PMI RESEARCH & DEVELOPMENT

Statistical Analysis Plan

P1-PMC-01-JP

Study Title:	An observational cohort study in Japan to assess the patterns of product use and changes in health status associated with the use of HeatSticks with the IQOS tobacco heating system
Short Title:	Japanese Post-Market Cohort Study
EUDRACT Number:	Not applicable
Product Name:	IQOS
Study Number:	P1-PMC-01-JP
Sponsor:	Philip Morris International Quai Jeanrenaud 5 2000 Neuchatel
Version Number:	3.0
Revision Date:	27APR2018
Authors:	[redacted], Sr. Biostatistician, [redacted]

1. Approval Signatures

Sponsor approval:

[redacted] 30 APR 2018
Date

Study Statistician
Philip Morris International

[redacted] 02 May 2018
Date

Study Scientist
Philip Morris International

[redacted] 02 May 2018
Date

Director Population Risk Assessment
Philip Morris International

[redacted] 30 Apr 2018
Date

Medical Safety Officer
Philip Morris International

[redacted] approval:

Prepared by: [redacted]
[redacted] Statistical Lead [redacted]
Date

Approved by: [redacted]
[redacted] Statistical Programming Lead
Date

Approved by: [redacted]
[redacted] Lead Epidemiologist [redacted]
Date

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3. INTRODUCTION

This statistical analysis plan (SAP) has been developed to supplement the statistical analysis described in the Japanese Post-Market Cohort Study protocol P1-PMC-01-JP (final 7.0 dated 15 December 2017).

The study was terminated in March 2018 during recruitment of the second wave of participants. The main reason for study termination were challenges with recruitment, retention and response rate which limited the statistical analysis and the evaluability of the protocol objectives. In addition to this, [redacted] produced a scientific report (February 5th 2018) that identified several study design flaws and limitations that prevent meaningful interpretation of the results. Due to study termination and in light of the scientific report, PMP and [redacted] agreed upon a reduced scope statistical analysis that is described in the current SAP. All changes to the study protocol and SAP v2.0 are detailed in Section 8. This reduced scope statistical analysis will be conducted at once on the wave 1 participants. This SAP describes the methodology and considerations of the planned analyses and a list of all the tables, listings, figures (TLFs) for this study. A detailed description of the planned TLFs will be provided in a separate TLFs shell document. Any changes to the TLF shells numbering or to the title of the TLFs will not require an amendment to this SAP.

Any changes to the analyses described in this document or additional analyses performed to supplement the planned analyses, will be described in the cohort study report (CSR).

The preparation of this SAP is based on the following documents:

- International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" (**ICH Guidelines E9 1998**).
- European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, Chapter 5: Statistical and epidemiological analysis plan (Revision 6, dated July 2017).
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" (**ICH Guideline E3 1995**).
- Case Report Form (CRF) for Wave 1 (final 4.0 dated 27 September 2016).
- CRF ([redacted] Part 1 of 2) (final 4.0 dated 06-Jul-2017).
- CRF ([redacted] Part 2 of 2) (final 2.0 dated 10-Jul-2017).
- LYFE Scientific Report [redacted] Version 1 05 February 2018.

3.1 Revision History

Version	Date of Revision	Revision
1.0	02 December 2016	Final version 1
2.0	31 August 2017	The revision is triggered by protocol amendment v5.0 and termination of clinical sub-study.
3.0	27 April 2018	The revision is triggered by the study termination.

3.2 Background

3.2.1 Smoking-Related Diseases and Harm Reduction Strategy

Tobacco use is a major public health problem worldwide as it is a well-known risk factor for many life threatening diseases. Tobacco use leads most commonly to cardiovascular and pulmonary disease and is a major risk factor for myocardial infarction, stroke, chronic bronchitis, cancers of mouth, throat, voice box and pancreas (4). Half of all long-term smokers will die of a tobacco-related condition (5).

The best way to reduce the adverse health consequences of smoking is to quit smoking (6, 7). Because of the impact that smoking has on health and the fact that total smoking cessation is difficult to achieve (8, 9), the food and drug administration (FDA) drafted guidelines for application of modified risk tobacco products (MRTPs) that would either have reduced exposure to tobacco toxicants and/or reduced risk of developing tobacco-related diseases (10). For those smokers who are not willing to quit, Philip Morris Products (PMP) is developing alternative approaches by developing products with the potential to reduce the risks of tobacco-related diseases under the FDA draft guidelines for MRTP (10).

PMP's approach to scientifically assessing the risk-reduction potential of its candidate MRTPs is described in the reference document (11). Smoking cessation is the only intervention proven to reduce the risk of smoking-related diseases in smokers. Accordingly, PMP utilizes smoking cessation/smoking abstinence as the benchmark for assessing the risk reduction potential of its candidate MRTPs. The Institute of Medicine (IOM) observed that cessation is the "gold standard" for assessing risk reduction, and that "the closer risks and exposures from the MRTP are to cessation products, the more confident a regulator can be of achieving a net public health benefit" (12). PMP has already conducted studies and plans to conduct further clinical studies which observe measurable changes in blood chemistry, risk factors and health effects in smokers who switch to a candidate MRTP, comparing the changes with those observed in both smokers who continue smoking combustible cigarettes (CC) and smokers who stop using tobacco products.

Assessments of patterns of use of the candidate MRTPs are vital to determine population harm.

3.2.2 Description of the PMI's First Candidate MRTP and Scientific Findings

Thousands of chemicals - "smoke constituents" - are formed when tobacco is burned or combusted. More than 5000 smoke constituents have been identified (13, 14), and more than 100 of them have been categorized as harmful and potentially harmful constituents (HPHCs) (15). PMP's focus has been on the development of products that do not combust tobacco but heat tobacco while replicating the "smoking experience" as much as possible. The approach being used by heating tobacco at significantly lower temperatures than CC limits pyrolysis and combustion. PMP believes that such heat-versus-burn products present the best opportunity for reducing harm as they produce vastly lower levels of HPHCs and are more likely to be accepted by smokers as substitutes for cigarettes. Important to this effort has been providing nicotine in a way that closely parallels CC and closely replicate taste, sensorial experience and ritual of that of a CC.

The product developed by PMP, and to be assessed in this study, is the IQOS Tobacco Heating System (THS) (referred to as the IQOS). With this product, the heating of the tobacco is maintained below 400°C, a temperature much lower than what is observed for CC, which can reach 900°C. The IQOS is composed of the 'Tobacco Stick Holder', dedicated special IQOS HeatSticks, a Charger, and different accessories. The energy of the IQOS Tobacco Stick Holder is sufficient to maintain approximately a 6-minute session. Unlike CC, the IQOS HeatSticks do not burn down during their consumption and their lengths remain constant after use.

