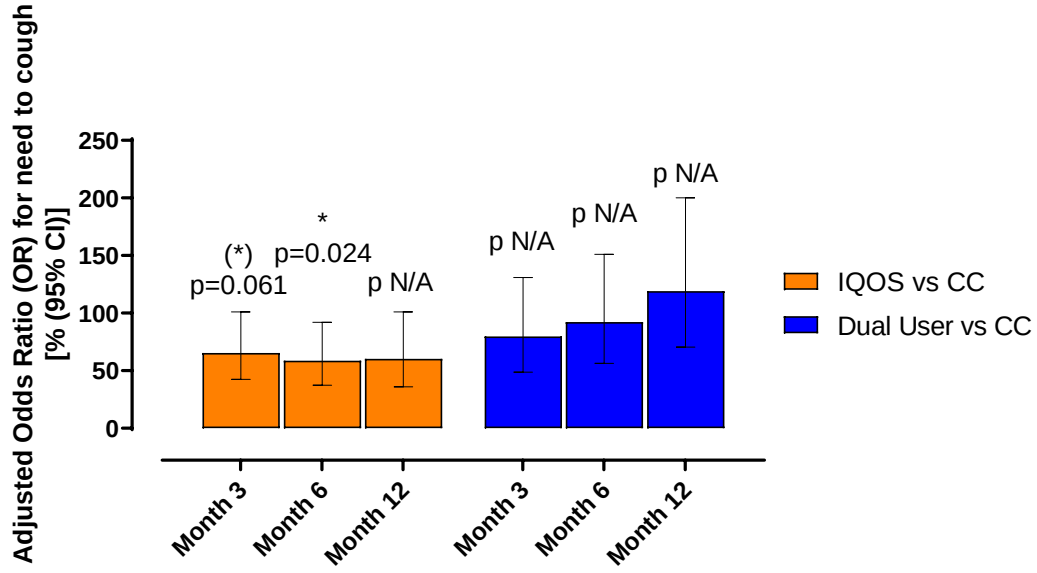

Figure 5Adjusted Odd Ratios for Need to Cough (FAS-EX) According to Actual Product Use (FAS-EX)

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Predominant *IQOS* users: After 6 months, the likelihood to self-report a regular need to cough was statistically significantly lower in THS users compared to CC users. This lower odd was already observed after 3 months of switching to THS, although not statistically significant. Similarly, it was lower at 12 months with a p-value close to 5%.

Dual-users: The likelihood to self-report the need to cough was not notably different between dual users and CC users, with an OR ranging from approximately 80% to 120% over the course of the study.

1.1.1.2.5. Exposure to HPHC and Product Use

Predominant *IQOS* users: Exposure to seven HPHCs was statistically significantly reduced in THS users by 21% to 52% after 3 months, and by 16% to 49% after 6 months (Figure 6).

Reductions at 6 months were much less pronounced than at 3 months, and less pronounced than in previous reduced exposure studies of 3 month duration (REXA-07-JP and REXA-08-US), where reductions for these BoExp ranged from 34% to 91%[1]. However, in the ERS-09-US study, subjects could use many more cigarettes than in the two 90-days studies, and still be categorized in the THS group (i.e., <30% cigarette use in the ERS-09-US study vs no more than 0.5 uses of any tobacco or nicotine containing product per day on average and no more than two uses on a single day in the two 90-days studies). With this rule, in the ZRHR-ERS-09-EXT-US study, THS users smoked on average 1.62 cigarette/day (and used 16.5 tobacco heatsticks), while in the REXA-07-JP and REXA-08-US studies, they smoked, respectively, 0.1 and 5.4 cigarette/day (FAS population), and used 21.5 and 20.7 tobacco heatsticks.

Dual users: reductions ranged from -16% to -1% and from -13% to -3% after 3 and 6 months, respectively (Figure 6). This finding emphasizes the importance of using *IQOS* exclusively to obtain the maximum benefit.

At month 12, only total NNN and 2-CyEMA were assessed. Results were consistent with earlier time points in both THS-use and Dual-use categories.

[1] *IQOS* 2.4 MRTPA submitted on Dec 5, 2016, section 6.1.3.4 Reduced Exposure – Overview of Studies

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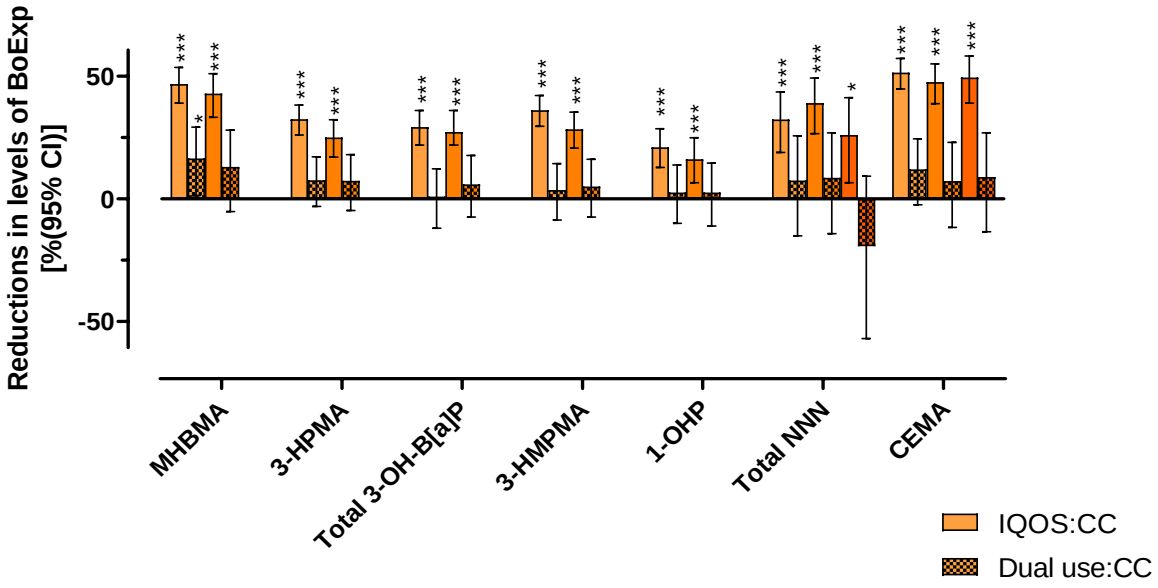

Figure 6Relative Reductions in Levels of BoExp at Months 3, 6 and 12, According to Actual Product Use (FAS-EX)

Legend: *: p<0.05; **: p<0.01; ***: p<0.001

Exposure to nicotine was comparable between THS-use, Dual-use and CC-use categories, based on urinary NEQ levels (Figure 7), and on plasma nicotine and cotinine concentrations (not shown) at Month 3, Month 6, and Month 12, indicating that subjects were titrating their nicotine levels throughout the study, regardless of their pattern of product use.

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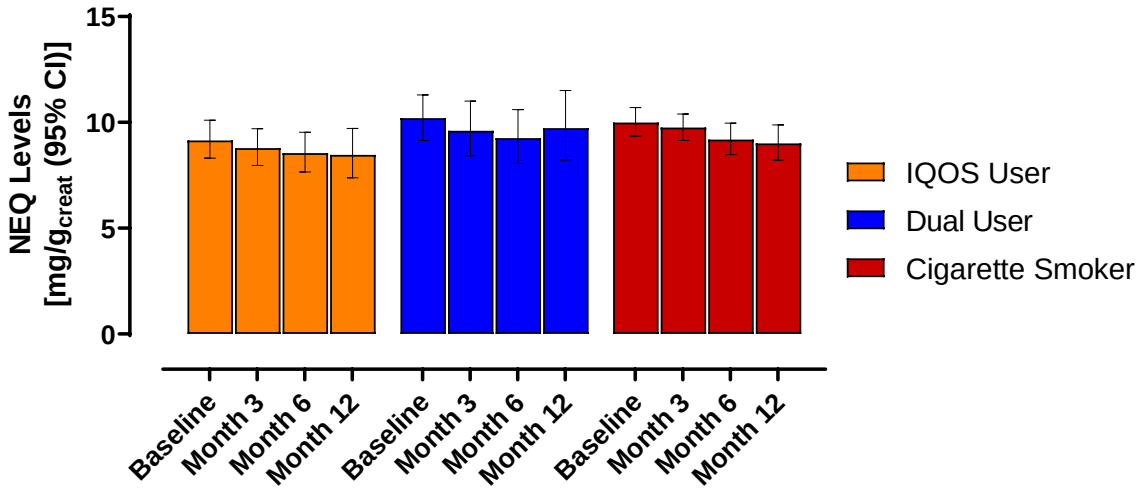

Figure 7 Levels of Urinary NEQ (adjusted to creatinine) at Months 3, 6 and 12, According to Actual Product Use (FAS-EX)

In coherence with the NEQ levels, product use did not change much from baseline in either of the product use categories, as shown in Figure 8, except for a slight decrease of in the CC-use group. This is in line with subjects' self-reported scores related to their product experience that were similar between *IQOS* and CC users for aversion, psychological reward, craving reduction, enjoyment of respiratory tract sensation, and smoking satisfaction throughout the study (not shown). A slightly lower psychological reward score in the *IQOS*-use compared to the CC use at Month 12 is however to be noted (not shown). Figure 8 further shows the amount of self-reported daily cigarette use (in red) on top of *IQOS* sticks (in orange), confirming that the *IQOS* group was indeed smoking a few cigarettes on top of using *IQOS*.

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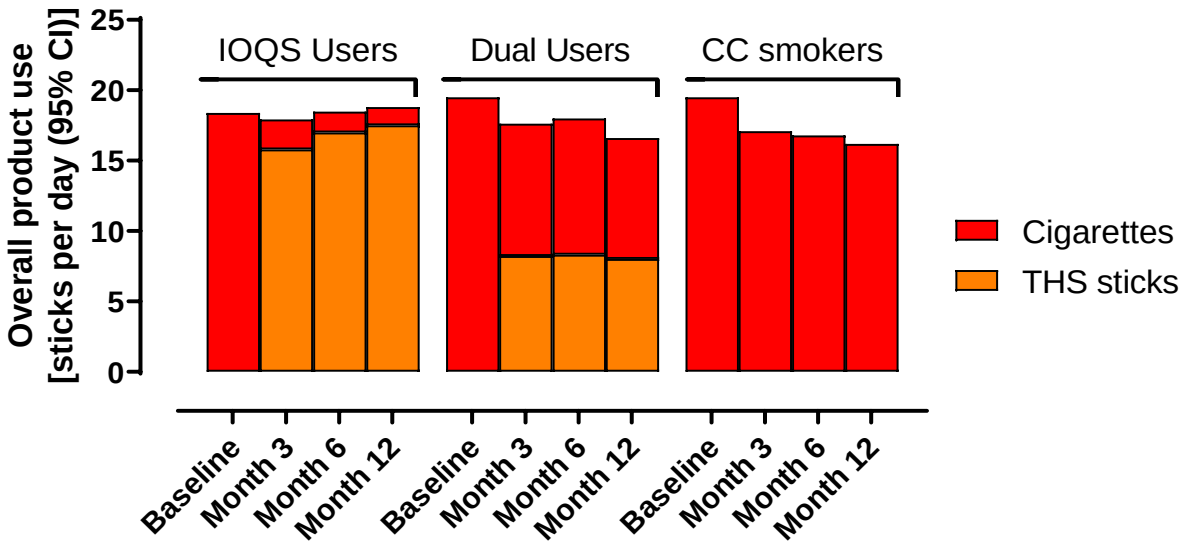

Figure 8 **Average Daily Products Used by 12 Month Product Use Category (FAS-EX)**

1.1.1.2.6. Safety Findings

In the overall Safety Population, 42 serious adverse events (SAE)s were reported by 31 subjects (3.1%); 19 SAEs in 16 subjects (3.4%) in the *IQOS* arm and 23 SAEs in 1 subjects (3.1%) in the CC arm. In the *IQOS* arm, of the 19 SAEs, serious criteria was fatal for 2 SAEs, life-threatening for 1 SAE, and required hospitalization for 17 SAEs. In the CC arm, seriousness criteria was fatal for 1 SAE, required hospitalization for 21 SAEs, resulted in disability/incapacity for 1 SAE, and involved other serious or important medical events for 3 SAEs. Of note, in 4 of the 42 SAEs, more than one seriousness criteria was selected.

There were no SAEs related to *IQOS* reported by any randomized subjects, while 3 SAEs reported by 3 randomized subjects were considered related to CC. No randomized subjects were discontinued due to SAEs related to *IQOS* or CC.

There were very few clinically relevant findings in clinical laboratory evaluations, vital signs, or ECG data, with comparable changes from Baseline to Month 6 and Month 12 between *IQOS* and CC arms.

As per 12-month product use categories, the most common AEs were upper respiratory tract infection (*IQOS*-use category [8.7%], Dual-use category [6.9%], CC-use category [9.2%] and Other-use category [7.5%]). Blood triglycerides increased were reported in 4.1% of subjects in the *IQOS*-use category, 3.8% of subjects in the Dual-use category, 6.0% of subjects in the CC-use category, and 0.9% of subjects in the Other-use category. Hypertension was reported by 3.7% of subjects in the *IQOS*-use category, 5.7% of subjects in the Dual-use category, 6.0% of subjects in the CC-use category, and 3.8% of subjects in the Other-use category. All other AEs by PT were

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reported in <5% of subjects within a product use category.

The incidence and frequency of AEs related to *IQOS* or CC were comparable between the 12-month product use categories (9 AEs in 7 subjects [2.9%] in the *IQOS*-use category, 5 AEs in 4 subjects [2.5%] in the Dual-use category, 9 AEs in 9 subjects [2.1%] in the CC-use category and 2 AEs in 2 subjects [1.9%] in the Other-use category). The most frequent AEs related to *IQOS* or CC were cough, productive cough and weight increased.

There were very few clinically relevant findings in clinical laboratory evaluations, vital signs, or ECG data, with comparable changes from Baseline to 6 and 12 months across categories.

1.1.1.2.7. Study Conclusions

In predominant *IQOS* users, reduction of exposure to HPHCs was associated with a favorable change (interpreted in the context of what is observed when stopping smoking) in trajectory after 12 months in all the eight core BoPH versus continued cigarette smoking as reported in the initial 6-month study, as reported in the literature on smoking cessation and as shown in the PMP's smoking cessation study (section 1.1.2). These favorable changes were observed despite the allowed use of up to 30% of cigarettes.

In the dual-users, the magnitude of favorable changes (both BoPH and BoExp) was detectable but lower throughout the study due to the higher cigarette consumption in the dual users (dose response to smoking intensity).

Exposure to nicotine was comparable between across product use categories while product consumption, remained overall stable for the whole study duration. Overall, the product was well accepted by subjects based on their self-reporting of *IQOS* experience and safety data.

