PMI RESEARCH & DEVELOPMENT

Assessment Study Protocol

Study title:	Assessment of passive environmental tobacco aerosol exposure through IQOS (Tobacco Heating System [THS] with Marlboro Heatsticks) in a restaurant setting where IQOS use, but not cigarette smoking, is allowed
Study number	P1-PES-01-JP
Short title	Real Life Passive Exposure Assessment of IQOS
Registration number:	Not assigned
Product name:	IQOS (Tobacco Heating System (THS) with Marlboro Heatsticks)
Sponsor:	Philip Morris Reduce Risk Products Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version number:	1.0, Final
Revision date:	10th October 2017
Authors:	[redacted], PhD, Lead Study Scientist [redacted], PhD, Study Scientist [redacted], PhD, Study Biostatistician [redacted], MD, Study Scientist [redacted], PhD, Study Biostatistician

PROTOCOL AUTHORISATION

Assessment of passive environmental tobacco aerosol exposure through IQOS (Tobacco Heating System (THS) with Marlboro Heatsticks) in a restaurant setting where IQOS use, but not cigarette smoking, is allowed

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the methods to be used, as well as with the moral, ethical, and scientific principles governing epidemiological research as set out in the current Declaration of Helsinki and the guidelines on Good Epidemiological Practice (GEP).

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Dr.Takao Ohki, MD, PhD, Prinicpal Investigator (Print)	
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SYNOPSIS

Sponsor:

Philip Morris Products S.A.
Quai Jeanrenaud 5
2000 Neuchâtel
Switzerland

Name of Product:

IQOS (Tobacco Heating System [THS] with Marlboro Heatsticks)

Study Title:

Assessment of passive environmental aerosol exposure through IQOS (Tobacco Heating System (THS) with Marlboro Heatsticks) in a restaurant setting where IQOS use, but not cigarette smoking, is allowed

Study Number:

P1-PES-01-JP

Short Title:

Real Life Passive Exposure Assessment of IQOS

Registration number:

NA

Study Location:

This single-site, restaurant-based study, will be conducted in Japan.

Primary Objectives and Endpoints:

1) To estimate the mean change in levels of urinary biomarker of exposure (BoExp) to selected tobacco specific harmful and potentially harmful constituents (HPHC)s representative of environmental tobacco smoke (ETS) after passive exposure to IQOS in a planned restaurant event ('Exposure Event') where IQOS use, but not cigarette smoking, is allowed. Mean change in BoExp will be estimated for the Passive Exposure Group and stratified by product use status.

Co-primary Endpoints (measured before the start and in the last sample collected prior to the individual participants' end of the Events):

- Nicotine
    - BoExp to Nicotine: Nicotine equivalents (NEQ): molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide in spot urine (expressed as concentration adjusted to creatinine)
- Tobacco Specific Nitrosamines (TSNAs): 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N-nitrosonornicotine (NNN)
    - BoExp to Tobacco Specific Nitrosamines (TSNAs): Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL) and Total N-nitrosonornicotine (Total NNN) in spot urine (expressed as concentration adjusted to creatinine)

Secondary Objectives and Endpoints:

1. To evaluate Indoor Air Quality (IAQ) through the assessment of concentrations of select HPHCs representative of ETS in the air of the participating restaurant where both the Non-Exposure and Exposure Events will occur.

Endpoints (measured before the start and during the Event):

- ISO measurement standards for ETS (ISO Norm 18144:2003)[1]
    - 3-Ethenylpyridine (3-EP) [$\mu g/m^3$]
    - Nicotine [$\mu g/m^3$]

[1] ISO Norms related to ETS (15593:2001, 18145:2003 and 11454:1997) are out of scope for indoor air collection as combustion does not occur in THS.

- Carbonyls
    - Acetaldehyde [µg/m3]
    - Acrolein [µg/m3]
    - Crotonaldehyde [µg/m3]
    - Formaldehyde [µg/m3]

- Tobacco Specific Nitrosamines
    - NNN [µg/m3]
    - NNK [µg/m3]
- Real-time measurements of PM1-PM10 suspended particles in air.

2. To evaluate the levels of exposure to additional selected HPHCs representative of ETS during both the Non-Exposure Events and Exposure Events in the study participants.

Endpoints (measured before the start and in the last sample collected prior to the individual participants' end of the Non-Exposure Events):

- Nicotine
    - BoExp to Nicotine: NEQ: molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide in spot urine (expressed as concentration adjusted to creatinine)
- TSNAs: NNK and NNN
    - BoExp to TSNAs: Total NNAL and Total NNN in spot urine (expressed as concentration adjusted to creatinine

Endpoints (measured before the start and in the last sample collected prior to the individual participants' end of the Non-Exposure and Exposure Events):

- Carbonyls
    - BoExp to crotonaldehyde: 3-hydroxy-1-methylpropylmercapturic acid (HMPMA) (concentration adjusted for creatinine)
    - BoExp to Acrolein: 3-hydroxypropylmercapturic acid (3-HPMA) in spot urine (concentration adjusted for creatinine)

- Volatile Organic Compounds
    - BoExp to Benzene: S-phenylmercapturic acid (S-PMA) (concentration adjusted for creatinine)

- Ethylene Oxide
    - BoExp to ethylene oxide: 2-hydroxyethyl mercapturic acid (HEMA) (concentration adjusted for creatinine)

Study Hypothesis:

There are no formal statistical hypotheses to be tested in this study. The research objective is to assess the level of BoExp to selected HPHCs representative of ETS in study participants after passive exposure to IQOS use in a restaurant setting where IQOS use, but not cigarette smoking, is allowed.

Study Design:

This study is a non-interventional observational study designed to assess the impact of environmental tobacco aerosol exposure in Non-Smokers exposed to IQOS in a real-life restaurant setting. Three types of participant with the following characteristics will be enrolled in this study: 1) Non-Smokers; 2) Cigarette Smokers and 3) IQOS Users. IQOS Users will be assigned to either the Passive Exposure or Active Exposure Group (see below).

There are three steps in the core study design:

- Identification and consent of participants;
- Non-Exposure dinner events ('Non-Exposure Event') of 4h duration for the individual participant, where no use of any tobacco or nicotine containing product is allowed, designed to establish background measurements in the absence of exposure to IQOS;
- Exposure dinner Events ('Exposure Event') with 4h of exposure for the individual participants in the Passive Exposure Group, designed to measure BoExp to selected HPHCs representative of ETS in all participants.

A sufficient number of Non-Exposure Events and Exposure Events will be conducted depending on the size of the selected location and to ensure the following minimum number of participants in the respective groups:

Non-Exposure Event:

- Non-Exposed Group (no product use): a minimum of 169 participants comprised of Non-Smokers, IQOS-users not using IQOS or any other tobacco or nicotine-containing product, and cigarette (CC) smokers not using cigarettes or any other tobacco or nicotine-containing product for the duration of the Non-Exposure event;

Exposure Event:

- Passive Exposure Group (no product use): a minimum of 169 participants passively exposed comprised of Non-Smokers, IQOS-users not using IQOS or any other

tobacco or nicotine-containing product, and CC smokers not using cigarettes or any other tobacco or nicotine-containing product for the duration of the Exposure Event;

- Active Exposure Group (IQOS Use): 20% ± 5% of the available seats at the Event location will be occupied by current IQOS Users using IQOS exclusively for the duration of the Exposure Event.

Figure 1 below presents an example of the study schematic with the currently planned number of events.

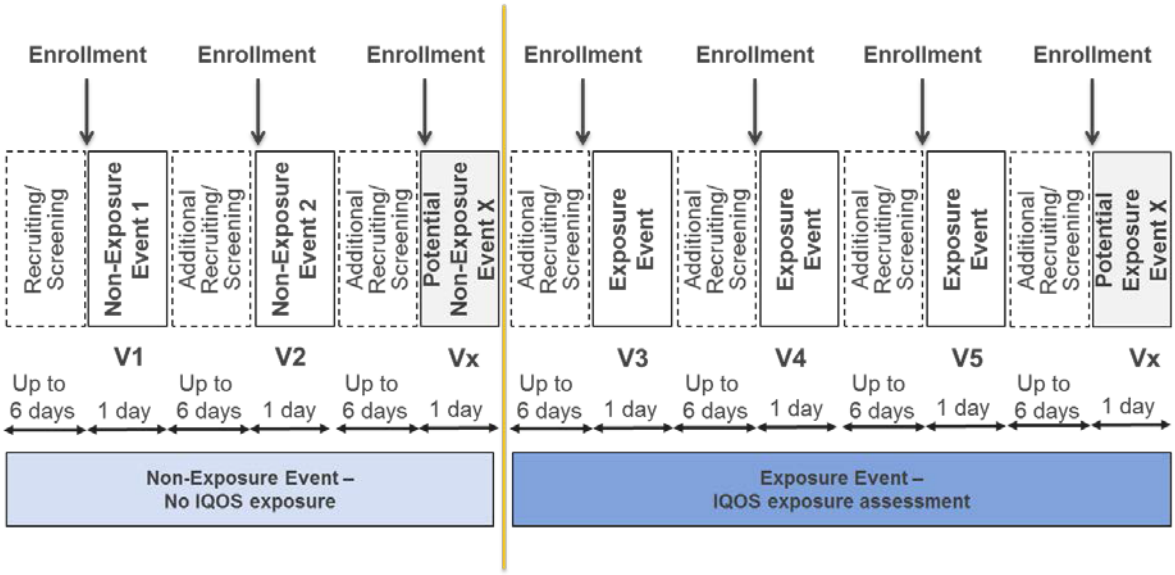

Figure 1 - Study Design

If necessary, additional Non-Exposure and Exposure Events might be conducted to achieve the required number of participants.