The non-clinical assessment of IQOS supported the initiation of the clinical studies (16). No new or increased toxicological hazard in the product's aerosol was detected compared with CC smoke and aerosol chemistry studies have shown a reduction of up to 90% in HPHC's (16). Several clinical studies have been conducted on an earlier version of IQOS (THS 1.0), in Europe, Asia, Africa and the United States. All studies showed reductions in exposure to the majority of measured HPHCs from both aerosol fractions, total particulate matter (TPM) and gas vapor phase (GVP), in participants using the THS 1.0 as compared to participants continuing smoking CC, both, in controlled and ambulatory setting. THS 2.1, the immediate predecessor of the non-menthol current IQOS, was tested in two exploratory clinical studies to measure the nicotine pharmacokinetic (PK) profile (17) and to assess the reduction of exposure to HPHCs when switching from CC to THS 2.1 (18). The observed nicotine PK profile for THS 2.1 was similar to CC and there were significant reductions in the exposure to the majority of selected HPHCs. In 2013, eight clinical studies were initiated in US, Europe, and Japan in order to evaluate the nicotine PK profile, to demonstrate reduced exposure, and to determine functional and biological changes following the switching from CC to THS in smokers as compared to smokers continuing smoking CC and smoking abstinence (SA). The reporting of the results is currently ongoing.

Clinical studies conducted and ongoing so far on about 3000 participants revealed no safety

concern for THS 2.2 and its earlier prototypes.

3.3 Study Rationale

In order to support PMP's pre-clinical and clinical programs in assessing the exposure and risk reduction of the IQOS, post-marketing and in particular observational data is needed to collect information on how the product is used in the 'real world' (19). This study will therefore allow us to assess the patterns of product use and changes in health status associated with the use of the IQOS, compared to CC smokers.
Originally, the study included a Clinical Sub-Study which would further assess the population level differences in levels of Biomarkers of Exposure (BoExp) to HPHC contained in cigarette smoke, Clinical Risk Endpoints (CREs) and self-reported health outcomes and health related events between CC smokers, IQOS users and never-smokers. However, as recruitment into this part of the study was extremely low and there was little interest in participation from those enrolled in what was called the Main Study, it was decided to terminate the Clinical Sub-Study earlier than planned..

The Main Study was terminated in March 2018 as described in Section 3 of this SAP. The changes from the analyses described in the protocol are detailed in Section 8.

4 ABBREVIATIONS OF TERMS

Abbreviations

AE	Adverse event
BoExp	Biomarker of exposure
CASI	Computer assisted self-interview
CB_i	Current behavior
CC	Combustible cigarette
CC_i	Current CC smoker at measurement time i
COPD	Chronic obstructive pulmonary disease
CPD_i	Average CC consumption
CRE	Clinical risk endpoint
CRF	Case report form
CRO	Contract research organization
CSR	Cohort study report
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ePD_i	Average number of e-cigarettes per day
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
GVP	Gas vapor phase
HnB	Heat-not-burn products
$HnBPD_i$	Average consumption of HnB per day
HPHC	Harmful and potentially harmful constituent
IB	Initial behavior
ICF	Informed consent form
IOM	Institute of Medicine
MCEQ	Modified cigarette evaluation questionnaire
MI	Myocardial infarction

MRTPs	Modified risk tobacco products
MT(i)	Measurement time
OTP	Other tobacco products
$OTPD_i$	Average consumption of other tobacco products per day
PK	Pharmacokinetic
PMI	Philip Morris International
PMP	Philip Morris Products S.A.
PRI-P	Perception risk instrument
QSU-b	Questionnaire on smoking urges – short form
SA	Smoking abstinence
SAP	Statistical analysis plan
SD	Standard deviation
SES	Socio-economic status
SRCQ	Self-reported changes questionnaire
ST_i	Study Time
THS	Tobacco heating system
TLF	Tables, listings, figures
TPM	Total particulate matter
VAS	Visual analog scale

5 STUDY OBJECTIVES AND ENDPOINTS

The objectives and endpoints of the Study are:

1. To characterize and describe patterns of use of tobacco and nicotine containing products
   Endpoints:
   - Mean number of cigarettes smoked (per day and/or per week) over time
   - Mean number of IQOS HeatSticks used (per day and/or per week) over time
   - Mean number of times e-cigarettes are used (per day and/or per week) over time
   - Product use patterns over time (individual and dual/poly use patterns)
   - Rate of increase or decrease in product use over time
2. To identify intra-individual product use trajectories over time
   Endpoints:
   - Product switching
   - Uptake of products
   - Rate of tobacco and nicotine product use transitions, within a given timeframe
3. To describe the cessation rates of tobacco and nicotine containing products including CC over time
   Endpoints:
   - Rate of cessation of tobacco or nicotine containing products use, overall as well as by consumption within a given timeframe
   - Rate of cessation from CC use overall as well as by consumption within a given timeframe
     Note: Objective 3 will not be assessed due to study termination (details are given in Section 8).
4. To identify and assess the motivations for quitting tobacco use and to characterize the quit attempts by product use over time
   Endpoints:
   - Rate and number of participants that want to quit
   - Reasons for wanting to quit
   - Rate and number of self-reported quit attempts
   - Characteristics of the quit attempts, including:
     - Length of quit attempt
     - Type of product used to help in quit attempt (if applicable)
     - Reasons for quit attempt
     - Outcome of quit attempt

     Note: Objective 4 will not be assessed due to study termination (details are given in Section 8).

5. To characterize the users of tobacco and nicotine containing products over time
   Endpoints:
   - Demographics and socio-economic characteristics of tobacco and nicotine containing products users
   - Smoking history of tobacco and nicotine containing products users
   - Pre- IQOS tobacco and nicotine containing product usage and behaviors
6. To assess subjective effects including urge to smoke, product reinforcement and self-observed aesthetic improvements over time
   Endpoints:
   - Total Score and Factor scores from the Questionnaire on Smoking Urges-brief version (QSU-b) by product use
   - Subscales from the Modified Cigarette Evaluation Questionnaire (MCEQ) in IQOS users
   - Self-Reported Changes Questionnaire (SRCQ) in IQOS users

   Note: Objective 6 will not be assessed due to study termination (details are given in Section 8).
7. To assess the perception of risk associated with tobacco and nicotine containing products by product use over time
   Endpoints:
   - Perceived Risk Instrument (PRI-P) to measure perception of risk associated with using CC, IQOS and e-cigarettes based on exposure group at the time of assessment using the following domains:
     - Perceived Health Risk
     - Perceived Addiction Risk
     - Perceived Harm to Others

   Note: Objective 7 will not be assessed due to study termination (details are given in Section 8).
8. To assess the strength of nicotine dependence by product use over time
   Endpoints:
   - Score from the Fagerström test for Nicotine Dependence (FTND) questionnaire.