Our findings indicates that switching to *IQOS* is likely to translate further into reduction of disease risk because:

- Quitting cigarette smoking is well established to reduce the risk of the main diseases attributable to smoking (CVD, COPD, and lung cancer), and
- BoPH response when switching was similar to quitting cigarette smoking.

In the context of harm reduction strategy, *IQOS* is likely to play a critical role to reduce the risk of smoking-related diseases in smokers who wish to continue smoking while providing an acceptable and satisfactory alternative to smokers with regards to nicotine delivery, subjective effects, and safety. Results of the study have been released on ClinicalTrials.gov.

1.1.2. *SA-SCR-01 Study*

The 12-month smoking cessation response study (SA-SCR-01 Study) was conducted in smokers willing to quit smoking to assess the magnitude of changes of all the BoPH assessed in the "Exposure Response Study (both ZRHR-ERS-09-US and ZRHR-ERS-09-EXT-US) after smoking cessation. It was meant to serve as a benchmark of changes, in quitters who were verified via

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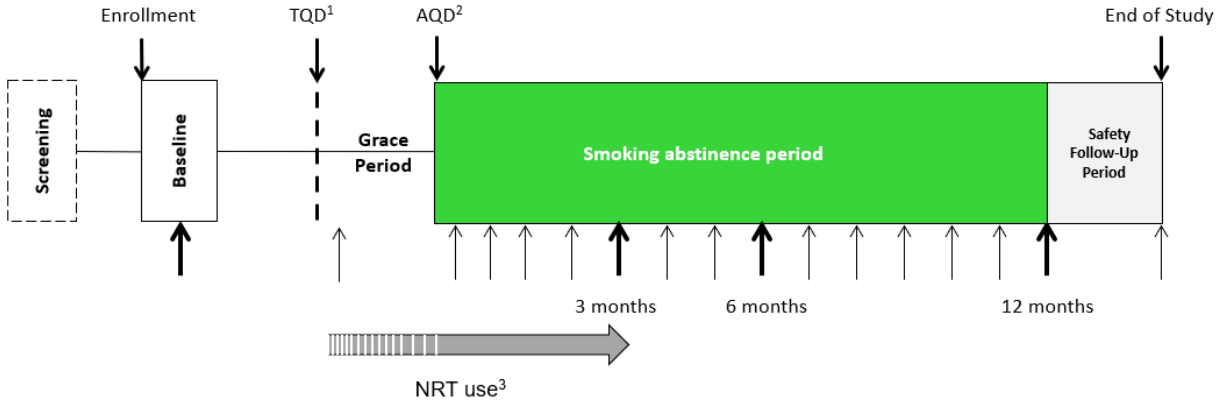
multiple biochemical methods for continuous and full abstinence from cigarette smoking. The results of this study were used to perform a cross-study comparison with the results obtained on switching from cigarettes to *IQOS* use for 12 months for contextualization and evaluate reduced risk potential of *IQOS* (section 1.1.3 and 1.1.4).

1.1.2.1. SA-SCR-01 Design Summary

A brief description of the study design is provided in Figure 9, while a summary of the main endpoints and methodology is provided in Table 4.



1 Target quit date (TQD) was within 1–14 days of checkout of V2
2 Actual quit date (AQD) was within 14 days of TQD (grace period with occasional CC use)
3 Smoking abstinence (SA)
4 Use of NRT was only allowed for up to 3 months (+2 weeks) after the start date of NRT. NRT could be started at any time between the TQD and 1 week after the AQD

Abbreviations: AQD, actual quit date; CC, cigarettes, CO, carbon monoxide; NRT, nicotine replacement therapy; TQD, target quit date; V, visit.

Figure 9 Scheme of the SA-SCR-01 Study

Table 4 Methodology of the SA-SCR-01 Study

Study Title: A multi-center, multi-region smoking cessation study to understand the biological and functional changes related to smoking cessation in healthy smokers who are continuously abstinent from smoking for one year. ClinicalTrials.gov: ID NCT02432729.
Goal: to determine the effect of quitting cigarette for 12 months on a broad range of BoPH and BoExp .
Hypothesis: This study had no formal pre-specified hypotheses associated with the study objectives. **Evaluation Criteria:** The study targeted to describe the estimates of the effect of quitting cigarette and their associated 95% CI at Week 52.

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Sample size was estimated based on FEV1 change upon cessation and predicted continuous abstinence rate to be able to estimate the cessation effect after 52 weeks on FEV_1%pred with a 90% probability of obtaining a margin of error (half-width of the 95% CI) of ± 1% pred.Other endpoints are assumed to exhibit a larger effect size than FEV_1%pred and thus would result in smaller sample size estimates.

Study Design:

This was a multi-region, multi-center, ambulatory study conducted in the US, Japan and Europe (43 sites). Smokers who were motivated to quit smoking within the next 30 days at the Screening Visit (V1) were enrolled. From AQD onwards at Week 2 (V5) the study intended to achieve at least 190 successful quitters at the end the study.

Screening Period (1 to 42 days prior to enrollment)

Subject's eligibility to the study was verified at V1. Subjects were provided with urine containers and instructions for the 24 hour urine home collection at the end of V1.

Baseline Visit - V2 (from check-in to check-out from the site)

Twenty-four-hour urine collection started in the morning of the day prior to V2 and ended 24 hours later in the morning of V2. Enrollment of the subject took place after collection of the cooled urine container(s) filled with his/her 24-hour urine and re-check of inclusion criteria number 4 and 6. Then, procedures and data collection were completed. All subjects could continue smoking their preferred brand of cigarette (CC). Before check-out, subjects were asked to define their targeted quit date (TQD,).

From Check-out of V2 to AQD (28 days for each subject)

This period identified subjects who were motivated and likely to quit and remain continuously abstinent from smoking cigarettes over the study. The period started from check-out of V2 and ended with the actual quit date (AQD, Day 1) including the TQD, V3 and the Grace Period (maximum of 14 days was allowed from TQD, during which occasional use of nicotine and or/tobacco-containing products was accepted). The subjects were asked to come to the clinic for V3 within 24 to 48 hours after their defined TQD. The latest possible day for the AQD was defined as the last day of the Grace Period (*i.e.*, TQD + 14 days).

The Smoking Abstinence Period (from the AQD up to the check-out of V17 [week 52]):

From the AQD, subjects were asked to come on site at week 1 (V4), at week 2 (V5) and then on a monthly basis at week 4 (V6), at week 9 (V7), at week 13 (Month 3, V8), at week 17 (V9), at week 22 (V10), at week 26 (Month 6, V11), at week 30 (V12), at week 35 (V13), at week 39 (V14), at week 43 (V15), at week 48 (V16), and at week 52 (Month 12, V17). Visits were scheduled based on the AQD. A time window of ± 8 days was allowed for the visits, with the exception of V4 (± 3 days) and V5 (± 3 days).

The V8 (Month 3), V11 (Month 6), and V17 (Month 12) correspondeded to full assessment visits at site(s) where 24-hour urine and blood sampling were collected for analysis of BoExp and BoPH. The collection of the 24-hour urine started at home in the morning the day before the visit and ended 24 hours later in the morning of the day of the visit to the clinic.

The Safety Follow-Up Period and Phone Contact (28 days after the check-out of V17 [V18 (±3 days); week 56]):

A subject who completed V17, or a subject who discontinued from the study prematurely (early termination), entered a 28-day Safety Follow-Up Period during which spontaneously reported new AEs/SAEs were recorded, and the active follow-up of ongoing AEs/SAEs was done by the site. The EOS of the entire study was the end of the Safety Follow-Up Period of the last subject.

Type of blinding: None.

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Subjects:

Number of Subjects (Planned and Analyzed):

Enrolled Population:	1184subjects
Abstinent 3m Set	720 subjects
Abstinent 6m Set	450 subjects
Abstinent 12m Set	358 subjects

Main criteria for Inclusion:

Male or female smoking healthy subjects with no restriction on race and ethnicities, who had smoked at least 10 CCs per day on average for the last 12 months and who had been smoking for at least the last 10 years were enrolled. The following main inclusion criteria had to be met:

- Subject had signed the informed consent form (ICF) and was able to understand the information provided in the ICF;
- Subject was aged from 30 to 65 years old (inclusive);
- Smoking, healthy subject as judged by the Investigators based on all available assessments from the Screening Period (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG, concomitant medications and medical history);
- The subject was willing to quit smoking within the next 30 days, as assessed by the Prochaska's 'Stage of Change' questionnaire.

Test product:

There was no test product, since this was a smoking cessation study. Subjects were free to use NRT for up to 3 months and were reimbursed if taking any.

Duration of Study:

The maximum total duration of the study for a subject was up to 66 weeks, including a 42-day screening period and a 28-day Safety Follow-Up period. The end of study (EOS) for a subject was defined as the end of the Safety Follow-Up Period of the last subject, unless the subject was lost to follow-up.

Objectives and Endpoints:

The objectives of this study were:

1. To describe the clinical, biological and functional changes in smokers who were continuously abstinent from smoking.

   <u>BoPH associated with cardiovascular disease at Month 3 (V8), Month 6 (V11), and Month 12 (V17):</u>

   - White blood cell count (WBC), platelet count, glycosylated hemoglobin (HbA1c), and carboxyhemoglobin (COHb) in blood
   - High and low density lipoprotein cholesterol (HDL-C, and LDL-C), myeloperoxidase (MPO), soluble intercellular adhesion molecule-1 (sICAM-1), apolipoprotein A1 and B (Apo A1 and Apo B), and high sensitivity C-reactive protein (hs-CRP) in serum
   - Fibrinogen and homocysteine in plasma
   - Albumin, 11-dehydrothromboxane B2 (11-DTXB2) and 8-epi-prostaglandin F2-alpha (8-epi-PGF2α) in urine (expressed as concentration adjusted to creatinine)

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BoPH associated with respiratory diseases at Month 3 (V8), Month 6 (V11), and Month 12 (V17):

- Spirometry (pre- and post-bronchodilator): Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, forced expiratory flow (FEF 25-75)
- Lung volume: vital capacity (VC), total lung capacity (TLC), functional residual capacity (FRC), inspiratory capacity (IC), at selected sites specialized for lung function testing
- Cough symptoms (intensity and frequency), amount of sputum production and bothersomeness of cough symptom from the cough questionnaire

BoPH associated with xenobiotic metabolism at Month 3 (V8), Month 6 (V11), and Month 12 (V17):

- Cytochrome P450 2A6 (CYP2A6) activity: molar metabolic ratio of *trans*-3-hydroxycotinine/cotinine in plasma

BoPH associated with genotoxicity at Month 3 (V8), Month 6 (V11), and Month 12 (V17):

- Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL) in urine (expressed as concentration adjusted to creatinine)

2. To describe the changes in biomarkers of exposure (BoExp) to harmful and potentially harmful constituents (HPHCs) in smokers who were continuously abstinent from smoking.

BoExp to HPHCs at Month 3 (V8), Month 6 (V11), and Month 12 (V17):

- BoExp to carbon monoxide (CO): CO in exhaled breath (expressed as ppm)*
- BoExp to nicotine: cotinine and nicotine in plasma and nicotine equivalents (NEQ) in urine[2]*
- BoExp to 1,3-butadiene : monohydroxybutenylmercapturic acid (MHBMA)*
- BoExp to acrolein: 3-hydroxypropylmercapturic acid (3-HPMA)*
- BoExp to acrylonitrile: 2-cyanoethylmercapturic acid (CEMA; or 2-CyEMA)*
- BoExp to benzo(a)pyrene: 3-hydroxybenzo(a)pyrene (B[a]P)*
- BoExp to pyrene: Total 1-hydroxypyrene (Total 1-OHP)*
- BoExp to crotonaldehyde: 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA)*
- BoExp to N-nitrosonornicotine: total N-nitrosonornicotine (Total NNN)*
- BoExp to 4-aminobiphenyl: 4-aminobiphenyl (4-ABP)
- BoExp to benzene: S-phenylmercapturic acid (S-PMA)
- BoExp to 1-aminonaphthalene: 1-aminonaphthalene (1-NA)
- BoExp to 2-aminonaphthalene: 2-aminonaphthalene (2-NA)
- BoExp to o-toluidine: o-toluidine (o-tol)
- BoExp to ethylene oxide: 2-hydroxyethylmercapturic acid (HEMA)
- BoExp to toluene: S-benzylmercapturic acid (S-BMA)

All BoExp measured in urine, were expressed as concentrations adjusted to creatinine. Only BoExp marked with " * " were assessed at Month 6 (V11) and Month 12 (V17).

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3. To describe the rate of continuous smoking abstinence at each visit following the actual quit date (AQD) of smoking cessation.
4. To monitor safety
    - Adverse events (AEs) / serious adverse events (SAEs)
    - Body weight
    - Vital signs
    - Spirometry
    - Electrocardiogram (ECG)
    - Clinical chemistry, hematology and urine analysis safety panel
    - Physical examination
    - Concomitant medications

Statistical Methods:

Analysis Populations

Screening population: All subjects who provide informed consent.

Full safety population: All subjects in the Screened Population who had been enrolled and had at least one evaluable safety assessment at Enrollment or later.

Enrolled Population: All subjects in the Full Safety Population excluding those from Site 515 in Japan. This site was closed due to findings identified during monitoring visits concerning the validity, reliability and integrity of data reported by the site.

Quitters population**:** All enrolled subjects with at least one evaluable BoPH, BoExP, or questionnaire assessment after AQD contributing to analysis at 3 or 6 months or 1 year with no major protocol deviations impacting the overall subject evaluability part of this population. Continuous cigarette abstinence throughout the study was assessed based on self-reported product use and biochemical verification**:** 1) no self-reported use of any tobacco or nicotine-containing products other than NRT from AQD onwards; 2) exhaled CO breath test result ≤ 10 ppm, performed at each visit from V4 onwards; 3) urine cotinine test result < 100 ng/mL (in spot urine collected at the study site), performed at each visit from month 5 (V10) onwards; and 4) free cotinine concentration result < 50 ng/mL in urine collected during the 24-hour in-home urine collection [2]. Participants were discontinued if they failed to meet any of these four criteria. Additionally, subjects were included in this population if the concentration of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) from the 24-hour urine collection at V11 (6 months). was <75.9 pg/mL, however, the subject was NOT discontinued from the study [3]. Depending on the period during which subjects in the Quitters Population continuously abstained from smoking (and with no major protocol deviations which impacted data evaluability), quitters were included in one or more abstinence sets (Abstinence3m, Abstinence6m, and Abstinence12m). These were the main populations of interest for analysis.

Stratification

Stratified presentations were conducted for all the abstinence sets for the descriptive summaries of BopHs using stratification criteria based on the following baseline subject characteristics:

- Sex (male, female);

[2] Nicotine equivalents (Neq) are defined as molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free *trans*-3'-hydroxycotinine, *trans*-3'- hydroxycotinine-glucuronide.

