PMI RESEARCH & DEVELOPMENT

Clinical Study Protocol

Study title:	A randomized, controlled, open-label, 4-arm parallel group study to evaluate the effect of switching from cigarette smoking to the use of *IQOS* in healthy adult current smokers on exercise capacity and trainability
Study number	P1-EXC-01-EU
Short title	Effect of switching from cigarette smoking to *IQOS* on exercise capacity
Registration number:	NCT03887117
Product name:	*IQOS*
Sponsor:	Philip Morris Products SA Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version number:	3.0
Date:	2 May 2019
Authors:	[redacted], Clinical Scientist [redacted], Biostatistician [redacted], Medical Safety Officer

SUMMARY OF CHANGES

Clinical Study Protocol

P1-EXC-01-EU

	Version	Date	Amendment
Second updated protocol	3.0	2 May 2019	Substantial changes. The cut-off for the exhaled CO level applied to confirm cigarette smoking status at V1 and V2, in addition to self-report and urine cotinine measurement, was lowered from >10ppm to >6ppm as supported by literature. Due to the 2-8 hours half-life of CO, confirmed smokers may have levels below >10 ppm especially in the morning after overnight abstinence (56,57).
First updated protocol	2.0	22 November 2018	Substantial changes. The mHealth device included in the first version of the protocol (Everion, Biovotion) has been replaced with another device (Vivofit 3, Garmin). Endpoints and protocol sections concerned have been updated.
Original protocol	1.0	14 September 2018	

The main purpose of the table above is to summarize the major update(s) between original clinical study protocol P1-EXC-01-EU (Final Version 1.0) dated 14 September 2018 , signed 18 September and its first updated version (Final Version 2.0) dated and signed 22 November 2018, and the changes between the first updated version dated and signed 22 November 2018 and its second updated version dated 2 May 2019

More precise details on the protocol sections changed are provided in the Appendix 5, with the list of changes, including the previous and the amended texts, as well as the reasons to change.

The new text has been highlighted in bold (e.g. **new text**) and deleted text has been crossed out (e.g. ~~deleted text~~).

SYNOPSIS

Sponsor:

Philip Morris Products SA
Quai Jeanrenaud 5
2000 Neuchâtel
Switzerland

Name of Product:

IQOS

Study Title:

A randomized, controlled, open-label, 4-arm parallel group study to evaluate the effect of switching from cigarette smoking to the use of *IQOS* in healthy adult current smokers on exercise capacity and trainability

Study Number:

P1-EXC-01-EU

Short Title:

Effect of switching from cigarette smoking to *IQOS* on exercise capacity

Registration number:

Not assigned

Study Location:

Germany

Objectives and Endpoints:

Objective

1. To evaluate changes in VO_2max in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoint (V3, V4 and V43)

- VO_2max as determined during maximal cycle ergometer exercise (expressed in absolute [$mL*min^{-1}$], weight-adjusted [$mL*kg^{-1}*min^{-1}$] and fat-free weight adjusted values [$mL*kg^{-1}*min^{-1}$])

2. To evaluate changes in exercise capacity in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints (V3, V4 and V43)

- Exercise capacity: time to complete a pre-defined work on a cycle ergometer (min:sec).

3. To assess the intensity of the exercise training in subjects participating in a training program switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent

Endpoints (V5-V42)

- Cumulative work produced during each training session (calories and calories/kg body weight)
- Average work rate during each training session (watt and watt/kg body weight)
- Average work rate during each interval during each training session (watt and watt/kg body weight)
- Time spent at 0-50%, 50-65%, 65-75%, 75-90%, >90% of maximal work rate during each training session (min:sec)
- Average heart rate (HR) during each training session (bpm)
- Time spent at 0-50%, 50-60%, 60-70% , 70-80 % and >80% of maximal HR during each training session (min:sec)

4. To evaluate changes in physiological parameters and perception of exertion and capacity in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints (V3, V43)

- Blood composition: Hemoglobin mass (g), red blood cell volume (mL), plasma volume (mL) and total blood volume (mL) as determined by CO re-breathing method
- Capillary blood lactate levels during VO_2max test (mmol/L)
- Perceived rate of exertion during VO_2max test (Borg Rating of Perceived Exertion (RPE) scale)

Endpoints (V3, V4 and V43)

- Respiratory parameters at VO_2max: Ventilation (L/min), respiratory rate, VCO_2 (L/min), Respiratory exchange ratio (RER) (VCO_2 / VO_2)
- Rating of Perceived Capacity (RPC) scale
- Heart rate (bpm) and oxygen uptake (mL/min) during VO_2max test

5. To monitor trends of daily physical activity levels during the study in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints (from V2 until V43)

- Aggregated data derived from the mobile health (mHealth) wearable for:
  - Cumulative number of steps per day
  - Sedentary minutes per day and % of time sedentary
  - Active minutes per day and % of time active
  - Very active minutes per day and % of time very active

6. To explore trends and changes in activity and sleep parameters through continuous measurements during the study*

Endpoints (from V2 until V43)

mHealth wearable measurements of steps, activity, distance, energy expenditure, sleep* Reporting of data for this objective will be subject to a separate report(s) (not part of the Clinical Study Report [CSR]).

7. To describe changes in biological health markers in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints (V3, V14, V28 and V43)

- High density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) (mg/dL)
- High sensitivity C-reactive protein (hs-CRP) (mg/L)
- Growth hormone (GH) (ng/mL)
- Hemoglobin A1C (HbA1c) (%)
- Resting blood pressure (mmHg)

- Resting HR (bpm)

8. To describe changes in weight, body fat and waist circumference in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints (V3, V4 and V43)

- Body fat percentage (%)
- Waist circumference (cm)

Endpoints V3-V43

- Body weight (kg)

9. To monitor levels of exposure to CO, nicotine, nitrosamines and acrylonitrile in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints

At all visits:

- Exhaled carbon monoxide (CO) (ppm)

At V3, V4, V14, V28 and V43

- Carboxyhemoglobin (COHb%) in blood (%)
- Nicotine equivalents (NEQ) in urine (adjusted for creatinine)
- Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in urine (adjusted for creatinine)
- 2-cyanoethylmercapturic acid (CEMA) in urine (adjusted for creatinine)

10. To describe the self-reported nicotine and tobacco containing product use over the duration of the study

Endpoints (measured daily from V2 to V43)

- Self-reported number of any nicotine/tobacco product used on a daily basis as reported in the product use diary
- Product use exposure

11. To monitor safety during the study

Endpoints

- Incidence of adverse events (AEs), serious adverse events (SAEs)
- Frequency of AEs, SAEs
- Incidence of *IQOS* device events including malfunction/misuse
- Frequency of *IQOS* device events including malfunction/misuse
- Vital signs changes from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
- Physical examination changes from baseline
- Electrocardiogram (ECG) changes from baseline (heart rate, PR, QRS, QT, QTcB, QTcF intervals)
- Spirometry changes from screening visit (V1) used as baseline (FEV1, FEV1 % predicted, FVC, FVC % predicted, and FEV1/FVC)
- Cough assessment changes from baseline (VAS and three Likert scales)
- Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel
- Concomitant medications

12. To assess perception of health and functioning in subjects switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent **

Endpoints (first interview between V2 and V3, second interview between V42 and V43)

- Changes in subjects' perception of health and functioning as determined by qualitative interviews based on the World Health Organization's International Classification of Functioning, Disability, and Health

** This objective will be assessed as a sub-study with a separate section of the Informed Consent Form (ICF), and the reporting will be subject of an appendix to the main CSR.

Study Hypothesis:

The study is descriptive; no statistical hypothesis will be tested.

Study Design:

This is a randomized, controlled, open-label, 4-arm parallel group study with stratification by daily cigarette consumption over the past 12 months prior to V1 as reported during V1 (i.e. 10 to 19 cigarettes or >19 cigarettes per day) and sex (Figure 1).

A sufficient number of healthy adult smokers will be screened and enrolled after checking that all eligibility criteria have been met, in order to reach 90 randomized subjects.

Smokers will be randomized as follows with a 5:5:5:3 ratio according to strata:

1. switch to *IQOS* use + participation in training program: ***IQOS*-1 arm**, 25 subjects
2. continue cigarette smoking + participation in training program: **Cigarette arm**, 25 subjects
3. smoking abstinence + participation in training program: **SA arm**, 25 subjects
4. switch to *IQOS* use only: ***IQOS*-2 arm**, 15 subjects

When 90 randomized subjects are reached, further enrollment will be stopped. Subjects already enrolled in the study will still be eligible for randomization. From randomization, subjects will be instructed to use their allocated product or stay smoking abstinent until the end of the study. Drop-outs will not be replaced.

Acute effect on VO_2max and exercise capacity of switching to *IQOS* will be assessed one week after randomization before initiating the training program, and the combined effect of switching and exercise training will be assessed one week after completion of the 12-week training program.

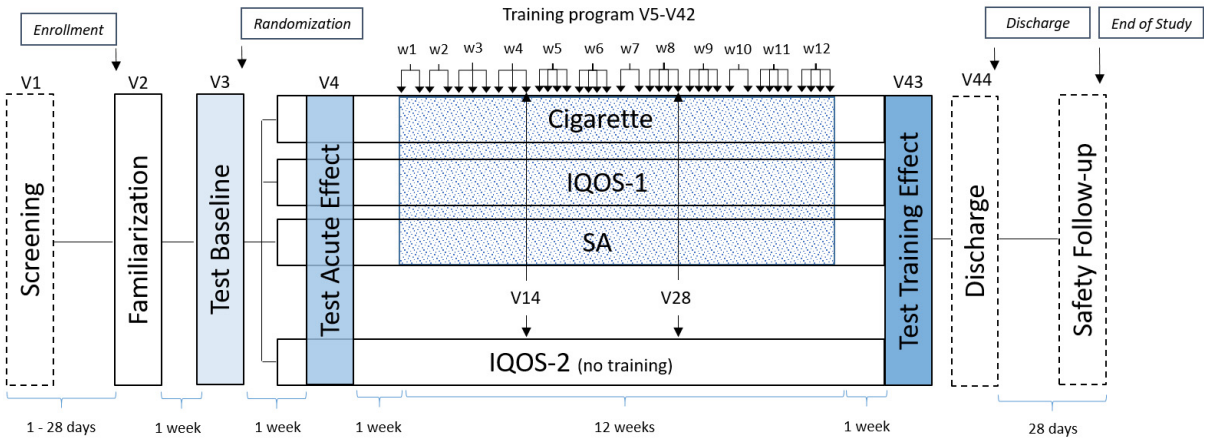

Figure 1 Study Design

Subjects will have serial visits at the investigational site as follows:

Screening, V1 (within 28 days prior to V2): No study-specific procedures will be performed before the Informed Consent Form (ICF) has been signed. The subject will also be invited to participate in a sub-study on perception of health and functioning and will sign a separate optional section of the ICF for this part of the study. Subjects will be invited to sign a separate optional consent form for collection of samples for biobanking.
A demonstration of *IQOS* and the mHealth wearable will be done by the site staff during the screening visit. All inclusion and exclusion criteria will be assessed. A VO_2max test will be performed as part of eligibility assessments. All eligible subjects will be invited to come to V2.
Enrollment and Familiarization, V2 (7±1 days prior to V3): Enrollment will take place after confirmation of smoking status (urine cotinine and exhaled CO) and negative urine pregnancy test, alcohol breath test and urine drug screen. After enrollment, vital signs will be assessed and subjects will perform an exercise capacity test for the purpose of familiarization. The exercise test consists of completing a pre-defined work (calories) on a bike ergometer (1). Before leaving the investigational site the subject will receive an mHealth wearable kit and will be trained on how to handle the device. Subjects will be instructed to wear the device all the time. Subjects will also receive a diary to record the daily use of tobacco and nicotine containing products.

Between V2 and V3, subjects having signed the optional section of the ICF will have an interview (by phone or computer) on the topic of health and functioning lasting around 60 minutes.

Baseline and Randomization, V3: Baseline assessments will be performed as listed in Appendix 1. Then, 30-60 min before start of the VO_2max test all subjects will smoke a cigarette (only if they are willing to). During the VO_2max test at rest and at each 25 W increase, the subject's lactate levels will be determined by capillary blood sampling and the rate of perceived exertion (RPE) will be assessed using the Borg RPE scale. After completing the VO_2max test, the subject will rest for 60±5min, after which the exercise capacity test will be performed. After completing exercise tests, total blood volume will be determined.
Subjects will thereafter be randomized into one of the 4 arms. Subjects randomized into *IQOS* arms will receive their *IQOS* starter kit and be trained on how to use the device. Subjects randomized into the SA arm will receive smoking abstinence support and will be allowed to use NRT upon request.
Acute effect, V4 (7±2 days after V3): Before the VO_2 max test, vital signs, exhaled CO, weight, body-fat and waist circumference measurements will be performed. 30-60 min before start of the VO_2max test subjects in cigarette and *IQOS* arms will smoke a cigarette or use a HeatStick, respectively (only if they are willing to). Subjects' VO_2max, maximal

heart rate and maximal work rate will be determined. After completing the VO_2max test, subjects will rest for 60±5min after which the exercise capacity test will be performed.
Training program, from V5 (15±2 days after V3) until V42 (99±2 days after V3): Subjects randomized into *IQOS*-1, cigarette and SA arms will participate in 38 supervised training sessions during a 12-week period using three different training protocols (Appendix 2).

Subjects randomized to the *IQOS*-2 arm will come for visits once a week for all assessments except the training. Subjects in the *IQOS*-2 arm will consequently only attend the following visits: V5, V7, V9, V14, V16, V19, V23, V28, V30, V33, V35 and V39.

At V14 and V28 (medical visits), safety, biological health marker and exposure marker assessments will be performed for all subjects.

Before each training, the following assessments will be conducted;

- Weight
- Exhaled CO
- 30-60 min before start of the training subjects in cigarette and *IQOS* arms will smoke a cigarette or use a HeatStick, respectively (only if they are willing to).

All trainings will be performed on a bike ergometer. The training intensity will be adjusted according to the subject's resting heart rate as determined by ECG at V3, and maximal heart rate as determined at the VO_2max test at V4 (acute test) . The work produced, the work rate and heart rate will be recorded for each training (as described in Objective 3).

Between V42 and V43, subjects having signed the optional section of the ICF will have an interview (by phone or computer) on the topic of health and functioning lasting around 60 minutes.

Training effect, V43 (106±2 days after V3):
Before the VO_2max test, biological health markers, exposure markers, vital signs, exhaled CO, weight, body-fat percentage and waist circumference measurements will be performed. Then, 30-60 min before start of the VO_2max test subjects in cigarette and *IQOS* arms will smoke a cigarette or use a HeatStick, respectively (only if they are willing to). Subjects' VO_2max will be determined as described for V3, including determination of lactate levels and perceived exertion rate. After completing the VO_2max test, the subject will rest for 60±5min, after which the exercise capacity test will be performed.
After completing exercise tests, total blood volume will be determined. Subjects will return the mHealth wearable, the product use diary and the *IQOS* device (if applicable).
Discharge, V44 (107±2 days after V3): Safety assessments will be conducted as listed in Appendix 1.

Safety follow-up period (from discharge at V44 or early termination plus 28 days):

After discharge on V44 or after early termination, subjects will enter a 28-day safety follow-up period during which AE/SAEs spontaneously reported by the subjects will be collected. Any non-serious AE that is ongoing at the time of discharge or early discontinuation will be followed-up by the Investigator or designee during the safety follow-up period until it has been resolved, stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition) or lost to follow up. The follow-up of the ongoing non-serious AEs will be done via a phone call performed until the end of the Safety Follow-Up Period. At the end of the safety follow-up period, all ongoing non-serious AEs will be documented as "ongoing" and no further follow-up information will be sought for them by the Investigator or designee. At that point, the Investigator will assess whether the subject should be referred to his/her General Practitioner to have their ongoing AEs addressed accordingly. SAEs will be followed up by the Investigator until resolution, stabilization or the determination of a plausible explanation for them was found, regardless of the end of the safety follow-up period. All subjects discontinued from the study at any time after enrollment, will enter the 28-day safety follow-up period.

Study population and Main Inclusion Criteria:

Inclusion criteria

1. Subject has signed the ICF.
2. Smoking, healthy subject based on safety laboratory, ECG, spirometry, vital signs, physical examination, medical history and Investigator's assessment.
3. Subject has been smoking for at least three years prior to V1.
4. Subject has been smoking ≥ 10 cigarettes per day over the last 12 months. Smoking status will be verified by a urinary cotinine ≥ 200 ng/mL and CO exhaled breath test > 6 ppm at both V1 and V2.
5. Subject does not plan to quit smoking within 6 months after V1.
6. Subject is aged between 21 and 65 years (inclusive).
7. Subject is available for the entire study period and willing to comply with study procedures.

Exclusion criteria

1. Subject performs more than 45 min of vigorous physical activity per week.
2. Inability to perform a VO_2max test at V1.
3. VO_2max > 50 mL.min^{-1} kg-^{1} for men and VO_2max > 40 mL.min^{-1} kg-^{1} for women as determined at V1.

4. For women only: subject is pregnant (does not have negative pregnancy tests at V1 and at V2) or is breastfeeding.
5. For women of childbearing potential: Female subject who does not agree to using an acceptable method of effective contraception during the entire study.
6. Subject has a BMI < 18.5 kg/m^2 or BMI ≥ 30 kg/m^2.

Investigational Products; Dose; and Mode of Administration:

IQOS arm: *IQOS* starter kit (*IQOS* device and packs of marketed HeatSticks of different variants) will be supplied to the subjects randomized to *IQOS*-1 and *IQOS*-2 arms at the end of V3. The short time between the randomization and the distribution of the device (same visit) does not allow subjects to purchase the device on-line and have it delivered on time (there is no physical shop in the study area). The distribution of the device by the study staff will also allow the subjects to benefit from the on-site guided trial to understand how to use the device properly. Subjects allocated to *IQOS* arms will be asked to buy their variant of choice of HeatSticks for their own use during the entire investigational period as HeatSticks will not be provided by the Sponsor.

Cigarette arm (comparator product): Subjects' own preferred brand of commercially available cigarettes will not be provided by the Sponsor but purchased by the subjects for their own use for the duration of the study.

Duration of Study:

The study duration per subject will be between approximately 20-25 weeks depending on length of visit windows. The study consists of a 1-28-day screening period (V1), a 1-day familarization visit (V2), up to 7±1 days interval between V2 and V3, followed by a 1-day baseline and randomization visit (V3). A 1-day acute effect test visit (V4) will be scheduled 7±2 days after V3, followed by a 12-week training program with training sessions 2-4 times per week (V5-V42) starting 15±2 days after V3 until 99±2 days after V3. A 1-day training effect test visit (V43) will be scheduled up to 7±2 days after V42 (106±2 days after V3), followed by a discharge visit (V44) up to 1±2 days after V43 (107 ±2 days after V3), and followed by a 28-week safety follow-up period. The end of the study for an individual subjects will be defined as V44 or the date of early termination plus the 28 days for the safety follow-up period. The end of the entire study is the latest date that an individual subject reaches the end of the study.

Statistical Methods:

Sample Size and Evaluation:

The sample size of 20 per arm (smoking abstinence with training, *IQOS* with training, continued cigarette smoking with training) was determined based on previously published

results, which reported a standard deviation of 14 mL/kg/min in VO_2max in the change between groups which continued smoking and those who were smoking abstinent after participating in a 12-week training program (2). This sample size allows a probability (power) of 90% that the half-width of the 95% confidence intervals between two arms have a precision of approximately 10.3 mL/kg/min. For example, if the mean difference in change between the cigarette arm and smoking abstinence arm was 12 mL/kg/min after training, we expect that if the experiment were repeated many times then on average 90% of the time the 95% confidence intervals of the mean differences between two arms will be within 1.7 and 22.3. To allow for a dropout rate of approximately 20%, the sample size will be 25 per arm. The *IQOS*-2 arm without training will mainly serve as a secondary analysis to the *IQOS*-1 arm with training, and the drop-out rate in this arm is expected to be lower. Therefore, only 15 subjects will be randomized to this arm.

Analysis Populations:

The main population for non-safety analysis will be the As Exposed Exercise Compliant Set.

Safety will be analyzed using the Safety Set.

1. As Exposed Exercise Compliant Set

The As Exposed Exercise Compliant Set (AEECS) consists of all randomized subjects who have at least one valid non-safety assessment after randomization, specifically we have

- post-randomization product (cigarette or *IQOS*) use experience if randomized to *IQOS*, *IQOS*-2 or cigarette arm or
- no product use if randomized to the SA arm,

and who attended at least 34 of 38 (~90%) of the exercise training sessions except the subjects in *IQOS*-2 arm. The AEECS will be analyzed by actual exposure (product use exposure).

2. Full Analysis Set

The Full Analysis Set (FAS) consists of all randomized subjects who have at least one post-randomization product (cigarette or *IQOS*) use experience if randomized to *IQOS*, *IQOS*-2 or cigarette arm, and who have at least one valid non-safety assessment after randomization. All subjects in the SA arm who fulfil these requirements, except the product use experience, are part of this set as well. The FAS will be analyzed by randomized study arm.

3. Safety Set

The Safety Set consists of all subjects enrolled with signed ICF who have at least one valid safety assessment during the course of the study. The Safety Set will be analyzed by actual exposure (product use exposure).

Endpoint analysis

A linear mixed effects model will be used to estimate the VO_2max values between each arm (*IQOS*-1, SA arm) versus cigarette arm one week after randomization (V4) and after completion of the 12-week training program (V43). The dependent variable will be VO_2max with baseline VO_2max, arm, sex, age and cigarette consumption as covariates. Appropriate contrasts will be constructed to report an estimate of the difference in VO_2max and its 95% confidence intervals within and between each arm. The same analysis will be performed for SA vs *IQOS*-1 arm. Other covariates may be added as deemed appropriate.

To estimate the VO_2max values between *IQOS*-1 and *IQOS*-2 arms, the same linear mixed effects model will be used to model the VO_2max at V43. The same analysis will be repeated for weight-adjusted and fat-free weight adjusted VO_2max.

A linear mixed model will be used to estimate the difference in exercise capacity between each arm (*IQOS*-1, SA arm) versus cigarette arm one week after randomization (V4) and after completion of the 12-week training program (V43). The dependent variable will be the time to complete the test in seconds with baseline exercise capacity (in seconds), arm, sex, age and cigarette consumption as fixed effects. Appropriate contrasts will be constructed to report an estimate of the difference in change in exercise capacity time at V3 and V43 and its 95% confidence intervals as an estimate of the acute effect and training effect, respectively. Other covariates may be added as deemed appropriate. The same analysis will be performed for SA vs *IQOS*-1 arm as well. To estimate the change in exercise capacity between *IQOS*-1 and *IQOS*-2 arm the same linear model will be used to model the change between arms at V43.

An appropriate statistical model will be used to estimate the intensity of exercise training in the various arms over time. Further details will be provided in the SAP.

Estimates of variability from the statistical model (VO_2max, exercise capacity, intensity of exercise training) will be reported and may be used to power future similar studies.

Descriptive statistics will be used to present various measures assessing the VO_2max, exercise capacity, intensity of exercise training in each arm.

An appropriate statistical model will be used to estimate the changes in physiological parameters and perception of exertion and capacity whilst adjusting for covariates such as age, sex, cigarette consumption or any other clinically relevant covariates of interest. The difference between arms will be estimated and reported together with its 95% confidence intervals. Other covariates may be added as needed.

Descriptive statistics of the various measures of physical activity as measured by the mHealth wearable device will be reported. An appropriate statistical (linear or non-linear) model will be used to estimate the levels of activity taking into account clinically relevant covariates and repeated measures over time. Comparisons of physical activity levels for *IQOS*-1 and *IQOS*-2 arm will be reported based on the chosen statistical model.