   Note: Objective 8 will not be assessed due to study termination (details are given in Section 8).
9. To describe the rates of self-reported signs, symptoms and diagnoses by product use over time
   Endpoints:
   - Signs and symptoms
   - Cardiovascular disease diagnoses: myocardial infarction, stroke, new diagnoses of hypertension, unstable angina, or other cardiovascular diseases
   - Respiratory diseases diagnoses: new diagnoses of chronic obstructive pulmonary

disease (COPD), or other respiratory diseases, including asthma exacerbations
- Malignancies diagnoses: all malignancies, including smoking-related malignancies (i.e., lung, larynx, and bladder)

Note: Objective 9 will not be assessed due to study termination (details are given in Section 8).

10. To summarize the number of health-related events (hospitalizations) over time
    Endpoints:
    - Rate of prevalence of emergency room visits and/or hospitalization reported by product use over time
    - Frequency of diagnoses associated with emergency room visits and/or hospitalizations reported over time

    Note: Objective 10 will not be assessed due to study termination (details are given in Section 8).
11. To assess coughing by product
    Endpoints:
    - Cough impact assessed by Visual Analog Scale (VAS)
    - Frequency and intensity of cough using the cough assessment.

    Note: Objective 11 will not be assessed due to study termination (details are given in Section 8).

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

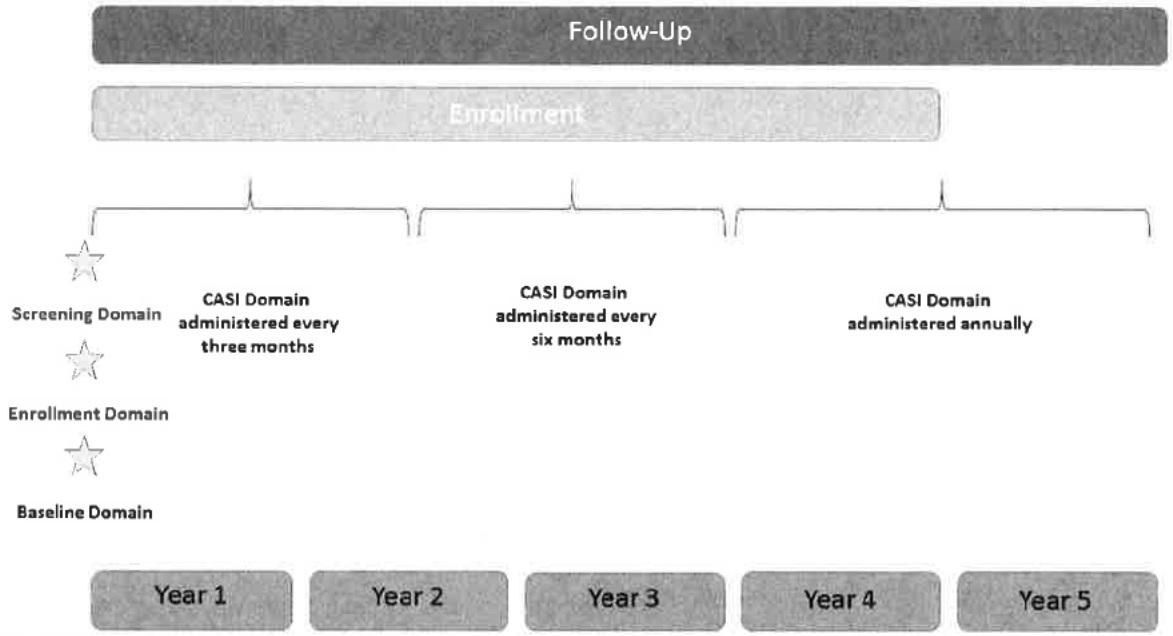
This is a prospective, open-label, observational cohort study of Japanese adults, legally authorized to purchase tobacco products in Japan. The Study will describe the patterns of use of tobacco and nicotine containing products and self-reported health outcomes and health related events in CC smokers and IQOS users.

Participants will be recruited into the cohort in four annual waves of 1000 participants per year (500 IQOS users and 500 CC smokers) until reaching the total study sample size of 4000 participants (2000 per exposure group). The aim of these annual waves is to ensure the recruitment of new IQOS users, even as the demographic characteristics of new IQOS users might change over time.

For IQOS users, the date of initiation of IQOS use is the trigger for all study assessments in the Study. The CC smoker's questionnaire timing will be based on the date of enrollment.

All participants enrolled in the Study will answer the computer assisted self-interviews (CASIs) which will include the following questionnaires: demographic information, smoking history, detailed product use, lifestyle assessments, socio-economic status questionnaire (SES), QSU-b, PRI-P, FTND, intention to stop questionnaire, self-reported health outcomes (symptoms and diagnoses) and health related events (hospitalizations) questionnaire, and cough assessment questionnaire, while IQOS users will also be administered the MCEQ and SRCQ.

Figure 1 Study Design



CASI= Computer assisted self-interview.

The study was terminated in March 2018 during the recruitment of wave 2 participants (Year 2).

6.2 Study Population

6.2.1 Selection of Study Population

4000 participants were to be enrolled in the Study, including 2000 IQOS users and 2000 CC smokers. However the study was terminated during the recruitment of wave 2 participants.

The study will enroll Japanese adults legally authorized to buy tobacco products in Japan.

6.2.2 Inclusion Criteria

At screening, each participant must meet the following criteria in order to be enrolled:

Table 1 Inclusion Criteria

Inclusion Criteria
1. Adults legally authorized to buy tobacco products in Japan (20 years of age)
2. Japanese
3. Participant is able to understand the information provided in the informed consent form (ICF)
4. Signed ICF
5. Willing to participate in the study and has access to the internet
6. For IQOS users: o Is currently using IQOS HeatSticks, and o Has used at least 100 IQOS HeatSticks in their lifetime, and o Has used IQOS HeatSticks for at least 2 months NOTE: The use of IQOS HeatSticks defines the user as an IQOS user, regardless of other tobacco or nicotine product use
7. For CC smokers: o Is currently using CC, and o Is not currently using IQOS HeatSticks, and o Has used at least 100 CC in their lifetime

6.2.3 Exclusion Criteria

Participants who meet any of the following exclusion criteria at screening must not be enrolled into the study.

Table 2 Exclusion Criteria

Exclusion Criteria
1. Tobacco industry employees
2. Employed by the Sponsor, Contract Research Organization (CRO) or Clinical Site
3. For IQOS users: o More than 12 months of IQOS use
4. For former smokers: o Is not currently using CC, and o Is not currently using IQOS HeatSticks, and o Has used at least 100 CC and/or 100 IQOS HeatSticks in their lifetime

6.2.4 Discontinuation of Participants from the Study

Participants are free to withdraw from the study at any time. Participants can log into the Study Website at any time to discontinue from the Study. If a participant decides to withdraw, they will be asked to record the reason for discontinuation, although they are not obliged to disclose it. Data collected for enrolled participants prior to the participant's withdrawal will be kept in the database and used in the analysis.