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- Region (Japan, US and EU). Centers from UK, Poland and Germany were pooled to region EU.

Stratified presentations were also conducted for:

- Demographics by sex and by region for the Enrolled Population and for all the abstinence sets;
- Quitting rates (*i.e.*, rate of subjects continuously smoking abstinent) over study visits by region, and by country within Europe for the Enrolled and Quitters populations;
- Adverse events by region.

Clinical, Biological and Functional Changes
BoPH including the 8 core BoPH data were summarized at Baseline, V8, V11 and V17. The level of BoPH and their change from Baseline were presented descriptively.

Apart from WBC (total and counts), HbA1c, LDL-C, HDL-C, Apo A1, Apo B, Apo B/Apo A1, respiratory diseases, xenobiotics and genotoxicity markers, the BoPH values were log-transformed ($base_e$) prior to the analysis. These endpoints were analyzed in the logarithmic scale and summary estimates were back-transformed to provide results in the original scale. Summaries were only presented on the original scale. The geometric mean and CV were presented in addition to the (arithmetic) mean and standard deviation (SD).

Summary statistics included the mean change from baseline with 95% confidence interval (CI). Absolute and percent change from baseline was summarized for endpoints analyzed in the real and logarithmic scale, respectively.

Urinary markers (albumin, 11-DTXB2 and 8-epi-PGF2α) were summarized adjusted for creatinine. The percent of change from Baseline in the concentration adjusted for creatinine, and the quantity excreted was also summarized.

Biomarkers of Exposure to HPHCs
The level of BoExp parameters (CO in exhaled breath, S-BMA NEQ, cotinine and nicotine in plasma, MHBMA, 3-HPMA, 2-CyEMA, B[a]P, Total 1-OHP, 3-HMPMA, Total NNN, 4-ABP, S-PMA, 1-NA, 2-NA, o-tol, HEMA) and their change from Baseline was summarized at Baseline, V8, V11, and V17 descriptively for the abstinence sets.

Exhaled CO was described within the abstinence sets. All other BoExp were log-transformed prior to the analysis. Summaries were presented on the original scale.

Concentration of BoExp in urine was summarized adjusted for creatinine and summarized as percent of change from Baseline and quantity excreted.

Nicotine exposure: The level of NEQ adjusted for creatinine, nicotine and cotinine in plasma was summarized.

Continuous smoking abstinence**:** Continuous smoking abstinence was summarized at V4 to V17, as well as the quitting status reported at V18, for the Quitters Population and abstinence sets.

Time-to-event analysis using Kaplan-Meier (KM) methodology was adopted to describe the estimated rate of subjects who were continuously abstinent from cigarettes from AQD to V17. Time from AQD nominal visit was used to calculate the time-to-relapse event or censoring (duration of abstinence only partially known as subject has left the study before relapse). Relapse events were defined as non-adherence to continuous abstinence. Subjects without an event at the time of analysis were censored at the last visit where adherence was demonstrated.

The number of subjects at risk of relapse event, number of events and estimated continuous abstinence rates and 95% CI (using the log-log transformation) was presented from AQD to V17. Summaries and graphs were produced overall and by region for the Quitters Population at each visit following the AQD of smoking cessation and also summarized by country within Europe.

Safety Analyses:
Adverse events (including SAEs, AEs leading to discontinuation, and AE leading to death) were summarized for the Safety Population. AEs were categorized by System Organ Class and preferred term (PT) and coded using the

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Medical Dictionary for Regulatory Activities (MedDRA, Version 18.0). Respiratory symptoms (cough assessment questionnaire), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), spirometry parameters, ECG data, clinical laboratory safety parameters (clinical chemistry, hematology, and urinalysis), concomitant medication, body mass index, body weight, height and waist circumference and physical examination were summarized.

Questionnaires:

Lifestyle Assessment: The change from Baseline was calculated for the numeric items at V8, V11 and V17. The responses to the individual items and change from Baseline were summarized for the abstinence sets. The number and percentage of subjects reporting living in a household with one or more smokers was also summarized, as well as the shift from Baseline.

Cough-VAS Questionnaire: The change from Baseline was calculated for the VAS score evaluating the level of cough bother at V8, V11 and V17. For the calculation of the change from Baseline, missing VAS values was imputed with zero when no cough was reported. To evaluate cough symptoms, participants were asked if they had experienced a regular need to cough within the previous 24 hours, assessed its intensity by completing a visual analogue scale (VAS), and answered 3 Likert scale questions. These questions, based on a 24-hour recall, assessed the bothersomeness, intensity, and frequency of cough, and the amount of sputum production. Questions and instructions were provided in the participant's language.

The VAS score and change from Baseline and 3 Likert scales measuring the intensity, the frequency of cough and the amount of sputum production was listed and summarized for all subjects who filled in the questionnaire from the abstinence sets. The number and percentage of subjects reporting a cough was also summarized, as well as the shift from Baseline.

1.1.2.2. SA-SCR-01 Results Summary (12 Month Abstinence Set)

1.1.2.2.1. Demographics and Baseline Characteristics

Overall, subjects' characteristics were well balanced between the different groups, with a comparable sex ratio, as summarized in Figure 10 for the 12-month abstinence set, except for races, which were guided by the regions in which the study was conducted and for gender. In the US, the majority of subjects were white, with 15.1% black or African American in the 12-months abstinence set. A higher proportion of female subjects than male subjects were enrolled across in the US subjects, while this proportion was much lower in Japan. The mean BMI for the overall 12-month abstinence set was approximately 25 kg/m^2 with a higher proportion of obese subjects in the US (23.3% vs 10.3% in the overall population). FTND scores were notably lower in Japan than in the other regions.

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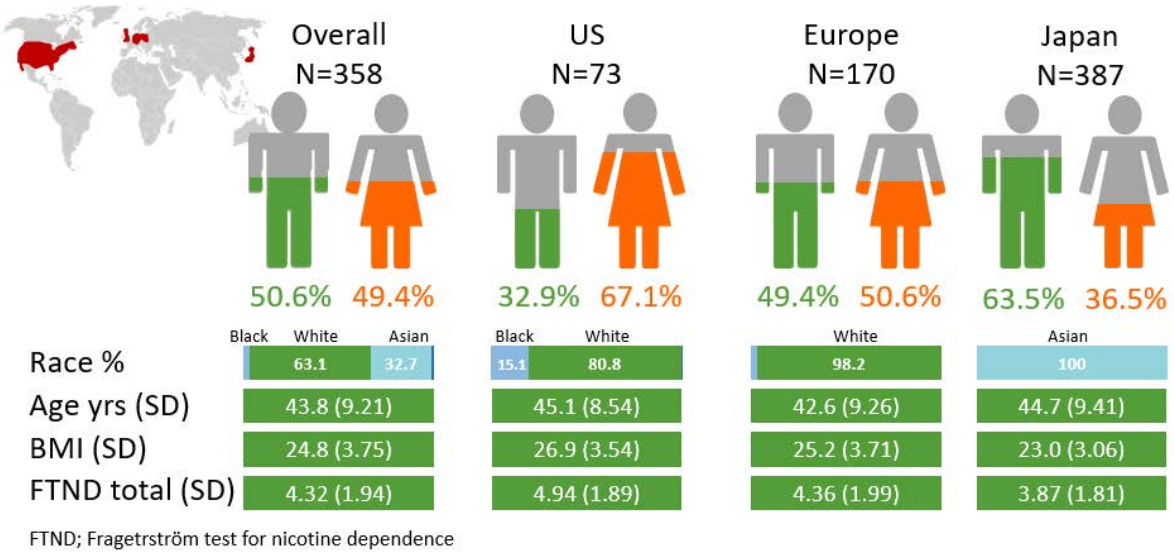

Figure 10 Summary of Demographic Data of the Quitters, Overall and by Region (Abs12mo Set)

1.1.2.2.2. Rate of Continuous Smoking Abstinence and Exposure to HPHC

The overall continuous abstinence rate was higher until Month 5 (81%) and decreased at Month 6 (58.8%) due to 170 subjects declared non-abstinent at Month 6, following the implementation of more rigorous compliance measures (i.e., urine analysis of cotinine and NNAL levels) (Figure 11). Among the different regions, at Month 12. Across regions, subjects from Japan had the highest adherence rate to continuous smoking abstinence than other regions: Japan: 54%, Europe: 48.8%, US: 49.7%.

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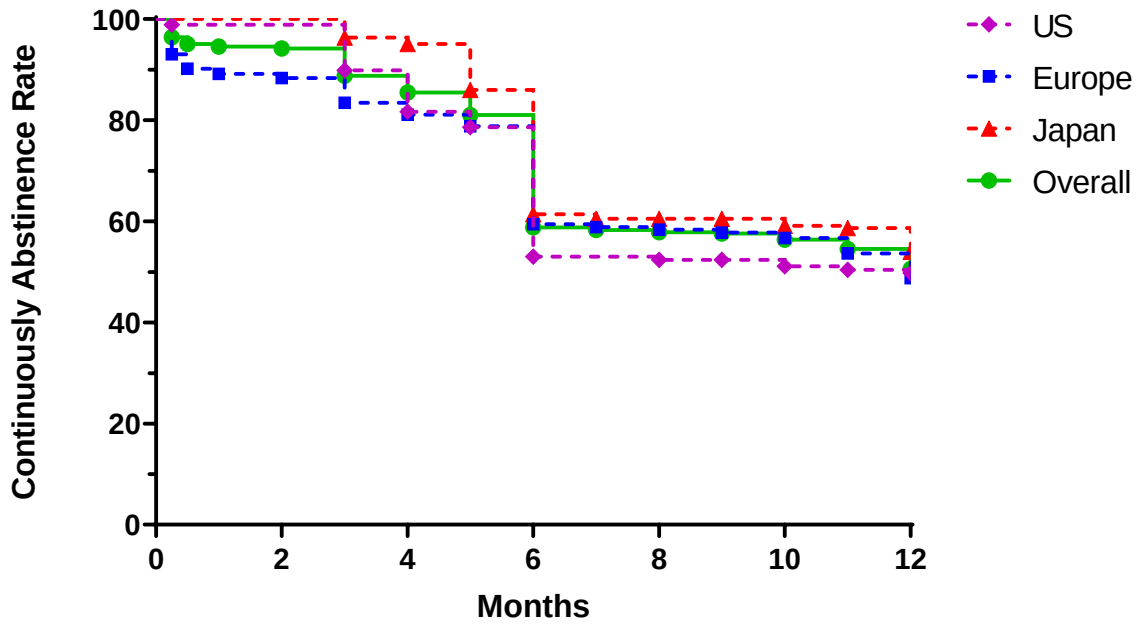

Figure 11 **Rate of Continuous Smoking Abstinence over Time by Region and Overall - Quitters Subjects**

As expected, marked and sustained reduction from Baseline in BoExp levels was observed over the course of the study (except for S-BMA, not reported on the graph, as it was found not to be able to distinguish smokers from non-smokers) (Figure 12). Exhaled CO levels were also reduced over time (by around 3 ppm at each time point, versus around 15 ppm at Baseline). Exposure to nicotine, as evaluated with NEQ levels) was also substantially reduced from Baseline. Not all BoExp were measured at each time point.

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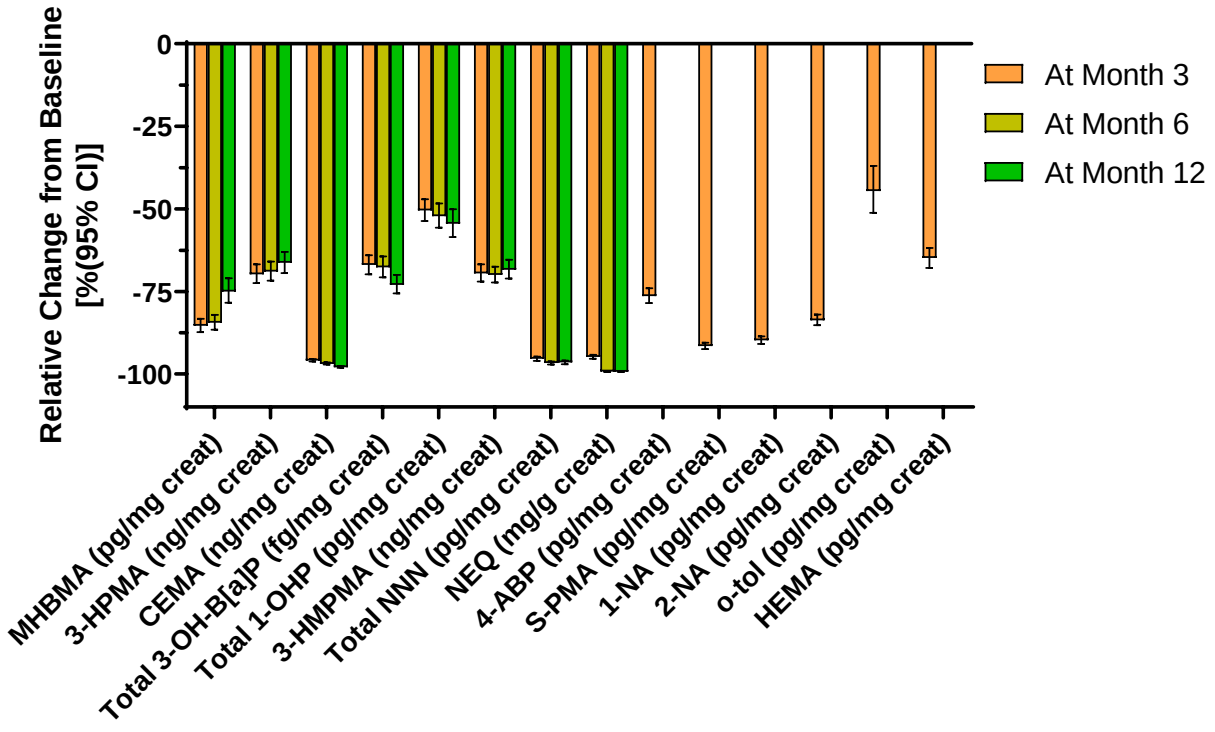

Figure 12 Relative Changes from Baseline of Levels of BoExp over Time Overall - Quitters Subjects (Abs12mo Set)

Reductions across regions were all comparable, despite some notable differences in the baseline levels (not shown). Total NNAL and total NNN were higher at baseline in the US than in the other regions, probably due to differences in the tobacco blends used in the US, where Burley tobacco is more commonly used, which is known to contain more tobacco specific nitrosamines [4].

1.1.2.2.3. Changes in BoPH Over Time

Results of the eight core BoPH tested in the ZRHR-ERS-09-EXT study are summarized below (Table 5 and Figure 13).