Participant Identification and Enrollment:

Participant candidates will be identified via two methods: 1) Philip Morris – Japan (PM-JP) Product Databases, and/or 2) using panels of candidate volunteers provided by participant recruitment vendor(s). The candidates will be sent information of study details through a Study Information Website. Candidates interested in participation will then be invited to provide informed consent through the Study Registration Website. After completion of informed consent, the web system proceeds to a "screening domain" of a Computer Assisted Self-Interview (CASI) that is a set of questions and questionnaires to evaluate the participants' eligibility for participation (i.e., inclusion and exclusion criteria). At the end of the "screening domain" eligible participants will be directed to the "enrollment domain" to confirm their participation in the study, and to select their preferred dates for participation.

Participants may attend a maximum of one Non-Exposure Event and one Exposure Event. Once participant confirms participation in the study, they are considered enrolled. No data will be recorded in the Study Database for the potential participants that do not consent to participate in the study. After consenting to participate in the study, participants can withdraw from the study at any time, but all data already provided by them, with the exception of their contact details, will be retained in the Study Database and analyzed as per the analysis plan. The contact details including personal information and personal identifiers will be kept separate from the study data.

Study Population and Main Criteria for Inclusion/Exclusion:

Main Criteria for Inclusion:

A sufficient number of female or male Japanese adult IQOS Users, CC smokers or Non-Smokers to ensure the required number of participants meeting the following main inclusion criteria will be enrolled in the study:

- Participant is able to understand the information provided in the Subject Information Sheet (SIS) and informed consent form (ICF) (confirmed by signing the ICF) and has signed the ICF..
- Adults legally authorized to buy tobacco products in Japan (20 years of age).
- Participant is Japanese as self-reported.
-
- Willing to participate in the study, comply to study procedures and has access to the Internet.
- Participant is an active IQOS User, or CC smoker, or Non-Smoker as self-reported by the participants and as defined in this protocol.

Criteria for Exclusion:

- Participant with a medical history of severe cardiovascular or respiratory diseases *(e.g.,* stroke, acute cardiovascular event, or pulmonary thrombosis) in the last 12 months as self-reported.
- Participant with currently active cancer or history of cancer within the last 5 years as self-reported.
- Female participant who is pregnant or breast-feeding as self-reported.
- Participant, or their first-degree relatives (parent or child), is a current or former employee of the tobacco industry.

- Participant, or their first-degree relatives (parent or child), is an employee of PMI, [redacted] vendors, the restaurant or the event location.

Specific to participants who are Non-Smokers:

- Participant lives in a household with users of tobacco or nicotine-containing products, or is exposed to the use of tobacco or nicotine-containing products at the workplace.

Investigational Products, Dose, and Mode of Administration:

The product tested in this study is the Tobacco Heating System (THS) with *Marlboro Heatsticks*, marketed in Japan under the brand name IQOS and referred to as IQOS in this protocol. All versions of IQOS and *Marlboro Heatsticks* that have been available for sale in Japan prior or at the time of study start or becoming available during the course of the study are allowed to be used in this study.

***Test product*:** IQOS. Participants in the Active Exposure Group (IQOS use) will be asked to bring their own IQOS device and *HeatSticks* for their own use during the entire study period as *HeatSticks* will not be provided by the Sponsor. Participants in the Active Exposure Group will use IQOS *ad libitum* with no *HeatSticks* variants restrictions.

Duration of Study:

The maximum duration of passive exposure in the Passive Exposure Group will be approximately 4h not exceeding 5h). The maximum duration of Active IQOS use by participants in the Active Exposure Group will be up to 8h (±15 min). Each participant can participate in a maximum of one Non-Exposure Event and a maximum of one Exposure Event.
The overall duration of the study is currently planned for 6 weeks, but might be extended based on the number of events needed to secure the necessary number of participants.
End of Study for a participant is defined as the end of the Non-Exposure Event or the last Exposure Event they participated in. The overall End of the Study is defined as the end of the last Exposure Event.

Indoor Air Quality Measurements:

For Non-Exposure Events, IAQ measurements will be performed at the Event location for up to 3h prior to the start of the Event and for 3h after the last participant has entered the Event for 1h. For Exposure Events, IAQ measurements will be performed at the Event location for up to 3h prior to start of the Exposure and for 3h after the last participant has been exposed for 1h to quantify and differentiate background exposure and to assess the impact of IQOS use on IAQ. Study samples will be collected at each Event (Non-Exposure and each

Exposure Event) at the Event location.

To collect IAQ samples, three mobile sampling set-ups for indoor air pollutants will be used. The set-up consists of 3 aluminum sampling cases with 5 flow-controlled pumps. Each sampling case is equipped with:

- 2 x AD-4 traps for Nicotine and 3-EP collection operated at a flow rate of 1.0 L/min for 3h;
- 2 x 1 DNPH-silica traps for carbonyl collection (acetaldehyde, acrolein, crotonaldehyde and formaldehyde) operated at a flow rate of 1.2 L/min sequentially for 1h;
- 2 glass fiber filters (Cambridge filters) spiked with ascorbic acid for TSNAs (NNN, NNK), operated at a flow rate of 1.0 L/min for 3 h.

The position of the sampling cases will be inside the breathing zone as described by ASHRAE.[2]

Additionally, two small instruments in front of the sampling cases will electronically record the ambient temperature and relative humidity. Furthermore, two portable instruments, used for on-line PM1-PM10 particle measurements will be used. The equipment are the property of PMI and will be used by a PMI trained scientist according to the ISO accredited method PMI-RRP-WKI-111642 “Dust Trax characterization for real time monitoring of aerosol mass concentration”.

A total of 18 tubes per Event will be collected which will be analyzed using validated analytical methods at Analytisch-biologisches Forschungslabor [ABF] Munich.

Statistical Methods:

The Compliant Exposure Set will consist of all enrolled participants who have signed the ICF, have participated in either a Non-Exposure Event or an Exposure Event, have provided two urine samples (at minimum, one urine sample prior to the start of the event and one urine sample after a minimum of 2h of individual participation in the Non-Exposure or Exposure Event), and are compliant with the Event Groups (Non-Exposure vs. Passive Exposure vs.

[2] ASHRAE, 2016. ANSI/ASHRAE Standard 62.1-2016. Ventilation for acceptable indoor air quality. Atlanta, GA: American Society of Heating, Refrigerating and Air-Conditioning Engineers.

Active Exposure).

The Active Exposure Set (PP) will consist of all enrolled participants who have signed the ICF, have participated in an Exposure Event, have provided two urine samples (at minimum, one urine sample prior to the start of the Event and one urine sample after a minimum of 2h after the start of the Active Exposure), and were in the Active Exposure Group.

Descriptive statistics for continuous variables will include the number of participants, number and percent of participants 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) for each product exposure, and summary across all participants. In addition, the results may be presented as a stratified summary as defined in the Statistical Analysis Plan (SAP).

Analysis of the Primary Endpoint:

The primary endpoints will be the pre-event urinary BoExp and latest post two hour urinary BoExp observation. A linear mixed effects model with event type, IAQ, duration of exposure (time between pre-event collection and last post exposure collection), product use status and product use status and event type interaction will be modelled as fixed effects with a random subject effect. Other covariates or interactions terms may be added as needed. Appropriate contrasts will be constructed to determine the effect of passive exposure to IQOS aerosol during the Exposure Event on the mean change in levels of urinary BoExp to selected tobacco specific HPHCs together with the 95% confidence intervals (CIs). Other contrasts can be constructed to determine the change in urinary BoExp for subjects with other smoking status after passive exposure to IQOS usage.

Analysis of the Secondary Objectives:

A similar statistical model as described in the analysis of the primary endpoint will be used to evaluate the levels of exposure to additional selected HPHCs representative of ETS during both the Non-Exposure Events and Exposure Events in the study population. The results will also be looked at stratified by incoming smoking status.

Additional analysis may be defined in the SAP and performed and reported in the Assessment Study Report.

Analysis of the Active Exposure Group:

The primary endpoints will look at the change between the pre-event urinary BoExp and latest post two-hour urinary BoExp observation. A linear mixed effects model with IAQ, duration of exposure (time between pre-event collection and last post exposure collection) and number of sticks used during the event, will be modelled as fixed effects with a random subject effect. Other covariates or interaction terms may be added as needed. Appropriate contrasts will be constructed to determine the effect of active exposure to IQOS usage during the Exposure Event on the mean change in levels of urinary BoExp to selected tobacco specific HPHCs together with the 95% confidence intervals (CIs).

Data processing and analysis of IAQ samples:

The IAQ data will be processed at ABF and the individual results per compound will be summarized and tabulated.

An analysis of variance (ANOVA) design will be applied as the quantitative results of the IAQ sessions will be compared per compound. The mean, standard deviation, relative standard deviation, minimum and maximum will be computed per compound and the number of observations will be indicated. A significance level set at 0.05 will be used to determine equality between sessions.

Sample Size:

The sample size of approximately 169 participants in the Exposure and Non-Exposure Events each is based on the expected exposure of a Non-Smoker when exposed to cigarette smoke as documented in the literature. Variability of exposure levels and method variability were furthermore considered to estimate the sample size needed.

Adverse Events and Participants Safety and Well-Being:

As this study is observational by design and is conducted in a post-market setting, adverse event (AE) reporting will follow the Sponsor's already established post-market Safety Surveillance Procedures for spontaneously-reported events. All study personnel and study participants will be reminded of the product quality complaints (including AEs) hotline that has been established for all users of IQOS in Japan.

In the event that a medical event occurs in any of the study participants the study staff will be advised to call local emergency number to ensure appropriate medical treatment. The related cost for emergency treatment and transportation will be borne by the Sponsor.

Security personnel will be on site at the event location to ensure secure and ordered conduct at the event.