Participants may be discontinued from the Study for any of the following reasons:

- Withdrawal of informed consent.
- The Sponsor terminates the study. If the Sponsor decides to prematurely terminate the study, the participant will be promptly informed.
- Lost to follow-up.

Participants that discontinue from the Study cannot re-enter the study.

7 DERIVED AND COMPUTED VARIABLES

7.1 General Definition

7.1.1 Types of Missing Data

There are many potential sources of missing data in the study data and it will be important to identify and categorize the different types of missing data.

7.1.1.1 IQOS CASI was missed due to the Study Design

During the first year, IQOS participants may enter the study between 2 and 12 months of product use. All IQOS participants will complete their baseline questionnaire at time of entry (baseline CASI). After the baseline CASI, the next CASI is dependent on the exposure time to IQOS. IQOS participants will not complete a CASI if their baseline CASI is within the timeframe (± 4 weeks of the next required CASI).

7.1.1.2 CASI was missed by Participant

The study participant did not complete a CASI despite being enrolled in the study. For IQOS users during the first year of the study if the Baseline CASI is conducted within the assessment window for a specific CASI, the Baseline will be used in the assessment of the time-point.

7.1.1.3 Questionnaire Missed

The CASI is incomplete. There are some data collected at the time-point; however there is one or more questionnaire within the CASI that was/were completely missed.

7.1.1.4 Questions Missed

The questionnaire is incomplete. There are some data collected within a questionnaire for a time-point, however there are one or more questions within the questionnaire that were missed or not answered.

7.1.1.5 Inconsistent Data

Data are present in questionnaires but there are inconsistencies. In this case, some answers will take precedence over others when they contradict each other. The rules for handling inconsistent data will be described in the Appendix data-handling document separately from the SAP.

7.1.2 Definitions of Time

There are four major definitions of time

1) Study time (for each participant)
2) IQOS time
3) Annual Wave
4) Measurement Time

7.1.2.1 Study Time

Study time (STi) is the time of the participant in the study, starting with the completion of the baseline CASI. For participants that enter the study as CC smokers, STi will drive the timing of the subsequent CASIs.

7.1.2.2 IQOS Time

IQOS time is the time since initiating IQOS. A participant is required to have between 2-12 months of IQOS use to enter the study, and 100 IQOS HeatSticks used during their lifetime to be considered an IQOS user, IQOS time will be based on the date of initiation of IQOS.

7.1.2.3 Annual Wave

Annual wave is an identifier for each subject in the Study based on the wave in which they were enrolled. Information on the wave in which the subjects are enrolled in will come from the system.

7.1.2.4 Measurement Times

Measurement Times (MT(i)) i= 0,1,2,….,11 is defined in months as follows

MT(0)= 0 as the baseline;

MT(1)= 3 months; MT(2)= 6 months ; MT(3)= 9 months; MT(4)= 12 months;

MT(5)=15 months; MT(6)= 18 months; MT(7)= 24 months; MT(8)= 30 months; MT(9)= 36 months; MT(10)= 48 months; MT(11)= 60 months

Note: Due to study termination MT from MT(7) onwards are not applicable.

Results overtime for participants that entered the study as CC smokers will be presented by MT. For IQOS users MT(i) corresponds to IQOS time.

7.1.3 Product Use

7.1.3.1 Consumption (Sticks per Day)

Consumption at a Measurement time

At a MT(i), this is the number that a participant reports in their questionnaire as the average number used per day (current use). Participants will only be presented at MT(i) for which they have answered about their product use. For participants that entered the study as IQOS users this will be presented by IQOS time.

7.1.3.2 Individual Product Use at a Measurement Time

Products will be combined to three categories:

1) CC including Manufactured cigarettes and roll- your-own cigarettes,

2) THS (Marlboro Heatsticks with IQOS device],

3) Other tobacco product use (OTP) including other Heat-not-Burn products (Ploom with Mevius/ Planissimo/ Gold/ Lugano/ Orchard/ Cooler Pods and Glo), e-cigarettes, and all other product use.

Weekly numbers of consumption will need to be converted to daily numbers, in order to classify the population into several product use patterns described in Section 7.1.4.

The THS and CC consumption over a period ending at MT(i) will be calculated as the average number of THS per Day ($THSPD_i$) and Cigarettes per Day (CPD_i), respectively, over the period MT(i-1) to MT(i). For the CPD_0 and other products missing at study entry (from product use questionnaire), the information can be obtained from the smoking history of Wave 1 EXCO database (previously reported).

Consumption of other product types will be calculated in analog manner for descriptive purposes (e.g., average consumption of other tobacco products per day [$OTPD_i$] including all other products used). For occasional daily use (or occasional weekly use), it will be treated the same as daily use (or weekly use).

7.1.4 Average Consumption

Percent consumption of THS, CC, OTP, e-cig, and HnB will be calculated with respect to THSPD, CPD, OTPD, ePD, HnBPD use calculated at MT_i based on reported use in the Product use questionnaire as:

$$\%THS_i = 100 * \frac{THSPD_i}{THSPD_i + CPD_i + OTPD_i}$$

$$\%CC_i = 100 * \frac{CPD_i}{THSPD_i + CPD_i + OTPD_i}$$

$$\%OTP_i = 100 * \frac{OTPD_i}{THSPD_i + CPD_i + OTPD_i}$$

$$\%e - cig_i = 100 * \frac{ePD_i}{THSPD_i + CPD_i + OTPD_i}$$

$$\%HnB_i = 100 * \frac{HnBPD_i}{THSPD_i + CPD_i + OTPD_i}$$

where $THSPD_i$ is the average daily THS consumption (Marlboro Heatsticks with iQOS device), CPD_i is the average daily Cigarettes consumption at MT_i, $OTPD_i$ is the average daily other tobacco products consumption, ePD_i is the average daily e-cigarette products consumption, and $HnBPD_i$ is the average daily HnB products consumption. ePD and HnBPD are also included in OTPD.

7.1.5 Definitions of Behavior

Current Behavior (CB) at MT(i), will be denoted CB(i) and will be defined as described in Table 3:

Initial Behavior (IB) is the behavior at enrollment.