For each of the biological markers descriptive statistics will be employed to assess the difference between arms. An appropriate statistical model may be employed to estimate differences across arms at V43.

For weight, body fat and waist circumference, descriptive statistics will be employed to assess the changes for each arm. An appropriate statistical model may be employed to estimate differences across arms at V43.

To monitor levels of exposure to CO descriptive statistics of exhaled CO will be summarized and presented for each arm. Descriptive statistics of COHb% in blood, NEQ, NNAL and CEMA in urine will be summarized and presented for each arm. An appropriate statistical model may be employed to estimate differences across arms during the visits where these are measured.

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AE	Adverse event
AEECS	As Exposed Exercise Compliant Set
BMI	Body mass index
BoExp	Biomarker of exposure
Bpm	Beat per minute
CEMA	2-cyanoethylmercapturic acid
CI	Confidence interval
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events and common toxicity criteria
CTMS	Clinical trial management system
CV (documentation)	Curriculum vitae
CV (statistics)	Coefficient of variation
DMP	Data management plan
ECG	Electrocardiogram
EOS	End of study
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström test for nicotine dependence (revised version)
FVC	Forced vital capacity
GCP	Good Clinical Practice
GH	Growth hormone
Hb	Hemoglobin

HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HPHCs	Harmful and potentially harmful constituents
HR	Heart rate
hs-CRP	High sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational product
IPAQ	International Physical Activity Questionnaire
LDL	Low-density lipoprotein
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
NEQ	Nicotine equivalents
NNAL	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NRT	Nicotine replacement therapy
PMI	Philip Morris International
QC	Quality control
RPC	Rating of Perceived Capacity
RPE	Rate of Perceived Exertion
SA	Smoking abstinence
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedure
SPI	Summary of Product Information
[redacted]	[redacted]

ULN	Upper limit of the normal range
ULOQ	Upper limit of quantification
VAS	Visual analogue scale
VLDL	Very low density lipoprotein
VO_2max	Maximal oxygen uptake
WBC	White blood cell (count)
WHO	World Health Organization

Explanation of Terms

The following special terms are used in this protocol:

Cigarette	The term 'cigarette' refers to commercially available cigarettes (manufactured) and excludes cigars, pipes, bidis, and other nicotine-containing products.
End of study (EOS)	The EOS for a subject is defined as discharge on Visit 44 or the date of early termination of the subject plus the 28 days for the safety follow-up period. The EOS of the entire study is the end of the safety follow-up period of the last subject.
Randomization	Allocation of the respective product at any time on V3 utilizing an interactive web and voice response system (IxRS). In the end of V3, the subjects will be individually informed about the product they are randomized to prior to the first product use.
Screening failure	All subjects that are not enrolled because they violate the entry criteria prior to enrollment are considered as screening failures. Re-screening of these subjects will not be permitted.

1 ETHICS AND REGULATIONS

1.1 Independent Ethics Committee (IEC) Approval

Prior to the start of the study, the study protocol, together with its associated documents (informed consent form [ICF] including the subject information sheet and the informed consent, subject recruitment procedures [*e.g.*, advertisements], written information including questionnaires and written instructions to be provided to the subjects, Summary of Product Information [SPI] including available safety information, curriculum vitae of the Investigator and/or other evidence of qualifications and any other documents requested by an Independent Ethics Committee [IEC]), will be submitted for review and approval to the relevant IEC. The IEC shall be appropriately constituted and perform its functions in accordance with the International Conference on Harmonization (ICH) Tripartite Guidance for Good Clinical Practice (GCP) (3) and local requirements, as applicable.

In accordance with GCP, a written confirmation of the IEC approval should be provided to the Sponsor. This should identify the study (name of the Investigator, study number, and title) and the documents that have been approved by the IEC, with dates and version numbers, as well as the date of approval. The composition of the IEC, including the name and occupation of the chairperson, will be supplied to the Sponsor together with a GCP compliance statement.

The written approval from the IEC will be filed in the Investigator Site File (ISF), and a copy will be filed in the Study Master File (SMF) at the Sponsor or designated organization. The study must not start at an investigational site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC.

Any substantial change or addition to this protocol will require a written protocol amendment that must be approved by the Sponsor and the Investigator. All amendments will be submitted to the IEC, and substantial amendments will only be implemented after approval by the IEC.

These requirements for approval should in no way prevent any action from being taken by the Investigator or by the Sponsor in order to eliminate immediate hazards to the subjects. If such a change to the protocol is felt to be necessary by the Investigator, and is implemented for safety reasons, the Sponsor and the IEC should be informed immediately. The Investigator is responsible for local reporting (*e.g.*, to the IEC) of serious adverse events (SAEs) that occur during the study, according to local regulations.

Relevant safety information should be submitted to the IEC during the course of the study in accordance with national regulations and requirements. Medically qualified study personnel will be available during the study.

1.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (4) and are consistent with ICH/GCP guidelines (3) and applicable regulatory principles.

The Investigator agrees to conduct the study in compliance with the protocol agreed with the Sponsor and approved by the IEC. The Investigator and the Sponsor must sign the protocol (and protocol amendments, if applicable) to confirm this agreement. A copy of the Declaration of Helsinki should be located in the ISF.

1.3 Subject Information and Consent

1.3.1 Informed Consent Form for Study Participation

At the beginning of V1, the Investigator will ensure that each subject has been given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study, and the Investigator will answer all questions the subject might have to his/her full satisfaction. The subject will have sufficient time for consideration of his/her participation in the study and will be notified that he/she is free to withdraw his/her participation at any time without penalty or loss of benefits to which she/he may be otherwise entitled.

Once the subject has received all the necessary information and sufficient time for consideration, and if he/she agrees to participate in the study, the subject and the person who conducted the informed consent discussion during V1 will both sign, date and time the ICF. The ICF includes both the subject information sheet and informed consent. No study-specific procedures will be performed before informed consent is obtained and the ICF has been signed (including date and time). All subjects will be invited to participate in an optional sub-study on health and functioning and will sign a separate section of the ICF for this part.

The original, dated and signed ICF must be kept by the Investigator and filed in the ISF at the investigational site or with the subject's files and a copy must be given to the subject.

The subject will be informed that if he/she withdraws from the study, the data collected until the point of withdrawal will be maintained as part of the study data and the samples collected prior to withdrawal will be analyzed, unless he/she refuses in writing. The subject will be informed that additional data analyses not mentioned in the protocol or the statistical analysis plan might be performed with the collected data at a later time. If any additional analyses will be performed, they will fully be covered by data confidentiality, as for the main analyses described in this protocol.

For the purpose of exploratory digital biomarker scientific research the subjects will need to consent that data collected continuously throughout the study with the mHealth wearable

device will be stored by the Sponsor. The subjects will be informed that following completion of this study, analysis of these data of exploratory nature will be conducted to provide better understanding of changes in activity and sleep patterns in healthy smokers switching to *IQOS* or being smoking abstinent vs continued cigarette smoking.

1.3.2 Informed Consent Form for Biobanking

In addition to the ICF for the participation in the study, each subject will be asked to provide his/her separate optional consent for the collection of samples and storage for long-term biobanking. Samples to be collected include blood, urine, saliva and sweat samples.

Biobanking samples will be collected using commonly accepted methods for the purpose of identification and validation of new biomarkers indicative of the underlying biological processes related to the exposure to potentially harmful compounds, disease risk and health status. A part of the biobanking samples will also be used for the development and validation of methods to perform the measurements under the quality management system. The biobanking samples will be analyzed using non-targeted analytical methods such as molecular, metabolomics, proteomics, lipidomics, and transcriptomics profiling. The identified biomarker quantification will subsequently be confirmed using established targeted methods. The analyses performed will be covered by data confidentiality, as for the main analyses described in this protocol.

Subjects will be given full and adequate oral and written information about the purpose of biobanking, and the Investigator will answer all questions the subject might have to their full satisfaction. The subject will be notified that he/she is free to withdraw consent at any time. Once the subject has received all the necessary information, and if he/she agrees to participate, this will be documented by the date, time and signature of both, the subject and the Investigator who conducted the informed consent discussion. The subject's consent to collection of any samples for long-term storage in a biobank is not a requirement for participation in the study.

1.3.3 Amendment to the Informed Consent Form

If a protocol amendment is required, an amendment may be required to the ICF. If revision of the ICF is necessary, the Investigator or designee will, with the support of the Sponsor or authorized representative, ensure that the documents have been reviewed and approved by the IEC before study participants are required to re-sign and time and date the ICF.

1.4 Good Clinical Practice and Regulatory Requirements

The procedures set out in this clinical study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by the principles of the current version of the ICH

guidelines on GCP and will carry out the clinical study in accordance with these principles if applicable. Although these guidelines were written specifically to set a standard for pharmaceutical development, they nevertheless provide a robust and ethical framework for conducting clinical studies of tobacco products.

2 INTRODUCTION

2.1 Background

2.1.1 Smoking and Exercise Capacity

Insufficient physical activity is a leading risk factor for global mortality, and according to WHO 23% of adults are being insufficiently physically active (5). Improvement in cardiorespiratory fitness, quantified by measuring the maximal oxygen uptake (VO_2max) is independently associated with 13% reduction in all-cause mortality, highlighting the clinical benefit associated with exercise training and physical activity (6) . Exercise training is the most effective lifestyle intervention for increasing cardiorespiratory fitness.

In addition to causing adverse health effects and disease, cigarette smoking has been shown to adversely affect cardiorespiratory fitness and exercise performance, and lower VO_2max values have been reported in smokers as compared to non-smokers. The carbon monoxide (CO) present in the cigarette smoke has >200 times stronger affinity for hemoglobin (Hb) as compared to oxygen thus in the presence of CO the formation of carboxyhemoglobin (COHb) easily occurs (7), which consequently limits oxygen transport to the exercising skeletal muscles. While it has been suggested that COHb% levels below 4% only exerts mild effects on VO_2max, there is a marked decrease in VO_2max above this threshold (8). In smokers, COHb% values of 3-15 is within the expected range (9), and upon smoking abstinence, these values decrease to levels found in non-smokers (10, 11).

Beyond limiting exercise capacity, it has likewise been demonstrated that cigarette smoking limits the training response associated to exercise training, i.e. exercise trainability (7). Cooper et al. assessed the effect of 6 weeks of training on a 12-minute field test and showed that the training response was significantly impaired in the smoking as compared to the non-smoking participants (12). Another study, assessing the effect of smoking cessation on exercise performance in 109 female smokers, demonstrated that women who underwent a 12-week exercise training program and quit smoking improved exercise performance over those who continued smoking (2).

The other main component in cigarettes that may influence exercise is nicotine. In regard to exercise, the main line of action of nicotine is exerted through an increase in adrenaline and noradrenaline release from peripheral nerve endings and the adrenal medulla. While this increases submaximal heart rate and contractility, and thereby cardiac minute volume, it has no consequences on submaximal exercise performance, as the O_2 extraction in the skeletal muscle will decrease in order to keep the total oxygen uptake constant (13). Bolinder et al., assessed the influence of prolonged nicotine exposure on maximal physical working capacity, and cardiovascular response to exercise in 144 smokeless tobacco users, smokers and non-

tobacco users. Smokeless tobacco users had similar VO_2max as non-users whereas significantly lower VO_2max was found for smokers. The findings indicate that use of smokeless tobacco not generating CO does not significantly influence exercise capacity in healthy, physically well-trained men (14). Results from a randomized controlled cross-over study on a tobacco heating device (previous prototype of *IQOS*), with CO reduced by > 90% (15), indicated acute improvements in exercise performance parameters, such as maximal workload and heart rate response, in 18 male smokers switching to this product or being smoking abstinent (16). Altogether, these studies suggest that the effects of cigarette smoking on exercise performance and trainability are mainly triggered by an induced elevation in COHb% whereas the effect of nicotine is minor.

Studies have also suggested that smokers stopping smoking tend to maintain a healthier physical activity level compared to those continuing to smoke (17). Physical activity is commonly assessed using self-reported questionnaires, which are limited by recall and response biases. Thus, activity tends to be over- or underestimated with regards to activity frequency, duration, and intensity (18). Recent advancements in mobile health (mHealth) wearable technology have provided clinicians and researchers with new opportunities to collect objective data from research participants with greater frequency than conventional data collection methods, outside of structured research settings during activities of daily living in a non-invasive manner.

2.1.2 Description of the Product and Scientific Findings

Philip Morris International's Tobacco Heating System *IQOS* is a novel tobacco product that heats a specifically designed tobacco stick (HeatSticks) within a precisely controlled temperature range rather than burning it. Lowering the temperature below 400 °C substantially reduces levels of harmful and potentially harmful constituents (HPHCs) including a reduction of CO > 95% (19). *IQOS* is composed of the Holder and dedicated HeatSticks. In this document, unless otherwise specified, *IQOS* refers to the device with HeatSticks. No other tobacco sticks should be used with the device. A Charger allows to recharge the Holder after each use. Unlike cigarettes, the HeatSticks do not burn down during their consumption and their lengths remain constant after use. *IQOS* has been commercialized in Germany since 2016. With this product, the heating of the tobacco is maintained below 350°C, a temperature much lower than what is observed for cigarette, which can reach 900°C.

PMI has undertaken a comprehensive assessment program on *IQOS*, including pre-clinical and clinical studies, aiming to demonstrate that *IQOS* is a reduced risk product[1]. The non-clinical

[1] Reduced risk products ("RRPs") is the term used by PMI to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

assessment of *IQOS*, consisting of the aerosol chemistry analysis, *in vitro* and *in vivo* studies, supported the initiation of clinical studies, as no new or increased toxicological hazard in the product's aerosol was detected when compared with cigarette smoke. Results from pre-clinical in vivo studies comparing cigarette smoke with *IQOS* aerosol in continuous inhalation show that exposure to *IQOS* aerosol, at multiple concentrations, results in a dramatically lower systemic toxicity, extensively reduced lung inflammation and reduced histopathological changes in the nasal epithelium as well as lung tissue compared to cigarette smoking (20, 21). Furthermore, exposure to *IQOS* aerosol in mice does not enhance cardiovascular disease or emphysema, as cigarette smoke does, and switching from cigarette smoke to *IQOS* aerosol exposure halts e.g., aortic plaque growth in a similar manner as smoking cessation (22, 23).

Several clinical studies have been conducted with *IQOS*, in Europe, Asia and the United States, in order to evaluate the nicotine pharmacokinetics (PK) profile (24-28), to demonstrate reduced exposure (29, 30), and to determine functional and biological changes when adult smokers from cigarettes to *IQOS* use compared to smokers continuing smoking cigarettes (31-33). The PK studies demonstrated similar nicotine absorption in subjects using *IQOS* and subjects smoking cigarettes (34). The Reduced Exposure studies showed reductions from 47% to 98% in the controlled 5-day (10, 11), and from 32% to 94% (35) in the 3-month ambulatory settings, in the levels of biomarkers of exposure (BoExp) to selected HPHCs in subjects using *IQOS* compared to subjects continuing smoking cigarettes. Importantly, the magnitude of reductions in the BoExp levels when using *IQOS* were comparable to those observed when smokers stopped smoking cigarettes (10, 11, 35). The 3-month studies also indicated favorable biological and functional changes in clinical risk endpoints linked to smoking-related diseases (36). A 6-month Exposure Response study (33) with the specific aim to demonstrate favorable changes in clinical risk endpoints in smokers switching from cigarettes to *IQOS* succeeded to meet its primary objective: all eight of the primary clinical risk endpoints moved in the same direction as observed for smoking cessation in the group who switched to *IQOS*, with statistically significant changes in five of the eight endpoints compared with on-going smoking. These clinical risk endpoints are associated with diseases including heart and lung diseases, covering multiple organ systems, disease pathways, and biological mechanisms such as inflammation and oxidative stress (37). The reporting of the 6-month extension of the Exposure Response study (38) is ongoing.
Post-marketing studies have been initiated in order to have a better understanding of the product use behaviors (39). Safety data available from the clinical studies conducted to date show a similar short-term safety profile for *IQOS* than for cigarettes. PMI is now launching a series of new clinical studies to better understand whether switching to *IQOS* can have beneficial effects on health outcomes (40). Further product information can be found in the Summary of Product Information (SPI) (41).

2.2 Purpose of the Study

This study is part of the global clinical assessment program of *IQOS* which is designed to provide scientific evidence to further substantiate the potential of reduced risk of using *IQOS* as compared to smoking cigarettes. The main goals of this exploratory study are to assess whether switching from cigarette smoking to using *IQOS* will influence 1) VO_2max and exercise capacity, 2) ability to perform exercise training and thereby influence 3) VO_2max after 12 weeks of exercise training, 4) physiological parameters and biological health markers, and finally 5) physical activity levels in daily life.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

Subjects who participate in this study will benefit from repeated, detailed health check-ups. The VO_2max test performed for screening purpose will allow subject to know their maximum exercise capacity and their level of cardiorespiratory fitness as compared to norms adjusted for sex and age. Advice on health risk associated with tobacco smoking, and smoking cessation advice will be provided at V1 and V2 and then on a monthly basis until the end of the study. Subjects who are motivated to quit using tobacco-containing products (e.g. *IQOS* and/or cigarette) are to be referred for additional smoking cessation counselling and the standard of care to support smoking cessation will be applied.

Subject being randomized into an arm including participation in the training program (cigarette, SA and *IQOS*-1 arms) will benefit from a personalized 12-week exercise training program.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures

- Risks related to blood sampling (*e.g.*, excessive bleeding, fainting, hematoma, paresthesia or infection).
- Risk related to spirometry testing procedures (*e.g.*, dizziness or fainting). Administration of salbutamol for the spirometry testing may potentially elevate blood pressure, increase the heart rate and cause tremor, inner agitation, palpitation due to sinus tachycardia, muscle cramps or headaches. However, these effects are limited after single use and only more frequent following repeated use and oral administration.
- Risk related to VO_2max test may include muscle cramps, muscle strain, delayed muscle soreness (1 to 2 days afterwards), light headedness, fatigue, and in rare instances, heart attack. These symptoms are expected physiological responses and are similar to what may occur if the subject undertakes a strenuous run or bike-ride by him- or herself.

- Risks related to exercise training include muscle cramps, muscle strain and delayed muscle soreness 1 to 2 days afterwards, fatigue. These symptoms are expected physiological responses and are similar to what may occur if the subject undertakes a strenuous run or bike-ride by him- or herself.

All risks related to study procedures will be explained in detail to the subjects. Mitigation will include:

- Using accepted research and scientific standards, (*e.g.*, blood samples not to exceed local blood donation standards).
- Before performing the first VO_2max test at V1, subjects will undergo medical examinations and their medical history will be assessed. All exercise testing will be performed by trained study personnel and be medically supervised.
- Exercise training sessions will be supervised and performed on stationary bikes. During stationary bike ergometer exercise, the exerted loads on especially the knee joints and back will be smaller than during running exercise (42).
- Medical assessment of all study participants with follow-up of those who have experienced an AE/SAE.

2.3.3 Anticipated Foreseeable Risks due to Investigational Product (*IQOS*/Cigarette)

A substantial body of evidence already exists on *IQOS* and its development product, Tobacco Heating System (THS) (please refer to SPI (41)). Adverse events (AEs) reported so far seem to be mostly in line with the side effects that can be observed while using NRT. Cigarette smoking causes pulmonary, cardiovascular diseases and other serious diseases in smokers.

2.3.4 Unforeseeable Risks

The possibility of unforeseeable events/risks will be explained at V1. Non-expected malfunction of *IQOS* may lead to unforeseeable risks. Subjects will be informed that *IQOS* is not demonstrated yet to be less harmful than cigarettes. Mitigation will include close monitoring and medical supervision to detect any unforeseeable risks or safety signals at the earliest time possible.

3 STUDY OBJECTIVES

3.1 Objectives and Endpoints

The objectives of this study are:

Objective

1. To evaluate changes in VO_2max in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoint (V3, V4 and V43)

- VO_2max as determined during maximal cycle ergometer exercise (expressed in absolute [$mL*min^{-1}$], weight-adjusted [$mL*kg^{-1}*min^{-1}$] and fat free weight-adjusted [$mL*kg^{-1}*min^{-1}$] values)

2. To evaluate changes in exercise capacity in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints (V3, V4 and V43)

- Exercise capacity: time to complete a pre-defined work on a cycle ergometer (min:sec)

3. To assess the intensity of the exercise training in subjects participating in a training program and switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent

Endpoints (V5-V42)

- Cumulative work produced during each training session (calories and calories/kg body weight)
- Average work rate during each training session (watt and watt/kg body weight)
- Average work rate during each interval during each training session (watt and watt/kg body weight)
- Time spent at 0-50%, 50-65%, 65-75%, 75-90%, >90% of maximal work rate during each training session (min:sec)
- Average heart rate (HR) during each training session (bpm)
- Time spent at 0-50%, 50-60%, 60-70% , 70-80 % and >80 % of maximal HR during each training session (min:sec)

4. To evaluate changes in physiological parameters and perception of exertion and capacity in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints (V3, V43)

- Blood composition: Hemoglobin mass (g), red blood cell volume (mL), plasma volume (mL) and total blood volume (ml) as determined by CO re-breathing method
- Capillary blood lactate levels during VO_2max test (mmol/L)
- Perceived rate of exertion during VO_2max test (Borg Rating of Perceived Exertion (RPE) scale)

Endpoints (V3, V4 and V43)

- Respiratory parameters at VO_2max: Ventilation (L/min), respiratory rate, VCO_2 (L/min), Respiratory exchange ratio (RER) (VCO_2 / VO_2)
- Rating of Perceived Capacity (RPC) scale
- Heart rate (bpm) and oxygen uptake (mL/min) during VO_2max test

5. To monitor trends of daily physical activity levels during the study in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints (from V2 until V43)

Aggregated data derived from the mobile health (mHealth) wearable for:

- Cumulative number of steps per day
- Sedentary minutes per day and % of time sedentary
- Active minutes per day and % of time active
- Very active minutes per day and % of time very active

6. To explore trends and changes in activity and sleep parameters through continuous measurements during the study*

Endpoints (from V2 until V43)

mHealth wearable measurements of steps, activity, distance, energy expenditure, sleep* Reporting of data for this objective will be subject to a separate report(s) (not part of the Clinical Study Report [CSR]).

7. To describe changes in biological health markers in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints (V3, V14, V28 and V43)

- High density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) (mg/dL)
- High sensitivity C-reactive protein (hs-CRP) (mg/L)
- Growth hormone (GH) (ng/mL)
- Hemoglobin A1C (HbA1c) (%)
- Resting blood pressure (mmHg)
- Resting HR (bpm)

8. To describe changes in weight, body fat and waist cirumference in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints (V3, V4 and V43)

- Body fat percentage (%)
- Waist circumference (cm)

Endpoints (V3- V43)

- Body weight (kg)

9. To monitor levels of exposure to CO, nitrosamines and acrylonitrile in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training)

Endpoints

At all visits:

- Exhaled carbon monoxide (CO) (ppm)

At V3, V4, V14, V28 and V43

- COHb% in blood (%)
- Nicotine equivalents (NEQ) in urine (adjusted for creatinine)
- Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in urine (adjusted for creatinine)
- 2-cyanoethylmercapturic acid (CEMA) in urine (adjusted for creatinine)

10. To describe the self-reported nicotine and tobacco containing product use over the duration of the study

Endpoints (measured daily from V2 to V43)

- Self-reported number of any nicotine/tobacco product use on a daily basis as reported in the product use diary
- Product use exposure

11. To monitor safety during the study

Endpoints

- Incidence of adverse events (AEs), serious adverse events (SAEs)
- Frequency of AEs, SAEs
- Incidence of *IQOS* device events including malfunction/misuse
- Frequency of *IQOS* device events including malfunction/misuse
- Vital signs changes from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
- Physical examination changes from baseline
- Electrocardiogram (ECG) changes from baseline (heart rate, PR, QRS, QT, QTcB, QTcF intervals)
- Spirometry changes from screening visit (V1) used as baseline (FEV1, FEV1 % predicted, FVC, FVC % predicted, and FEV1/FVC)
- Cough assessment changes from baseline (VAS and three Likert scales)
- Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel
- Concomitant medications

12. To assess perception of health and functioning in subjects switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent **

Endpoints (first interview between V2 and V3, second interview between V42 and V43)

- Changes in subjects' perception of health and functioning as determined by qualitative interviews based on the World Health Organization's International Classification of Functioning, Disability, and Health

** This objective will be assessed as a sub-study with a separate section of the Informed Consent Form (ICF), and the reporting will be subject of an appendix to the main CSR.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, controlled, open-label, 4-arm parallel group study with stratification by daily cigarette consumption over the last 12 months prior to V1 as reported during V1 (i.e., 10 to 19 cigarettes or >19 cigarettes per day) and sex (Figure 2).