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ABBREVIATIONS AND DEFINITION OF TERMS

3-HPMA	3-hydroxypropylmercapturic acid
AE	Adverse Events
ANOVA	Analysis of Variance
BKG	Background
BoExp	Biomarker of Exposure
CASI	Computer Assisted Self Interview
CC	Cigarette
CI	Confidence Interval
CRF	Case Report Form
CVD	Cardiovascular Disease
DMP	Data Management Plan
DNHP	2,4-Dinitrophenylhydrazine
EA	Environmental Aerosol
ETS	Environmental Tobacco Smoke
GC-MS	Gas chromatography–mass spectrometry
GEP	Good Epidemiological Practice
HEMA	2-hydroxyethyl mercapturic acid
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
HPHC(s)	Harmful and Potentially Harmful Constituent(s)
IAQ	Indoor Air Quality
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
NEQ	Nicotine Equivalents

NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
PMI	Philip Morris International
PMP	Philip Morris Products S.A.
SAP	Statistical Analysis Plan
SD	Standard Deviation
S-PMA	S-phenylmercapturic acid
Total NNAL	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
Total NNN	Total N-nitrosonornicotine
THS	Tobacco Heating System
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 IQOS with *HeatSticks*, cigars, cigarillos, e-cigarettes, hand-rolled cigarettes, pipes, hookah, bidis, and other tobacco- or nicotine-containing products.
End of study	The end of the study for an individual participants will be defined as the end of the Non-Exposure Event or the last Exposure Event he/she participated in. The end of the entire study is defined as the end of the last participant's individual end of the study/the end of the last Exposure Event.
HeatSticks	*Marlboro HeatSticks* are designed to be used with IQOS only. Each *HeatStick* is composed of: tobacco plug; hollow acetate tube; polymer-film filter; mouth piece filter; outer and mouth-end papers.
IQOS	Unless otherwise specified, IQOS in this document refers to PMI's Tobacco Heating System (THS) with *Marlboro HeatSticks* as available for purchase in the Japanese market. No other tobacco sticks should be used with the IQOS device.
IQOS User (IQOS)	• Used at least 100 HeatSticks • Uses IQOS daily > 1/day • Uses a cigarette less than daily • Uses less than 30 cigarettes/month • IQOS is > 95% of product use (all tobacco/nicotine product use) – excluding other products (e-cig/Ploom/etc.)
Cigarette Smoker (CC)	• Used at least 100 cigarettes • Uses cigarettes daily > 1/day • Uses IQOS less than daily • Uses less than 30 HeatSticks/month • Cigarette is > 95% of product use (all tobacco/nicotine product use)
Non-Smoker (NS)	• Abstinent for at least 12 months from the use of any nicotine and/or tobacco-containing product based on self-reporting. • Must not be exposed to cigarette smoke or IQOS use in any other substantial way (family, partner, other, or workplace).

1 ETHICS AND REGULATIONS

1.1 Independent Ethics Committee (IEC) / Institutional Review Board (IRB) Approval

Prior to the start of the study, the study protocol, together with its associated documents (informed consent forms [ICF] which include the participant information sheet and informed consent, participant recruitment procedures, written information to be provided to the participants, and any other documents requested by the Independent Ethics Board [IEC]/Institutional Review Board [IRB]), will be submitted for review and approval to the relevant IEC/IRB. The IEC/IRB shall be appropriately constituted in accordance with the International Epidemiological Association (IEA) Guidance for Good Epidemiological Practice (GEP) [1] and the Ethical Guidelines for Medical and Health Research Involving Human Subjects [2].

A written confirmation of the IEC/IRB approval should be provided to the Sponsor. This should identify the study (Principal Investigator's name, study number, and title) and the documents that have been approved by the IEC/IRB, with dates and version numbers, as well as the date of approval. The composition of the IEC/IRB, including the name and occupation of the chairperson, should be supplied to the Sponsor.

The written approval from the IEC/IRB will be filed in the study master file at the Sponsor or designated organization. The study must not start before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB.

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

These requirements for approval should in no way prevent any action from being taken by the Sponsor in order to eliminate immediate hazards to the participants. If such a change to the protocol is felt to be necessary by the Principal Investigator, and is implemented for safety reasons, the Sponsor and the IRB should be informed immediately.

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 2013 [3] and are consistent with GEP [1], and the Ethical Guidelines for Medical and Health Research Involving Human Subjects [2]. The Principal Investigator agrees to conduct the study in compliance with the protocol agreed upon with the Sponsor and approved by the IEC/IRB. The Principal 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 Principal Investigator study file.

1.3 Subject Information and Consent

1.3.1 Informed Consent Form for Study Participation

Before the "screening domain" is administered, the participant will be informed about the nature and purpose of the study via the Study Website. Participants interested in participating in the study initiate the informed consent process by clicking on the link from the Study Website that will re-direct them to a Computer-Assisted Self-Interview (CASI) to assess eligibility, register for the study, and give informed consent. The ICF will be administered electronically for participants and will be recorded in the Study Database. Participants will be informed that they are free to discontinue their participation at any time.

No data will be recorded in the Study Database for the potential participants that do not consent to participate in the study. Participants will be informed that after consenting for participation in the study, they can withdraw from the study at any time, but that all data already provided by the participant with the exception of their contact details, and all samples collected from the participant until the time of withdrawal will be retained in the database and/or analyzed as per the analysis plan. The contact details including personal information and personal identifiers will be kept separate from the study data. They will also be informed and will be asked to provide their consent for any additional data analyses not mentioned in the protocol or the Statistical Analysis Plan (SAP) that may be performed with the collected data at a later time. Any additional analysis performed will be covered by data confidentiality, as for the main analysis described in this protocol.

1.3.2 Amendment to the Informed Consent Form

If a protocol amendment is required, an amendment may be required to one or more of the ICFs. If revision of the ICF is necessary, the Principal Investigator will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by a relevant IEC/IRB before participants are required to re-sign the ICF.

1.4 Good Epidemiological Practice

The procedures set out in this observational study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and the Principal Investigator abides by the principles of the guidelines on GEP [1]. These guidelines apply specifically to epidemiological studies and therefore provide a robust and ethical framework for conducting observational studies. In

addition, the Principal Investigator will carry out the study in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects [2][.

1.5 Risk Minimization

There are no anticipated specific risks from participating in this observational study as the study is conducted to reflect a real-life setting utilizing an existing IQOS-only restaurant in Japan. Study participation is by invitation only.

2 INTRODUCTION

2.1 Background

2.1.1 Smoking-Related Diseases and Harm Reduction Strategy

Public health authorities, including the World Health Organization (WHO), have concluded that exposure to Environmental Tobacco Smoke (ETS), also named secondhand smoke, which is a mixture of sidestream smoke (tobacco smoke which is emitted from the lit end of a cigarette or cigar) and exhaled smoke, causes heart disease, cancer, as well as respiratory disease and other conditions. The U.S. Environmental Protection Agency, the U.S. National Toxicology Program, the U.S. Surgeon General, and the International Agency for Research on Cancer have all classified ETS as carcinogenic [4-8].

For cardiovascular disease (CVD), it is estimated that ETS increases the risk of heart disease by ~30%, accounting for at least 35,000 deaths annually in the United States [9]. Six meta-analyses have been published summarizing data reported over the last 30 years [10-15] yielding relative risks of heart disease from ETS exposure ranging between 1.2 and 1.3. In 2004, Whincup et al published a 20-year prospective study of ETS exposure and coronary heart disease that estimated that the risk associated with ETS exposure was between 1.45 (95% CI, 1.10 to 2.08) and 1.57 (95% CI, 1.08 to 2.28), depending on the level of ETS exposure [16].

A literature review and meta-analysis to systematically evaluate the association between ETS and lung cancer in Japan identified four cohort studies and five case-control studies on which a quantitative synthesis was conducted only for ETS exposure in the home during adulthood. The pooled relative risk of lung cancer associated with secondhand smoke exposure was 1.28 (95% confidence interval: 1.10-1.48). The authors concluded that ETS exposure in the home during adulthood results in a statistically significant increase in the risk of lung cancer [17].

These results are in line with the estimate of the U.S. Surgeon General who estimates that ETS increases a nonsmoker's chances of developing lung cancer by 20 to 30 percent [11] .

Philip Morris International (PMI) develops, assesses and commercializes a portfolio of innovative products that have the potential to reduce the risk of smoking-related diseases in

comparison to smoking cigarettes. The objective is to develop products that (1) significantly reduce the risk of smoking-related disease compared to continued smoking of cigarettes and (2) are accepted by smokers as substitutes for cigarettes.

One of these novel products is the Tobacco Heating System (THS) which is commercialized in Japan since November 2014 under the brand name IQOS and uses tobacco sticks called *HeatSticks* (sold in Japan as *Marlboro Heatsticks*). IQOS heats the tobacco instead of burning it and the temperature is maintained below 350°C, a temperature much lower than what is observed for cigarettes, which can reach 900°C. More than 6000 smoke constituents have been identified when the tobacco is burned or combusted [18], and more than 100 of them have been categorized as harmful and potentially harmful constituents (HPHCs) [19]. By heating the tobacco instead of burning it, an aerosol is produced that is not the product of combustion and therefore many of the chemical reactions associated with combustion do not take place. As a result IQOS produces an aerosol with significantly lower levels of HPHCs than cigarette smoke, which is the key to THS's potential to reduce the risk of smoking-related disease as HPHCs are formed primarily through combustion and pyrolysis in cigarettes.

IQOS is composed of the Tobacco Stick Holder and a Charger which recharges the Holder after each use. IQOS was designed to be used with dedicated Tobacco Sticks, the *HeatSticks*.