Table 3 Current Behaviors Definitions

CB(i)	Notation at MT(i)	Definition
Primarily THS	**Prim_THS$_i$**	• ≥70% consumption from THS
Primarily CC	**Prim_CC$_i$**	• ≥70% consumption from CC
Mixed THS-CC	**Mix_THS_CC$_i$**	• Consumption from THS in (30%-70%) AND consumption from CC in (30%-70%)
Mixed THS-OTP	**Mix_THS_OTP$_i$**	• Consumption from THS in (30%-70%) AND consumption from OTP in (30%-70%)
Mixed CC-OTP	**Mix_CC_OTP$_i$**	• Consumption from CC in (30%-70%) AND consumption from OTP in (30%-70%)
Non-User/Smoker	**Non_Smoker$_i$**	• Total consumption = 0
Other	**Other$_i$**	• None of the above and no 'missing'

Note: OTP includes other HnB except THS
Note: ePD is considered as one of the OTP when we determine the CB.

7.1.6 Definitions of Pack-Years

Pack-Years are calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. Pack-years are calculated by summing the trapezoids of cigarettes smoked (either from manufactured and/or hand-rolled cigarettes) from Smoking History Questions 8--13 at baseline of [redacted] database of Wave 1 participants. Baseline product use will be used when calculating the trapezoid of cigarettes smoked. Pack-years are calculated

up to 20 years of smoking history. Pack-years will be categorized into 5 pack-years groups (e.g. 0-5, >5-10, >10-15…).

7.1.7 Definition of Duration as a CC Smoker at Baseline

The duration of CC smoking over a lifetime at baseline will be calculated as the difference between the age of the participant at study entry and the age at which the participant initiated smoking, subtracting the total sum of the duration of quit times.

7.2 Questionnaires

7.2.1 Socio-Economic Status Questionnaire

There is no scoring for SES or missing data imputation.

7.2.2 Smoking History Questionnaire

There is no scoring for this questionnaire or missing data imputation.

8 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

Changes listed below are changes as compared to P1-PMC-01-JP Study Protocol version 7. Due to study termination and in light of the outcome of the scientific report, PMP and [redacted] agreed upon a reduced scope statistical analysis.

The reduced sample size, the limitations of the study design, and the shorter follow-up have made some of the planned objectives either not assessable or uninformative. The new statistical analysis will focus on a subset of the objectives and endpoints described in the protocol (see below):

1. To characterize and describe patterns of use of tobacco and nicotine containing products
   Endpoints:
   - Mean number of cigarettes smoked (per day and/or per week) over time
   - Mean number of IQOS HeatSticks used (per day and/or per week) over time
   - Mean number of times e-cigarettes are used (per day and/or per week) over time
   - Product use patterns over time (individual and dual/poly use patterns)
2. To identify intra-individual product use trajectories over time
   Endpoints:
   - Behaviors transitions over time
   - Uptake of products
   - Rate of tobacco and nicotine product use over time
5. To characterize the users of tobacco and nicotine containing products over time
   Endpoints:
   - Demographics and socio-economic characteristics of tobacco and nicotine containing products users
   - Smoking history of tobacco and nicotine containing products users
   - Pre-IQOS tobacco and nicotine containing product usage and behaviors
3. All other objectives and endpoints will not be assessed. Beyond the aforementioned study limitations that affect all the objectives transversally, a detailed rationale of specific limitations for each non assessed objective is given below. To describe the cessation rates of tobacco and nicotine containing products including CC over time. The rationale why objective 3 will not be assessed consists of:
   - Cessation is defined as having quit smoking for at least one year, and is recorded as a behavioral change at each time-point, an actual date is never recorded.
   - With longer follow-up, cessation will be considerably misclassified, due to the discrepancy between the definition and the variation in timing of data collection.

4. To identify and assess the motivations for quitting tobacco use and to characterize the quit attempts by product use over time. The rationale why objective 4 will not be assessed consists of:
   - The 'intention to quit questionnaire' asks, which product the subjects would like to quit at a given time-point; due to missing data for IQOS users this will not effectively capture why subjects switched to IQOS.
   - Self-reported quit attempts will be heavily biased.
6. To assess subjective effects including the urge to smoke, product reinforcement and self-observed aesthetic improvements over time. The rationale why objective 6 will not be assessed consists of:
   - As stated in the objective these are subjective questionnaires (QSU-b, SRCQ, mCEQ), and are better reported as intra-individual changes.
   - There is no baseline to reference for the IQOS users, who may be systematically different from CC smokers, precluding any comparison.
   - Within group comparisons over time are limited due to lack of a baseline in IQOS users and re-classification of subjects at each time-point, based on current behavior but independent of previous behavior.
7. To assess the perception of risk associated with tobacco and nicotine containing products by product use over time. The rationale why objective 7 will not be assessed consists of:
   - There is no baseline to reference for the IQOS users, who may be systematically different from CC smokers, precluding any comparison.
   - Within group comparisons are limited over time, due to lack of a systematic baseline in IQOS users and re-classification of subjects at each time-point, based on current behavior.
8. To assess the strength of nicotine dependence by product use over time. The rationale why objective 8 will not be assessed consists of:
   - There is no baseline to reference for the IQOS users, who may be systematically different from CC smokers, precluding any comparison.
   - Within group comparisons are limited over time, due to lack of a baseline in IQOS users and re-classification of subjects at each time-point, based on current behavior but independent of previous behavior.
9. To describe the rates of self-reported signs, symptoms and diagnoses by product use over time. The rationale why objective 9 will not be assessed consists of:

- Validity of self-reported health data is highly questionable, especially in this specific study population.
- Tobacco leads to long-term chronic diseases, there will not be observed changes in health outcomes with this short follow-up.
- Potential prodromal effects in IQOS users would lead to higher levels of events in this group in the short-term.
- CC smokers are older than IQOS users and would be expected to have a higher number of events.

10. To summarize the number of health related events (hospitalizations). The rationale why objective 10 will not be assessed consists of:
    - Subjects with health issues (e.g. hospitalizations) are more likely to drop-out leading to biased results.
11. To assess coughing by product use. The rationale why objective 11 will not be assessed consists of:
    - There is no baseline to reference for the IQOS users, who may be systematically different from CC smokers, precluding any comparison.
    - Within group comparisons are limited over time, due to lack of a baseline in IQOS users and re-classification of subjects at each time-point, based on current behavior but independent of previous behavior.

Other changes from the protocol consisted of:

- The analysis will be performed on wave 1 participants whose data were collected through the [redacted] CRF. All data collected up to study termination will be listed (see Table 4).
- Re-definition of CBs as described in Table 3
  - CBs as defined in Final SAP v2.0 (31AUG2017) were used for topline tables and will appear in the final analysis datasets using different variable names from the newly defined behaviors.
  - CBs were reduced due to study termination and the limited sample size.
- The definition of CASI missed by participant (see Section 7.1.1.2) has been clarified.
- Separate presentation for CC smokers and IQOS users
  - There is no baseline to reference for the IQOS users, who may be systematically different from CC smokers, precluding any comparison.