A sufficient number of healthy adult smokers will be screened and enrolled after checking that all eligibility criteria have been met, in order to reach 90 randomized subjects.

Smokers will be randomized as follows with a 5:5:5:3 ratio according to strata:

1. switch to *IQOS* use + participation in training program: ***IQOS*-1 arm**, 25 subjects
2. continue cigarette smoking + participation in training program: **Cigarette arm**, 25 subjects
3. smoking abstinence + participation in training program: **SA arm**, 25 subjects
4. switch to *IQOS* use only: ***IQOS*-2 arm**, 15 subjects

When 90 randomized subjects are reached, further enrollment will be stopped. Subjects already enrolled in the study will still be eligible for randomization. From randomization, subjects will be instructed to use their allocated product or stay smoking abstinent until the end of the study. Drop-outs will not be replaced.

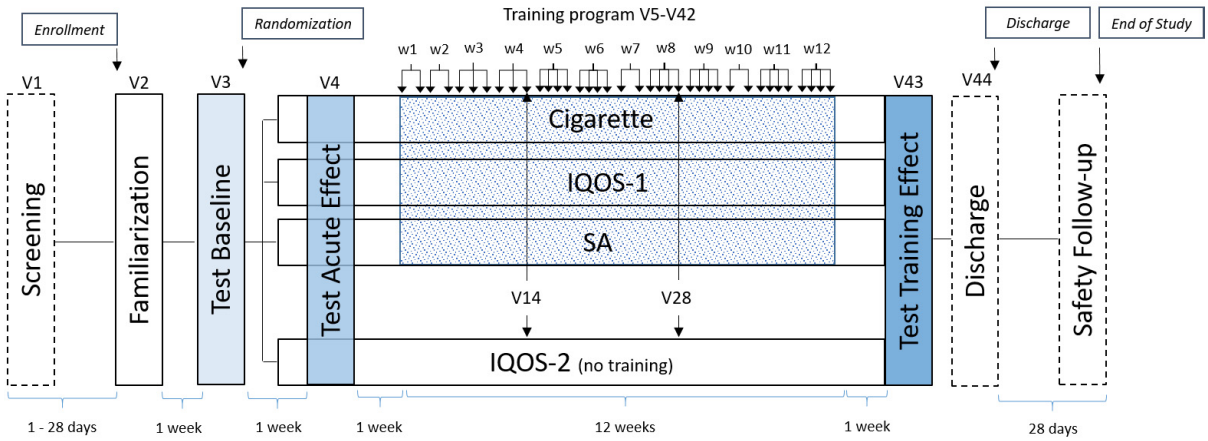

Figure 2 Study Design

Subjects will have serial visits at the investigational site as follows:

Screening, V1 (within 28 days prior to V2): No study-specific procedures will be performed before informed consent is obtained and the ICF has been signed. The subject will also be invited to participate in a sub-study on perception of health and functioning and will sign a separate optional section of the ICF for this part of the study. Subjects will be invited to sign a separate optional consent form for collection of samples for biobanking.
All inclusion and exclusion criteria will be assessed. A demonstration of *IQOS* and the mHealth wearable will be done by the site staff during the screening visit. A VO_2max test will be performed as part of eligibility assessments. All eligible subjects will be invited to come to V2.
Enrollment and Familiarization 1, V2 (7±1 days prior to V3): Enrollment will take place after confirmation of smoking status (urine cotinine and exhaled CO) and negative urine pregnancy test, alcohol breath test and urine drug screen. After enrollment, vital signs will be assessed and subjects will perform an exercise capacity test for the purpose of familiarization. The exercise test consists of completing a pre-defined work (calories) on a bike ergometer (1). Before leaving the investigational site the subject will receive an mHealth wearable kit and will be trained on how to handle the device. Subjects will be instructed to wear the device all the time. Subjects will also receive a diary to record the daily use of tobacco and nicotine containing products.

Between V2 and V3, subjects having signed the optional section of the ICF will have an interview (by phone or computer) on the topic of health and functioning lasting around 60 minutes.

Baseline and Randomization, V3: Baseline assessments will be performed as listed in Appendix 1. Then, 30-60 min before start of the VO_2max test all subjects will smoke a cigarette (only if they are willing to). During the VO_2max test at rest and at each 25 W increase, the subject's lactate levels will be determined by capillary blood sampling and the rate of perceived exertion will be assessed using the Borg RPE scale. After completing the VO_2max test, the subject will rest for 60±5min, after which the exercise capacity test will be performed. After completing exercise tests, total blood volume will be determined.
Subjects will thereafter be randomized into one of the 4 arms. Subjects randomized into *IQOS* arms will receive their *IQOS* starter kit and be trained on how to use the device. Subjects randomized into the SA arm will receive smoking abstinence support and will be allowed to use NRT upon request.
Acute effect 1, V4 (7±2 days after V3): Before the VO_2 max test, vital signs, exhaled CO, weight, body-fat and waist circumference measurements will be performed. 30-60 min before start of the VO_2max test subjects in cigarette and *IQOS* arms will smoke a cigarette or use a HeatStick, respectively (only if they are willing to). Subjects' VO_2max, maximal heart rate and maximal work rate will be determined. After completing the VO_2max test, the subject will rest for 60±5min after which the exercise capacity test will be performed.

Training program, from V5 (15±2 days after V3) until V42 (99±2 days after V3): Subjects randomized into *IQOS*-1, cigarette and SA arms will participate in 38 supervised training sessions during a 12-week period using three different training protocols (Appendix 2).

Subjects randomized to the *IQOS*-2 arm will come for visits once a week for all assessments except the training. Subjects in the *IQOS*-2 arm will consequently only attend the following visits: V5, V7, V9, V14, V16, V19, V23, V28, V30, V33, V35 and V39.

At V14 and V28 (medical visits), safety and biological health marker and exposure marker assessments will be performed for all subjects.

Before each training, the following assessments will be conducted;

- Weight
- Exhaled CO
- 30-60 min before start of the training subjects in cigarette and *IQOS* arms will smoke a cigarette or use a HeatStick, respectively (only if they are willing to).

All trainings will be performed on a bike ergometer. The training intensity will be adjusted according to the subject's resting heart rate as determined by ECG at V3 and maximal heart rate as determined at the VO_2max test at V4 (acute test). The work produced, the work rate and heart rate will be recorded for each training (as described in Objective 3).

Between V42 and V43, subjects having signed the optional section of the ICF will have an interview (by phone or computer) on the topic of health and functioning lasting around 60 minutes.

Training effect, V43 (106±2 days after V3):

Before the VO_2max test, biological health markers, exposure markers, vital signs, exhaled CO, weight, body-fat percentage and waist circumference measurements will be performed. Then, 30-60 min before start of the VO_2max test subjects in cigarette and *IQOS* arms will smoke a cigarette or use a HeatStick, respectively (only if they are willing to). Subjects' VO_2max will be determined as described for V3, including determination of lactate levels and perceived exertion rate. After completing the VO_2max test, the subject will rest for 60±5min, after which the exercise capacity test will be performed. After completing exercise tests, total blood volume will be determined.

Subjects will return the mHealth wearable, the product use diary and the *IQOS* device (if applicable).

Discharge, V44 (107±2 days after V3): Safety assessments will be conducted as listed in Appendix 1.

Safety follow-up period (from discharge at V44 or early termination plus 28 days):

After discharge on V44 or after early termination, subjects will enter a 28-day safety follow-up period during which AE/SAEs spontaneously reported by the subjects will be collected. Any

non-serious AE that is ongoing at the time of discharge or early discontinuation will be followed-up by the Investigator or designee during the safety follow-up period until it has been resolved, stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition) or lost to follow up. The follow-up of the ongoing non-serious AEs will be done via a phone call performed until the end of the Safety follow-up period. At the end of the safety follow-up period, all ongoing non-serious AEs will be documented as "ongoing" and no further follow-up information will be sought for them by the Investigator or designee. At that point, the Investigator will assess whether the subject should be referred to his/her General Practitioner to have their ongoing AEs addressed accordingly. SAEs will be followed up by the Investigator until resolution, stabilization or the determination of a plausible explanation for them was found, regardless of the end of the safety follow-up period. All subjects discontinued from the study at any time after enrollment, will enter the 28-day safety follow-up period.

4.2 Rationale for Study Design

PMI is now launching a series of new clinical studies to better understand the additional benefits the reduced exposure of *IQOS* can offer to its consumers. Because of the recognized adverse effects of smoking on exercise capacity, this exploratory study is part of the program. The overall objective of the *IQOS* design is to provide an acceptable alternative to cigarettes for current, adult smokers, with substantial reduction of exposure to HPHCs by its aerosol compared to cigarette smoke.

Based on the well-known role of hemoglobin in blood oxygen transport and the formation of COHb upon CO exposure, it is assumed that when cigarette smokers switch to a smoke- and CO-free product, such as *IQOS*, their exercise capacity and response to exercise training will increase as a consequence of normalization of COHb levels and increased blood oxygenation. In order to explore this assumption, and to further assess the role of CO, smokers will be randomized to switching to *IQOS* use (*IQOS*-1, *IQOS*-2), continuing cigarette smoking and smoking abstinence (SA). In a previous study an effect on VO_2max already after 8h of smoking abstinence has been reported (9). In this study the acute effect of switching to *IQOS* will be assessed one week after randomization. In order to assess the impact on the response to exercise training, all subjects besides the *IQOS*-2 arm, will participate in a 12-week exercise training program. Whereas a reduced CO exposure in the SA-arm and the *IQOS*-1 arm is thought to favorably impact response to training, continued exposure to CO in the cigarette arm would reduce the training effect in sedentary healthy smokers.

The training program designed for this study is based on previous studies demonstrating that in order to achieve improvements in cardiorespiratory fitness the optimal training frequency consists of at least 3 training sessions at a moderate intensity (~65% of maximal workload) per week (43). A bike exercise is recommended as compared to running due to the lower risk of

injuries (42, 44.) The *IQOS*-2 arm will allow to assess the impact on simply switching to a smoke-free product on VO_2max and exercise capacity.

This study is designed as an *ad libitum* study without product use restriction in order to mimic as closely as possible "real life" conditions. Subjects randomized to the cigarette and *IQOS* arms will be asked to buy their own cigarettes or HeatSticks respectively, according to their needs for the study, in order to minimize any changes in their smoking behavior. Subject randomized to the SA arm will be instructed to stay smoking abstinent until the end of the study. Subjects in the SA arm will receive smoking abstinence support and, in order to prevent relapse to cigarette smoking (i.e. CO exposure) during the intense training program, subjects will be allowed to use nicotine replacement therapy. Other drugs to aid smoking abstinence have been approved in Germany (e.g., bupropion and varenicline). However, since information on their effect on the study endpoints is sparse, their use will not be allowed in this study.

Similarly to smoking cessation (45), there is evidence that physical activity and exercise training have a favorable impact on biological health markers, such as markers for inflammation (46), lipid metabolism (47, 48) and blood glucose regulation (49). In this study the impact of switching to *IQOS*, alone or in combination with participation in an exercise training program, on a selected number of health markers will be assessed. It is expected that *IQOS* effects will be close to the ones observed in the SA arm.

Mobile health technology will be used in the study to explore the impact on switching from smoking to using *IQOS* on physical activity in daily real-world living conditions. The wearable will enable non-invasive recording of physical activity in an objective manner throughout the study.

4.3 Appropriateness of Measurements

The VO_2max test is the only direct test to determine maximal oxygen uptake in humans and is considered to be the metric that defines the limits of the cardiopulmonary system (50). To assess exercise performance in this study, a laboratory-based exercise capacity test will be performed which includes the advantages of the controlled settings provided in a laboratory. The combination of these two tests provide a complete evaluation of exercise capacity. The determination of blood lactate levels during incremental exercise (51) and blood volume before and after the exercise interventions (52) provides an additional measure of exercise capacity but which is independent of subject motivation.

All laboratory-based exercise tests will be conducted on a bike ergometer and not on a treadmill since 1) all exercise training sessions will be performed on bike ergometers 2) workloads can be determined more accurately, 3) the test procedure itself is easier as subject movement is smaller and 4) it may be difficult for especially untrained individuals to coordinate their limbs during fast maximal treadmill running which can lead to false low values.

In addition to self-reporting of product use, to assess exposure to CO, nicotine, tobacco-specific nitrosamines and acrylonitrile (a tobacco combustion constituent), exhaled CO and COHb levels, and NEQ, NNAL and CEMA concentrations in urine will be measured throughout the study.

4.4 Study Duration

The study duration per subject will be between approximately 20-25 weeks depending on length of visit windows. The study consists of a 1-28-day screening period (V1), a 1-day familarization visit (V2), up to 7±1 days interval between V2 and V3, followed by a 1-day baseline and randomization visit (V3). A 1-day acute effect test visit (V4) will be scheduled 7±2 days after V3, followed by a 12-week training program with training sessions 2-4 times per week (V5-V42) starting 15±2 days after V3 until 99±2 days after V3. A 1-day training effect test visit (V43) will be scheduled up to 7±2 days after V42 (106 ±2 days after V3), followed by a discharge visit (V44) up to 1±2 days after V43 (107 ±2 days after V3), and followed by a 28-day safety follow-up period. The end of the study for an individual subjects will be defined as V44 or the date of early termination plus the 28 days for the safety follow-up period. The end of the entire study is the latest date that an individual subject reaches the end of the study.

5 STUDY POPULATION

5.1 Selection of Study Population

5.1.1 Inclusion Criteria

Subjects who meet all the following inclusion criteria can be enrolled into the study:

Inclusion Criteria	Rationale	Screening	Enrollment V2
1. Subject has signed the ICF.	Administrative	x	
2. Smoking, healthy subject based on safety laboratory, ECG, spirometry, vital signs, physical examination, medical history and Investigator's assessment.	Safety	x	
3. Subject has been smoking for at least three years prior to V1.	Effect	x	
4. Subject has been smoking ≥ 10 cigarettes per day over the last 12 months. Smoking status will be verified by a urinary cotinine ≥ 200 ng/mL and CO exhaled breath test > 6 ppm both at V1 and V2.	Effect	x	x
5. Subject does not plan to quit smoking within 6 months after V1.	Safety	x	
6. Subject is aged between 21 and 65 years (inclusive).	Safety	x	
7. Subject is available for the entire study period and willing to comply with study procedures.	Effect	x	

5.1.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria must not be enrolled into the study:

Exclusion Criteria	Rationale	Screening	Enrollment V2
1. Subject has a clinically relevant disease which requires medication (including but not limited to gastrointestinal, renal, hepatic,	Safety	x	

Exclusion Criteria	Rationale	Screening	Enrollment V2
neurological, hematological, endocrine, oncological, urological, immunological, pulmonary [such as but not limited to pulmonary oedema, asthma], and cardiovascular [such as, but not limited to myocardial infarction, unstable angina, uncontrolled arrhythmias, heart failure], disease) or any other clinically significant medical condition (including abnormal safety laboratory result as per CTCAE), which as per the judgment of the Investigator would jeopardize the safety of the subject.			
2. Subject who has forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <0.7 and FEV_1 <80% predicted value at post-bronchodilator spirometry (GOLD, 2017).	Safety	x	
3. Subject with asthma condition (FEV_1/FVC < 0.75 and reversibility in FEV_1 (in both > 12% and > 200 mL) from pre to post-bronchodilator values.	Safety	x	
4. Subject has clinical significant abnormalities of ECG at V1.	Safety	x	
5. Subject performs more than 45 min of vigorous physical activity per week.	Effect	x	
6. Inability to perform a VO_2max test at V1.	Safety	x	
7. VO_2max >50 $mL.min^{-1}kg^{-1}$ for men and VO_2max >40 $mL.min^{-1}kg^{-1}$ for women as determined at V1.	Effect	x	
8. Subject takes medication influencing blood volume such as erythropoietin, diuretics and beta blockers, or diabetic medications.	Effect	x	
9. Subject cannot participate in the study for any reason other than medical as per the Investigator's judgment (e.g. psychological and/or social reason)	Administrative	x	
10. For women only: subject is pregnant (does not have negative pregnancy tests at V1 and at V2) or is breastfeeding.	Safety	x	x

Exclusion Criteria	Rationale	Screening	Enrollment V2
11. For women of childbearing potential[2]: female subject who does not agree to using an acceptable method of effective contraception [3] during the entire study.	Safety	x	
12. Subject has a BMI < 18.5 kg/m^2 or BMI ≥ 30 kg/m^2.	Safety	x	
13. Subject has positive serology test for HIV, Hepatitis B or Hepatitis C.	Safety	x	
14. Subject has a positive alcohol breath test and/or a history of alcohol use disorder (both V1 and V2).	Administrative	x	x
15. Subject has a positive urine drug screen.	Administrative	x	x
16. The subject has been previously screened for this study.	Administrative	x	
17. The subject, or one of their family members (e.g., spouse, parent, sibling or child), is a current or former employee of the tobacco industry.	Administrative	x	
18. The subject, or one of their family members (e.g. spouse, parent, sibling or child), is an employee of the investigational site or any other parties involved in the study.	Administrative	x	
19. Subject is legally incompetent, or physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, prisoners, or subjects who are involuntarily incarcerated).	Administrative	x	

[2] Women who are not of childbearing potential meet at least one of the following criteria: Have undergone hysterectomy or bilateral tubal ligation, Have medically confirmed ovarian failure, or Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause).

[3] Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception containing progesterone only, vasectomized partner(s), from screening until the end of the safety follow-up period.

Exclusion Criteria	Rationale	Screening	Enrollment V2
20. Subject has donated or received whole blood or blood products within 3 months prior to V1.	Safety/ Effect	x	

5.2 Discontinuation of Subjects from the Study

Discontinued subjects will include both, subjects who withdraw from the study (subject's decision) and subjects who are discontinued from the study by the decision of the Investigator.

A subject can only be discontinued from the study after enrollment.

Subjects will be informed that they are free to withdraw from the study at any time. Subjects should be questioned for the reason of withdrawal from the study, although they are not obliged to disclose it.

If the subject withdraws from the study, he/she will be asked to perform the early termination procedures (Section 9.6) as soon as possible after the time of withdrawal unless the subjects refuses to do it in writing.

If a subject expressed his/her wish to quit the study during a visit planned for clinical assessments, he/she will be asked whether he/she would agree to still do the clinical assessments planned for this visit, but with no obligation.

After the time of study termination, independent of the reason of discontinuation (for example, withdrawal of consent, or at the Investigator's decision etc.), the subject will enter into the 28-day period of safety follow-up.

Discontinuation from the study

Subjects must be discontinued from the study for any of the following reasons:

1. Withdrawal of informed consent.
2. Discontinuation is considered to be in the interest of the subjects from a safety perspective as judged by the Investigator.
3. Positive or unclear pregnancy test.
4. The Sponsor or Investigator terminates the study or the study terminates at the investigational site. If the Sponsor or the Investigator decides to prematurely terminate the study, the subject will be promptly informed. The Investigator should report the fact and the reason in writing to the IEC.

5. Subjects becomes an employee of the investigational site or any other parties involved in the study.
6. Lost to follow-up.
7. Violation of eligibility criteria after enrolment (i.e. if an eligibility criteria violation is retrospectively discovered after enrolment during the course of a study).

Subjects may be discontinued from the study for the following reasons:

1. Non-compliance with the study procedures based on the judgment of the Investigator.

For subjects who are discontinued, the reason for discontinuation should be documented in the source documents and in the CRF and subjects will undertake early termination procedures (Section 9.6).

IQOS and cigarette arms:

The switch to different variants of HeatSticks as well as the use of other tobacco- or nicotine-containing products will not lead to discontinuation.

SA arm:

The use of any tobacco- or nicotine-containing products will not lead to discontinuation.

5.3 Lost to Follow-up

The date of the last contact with the subject (e.g., last visit, last phone call) should be recorded in the source document.

After the last contact, reasonable number of attempts to contact the subject (including written correspondence and phone calls) should be done and documented in the source documents by the site. Following the contact attempts, if the Investigator(s) or designee(s) decides to discontinue the subject with the reason of lost to follow-up, the discontinuation date will be recorded. The discontinuation date for the subjects will be the date the subject was determined to be lost to follow-up and will correspond to the date of the EOS of the subject.

If the site has lost track of the subject, the discontinuation date cannot exceed the maximum number of study weeks (i.e. 25), then the Investigator(s) or designee(s) will discontinue the subject with reason as lost to follow-up.

5.4 Violation of Selection Criteria

Subjects who violate the entry criteria prior to enrollment will be considered as screening failures. Re-screening of these subjects will not be permitted.

6 INVESTIGATIONAL PRODUCTS/ REFERENCE ARM

6.1 Description of Investigational Products

6.1.1 Test Product

The product tested in this study is the Tobacco Heating System with Heatsticks, marketed in Germany under the brand name *IQOS* and referred to as *IQOS* in this protocol. All versions of *IQOS* and Heatsticks available for sale in Germany at the time of study start or becoming available during the course of the study are allowed to be used in the context of this study. The *IQOS* is composed of the following components: a tobacco HeatStick, a Holder and a Charger (Table 1), as well as a cleaning tool, a power supply, and a USB cable. The product user guide will be provided as part of the *IQOS* starter kit.

The product is provided to study subjects free of charge in the framework of the study due to the short time between the randomization and the distribution of the device (same visit) which does not allow subjects to purchase the device on-line and have it delivered on time (there is no physical shop in the study area). The distribution of the device by the study staff will also allow the subjects to benefit from the on-site guided trial to understand how to use the device properly. Subjects will then buy their preferred variant of Heatsticks by themselves.

Table 1 Test Product (*IQOS*)

HeatStick*:*	The HeatStick is designed to function with the Holder. The HeatStick is made up of: tobacco plug, hollow acetate tube, polymer-film filter, mouth piece filter, outer and mouth-end papers. All materials have been evaluated with regards to their toxicological potential and have been approved for use. The tobacco plug is made from tobacco, glycerin, water, guar gum, cellulose, propylene glycol, natural and artificial flavorings. The average amount of nicotine in the tobacco plug is 4.3-5.4 mg/stick per HeatStick.
Holder:	The Holder is a slim electrical heating unit that heats the *HeatStick* in a controlled manner by using a heater blade. The Holder stores enough energy for a single experience, delivering puffs over a period of about 6 minutes or 14 puffs (whichever comes first). A Light Emitting Diode indicates the end of the experience. Once this cycle is complete, the Holder must be recharged before a new HeatStick can be used.
Charger:	The power supply for the Holder is the Charger. The Charger holds enough energy for approximately 20 uses of the Holder and can be recharged from household power. The Charger stores the Holder when not in use, and provides a secure environment for the cleaning process of the heater blade.

The overall objective of the product design is to provide an acceptable experience in which the HPHCs levels in the aerosol are substantially reduced in comparison with the smoke of a cigarette (19, 53). A summary of description of the product, pre-clinical and clinical data available on *IQOS* is provided in the SPI (41).