Various pre-clinical and clinical studies have been conducted and in summary, the scientific evidence available to date has shown that:

1. The aerosol of IQOS contains on average 90 to 95% lower levels of HPHCs compared to the smoke from a standard reference cigarette [20].
2. The aerosol of IQOS is on average 90% less toxic compared to the smoke of a standard reference cigarette (cytotoxicity, bacterial, and mammalian mutagenicity) [21].
3. In animal models, continuous inhalation and exposure to IQOS aerosol, even at a multiple of the aerosol concentration, resulted in a dramatically lower systemic toxicity, extensively reduced lung inflammation and histopathological changes in the nasal epithelium as well as lung tissue [22]. Furthermore, in an $Apoe^{-/-}$ mouse model, exposure to IQOS aerosol does not enhance cardiovascular disease or emphysema, when compared to cigarette smoke, and switching from cigarette smoke to IQOS aerosol exposure results in a reversal of the aortic plaque growth in a similar manner as Smoking Cessation (SC) [22].
4. PK studies demonstrated comparable nicotine exposure in subjects using IQOS as in subjects using cigarettes [23-26]
5. The exposure reduction to selected HPHCs in current adult smokers switching to IQOS is scientifically substantiated compared to cigarette smoking and is close to

what is observed in adult smokers who stop smoking for the duration of our clinical studies [27-31].

6. Improvements of cardiovascular and other clinical risk endpoints have been observed in healthy adult smokers who switched to IQOS, similarly to what has been observed in smoking abstinence over a period of up to 3 months [29-31].
7. No safety signals have been detected indicating any new or increased risks of health issues in smokers switching from smoking cigarettes to IQOS.
8. As indicated in markets where IQOS is now available, IQOS has been accepted by smokers (with over 3 million adult users to-date) and appears to be an acceptable substitute for current adult smokers with various smoking habits and patterns.

An IAQ study conducted showed that, out of 23 analytes assessed, only 2 HPHCs, namely nicotine and acetaldehyde, as well as glycerin were detectable in air following the use of IOQS but at levels that were much lower than the thresholds defined in existing air quality guidelines. These results indicated that IQOS is not a source of ETS. The study therefore showed that, based on existing indoor air quality guidelines, there is no impact on the overall Indoor Air Quality (IAQ) when using IQOS in an indoor environment [32, 33].

2.2 Purpose of the Study

The purpose of the study is to show that Non-Smokers exposed to IQOS in a restaurant setting (i.e., through planned dinner "Events") do not have higher urinary levels of Biomarkers of Exposure (BoExp) to selected HPHCs representative of ETS compared to the urinary levels of BoExp to selected HPHCs representative of ETS caused by background exposure in Non-Smokers before IQOS exposure. Furthermore the impact of passive IQOS exposure on IQOS Users and Cigarette Smokers not using any nicotine or tobacco containing nicotine product will be investigated. The addition of IQOS Users who don't use IQOS, and Cigarette Smokers who don't use any nicotine or tobacco products, allows for of the assessment of individuals with varying levels of exposure to HPHCs in their personal lives, in order to assess whether there is any measurable additive exposure from IQOS. Relatedly, the study will also evaluate IAQ through the assessment of concentrations of selected HPHCs representative of tobacco-specific and IAQ markers in the air during the Event.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

There are no major benefits from participating in this study for the overall study population other than to collaborate in the understanding of how the use of IQOS affects by-standers in a real-life setting.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures

There are no anticipated risks from participating in this study. The study is conducted in a real-life setting in an IQOS-only restaurant in Japan where participation of study participants is by invitation-only.

2.3.3 Unforeseeable Risks

It is unlikely that any unforeseeable risks will occur from participating in this observational study. However, the possibility of unforeseeable events/risks will be explained when information about the study is provided. Non-expected malfunction of IQOS may lead to unforeseeable risks. Participants will be informed that IQOS is not demonstrated yet to be less harmful than cigarettes. Mitigation will include close monitoring to detect any unforeseeable risks at the earliest time possible.

3 STUDY OBJECTIVES

3.1 Primary Objective and Endpoints

The primary objective of this study is:

1) To estimate the mean change in levels of urinary biomarker of exposure (BoExp) to selected tobacco specific harmful and potentially harmful constituents (HPHC)s representative of environmental tobacco smoke (ETS) after passive exposure to IQOS in a planned restaurant event ('Exposure Event') where IQOS use, but not cigarette smoking, is allowed. Mean change in BoExp will be estimated for the Passive Exposure Group and stratified by product use status.

   Co-primary Endpoints (measured before the start and in the last sample collected prior to the individual participants' end of the Events):

   - Nicotine
     - BoExp to Nicotine: Nicotine equivalents (NEQ): molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide in spot urine (expressed as concentration adjusted to creatinine)

   - Tobacco Specific Nitrosamines (TSNAs): 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N-nitrosonornicotine (NNN)
     - BoExp to Tobacco Specific Nitrosamines (TSNAs): Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL) and Total N-

nitrosonornicotine (Total NNN) in spot urine (expressed as concentration adjusted to creatinine)

3.2 Secondary Objectives and Endpoints

Secondary objectives of this study are:

1. To evaluate IAQ through the assessment of concentrations of select HPHCs representative of ETS in the air of the participating restaurant where both the Non-exposure and Exposure Events will occur.

   Endpoints (measured before the start and during the Event):

- International Organization for Standardization (ISO) measurement standards for ETS (ISO Norm 18144:2003)[3]
  - 3-Ethenylpyridine (3-EP) [µg/m^3]
  - Nicotine [µg/m^3]

- Carbonyls
  - Acetaldehyde [µg/m3]
  - Acrolein [µg/m3]
  - Crotonaldehyde [µg/m3]
  - Formaldehyde [µg/m3]

- Tobacco Specific Nitrosamines
  - N-nitrosonornicotine (NNN) [µg/m3]
  - 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [µg/m3]
- Real-time measurements of PM1-PM10 suspended particles in air.

2. To evaluate the levels of exposure to additional selected HPHCs representative of ETS during both the Non-Exposure Events and Exposure Events in the study participants.

Endpoints (measured before the start and in the last sample collected prior to the individual participants' end of the Non-Exposure Events):

- Nicotine

[3] ISO Norms related to ETS (15593:2001, 18145:2003 and 11454:1997) are out of scope for indoor air collection as combustion does not occur in THS.

- BoExp to Nicotine: NEQ: molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide in spot urine (expressed as concentration adjusted to creatinine)

- TSNAs: NNK and NNN
  - BoExp to TSNAs: Total NNAL and Total NNN in spot urine (expressed as concentration adjusted to creatinine

Endpoints (measured before the start and in the last sample collected prior to the individual participants' end of the Non-Exposure and Exposure Events):

- Carbonyls
  - BoExp to crotonaldehyde: 3-hydroxy-1-methylpropylmercapturic acid (HMPMA) (concentration adjusted for creatinine)
  - BoExp to Acrolein: 3-hydroxypropylmercapturic acid (3-HPMA) in spot urine (concentration adjusted for creatinine)

- Volatile Organic Compounds
  - BoExp to Benzene: S-phenylmercapturic acid (S-PMA) (concentration adjusted for creatinine)

- Ethylene Oxide
  - BoExp to ethylene oxide: 2-hydroxyethyl mercapturic acid (HEMA) (concentration adjusted for creatinine)

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This study is a non-interventional observational study designed to assess the impact of environmental tobacco aerosol exposure in Non-Smokers exposed to IQOS in a real-life restaurant setting (henceforth referred to as the 'Event'). Three types of participant with the following characteristics will be enrolled in this study: 1) Non-Smokers; 2) Cigarette Smokers and 3) IQOS Users. IQOS Users will be assigned to either the Passive Exposure Group (not using IQOS during the Exposure Events) or Active Exposure Group (using IQOS during the Exposure Events - see below).

There are three steps in the core study design:

1. Identification and consent of participants;
2. Non-Exposure dinner events ('Non-Exposure Event') of 4h duration for the individual participant where no use of any tobacco or nicotine-containing product is allowed, designed to establish background measurements in the absence of exposure to IQOS;
3. Exposure dinner Events ('Exposure Event') with 4h of exposure for the individual participants in the Passive Exposure Group, designed to measure BoExp to selected HPHCs representative of ETS in all participant groups.

A sufficient number of Non-Exposure Events and Exposure Events will be conducted depending on the size of the selected location and to ensure the following minimum number of participants in the respective groups:

Non-Exposure Event:

- Non-Exposed Group (no product use): a minimum of 169 participants comprised of Non-Smokers, IQOS-users not using IQOS or any other tobacco or nicotine-containing product and CC smokers not using the cigarettes or any other tobacco or nicotine-containing product for the duration of the Non-Exposure Event;

Exposure Event:

- Passive Exposure Group (no product use): a minimum of 169 participants passively exposed comprised of Non-Smokers, IQOS-users not using IQOS or any other tobacco or nicotine-containing product and CC smokers not using the cigarettes or any other tobacco or nicotine-containing product for the duration of the Exposure Event;
- Active Exposure Group (IQOS Use): 20% ± 5% of the available seats at the Event location of current IQOS Users using IQOS for the duration of the Exposure Event.

If necessary, additional Non-Exposure and Exposure Events might be conducted to achieve the necessary number of participants.

Figure 2 below presents an example of the study schematic with the currently planned number of events.