In the overall 12 month abstinent set, all the levels BoPH changed from baseline in the direction reported in the literature (favorable changes considering that smoking cessation is known to decrease disease risk [5]) and in a time-dependent manner with the exception of HDL-C, which showed consistently favorable changes but inconsistent magnitude of effect throughout time, with higher changes observed at Month 3 than at Month 12. A possible explanation to explain this observation, could be the weight gain, which was higher in the SA-SCR-01 study than in the ZRHR-ERS-09-EXT study, even though this would need to be confirmed.

Specifically, the following findings throughout the study were observed relative to baseline:

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- An increase in HDL-C at 3 and 6 months, which was less marked after 12 months.
- A decrease from baseline in total WBC count, suggestive of a lower inflammation.
- A small decrease of FEV_1 (%pred) post bronchodilator (BD) over time, indicative of the known effects of ageing on lung function. Of note, most of the other lung function parameters (not shown here) remained similar at 3 and 6 months. Our findings are in line with the absolute change of FEV_1 reported in the literature in healthy smokers following one year of cigarette quitting: up to ca 50 ml/year [6], which is about the volume that was lost during this study (ca. 50 mL).
- A reduction in sICAM-1 levels indicative of a possible improvement in endothelial function. The concentration of urinary albumin adjusted for creatinine remained similar to Baseline over the course of the study.
- A decrease in 11-DTXB2 and fibrinogen concentration, likely reflecting a positive change in the platelet function.
- A decrease in 8-epi-PGF2α levels, possibly indicating an amelioration of oxidative stress, however, this was not supported by levels of MPO, which instead increased at 6 and 12 months (not shown here). No plausible explanation was found to explain this discrepancy.
- A substantial decrease in COHb level, which should be overall beneficial for the cardiovascular system.
- A marked decrease in total NNAL urinary level, indicative of less exposure to carcinogens.

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Table 5 Changes from Baseline in the Eight Core BoPHs after Quitting Completely Cigarette at 6 and 12 months (Abs12mo Set)

		Change (SD) from baseline (CV%) 95% CI	
		Month 6	**Month 12**
Lipid metabolism	HDL-C (mg/dL)	1.6 (9.73) 0.646, 2.55	0.856 (10.4) -0.285, 2
Inflammation	WBC count (GI/L)	-0.629 (1.48) -0.768, -0.491	-0.545 (1.68) -0.721, -0.37
Platelet function	11 DTXB2 concentration* adjusted for creatinine	-24.9 (65.7) -29, -20.5	-22.2 (66.8) -27, -17
Oxidative stress	epi-PGF2α concentration adjusted for creatinine*	-16.2 (45.3) -19.5, -12.7	-18.8 (45.8) -22.4, -15
Endothelial Dysfunction	Soluble Intercellular Adhesion Molecule-1*	-11.8 (20.5) -13.5, -10.1	-13.2 (24.2) -15.4, -11
Acute Cardiovascular Effect	Carboxyhemoglobin*	-73.7 (138) -76.3, -70.8	-71.5 (157) -74.7, -67.8
Lung Function	FEV_{1pred} post BD	-0.0527 (0.245) -0.0792, -0.0263	-0.0491 (0.238) -0.0755, -0.0227
Genotoxicity	Total NNAL*	-95.9 (194) -96.4, -95.3	-96.1 (200) -96.6, -95.5

* Corresponds to relative changes from baseline

Abbr.: 8-epi-PGF2α = 8-epi-prostaglandin F2α, 11-DTX-B2 = 11-Dehydrothromboxane B2, COHb = Carboxyhemoglobin, CRE = clinical risk endpoint, FEV1 = Forced expiratory volume in 1 second, HDL-C = High density lipoprotein Cholesterol, NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, WBC = White blood cells, BD: bronchodilator.

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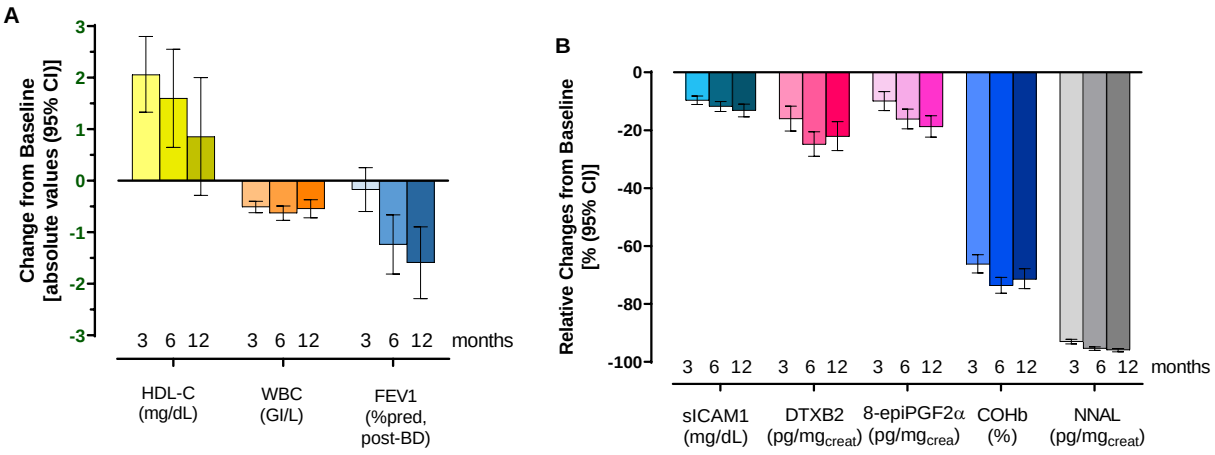

Figure 13 Differences (A) and Relative Changes (B) from Baseline of Eight BoPH after 3, 6 and 12 Months of Smoking Cessation (Abs12mo Set)

Changes across regions were overall comparable, however, with notable differences in some baseline values, such as, for example, for HDL-C, which was lower at baseline in the US population, and higher in Japan. The US population generally had a less "favorable" BoPH profile at baseline, which could be due to its overall higher BMI and inclusion of more obese subjects than in the other regions.

1.1.2.2.4. Need to Cough (Abs12mo Set)

The percent of subjects who self-reported a regular need to cough was 34.4, 11.7, 10.6, and 11.2 at baseline, 3, 6 and 12 months, respectively, therefore indicating an amelioration of cough symptoms after smoking cessation. Similar results were observed for each region.

1.1.2.2.5. Safety Findings (Abs12mo Set)

Overall, SAEs were reported in a small proportion of subjects overall (17 subjects [1.4%]; 20 events) with one fatal AE reported in one US subject. No SAEs were related to study procedures and no deaths or subjects' discontinuation from the study due to any AE were reported in the Abstinence12m Set. Incidence of AEs for the subjects in the Abstinence12m Set was similar to that of the Enrolled Population.

Overall, 2083 AEs were reported in 701 subjects (59.2%) in the Enrolled Population (Full Safety Population excluding subjects from site 515 closed due to findings during monitoring visits). In most of these subjects, the AEs were considered as either mild or moderate in severity with 28 AEs being considered as severe. The proportion of subjects reporting AEs was higher in Europe than in the other regions; 384 subjects (76.8%) reported 1296 AEs in Europe, 169 subjects (48.4%) reported 534 events in the US, and 148 subjects (44.2%) reported 253 events in Japan. Overall, 390 AEs in 216 subjects (18.2%) were assessed as being related to the study procedures. The most common AEs were nasopharyngitis, upper respiratory tract infections, and weight increased. The

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most common AEs related to study procedures were drug withdrawal syndrome and weight increased. The majority of the subjects in the Enrolled Population had normal clinical chemistry, hematology, and urinalysis values at all the time points. Mean changes from Baseline in vital signs, physical examination, ECG and spirometry parameters were small and similar across all three regions.

1.1.2.2.6. Study Conclusions

In the SA-SCR-01 study, substantial decreases in exposure to HPHCs were observed after 3, 6 and 12 months of continuous smoking abstinence. This was likely associated with a favorable changes impact on lipid metabolism as indicated by an increase in HDL-C, a decrease in the inflammatory status as indicated by a decrease in WBC, a decrease in platelet activation as indicated by a decrease in 11-DTXB2, a decrease in oxidative stress as indicated by a decrease in the levels of 8 epi-PGF2α, and favorable changes in endothelial function as indicated by the decrease in sICAM-1. This was supported by changes of supportive BoPH not summarized here.

The observed favorable impact on the majority of mechanistic pathways which occur altogether upon smoking cessation provide comprehensive and coherent information and provide mechanistic understanding on how the risk of diseases can decrease in smokers who continuously stop smoking.

Because, quitting cigarette is known to decrease the risk the main disease attributable to smoking long term [5], we interpret the changes of BoPH trajectory from baseline as being indicative of further risk reduction. Importantly, the outcomes of this study offer the possibility to position the changes in BoExp and BoPH associated with switching to *IQOS*, and thus, its potential for harm reduction.

In subjects abstinent over 12 months, FEV_1 post-bronchodilator and FEV_1%predicted post-bronchodilator plateaued from Baseline to Month 6 and slightly decreased at Month 12.

Results of the study have been released on ClinicalTrials.gov.

1.1.3. *Cross-Study Analysis on the Core 8 BoPH in the ZRHR-ERS-09-US study (P1-ERS-EXT-SCR-PH-SHP)*

1.1.3.1. P1-ERS-EXT-SCR-PH-SHP Design Summary

The purpose of this integrated cross study analysis was to evaluate the magnitude of effects of the changes observed in smokers for BoExp and the eight core BoPH after switching from cigarette to predominant *IQOS* use relative to continuous abstinence smoking cessation against current smoking over a one year period.

The cross-study analysis pooled the data from three studies:

- ZRHR-ERS-09-US (NCT02396381) and its extension ZRHR-ERS-09-EXT-US (NCT02649556).

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- SA-SCR-01 (NCT02432729)

This pooled data resulted in an "observational study like" with potential imbalanced subject's characteristics between study groups at baseline.

To account for the baseline imbalance and minimize bias:

- Japanese population was excluded from post-Hoc analysis. It was considered to have baseline characteristics that differ from the European and American populations
- A propensity-score-weighing based approach was implemented in order to adjust the analysis for the potential imbalance of baseline characteristics between study groups. As a result, age, body mass index (BMI), smoking intensity, Fagerström test for Nicotine Dependence (FTND) score, sex, and ethnicity were used in Propensity Score Weighting for ATT Analysis.

In this analysis, three product use groups determined from subjects' self-reported product use were considered:

IQOS-users:	• Subjects completing the extension of the Exposure Response Study • Daily users of *IQOS* or cigarettes • *IQOS* use representing at least 70% of the total of *IQOS* (up to 30% cigarette use) over 12 months according to self-reporting
Smokers (CC-use category):	• Subjects completing the extension of the Exposure Response Study • Daily users of *IQOS* or cigarettes • *IQOS* use representing less than 1% of the total of *IQOS* and cigarettes use over 12 months according to self-reporting
Smoking abstinent subjects (Abstinence category):	• Subjects completing the Smoking Cessation Study • No self-reporting of any tobacco or nicotine-containing product other than Nicotine Replacement Therapies over 12 months • Adherent to various biochemical verifications

To account for potential bias of self-reported product use in the *IQOS* and smoking abstinence groups mentioned above, biochemical verification was used to detect the intensity of concomitant use of cigarette to evaluate adherence in the predominant *IQOS* group.

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The BoExp used for verification was 2-CyEMA (urinary concentrations), a BoExp for acrylonitrile, which is produced only with tobacco combustion. A dose relationship between number of cigarettes used daily and 2-CyEMA was observed in Theophilus et al. [7]**.** The threshold applied was of 47 ng/mg creatinine, based on former internal analyses and on levels of 46.98 described by Rostron et al. (under the designation of 2-CyEMA) in the Population Assessment of Tobacco and Health (PATH) study for participants using between 0 and 4 cigarette per day [8]. The implementation of this threshold in the predominant *IQOS* users (allowed up to 30% cigarette consumption use in addition to using *IQOS*) and smoking abstinence groups intended to exclude subjects who smoke more than 4 cigarettes/day. By limiting concomitant cigarette consumption to the minimum, we expected to observe higher magnitude of favorable effects on BoExp and BoPH associated with *IQOS* use.

A brief description of the methodology of this new analysis is provided in Table 6.

Table 6 Methodology of the P1-ERS-EXT-SCR-PH-SHP Cross-Study Analysis

Study Title: A Cross-Study Analysis to Determine the Effect of Smoking Abstinence Preserved After Switching from Cigarette Smoking to THS 2.2 use	
Goal of the Study: To understand how close if the effect of THS use relative to smoking abstinence against cigarette smoking.	
Hypothesis: The study was exploratory with no confirmatory hypothesis being tested. Point and interval estimates (and accompanying p-values) were presented. **Evaluation Criteria:** The statistical tests were two-sided and conducted at the 5% level, and all quoted confidence intervals are two-sided 95% confidence intervals, with no multiplicity adjustment.	
Subjects:	
Number of Subjects included in the WAFAS-EX analysis set	
Total:	725 subjects
THS	167 subjects
CC	315 subjects
SA	243 subjects
Number of Subjects included in the WAFAS-2-CyEMA analysis set	
Total:	609 subjects
THS	51 subjects (69% of the WAFAS-EX removed)
CC	315 subjects
SA	243 subjects
Main criteria for Inclusion: Please refer to sections 1.1.1.1 and 1.1.2.1 for the inclusion/exclusion criteria in the studies.	

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Because only subjects from the US were enrolled in the ZRHR-ERS-09-EXT-US study while the SA-SCR-01 study population also included subjects from different countries in the EU, and in Japan, data from subjects enrolled in JP were not included in this integrated analysis due to different lifestyle and biological differences that were not accounted for in the assessed baseline characteristics.

Test product:

Test product: THS 2.2 (tobacco flavor); provided by the sponsor.

Reference product: commercially available cigarettes (subjects' own usual brand; regular or menthol); purchased by the subjects.

No test product in the SA-SCR-01 study, which was a smoking cessation study.

Duration of Study:
The maximum total duration of the SA-SCR-01 study for a subject was of 66 weeks (including a 42-day screening period and a 28-day safety follow-up period, while the entire extension study duration per subject was 26 weeks of exposure (6 months) plus 28 days of safety follow-up, in addition to the 26 weeks of the initial phase of the study (ERS).

Main objective and endpoints:

- To determine the effects after 12 months on the 8 BoPH defined in the primary objective of the first 6-months period of switching from cigarette to THS or becoming smoking abstinent (SA), compared to continued smoking (switching to THS was also compared to becoming SA).