Stratified presentation will be limited to sex and age group at entry and IB, CB where applicable.

- Wave of enrollment (strata) is no longer applicable because of study termination.

9 ANALYSIS POPULATIONS

There are no assessments of safety captured as part of this study, therefore there are no planned safety analysis and no safety population defined.

9.1 Enrolled Population

All participants that were enrolled in the study are considered as the enrolled population. All the analyses will be performed on the enrolled population.

9.2 Protocol Deviations

Protocol deviations are defined as deviations from the study procedures, including but not limited to any violation of inclusion/exclusion criteria. Any other protocol deviations identified during the study will be recorded into the protocol deviation tracker. All deviations will be reviewed and each deviation will be classified as major or minor.

9.2.1 Major Protocol Deviations

Participants with major protocol deviations will be identified and reviewed prior to the final analysis.

The categories for the major deviations may include, but are not limited to the following deviation:

- Eligibility criteria violation

9.2.2 Minor Protocol Deviations

Minor protocol deviations will be identified and reviewed prior to the final analysis.

The categories for the minor deviations may include, but are not limited to the following deviations:

- CASI questionnaire not done
- Missing product use questionnaire at any specific time-point.

Protocol deviations will be derived programmatically and recorded in the protocol deviation tracker, that will be transferred to the biostatistics team after database lock.

10 PLANNED STATISTICAL METHODS

10.1 General Considerations

This study is observational in nature, and is self-sourced: data will be subject to analysis/data-handling rules, but no data cleaning or updates. Therefore, the Study analysis may be performed at any point during the study, after the SAP is approved.

Product safety is not reported within the study and is not being captured in association with study participants therefore it cannot be summarized.

The statistical evaluation will be performed using SAS®, version 9.2 or later.

10.1.1 Stratified Presentation

- Analyses will be stratified and reported separately by product group at study entry
- Analyses may be further stratified by the following factors:
    - IB (as defined in Section 7.1.5)
    - Sex: male and female
    - Age group at study entry: age group will be categorized into 10 year groups. For example, 20-29, 30-39, etc.
    - CB at each time-point.

Additional stratification variables may be investigated throughout the study.

10.1.2 Descriptive Statistics

Data presented in listings will be ordered by group of use at study entry (cohort or IB), and then by the participant number, unless otherwise specified.

Descriptive statistics will be provided for all measurements and defined behaviors at MT(i) for CC smokers, and IQOS time for IQOS users.

Descriptive statistics for continuous variables will include number of participants (n), number and percent of participants with data, mean, standard deviation (SD), median, 95% confidence interval (CI), minimum and maximum. For categorical variables absolute and relative (%) frequency for categorical data will be presented.

Counts of missing data will be provided in all tables for information only. Percentages will not include the missing category and will be calculated from the number of participants with

available (non-missing) data.

10.1.3 Definitions for Statistical Data Analysis

The detailed definitions are specified previously in Section 7.

10.1.4 Handling of Missing Values

The Study will consist of missing data for multiple reasons and it is important to distinguish between the different types of missing data:

(1) CASIs are missing due to the design of the study.

a. IQOS users do not have CASI time-points prior to enrolling in the study – in this case the missing time-point will be missing and there is no THS product use data collected in the Smoking History questionnaire.

b. IQOS users will not complete a CASI if their Enrollment CASI is within the timeframe (± 4 weeks of the next required CASI) – in this case the Enrollment CASI will serve as the data for the missing CASI.

(2) Participant starts but does not complete the CASI for a specific time-point. The available data will be used. Regarding time-point specific data, the participant will only be included at time-points where they provide data. For averages over a period of time the mean will be calculated based on the data that does exist.

(3) Participant misses an entire CASI – the participant will be excluded from the time-point that is missing.

(4) Product use at MT(i) if missing, can be interpolated by averaging across neighboring product use at MT(i-1) and MT(i+1). Interpolated values will be flagged in the listing.

10.1.4.1 Insufficient Data for Analysis/Presentation

If there are no values/events at the general value, then the break up should not be presented.

For categories of summaries that have <4 subjects, only the number of subjects and the minimum and maximum will be shown.

10.1.5 Multiple Comparisons/Multiplicity

Not applicable.

10.1.6 Confidence Intervals

Unless stated otherwise, all CIs will be two-sided 95% CIs.

10.2 Disposition of Participants Including Protocol Deviations

Tables and listings on participant disposition will be presented for all enrolled participants in the Study.

Disposition related tables will present frequencies of participants completing each time-point by cohort (Table 14.2.1.1.1). Another table will present the distribution of behavior groups for the IQOS users cohort at study entry (Table 14.2.1.2.1). The table will show the distribution for all possible CASI at entry (3 months, 6 months, etc.). The disposition tables will be repeated by sex and age group (Tables 14.2.1.1.2, 14.2.1.1.3, 14.2.1.2.2 and 14.2.1.2.3).

The number of participants at each time-point is defined as all participants who are enrolled on or prior to the time-point unless their participation has been terminated prior to the time-point.

Participant data listings present separately for related information of disposition and attendance (Listing 14.3.1.1 to 14.3.1.3).

Protocol deviations will be tabulated by cohort (Table 14.2.1.3). The protocol deviations information will also be presented in the listing (Listing 14.3.2).

10.3 Demographic and Other Baseline Characteristics

Demographic data will be presented by frequency distributions for categorical data such as sex, and by summary statistics for continuous variables. Tobacco and nicotine containing products use, and IB, are defined based on the product use questionnaire at screening. The following information will be summarized by cohort group and IB respectively (Table 14.2.1.4.1 and 14.2.1.4.2):

- Demographics and Baseline Characteristics (age, sex)
    - Age (years) will be derived as: (ICF date – birth date) / 365.25
- Pack-year summary and years of smoking (see sections 7.1.6 and 7.1.7)
    - Pack-year and years of smoking will be presented in two ways:
        - mean, SD, median and 95% CI, minimum and maximum
        - group of five pack-years/years of smoking.
- Months of THS use before study entry for IB as IQOS user
- Where do you live? (8 Regions and the details as well)

The prefectures listed in "Where do you live" are collapsed into the following eight areas:

- Hokkaidô: Hokkaidô
- Tohoku: Aomori, Iwate, Miyagi, Akita, Yamagata
- Kanto: Fukushima, Ibaraki, Tochigi, Gunma, Saitama, Chiba, Tôkyô, Kanagawa
- Chubu: Niigata, Toyama, Ishikawa, Fukui, Yamanashi, Nagano, Gifu, Shizuoka, Aichi
- Kansai: Mie, Shiga, Kyôto, Ôsaka, Hyôgo, Nara, Wakayama
- Tyugoku: Tottori, Shimane, Okayama, Hiroshima, Yamaguchi
- Shikoku: Tokushima, Kagawa, Ehime, Kôchi
- Kyusyu: Fukuoka, Saga, Nagasaki, Kumamoto, Ôita, Miyazaki, Kagoshima, Okinawa

Corresponding information is provided in participant data listings (Listing 14.3.2.3.1).