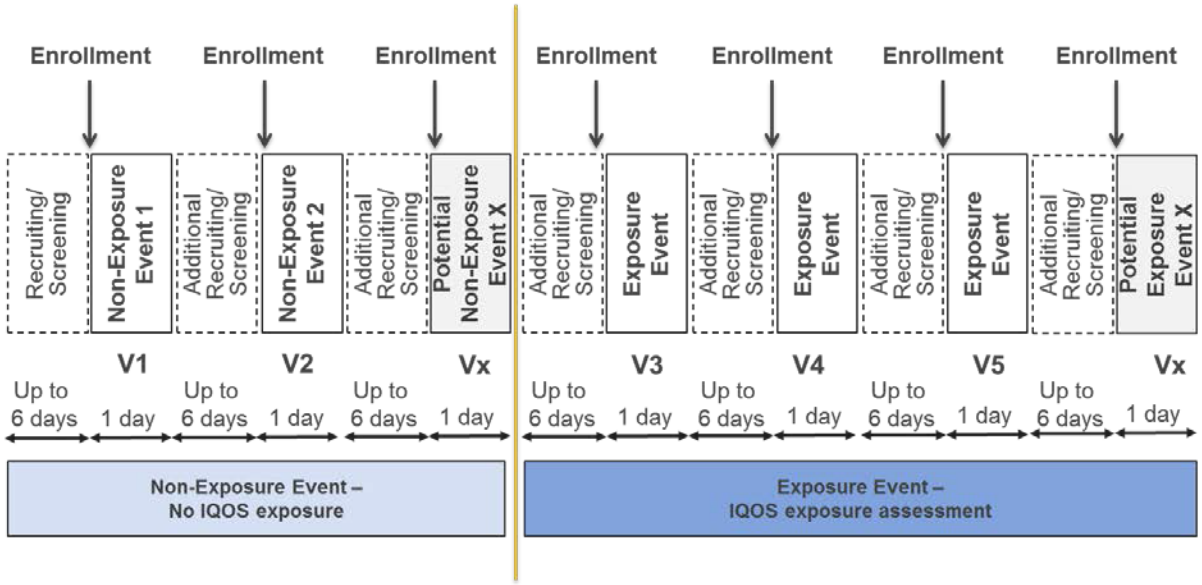

Figure 2 - Study Design

Table 1 below presents the four participant groups, measures of interest, and sample sizes, according to event type (Non-Exposure Event and Exposure Event).

Table 1 Relative Exposure/participants groups, measures and sample sizes, according to event type (Non-exposure vs Exposure)

Variable	Non-Exposure Event	Exposure Event
Participants (group sizes can vary by ± 5%)		
Sample Size required for Non-Exposure and Passive Exposure Group	N = 169	N = 169
• Group 1: Non-Smokers	50%	50%
• Group 2: Cigarette Smokers	25%[1]	25%[1]
• Group 3a: IQOS Users (not using IQOS)	25%[1]	25%[1]
Total	**100% participants in Non-Exposure Events**	**100% participant passively exposed in Exposure Events**
• Group 3b: IQOS Users (using IQOS)	n/a	20% of the total number of available seats in the event location[2]
Measures		
• Urine (void)	Before Start of the Event, as of ≥2h after start of the Event until the end of the Event (last void analyzed only).	Before Start of the Event, as of ≥2h after start of the Exposure until the end of the Event (last void analyzed only).
• Indoor Air Quality measures	For up to 3h prior to start of the Event; for 3h after the last participant has entered the Event for 1h.	For up to 3h prior to start of the Exposure; for 3h after the last participant has entered and has been exposed for 1h.

[1] Participants refrain from using any tobacco or nicotine products, including IQOS and/or cigarettes.

[2] Participants create the exposure to environmental tobacco aerosol through IQOS use.

4.1.1 Step 1: Identification of Participants and Informed Consent: Screening and Enrollment

This step involves the identification of participants, and obtaining informed consent prior to the study (Non-Exposure or Exposure Events). Current adult IQOS Users and Cigarette Smokers will be identified and invited to participate through PMI's product database. A vendor will identify and recruit Non-Smokers from a panel of existing participants used for other research and survey purposes. Additionally, public advertisements might be used.

Potential candidates for participation in the study will be sent a link to a study website to provide information on study details and to complete a Computer-Assisted Self-Interview (CASI) system to assess eligibility and obtain informed consent. After completion of informed consent, the web system proceeds to a "screening domain" of the CASI which is the set of questions and questionnaires to evaluate the participants' eligibility for participation (i.e., inclusion and exclusion criteria, eligible participants).

At the end of the "screening domain" eligible participants will be directed to the "enrollment domain" to confirm their participation in the study. Eligible participants will be presented with the available dates for the Non-Exposure and Exposure Events and asked to confirm his / her preferred dates for participation in maximum one Non-Exposure Event and maximum one Exposure Event. Once a participant confirms participation in the study, they are considered enrolled in the study.

No data will be recorded in the Study Database for the potential participants that do not consent to participate in the study. After consenting for participation in the study, participants can withdraw from the study at any time.. The contact details of the participants, including personal information and personal identifiers will be kept separate from the study data. Subjects will only be compensated for the Non-Exposure or Exposure events they participated in.

4.1.2 Step 2: Non-Exposure Events

The Non-Exposure Events are planned dinner events of 4-hour duration for the individual participant in a restaurant setting with a sufficient number of events ensuring a minimum 169 participants with the following smoking phenotypes: 50% (±5%) of participants are Non-Smokers, 25% (±5%) of participants are IQOS Users (not using IQOS), 25% (±5%) of participants are Cigarette Smokers (not smoking) who are invited to attend a dinner party and enrolled into the study at no cost to them (see Table 1). The Non-Exposure Events are both nicotine- and tobacco-free (i.e., no nicotine or tobacco products are allowed to be used), and participants must agree to this study requirement. This step allows for non-exposure measurements to be obtained in order to estimate levels of primary endpoints in the absence of IQOS exposure.

IAQ measurements will be sampled for up to 3h prior to the start of the Event and for 3h after the last participant has entered the Event for 1h. Urine specimens per person will be collected for analysis as follows:

The first urine sample will be collected prior to the start of the Event. For the second urine sample, collection will start with the first void after 2 hours of participation in the event to allow sufficient exposure to the event environment to have occurred and therefore detection of BoExp in the urine characterizing the background exposure. From the 2h time point onwards every subsequent void will be collected and the previous urine sample discarded with the last void collected ideally at the end of the 4h exposure period. Only the first and the last urine sample taken (ideally after 4h of participation in the Event) will be analyzed. The time of urine collection will be recorded to ensure that only urine samples taken after 2 hours of participation in the Non-Exposure Event are analyzed.

Urine specimens will also be used to confirm self-reported non-smoking status of the invited participants. Participants who misstate their non-smoking status will not be included in the final analysis.

A fixed menu of food and non-alcoholic and alcoholic beverages typically served in Japanese restaurants will ensure homogeneity of types of potential confounders of both IAQ endpoints and BoExp in the unexposed participant group. The overall amount of food consumed per food type and beverages consumed by type will be recorded.

4.1.3 Step 3: Exposure Events

This step comprises the Exposure Events which will occur in the same restaurant setting as the Non-Exposure Events in order to control for restaurant-related exposures that could confound study results. The first of the Exposure Events will occur within 4 weeks of the Non-Exposure Events and will replicate both the meal, beverages and restaurant dynamics (i.e. same location, air ventilation and table setting) of the Non-Exposure Event.

Exposure Event participants may or may not have attended a Non-Exposure Event, as this is not a study requirement. Participants attend the dinner event at no cost to themselves. These participants represent the same product use phenotypes as in the Non-Exposure Events, except that IQOS Users will be assigned for the Exposure Events to either a) IQOS Users who will use IQOS during the dinner event, or b) IQOS Users who agree not to use IQOS (or any nicotine or tobacco product) during the dinner event (see Table 1).

The Exposure Events will include a minimum of 169 passively exposure participants with the following product use phenotypes: 50% (±5%) Non-Smokers, 25% (±5%) IQOS Users who refrain from using any nicotine or tobacco product, and 25% (±5%) Cigarette Smokers who refrain from using any nicotine or tobacco products.

In addition, a total of 20% ± 5% of the available seats at the Event location of actively exposed IQOS Users (who use IQOS during the event) will participate in each of the Exposure Events.

Participants actively using IQOS will enter the event location first and start using IQOS *ad-libitum* for 1h prior to the other participants (passive Exposure Group) entering the event location.

IAQ measurements will be sampled for up to 3h prior to the start of the Event and for 3h after the last participant was exposed for 1h. Urine specimens per person will be collected for analysis as follows:

The first urine sample will be collected prior to the start of the event. For the second urine sample, collection will only start with the first void after 2 hours of IQOS exposure to allow sufficient exposure to have occurred and therefore detection of BoExp in the urine. From the 2h time point onwards every subsequent void will be collected and the previous urine sample discarded with the last void collected ideally at the end of the 4h exposure period. Only the first and the last urine sample taken (ideally after 4h of exposure) will be analyzed. The time of urine collection will be recorded to ensure that only urine samples taken after 2 hours exposure to IQOS are analyzed.

A fixed menu of food and non-alcoholic and alcoholic beverages typically served in Japanese restaurants will ensure homogeneity of types of potential confounders of both IAQ endpoints and BoExp in the unexposed and passively-exposed participant groups. The overall amount of food consumed per food type and beverages consumed by type will be recorded.

4.2 Rationale for Study Design

IQOS is currently used by over 2 million users in Japan. Various restaurants and bars exist where IQOS use is allowed but not CC smoking. This observational study will determine the impact of IQOS use on IAQ and the impact of exposure to environmental tobacco aerosol through measurement of BoExp in urine representative of ETS in a restaurant setting where IQOS use, but not smoking, is allowed.

4.3 Appropriateness of Measurements

Nicotine is one of the markers for ETS, however ETS covers several other markers. In this study, ISO Norms related to ETS (15593:2001, 18145:2003 and 11454:1997) are out of scope for indoor air collection as combustion does not occur in THS. Indoor Air Quality Markers selected for assessment in this study are based on:

1. ISO measurement standards for ETS (ISO Norm 18144:2003)[4]
2. Their relevance for air quality
3. Their relative abundance in THS2.2 aerosol (i.e. the most abundant)
4. Gas-phase tobacco non-specific markers

The BoExp endpoints to assess passive exposure in humans are accepted biomarkers of exposure to ETS, and were furthermore selected based on the following criteria:

1. Availability of a validated analytical method
2. Measure is known to be directly or indirectly affected by the use of tobacco product
3. Timeframe of metabolic decay in the perspective of the study duration
4. Robustness of the method (rapid, simple, accurate)
5. Limited exposure through other sources than tobacco

4.4 Study Duration

The maximum duration of participants in the Passive Exposure Group will be approximately 4h (not exceeding 5h). The maximum duration of active IQOS use by participants in the Active Exposure Group will be up to 8h (±15 min). Each participant can participate in maximum one Non-Exposure Event and maximum one Exposure Event.
The overall duration of the study is currently planned for 6 weeks, but might be extended based on the number of events needed to secure the necessary number of participants..
End of Study for a participant is defined as the end of the Non-Exposure Event or the last Exposure Event he/she participated in. The overall End of the Study is defined as the end of the last Exposure Event.