Endpoints:
- High density lipoprotein cholesterol (HDL-C) in serum
- White blood cell total count (WBC) in blood
- Soluble Intercellular adhesion Molecule 1 (sICAM-1) in serum
- 11-dehydrothromboxane B2 (11-DTX-B2) in urine (expressed as concentration adjusted for creatinine)
- 8-epi-prostaglandin F2α (8-epi-PGF2α) in urine (expressed as concentration adjusted for creatinine)
- Carboxyhemoglobin (COHb) % in blood
- Forced expiratory volume in 1 second (FEV_1 post-bronchodilator, expressed as % predicted [FEV1 %pred])
- Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL) in urine (expressed as concentration adjusted for creatinine)

Secondary objectives and endpoints:

- To determine the effects after 3 and 6 months on the eight core primary BoPH defined in the primary objective of the first 6-months period the of switching from cigarette to THS or becoming SA, compared to continued smoking (switching to THS was also compared against becoming SA).

Endpoints:
Same as for main objective (above)

- To determine the effects after 3, 6, and 12 months on the biomarkers of exposure (BoExp) of switching from CC to THS, or becoming SA, compared to continued smoking (switching to THS was also compared against becoming SA).

Endpoints:
BoExp to carbon monoxide (CO):
- CO in exhaled breath (expressed as ppm)

BoExp to various HPHCs in urine (expressed as concentration adjusted for creatinine):
- BoExp to 1,3 butadiene: monohydroxybutenylmercapturic acid (MHBMA)*
- BoExp to acrolein: 3-hydroxypropyl-mercapturic acid (3-HPMA)*

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- BoExp to N-nitrosonornicotine: total N-nitrosonornicotine (Total NNN)
- BoExp to acrylonitrile: 2-cyanoethylmercapturic acid (2-CyEMA or CEMA)
- BoExp to benzo[a]pyrene: 3-hydroxybenzo(a)pyrene (3-OH-B[a]P)*
- BoExp to crotonaldehyde: 3-hydroxy-1-methyl propyl mercapturic acid (HMPMA)*
- BoExp to pyrene: Total 1-hydroxypyrene (total 1-OHP)*

(Note: BoExp indicated with an asterisk * were not measured at month 12 during the ZRHR-ERS-09-EXT-US study. For these BoExp, the analyses were conducted similarly to the other BoExp up to month 6.)

Statistical Methods:

The subjects in the Full Analysis Set – As Exposed (FAS-EX) as defined in ZRHR-ERS-09-EXT-US who completed the 12-month study period and the ones from the Abstinence 12 Months (Abs12M) dataset as defined in SA-SCR-01 (excluding subjects coming from Japanese sites) were pooled to form the Augmented FAS-EX (AFAS-EX) analysis set. The main product use category variable was retrieved from ZRHR-ERS-09-EXT-US. Subjects labelled as "Dual-use" or "Other-use" were not used in any analysis and thus excluded from the AFAS-EX analysis set. For subjects in Abs12M, the product use category variable was created and populated as "SMK_ABS" (Smoking Abstinence) when merging the datasets.

To ensure balanced baseline characteristics between subjects of different product use categories, a propensity score weighting method was used, and weights were computed to estimate an average treatment effect on the treated (ATT). The ATT compares the effect of the product use categories on subjects that were likely to select THS use and were able and willing to use it for 12 months. These weights were assigned to the subjects and the Weighted Augmented Full Analysis Set – As Exposed (WAFAS-EX) was formed and used as the main analysis set. Propensity score included Age, body mass index (BMI), Smoking intensity, Fagerström Test for Nicotine Dependence (FTND) score as continuous covariates, while sex and race were accounted for as categorical covariates.

Separately for each endpoint, a linear mixed effects model was fit, using the weights derived based on the propensity score method. The model included the following covariates: baseline of endpoint, age, sex, product use category, visit, and interaction between product use category and visit. An unstructured covariance matrix was used to model the relationships between the repeated measurements per subject and a robust sandwich estimator was used to estimate the variances. For endpoints assumed to follow a log-normal distribution, a log-transformation before entering the model (using the natural logarithm) was applied and the results were exponentiated back to the original scale.

Furthermore, creatinine adjusted 2-cyanoethylmercapturic acid (2-CyEMA) was used as a tool for assessing adherence to THS and SA. A biochemically verified subpopulation of AFAS-EX using a cut-off of 47 ng/mg creatinine for 2-CyEMA in "THS-use" and "SMK_ABS" subjects was identified. These subjects with a 2-CyEMA value above the cut-off (at month 12) were excluded from AFAS-EX and the resulting population was called AFAS-CyEMA (subjects with a missing value of 2-CyEMA at month 12 were not excluded). Using the same propensity score approach as described in the previous paragraph to this reduced AFAS-2-CyEMA analysis set led to the creation of the WAFAS-2-CyEMA analysis set.

The main estimand was an Average Treatment effect among the Treated and was defined as follows:

Product Use Under Evaluation: CC use, THS use, and SA (adherence/abstinence was up to month 12).

Main Endpoints: see endpoints defined in the primary objective of the first 6-months period.

Target population: THS users satisfying inclusion/exclusion criteria as detailed in the clinical study protocols of the various studies (excluding subjects from Japan).

Population-level summary: the pairwise mean differences between the three product use categories in endpoint values at month 12 (for log-normally distributed endpoints, differences was replaced by ratios).

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Intercurrent events:

- Subject's non-adherence. Non-adherence was out of the scope of this estimand. Consequently, non-adherent subjects were excluded according to self-reported product use.
- Subject's discontinuation. Discontinuation was out of the scope of this estimand. Consequently, subjects who did not complete the study were excluded.
- Intermittent missing data were not imputed.

Additional analyses using the Average Treatment Effect (ATE) estimand and propensity score matching instead of weighting were also performed.

1.1.3.2. P1-ERS-EXT-SCR-PH-SHP Results Summary

1.1.3.2.1. Analysis Sets

The two main analyses of interest were the WAFAS-EX-ATT and the WAFAS-EX-2-CyEMA-ATT. Following adjustment with propensity scores (ATT weighting for all the variables), the standardized mean differences and variance ratios of each covariate of the two analysis sets confirmed a better balance of the baseline covariates across all three pairwise comparisons of product use categories (CC, *IQOS*, and SA).

Pooled Full Analysis Set – WAFAS-EX – Baseline Characteristics (Self-Reported Product Use Only)

A total of 725 subjects (167 *IQOS*, 315 CC, and 243 SA) were included.

Their mean (SD) age was 44.5 (9.47) years; males were 395 (54.5%). Their mean smoking duration was 25.4 (9.61) years with an average daily consumption of 18.5 (7.15) cigarettes.

Pooled Full Analysis Set – WAFAS-2-CyEMA – Baseline Characteristics (Self-Reported product use and 2-CyEMA threshold)

A total of 609 subjects (51 *IQOS*, 315 CC, and 243 SA) were included. Compared to the WAFAS-EX analysis set, 116 subjects out of 167 were removed from the *IQOS* group, which represents 69% of the initial group. No SA subject had a 2-CyEMA value above 47 ng/mL.

Their mean (SD) age was 44.4 (9.40) years; males were 328 (53.9%). Their mean smoking duration was 25.1 (9.65) years with an average daily consumption of 18.4 (7.18) cigarettes.

1.1.3.2.2. Changes in BoPH Over Time

Irrespective of the analysis sets presented in this document, significant favorable differences in all the examined parameters were seen in both the SA and *IQOS* groups compared to the cigarette group (Figure 14).

In absence of biochemical (2-CyEMA) verification WAFAS-EX-ATT analysis (Figure 14, A&B): The levels of the eight core BoPH were statistically significantly different from the cigarette group for SA at most timepoints, while changes in *IQOS* group were consistent, however,

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not always statistically significant. Changes were generally lower in the *IQOS* versus SA, except for FEV_1, where results were rather comparable. The later suggest that the switching to *IQOS* effect may not be as impactful as quitting smoking over a one-year period. This can, however, be explained by the concomitant use of cigarette allowed (up to 30% of the total consumption) in addition to *IQOS*.

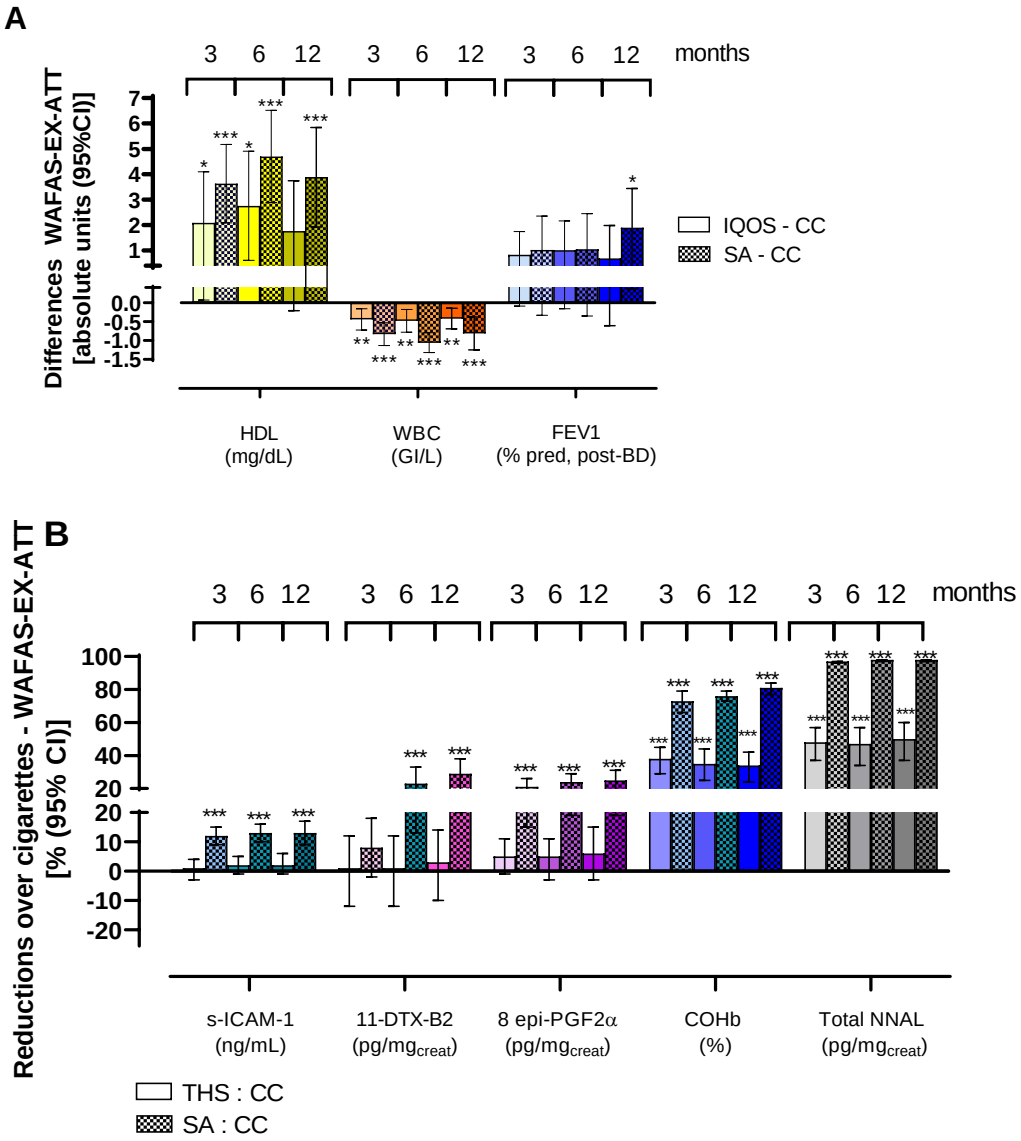

Figure 14 Differences (A) and Reductions (B) Between *IQOS*-Use vs Cigarette-Use, and Smoking Abstinence vs Cigarette-Use for the Eight Selected Co-Primary Endpoints at Months 3, 6 and 12 (WAFAS-EX-ATT Analysis Set)

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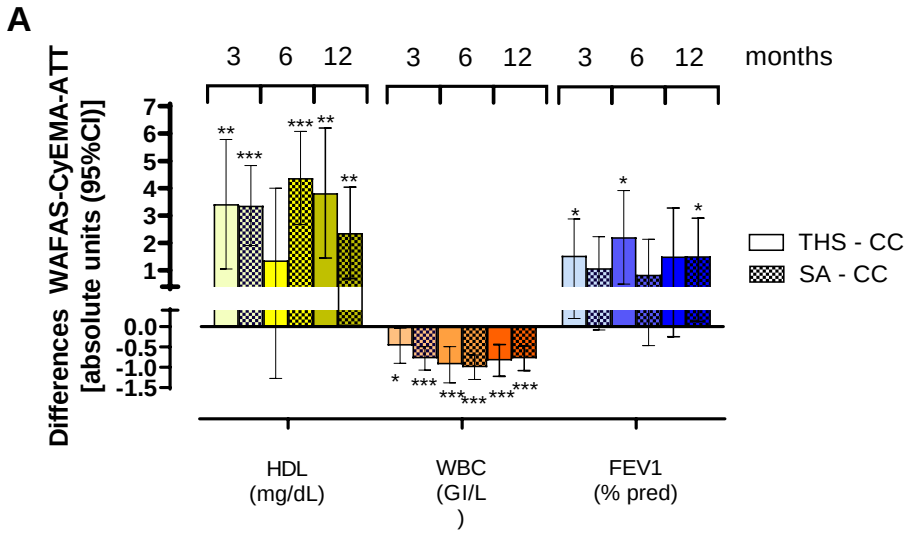
Note: Reductions were obtained as follows: (1-ratio)*100.

Legend: *: p<0.05; **: p<0.01; ***: p<0.001

With biochemical (2-CyEMA) verification, WAFAS-2-CyEMA-ATT analysis (Figure 15, A&B)**:** exclusion of subjects smoking more than 4 cigarettes/day (subjects with 2-CyEMA >47 ng/mg creatine) generally resulted in a more pronounced favorable effect (compared to the cigarette group) throughout the study in the *IQOS* users compared to the analysis without biochemical verification (WAFAS-EX-ATT), in particular for HDL (except at 6 months).

The change in trajectory was similar between *IQOS* and SA groups relative to the cigarette group with statistical differences observed for HDL-C and 8-epi-PGF2α at 12 months.

The favorable impact of *IQOS* on WBC, COHb and total NNAL was comparable in magnitude to SA, however, it was still slightly lower for the five remaining BoPH.