The tables will be presented in the same manner for socio-economic characteristics (SES) tables (Table 14.2.1.5.1 to 14.2.1.5.2).

An additional table (Table 14.2.1.6.1) will present demographic characteristics for participants that (after enrollment) started IQOS vs. those who did not in the CC smokers' cohort. Among those who started IQOS, this table will also distinguish dual (THS+CC) users and THS exclusive users. A similar table (Table 14.2.1.6.2) will present demographics characteristics for participants that (after enrollment) stopped IQOS vs. those who continued in the IQOS users' cohort. Among those who stopped IQOS, this table will also distinguish those stopping THS exclusively and those who stopped all tobacco products. Table 14.2.1.6.3 will present demographic characteristics for participants that (after enrollment) stopped all tobacco products vs. those who continued in the CC smokers' cohort. Those who only stopped CC will be documented separately.
Participants starting IQOS after enrolment are defined as those that consumed at least one heat-stick per day at their last evaluable assessment.
Participants that stopped IQOS/CC/OTP are defined as those having a consumption of 0 in the corresponding category at their last evaluable assessment.

Corresponding information is provided in participant data listings (Listing 14.3.2.3.2 and 14.3.2.3.3).

10.4 Measurements of Product Compliance

Not applicable.

10.5 Extent of Exposure (Product Consumption)

Details of product used are specified in Section 7.1.3 and 7.1.4.

10.6 Planned Statistical Analyses

10.6.1 Product Use Level

To assess objective 1, the following analysis will be conducted.

Summary table of the use of tobacco and nicotine containing products over time for all enrolled participants in the CC cohort at enrollment (Table 14.2.2.1.1). For the IQOS users cohort there will be two summary tables. Table 14.2.2.2.1 will describe product use for each CB at each IQOS time. Table 14.2.3.1 will describe the flow of product use overtime, separately for those who have started the study at IQOS time 3 months, 6 months, 9 months and 12 months and overall (regardless of the IQOS time at enrollment). These tables will summarize:

- Mean number of cigarettes smoked (per day) - CPD(i)
- Mean number of THS Tobacco Sticks used (per day)- THSPD(i)
- Mean number of Heat-not-Burn products used (per day)- HnBPD(i)
- Mean number of other cigarettes product used (per day)- OTPD(i)
- Mean number of e-cigarettes used (per day)- ePD(i)
- Percent of cigarettes used (%CC)
- Percent of THS Tobacco Sticks used (%THS)
- Percent of Heat-not-Burn products used (%HnB)
- Percent of other cigarette products used (%OTP)
- Percent of e-cigarettes used (%e-cig)

All the above tables will be repeated by sex and age group (Tables 14.2.2.1.2, 14.2.2.1.3, 14.2.2.2.2, 14.2.2.2.3, 14.2.2.3.2 and 14.2.2.3.3).

The following figures will be provided at each MT(i).

- Bar chart of mean consumption of CPD(i), THSPD(i), HnBPD(i), OTPD(i), ePD(i), with 95% at each (applicable) IQOS time, separately for participants that entered at CASI 3 months, 6 months, 9 months and 12 months and overall (Figure 14.1.2.1).

Corresponding information is provided in participant data listings (Listing 14.3.2.4.1).

10.6.2 Product Use Patterns

The table of current behavior, CB(i), at MT(i) will provide the information of product use patterns (Table 14.2.2.4.1) for CC smokers cohort. In the IQOS users cohort a similar table (Table 14.2.2.5.1) of CB(i) over IQOS time will be displayed by month of enrollment (i.e. separately for enrollment at 3 months, 6 months, 9 months and 12 months CASI) and overall. Other product use patterns, like uptake of HnB products for CC cohort by CB(i) (Table

14.2.2.6.1), and description of use of HnB and THS Brand products, cigarettes, e-cigarettes, smokeless tobacco pipe, roll-your-own cigarettes, cigars/pipes/kiseru, and chewing tobacco/snus/snuff use for IQOS users (Table 14.2.2.7.1) cohort will be presented.

Uptake of product (not CC) is defined based on the product use questionnaire, as when a participant uses at MT(i) an HnB or THS product and was not using that product at the previous time-point (Table 14.2.2.6.1). Frequency of HnB product and THS brand, cigarettes and e-cigarettes, smokeless tobacco pie, roll-your-own cigarettes, cigars/pipes/kiseru and chewing tobacco/snus/snuff use will also be summarized by each IQOS time-point no matter the participant uses it previously or not (Table 14.2.2.7.1).

Additional product transition table will also be provided between CB(i-1) and CB(i) (Table 14.2.2.8).

The following outputs will be repeated by sex and age group:

- Descriptive Statistics of CB in the CC smokers cohort (Table 14.2.2.4.2 to 14.2.2.4.3)
- Descriptive Statistics of CB in the IQOS users cohort (Table 14.2.2.5.2 to 14.2.2.5.3)
- Descriptive Statistics of Uptake of HnB Products by CB in the CC smokers cohort (Table 14.2.2.6.2 to 14.2.2.6.3)
- Descriptive Statistics of THS and OTP use in the IQOS users cohort (Table 14.2.2.7.2 to 14.2.2.7.3)

A Sankey diagram will display the flow of CB(i) over time for the CC smokers and IQOS users separately (Figures 14.1.2.2.1 and 14.1.2.3.1). Figure 14.1.2.3.1 will include, within the band, the numbers of participants already enrolled or newly enrolled for each IQOS time. Those lost to follow-up will be documented in a band as well. For IQOS users the diagram will be repeated separately for those enrolled at IQOS time 3 months, 6 months, 9 months and 12 months (Figure 14.2.4.1). Figures will be repeated by sex and age-groups (14.1.2.2.2, 14.1.2.2.3, 14.1.2.3.2, 14.1.2.3.3, 14.1.2.4.2, 14.1.2.4.3).

Corresponding information is provided in participant data listings (Listing 14.3.2.4.2).

11 ANALYSES AND REPORTING

11.1 Interim Analyses and Data Monitoring

Not applicable due to study termination (details in Section 8).

11.2 Safety Reporting

Not applicable.

11.3 Topline Results

Not applicable.

11.4 Final Analyses

The list of all tables, figures and listings to be presented at final analysis are presented in Table 4 below.