5 STUDY POPULATION

A sufficient number of female or male Japanese adult IQOS Users, CC smokers, or Non-Smokers to achieve 169 participants in each of the Non-Exposed and Passive Exposure Groups, who meet the Inclusion criteria below, will be enrolled in the study. In addition a sufficient number of IQOS Users, actively using the product during Exposure Events, will be enrolled to ensure that 20% ± 5% of the available seats of the event location are occupied by

[4] ISO Norms related to ETS (15593:2001, 18145:2003 and 11454:1997) are out of scope for indoor air collection as combustion does not occur in THS.

IQOS Users actively using IQOS during the Exposure Event. Distribution of adult IQOS Users, CC smokers or Non-Smokers to these groups are outlined in Table 1.

5.1 Selection of Study Population

5.1.1 Inclusion Criteria

Participants who meet the following primary inclusion criteria will be enrolled:

- Participant is able to understand the information provided in the Subject Information Sheet (SIS) and informed consent form (ICF) (confirmed by signing the ICF) and has signed the ICF.
- Adults legally authorized to buy tobacco products in Japan (20 years of age).
- Participant is Japanese as self-reported.
- Willing to participate in the study, comply to study procedures and has access to the Internet.
- Participant is an active IQOS User, CC smoker or Non-Smoker as self-reported and as defined in Table 2.

Table 2 Definition of an IQOS User, Cigarette User or Non-Smoker

Category label	General description
IQOS User (IQOS)	• Used at least 100 *HeatSticks* • Uses IQOS daily > 1/day • Smokes a cigarette less than daily • Smokes less than 30 cigarettes/month • IQOS is > 95% of tobacco/nicotine product (all product use) – excluding other products (e-cig/Ploom/etc.)
Cigarette Smoker (CC)	• Used at least 100 cigarettes • Smokes cigarettes daily > 1/day • Uses IQOS less than daily • Uses less than 30 *HeatSticks*/month • Cigarette is > 95% of tobacco/nicotine product (all product use)
Non-Smoker (NS)	• Abstinent for at least 12 month from the use of any nicotine and/or tobacco-containing product based on self-reporting. • Must not be exposed to tobacco or nicotine-containing products use in any other substantial way (family, partner, workplace, etc.).

Note: Details of the product use categories will be reported in the SAP.

5.1.2 Exclusion Criteria

Participants who meet any of the following Exclusion Criteria may not be enrolled in the study:

- Participant with a medical history of severe cardiovascular or respiratory diseases (e.g., stroke, acute cardiovascular event, pulmonary thrombosis) in the last 12 months as self-reported.
- Participant with currently active cancer or history of cancer within the last 5 years as self-reported.
- Female participant who is pregnant or breast-feeding as self-reported.
- Participant is a current or former employee of the tobacco industry or their first-degree relatives (parent and child).

- Participant is an employee of PMI, [redacted] vendors, restaurant/event location employee or their first-degree relatives (parent and child).

Specific to participants who are Non-Smokers:

- Participant lives in a household with users of tobacco or nicotine-containing products, or is exposed to the use of tobacco or nicotine-containing products at the workplace.

5.2 Discontinuation of Subjects from the Study

Discontinued participants will include both, participants who withdraw from the study (participants' decision) and participants who are discontinued from the study by the decision of the Principal Investigator. Participants can only be discontinued from the study after enrollment. Participants will be informed that they are free to withdraw from the study at any time. Participants should be questioned for the reason of withdrawal from the study, although they are not obliged to disclose it.

If the patient withdraws from the study during an Event, he/she will be asked whether he/she would agree to still check out procedures (section 9.3), but with no obligation.

Discontinuation from the study

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

1. Withdrawal of informed consent.
2. The Sponsor terminates the study. If the Sponsor or the Principal Investigator decides to prematurely terminate the study, the participants will be promptly informed. The Sponsor should report the fact and the reason in writing to the IEC/IRB.
3. Participant becomes an employee of any other parties involved in the study.
4. Use of any tobacco or nicotine-containing product (if not allowed).

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

1. Non-compliance to the study procedures based on the judgment of the Principal Investigator.
2. The number of participants has exceeded the number of necessary participants in the Non-Exposure or Exposure Groups.

5.3 Lost to Follow-up

If a participant has been enrolled in the study via the Study Website but does not show up at the scheduled events, no attempt to follow-up with the participant will be made and the participant will be marked as "no show".

5.4 Violation of Selection Criteria

Any participant who is in violation of selection criteria as checked at Screening or prior to each Event shall be discontinued from the study.

6 INVESTIGATIONAL PRODUCTS

6.1 Description of Investigational Products

The product tested in this study is the Tobacco Heating System (THS) with *Marlboro Heatsticks*, marketed in Japan under the brand name IQOS and generally referred to as IQOS in this protocol. All versions of IQOS and *Marlboro Heatsticks* available for sale in Japan at the time or prior to the Study start or becoming available during the course of the Study are allowed to be used in the context of this study. IQOS is composed of the following components: a tobacco *HeatStick*, a Holder and a Charger (Table 3), as well as a cleaning tool, a power supply, and a USB cable.

Table 3 Test Product (IQOS)

Component	Description
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 consecutive 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 [20, 34]. A summary of description of the product, pre-clinical and clinical data available on IQOS is provided in the SPI [35].

6.2 Use of Investigational Product(s)

Participants in the Active Exposure Group (IQOS use) will be asked to bring their own IQOS device and *HeatSticks* for their own use during the entire study period as *HeatSticks* will not be provided by the Sponsor. Participants in the Active Exposure Group will use IQOS *ad libitum* with no *Heatsticks* variant restrictions.

Urine samples collected during the study will also be used to verify self-reported smoking status as well as compliance with protocol restrictions on IQOS and cigarette use during the events.

6.2.1 From Screening to Event Participation

There are no restrictions on use of IQOS or cigarettes or any other tobacco or nicotine-containing products during screening until participation in any of the events.

6.2.2 Non-Exposure Event

Participants will not be permitted to use IQOS, cigarettes or any other tobacco or nicotine-containing products during the 4-hour Non-Exposure Event.

6.2.3 Exposure Event

IQOS Users assigned to the Active Exposure Group will be permitted to use exclusively IQOS during the 4-hour Exposure Event. All other participants will not be allowed to use any tobacco or nicotine-containing products for the duration of their participation in the event.

6.2.4 In-between Event Participation

There are no restrictions on use of IQOS, cigarettes, or any other tobacco or nicotine-containing products, during the periods between participation in Events.

6.3 Method for Assigning Subjects to Study Groups

In the Non-Exposure Events, participants will be assigned to the IQOS User Group, Cigarette Smoker Group, or Non-Smoker Group based on self-reported smoking status.

The same applies to the Exposure Events with the exception that IQOS Users will be assigned during the enrollment process to be either an IQOS User who is allowed to use IQOS during the Event (Active Exposure Group), or an IQOS User who is not allowed to use any tobacco or nicotine-containing products for the duration of their participation in the event. The assignment to either of the two groups will be automatically done by the system with the Active Exposure Group to be filled first to ensure that the necessary sample size for the Active Exposure Group can be assured for each of the events.

6.4 Blinding

There is no blinding in this study.

6.5 Investigational Product Accountability and Compliance

6.5.1 Dispensing Investigational Product

Participants in the Active Exposure Group will be asked to bring their own *HeatSticks* for their own use during the entire study period as *HeatSticks* will not be provided by the Sponsor. Participants in the Active Exposure Group will use IQOS *ad libitum* with no flavor restrictions.

6.5.2 Adherence to allocated Exposure

Adherence to allocated Exposure, no use of any tobacco or nicotine-containing product during the Non-Exposure Events and no use of any tobacco or nicotine-containing product during the Exposure Events, with the exception of the Active Exposure Group, will be monitored by the staff at the Event location. Any product use by any participant in the Passive Exposure Group and any product use other than IQOS in the Active Exposure Group will lead to the discontinuation of the participant from the study.

6.6 Restrictions

6.6.1 General Restrictions

As the study objective is to represent a real life setting, no restrictions apply to any of the participants other than stated in the Inclusion/Exclusion criteria (i.e., with regards to smoking prior to the events, wearing perfume, dress code, etc.)

6.6.2 Dietary Restrictions

For the duration of an Event, participants will only be allowed to consume food and drinks provided at the Event location. Participants will not be allowed to bring in their own food or beverages. The food and beverages served during the event represent a typical and often requested choice in Japanese restaurants, however it can only represent a sub-selection of choices available in the variety of restaurant settings.

6.6.3 Product Use Restrictions

Participants in the Active Exposure Group will only be allowed to use IQOS. IQOS use in the Active Exposure Group is not limited in terms of *HeatStick* variants or number of *HeatSticks* used. . All other participants will not be allowed to use any tobacco or nicotine containing product for the duration of the event. Any product use other than allocated will be recorded by the study staff and checked by the Principal Investigator or designee.

7 STUDY PROCEDURES

An overview of all study procedures is shown in the schedule of events (see Appendix A). In this section, only the expected/planned time points for the various measurements are described.

7.1 Informed Consent

Prior to participating in any Event, the participant will be asked to provide their consent to participate to the study (ICF) (section 1.3.1).