6.1.2 Comparator and Baseline Product

Cigarette (comparator product): subjects's own preferred brand of commercially available cigarettes.

6.2 Packaging and Labeling

An *IQOS* starter kit (*i.e.*, *IQOS* device and a selection of HeatSticks variants available on the German market) will be supplied to the site by the Sponsor or authorized representative in packages that protect against deterioration during transport and storage.

The Sponsor or authorized representative will label the *IQOS* starter kit in local language ensuring adherence to local regulatory requirements. This will include at least the following information:

- Statement 'For investigational use only'
- Name and address of the Sponsor (if the Sponsor resides outside Germany, name of the Sponsor and name of the country where the Sponsor is located, and name and address of the clinical trial in-country representative)
- *IQOS* device serial number.

6.3 Use of Investigational Product(s)

The study is designed as an *ad libitum* use study. The subjects will be allowed to use their allocated products (cigarette or *IQOS*) according to their need. There will be no restrictions on the variants of HeatSticks used.

6.3.1 From Enrollment to Randomization

From screening visit (V1) to randomization (V3), all subjects will be allowed to continue smoking *ad libitum* their preferred usual brand of cigarettes. 30-60 min before start of baseline VO_2 max at V3, subjects will smoke a cigarette. However, subjects will never be forced to smoke, and will only smoke if they are willing to.

At randomization, subjects allocated to the *IQOS* arm, since they will not be able to purchse the device on time to start the trial (there is no physical store in the study area), will be supplied with an *IQOS* starter kit (*i.e.*, *IQOS* device and a selection of HeatStick variants available on the German market). Subjects will benefit from a guided trial to understand how to properly use the device and will have to return it at the end of the trial. Subjects will have to purchase their own HeatSticks for use during the study (available throughout the country).

6.3.2 Investigational Period

6.3.2.1 *IQOS* arms

IQOS arm: subjects randomized into *IQOS*-1 and *IQOS*-2 arms will be instructed to use exclusively *IQOS ad libitum*. The switch to different variants of HeatSticks as well as the use of other tobacco- or nicotine-containing products will not lead to discontinuation (see Section 5.2). 30-60 min before start of VO_2 max at V4, and V43 and 30-60 min before start of each training V5-V42, subjects will use a HeatStick. However, subjects will never be forced to use *IQOS*, and will only use a HeatStick if they are willing to.

6.3.2.2 Cigarette arm

Cigarette arm: subjects randomized to the cigarette arm will be instructed to continue smoking their cigarettes *ad libitum*. The switch to different cigarette brands and the use of other tobacco- or nicotine-containing products will not lead to discontinuation (see Section 5.2). 30-60 min before start of VO_2 max at V4 and V43 and before each training V5-V42, subjects will smoke a cigarette. However, subjects will never be forced to smoke, and will only smoke if they are willing to.

6.3.2.3 SA arm

SA arm: As of randomization on V3 until V43, subjects in the SA arm will be instructed to abstain from smoking cigarettes or using any other tobacco- or nicotine-containing products. Use of NRT will be allowed as per subjects request and will be provided by the site. If NRT patches are used they should be removed before and during exercise tests and trainings.

6.3.3 Safety Follow-up Period

During the safety follow-up period (*i.e.* as of V44 or prematurely discontinued), all subjects will be free to smoke their own cigarettes, or use any other nicotine-containing product of their choice.

6.3.4 Stopping rules for Investigational Product

For safety purposes, use of the IP should be temporarily reduced or stopped in the event of any signs suggesting nicotine overexposure, e.g., gastrointestinal disturbance (nausea, vomiting, diarrhea, stomach, or abdominal pain), cold sweats, headache, dizziness, and breathing problems or any reasons at the discretion of the Investigator.

6.4 Method for Assigning Subjects to Study Arms

Randomization will be done through the Interactive Web and Voice Response System (IXRS) at any time during the visit. Subjects will be informed about their study arm allocation at the end of V3. Subjects will be randomized in one of the four study arms:

- Cigarette arm with training program
- *IQOS*-1 arm with training program
- SA arm with training program
- *IQOS*-2 arm without training

in a 5:5:5:3 ratio using a stratified randomization based on daily cigarette consumption over the 12 months prior to V1 (10-19 cigarettes/day vs. >19 cigarettes/day), and sex. All subjects will be instructed to adhere to their assigned product/regimen until they complete the study.

6.5 Blinding

6.5.1 Blinding of site staff

This is an open-label study and the site staff performing study assessments will therefore not be blinded by the smoking status.

6.5.2 Blinding of data

There will be additional, even though limited, degree of blinding during the conduct of the study, including the data review and data analysis process. In particular, PMI and contract research organization (CRO) personnel will be blinded as summarized in Table 2

Table 2 Blinding

Blinded Study Personnel	Blinded data	End of Blinding Period
PMI and CRO Study Statisticians	VO_2max and exercise capacity test results after randomization	After database lock.
PMI Clinical Scientist	VO_2max and exercise capacity test results after randomization	After the finalization of PMI blind database review. Can be actively un-blinded when appropriate.

Any PMI and CRO personnel who are not listed in Table 2 will be unblinded by default.

Unblinded information will not be shared with the blinded study team, until the end of the blinding period. PMI will receive blinded and unblinded data for the pre-analysis data review as planned in the data review plan. Unblinded data will only be reviewed by the unblinded study team.

6.6 Investigational Product Accountability and Adherence

6.6.1 Dispensing Investigational Product

Due to the lack of availability of the device in physical stores in the study area subjects allocated to the *IQOS* arms will be supplied with an *IQOS* starter kit (*IQOS* device and a

selection of HeatStick variants available on the German market) at V3 after randomization. Subjects randomized to the *IQOS* arms will purchase their HeatSticks variants, as it will not be provided by the Sponsor.

In case the device needs replacement due to a device malfunction or in case of loss/theft of the device, the subjects will need to contact the site. In case a subject decides to purchase their own device, these will not be replaced by the site. Subjects allocated to the cigarette arm will buy cigarettes for their own use for the entire duration of the study.

6.6.2 Storage and Accountability

The Investigator or a designated study collaborator will be responsible for the storage and accountability of the *IQOS* devices and HeatSticks to be distributed only once at V3, together with the device. The *IQOS* devices (charger and holder) as well as HeatSticks (to be distributed only once at V3, together with the device) will be stored in a secured storage site with access limited to authorized personnel only.

A sufficient number of *IQOS* starter kit will be stored at site, to be delivered to subjects allocated to the two *IQOS* arms only. A few additional devices will be stored in case a subject needs to have his/her *IQOS* device replaced. Full accountability of the distributed *IQOS* starter kit and replacement devices, if any, will be ensured by the designated study collaborator and recorded in IP accountability logs. This includes but is not limited to the record of the device serial number, HeatSticks batch number, the quantity of devices and HeatStick packs delivered per subject, date of delivery, total quantity available at site, the quantity of devices returned to the site at the end of the study.

Except for the initial packs of HeatSticks delivered within the *IQOS* starter kit at V3, neither HeatSticks nor cigarettes will be stored at site during the study as they will be bought by the subjects throughout the study.

6.6.3 Investigational Product Retention

The subjects will return the *IQOS* device (Charger and Holder), including replacement devices to the study site at V43 or upon early discontinuation. The study site will return to the Sponsor or authorized representative the *IQOS* device (Charger and Holder) upon study completion. This does not apply to devices purchased by the subjects.

6.6.4 Adherence to Investigational Products and Reference Arm

Adherence to the allocated product or reference arm will be monitored using self-reported tobacco and nicotine containing product use as reported in the product use diary (Section 7.11.8).

6.7 Restrictions

6.7.1 Product Use Restrictions

There will be no restriction on allocated product use.

6.7.2 Dietary Restrictions

Subejcts will be asked not to consume any caffeine- or alcohol-containing products 12 h prior to VO_2max and exercise capacity test.

Before safety laboratory and biological health markers blood collections at V3, V14, V28, V43 and V44 subjects will be required to fast for at least 8 h.

6.8 Concomitant Medication

Medications will be allowed and carefully monitored during the study by the Investigator or designee. The Investigator or designee is responsible for the medical care including medication of the subjects during their participation in the study. Any decisions regarding the prescription of medication will be taken in the best interest of the subject. The use of any concomitant medication must be fully documented in the source document and transcribed into the CRF. All medication taken within 4 weeks prior to the ICF signature will be considered prior medication. All medication taken from screening visit to end of the safety follow-up period will be considered concomitant medication.

Records of medication taken include the drug name (preferably both generic and trade name), route of administration (e.g., oral, intravenous), total daily dose/unit (e.g., expressed in mg, mL or IU), indication, the start and if applicable, the stop date (day, month and year). Any therapy changes (including changes of regimen) during the study have to be documented.

7 STUDY PROCEDURES

Personnel performing or recording study measurements must have appropriate and fully documented training. Quality control (QC) measures must be defined, implemented and documented. All study procedures are provided as an overview in the schedule of events (Appendix 1).

In this section, only the expected/planned time points for the various measurements are given. Considering that not all study participants can have a procedure at the same time point, adequate time windows are given for each study procedure and each time point in Section 9. Site personnel will adhere to the site's standard operating procedures (SOPs) for all activities relevant to the quality of the study. Appropriate medical advice will be provided to the subjects in case of any medical findings requiring health care.

7.1 Informed Consent

Prior to any study assessment being performed, the subjects will be asked to provide his/her written consent to participate to the study (ICF) (Section 1.3.). During the consent process, the Investigator or designee obtaining consent must inform each subject of the nature, risks and benefits of, and alternatives to study participation. In addition, each subject must review the ICF and must have sufficient time to understand and have adequate opportunity to ask questions. The ICF must be signed and dated (date and time) prior to undertaking any study specific procedures. A copy of the signed ICF must be given to the subject.

Subjects will be invited to participate in an optional sub-study assessing health and functioning through qualitative interviews (Section 7.11.9) and will sign a separate section of the ICF if they wish to participate.

In addition to the ICF for study participation, the subject will be asked to provide his/her separate optional consent for the collection and storage of samples for long-term biobanking.

7.2 Information on the Risk of Smoking and Smoking Cessation Advice and Debriefing on *IQOS*

All subjects included in the study will be advised that the best way of preventing the development of smoking-related diseases is to stop smoking. Only subjects who are not planning to quit smoking cigarettes will be eligible for the study.

From V1 onwards, information on the risks of smoking and smoking cessation advice will be given to all subjects (Appendix 1). This will take the form of a brief interview according to WHO recommendations (54). In addition, a debriefing of subjects will be done to address any intended or unintended beliefs participants have about *IQOS*. The goal of the debriefing is to

ensure that subjects have an accurate understanding of *IQOS* risks including an understanding that *IQOS* has not yet been demonstrated to be less harmful than cigarettes.

Any enrolled subject, who is willing to attempt quitting during the study will be encouraged to do so and will be referred to appropriate medical services.

7.3 Questions on Smoking History/Habits and Plan to Quit Smoking.

Subject will be questioned for their smoking history and self-reported current tobacco and nicotine containing product use over the past 12 months at V1. The subject will also be asked if he/she is planning to quit smoking within 6 months after V1. This information will be used to assess their eligibility for the study.

7.4 Demonstration of *IQOS*

IQOS including HeatSticks will be presented to all subjects by the Investigator or designated study collaborator at V1.

7.5 Clinical Assessments

7.5.1 Demographic Data

Demographic data (sex, date of birth, race) will be recorded at V1.

7.5.2 Medical History, Concomitant Disease, Previous and Ongoing Medications

Relevant medical history and any concomitant disease will be documented at V1. Medical history is defined as any condition that started and ended prior to ICF signature. A concomitant disease is defined as any condition that started prior to ICF signature and is still ongoing at V1. The final status of any concomitant disease (i.e stop date or ongoing) should be verified at each visit.

Prior medication taken within 4 weeks prior to screening and any ongoing medication at screening needs to be documented. Any medication which is started prior to screening and is still being taken by the subject at screening or thereafter will be considered as concomitant medication. Medication initiated after the screening visit will also be referred to as concomitant medication. This applies to both prescription and over-the-counter products. If the use of a concomitant medication cannot be avoided for the subject's safety, it must be fully documented in the Source Document and CRF (see Section 6.8).

7.5.3 Physical Examination

A full physical examination will include review of general appearance, skin, head, eyes, ears, nose and throat, thyroid gland, chest, lungs, back, abdomen, dentition, cardiovascular, gastrointestinal, musculoskeletal and neurological systems. The physical examination is to be conducted by the Investigator or a designated fully trained representative.

7.5.4 Body Height, Weight and Body Mass Index (BMI)

Body height and weight will be recorded and BMI will be calculated using the following formula:

$$BMI = \frac{\text{weight in kilograms}}{\text{height in meters}^2} \quad (kg/m^2)$$

The BMI will be used to assess eligibility for enrollment at V1.

The fat-free weight is defined as:

Fat-free weight =	Weight in kilograms * (100 – body fat percentage)/100 kg

Weight will be recorded throughout the study (Appendix 1).

7.5.5 Vital Signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate will be recorded. All measurements will be made in supine position after the subject has rested for at least 5 minutes in a supine position. The subject should have abstained from smoking or using *IQOS* for at least 15 minutes prior to measurement.

7.5.6 Spirometry

All personnel performing spirometry testing must have the appropriate training with the record of the training. Quality control measures should be available and be properly documented.

The spirometry test will be performed in accordance with the 2005 guideline of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry (55).

Pre and post- bronchodilator spirometry assessments will be performed. Each assessment requires at least three valid spirometry tests. The ratio of forced expiratory volume in one second (FEV1) / forced vital capacity (FVC) will be calculated from the highest acceptable FEV1 and the highest acceptable FVC, respectively.

The results from FEV1 and the ratio FEV1 to FVC at V1 will be used for eligibility criteria to assess COPD and asthma conditions. All spirometry testing will be recorded in sitting position after resting for at least 15 minutes in sitting position. The subject should have abstained from smoking or using *IQOS* for at least 1 hour prior to testing. All post-bronchodilator spirometry testing will be performed 15-30 minutes post administration of around 400 µg of salbutamol/albuterol (usually equivalent to 4 puffs assuming 100 µg/puff). The time of salbutamol/albuterol inhalation and time of spirometry assessment will be recorded in the source document.

7.5.7 Electrocardiogram

ECG testing will be performed as per the site's local practice. A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in a supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QT interval corrected according to Bazett's formula and Fridericia's formula. Every ECG has to be assessed as normal, abnormal – clinically not relevant, or abnormal – clinically relevant. A diagnosis has to be provided on the CRF for all ECGs assessed as abnormal – clinically relevant. All ECG print-outs will be interpreted by a qualified physician. Any print-outs of ECGs on thermo-sensitive paper must be photocopied.

7.5.8 Body-fat Percentage and Waist Circumference

Body-fat percentage based on skinfold caliper measurements and waist circumference will be performed as per the site's practice. Mesurements should be performed by the same trained site collaborator and using the same instrument.

7.5.9 Determination of Blood Composition and Volume

Hemoglobin mass (Hb_{mass}) will be quantified using an automated system (e.g. OpCO, Detalo Instruments, Denmark or similar). First, a venous blood sample will be drawn to measure hemoglobin, hematocrit and COHb, after which the CO re-breathing procedure will be performed. Using the system a precise volume of CO is inhaled and re-breathed by the subject

for 10 min. During the re-breathing period 100% O_2 is administered to the subject on a demand basis, and due to the small volume of CO administered and the continuous O_2 supplementation arterial O_2 is barely affected. After completion of the re-breathing procedure COHb will be measured again. Then based on the resulting increase in COHb, the mass of hemoglobin will be calculated. Red blood cell volume, plasma volume and blood volume will be derived from measures of $Hb_{mass,}$ [Hb] and hematocrit.

7.6 Exercise Testing and Training

7.6.1 VO_2max Test and Blood Lactate Levels

Subjects will perform an incremental cycling test to volitional fatigue on an electronically braked cycle ergometer (such as Monark E839, Varberg, Sweden). To measure oxygen uptake and determine VO_2max an online gas collection system (e.g. COSMED CPET) will be used where O_2 and CO_2 concentration in the expired gas are continuously measured and monitored as breath-by-breath values.

Subjects will be asked to refrain from heavy exercise 24h prior to the test, and consuming caffeine or alcohol 12h prior to the test. Measurements will begin with the subjects resting for 3 min seated on the bike ergometer whereafter the workload will be increased by 25W every 60 sec until volitional fatigue. Subjects should keep cadence between 60 and 90 rpm during the test. Mean VO_2max will be determined as the highest O_2 value averaged over 30 s for each subject. At VO_2max the following parameters will be recorded: ventilation (l/min) respiratory rate, VCO_2 (l/min), respiratory exchange ratio (RER, [VCO_2 / VO_2]).

In addition at V4, the maximal heart rate and the maximal work rate will be recorded in order to design the training program.

At V3 and V43, capillary (fingertip or earlobe) blood samples will be obtained at rest and at each 25W workload increased and analysed for lactate (e.g. Radiometer ABL80 or similar). Blood collection should be started 40-45 seconds into the workload and no blood sample should be obtained at maximal effort. The final blood sample should be obtained within 5 minutes after termination of the bike exercise. Heart rate and oxygen uptake (VO_2) will be recorded at rest at each 25W increase.

After the test subjects will rest for 60±5 min and will be offered water *ad libitum* and a light snack e.g. fruit, chocolate or bar. The snack has to be consumed at least 30 min before the upcoming exercise capacity test (not applicable for V1).

7.6.2 Exercise Capacity Test

Subjects will perform an exercise capacity test during which they will complete a given workload as quickly as possible. The criteria for completion of the test is the completing of a pre-defined relative work determined based on the highest wattage level reached at VO_2max test times 1.25 (i.e. 200 W x 1.25 = 250; 250 kcal to be completed). The highest wattage reached at the VO_2max test at V1 will be used for the test at V2, and at the VO_2max test V3 will be used for the tests at V3, V4 and V43. This relative workload determination is selected for the exercise capacity tests because it i.) controls for differences in baseline aerobic capacity across subjects, and ii.) standardizes the time of completion of all baseline tests at approximately 20 minutes.

7.6.3 Exercise Training

Subjects randomized into the *IQOS*-1, cigarette and SA arms will participate in a 12-week training program consisting of 38 training sessions (V5-V42). All training sessions will be performed at the investigational site using stationary bikes, and will be supervised by designated site personnel.

Different training programs will be circulated to provide the study participants with differentiated training inputs and make the training sessions less monotonous. Each training session will last 40 min with a training intensity ranging between 60-85%. The target exercise heart rates are based on the subject's resting (HR_{rest}; obtained during ECG at V3) and maximal heart rate (HR_{max}) obtained during the acute effect VO_2max test at V4. The formula to be used for exercise heart rates is: Target exercise heart rate = ((HR_{max} – HR_{rest}) * intensity) + HR_{rest} with intensity as fraction of 1.

7.7 Biomarker Assessment

7.7.1 Exhaled Carbonmonoxide (CO)

Carbon monoxide (CO) in exhaled breath will be measured using the a Smokerlyzer® device, such as the Micro 4 Smokerlyzer® or similar. At V1 and V2, a cut-off of >6 ppm for confirming cigarette smoking status will be applied (56)(57).

7.7.2 Carboxyhemoglobin (COHb)

Venous blood samples will be collected and COHb measured by a designated laboratory.

7.7.3 Urine Biomarkers of Exposure

Spot urine will be collected to measure concentrations of NEQ, NNAL, CEMA and creatinine. The urine collection should be performed as late as possible during the day.

7.7.4 Biological Health Markers in Blood

Venous blood samples will be collected for measurement of HDL, LDL, VLDL, hs-CRP, GH and HbA1c (%). Blood samples will be taken after at least 8 hours of fasting (Section 6.7.2).

7.8 Laboratory Assessments

7.8.1 Clinical Chemistry, Hematology, and Urinalysis for Safety Panel

Hematology, clinical chemistry, serology and urinalysis safety panel will be measured at local laboratory except for urine drug screening, urine cotinine screening,, alcohol breath test and urine pregnancy test, these tests will be performed at site

Blood samples will be taken after at least 8 hours of fasting (Section 6.7.2) except at screening (V1) and early termination. Parameters to be measured are listed in Table 3.

Table 3 Clinical Laboratory Parameters for Safety Panel

Hematology	Clinical Chemistry	Urinalysis
• Hematocrit • Hemoglobin • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood cell (RBC) count• White blood cell (WBC) count • Differential WBC count: - Neutrophils - Basophils - Eosinophils - Lymphocytes - Monocytes	• Albumin • Total protein • Alkaline phosphatase (AP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Blood urea nitrogen (BUN) • Creatinine • Gamma-glutamyl transferase (GGT) • Glucose • Lactate dehydrogenase (LDH) • Potassium • Sodium • Total bilirubin • Direct bilirubin • Total cholesterol (TC) • Triglycerides (TG)	• pH • Bilirubin • Glucose • Nitrite • Red blood cell traces • Protein • Specific gravity

7.8.2 Serology

At V1, a test for hepatitis B (HbsAg), hepatitis C (HCV antibody), and human immunodeficiency virus (anti-HIV1/2) will be performed. In case of positive results, the subject will be referred to appropriate medical care.

7.8.3 Urine Drug Screening

At V1 and V2, urine drug screen (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone, methamphetamines, phencyclidine, tricyclic antidepressants) will be performed by the personnel at the investigational site.

7.8.4 Urine Cotinine Screening

At V1 and V2, a urine dip-stick cotinine test with a threshold of ≥ 200 ng/mL will be performed at the investigational site to confirm subject's smoking status.

7.8.5 Alcohol Breath Test

At V1 and V2, a breath alcohol test will be performed at the investigational site using a breathalyzer device.

7.8.6 Urine Pregnancy Test

A urine pregnancy test will be done at the investigational site for all female subjects at V1-V3 V5, V14, V28 and V44.

Subjects with a positive pregnancy test at V1 or at V2 will not be enrolled and will be considered screening failures. In any case of a positive urine pregnancy test, the Investigator will inform the subject about the risks associated with smoking during pregnancy.

All pregnancies detected during the study must be reported and handled as described in Section 8.5. Pregnancies detected after enrollment will lead to discontinuation from the study.

7.9 Sample Handling, Storage, and Shipment

Detailed procedures for sample collection and handling of samples are described in the laboratory manual. Safety laboratory samples will be destroyed as per the laboratory's standard procedures. For blood and urine samples collected for biological health marker and exposure marker analysis at least one sample should be kept at least up until the finalization of the bioanalytical reports and the database is locked unless stability for analysis is exceeded.

7.9.1 Blood Samples

Venous blood samples will be collected by qualified and trained site personnel. Subjects should be in a seated position during blood collection. The maximal volume of blood drawn for each subject will be approximately 235 mL, which includes approximately 55 mL for safety and serology analysis, approximately 100 mL for biological health markers, COHb, and blood volume determination and 80 mL for biobanking.

Capillary blood sampling will be performed for determination of lactate levels and will be analyzed on-site.

7.9.2 Urine Samples

Spot urine samples will be used for the urine drug screen, urine cotinine screen, urine pregnancy test, safety urinalysis, NEQ, NNAL, CEMA and creatinine analysis, and for biobanking.

7.9.3 Long-Term Storage (Biobanking)

If a subject gives consent for biobanking, additional samples of urine, blood, plasma, saliva will be collected at V3, V14, V28 and V43, and sweat at V3 and V43.