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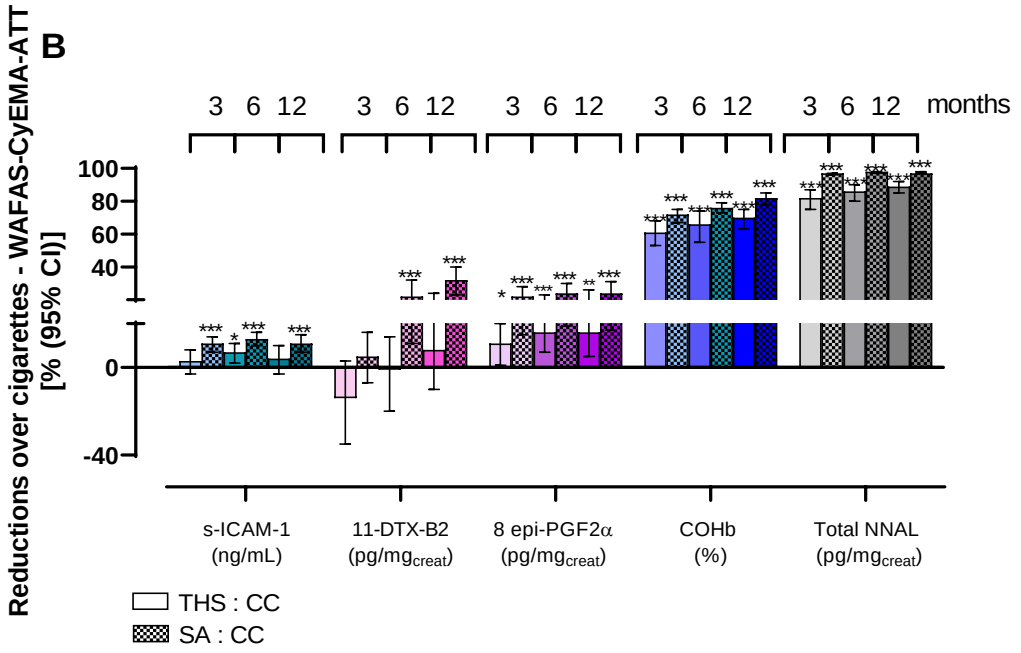

Figure 15 Differences (A) and Reductions (B) Between *IQOS*-Use vs Cigarette-Use, and Smoking Abstinence vs Cigarette-Use for the Eight Selected Co-Primary Endpoints at Months 3, 6 and 12 (WAFAS-2-CyEMA-ATT Analysis Set)

Note: Reductions were obtained as follows: (1-ratio)*100.

Legend: *: p<0.05; **: p<0.01; ***: p<0.001

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Table 7 Overview of the Eight Core Primary BoPH Defined in the Primary Objective of the ZRHR-ERS-09-US study

	Comparison	SA vs. CC			*IQOS* vs. CC			*IQOS* vs. SA		
Endpoint	**Month**	**3**	**6**	**12**	**3**	**6**	**12**	**3**	**6**	**12**
HDL-cholesterol (mg/dL)[1]	**WAFAS-EX**	3.63***	4.7***	3.89***	2.09*	2.76*	1.77 (0.08)	-1.55 (0.143)	-1.94 (0.111)	-2.11 (0.063)
	WAFAS-2-CyEMA	3.37***	4.38***	2.37**	3.42**	1.37 (0.31)	3.82**	0.05 (0.968)	-3.01*	1.45 (0.237)
Leukocytes (GI/L)[1]	**WAFAS-EX**	-0.83***	-1.06***	-0.81***	-0.44**	-0.48**	-0.42**	0.39*	0.58***	0.39 (0.08)
	WAFAS-2-CyEMA	-0.78***	-1***	-0.78***	-0.47*	-0.93***	-0.83***	0.31 (0.142)	0.07 (0.758)	-0.04 (0.83)
FEV1 (%pred)[1]	**WAFAS-EX**	1.02 (0.138)	1.05 (0.141)	1.9*	0.83 (0.077)	1.01 (0.092)	0.69 (0.298)	-0.19 (0.795)	-0.04 (0.954)	-1.21 (0.159)
	WAFAS-2-CyEMA	1.08 (0.069)	0.84 (0.208)	1.52*	1.54*	2.21*	1.51 (0.092)	0.47 (0.551)	1.37 (0.134)	0 (0.996)
sICAM-1 (ng/mL)[2]	**WAFAS-EX**	0.88***	0.87***	0.87***	0.99 (0.737)	0.98 (0.17)	0.98 (0.213)	1.13***	1.13***	1.13***
	WAFAS-2-CyEMA	0.89***	0.87***	0.89***	0.97 (0.322)	0.93*	0.96 (0.243)	1.09**	1.07*	1.08*
11-dehydro TXB2 (pg/mg creat)[2]	**WAFAS-EX**	0.92 (0.117)	0.77***	0.71***	0.99 (0.898)	0.99 (0.852)	0.97 (0.638)	1.08 (0.209)	1.29***	1.37***
	WAFAS-2-CyEMA	0.95 (0.41)	0.78***	0.68***	1.14 (0.112)	1.01 (0.861)	0.92 (0.345)	1.2*	1.3***	1.35**
8-epi PGF 2a (pg/mg creat)[2]	**WAFAS-EX**	0.79***	0.76***	0.75***	0.95 (0.122)	0.95 (0.201)	0.94 (0.176)	1.19***	1.26***	1.25***
	WAFAS-2-CyEMA	0.78***	0.76***	0.76***	0.89*	0.84***	0.84**	1.14*	1.11*	1.11 (0.101)
COHb (%)[2]	**WAFAS-EX**	0.27***	0.24***	0.19***	0.62***	0.65***	0.66***	2.35***	2.69***	3.42***
	WAFAS-2-CyEMA	0.28***	0.24***	0.18***	0.39***	0.34***	0.3***	1.37**	1.43*	1.64***
Total NNAL (pg/mg creat)[2]	**WAFAS-EX**	0.03***	0.02***	0.02***	0.52***	0.53***	0.5***	16.48***	21.94***	20.54***
	WAFAS-2-CyEMA	0.03***	0.02***	0.03***	0.18***	0.14***	0.11***	5.63***	5.63***	4.09***

Note: The table contains effect sizes for all contrasts at all timepoints. If the parameter is analyzed in its original scale (indicated by the superscript [1]), the effect size for the contrast x vs. y is the difference of LS-means x – y. If the parameter is analyzed on the log-scale (indicated by the superscript [2]), the effect size for the contrast x vs. y is the ratio x over y (obtained by exponentiating the difference of LS-means x - y obtained on the log-scale).

Legend: *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$. p-values ≥ 0.05 are provided in parentheses.

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1.1.3.2.3. Exposure to HPHCs and Product Use

In absence of biochemical (2-CyEMA) verification WAFAS-EX-ATT analysis (Figure 16): Exposure was reduced in both predominant *IQOS* and SA groups relative to the cigarette one throughout the study, except for nicotine, as expected (assessed by NEQ levels). However, the magnitude of exposure was lower for *IQOS* versus SA. As highlighted before, these lower reductions are likely due to the allowed cigarette use (up to 30% of the total product consumption).

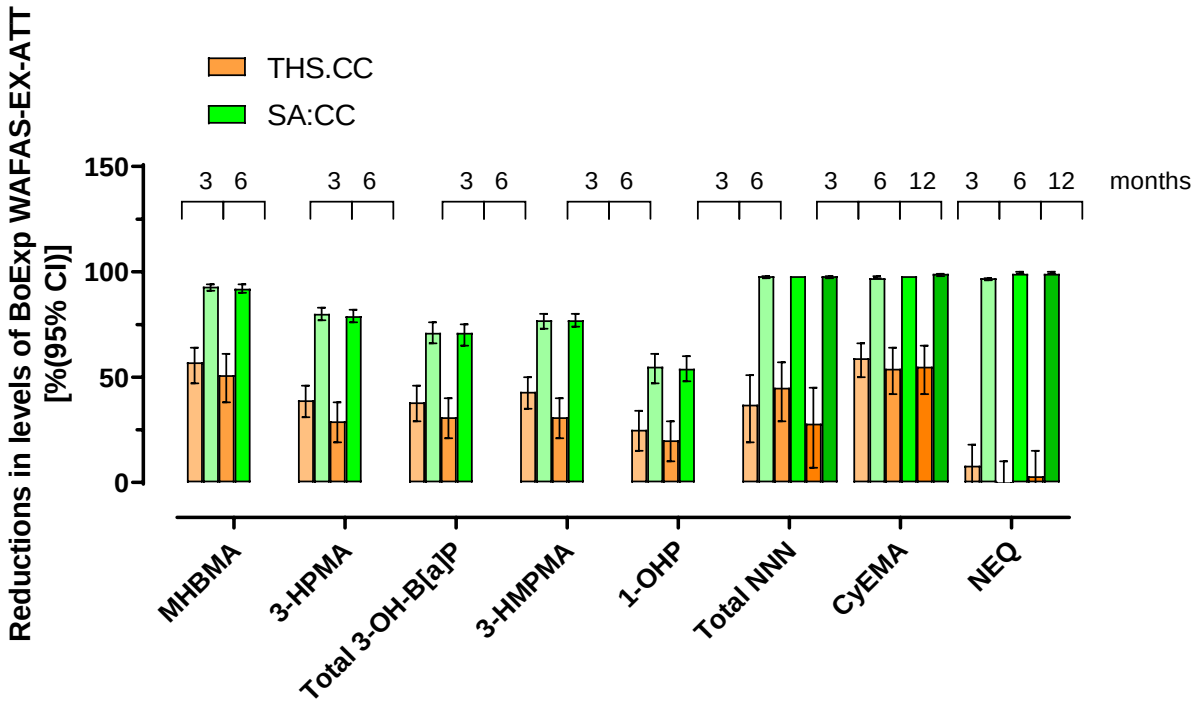

Figure 16 Reductions of Exposure to HPHCs Between *IQOS*-Use vs Cigarette-Use, and Smoking Abstinence vs Cigarette-Use at Months 3, 6 and 12 (WAFAS-EX-ATT Analysis Set)

Note: p-values are not represented on the graph, as they were all <0.001, when compared to levels of Cigarette use (the only exceptions being for the comparison between *IQOS* and CC for Total NNN at month 12 where the p-value was <0.05 and for NEQ at 3, 6 and 12 month where the p values were >0.05).

With biochemical (2-CyEMA) verification WAFAS-EX-2-CyEMA-ATT analysis (Figure 17): When excluding subjects who smoked more than 4 cigarettes/day in predominant *IQOS* users (2-CyEMA > 47 ng/mg creatinine), the magnitude of exposure reduction reached, upon *IQOS* user that of the SA group, thereby confirming the dose response to cigarette smoking. No major difference in NEQ levels were observed between *IQOS* and cigarette users, as expected, even though there were some levels of reductions in the THS users.

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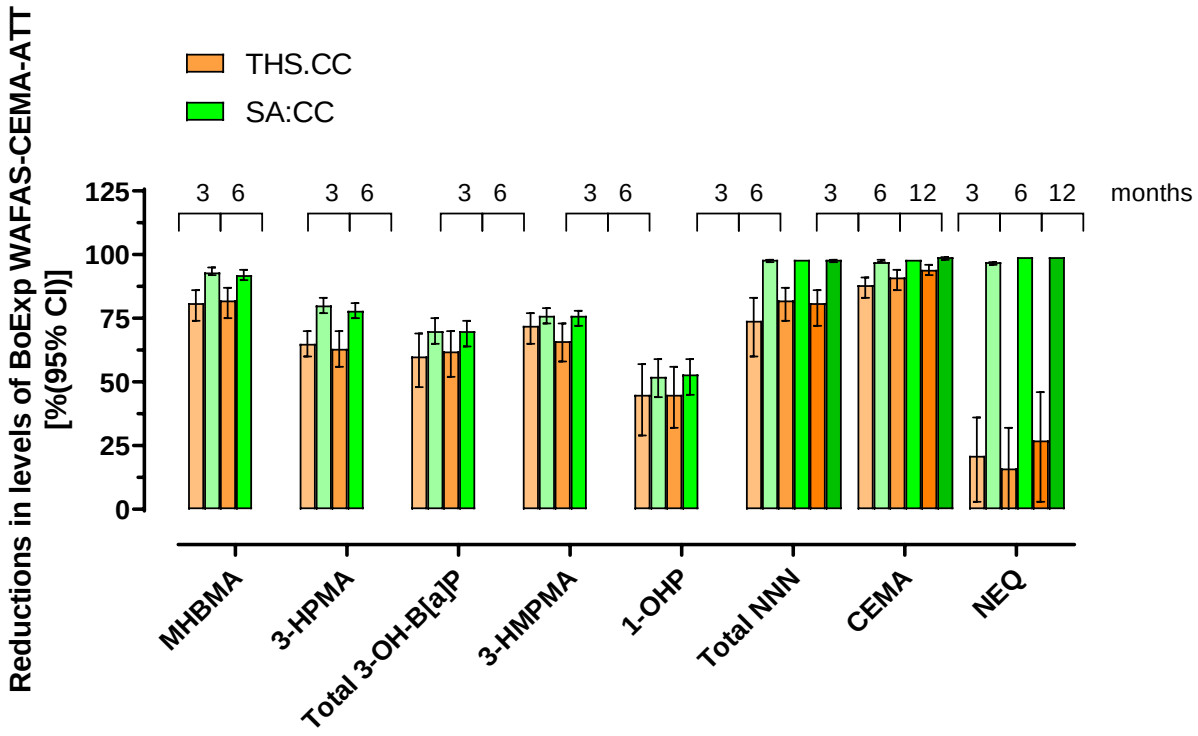

Figure 17 Exposure Reductions Between *IQOS*-Use vs Cigarette-Use, and Smoking Abstinence vs Cigarette-Use at Months 3, 6 and 12 in Biochemically Verified Groups (WAFAS-2-CyEMA-ATT Analysis Set)

Note: p-values are not represented on the graph, as they were all <0.001, when compared to levels of cigarette (CC) group, except for NEQ in the THS group at 3, 6 and 12 months (at 3 and 12 months p* <0.05-0.01 and 6 months p>0.05).

When comparing the magnitude of exposure reduction over one year to former PMP's studies of 3 months intervention with *IQOS*, namely the "reduced exposure studies" mentioned in section 6-1-health-risk-investigations paragraph 4.1, they were comparable, as summarized below (Table 8).

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Table 8 Magnitude of Exposure Reduction in Former PMP' Reduced Exposure Studies Compared to the Exposure Response (and Extension) Study (WAFAS-2-CyEMA-ATT)

BoExp	ERS (WAFAS-2-CyEMA-ATT set) (ranges of reductions in %)	REX studies[3] (ranges of reductions in %)
MHBMA	81-82%	77-92%
3-HPMA	63-65%	47-58%
3-OH-B[a]P	60-62%	70-73%.
3-HMPMA	66-72%	57-77%,
1-OHP	45%	52-61%
NNN	74-82%	60-80%
CyEMA	88-94%	79-87%

Over 12 months, product use, as self-reported, did not change between the two analyses sets, as shown in Figure 18 except for a slightly higher daily consumption of *IQOS* Heatsticks in the *IQOS* users verified biochemically with 2-CyEMA.