7.2 Debriefing on IQOS

A debriefing of participants will be done at each Event to address any intended or unintended beliefs participants may have about IQOS, and to inform participants on the current status of knowledge about IQOS. The goal of the debriefing is to ensure that participants have an accurate understanding of product risks including an understanding that IQOS has not been demonstrated to be less harmful than cigarettes.

7.3 Main Assessments

7.3.1 Questionnaires

The participant questionnaires used in this study will be entered by the participant directly in the CASI survey. All questionnaires, as well as instructions will be provided in Japanese (the local language).

See Appendix A for the time points of assessment.

7.3.2 Demographics

Demographic data corresponding to inclusion/exclusion criteria (i.e., sex, age, and ethnicity) will be recorded in the screening domain.

See Appendix A for the time points of assessment.

7.3.3 Self-reported tobacco and nicotine-containing product use

The self-reported tobacco and nicotine-containing product use questionnaire will be administered at enrollment within the CASI and during the check-in procedures of each event to confirm self-reported product use status.

See Appendix A for the time points of assessment.

7.3.4 Self-Reported Health Outcomes and Events Questionnaire

A self-reported health outcomes questionnaire will be administered at enrollment within the CASI and during the check-in procedures of each event to confirm self-reported health status. The self-reported health outcomes and events questionnaire will focus on diagnoses of smoking-related disease and if the participant is pregnant or breastfeeding.

7.3.5 Recording of IQOS Use

IQOS product use will be periodically counted and recorded at each Exposure Event by the study personnel to evaluate the total number of *HeatSticks* used during the Exposure Event overall.

7.3.6 Recording of Food and Alcohol Consumption

Overall use of alcohol will be recorded at each Event using alcohol drink tickets. The overall food consumption per food type will be recorded at each event.

7.3.7 Biomarker of Exposure Assessment in Urine

All bioanalytical assays will be carried out using validated methods. The bioanalytical methods used will be documented in the Bioanalytical Plans/Reports. A list of laboratories is provided in Appendix B.

Spot urine will be collected at each Non-Exposure Event before the start of the Event and as of ≥2h after start of the Event until the end of the Event (last void analyzed only). For Exposure Events, urinary samples will be collected before the start of the Event and as of ≥2h after start of the Exposure until the end of the Event (last void analyzed only) for analysis of:

Creatinine, NEQ, a set of BoExp to nicotine; total NNAL, a biomarker for NNK; total NNN, a BoExp for NNN; 3-HPMA, a BoExp to acrolein; 3-HMPMA, a BoExp to crotonaldehyde; HEMA, a BoExp to Ethylene Oxide. Creatinine will be measured for normalization of urinary BoExp.

7.3.8 Assessment of Indoor Air Quality

For Non-Exposure Events, IAQ measurements will be performed at the Event location for up to 3h prior to the start of the Event and for 3h after the last participant has entered the Event for 1h. For Exposure Events IAQ measurements will be performed at the Event location for up to 3h prior to start of the Exposure and for 3h after the last participant has been exposed for 1h to quantify and differentiate background exposure and to assess the impact of IQOS

use on IAQ. The sample collection starts one hour after the entry of the participants in order to sample a homogeneous atmosphere during the collection time (i.e., 3 hours).

Study samples will be collected at each Event (Non-Exposure and each Exposure Event) at the Event location.

To collect IAQ samples, three mobile sampling set-ups, for indoor air pollutants will be used. The set-up consists of 3 aluminum sampling cases with 5 flow-controlled pumps. Each sampling case are equipped with:

- 2 x AD-4 traps for Nicotine and 3-EP collection operated at a flow rate of 1.0 L/min for 3h;
- 2 x 1 DNPH-silica traps for carbonyl collection (acetaldehyde, acrolein, crotonaldehyde and formaldehyde) operated at a flow rate of 1.2 L/min sequentially for 1h
- 2 glass fiber filters (Cambridge filters) spiked with ascorbic acid for TSNAs (NNN; NNK), operated at a flow rate of 1.0 L/min for 3h.

The position of the sampling cases will be inside the breathing zone as described by ASHRAE.[5]

Moreover, two small instruments in front of the sampling cases are electronically recording the ambient temperature and relative humidity. In addition, two portable instruments, used for on-line PM1-PM10 particle measurements will be used. The equipment are the property of PMI and will be used by a PMI-trained scientist according to the ISO accredited method PMI-RRP-WKI-111642 “Dust Trax characterization for real time monitoring of aerosol mass concentration”.

The analytical methods to be applied at the analyzing laboratory (see Appendix B.) for the air samples are listed in Table 4.

[5] ASHRAE, 2016. ANSI/ASHRAE Standard 62.1-2016. Ventilation for acceptable indoor air quality. Atlanta, GA: American Society of Heating, Refrigerating and Air-Conditioning Engineers.

Table 4 Constituents selected, technology and trap used for indoor air collection

Chemical class (constituents)	Analytical method / Technology	Trap to collect the air
Carbonyls (formaldehyde, acetaldehyde, acrolein, crotonaldehyde)	LC-MS/MS	DNPH-coated silica cartridge
Tobacco-specific markers (Nicotine, 3-ethenylpyridine)	GC-MS	XAD-4
Tobacco-specific nitrosamines (NNN; NNK)	LC-MS/MS	Ascorbic acid-spiked glass fiber filters

Notes: LC-MS/MS = Liquid chromatography-tandem mass spectrometry; GC-MS = Gas chromatography–mass spectrometry; DNHP = 2,4-Dinitrophenylhydrazine; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN = N-nitrosonornicotine

A total of 18 tubes per Event will be collected. Table 5 shows the repartition of samples.

Table 5 List of samples generated for the main study.

Purpose	Non-Exposure Event		Exposure Event		
	Event 1	Event 2	Event 3	Event 4	Event 5
Nature of sample (duration)	BKG (3h) then EA (3h)	BKG (3h) then EA (3h)	BKG (3h) then EA (3h)	BKG (3h) then EA (3h)	BKG (3h) then EA (3h)
Sample ID	BKG1/ EA1	BKG2/EA2	BKG3/EA3	BKG4/EA4	BKG5/EA5

Notes: BKG = Background; EA= Environmental Aerosol

7.4 Sample Handling, Storage, and Shipment

Participating laboratories for the analyses of urinary samples are listed in Appendix B. Detailed procedures for handling of samples are described in a separate Laboratory Instruction Manual. All samples will be destroyed post database lock or post finalization of the bioanalytical reports depending on which one is coming the latest.

For urinary samples, the collected samples will be stored at 4°C up to 24h after the collection period. Longer storage periods will be at ≤ -20°C. Samples will be shipped on dry ice to Celerion, USA, within a few days after completion of the study. Several shipments might be considered to respect the stability of the samples.

For IAQ assessment, the collected samples will be stored at 4°C up to 12h after the collection period. Longer storage periods will be at ≤-20°C. Samples will be shipped on dry ice to ABF Munich, Germany, within a few days after completion of the event. Extraction will be done by ABF. Weekly shipments will be considered to respect the stability of the samples, especially for DNPH cartridges.[6]

8 ADVERSE EVENTS, PARTICIPANTS SAFETY AND WELL-BEING

As this study is observational by design and is conducted in a post-market setting, adverse event (AE) reporting will follow the Sponsor's already established post-market Safety Surveillance Procedures for spontaneously-reported events. All study personnel and study participants will be reminded of the product quality complaints (including AEs) hotline that has been established for all users of IQOS in Japan.

In the event that a medical event occurs in any of the study participant the study staff will be advised to call local emergency number to ensure appropriate medical treatment. The related cost for emergency treatment and transportation will be carried by the Sponsor.

Security personnel will be on site at the event location to ensure secure and ordered conduct at the event.

9 STUDY ACTIVITIES

If no start time for the procedures is provided, then the procedure can be performed at any time during the visit. Assessments will be conducted only by qualified and trained site personnel.

A detailed schedule of assessments can be found in Appendix A.

9.1 Screening and Enrollment

Screening will be done entirely online as detailed in Section 4.1.1.

Table 6 shows the assessments that will be performed at the screening and enrollment:

[6] Stability Carbonyl samples on DNPH cartridges: up to 2 weeks in the freezer after collection. Stability of eluate of Carbonyls samples collected on DNPH cartridges: up to 3 months when stored at – 20 °C. Stability nicotine samples on XAD-4 tubes: up to 8 weeks in the freezer after collection, stability of eluate of nicotine samples collected on XAD-4 tubes: up to 2months when stored at – 20 °C.

Table 6 Schedule – Screening and Enrollment

Time	Sample collection	Procedures	Additional information
Start of procedure		**Screening, Enrollment and Baseline**	
Online Information and Questionnaire		ICF signature	
		Demographics data	Sex, date of birth, ethnicity
		Tobacco or nicotine-containing product use self-reporting	Participants will be questioned on their product use history.
		Self-Reported Health Outcomes and Events Questionnaire	
		Readiness to comply to study procedures	
		Verification of eligibility	All eligibility criteria must be checked and met to continue to enrollment.
		Selection of participation dates for Non-Exposure and Exposure Events	
		Enrollment	If all eligibility criteria are met.
Assignment of IQOS Users		Assignment of IQOS Users into the Active Exposure of Passive Exposure Group	Participants who are self-reported IQOS Users
		Confirmation email to subject	Needs to be presented during check-in procedure at the event.
End of Screening and Enrollment			

Abbreviations: ICF = Informed Consent

9.2 Recruitment Period

Recruiting for this study will be open for the entire study period as outlined in Figure 2.

9.3 Study Period

Procedures to be conducted during the Non-Exposure Event are detailed in section 4.1.2 and Table 7. Procedures for the Exposure Event are detailed in section 4.1.3 and Table 8.