Urine:
Samples will be collected from the spot urine for:

- lipidomic profiling: 2 x approximately 2 mL
- proteomic profiling: 2 x approximately 10 mL
- metabolomics profiling: 2 x approximately 10 mL

Whole blood:

- transcriptomic profiling: 2 x 2,5 mL will be collected
- proteomic profiling: 5 mL will be collected to obtain 4 x 0.5 mL of plasma
- metabolomics profiling: 5 mL will be collected to obtain 4 x 0.5 mL of plasma
- lipidomics profiling: 5 mL will be collected to obtain 2 x 1 mL of plasma

Saliva:

- 4 x approximately 1mL saliva will be collected using a dedicated saliva collection kit for molecular profiling.

Sweat:

- 2 x at least approximately 40µL will be collected using a sweat collection system (Macroduct®Sweat Collection system, ELITechGroup) for molecular profiling.

Samples will be sent to the designated biobank facility and stored for 10 years as of final CSR. The biobank facility will follow their procedures for destruction of banked samples if a subject withdraws consent for long-term biobanking.

7.10 Mobile Health (mHealth) Wearable

Subjects will wear a mHealth device (Vivofit 3, Garmin), which is worn on the wrist, for the recording of their physical activity including daily step count and intensity minutes. Three intensity levels of physical activity will be recorded; 1) sedentary - little to no activity monitored (e.g. minimal movement, sitting, resting, or sleeping); 2) active – some activity monitored (e.g. a brisk walk); 3) very active- high activity monitored (e.g.running or speed walking).

The wearable will simultaneously record energy expenditure, distance and sleep as described in objective 6, however the analysis and reporting of this data will not be part of the CSR but reported separately.

Subjects will be trained on how to wear (i.e. correct positioning) and handle the device in accordance with the user guide. Subjects will be instructed to wear the device on their non-dominant wrist and to wear it all the time. As part of the wearable device kit subjects will also receive a mobile phone with Bluetooth and wireless internet connectivity through which data will be transferred from the wearable device. Between V2 and V3, baseline data will be collected, and as of randomization at V3 data will be collected during the investigational period until V43.

The Vivofit 3 device records accelerometer data continuously and transfers data aggregated on a 15-min basis to the data storage cloud. For the parameters to be analyzed as part of the study (objective 5; steps and activity) data transferred from the wearable device to the clinical database will be aggregated on a per 24-hour level. In addition, wear time per day will be monitored. Parameters listed in objective 6 will be transferred from the wearable device on a per 15-min level to the storage cloud. Further details on device set-up, subject account creation, device pairing and mapping, and data flow and storage will be given in a dedicated plan.

7.11 Questionnaires

7.11.1 Fagerström Test for Nicotine Dependence (Revised Version)

Subjects will complete the FTND questionnaire in its revised version (58).

The questionnaire consists of six questions. The FTND total score determines the subject's dependence on nicotine in three levels: mild (0-3 points), moderate (4-6 points), and severe (7-10 points).

7.11.2 Product preference

On V3, the following question will be asked to all subjects

"Which product would you prefer to be randomized to?"

- *IQOS*
- Cigarette
- Smoking abstinence
- No preference

The product preference question needs to be asked before randomization. As an instruction to answer this question, subjects will be informed that their response will not influence the randomization process.

7.11.3 Lifestyle questionnaire

Subjects will be asked questions to capture baseline covariates such as, diet, alcohol intake, sleep deficit, and exposure to passive smoking at V3.

7.11.4 Assessment of Cough-VAS and Likert Scales

Subjects will assess cough on a Visual Analogue Scale (VAS) and on three Likert scales.

Subjects will be asked if they have experienced a regular need to cough (*e.g.*, whether they have coughed several times in the previous 24 hours prior to assessment). If the answer is 'yes', subjects will be asked to complete a VAS and 3 Likert scales. On the VAS, subjects will assess how bothersome their cough was during the previous 24 hours. The VAS ranges from "not bothering me at all" to "extremely bothersome". Furthermore, subjects will assess the intensity and frequency of cough and the amount of sputum production during the previous 24 hours on Likert scales.

- The intensity of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with 1 = very mild – 2 = mild – 3 = moderate – 4 = severe – 5 = very severe.
- The frequency of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with 1 = rarely – 2 = sometimes – 3 = fairly often – 4 = often – 5 = almost always.
- The amount of sputum production will be assessed on a 4-point Likert scale ranging from 0 to 3, with 0 = no sputum – 1 = a moderate amount of sputum – 2 = a larger amount of sputum – 3 = a very large amount of sputum.

Symptoms or worsening of symptoms documented in the VAS do not need to be documented as additional AEs because the VAS will be analyzed as part of the final report. However, it is at the discretion of the Investigator to decide whether to document such symptoms as additional AEs. The main source for AE collection will be the face-to-face interview between the subject and investigational site staff using, open, non-directive questions (see Section 8.2.1).

7.11.5 International Physical Activity Questionnaire (IPAQ) - short form

At V1 subjects' physical activity levels will be assessed using the short version of the IPAQ. This questionnaire was developed by a group of experts in 1998 to facilitate surveillance of physical activity based on a global standard (59). The IPAQ has since become the most widely used physical activity questionnaire (60) with two versions available: the 31 item long form (IPAQ-LF) and the 9 item short form (IPAQ-SF). The short form records the activity of four intensity levels: 1) vigorous-intensity activity such as aerobics, 2) moderate-intensity activity such as leisure cycling, 3) walking, and 4) sitting.

7.11.6 Borg Rate of Perceived Exertion (RPE) Scale

During VO_2max test (only at V3 and V43) subjects will rate their perceived exertion on the Borg RPE scale at rest and then at each 25W increase (61). The Borg RPE scale is a way of measuring physical activity intensity level. It is based on the physical sensations a person experiences during physical activity, including increased heart rate, increased respiration or breathing rate, increased sweating, and muscle fatigue.

The scale ranges from

- 6- no exertion at all,
- 7.5 – extremely light,
- 9 – very light,
- 11 – light,
- 13 somewhat hard,
- 15- hard,
- 17-very hard,
- 19- extremely hard, to
- 20- maximal exertion.

A high correlation exists between a person's perceived exertion rating times 10 and the actual heart rate during physical activity (61).

7.11.7 Rate of Perceived Capacity (RPC) Scale

To predict maximal exercise capacity, the rating of perceived capacity (RPC) scale was developed based on metabolic equivalents (METs) (62). MET values from 1 to 20 for men and 1 to 18 for women are listed on a progressive scale and linked to physical activities. Subjects will rate their perceived capacity by choosing the most strenuous activity and the corresponding MET value that they could sustain for 30 min.

7.11.8 Product Use Diary

Subjects will enter the number of HeatSticks, cigarettes, or/and other tobacco and nicotine-containing products used per day in a product use diary from V2 until the discharge at V43. Before the diary is delivered to the subjects, subjects will be trained by site staff on how to complete it. The product use diary will be supplied by Sponsor and distributed to the subjects by the investigational site personnel.

7.11.9 Qualitative Interviews on Health and Functioning (sub-study)

Subjects that have signed the optional section of the ICF for the sub-study on health on functioning will have a one-hour, qualitative interview over the phone or computer between

V2 and V3, and at the end of the study between V42 and V43. Questions during the interview will be open-ended and will focus on subjects' current state of health and functioning, experiences during the training program, and changes in health and functioning as a result of the training program. The protocol for the sub-study is available in Appendix 4.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

An adverse event is defined as any health-related event which is adverse or unfavorable and which either starts after ICF signature or represents a worsening of a health – related condition that existed at the time of that signature. Careful medical judgment is required to establish whether a clinical finding (including an abnormal laboratory result) is a true AE or just a manifestation of a preexisting health – related condition. An AE may or may not have a causal relationship with the study procedures or with the use of investigational product (cigarette or *IQOS*).

8.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed in the above definitions.

"Life-threatening" means that the subject was at immediate risk of death from the event. It might have caused death if it had occurred in a more serious form.

7.1.3. Conditions Existent Before the Start of the Period of Collection of AEs (ICF Signature)

Clinical conditions that existed before the start of the period of collection of AEs and still ongoing at V1 (concomitant disease), and whose severity remained unchanged after that point,

should not be considered AEs and should not be captured as such. This includes medical therapies or surgical interventions that had been planned before the start of the period of collection of AEs regardless of involving admissions to hospital, if the medical condition to be addressed did not worsen after the start of the collection period. Otherwise, any medical condition that existed before the start of the period of collection and still ongoing at V1 (concomitant disease) and whose severity increased after that point is to be captured as a non-serious AE or an SAE, depending on the seriousness criteria met.

8.2 Assessment of Adverse Events

8.2.1 Collection of Information

Any non-serious AE occurrence during the study must be documented in the subject's medical records in accordance with the Investigator's normal clinical practice and on the AE page of the CRF. SAEs that occur during the study must be documented in the subject's medical record, on the AE CRF, and on the SAE form.

AEs should be collected mainly via face-to-face interview with the subject through spontaneous reporting or by the use of consistent, open, non-directive questions from the Investigator or designee(s) (e.g., "Have you had any health problems since you were last asked? or "How have you been feeling since you were last asked?").

Information recorded will include: verbatim description of the AE/SAE, start and stop dates, seriousness, severity (intensity), action taken (e.g., whether or not the AE/SAE led to the subject's withdrawal from the study), and outcome (e.g., resolved, stabilized).

Information to be recorded about an SAE should also include, whenever possible, onset and resolution dates and times, circumstances leading up to the event, clinical elements such as clinical course, specific vital signs and test results that may explain the pathophysiology of the event, as well as alternative explanations to its occurrence.

Whenever a medically meaningful diagnosis is available to comprise a set of reported signs and/or symptoms, it should be preferentially provided as the AE or SAE term, rather than the individual signs and/or symptoms. Otherwise, each one of those signs and/or symptoms should be reported separately as event terms.

8.2.2 Period of Collection

AEs (including SAEs) will be collected from the time of ICF signature until the EOS.

Any AEs which occur during the screening period will be captured by the study site staff and assessed by the Investigator or designee(s) in order to establish relationship to study procedures.

During a 28-day safety follow-up period there will be recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site. In general, all AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found and until the end of the study. The follow-up of the ongoing non-serious AEs will be done via a phone call performed until the end of the Safety follow-up period. Any AEs or SAEs that are ongoing at the end of the safety follow-up period will be managed as described in Section 8.2.6.

SAEs spontaneously reported to the Investigator after the end of the safety follow-up period and considered related to the *IQOS* must also be reported to the Sponsor.

8.2.3 Intensity of Adverse Event

The Investigator must assess the intensity of each reported AE according to the following grading scale:

Mild: Easily tolerated, not interfering with normal everyday activities.

Moderate: Interferes with normal everyday activities, but the subject is still able to function.

Severe: Incapacitating and requires medical intervention.

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

The Investigator must assess the causal relationship between the exposure to the IP (cigarette or *IQOS*) and each of the reported AEs, using the classification system and the criteria described below. The same assessment must be made separately regarding the causal relationship between the study procedures and each of the reported AEs:

Not related: The temporal relationship of the adverse event to IP administration or study procedure(s) makes a causal relationship unlikely, or concomitant medication, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Related: The temporal relationship of the adverse event to IP administration or study procedure(s) makes a causal relationship possible, and concomitant medication, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

8.2.5 Expectedness

Any AE assessed as related to the IP (cigarette or *IQOS*) will be assessed for its expectedness. An AE will be regarded as “unexpected” if its nature or severity is not consistent with information already recorded about *IQOS* in current version of SPI. The assessment of

expectedness with the cigarette will be based on the judgement of the PI relying on the available safety information on cigarette in the literature.

8.2.6 Follow-up of Non-Serious and Serious Adverse Events

Any non-serious AE that is ongoing at the time of discharge or early termination will be followed-up by the Investigator during the follow-up period until it has been resolved, stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition). The follow-up of the ongoing non-serious AEs will be done via a phone call performed until the end of the Safety follow-up period.

At the end of the safety follow-up period, all ongoing non-serious AEs will be documented as "ongoing" and no follow-up information will be sought on them anymore by the Investigator. At that point, the Investigator will assess whether the subject should be referred to his/her General Practitioner to have their ongoing AEs addressed accordingly.

All SAEs will be followed up by the Investigator or designee, despite their continuation after the end of the safety follow-up period, until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition).

8.3 Reporting of Serious Adverse Events

Any SAE observed *during* the study, whether or not attributable to the IP (cigarette or *IQOS*), or to any study procedures, must be reported **within 24 hours of first awareness** to [redacted] and Sponsor, as described in the respective safety management plan (SMP).

SAEs considered related to the *IQOS* and spontaneously reported *after* the end of study must also be reported **within 24 hours of first awareness** to [redacted] and Sponsor for safety surveillance purposes

All the SAE report forms must be sent as an attachment to an e-mail message to [redacted] and Sponsor:

[redacted]**:** **E-mail:** [redacted]
Fax: [redacted]
Address: [redacted]

Sponsor:	**E-mail:**	[redacted]@pmi.com
	Phone:	+ 41 [redacted]
	Address:	Philip Morris Products S.A. R&D Innovation Cube 5 Quai Jeanrenaud 2000 Neuchâtel Switzerland

As further information regarding an already reported SAE becomes available to any of the parties involved in this study, such follow-up information should be reported on a new SAE report form, marked as a follow-up report and submitted to [redacted] and Sponsor according to the same timelines described above. The follow-up SAE report form must include the minimum information required for form completion and only changed/new information needs to be specified. Information provided in the follow-up SAE report form supersedes any information that was initially reported. The SAE report form to be used in this study is provided as a separate document. All SAEs will also be recorded on the relevant CRF page, in addition to the SAE report form.

The Investigator or designee is responsible for submitting the relevant reports of SAEs that occur during the study to the local IEC, according to local regulations and in accordance with the respective safety management plan (SMP).

8.4 Reporting and of Other Events Critical to Safety Evaluation

8.4.1 Abnormal Results of Laboratory Tests

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the Investigator and assessed for clinical significance according to its severity. The severity of abnormal laboratory test result must be assessed using CTCAE version 4.03 grading scales (Appendix 3).

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the Investigator and assessed for clinical significance according to its severity. Whenever that grading scheme is not available for the laboratory result of concern, the Investigator should assess the severity and the clinical significance of that result using his/her medical judgment.

Subjects with clinically significant abnormal laboratory values at Screening will not be enrolled. Abnormal laboratory test results detected at the Screening Visit whose CTCAE grades are 2 or higher or still are CTCAE grade 1 and deemed clinically significant are usually

concomitant disease or a manifestation of one and must be recorded accordingly. However, in some instances, they may be assessed as AEs (and therefore must be handled according to the directions in Section 8.2) or as manifestations of already reported AEs. This decision will require a careful assessment of the abnormal result within the clinical context on a case-bycase basis and will depend on the Investigator's medical judgment.

Abnormal laboratory test results detected after the screening visit whose CTCAE grades are 2 or higher or still are CTCAE grade 1 and deemed clinically significant must be either recorded as AEs (and handled according to the directions in Section 8.2) or linked to a concomitant disease or still to an already reported AE.

The principles for assessing and reporting abnormal laboratory test results, emerging after the screening Visit, using CTCAE 4.03 grading scales are set up in Table 4:

Table 4 Principles for assessing and reporting abnormal laboratory test results

Grading	Clinically significant?	Is it a grade increase from previous results in study?§	Report?
Grade 1	No	Not applicable	No
Grade 1	Yes	No	No*
Grade 1	Yes	Yes	Yes, as AE or linked to an already reported AE
Grade 2 or higher	No/Yes	No	No*
Grade 2 or higher	No/Yes	Yes	Yes, as AE or linked to an already reported AE

*in this situation, this abnormal lab test result is either a manifestation of a concomitant disease or of an already reported AE.

§ grade increase in this context means the value is higher than the one from the screening visit.

In general, laboratory values will be recorded as “increased <lab parameter>” or “decreased <lab parameter>” to ensure consistency of recording/coding.

8.4.2 Reporting other abnormal findings

The other abnormal findings (except abnormal results of laboratory tests) discovered during different clinical assessments (e.g., ECG, spirometry, physical examination, vital signs, body weight) should be evaluated for the clinical significance by the Investigator/designee based on

his/her medical judgement. All abnormal clinical significant test results or clinical examination findings can, at the discretion of the Investigator, be reported as AEs and handled according to the directions from Section 8.2.

8.5 Reporting and Follow-Up of Pregnancies

8.5.1 Period of Collection and Follow-up

In case of pregnancies detected between the time of signature of the ICF and enrollment of the subject, the subject will be considered as a screening failure. In that situation, the pregnancy will not be reported to the Sponsor, however, the identified pregnancy(ies) must be captured in the screening failure CRF. No pregnancy form will be filled.

In case of pregnancies detected between enrollment and prior to randomization, subject will be discontinued, and reported as "enrolled but not randomized" subject. Early termination procedures shall apply. No pregnancy form will be filled.

Any pregnancy detected after randomization must be reported by the Investigator within 24 hours. This also includes pregnancies spontaneously reported to the Investigator after the end of the study for a subject.

Any pregnancy that was potentially associated with exposure to IP (*IQOS* or cigarette) will be followed-up until an outcome is reached (e.g., normal delivery, spontaneous abortion, or voluntary termination) and also until 8 weeks after delivery.

Any pregnancy complication, adverse pregnancy outcome or maternal complications will be recorded as an AE accordingly.

8.5.2 Reporting of Pregnancies

A dedicated pregnancy form will be used to report pregnancy cases.

The procedure to report a pregnancy and provide any additional/follow-up information to UBC Pharmacovigilance and Sponsor is the same and performed within the same timelines as the one described for an SAE (Section 8.3).

The Investigator is responsible for informing the corresponding IEC of any pregnancy case that was reported during the study, as determined by local regulations.

8.6 Adverse Events Leading to Discontinuation

Subjects who are discontinued from the study because of an AE will undergo the early termination procedures (Section 9.6), as soon as practical after discontinuation, and will enter the 28-day safety follow-up period. In general, AEs will be followed-up until resolved,

stabilized (i.e., no worsening of the event), or a plausible explanation has been found and until the end of the study. Any AEs or SAEs that are ongoing at the end of the safety follow-up period will be managed as described in Section 8.2.6.

8.7 Investigational Product Malfunction and Misuse

Any occurrences of device events, including *IQOS* malfunction (e.g., holder does not charge when inserted into the charger) or misuse by a subject (use not in accordance with its label and instructions), will be documented by the Investigator or his/her designee using a device issue log.

Investigational product misuse may result in use-related hazards (Section 2.3.4).

Furthermore, any misuse or malfunction of *IQOS* that leads to an AE/SAE will follow the same processes as described above for the reporting of the AE/SAE.

9 STUDY ACTIVITIES

The procedure can be performed at any time during the visit, unless otherwise specified. Assessments will be conducted only by qualified and trained site personnel.

9.1 Screening

The screening visit can be performed on more than one day but has to be completed (including safety laboratory results) within 28 days prior to V2. The sequence of assessments/events before VO_2max test is given for illustrative purposes. The VO_2max test should only be performed after all clinical assessment have been performed and the subject is judged healthy without any contraindication to perform exercise testing as per the Investigator's judgement. If the inclusion and exclusion criteria are satisfactorily met, the site staff will contact the subject to arrange his/her next visit (V2) to the site.

Table 5 shows the procedures that will be performed at V1:

Table 5 Time Schedule – V1

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V1**	
		Informed consent for study participation	Including section on optional participation in sub-study interviews
After ICF signature		Informed consent for biobanking	Optional
		Information on the risk of smoking, smoking cessation advice and debriefing on *IQOS*	
		Demographic data collected (sex, date of birth/age, and race)	
		Medical history/concomitant disease	
		Prior medication (within 4 weeks prior to V1) and concomitant medication	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V1**	
		Questionnaire on tobacco and nicotine containing product use history and habits to assess smoking history	
		IPAQ-short	
		Vital signs (blood pressure, pulse rate, respiratory rate)	After resting for at least 5 minutes in supine position
		Collection of spot urine for: • Urinalysis safety panel • Urine drug screen • Urine cotinine test • Urine pregnancy test	
	√	Clinical laboratory parameters (hematology, clinical chemistry)	
	√	Serology (HIV, hepatitis B and C)	
		Physical examination	
		Height, weight, calculation of BMI	
		IQOS demonstration	Without product use
		mHealth wearable demonstration	
		Alcohol breath test	
		CO breath test	
		Spirometry	Has to be done at least 1 hour after smoking After resting in sitting position for at least 15 minutes prior to testing.
		ECG	After resting for at least 10 minutes in supine position prior to recording.

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V1**	
After having performed all clinical assessments		VO_2max test	Exercise testing should be performed at least 30 min after spirometry assessments. VO_2max and the work produced will be recorded. After completing the test water will be provided *ad libitum*.
		AE/SAE recording	At any time during the day. If the V1 is performed on two separate days, the AE/SAE questions will be asked again
		Readiness to comply with study procedures	
		Inclusion/exclusion criteria check	

Abbreviations:

AE = Adverse event; BMI = Body mass index; CO = Carbon monoxide; ECG = Electrocardiogram; HIV = Human immunodeficiency virus; IPAQ= International Physical Activity Questionnaire; SAE = Serious adverse event.

9.2 Enrollment and Familiarization with Exercise Test

Visit 2 (V2) will be scheduled 7±1 days prior to V3 (randomization).

Table 6 shows the procedures that will be performed at V2.

Table 6 Time Schedule – V2 Enrollment and Exercise Capacity Test

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V2**	
Prior to enrollment		Collection of spot urine for: • Urine cotinine test • Urine drug screen • Urine pregnancy test	Confirmation of eligibility. Has to be done in the morning prior to enrollment
		Confirmation of smoking status by CO breath test.	
		Alcohol breath test	
		Enrollment	
After enrollment		Vital signs (blood pressure, pulse rate, respiratory rate)	After resting for at least 5 minutes in supine position
		Information on the risk of smoking, smoking cessation advice	
		Exercise capacity test – bike ergometer	Work to complete will be based on the highest wattage level reached during VO_2max test during V1. After completing the test water will be provided *ad libitum*.
		mHealth wearable kit distribution and training on how to wear, handle and charge the device	
		Product use diary distribution	
		Concomitant medication	
		AE/SAE recording	At any time during the day.

Abbreviations:
AE = Adverse event; CO = Carbon monoxide; SAE = Serious adverse event.

During the 7±1 days between V2 and V3, subjects having signed the optional section of the ICF will have an interview (by phone or computer) on the topic of health and functioning lasting around 60 minutes.

9.3 Baseline and Randomization

Table 7 shows the procedures that will be performed at V3. All baseline assessments should be performed before randomization.

Table 7 Time Schedule – V3 Baseline

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V3**	
		Urine pregnancy test	
Before breakfast/ snack	√	Clinical laboratory parameters (hematology, clinical chemistry and urinalysis)	At least 8 hours of fasting Hematocrit and Hemoglobin results will also be used to calculate blood volume
	√	Biological health markers	At least 8 hours of fasting
	√	Biobank blood collection	Only if optional ICF signed At least 8 hours of fasting
		Breakfast/Snack	
		Biobank saliva and sweat collection	Only if optional ICF signed
		FTND questionnaire	
		Lifestyle questionnaire	
		RPC scale	
		Vital signs (blood pressure, pulse rate, respiratory rate)	After resting for at least 5 minutes in supine position
		ECG	After resting for at least 10 minutes in supine position prior to recording.
		Physical examination	
		Weight, body fat percentage and waist circumference	
		Cough assessment questionnaire (VAS scale, and 3 Likert scales)	
		CO breath test	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V3**	
30-60 min before VO_2max test		Smoke a cigarette	Only subjects willing to
After all clinical assessments		VO_2max test	HR and VO_2 will be recorded at rest and at each 25W increase
During VO_2max test		Borg RPE scale	At rest and at each 25W increase
During VO_2max test	√	Capillary blood lactate sampling to measure lactate levels	At rest and at each 25W increase
Before start of exercise capacity		Snack and water *ad libitum*	Snack to be consumed at least 30 min before start of exercise capacity test
60±5min after VO_2max test		Exercise capacity test – bike ergometer	Work to complete will be based on the highest wattage level reached during VO_2max test at V3. After completing the test water will be provided *ad libitum*.
After exercise capacity test Before CO-rebreathing	√	COHb	Results will be used to assess 1) CO exposure and 2) to calculate blood volume
After exercise capacity test	√	Determination of blood volume by CO-rebreathing	Blood will be sampled after CO-rebreathing for COHb determination
As late as possible during the day/visit		Spot urine collection for urinary exposure markers and biobanking	Collection of urine for biobanking only if optional ICF signed
		Concomitant medication	
		AE/SAE recording	At any time during the day.
Before randomization		Product preference question	As an instruction to answer this question, subjects will be informed that their response will not influence the randomization process.