Table 4 List of Results Produced at Final Analysis

TLF no	Title
TABLES	
Table 14.2.1.1.1	Subject Attendance by Cohort– Enrolled Population
Table 14.2.1.1.2	Subject Attendance by Cohort and Sex – Enrolled Population
Table 14.2.1.1.3	Subject Attendance by Cohort and Age Group – Enrolled Population
Table 14.2.1.2.1	Distribution of Behavior Groups in the THS Users Cohort at Enrollment – Enrolled Population
Table 14.2.1.2.2	Distribution of Behavior Groups in the THS Users Cohort at Enrollment by Sex – Enrolled Population
Table 14.2.1.2.3	Distribution of Behavior Groups in the THS Users Cohort at Enrollment by Age Group – Enrolled Population
Table 14.2.1.3	Protocol Deviations – Enrolled Population
Table 14.2.1.4.1	Demographics and Baseline Characteristics at Enrollment– Enrolled Population
Table 14.2.1.4.2	Demographics and Baseline Characteristics by Initial Behavior – Enrolled Population
Table 14.2.1.5.1	Descriptive Statistics of Socio-Economic Status Questionnaire – Enrolled Population
Table 14.2.1.5.2	Descriptive Statistics of Socio-Economic Status Questionnaire by Initial Behavior – Enrolled Population
Table 14.2.1.6.1	Characteristics of Participants that Started THS after Enrollment – Enrolled Population
Table 14.2.1.6.2	Characteristics of Participants that Stopped THS after Enrollment – Enrolled Population
Table 14.2.1.6.3	Characteristics of Participants that Stopped all Tobacco Products after Enrollment – Enrolled Population
Table 14.2.2.1.1	Descriptive Statistics of Tobacco and Nicotine Containing Products (CC Smokers) at Enrollment – Enrolled Population
Table 14.2.2.1.2	Descriptive Statistics of Tobacco and Nicotine Containing Products (CC Smokers) at Enrollment by Sex – Enrolled Population
Table 14.2.2.1.3	Descriptive Statistics of Tobacco and Nicotine Containing Products (CC Smokers) at Enrollment by Age Group – Enrolled Population
Table 14.2.2.2.1	Descriptive Statistics of Tobacco and Nicotine Containing Products (THS Users) by Current Behavior and Timepoint – Enrolled Population

Listing 14.3.2.2.6.1	Product Use
Listing 14.3.2.2.6.2	Current Behavior and Tobacco/Nicotine Containing Products Average Consumption
Listing 14.3.2.2.6.3	Current Event
Listing 14.3.2.2.6.4	Intention to Stop Questionnaire
Listing 14.3.2.2.6.5	Smoking Urges-brief (QSU-b)
Listing 14.3.2.2.6.6	Total and Factor Score of Smoking Urges-brief (QSU-b)
Listing 14.3.2.2.6.7	Modified Cigarette Evaluation Questionnaire (MCEQ)
Listing 14.3.2.2.6.8	Subscale Scores from Modified Cigarette Evaluation Questionnaire (MCEQ)
Listing 14.3.2.2.6.9	Self-Reported Changes Questionnaire (SRCQ)
Listing 14.3.2.2.6.10	Perception of Risk Associated with Using CCs
Listing 14.3.2.2.6.11	Perception of Risk Associated with Using MRTPs
Listing 14.3.2.2.6.12	Perception of Risk Associated with Using NRTs
Listing 14.3.2.2.6.13	Perception of Risk Associated with Using ENDs
Listing 14.3.2.2.6.14	Subscale Scores from Perception of Risk Associated with Using CCs
Listing 14.3.2.2.6.15	Subscale Scores from Perception of Risk Associated with Using MRTPs
Listing 14.3.2.2.6.16	Subscale Scores from Perception of Risk Associated with Using NRTs
Listing 14.3.2.2.6.17	Subscale Scores from Perception of Risk Associated with Using ENDs
Listing 14.3.2.2.6.18	Fagerström Test for Nicotine Dependence (FTND) Questionnaire
Listing 14.3.2.2.6.19	Total Score of Fagerström Test for Nicotine Dependence (FTND) Questionnaire
Listing 14.3.2.2.6.20	Health Outcome Questionnaire
Listing 14.3.2.2.6.21	Cough Assessment
Listing 14.3.2.2.6.22	Lifestyle Assessment
Listing 14.3.2.2.8.1.1	Clinical Risk Endpoints (CREs) Values Associated with Cardiovascular Disease
Listing 14.3.2.2.8.1.2	Clinical Risk Endpoints (CREs) Values Associated with Respiratory Disease
Listing 14.3.2.2.8.2	Vital Signs

*These listings will be produced on SDTM data only. Derived variables will not be presented.

11.5 ClinicalTrials.gov Reporting

No additional analysis will be done for presentation of results in ClinicalTrials.gov.

12 DATA PRESENTATION

In general, Arial 10 point font will be used for the content of TLFs; exceptionally 8 point font will be used when necessary to allow for large tables and/or listings to fit within the page limits. Font will be single spaced with 0 point spacing before and after each paragraph.

Title text will be Arial 12 point bold font with 0 point spacing before the title, and 12 point spacing after the paragraph.

13 APPENDICES

Appendix 1 Schedule of Events

Assessments		Screening Domain	Baseline Domain	Observational Period (in months of exposure to IQOS)										
	Study Month[a]			Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 24	Month 30	Month 36	Month 48	Month 60
	Time Point	t_0	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9	t_{10}	t_{11}
ICF		•												
Inclusion and exclusion criteria		•												
Participant characteristics and contact details		•												
Enrollment		•												
Demographics			•											
SES questionnaire			•				•			•		•	•	•
Core Questionnaire		•		•	•	•	•	•	•	•	•	•	•	•
Lifestyle assessment			•	•	•	•	•			•		•	•	•
MCEQ[b]			•	•	•	•	•			•				
QSU-b			•	•	•	•	•							

Assessments		Screening Domain	Baseline Domain	Observational Period (in months of exposure to IQOS)										
	Study Month[a]			Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 24	Month 30	Month 36	Month 48	Month 60
	Time Point	t_0	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9	t_{10}	t_{11}
Fagerström Test for Nicotine Dependence			•	•	•	•	•	•	•	•	•	•	•	•
Perceived Risk Instrument (PRI-P)			•				•			•		•	•	•
SRCQ[b]				•	•	•	•							
Self-reported signs and symptoms & health outcomes questionnaires			•			•	•			•	•	•	•	•
Cough assessment questionnaire			•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations ICF = Informed consent form; MCEQ = Modified Cigarette Evaluation Questionnaire; SES = Socio-economic status; QSU-b = Questionnaire for Smoking Urges-brief;

[a]Study months – for IQOS users the study months are calculated from the self-reported date that they stated using IQOS, for CC smokers the study months are equivalent to months of follow-up.

[b]For IQOS users only

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