[3] Section 6-1-health-risk-investigations Table 1

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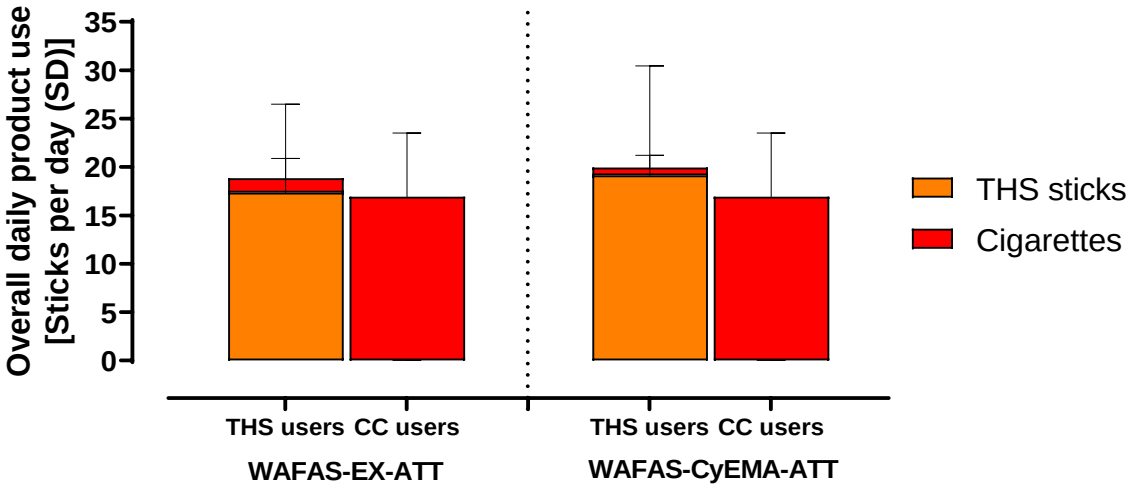

Figure 18 Average Daily Products Used Over 12 Months in the Two Main Analysis sets (WAFAS-EX-ATT and WAFAS-2-CyEMA-ATT)

Product consumption data indicates that the reduction of exposure observed in the WAFAS-2-CyEMA-ATT analysis was not influenced by the number *IQOS* Heatsticks used daily, but rather by the concomitant use of cigarettes, which was likely under-reported in the *IQOS* user group.

1.1.3.2.4. Study Conclusions

After pooling and weighing of from the ZRHR-ERS-09-US, ZRHR-ERS-09-EXT-US, and SA-SCR-01 studies, significant differences in BoExp and BoPH upon smoking cessation relative to continued smoking.

For each analyzed endpoint, subjects from the SA group showed significant statistical differences versus the CC group at month 12, and the magnitude of the differences was not notably different between the two main analysis strategies (i.e., WAFAS-EX and WAFAS-2-CyEMA). These results are coherent with the fact that no subjects was excluded from the analysis set with biochemical verification (none of the subjects were identified to smoke >4 cigarettes/day). as these studies were conducted in healthy smokers. Changes within “normal ranges” in healthy smokers are interpreted as favorable effects, although, as expected, not clinically relevant.

Considering that smoking cessation decreases disease risk, the favorable effect observed of SA on BoExp and BoPH (changes in trajectory (increase or reduction in levels) and the magnitude of their changes as favorable effects), is used as a benchmark to evaluate reduced risk associated with *IQOS* use relative to cigarette.

Like the smoking cessation effect, predominant *IQOS* use followed similar changes in trajectory in all of the endpoints investigated but the magnitude of effect was generally lower than SA. In absence of exclusion of subjects who smoked >4 cigarettes/day, statistical differences were

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observed at 12 months for all BoExp measured with three out of the eight core set of BoPH (COHb, total NNAL that could be also considered as BoExp, and WBC); Importantly, with the exclusion of subjects who smoked >4 cigarettes/day, the magnitude of effect was notably more pronounced at 12 months. These findings verify our initial our initial hypothesis that the magnitude of the favorable effects on biomarkers is dose dependent to the daily cigarette consumption. In this analysis, statistical differences were found for all BoExp and with 5 out of the eight core set of BoPH (COHb, total NNAL, WBC, HDL-C, and 8-epi-PGF2α). FEV1%pred was not statistically different at 12 months for *IQOS* relative to cigarettes while it was at 6 months.

Taken together, these results underline the potential of *IQOS* for tobacco harm reduction. Additional studies are required to understand how this translates into disease risks and how strict adherence to *IQOS* use (without any use of CC) may impact the results.

1.1.4. *Cross-Study Analysis on Lung Function (P1-ERS-EXT-SCR-PH-RESP)*

1.1.4.1. P1-ERS-EXT-SCR-PH-RESP Design Summary

Like for the study described in the previous section (1.1.3), this integrated post-hoc analysis was developed to define the cross-study analysis of data pooled from the same three studies, i.e., ZRHR-ERS-09-US (NCT02396381) and its extension ZRHR-ERS-09-EXT-US (NCT02649556), and SA-SCR-01 (NCT02432729) with a particular focus on respiratory function (spirometry parameters).

Similarly to the P1-ERS-EXT-SCR-PH-SHP, the analysis used 2-CyEMA biochemical verification (section 1.1.3.1).

The methodology applied was identical to the P1-ERS-EXT-SCR-PH-SHP analysis, therefore, the summary provided in Table 6 applies here as well, except for the endpoints, which are listed below in Table 9 (for endpoints not expressed on a continuous scale, a generalized linear mixed model was used instead of a linear mixed model).

Table 9 Endpoints of the P1-ERS-EXT-SCR-PH-SHP Cross-Study Analysis

Study Title: A Cross-Study Analysis to Determine the Effects of Switching from Cigarette Smoking to THS 2.2 Use and Smoking Abstinence on Endpoints Associated with Respiratory Function
Main objective and endpoints: • **Spirometry:** Endpoints: o Lung function pre- and post-bronchodilator: ▪ Best FEV1, expressed in L* ▪ %pred FEV1*# ▪ FEV1/FVC, expressed as ratio and %pred*

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- bronchodilator reversibility in FEV1, expressed in % and mL*
- FEF 25-75%, expressed as L/s and %pred*
- Best FVC, expressed as L*
- %pred FVC*

o Lung volume pre-bronchodilator:

- FRC, expressed in L and %pred
- VC, expressed in L and %pred
- TLC, expressed in L and %pred
- IC, expressed in L and %pred
- RV, expressed in L and %pred

- **Cough questionnaire[#]:**
  Endpoints:
  - Regular Need to Cough (binary response)
  - Cough Impact Scale (visual analog scale (VAS) from 0 to 100)
  - Cough Intensity Scale (5-level Likert scale)
  - Cough Frequency Scale (5-level Likert scale)
  - Sputum Production (4-level Likert scale)

Secondary objectives and endpoints:

- To determine the effects after 3 and 6 months on endpoints associated with the lung function of switching from CC to THS 2.2 or becoming SA, compared to continuous smoking (switching to THS 2.2 was also compared against becoming SA).

Endpoints:
Same as for main objective (above)

* Lung function endpoints pre-bronchodilator indicated with an asterisk were not measured at month 3 during the ZRHR-ERS-09-EXT-US study. For these endpoints, the planned analyses were conducted similarly to the other endpoint without month 3.

[#] In the cough questionnaire, the VAS and 3 Likert questions were only asked to the subjects answering 'yes' to the regular need to cough question.

1.1.4.2. P1-ERS-EXT-SCR-PH-RESP Results Summary

1.1.4.2.1. Analysis Sets

The main analyses were the WAFAS-EX-ATT and the WAFAS-EX-2-CyEMA-ATT as for the P1-ERS-EXT-SCR-PH-SHP post-hoc analysis. The summary presented in section 1.1.3.2.1 therefore also applies here.

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1.1.4.2.2. Changes in Spirometry Endpoints over Time

In healthy smokers, FEV_1 changes over one year upon smoking cessation are reported to be clinically relevant yet and impact on other lung functions parameters not necessarily expected. The analysis presented hereby explored the effect of *IQOS* on other lung function parameters versus SA and continued smoking.

Results for best FEV_1, %pred FEV_1 and %pred FEF 25-75% along with statistically significant differences are presented in Figure 19 pre- and post-bronchodilator (BD).

With (WAFAS-2-CyEMA-ATT [figures B, D, F]) or without biochemical verification (WAFAS-EX-ATT [figures A, C, E]), favorable changes were observed both for SA and *IQOS* groups relative to cigarette group. As an example, at 12 months, the difference in the best FEV_1 value between *IQOS* and cigarette ranged from 10 to 60mL across both analyses while FEV1%pred ranged from 0.44 to 1.87% and FEF25-75%pred pre-bronchodilator ranged from 1.04 to 4.99%.

In the biochemically verified *IQOS* group, the magnitude of the differences was more pronounced, got closer to that of the SA group although slightly lower.

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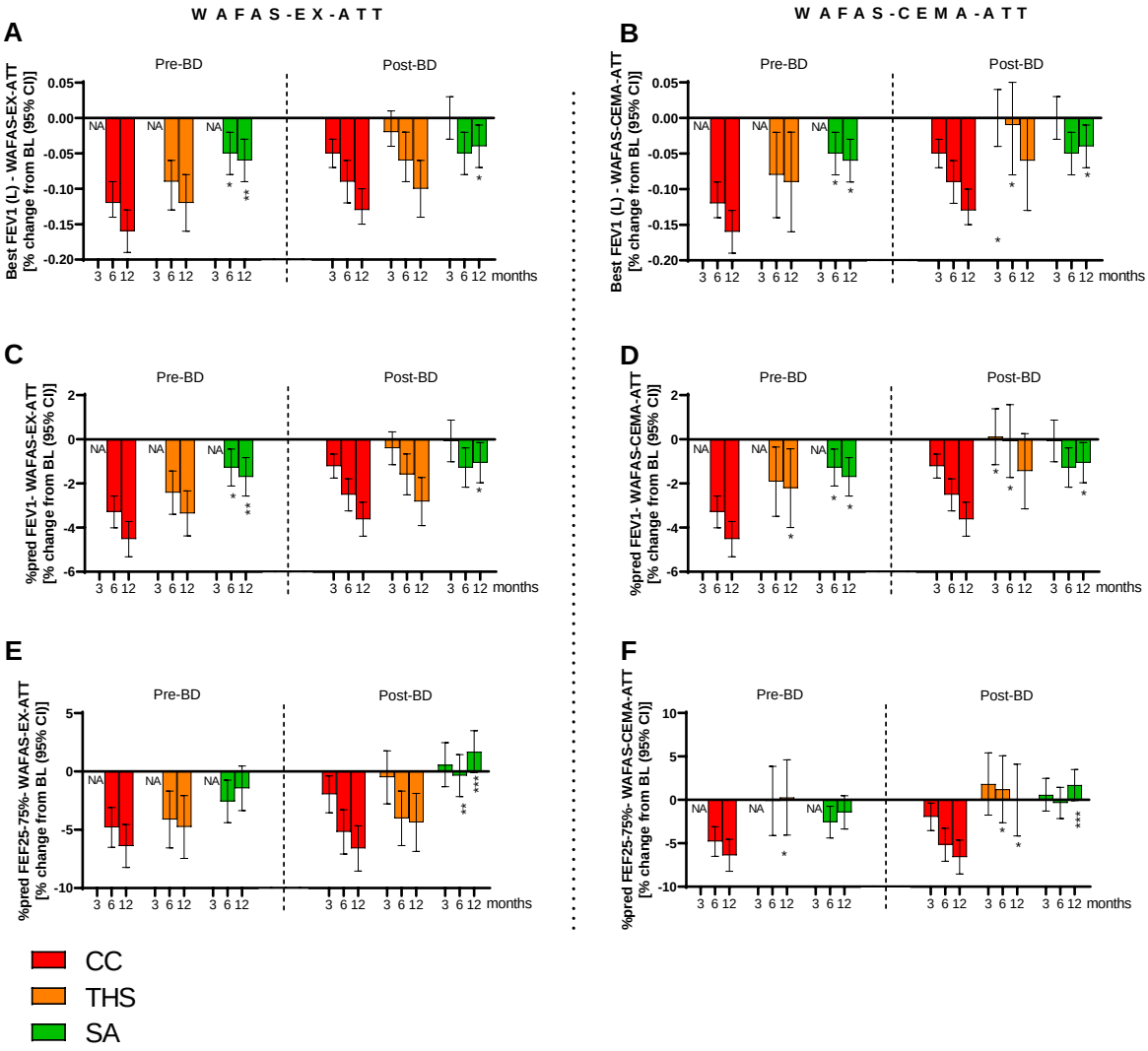

Figure 19 Change from Baseline for Best FEV1, %predFEV1 and %predFEF25%-75% in *IQOS*, SA and CC groups (WAFAS-EX-ATT and WAFAS-2-CyEMA-ATT analysis sets)

Legend: *: p<0.05; **: p<0.01; ***: p<0.001 (compared to CC).

1.1.4.2.3. Cough Questionnaire

With or without biochemical verification: Figure 21 (exclusion of smokers >4 cigarettes/day) (WAFAS-2-CyEMA)-ATT and Figure 20 (WAFAS-EX-ATT analysis set) respectively**:** *IQOS* and SA groups had lower probability (odds ratios) of regular need to cough than CC group at 12 months. *IQOS* users had slightly higher odds ratio than the SA, at all-time points.