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V3**	
		Randomization ***IQOS*-1 and *IQOS*-2 arms:** Distribution of IOQS starter kit to subjects randomized into and training on how to use the device. **SA arm**: Upon subject's request provision of NRT	

Abbreviations:

AE = Adverse event; CO = Carbon monoxide; COHb = Carboxyhemoglobin; ECG= Electrocardiogram; FTND = Fagerström Test for Nicotine Dependence (revised version); HR = Heart rate; NRT = Nicotine Replacement theray; RPC = Rating of Perceived Capacity; RPE = Rate of Perceived Exertion; SAE = Serious adverse event; VAS = Visual analogue scale

9.4 Exposure Period

9.4.1 Acute Effect Exercise Tests

Visit 4 (V4) will be scheduled up to 7±2 days after V3.

Table 8 shows the procedures that will be performed at V4:

Table 8 Time Schedule – V4 Acute Effect

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V4**	
		Vital signs (blood pressure, pulse rate, respiratory rate)	After resting for at least 5 minutes in supine position
	√	COHb	
		RPC scale	
		Weight, body fat percentage and waist circumference	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V4**	
		CO breath test	
30-60 min before VO_2max test		Subjects in *IQOS*-1 and *IQOS*-2 arms will use a HeatStick. Subjects in cigarette arm will smoke a cigarette.	Only subjects willing to.
		VO_2max test	HR and VO_2 will be recorded at rest and at each 25W increase HR at rest and maximal HR during VO_2max test will be recorded and used to set exercise training program intensities. Maximal work rate during VO_2max test will recorded and used to assess the work rates during exercise training program.
After VO_2max test		Snack and water *ad libitum*	Snack to be consumed at least 30 min before start of exercise capacity test.
60±5min after VO_2max test		Exercise capacity test – bike ergometer	Work to complete will be based on the highest wattage level reached during VO_2 max test at V3. After completing the test water will be provided *ad libitum*.
As late as possible during the day/visit		Spot urine collection for urinary exposure markers	
		Concomitant medication	
		AE/SAE and device event recording	At any time during the day.

Abbreviations:

AE = Adverse event; CO = Carbon monoxide; COHb = Carboxyhemoglobin; HR = Heart rate; RPC = Rating of Perceived Exertion; SAE = Serious adverse event.

9.4.2 Exercise Training Program

7±1 days after V4 all subjects besides those who are randomized to the *IQOS*-2 (no training) arm, will start a 12-week exercise training program, from V5 (15±2 days after V3) until V42 (99±2 days after V3) .

Subjects will attend trainings sessions 2-4 times per week and three different training programs will be circulated as described in Appendix 2. All trainings will be performed indoor on stationary bikes.

Subjects in the *IQOS*-2 arm will only attend V5, V7, V9, V14, V16, V19, V23, V28, V30, V33, V35 and V39 but not for training sessions.

Table 9 shows the procedures that will be performed at each training from V5 to V42.

Table 9 Time Schedule – ExerciseTrainings V5 to V42

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V5-V42**	
Before training		Urine pregnancy test	**V5 only**
Before training		Weight	
Before training		CO breath test	
30-60 min before the training		Subjects in *IQOS*-1 and *IQOS*-2 arms will use a HeatStick. Subjects in cigarette arm will smoke a cigarette	Only subjects willing to
		40-min bike exercise training	As per training program schedule in Appendix 2. The training intensity will be adapted for each subject based on the resting and maximal HR.
		Concomitant medication	
		AE/SAE and device event recording	At any time during the day.

Abbreviations:
AE = Adverse event; CO = Carbon monoxide; HR = Heart rate; SAE = Serious adverse event.

Table 10 describes the procedures that will be performed at medical visits after 4-week and 8-week of the training program. For subjects in *IQOS*-1, cigarette and SA arms medical assessments will be performed in conjunction with the training session on V14 and V28. Subjects in the *IQOS*-2 arm will attend these visits for medical assessments only.

V14 and V28 will be scheduled in the end of the 4th week (40±2 days after V3) and 8th week (68±2 days after V3) of the training program, respectively.

Table 10 Time Schedule – Medical Visits V14 and V28

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V14 and V28**	
		Urine pregnancy test	
Before breakfast/ snack	√	Clinical laboratory parameters (hematology, clinical chemistry and urinalysis)	At least 8 hours of fasting
	√	Biological health markers	At least 8 hours of fasting
	√	Biobank blood collection	Only if optional ICF signed At least 8 hours of fasting
		Breakfast/snack	
		Biobank saliva collection	Only if optional ICF signed
		Weight	
		Vital signs (blood pressure, pulse rate, respiratory rate)	After resting for at least 5 minutes in supine position
	√	COHb	
		ECG	After resting for at least 10 minutes in supine position prior to recording.
		Physical examination	
		CO breath test	
		Cough assessment questionnaire (VAS scale, and 3 Likert scales)	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V14 and V28**	
As late as possible during the day/visit		Spot urine collection for urinary exposure markers and biobanking	Collection of urine for biobanking only if optional ICF signed
		Information on the risk of smoking, smoking cessation advice	
		AE/SAE and device event recording	At any time during the day.
		Concomitant medication	

Abbreviations:

AE = Adverse event; CO = Carbon monoxide; COHb = Carboxyhemoglobin; SAE = Serious adverse event; VAS = Visual Analogue Scale

During the 7±1 days between V42 and V43, subjects having signed the optional section of the ICF will have an interview (by phone or computer) on the topic of health and functioning lasting around 60 minutes.

9.4.3 Training Effect Exercise Tests

Visit 43 (V43) will be scheduled 106±2 days after V3, and 7±2 days after V42.

Table 11 shows the procedures that will be performed at V43

Table 11 Time Schedule – V43 Training Effect Exercise Tests

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V43**	
Before breakfast/ snack	√	Biological health markers	At least 8 hours of fasting
	√	Biobank blood collection	Only if optional ICF signed At least 8 hours of fasting
		Breakfast/snack	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V43**	
		Biobank saliva and sweat collection	Only if optional ICF signed
		Vital signs (blood pressure, pulse rate, respiratory rate)	After resting for at least 5 minutes in supine position
		Weight,body fat percentage and waist circumference	
		RPC scale	
		CO breath test	
30-60 min before VO_2max test		Subjects in *IQOS*-1 and *IQOS*-2 arms will use a HeatStick. Subjects in the cigarette arm will smoke a cigarette.	Only subjects willing to.
After all clinical assessments		VO_2max test	HR and VO_2 will be recorded at rest and at each 25W increase
During VO_2max test		Borg RPE scale	At rest and at each 25W increase
During VO_2max test	√	Capillary blood lactate sampling to measure lactate levels	At rest and at each 25W increase
After VO_2max test		Snack and water *ad libitum*	Snack to be consumed at least 30 min before start of exercise capacity test
60±5min after VO_2max test		Exercise capacity test – bike ergometer	Work to complete will be based on the highest wattage level reached during VO_2max test at V3. After completing the test water will be provided ad libitum.
After exercise capacity test Before CO-rebreathing	√	COHb	Results will be used to assess 1) CO exposure and 2) to calculate blood volume
After exercise capacity test	√	Determination of blood volume by CO-rebreathing	Blood will be sampled before CO-rebreathing to for Hematocrit and Hemoglobin and after CO-rebreathing for COHb determination

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V43**	
As late as possible during the day/visit		Spot urine collection for urinary exposure markers	
		Return of *IQOS* device	
		Return of mHealth wearable	
		Return of product use diary	
		Concomitant medication	
		AE/SAE and device event recording	At any time during the day.

Abbreviations:

AE = Adverse event; CO = Carbon monoxide; HR = Heart rate; RPC = Rating of Percieved Capacity; RPE = Rate of Exertion; SAE = Serious adverse event.

Visit 44 (V44) will be scheduled 107±2 days after V3. Table 12 shows the procedures that will be performed at V44.

Table 12 Time Schedule – V44 Discharge Safety Assessments

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V44**	
		Urine pregnancy test	
Before breakfast/ snack	√	Clinical laboratory parameters (hematology, clinical chemistry and urinalysis)	At least 8 hours of fasting
		Information on the risk of smoking, smoking cessation advice and debriefing on *IQOS*	
		Cough assessment questionnaire (VAS scale, and 3 Likert scales)	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V44**	
		Vital signs (blood pressure, pulse rate, respiratory rate)	After resting for at least 5 minutes in supine position
		Physical examination	
		Spirometry	Has to be done at least 1 hour after smoking After resting in sitting position for at least 15 minutes prior to testing.
		ECG	After resting for at least 10 minutes in supine position prior to recording.
		Concomitant medication	
		AE/SAE recording	At any time during the day.

Abbreviations:
AE = Adverse event; CO = Carbon monoxide; SAE = Serious adverse event.

9.5 Safety Follow-Up Period

After the procedures of discharge or at the time of early termination, subjects will enter a 28-day safety follow-up period during which new AE/SAEs spontaneously reported by the subject and concomitant medication used as treatment for AE/SAEs will be recorded. The follow-up of ongoing AEs/SAEs will be conducted by the study investigational site as described in Section 8.2.6.

9.6 Early Termination Procedures

The following early termination procedures will be performed if a subject is discontinued from the study unless the subject refuses to perform the assessments:

- AE/SAE recording
- Device event recording
- Concomitant medications
- Clinical laboratory parameters (hematology, clinical chemistry, and urinalysis safety panel)

- Physical examination
- Spirometry
- Urine pregnancy test
- Vital signs
- ECG
- Information on the risk of smoking, smoking cessation advice, and debriefing on *IQOS*
- Return of *IQOS* device, mHealth wearable and product use diary.

Safety laboratory (hematology and clinical chemistry) may be done in non-fasting or fasting state. If subjects withdraw from the study or are discontinued during a planned visit, assessments required as per protocol for early termination that have been already performed during the planned visit should not be conducted again.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

The Clinical Research Associate ("Monitor") will be responsible for the monitoring of the study. Monitoring will be performed according to CRO's Standard Operating Procedures (SOPs) and as per the agreed monitoring plan with the Sponsor.

The Investigator shall permit the Monitor to review study data as frequently as considered necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator shall access medical records for the Monitor in order that entries in the CRFs may be verified. The Investigator, as part of their responsibilities, is expected to ensure that the study adheres to GCP requirements.

An Investigator's meeting will be held prior to the site initiation visit. During this meeting, the general training of the study procedures and specific training on selected procedures will be done and documented.

Subsequent to the Investigator's meeting, and before the first subject is screened into the study, site initiation visit will be conducted by the Monitor and, if necessary, with the Sponsor or its authorized representative. The purpose of the site initiation visit will be detailed in the monitoring plan.

Communication by telephone, mail, and e-mail may be used as needed to supplement site visits. The Investigator and study personnel will cooperate with the Monitor, provide all appropriate documentation, and will be available to discuss the study.

The Monitor and the Sponsor's personnel will be available between visits, should the Investigator or other study collaborator at the sites need information and advice. Site visits will be made at regular intervals during the study. The frequency of the monitoring visits will be defined in the monitoring plan agreed with the Sponsor.

The Investigator, or a designated member of the Investigator's study collaborator, must be available during the monitoring visit to review the data and resolve any queries, and to allow direct access to the subject's records for source data verification.

10.2 Training of Collaborators

A formal meeting (Investigator meeting) will be conducted prior to site initiation. During this meeting, the Sponsor or its authorized representative will discuss the requirements of the clinical study protocol and related documents and will also provide training in the relevant

systems and other study-specific procedures. The activities of the Investigator meeting will be described in the monitoring plan.

In addition to the Investigator meeting, the Investigator will ensure that appropriate training relevant to the study is provided to all study collaborators involved in the study, and that any new information relevant to the performance of this study is forwarded to the study collaborator involved in a timely manner. The record of all individuals involved in the study will be maintained in the Site Investigator File.

10.3 Audits and Inspections

Good Clinical Practice regulations require that there are independent inspections of clinical program activities. Such inspections may be performed at any time before, during and/or after the study.

Authorized representatives of the Sponsor, regulatory agencies and/or the IEC may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP guidelines, and any applicable regulatory requirements. The Investigator will contact the Sponsor or the authorized representative immediately, if contacted by a regulatory agency about an inspection at their site.

The Investigator and study collaborator are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its authorized representative, and/or regulatory agencies. In signing this protocol, the Investigator understands and agrees to provide access to the necessary documentation and files.

11 DATA MANAGEMENT ACTIVITIES

All Data Management activities will be described in detail in the Data Management Plan (DMP) and documents specified therein.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

Data Collection Procedures:

The results from the clinical assessments will be recorded in the source data file by the Investigator or their authorized designee and then captured in the CRFs.

Trained study personnel will be responsible for capturing the data from the observations, tests, and assessments specified in the protocol and in the source documents, and transferring the data to the CRF according to the CRF Completion Guidelines.

The Investigator has ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. The CRF must be signed by the Investigator to attest that the data contained on the CRF are true and accurate. Any corrections made to source documents must be clearly recorded, without obscuring the original values and be accompanied by the date of change, reason for change, and identification of the person making the change. The CRF data will be verified against the source documents at the study site by the clinical research associate. Instances of missing or unclear data will be discussed with the Investigator for resolution.

11.1.2 Protocol Deviations

All protocol deviations will be entered into the Clinical Trial Management System (CTMS) or other approved format.

Information from the source documents will represent the primary source of protocol deviations. Information following site monitoring and other manual reviews will be documented in the site visit reports, follow-up letters, audit documentation, or other manual review and will be recorded and tracked in the CTMS or other approved format. Telecommunications and other verbal communications regarding deviations will be considered and handled as important communication, and documented and tracked as protocol deviations, as necessary.

Individual entries for protocol deviations that are recorded in the CTMS, or other approved format, following site monitoring and other manual reviews will be reviewed against the individual data points in the CRF database but will not be formally reconciled with the CRF database (e.g., their description or occurrence date). The overall procedures for managing

protocol deviations are described in the SOPs of the CRO Data Management Team. All deviations will be reviewed periodically, as determined at study start, to identify trends to improve monitoring and/or potential impact on the statistical analysis.

11.2 Data Handling

All study data will be managed by the Data Management Team at the CRO. The overall procedures for quality assurance of clinical study data are described in the SOPs of the CRO Data Management Team. The Data Management Team at CRO will prepare a DMP, to be reviewed and approved by the Sponsor, prior to the start of the study. This document will describe, in detail, the Data Management related procedures and processes.
All data of all subjects enrolled and screening failures who experience an AE during the study (from time of informed consent) will be captured. All data collected during the study is property of the Sponsor irrespective of the location of the database and the Data Management CRO.

11.2.1 Data Validation

The data will be validated as defined in the DMP and Data Validation Specifications. Discrepancies will be reported as defined in DMP and Data Validation Specifications.
Data queries will be raised for discrepant or missing data. All changes to data will be captured in the database with a comprehensive audit trail.

11.2.2 Coding

AEs, medical/surgical history, and prior/concomitant medication will be classified according to the terminology of the latest version of the following Dictionaries, at time of coding the first entry:

Medical history:	Medical Dictionary for Regulatory Activities (MedDRA®)
Adverse events / Procedures:	MedDRA®
Medications:	WHODrug Global
IQOS device issues and/or malfunctions:	C54451/Medical_Device_Problem_Codes_FDA_CDRH

11.2.3 Database Lock

When all outstanding Data Management issues have been resolved and all validation, quality review, and cleaning activities are complete, the database or selected data is/are declared soft locked. Access to change data in the soft-locked database or to change selected data at this time is limited.

After the data is reviewed by the Sponsor, resolution of all raised queries and QC of the changed data, database, or selected data upon Sponsor approval as applicable, is declared locked.

Any changes to the database after that time can only be made by written agreement between the Sponsor and the Data Management and Statistical Teams at the CRO. Any of those changes must be documented in the database log file.

After study completion, the study database will be transferred to the Sponsor in the format specified in the DMP and compliant with CDISC Study Data Tabulation Model (SDTM).

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Full details of the statistical analysis will be given in the Statistical Analysis Plan (SAP). Any changes to the planned statistical methods will be documented in the study report. The statistical evaluation will be performed using SAS®, version 9.2 or later.

12.1.1 Stratification Criteria

For the analysis of VO_2max and exercise capacity, the following stratification criteria will be used:

- Cigarette consumption at V1 (10 to 19 cigarettes, more than 19 cigarettes per day)
- Sex (male, female)

Additional stratified presentations (e.g. for demographic data by age and BMI) will be defined in the SAP.

12.1.2 Definitions for Statistical Data Analysis

In general, baseline value for any given variable will be the last assessment prior to randomization for the subjects randomized to either *IQOS*, cigarette or SA arms. Further details will be described in the SAP.

12.1.3 Descriptive Statistics

Descriptive statistics for continuous variables will include the number of subjects, number and percent of subjects with missing data, the mean and standard deviation, geometric means and coefficient of variation (CV), median, first and third quartiles, minimum and maximum, and 95% confidence interval (CI; based on a t-distribution if not otherwise stated) on the mean for each product use group, and summary across all subjects. For categorical variables descriptive statistics will provide the number of observations, absolute frequencies, and relative frequencies (percentages) of the observed values. In addition, the results may be presented as a stratified summary as defined in the SAP.

12.1.4 Handling of Missing Values and of Values outside the Detection or Quantification Limits

For laboratory parameters outside the limit of detection or quantification, the following imputation will be performed:

- Values below the lower limit of detection (LLOD) or quantification (LLOQ) will be imputed as 0.5 x LLOD or LLOQ.
- Values above the upper limit of detection (ULOD) or quantification (ULOQ) will be imputed as the ULOD or ULOQ.

The number of values below LLOD (or LLOQ) or above ULOD (or ULOQ) will be presented in each summary table, as well as the statistics on the other quantitative values.

However, if 50% or more data are below the lower limit or above the upper limit, only the number of values below the lower limit and above the upper limit will be reported in the summaries, together with minimum (if no value below the lower limit is present) and maximum (if no value above the upper limit is present) of the observed values, and no other statistics will be reported.

There will be no imputation of missing laboratory parameters.

For mHealth parameters that are missing:

- There will be no imputation and all available data will be analyzed as is.

12.1.5 Significance Level for Inferential Analysis

This study is of exploratory in nature and therefore no statistical hypothesis will be tested.

12.2 Determination of Sample Size and Power Consideration

The sample size of 20 per arm (smoking abstinence with training, *IQOS* with training, continued cigarette smoking with training) was determined based on previously published results, which reported a standard deviation of 14 mL/kg/min in VO_2max in the change between groups which continued smoking and those who were smoking abstinent after participating in a 12-week training program (2). This sample size allows a probability of 90% that the half-width of the 95% confidence intervals between two arms have a precision of approximately 10.3 mL/kg/min. For example, if the mean difference in change between the cigarette arm and smoking abstinence arm was 12 mL/kg/min after training, we expect that if the experiment were repeated many times then on average 90% of the time the 95% confidence intervals of the mean differences between two arms will be within 1.7 and 22.3. To allow for a dropout rate of approximately 20%, the sample size will be 25 per arm. The *IQOS*-2 arm without training will mainly serve as a secondary analysis to the *IQOS*-1 arm with training, and the drop-out rate in this arm is expected to be lower. Therefore, only 15 subjects will be randomized to this arm.

12.3 Product Use

Although subjects are being requested to use solely the product allocated to their respective study arm, it is considered that not all subjects randomized to the *IQOS* arms or to the cigarette arm will exclusively use the randomized product at all times during the study. Subjects may concomitantly use *IQOS* and cigarettes (dual use). To account for dual use of IOQS and cigarettes, adjustments for cigarette or *IQOS* use outside of the intended arms will be done statistically. Similarly, it is expected that subjects in the SA arm who should stay abstinent during the study may relapse to the use of tobacco or nicotine-containing tobacco products (e.g., cigarette or *IQOS*).

Actual product use exposure within an analysis period will be categorized based on self-reporting; further details will be provided in the SAP.

12.4 Analysis Populations

The main population for non-safety analysis will be the As Exposed Exercise Compliant Set. Safety will be analyzed using the Safety Set.

12.4.1 As Exposed Exercise Compliant Set

The As Exposed Exercise Compliant Set (AEECS) consists of all randomized subjects who have at least one valid non-safety assessment after randomization, specifically we have

- post-randomization product (cigarette or *IQOS*) use experience if randomized to *IQOS*, *IQOS*-2 or cigarette arm or
- no product use if randomized to the SA arm,

and who attended at least 34 of 38 (~90%) of the exercise training sessions except the subjects in *IQOS*-2 arm. The AEECS will be analyzed by actual exposure (product use exposure).

12.4.2 Full Analysis Set

The Full Analysis Set (FAS) consists of all randomized subjects who have at least one post-randomization product (cigarette or *IQOS*) use experience if randomized to *IQOS*, *IQOS*-2 or cigarette arm, and who have at least one valid non-safety assessment after randomization. All subjects in the SA arm who fulfil these requirements, except the product use experience, are part of this set as well. The FAS will be analyzed by randomized study arm.

12.4.3 Safety Set

The Safety Set consists of all subjects enrolled with signed ICF who have at least one valid safety assessment during the course of the study. The Safety Set will be analyzed by actual exposure (product use exposure).

12.5 Endpoint Analysis

To evaluate changes in VO_2max in subjects switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent.

A linear mixed effects model will be used to estimate the difference in VO_2max between each arm (SA arm, *IQOS*-1 arm) versus cigarette arm one week after randomization (V4) and after completion of the 12-week training program (V43). The dependent variable will be the VO_2max with baseline VO_2max, arm, sex, age and baseline cigarette consumption as covariates. Self-reported cigarette consumption and/or *IQOS* use will be added as a covariate as well. Appropriate contrasts will be constructed to report an estimate of the VO_2max and its 95% confidence intervals within each arm and also between SA arm, *IQOS*-1 arm vs cigarette arm. The comparison between SA vs *IQOS*-1 arm will be calculated as well.

To estimate the difference in VO_2max between *IQOS*-2 and other arms, the same model will be used to model the change between arms only at V43.

Other covariates may be added as deemed appropriate. The same analysis will be repeated for weight-adjusted and fat-free weight adjusted VO_2max. Estimates of variability from the statistical model will be reported and may be used to power future similar studies.

To evaluate changes in exercise capacity in subjects switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent

The linear mixed effects model as described above for VO_2max will be used to estimate the difference in exercise capacity between the *IQOS*-1 or SA arm versus cigarette arm one week after randomization (V4) and after completion of the 12-week training program (V43). The dependent variable will be the time to complete the test in seconds with baseline exercise capacity (in seconds) as a covariate.

Other covariates may be added as deemed appropriate. Estimates of variability from the statistical model will be reported and may be used to power future similar studies.

To assess the intensity of the exercise training in subjects switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent

An appropriate statistical model will be used to estimate the intensity of exercise training in the various (cigarette, *IQOS*-1 and SA) arms over time. The exercise intensity will be the endpoint with baseline exercise intensity, age, visit, sex and arm as covariates. Self reported

cigarette consumption and/or *IQOS* may also be used as a covariate. Further details will be provided in the SAP.

Estimates of variability from the statistical model will be reported and may be used to power future similar studies.

Descriptive statistics will be used to present various measures assessing the intensity of exercise training in each arm. This includes the cumulative work produced (calories and calories/kg body weight)), average work rate during each training session (watt and watt/kg body weight), average work rate during each interval during each training session (watt and watt/kg body weight), time spent at 0-50%, 50-65%, 65-75%, 75-90%, >90% of maximal work rate during each training session (min:sec), average heart rate (HR) during each training session (bpm) and time spent at 0-50%, 50-60%, 60-70% , 70-80 % and >80 % of maximal HR during each training session (min:sec).

To evaluate changes in physiological parameters and perception of exertion and capacity in subjects switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent

An appropriate statistical model will be used to estimate the differences in physiological parameters and perception of exertion and capacity whilst adjusting for covariates such as age, sex, cigarette consumption and/or *IQOS* use or any other clinically relevant covariates of interest. The difference between arms (*IQOS*-1/SA vs cigarette) will be estimated and reported together with its 95% confidence intervals. All other pairwise comparisons between arms will be estimated and reported as well.

To monitor trends of daily physical activity levels during the study in subjects switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent

Descriptive statistics of the various measures of physical activity as measured by the mHealth wearable device will be reported. An appropriate statistical (linear or non-linear) model will be used to estimate the levels of activity taking into account clinically relevant covariates such as sex, cigarette consumption and age, and repeated measures over time. Estimates for each arm and all pairwise comparisons between arms will be reported using an appropriate statistical model as defined in the SAP.

To describe changes in biological health markers in subjects switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent

For each of the biological markers descriptive statistics will be employed to assess the changes from baseline for each arm. An appropriate (linear or non-linear) statistical model may be employed to estimate differences across arms at V14, V28 and V43. Covariates such as age, sex, cigarette consumption and/or *IQOS* use or any other clinically relevant covariates of interest will be adjusted statistically and further defined in the SAP.

To describe changes in weight, body fat and waist circumference in subjects switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent

For weight, body fat and waist circumference, descriptive statistics will be employed to assess the changes for each arm. An appropriate statistical model may be employed to estimate differences across arms at V4 and V43. Covariates such as age, sex, cigarette consumption and/or *IQOS* use or any other clinically relevant covariates of interest will be adjusted statistically and further defined in the SAP.

To monitor levels of exposure to CO, nicotine, nitrosamines and acrylonitrile in subjects switching to *IQOS*, continuing to smoke cigarettes and being smoking abstinent

Descriptive statistics of exhaled CO will be summarized and presented for each arm. An appropriate statistical model may be employed to estimate differences across arms at the end of the study. Covariates such as age, sex, cigarette consumption and/or *IQOS* use or any other clinically relevant covariates of interest will be adjusted statistically and further defined in the SAP. Descriptive statistics of COHb% in blood, NEQ, NNAL and CEMA in urine will be summarized and presented for each arm. An appropriate statistical model may be employed to estimate differences across arms during the visits where these are measured.

In the paragraphs above we mention “any other clinically relevant covariates of interest”. This may for example refer to spot urine concentrations of CEMA adjusted for creatinine that may be considered as a covariate because they serve as biochemical verification of product use or smoking abstinence. The self reported cigarette use of each subject may be used in addition to CEMA. A subject’s product preference prior to randomization may also be used as a clinically relevant covariate of interest.

Safety endpoints collected during the course of the study will be reported and details will be given in the SAP.

12.6 Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be summarized as reported in Section 12.1.3 for the Full Analysis Set. Summaries will also be provided for other analysis sets if they differ from FAS and each other. There will be no formal comparison of baseline data, that is, no statistical hypothesis testing will be performed.

12.7 Interim Analysis

No interim analysis will be performed for this study.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigator's and Study Administrative Structure

13.1.1 Investigator

Investigator:	Dr. med. Dr. rer. nat. Armin Schultz [redacted]

13.1.2 Sponsor

Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland Tel: +41 58 242 2111 Fax: +41 58 242 2811
[redacted] Clinical Scientist	Phone: +41 [redacted] E-mail: [redacted]
[redacted] Biostatistician	Phone: +41 [redacted] E-mail: [redacted]
[redacted] Medical Safety Officer	Phone: +41 [redacted] E-mail: [redacted]

13.1.3 Other Responsibilities

Any SAEs or pregnancies will be handled by:

[redacted]
Switzerland.
Phone: +41 [redacted]
Fax: +41 [redacted]
E-mail: [redacted]

Any SAEs or pregnancies will be handled as per the instructions listed in Section 8.3.

13.2 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects and state of their health will be regarded as confidential. A statement to this effect will be written in the information provided to the subject. An agreement to disclose any such information will be obtained from the subjects in writing and signed by the subject, in compliance with all applicable data protection and privacy legislation.

The anonymity of subjects participating in this study will be maintained. Subjects will be identifiable by the Sponsor (or Sponsor's authorized representative) on CRFs and other documents by their subject (or randomization) number/code, sex and date of birth, but not by name, initial, or any other details relating to identifiable person (*e.g.*, address, health insurance ID card, medical chart number, etc.). The assignment of a subject number/code for subject identification will be based on the appropriate data protection rules.

Any documents that allow full identification of the subject (*e.g.*, the subjects's signed study participation ICF) must be maintained in confidence by the Investigator. If any document relating to this study shows a subject's name or any other details relating to an identifiable person (*e.g.*, address, health insurance ID card, medical chart number, etc.), the name or other identifiable details must be obscured before a copy of that document is supplied to the Sponsor or the Sponsor's authorized representative.

13.3 Access to Source Documentation

Subjects will be informed that, during the course of the clinical study, the Sponsor, any authorized representatives of the Sponsor, IEC, or regulatory authorities may inspect their medical records to verify the information collected, and ensure that all personal information made available for inspection is handled in the strictest confidence and in accordance with applicable data protection and privacy legislation.

The Investigator and all study site collaborators involved with the study must permit direct access to source data/documents for study related monitoring, audits, IEB review, and regulatory inspection(s).

13.4 Record Retention

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, are described in Section 8 of the ICH GCP Guidelines (3).

Essential documents must be retained by the Investigator for a minimum of:

- At least 15 years after completion or discontinuation of the study.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

Examples of essential records/documents include, but are not limited to:

- Signed informed consent documents for all subjects and study participation ICF.
- Subject identification code list, Screening Log and Enrollment Log (if applicable).
- Record of all communications between the Investigator and the IEC, composition of the IEC.
- Record of all communications/contact between the Investigator, Sponsor, and its authorized representatives.
- List of sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study.
- Investigator Logs.
- CRFs, study specific questionnaires (and associated data/scoring), subject diaries.
- AE reports and details of follow-up investigations, details of concomitant medication.
- All other source documents or any electronically captured study source data.
- Original medical/hospital records, if applicable (the medical files of study subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital or investigational site).
- Record of any body fluids or tissue samples collected and retained.

- Device Issue Log, IP Accountability Logs, dispensing records.
- Information regarding subjects' discontinuation and any follow-up.

It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained.

The Investigator must take measures to prevent accidental or premature destruction of these documents.

If the Investigator wishes to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

The Investigator must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, they must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements must be documented.

The Sponsor or Sponsor's authorized representative will maintain documentation relating to the study as long as the IP is on the market, and/or for 15 years after the CSR has been finalized.

13.5 Clinical Study Report

The Sponsor must ensure that a CSR for this study is prepared regardless of whether the study is completed or prematurely terminated.

The CSR will be written based on standards of the ICH Guideline for the Structure and Content of Clinical Study Reports. In certain circumstances, an abbreviated CSR may be acceptable. Submission of the CSR to the IEC will be complied with as requested by local requirements.

The results of the additional variables for analysis will be presented in reports separate from the CSR.

13.6 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

13.7 Publication and Disclosure Policy

This document contains data, information and trade secretes that are confidential and proprietary to the Sponsor. This document is being provided solely for the purpose of evaluation and/or conducting this clinical study for the Sponsor. Disclosure of the content of

this document is allowed only to study personnel, IEC, or duly authorized representatives of regulatory agencies for this purpose under the condition that confidentiality is maintained. The contents of this document may not be used in any other clinical study or disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations; however, prompt notice will be given to the Sponsor prior to any such disclosure.

The Sponsor plans to disclose details of the study protocol on a web-based, publicly available, clinical trial register database (e.g., ClinicalTrials.gov).

13.8 Insurance

The Sponsor is responsible for AEs and health damage of the subjects who are associated with the *IQOS* product which are used during the study, except for AEs and health damage of the subjects caused by a negligent or an intentional misconduct and/or significant deviation to the protocol of the Investigator or the Investigational site or the subjects. The Sponsor has taken out insurance to cover any bodily injury and property damage caused by the operations carried out by the insured.

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Appendix 1 **SCHEDULE OF EVENTS**

	Screening	Familiarization	Baseline	Exercise Tests Acute Effect	Training Visits	Medical Visit	Training Visits	Medical Visit	Training Visits	Exercise Tests Training Effect	Discharge / Early Termination	28-day Safety follow-up
Visit	**1**	**2**	**3**	**4**	**5-14**	**14**	**15-28**	**28**	**29-42**	**43**	**44**	
Informed consent[4]	•											
Inclusion/Exclusion	•	•[5]										
Advice on the risks of smoking/smoking cessation advice and debriefing on *IQOS*	•	•				•		•			•• - if ET	
Demographics	•											
Fagerstrom's test for nicotine dependence (FTND)			•									
Tobacco and nicotine containing product use history and habits	•											
Cotinine urine test	•	•										
Exhaled CO	•	•	•	•	•	•	•	•	•	•		
International Physical Activity Questionnaire (IPAQ-short)	•											
Urine drug screen[6]	•	•										
Alcohol breath test	•	•										

[4] ICF for study participation including section for optional participation in sub-study interviews, and separate ICF for optional biobanking.

[5] Urine pregnancy test, cotinine urine test, exhaled CO, alcohol breath test, urine drug screen will be performed at V2 before enrollment.

[6] Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone, methamphetamines, phencyclidine, tricyclic antidepressants,.

	Screening	Familiarization	Baseline	Exercise Tests Acute Effect	Training Visits	Medical Visit	Training Visits	Medical Visit	Training Visits	Exercise Tests Training Effect	Discharge / Early Termination	28-day Safety follow-up
Visit	**1**	**2**	**3**	**4**	**5-14**	**14**	**15-28**	**28**	**29-42**	**43**	**44**	
HIV, Hepatitis B and C	•											
Safety laboratory hematology, clinical chemistry and urinalysis	•		•			•		•			•• - if ET	
Cough assessment questionnaire (VAS scale, and 3 Likert scales)			•			•		•			•	
Urine pregnancy test	•	•	•		•[7]	•		•			•• - if ET	
Physical examination	•		•			•		•			•• - if ET	
ECG	•		•			•		•			•• - if ET	
Spirometry	•										•• - if ET	
Vital signs[8]	•	•	•	•		•		•		•	•• - if ET	
Height	•											
Weight	•		•	•	•	•	•	•	•	•		
BMI	•											
Medical history and concomitant diseases	•											
Concomitant disease status		•	•	•	•	•	•	•	•	•	•	
AE/SAE recording	•	•	•	•	•	•	•	•	•	•	•• - if ET	•[9]

[7] Urine pregnancy test will not be performed at each training but at V5 only.

[8] Systolic and diastolic blood pressure, respiratory rate, pulse rate.

[9] Spontaneous reporting of new AEs and active follow-up of AEs ongoing at V44.

	Screening	Familiarization	Baseline	Exercise Tests Acute Effect	Training Visits	Medical Visit	Training Visits	Medical Visit	Training Visits	Exercise Tests Training Effect	Discharge / Early Termination	28-day Safety follow-up
Visit	**1**	**2**	**3**	**4**	**5-14**	**14**	**15-28**	**28**	**29-42**	**43**	**44**	
Prior and concomitant medications	•	•	•	•	•	•	•	•	•	•	•• - if ET	•[10]
Lifestyle questionnaire			•									
Rating of Perceived Capacity (RPC) scale			•	•						•		
Product preference[11]			•									
Smoke a cigarette/Heatstick before VO_2max test/exercise training[12]			•	•	•		•		•	•		
Snack and water after VO_2max test	•		•	•						•		
Bike ergometer – VO_2max test[13]	•		•	•						•		
Readiness to comply with study procedures	•											
Enrollment		•										

[10] Only concomitant medications used for treatment of AE/SAEs ongoing at discharge at V43.

[11] Will be asked before randomization. As an instruction to answer this question, subjects will be informed that their response will not influence the randomization process.

[12] As per randomized arm before exercise tests and trainings. Only applies for exercise tests for subjects in IQOS-2 arm.

[13] The VO_2max test will be performed on a bike ergometer using a mouthpiece and nose clip. Measurements will begin with the subjects resting for 3 min seated on the bike ergometer whereafter the workload will be increased by 25W every 60 sec until volitional fatigue. Subjects should keep cadence between 60 and 90 rpm during the test. At V3, V4 and V43, heart rate and VO_2 will be recorded at rest and at each 25W increase.

	Screening	Familiarization	Baseline	Exercise Tests Acute Effect	Training Visits	Medical Visit	Training Visits	Medical Visit	Training Visits	Exercise Tests Training Effect	Discharge / Early Termination	28-day Safety follow-up
Visit	**1**	**2**	**3**	**4**	**5-14**	**14**	**15-28**	**28**	**29-42**	**43**	**44**	
Bike ergometer – Exercise capacity[14]		•	•	•						•		
mHealth wearable demonstration	•											
mHealth wearable distribution and training		•										
mHealth wearable return										•	• - if ET	
Randomization			•									
Demonstration of *IQOS*	•											
IQOS starter kit distribution and device return			•							•	•- if ET	
Product use diary Distribution/Return		•								•	• - if ET	
Bike ergometer 40-min training session[15]					•		•		•			
Body fat percentage			•	•						•		
Waist circumference			•	•						•		
Blood composition and volume (CO re-breathing method) including blood sample for hematocrit Hb and COHb before CO-			•							•		

[14] The time to complete a pre-defined work as fast as possible on a bike ergometer. The criteria for completion of the test is the completion of the pre-defined work (kcal) determined as 1.25 times the highest wattage reached during the VO2max test at V1 for the test at V2, and at V3 for the tests at V3, V4 and V43.

[15] Training sessions will be performed according to Appendix 2 and will be adjusted according to the subject's resting and maximal heart rate.

	Screening	Familiarization	Baseline	Exercise Tests Acute Effect	Training Visits	Medical Visit	Training Visits	Medical Visit	Training Visits	Exercise Tests Training Effect	Discharge / Early Termination	28-day Safety follow-up
Visit	**1**	**2**	**3**	**4**	**5-14**	**14**	**15-28**	**28**	**29-42**	**43**	**44**	
rebreathing, and COHb after CO-rebreathing.												
Perceived exertion - RPE Borg scale [16]			•							•		
Blood COHb%			•	•		•		•		•		
Capillary blood lactate levels[17]			•							•		
Blood sampling for biological health markers[18]			•			•		•		•		
Spot urine collection for urinary exposure markers (NEQ, NNAL, CEMA, creatinine)[19]			•	•		•		•		•		
Biobanking sample collection– blood, urine, saliva			•			•		•		•		
Biobanking sample collection- sweat			•							•		

[16] Rate of perceived exertion will be measured at rest and at every 25 W increase during the VO_2 max test until the end of the test.

[17] Capillary (fingertip or earlobe) blood samples will be obtained at rest and at each workload and analysed for lactate. Blood collection should be started 40-45 sec into the workload and no blood sample should be obtained at maximal effort. The final blood sample should be obtained 60 sec after termination of the bike exercise.

[18] Blood sampling will be performed on fasting state (at least 8 hours of fasting).

[19] Urine collection to be performed as late as possible during the day.

	Screening	Familiarization	Baseline	Exercise Tests Acute Effect	Training Visits	Medical Visit	Training Visits	Medical Visit	Training Visits	Exercise Tests Training Effect	Discharge / Early Termination	28-day Safety follow-up
Visit	**1**	**2**	**3**	**4**	**5-14**	**14**	**15-28**	**28**	**29-42**	**43**	**44**	
Qualitative interview on health and functioning[20]			•							•		
Discharge											•	

[20] Subjects that have signed the optional section of the ICF for the sub-study on health on functioning will have a one-hour, qualitative interview over the phone or computer between V2 and V3, and in the end of the study between V42 and V43.

Appendix 2 Exercise Training Program

A set of three different training programs will be used. Different programs will provide the study participants with differentiated training inputs and make the training sessions less monotonous. Each training session will last 40 min with a training intensity ranging between 60-85%.The target exercise heart rates are based on the resting (HR_{rest}; obtained during baseline ECG at V3) and maximal heart rate (HR_{max}) obtained during the acute effect VO_2max test at V4. The formula to be used for exercise heart rates is: target exercise heart rate = ((HR_{max} – HR_{rest}) * intensity) + HR_{rest} with intensity as fraction of 1. Training programs including intervals and intensities will be described in a dedicated manual.

Training programs will be circulated as described below:

	Visit	Training 1	Training 2	Training 3
Week 1	5	•		
	6		•	
Week 2	7			•
	8	•		
Week 3	9		•	
	10			•
	11	•		
Week 4	12		•	
	13			•
	14	•		
Week 5	15		•	
	16			•
	17	•		
	18		•	
Week 6	19			•
	20	•		

	21		•	
	22			•
Week 7	23	•		
	24		•	
Week 8	25			•
	26	•		
	27		•	
	28			•
Week 9	29	•		
	30		•	
	31			•
	32	•		
Week 10	33		•	
	34			•
Week 11	35	•		
	36		•	
	37			•
	38	•		
Week 12	39		•	
	40			•
	41	•		
	42		•	

Appendix 3 - Laboratory Values

ABNORMAL LABORATORY VALUES RATING: CLINICAL CHEMISTRY PARAMETERS

Serum Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Sodium – Hyponatremia (mmol/L) [0]	<LLN - 130	-	<130 - 120	<120
Sodium – Hypernatremia (mmol/L) [0]	>ULN - 150	>150 - 155	>155 - 160; hospitalization indicated	>160
Potassium – Hyperkalemia (mmol/L) [0]	>ULN - 5.5	>5.5 - 6.0	>6.0 -7.0; hospitalization indicated	>7.0
Potassium – Hypokalemia (mmol/L) [0]	<LLN - 3.0	<LLN - 3.0; symptomatic; intervention indicated	<3.0 - 2.5; hospitalization indicated	<2.5
Glucose – Hypoglycemia [0] (mg/dL) (mmol/L)	 <LLN – 55; <LLN – 3.0	 <55 – 40; <3.0 – 2.2	 <40 – 30; <2.2 – 1.7	 <30; <1.7
Glucose – Hyperglycemia: [0] Fasting (mg/dL) (mmol/L)	 >ULN-160; >ULN-8.9	 >160-250; >8.9-13.9	 >250-500; >13.9-27.8; hospitalization indicated	 >500; >27.8
Creatinine increased [0]	>1 – 1.5 x Baseline; >ULN – 1.5 x ULN	>1.5 – 3.0 x Baseline; >1.5 – 3.0 x ULN	>3.0 x Baseline; >3.0 – 6.0 x ULN	>6.0 x ULN
Albumin - Hypoalbuminemia [0] (g/dL) (g/L)	 <LLN – 3; <LLN - 30	 <3 – 2; <30 - 20	 <2; <20	 - -
Alkaline phosphatase increased [0]	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
ALT / AST increased [0]	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Gamma-glutamyl transferase (GGT) increased [0]	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN

Serum Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Blood bilirubin increased (total and direct) [0]	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
Cholesterol high [0] (mg/dL) (mmol/L)	>ULN - 300; >ULN - 7.75	>300-400; >7.75-10.34	>400-500; >10.34-12.92	>500; >12.92
Triglycerides - Hypertriglyceridemia [0] (mg/dL) (mmol/L)	150 – 300; 1.71 – 3.42	>300 – 500; >3.42 – 5.70	>500 – 1000; >5.70 – 11.40	>1000; >11.4

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; GGT = Gamma-glutamyl transferase; LLN = Lower limit of the normal range; ULN = Upper limit of the normal range.

Data Sources:

[0] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

ABNORMAL LABORATORY VALUES RATING: HEMATOLOGY PARAMETERS

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Anemia (Hemoglobin) [0] (g/dL) (mmol) (g/L)	<LLN-10.0 <LLN-6.2 <LLN-100	< 10-8.0 < 6.2-4.9 < 100-80	<8.0 <4.9 <80 Transfusion indicated	Life threatening consequences; urgent intervention indicated
Hemoglobin increase [0] – (g/dL)	Increase in >0 – 2 above ULN or above Baseline if Baseline is above ULN	Increase in >2 – 4 above ULN or above Baseline if Baseline is above ULN	Increase in >4 above ULN or above Baseline if Baseline is above ULN	-
WBC Decrease [0] - (cell/mm^3) (10^9/L)	<LLN – 3000; <LLN – 3.0	<3000 - 2000; <3.0 – 2.0	<2000 - 1000; <2.0 – 1.0	<1000; <1.0
Lymphocytes increase [0] (cell/mm^3)	-	>4,000 – 20,000	>20,000	-
Lymphocytes decrease [0] (cell/mm^3) (10^9/L)	<LLN – 800; <LLN – 0.8	<800 - 500; <0.8 – 0.5	<500 - 200; <0.5 – 0.2	<200; <0.2
Neutrophils Decrease [0] (cell/mm^3) (10^9/L)	<LLN – 1500; <LLN – 1.5	<1500 - 1000; <1.5 – 1.0	<1000 - 500; <1.0 – 0.5	<500; <0.5
Platelets decrease [0] (cell/mm^3) (10^9/l)	<LLN – 75,000; <LLN – 75.0	<75,000 – 50,000; <75.0 – 50.0	<50,000 – 25,000; <50.0 – 25.0	<25,000; <25.0

Abbreviations: LLN = Lower limit of the normal range; ULN = Upper limit of the normal range; WBC = White blood cell.

Data Source:

[0] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

ABNORMAL LABORATORY VALUES RATING: URINE ANALYSIS PARAMETERS

Urine	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Protein[0]	1+ proteinuria; urinary protein <1.0 g/24 hours	2+ proteinuria; urinary protein 1.0-3.4 g/24 hours	Urinary protein ≥3.5 g/24 hours	-

Data Source:

[0] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

Appendix 4 - Sub-study Protocol

Study Number: ABOUT-HF-ND-CE-01-GER

Study Title: Exercise Capacity Clinical Trial Qualitative Interviews – Concept Elicitation Interviews Study to Inform the Development of a Health and Functioning Questionnaire for users of tobacco and nicotine products.

Appendix 5 Changes in Protocol Amendment

The changes made in the different protocol versions are listed in the below table, including previous and amended texts, as well as the reasons to change. The new text has been highlighted in bold (e.g. **new text**) and deleted text has been crossed out (e.g. ~~old text~~). When text has been amended in several sections for the same reason, the reason for change is after the last section.

Changes from Version 2.0 to Version 3.0		
Section Number	Section Name	Changes
	General	The version number and the revision date were updated accordingly to the most current version and date. The clinical trials.gov registration number was added. The table containing the "Summary of changes" has been updated, referring to Appendix 5 for the detailed changes.
Synopsis, 3	Synopsis, Objectives	Old text Endpoints (V3, V4 and V43) • Exercise capacity: time to complete a pre-defined work (determined as 25% more work than the study subject produced during baseline VO_2max test) on a cycle ergometer (min:sec). Amended text Endpoints (V3, V4 and V43) • Exercise capacity: time to complete a pre-defined work ~~(determined as 25% more work than the study subject produced during baseline VO_2max test)~~ on a cycle ergometer (min:sec).
7.6.2	Exercise Capacity Test	Old text The criteria for completion of the test is the completing of a pre-defined relative work determined as 25% more work than was completed during the VO_2max test at V1 for the test at V2, and at the VO_2max test V3 for the tests at V3, V4 and V43.