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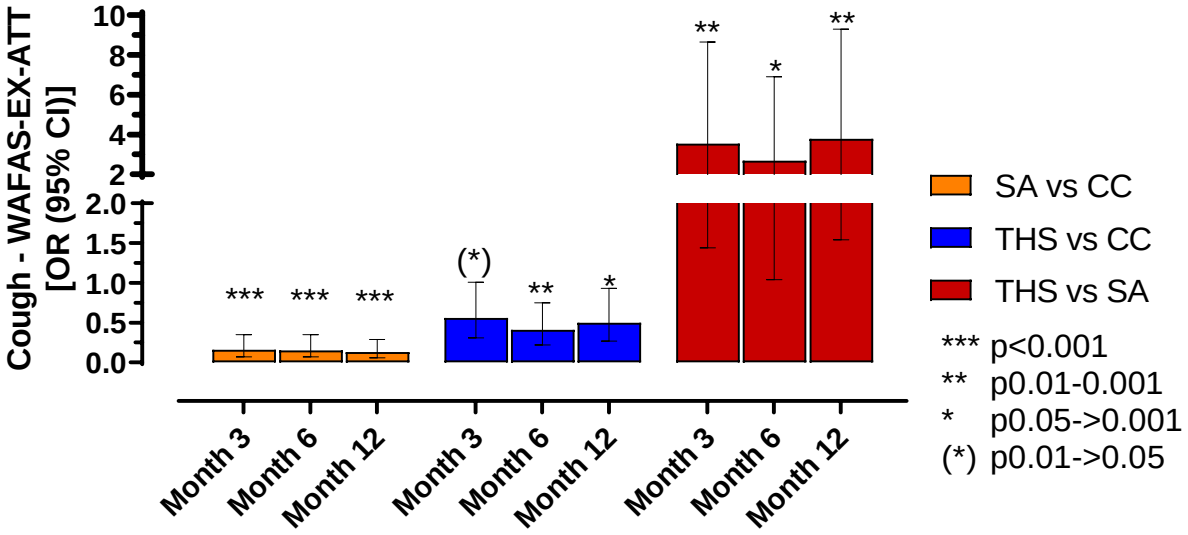

Figure 20 Adjusted Odds Ratios of the Presence of Regular Need to Cough based on ATT Weighting – WAFAS-EX

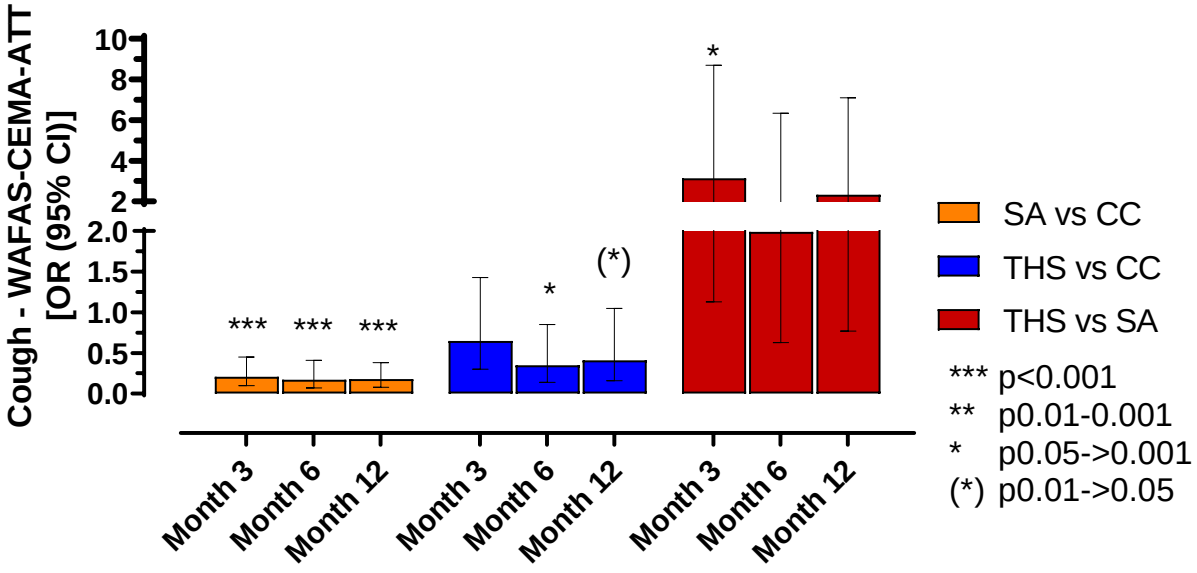

Figure 21 Adjusted Odds Ratios of the Presence of Regular Need to Cough based on ATT Weighting – WAFAS-2-CyEMA

1.1.4.2.4. Study Conclusions

This post pooled analysis coming from the ZRHR-ERS-09-US, ZRHR-ERS-09-EXT-US, and SA-SCR-01 studies generally indicate that *IQOS* use has beneficial impact on the main lung function

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parameters (e.g., FEV_1, FEV1/FVC post-bronchodilator and FEF 25-75% pre-bronchodilator) relative to continued smoking cigarettes at 12 months. This was associated with a reduction in the reporting of the need to cough. These effects were close to the effect of smoking cessation although slightly lower. In predominant *IQOS* users, the favorable effect was higher in magnitude when excluding subjects who smoked >4 cigarettes/day.

Additional studies are needed to understand how these favorable effects translate into disease risks.

1.1.5. *P1-OHS-01 Study*

The purpose of this study, conducted in Japan, was to demonstrate in subjects with generalized chronic periodontitis that switching from smoking cigarette to using *IQOS* improves the response to periodontal therapy (i.e., scaling and root planning, SRP) and the overall oral health status compared to continuing cigarette smoking. The study design was based on studies showing that smoking is a significant risk factor for periodontal disease [9-12] and on studies showing that the negative impact of tobacco use on periodontal disease is reversible, within a time frame of a few weeks to a few years, depending on the clinical endpoint assessed [13-18]. The healing of periodontal disease, as measured by the amelioration of different periodontal assessments such as reduction in periodontal pocket depth (PD), after a standard of care treatment, had been shown to be influenced by smoking (reviewed in [19]). If clinical attachment level (CAL) is the most clinically relevant endpoint, change in smokers vs non-smokers or quitters are sparser than data on PD. Therefore, PD was chosen as the primary endpoint. Even though the main primary endpoint was not met, the study is presented here to provide the exposure data on four selected HPHCs.

1.1.5.1. P1-OHS-01-JP Design Summary

A brief description of the study design is provided in Figure 22.

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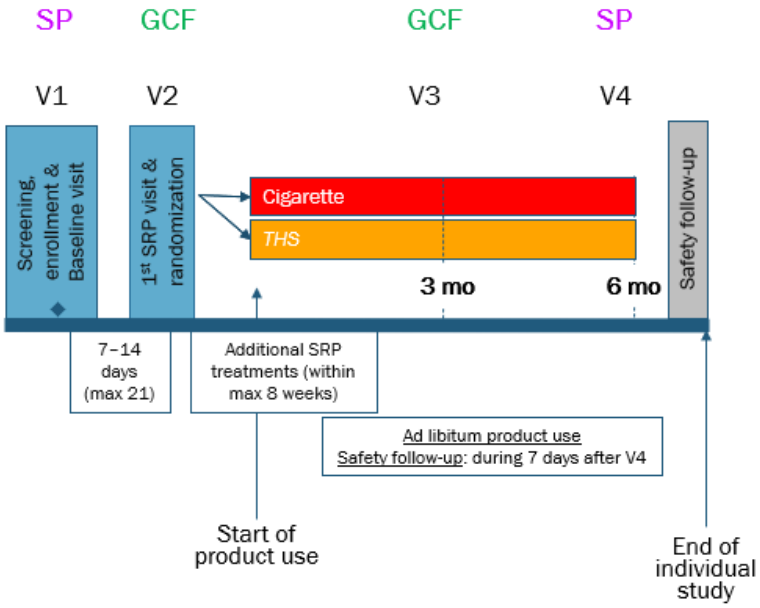

Abbreviations: SRP = Scaling and root planning, SP = subgingival plaque; GCF = gingival crevicular fluid, V = visit

Figure 22 Scheme of the P1-OHS-01-JP Study

The primary objective of the study was to demonstrate the effect of switching to IQOS use compared to continued cigarette smoking on the response of PD to mechanical periodontal therapy (SRP), with the endpoint being the mean PD reduction in all sites with initial PD ≥ 4 mm after mechanical periodontal therapy at 6 months. A series of other periodontal parameters, such as, for example, changes in CAL, bleeding on probing, and gingival inflammation were also assessed.

1.1.5.2. Study Conclusions

Reductions from baseline in PD and CAL were observed following the SRP treatments at 3 and 6 months in Japanese subjects with generalized chronic periodontitis who had smoked for at least 5 years prior to the screening. However, no statistically significant differences in reduction from baseline were found at any timepoints up to 6 months between subjects switching to the *IQOS* or dual use relative to continued cigarette smoking.

Most of the periodontal parameters improved following the SRP treatments, but no differences on the response after the SRP treatments were noted in the subjects who had switched to *IQOS* use or dual use, compared to the subjects had continued cigarette smoking. A trend for higher change in PD at dental sites with a baseline PD ≥ 7 mm was nevertheless observed in favor of *IQOS* relative to cigarettes.

As shown in previous PMP's studies [20-22], switching from cigarettes to *IQOS* results in comparable daily self-reported tobacco consumption (cigarettes and HeatSticks) to baseline (cigarettes only) and comparable nicotine exposure. Similar findings were observed throughout

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study, irrespective of the group. When switching to new product, *IQOS* users got satisfactory product experience to replace their cigarettes. For dual users, as nicotine exposure and daily tobacco consumption was comparable, they were likely not entirely satisfied by *IQOS* or needed more time to completely switch to *IQOS*. However, dual users were still significantly less exposed to HPHCs compared to cigarette smokers, even in an uncontrolled (ambulatory) and relatively long-term setting (6 months).

Taken together, the results of this study suggest that the SRP treatment by itself was at the origin of most of the favorable changes, and this could have masked a potential beneficial effect of switching to *IQOS* in these conditions. Even though a benefit of smoking cessation on SRP treatment effect has been reported in several publications, the data were not all consistent, and the differences were very small and time dependent. A number of publications on the effects of SRP in smokers vs non-smokers may have been biased by the absence of adjustment to appropriate covariates that were not necessary accounted for to be able to draw valid conclusions regarding the 'causal' effect of smoking, as highlighted in a study by Preus et al. [23]. Thus, our results appear to be in line with data from literature. The study design and the results were published [23].

In terms of exposure to HPHCs, as anticipated, no significant differences were found in NEQ levels from baseline among cigarette users, dual users and IQOS users at Month 6, which is in line with the overall self-reported consumption of tobacco products that did not increase throughout the study, in either of those product use categories.

On the other hand, compared to cigarette smokers, the reductions in the levels of urinary total NNAL and 2-CyEMA adjusted to creatinine in IQOS users were observed at 6 months, with reduction rates of 68.5% and 87.0%, respectively. Similar reductions were already observed at 3 months. No significant reduction was, however, observed in the dual users.

Results of the study have been released on ClinicalTrials.gov [24] and published in a scientific journal [25].

1.1.6. *P1-EXC-01-EU Study*

It is well established that smokers who engage in physical activity do not perform as well as non-smokers [26]. The purpose of the P1-EXC-01-EU study was therefore to explore whether switching from cigarette smoking to using *IQOS* for 12-weeks improved exercise tolerance compared to continued smoking. Because maximum oxygen consumption (VO_{2max}) during exercise testing is commonly used as an indicator of exercise tolerance, we designed this 12-week exploratory study using VO_{2max} as the main endpoint in subjects who underwent an intense training program while switching to *IQOS* or abstaining from smoking. Additional supportive physiological parameters and BoPH were assessed.

1.1.6.1. P1-EXC-01-EU Design Summary

A brief description of the study design is provided in Figure 23.

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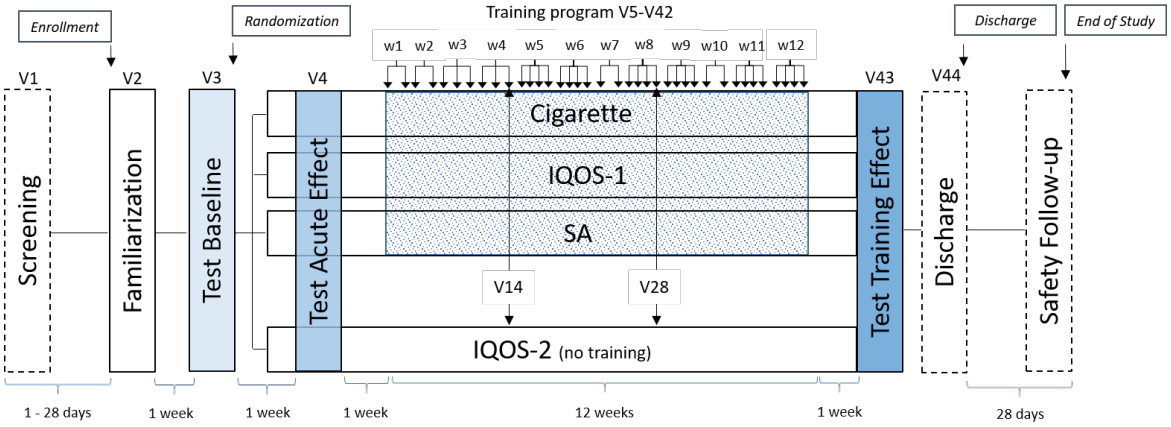

Abbreviations: V = visit; w = week; SA = smoking abstinence

Figure 23 Scheme of the P1-EXC-01-EU Study

The objectives of this study were all related to the exercise capacity of the subjects, as measured, for example, with the change in VO_{2max} after having switched to *IQOS*, with or without training sessions or with the amount of work produced during a training session. Levels of BoExp to nitrosamines and acrylonitrile were measured in spot urine, in order to assess the reduction of exposure to HPHCs in subjects switching to *IQOS* (with and without training), while nicotine equivalents (NEQ) were measured to assess whether switchers were absorbing nicotine to the same levels than at baseline.

1.1.6.2. Study Conclusions

Compared to continued smoking, observed improvements in exercise capacity were more apparent with SA than switching to *IQOS*. High variability was observed in the results across parameters assessed to evaluate the ability of subjects to exercise under different product use patterns. Most of the parameters were to be assessed during subject's maximal effort on the bike which were which were purely dependent on the willingness of subjects. It is likely that the maximal effort was not necessary reached for some subjects at all timepoints. Additional studies are necessary to explore further the effect of switching to *IQOS* on the ability to exercise.

In terms of exposure to HPHCs, changes from baseline in exposure to nitrosamines (creatinine-adjusted total NNAL) and acrylonitrile (creatinine-adjusted 2-CyEMA) in the *IQOS* product use groups were only slightly lower as those observed in the SA product use group, with changes ranging from -54.5% to -74.1% for total NNAL and from -76.8% to -93.2% for 2-CyEMA in the *IQOS* groups, while decreases in the SA product use group ranged from -72.5% to -89.5% (total NNAL) and from -80.3% to -91.4% (2-CyEMA). At V43, exposure to nicotine (NEQ) was slightly decreased from baseline in the Cigarette and *IQOS* groups while they were substantially decreased in the SA product use group (-90.5%). In the cigarette product use group, the BoExp NEQ, total NNAL and CEMA were similar to baseline.

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1.1.7. *Overall Conclusions of the New Studies*

As shown across all studies in a controlled or an ambulatory setting, switching from cigarette to *IQOS* resulted in a significant reduction of exposure to HPHCs with nicotine exposure and overall daily tobacco consumption remaining comparable to baseline.

All *IQOS* devices used in the submitted MRTP are built based on the same conceptual technology that prevents combustion of the tobacco. Scientific studies showed that the two authorized devices have:

These findings together with the well-established linear dose relationship between the magnitude of exposure of the human body to toxicants (as measured by biomarkers of exposure) and the level of toxicants found in smoke/aerosol under exclusive switching, make it is reasonable to assume that the reduced exposure demonstrated when switching to *IQOS* in human studies, is applicable to all *IQOS* devices with the blade heating system.

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