		Amended text The criteria for completion of the test is the completing of a pre-defined relative work determined ~~as 25% more work than was completed during~~ **based on the highest wattage level reached at VO_2max test times 1. 25 (i.e. 200 W x 1.25 = 250; 250 kcal to be completed). The highest wattage reached** at the VO_2max test at V1 **will be used** for the test at V2, and at the VO_2max test V3 **will be used** for the tests at V3, V4 and V43.
9.2 9.3 9.4.3	Enrollment and Familarization with Exercise Test – Table 6 Baseline and Randomization – Table 7 Training Effect Exercise Tests – Table 11	Old text Work to complete will be based on the work produced during VO_2max test during V1. Amended text Work to complete will be based on the ~~work~~**highest wattage level reached** ~~produced~~ during VO_2max test during V1.
Appendix 1	Schedule of events	Old text [14] The time to complete a pre-defined work as fast as possible on a bike ergometer. The criteria for completion of the test is the completion of the pre-defined work determined as 25% more work than was completed during the VO2max test at V1 for the test at V2, and at V3 for the tests at V3, V4 and V44. Amended text [14] The time to complete a pre-defined work as fast as possible on a bike ergometer. The criteria for completion of the test is the completion of the pre-defined work **(kcal)** determined as **1.**25 **times the highest wattage reached** ~~% more work than was completed~~ during the VO_2max test at V1 for the test at V2, and at V3 for the tests at V3, V4 and **V43**~~V44~~. Reason for change: To clarify how the work to be completed for the Exercise Capacity test is determined based on the subject's performance during the VO_2max test, accounting for the output of the exercise equipement

		installed on site. For the calculation of the work to be competed, the highest wattage reached at subject's VO_2max test is used and not the work produced during VO_2max test.
Synopsis, 4.1	Synopsis, Overall Study Design and Plan	Old text The subject will also be invited to participate in a sub-study on perception of health and functioning and will sign a separate optional section of the ICF for this part of the study. Amended text The subject will also be invited to participate in a sub-study on perception of health and functioning and will sign a separate optional section of the ICF for this part of the study. **Subjects will be invited to sign and separate optional consent form for collection of samples for biobanking.** Reason for change: To add the mention of the optional biobanking ICF in the Study Design and Plan sections as this was missing in the previous version.
Synopsis, 5.1.1	Synopsis, Inclusion criteria	Old text **Inclusion criteria** **[…]** 4. Subject has been smoking ≥ 10 cigarettes per day over the last 12 months. Smoking status will be verified by a urinary cotinine ≥ 200 ng/mL and CO exhaled breath test > 10 ppm at both V1 and V2. Amended text 4. Subject has been smoking ≥ 10 cigarettes per day over the last 12 months. Smoking status will be verified by a urinary cotinine ≥ 200 ng/mL and CO exhaled breath test >**6**~~10~~ ppm at both V1 and V2.
7.7.1	Exhaled Carbonmonoxide (CO)	Old text - Amended text

		At V1 and V2, a cut-off of >6 ppm for confirming cigarette smoking status will be applied (56) (57). Reason for change: The cut-off for the exhaled CO level applied to confirm cigarette smoking status at V1 and V2, in addition to self-report and urine cotinine measurement, was lowered from >10ppm to >6ppm as supported by literature. Due to the 2-8 hours half-life of CO, confirmed smokers may have levels below >10 ppm especially in the morning after overnight abstinence (56, 57).
7.6.3	Exercise Training	Old text Each training session will last 40 min with a training intensity ranging between 60-80%. Amended text Each training session will last 40 min with a training intensity ranging between 60-~~80~~5%. Reason for change: Correction of typhographical error.
7.9.3	Long-Term Storage (Biobanking)	Old text **Urine:** Samples will be collected from the spot urine for: • lipidomic profiling: 2 x 2 mL • proteomic profiling: 2 x 10 mL • metabolomics profiling: 2 x 10 mL **Whole blood:** • transcriptomic profiling: 2 x 2,5 mL will be collected • proteomic profiling:5 mL will be collected to obtain 4 x 0.5 mL of plasma • metabolomics profiling: 5 mL will be collected to obtain 4 x 0.5 mL of plasma • lipidomics profiling: 5 mL will be collected to obtain 2 x 1 mL of plasma **Saliva:** • 4 x 1mL saliva will be collected using a dedicated saliva collection kit for molecular profiling.

		Sweat: • 2 x 75 µL will be collected using a sweat collection system (Macroduct®Sweat Collection system, ELITechGroup) for molecular profiling. Amended text **Urine:** Samples will be collected from the spot urine for: • lipidomic profiling: 2 x **approximately** 2 mL • proteomic profiling: 2 x **approximately** 10 mL • metabolomics profiling: 2 x **approximately** 10 mL **Whole blood:** • transcriptomic profiling: 2 x 2,5 mL will be collected • proteomic profiling:5 mL will be collected to obtain 4 x 0.5 mL of plasma • metabolomics profiling: 5 mL will be collected to obtain 4 x 0.5 mL of plasma • lipidomics profiling: 5 mL will be collected to obtain 2 x 1 mL of plasma **Saliva:** • 4 x **approximately** 1mL saliva will be collected using a dedicated saliva collection kit for molecular profiling. **Sweat:** • 2 x **at least approximately** 40~~–75~~ µL will be collected using a sweat collection system (Macroduct®Sweat Collection system, ELITechGroup) for molecular profiling. Reason for change: To clarify that volumes of urine, saliva and sweat are approximate as collection method of these fluids may be more variable as compared to a blood draw.
9	Study Activities	Old text If no start time for the procedures is provided, then the procedure can be performed at any time during the visit. Amended text

		The procedure can be performed at any time during the visit, **unless other specified.**
9.3	Baseline and Randomization	Old text Table 7 shows the procedures that will be performed at V3 Amended text Table 7 shows the procedures that will be performed at V3. **All baseline assessments should be performed before randomization**. Reason for change: To clarify order of assessments during visits.
13.1.2	Sponsor	Old text Email [redacted] Amended text Email: [redacted] Reason for change: Change in email adress.
Appendix 3	**ABNORMAL LABORATORY VALUES RATING: HEMATOLOGY PARAMETERS**	Old text: WBC Decrease [0] - (cell/mm^3) (10^{-9}/L) Lymphocytes increase [0] (cell/mm^3) Lymphocytes decrease [0] (cell/mm^3) (10^{-9}/L) Neutrophils Decrease [0] (cell/mm^3) (10^{-9}/L) Platelets decrease [0] (cell/mm3) (10-9/l) Amended text: WBC Decrease [0] - (cell/mm^3) (10^{9}/L) Lymphocytes increase [0] (cell/mm^3)

		Lymphocytes decrease [0] (cell/mm^3) (10^{-9}/L) Neutrophils Decrease [0] (cell/mm^3) (10^9/L) Platelets decrease [0] (cell/mm^3) (10^9/l) Reason for change: Correction of typographical error such as 10^9 instead of 10^{-9}.
Appendix 4	**Sub-Study Protocol**	Please see summary of changes in the sub-study protocol.

Changes from Version 1.0 to Version 2.0		
Section Number	Section Name	Changes
	General	The version number and the revision date were updated accordingly to the most current version and date. A table containing the "Summary of changes" has been added, referring to this Appendix 5 for the detailed changes.
Synopsis, 3	Synopsis, Objectives	Old text 5. To monitor trends of daily physical activity levels during the study in subjects switching to IQOS (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training) Endpoints (from V2 until V43) • Aggregated data derived from the mobile health (mHealth) wearable for: ▪ Cumulative number of steps per day ▪ Energy expenditure (kcal) per day ▪ Daily move score

		Amended text 5. To monitor trends of daily physical activity levels during the study in subjects switching to *IQOS* (with and without training), continuing to smoke cigarettes (with training) and being smoking abstinent (with training) Endpoints (from V2 until V43) • Aggregated data derived from the mobile health (mHealth) wearable for: ▪ Cumulative number of steps per day ▪ ~~Energy expenditure (kcal) per day~~ ▪ ~~Daily move score~~ ▪ **Sedentary minutes per day and % of time sedentary** ▪ **Active minutes per day and % of time active** ▪ **Very active minutes per day and % of time very active**
Synopsis, 3	Synopsis, Objectives	Old text 6. To explore trends and changes in subject-generated physiological and behavioral parameters through continuous measurements during the study* Endpoints (from V2 until V43) mHealth wearable measurements of : • physiological parameters: heart rate, heart rate variability, interbeat interval, blood pulse wave, blood perfusion index, blood oxygenation (SpO2), skin temperature, core temperature, blood pressure, respiratory rate, energy expenditure • behavioral parameters: steps, activity levels Amended text 6. To explore trends and changes in ~~subject-generated physiological and behavioral~~ **activity and sleep** parameters through continuous measurements during the study* Endpoints (from V2 until V43)

		mHealth wearable measurements of : • **steps, activity, distance, energy expenditure, sleep** ~~physiological parameters: heart rate, heart rate variability, interbeat interval, blood pulse wave, blood perfusion index, blood oxygenation (SpO2), skin temperature, core temperature, blood pressure, respiratory rate, energy expenditure~~ • ~~behavioral parameters: steps, activity levels~~
4.2	Rationale for Study Design	Old text The wearable will enable non-invasive recording of physical activity and energy expenditure in an objective manner throughout the study. Amended text The wearable will enable non-invasive recording of physical activity and ~~energy expenditure~~ in an objective manner throughout the study. Reason for change: Replacement of Biovotion device with Garmin device and consequent alignement of captured parameters.
Synopsis, 4.1	Synopsis, Overall Study Design and Plan	Old text Before leaving the investigational site the subject will receive an mHealth wearable kit and will be trained on how to handle and charge the device. Amended text Before leaving the investigational site the subject will receive an mHealth wearable kit and will be trained on how to handle ~~and charge~~ the device. Reason for change: Garmin device does not need to be charged.
Synopsis 4.1	Synopsis Overall Study Design and Plan	Old text Subjects' VO_2max, resting and maximal heart rate and maximal work rate will be determined.

		[…] The training intensity will be adjusted according to the subject's resting and maximal heart rate as determined at the VO_2max test at V4 (acute test). Amended text Subjects' VO_2max, ~~resting and~~ maximal heart rate and maximal work rate will be determined. […] The training intensity will be adjusted according to the subject's resting **heart rate as determined by ECG at V3**, and maximal heart rate as determined at the VO_2max test at V4 (acute test).
7.6.1	VO_2max Test and Blood Lactate Levels	Old text In addition at V4, the resting heart rate, the maximal heart rate and the maximal work rate will be recorded in order to design the training program Amended text In addition at V4, ~~the resting heart rate~~ the maximal heart rate and the maximal work rate will be recorded in order to design the training program
7.6.3	Exercise Training	Old text The target exercise heart rates are based on the subject's resting (HR_{rest};lowest value during 3 min supine rest on ergometer) and maximal heart rate (HR_{max}) obtained during the acute effect VO_2max test at V4. Amended text The target exercise heart rates are based on the subject's resting (HR_{rest}; **obtained during ECG at V3** ~~lowest value during 3 min supine rest on ergometer~~) and maximal heart rate (HR_{max}) obtained during the acute effect VO_2max test at V4.
9.4.2	Table 9	Old text

		The training intensity will be adapted for each subject based on the resting and maximal HR recorded at VO_2max test V4. Amended text The training intensity will be adapted for each subject based on the resting and maximal HR ~~recorded at VO_2max test V4~~.
Appendix 1	Schedule of Events-Footnote	Old text [15] Training sessions will be performed according to Appendix 2 and will be adjusted according to the subject's resting and maximal heart rate as determined at VO_2max test at V4. Amended text [15] Training sessions will be performed according to Appendix 2 and will be adjusted according to the subject's resting and maximal heart rate ~~as determined at VO_2max test at V4~~.
Appendix 2	Exercise Training Program	Old text The target exercise heart rates are based on the resting (HR_{rest}; lowest value during supine rest on ergometer) and maximal heart rate (HR_{max}) obtained during the acute effect VO_2max test at V4. Amended text The target exercise heart rates are based on the resting (HR_{rest}; ~~lowest value~~**obtained** during~~supine rest on ergometer~~ **baseline ECG at V3**) and maximal heart rate (HR_{max}) obtained during the acute effect VO_2max test at V4. Reason for change: Clarification that the resting heart rate should be determined by ECG at V3 and not at V4.
Synopsis 4.1 4.4	Synopsis Overall Study Design and Plan Study Duration	Old text Acute effect, V4 (7±1days after V3) […] Training effect, V43 (106±1 days after V3) […] Discharge, V44 (107±1 days after V3)

		[…] A 1-day acute effect test visit (V4) will be scheduled 7±1 days after V3, followed by a 12-week training program with training sessions 2-4 times per week (V5-V42) starting 15±2 days after V3 until 99±2 days after V3. […] A 1-day training effect test visit (V43) will be scheduled up to 7±1 days after V42 (106±1days after V3), followed by a discharge visit (V44) up to 1±1 day**s** after V43 (107±1 days after V3), and followed by a 28-week safety follow-up period. Amended text Acute effect, V4 (7±~~1~~**2**days after V3) […] Training effect, V43 (106±~~1~~**2** days after V3) […] Discharge, V44 (107±~~1~~**2** days after V3) […] A 1-day acute effect test visit (V4) will be scheduled 7±**2**~~1~~ days after V3, followed by a 12-week training program with training sessions 2-4 times per week (V5-V42) starting 15±2 days after V3 until 99±2 days after V3. […] A 1-day training effect test visit (V43) will be scheduled up to 7±**2**~~1~~ days after V42 (106±~~1~~**2** days after V3), followed by a discharge visit (V44) up to 1±**2**~~1~~ day**s** after V43 (107±**2**~~1~~ days after V3), and followed by a 28-week safety follow-up period.
9.4.1 9.4.3	Acute Effect Exercise Tests Training Effect Exercise Tests	Old text Visit 4 (V4) will be scheduled up to 7±2 days after V3. […] Visit 43 (V43) will be scheduled 106±1days after V3, and 7±1 days after V42. […] Visit 44 (V44) will be scheduled 108±1 days after V3.

		Amended text Visit 4 (V4) will be scheduled up to 7±~~1~~**2** days after V3. […] Visit 43 (V43) will be scheduled 106±~~1~~**2** days after V3, and 7±~~1~~**2** days after V42. […] Visit 44 (V44) will be scheduled 10~~7~~**8**±~~1~~**2** days after V3 Reason for change: Visit windows were increased to allow more flexibility when scheduling site visits.
Synopsis 12.4.1	Synopsis As Exposed Exercise Compliant Set	Old text … and who attended at least 90% of the exercise training sessions except the subjects in *IQOS*-2 arm. The AEECS will be analyzed by actual exposure (product use exposure). Amended text and who attended at least **34 of 38 (**~90%**)** of the exercise training sessions except the subjects in *IQOS*-2 arm. The AEECS will be analyzed by actual exposure (product use exposure). Reason for change: To precise how many visits can be missed corresponding to ~10%.
1.3.1	Informed Consent Form for Study Participation	Old text The subjects will be informed that following completion of this study, analysis of these data of exploratory nature will be conducted to provide better understanding of physiological changes in healthy smokers switching to *IQOS* or being smoking abstinent vs continued cigarette smoking. Amended text The subjects will be informed that following completion of this study, analysis of these data of exploratory nature will be conducted to provide better understanding of ~~physiological~~ changes **in activity and sleep patterns** in healthy smokers switching to *IQOS* or being smoking abstinent vs continued cigarette smoking.

		Reason for change: Replacement of Biovotion device with Garmin device and consequent alignement of captured parameters.
2.3.1	Anticipated benefits	Old text Subjects who participate in this study will benefit from repeated, detailed health check-ups which may help to uncover undiagnosed medical conditions. Amended text Subjects who participate in this study will benefit from repeated, detailed health check-ups~~ which may help to uncover undiagnosed medical conditions~~. Reason to change: Alignement with wording in the ICF.
7.5.2	Medical History, Concomitqnt Disease, Previous and Ongoing Medications	Old text A concomitant disease is defined as any condition that started prior to ICF signature and is still ongoing at V1. Amended text A concomitant disease is defined as any condition that started prior to ICF signature and is still ongoing at V1**. The final status of any concomitant disease (i.e stop date or ongoing) should be verified at each visit.**
Appendix 1	Schedule of Events	Old text - Amended text **Concomitant disease status** (*line added in Schedule of Events*) Reason for change: Clarifiy the concomitant disease status should be checked during the study.
7.6.1	VO_2max Test and Blood Lactate Levels	Old text The final blood sample should be obtained within 60-seconds after termination of the bike exercise. Amended text

		The final blood sample should be obtained within ~~60 seconds~~ **5 minutes** after termination of the bike exercise. Reason for change: To allow for more time to collect the final blood sample while the subject is cooling down.
7.6.2	Exercise Capacity Test	Old text The criteria for completion of the test is the completing of a pre-defined relative work determined as 25% more work than was completed during the VO_2max test at V1 for the test at V2, and at the VO_2max test V3 for the tests at V3, V4 and V44. Amended text The criteria for completion of the test is the completing of a pre-defined relative work determined as 25% more work than was completed during the VO_2max test at V1 for the test at V2, and at the VO_2max test V3 for the tests at V3, V4 and ~~V44~~**43.** Reason to change: Mistake in the text.
7.8.3 Appendix 1	Urine Drug Screening Schedule of Events – footnote	Old text At V1 and V2, urine drug screen (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates) will be performed by the personnel at the investigational site. Amended text At V1 and V2, urine drug screen (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ~~and~~ opiates, **methadone, methamphetamines, phencyclidine, tricyclic antidepressants**) will be performed by the personnel at the investigational site. Old text [6]Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates. Amended text [6]Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine,~~ and~~ opiates, **methadone,**

		methamphetamines, phencyclidine, tricyclic antidepressants. Reason for change: The list was updated to accommodate all substances tested for by the site's standard test.
7.9.	Long-Term Storage (Biobanking)	Old text **Urine:** Samples will be collected from the spot urine for: • lipidomic profiling: 2 x 2 mL • proteomic profiling: 4 x 10 mL • metabolomics profiling: 4 x 10 mL **Saliva:** • 6 x 1mL saliva will be collected using a dedicated saliva collection kit for molecular profiling. Amended text **Urine:** Samples will be collected from the spot urine for: • lipidomic profiling: 2 x 2 mL • proteomic profiling: ~~4~~ **2** x 10 mL • metabolomics profiling: ~~4~~ **2**x 10 mL **Saliva:** • ~~6~~ **4** x 1mL saliva will be collected using a dedicated saliva collection kit for molecular profiling. Reason for change: Urine volumes were reduced as the expected volume of the spot urine collection may not allow for collection of the initially planned volume. Saliva volume was reduced to alleviate subject and site burden.
7.10	Mobile Health (mHealth) Wearable	Old text Subjects will wear an mHealth wearable device (Everion, Biovotion), which is worn on the upper arm, for the recording of their physical activity including daily step count and move score, and energy expenditure. Physical activity is routinely identified, analyzed, and evaluated on the basis of producing health benefits. The daily cumulative

		move score produced uses a 0 to 100 feedback scale (0-30 = poor, 30-59 = moderate, and 60-100 = good health effects). The score achieved varies according to the duration and intensity of the activity. Intensity accounts for the subject's heart rate, espiratory rate (derived from R-R intervals, i.e. time etween successive heart beats) (56, 57). The wearable will simultaneously record a range of physiological parameters as described in objective 6, however the analysis and reporting of this data will not be part of the CSR but reported separately. Subjects will be trained on how to wear (i.e. correct positioning), charge and handle the device in accordance with the user guide. Subjects will be instructed to wear the device all the time (~22-23h per day) except while charging and when showering or swimming (as per user guide instructions). The device should be charged once daily, preferably at the same time everyday. As part of the wearable device kit (device, armband, charger) subjects will also receive a mobile phone with Bluetooth and wireless internet connectivity through which data will be transferred from the wearable device. Subjects will wear the device in a blinded manner, i.e. they will not be able to see the data collected in order not to influence their behavior but will only be able to monitor battery levels. Between V2 and V3, baseline data will be collected, and as of randomization at V3 data will be collected during the investigational period until V43. The Everion device records physiological signals continuously on a per second level. For the parameters to be analyzed as part of the study (objective 5; steps, energy expenditure and move score) data transferred from the wearable device to the clinical database will be aggregated on a per 24-hour level. In addition, wear time per day will be monitored. Parameters listed in objective 6 will be transferred from the wearable device on a per second level to the storage cloud. Amended text Subjects will wear a~~n~~ mHealth ~~wearable~~ device (~~Everion, Biovotion~~**Vivofit 3, Garmin**), which is worn on the ~~upper~~

		~~arm~~ **wrist**, for the recording of their physical activity including daily step count and ~~move score, and energy expenditure~~ **intensity minutes**. **Three intensity levels of physical activity will be recorded; 1) sedentary - little to no activity monitored (e.g. minimal movement, sitting, resting, or sleeping); 2) active – some activity monitored (e.g. a brisk walk); 3) very active- high activity monitored (e.g.running or speed walking).** ~~Physical activity is routinely identified, analyzed, and evaluated~~ ~~on the basis of producing health benefits. The daily cumulative move score produced uses a 0 to 100 feedback scale (0-30 = poor, 30-59 = moderate, and 60-100 = good health effects). The score achieved varies according to the duration and intensity of the activity. Intensity accounts for the subject's heart rate, respiratory rate (derived from R-R intervals, i.e. time between successive heart beats) (56, 57).~~ The wearable will simultaneously record ~~a range of physiological parameters~~**energy expenditure, distance and sleep** as described in objective 6, however the analysis and reporting of this data will not be part of the CSR but reported separately. Subjects will be trained on how to wear (i.e. correct positioning)~~, charge~~ and handle the device in accordance with the user guide. Subjects will be instructed to wear the device **on their non-dominant wrist and to wear it** all the time ~~(~22-23h per day) except while charging and when showering or swimming (as per user guide instructions). The device should be charged once daily, preferably at the same time everyday.~~ As part of the wearable device kit ~~(device, armband, charger)~~ subjects will also receive a mobile phone with Bluetooth and wireless internet connectivity through which data will be transferred from the wearable device. ~~Subjects will wear the device in a blinded manner, i.e.they will not be able to see the data collected in order not to influence their behavior but willonly be able to monitor battery levels.~~ Between V2 and V3, baseline data will be collected, and as

		of randomization at V3 data will be collected during the investigational period until V43. The ~~Everion device~~**Vivofit 3 device** records ~~physiological signals~~ **accelerometer data** continuously ~~on a per second level~~**and transfers data aggregated on a 15-min basis to the data storage cloud**. For the parameters to be analyzed as part of the study (objective 5; steps~~, energy expenditure~~ and ~~move score~~**activity**) data transferred from the wearable device to the clinical database will be aggregated on a per 24-hour level. In addition, wear time per day will be monitored. Parameters listed in objective 6 will be transferred from the wearable device on a ~~per second~~**15-min** level to the storage cloud. Reason for change: Replacement of Biovotion device with Garmin device.
9.3	Baseline and Randomization Table 7 Footnote	Old text COHb = Carbon monoxide Amended text COHb= ~~Carbon monoxide~~**Carboxyhemoglobin** Reason for change: Mistake in the abbreviation.
Appendix 2	Exercise Training Program	Old text Each training session will last 40 min with a training intensity ranging between 60-80%. Amended text Each training session will last 40 min with a training intensity ranging between 60-**85**~~80%.~~ **Training programs including intervals and intensities will be described in a dedicated manual**. Reason for change: Clarification that a training manual will be prepared.

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