Table 7 Schedule – Non – Exposure Event

Time	Sample collection	Procedures	Additional information
Start of procedure		**Non-Exposure Event**	
IAQ Assessment	IAQ	See section 7.3.8	For 3h prior to the first participant entering the Event location
Arrival and Check-In		Participant Identification, check if ICF has been signed	
		Confirmation of demographics data	Sex, date of birth, ethnicity
		Tobacco or nicotine-containing product use self-reporting	Participant to fill questionnaire
		Readiness to comply to study procedures	
		Self-Reported Health Outcomes and Events Questionnaire	
Prior to entering the Event	U	Spot urine collection for NEQ, total NNAL, total NNN, 3-HPMA, HMPMA, HEMA and creatinine samples.	Process samples BoExp analysis according to laboratory manual/SHM.
During the Event		Dinner and Drinks	Food typically served in Japanese restaurants, soft-drinks, tea, alcoholic beverages as typically served in Japanese restaurants
IAQ Assessment	IAQ	See section 7.3.8	For 3h starting 1h after the last participant entered the Event.
During the Event as of 2h after entering the event	U	Spot urine collection for NEQ, total NNAL, total NNN, 3-HPMA, HMPMA, HEMA and creatinine samples.	Only last void to be kept for analysis (ideally the one prior to check-out). Prior voids to be discarded. Process samples BoExp analysis according to laboratory manual/SHM.
Check-Out prior to leaving the Event	U	Spot urine collection for NEQ, total NNAL, total NNN, 3-HPMA, HMPMA, HEMA and creatinine samples	
		Check if study questionnaires have been completed.	
Pick-Up of samples		Collection of samples for shipping to analyzing laboratories	

Confirmation that no other product than allowed as per protocol was used		PI or designee
End of the visit		

Abbreviations: IAQ = Indoor Air Quality; ICF = Informed Consent; SHM = Sample Handling Manual; BoExp = Biomarker of Exposure; NEQ = Nicotine Equivalents; total NNAL = Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; Total NNN = Total N-nitrosonornicotine; 3-HPMA = 3-hydroxypropylmercapturic acid; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; HEMA = 2-hydroxyethyl mercapturic acid; U = urine

Table 8 Schedule – Exposure Event

Time	Sample collection	Procedures	Additional information
Start of procedure		**Exposure Event**	
IAQ Assessment	IAQ	See section 7.3.8	For 3h prior to the first participant entering the Event location
Arrival and Check-In		Participant Identification, check if ICF has been signed	
		Confirmation of demographics data	Sex, date of birth, ethnicity
		Tobacco or nicotine-containing product use self-reporting	Participant to fill questionnaire
		Readiness to comply to study procedures	
		Self-Reported Health Outcomes and Events Questionnaire	
Check assignment of IQOS Users		Check assignment of IQOS Users into the Active Exposure of Passive Exposure Group	Participants who are self-reported IQOS Users and have brought their device and HeatSticks
Prior to entering the Event	U	Spot urine collection for NEQ, total NNAL, total NNN, 3-HPMA, HMPMA, HEMA and creatinine samples.	Process samples BoExp analysis according to laboratory manual/SHM.
"Priming" of Event location		The Active Exposure Group will enter the event location approximately 1h before the Passive Exposure Group to start using IQOS.	
During the Event		Dinner and Drinks	Food typically served in Japanese restaurants, soft-drinks, tea, alcoholic

			beverages as typically served in Japanese restaurants
In regular intervals, depending on product use (approximately every hour)		Regular count of used IQOS HeatSticks	PI or designee
IAQ Assessment	IAQ	See section 7.3.8	For 3h starting 1h after the last participant entered the Event.
During the Event as of 2h after entering the event and prior to leaving the Event	U	Spot urine collection for NEQ, total NNAL, total NNN, 3-HPMA, HMPMA, HEMA and creatinine samples.	Only last void to be kept for analysis (ideally the one prior to check-out). . Prior voids to be discarded. Process samples BoExp analysis according to laboratory manual/SHM.
		Check if study questionnaires have been completed.	
Pick-Up of samples		Collection of samples for shipping to analyzing laboratories	
Confirmation that no other product than allowed as per protocol was used			PI or designee
End of the visit			

Abbreviations: IAQ = Indoor Air Quality; ICF = Informed Consent; SHM = Sample Handling Manual; BoExp = Biomarker of Exposure; NEQ = Nicotine Equivalents; total NNAL = Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; Total NNN = Total N-nitrosonornicotine; 3-HPMA = 3-hydroxypropylmercapturic acid; HMPMA = 3-hydroxy-1-methylpropylmercapturic acid; HEMA = 2-hydroxyethyl mercapturic acid; U = urine

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

N/A

10.2 Training of Collaborators

A formal meeting will be conducted prior to the start of the study. During this meeting, the Sponsor or its authorized representative will discuss the requirements of the study protocol and related documents and will also provide training to the relevant systems and other study-specific procedures. The activities of this meeting will be described in the Event Coordination Plan.

10.3 Audits and Inspections

Good Epidemiological Practice guidelines do not specify independent inspections of study program activities, however, in order to guarantee adequate site performance, such inspections may be performed at any time before, during and/or after the study.
Authorized representatives of the Sponsor, regulatory agencies and/or an IRB/IEC may perform audits or inspections. 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, GEP guidelines [1], the Ethical Guidelines for Medical and Health Research Involving Human Subjects [2] and any applicable regulatory requirements. The Principal Investigator or designee will contact the Sponsor or the authorized representative immediately if contacted by a regulatory agency about an inspection at their site.
The Principal Investigator or designee 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. By signing this protocol, the Principal Investigator or designee understands and agrees to provide access to the necessary documentation and files.

11 DATA MANAGEMENT ACTIVITIES

All data management activities will be documented in the Data Management Plan (DMP) and documents specified therein. The electronic CASI system used to collect participant data will be FDA 21 CFR Part 11 compliant.

11.1 Data Capture

11.1.1 Data Capturing Tool, Case Report Forms and Study Records

All data collected during the screening and enrollment process will be collected through the CASI questionnaire. As the CASI questionnaire is administered directly to the subject it will be administered in Japanese. Any data that are reported in open-ended questions will be recorded in Japanese and translated to English.

Trained study personnel (Principal Investigator or his authorized designee(s)) at the event site will be responsible for performing the assessment specified in the protocol and documenting the results in the Source Data. These results will also be captured in the data capture tool.

The Principal Investigator has the ultimate responsibility for the collection and reporting of the data related to the assessments in the study and ensures that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring and available when required. The data capture tool for the study will be signed by the Principal Investigator to attest that the data contained in are true and accurate. Any corrections made to Source Data and/or data capturing tool must be recorded, without obscuring the original values, and must be accompanied by the date of change, reason for change and identification of the person making the change. Instances of missing or unclear data will be discussed with the Principal Investigator for resolution.

IAQ data will be recorded with the instrumentation listed above and analyzed and reported in a separate report. The results and discussion however will be integrated in the Assessment Study Report.

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, with the exception of the IAQ data (see above). The processed results of the IAQ data will be integrated on a dataset level after analysis. The overall procedures for quality assurance of study data are described in the SOPs of the CRO data management team. The data management team at the CRO will prepare a DMP, to be reviewed and approved by the Sponsor, prior to the go live of systems used to capture study data. This document will describe, in details, the data management-related procedures and processes.

All data collected during the study are declared property of the Sponsor, irrespective of the location of the database and the data management CRO.

Additional details are covered in the DMP.

11.2.1 Data Verification

The data will be validated as defined in the DMP. Discrepancies will be reported as defined in DMP and Data Validation Plan.

11.2.2 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 and QC of the changed data, database, or selected data upon Sponsor approval, as applicable, the database 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 Team 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 in Clinical Data Interchange Standards Consortium's Study Data Tabulation Model Data Structure Specifications, with the exception of the IAQ data, for which the raw data will be kept at ABF according to the vendor's data management process. The processed data will be provided to the Sponsor as defined in the DMP.

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 primary analysis, the following stratification criteria will be used:

1. Product use Status.
2. Event type.
3. Sex.

12.1.2 Definitions for Statistical Data Analysis

The following definitions of an IQOS User, Cigarette User or Non-Smoker will be used for this study and analysis of results.

Table 9 Definition of an IQOS User, Cigarette User or Non-Smoker

Category label	General description
IQOS User (IQOS)	• Used at least 100 *HeatSticks* • Uses IQOS daily > 1/day • Uses a cigarette less than daily • Uses less than 30 cigarettes/month • IQOS is > 95% of tobacco/nicotine product use (all product use) – excluding other products (e-cig/Ploom/etc.)
Cigarette Smoker (CC)	• Used at least 100 cigarettes • Uses cigarettes daily > 1/day • Uses IQOS less than daily • Uses less than 30 *HeatSticks*/month • Cigarette is > 95% of tobacco/nicotine product use (all product use)
Non-Smoker (NS)	• Abstinent for at least 12 month from the use of any nicotine and/or tobacco-containing product based on self-reporting. • Must not be exposed to tobacco or nicotine-containing products use

in any other substantial way (family, partner, other workplace).

Note: Details of the product use categories will be reported in the SAP.

12.1.3 Descriptive Statistics

Descriptive statistics for continuous variables will include the number of participants, number and percent of participants 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) for each product exposure, and summary across all participants. In addition, the results may be presented as a stratified summary as defined in the Statistical Analysis Plan (SAP).

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

For BoExp parameters:

- Values below the lower limit of quantification (LLOQ) will be imputed using LLOQ/2. For values above the upper limit of quantification (ULOQ), the ULOQ will be imputed.
- The number of values below LLOQ or above ULOQ will be presented in each summary table. If more than 50% of the data are below LLOQ, only the number and percentage of values below LLOQ will be reported in the summary together with the minimum and maximum values.

For CASI data:

Subject missing the complete CASI will not be considered for analysis. Those with incomplete CASI's will be analyzed based on the available data.

Further details will be provided in the SAP.

12.1.5 Significance Level for Inferential Analysis

Not applicable as there are no formal statistical hypotheses to be tested in this study.

12.2 Determination of Sample Size

The sample size of a minimum of 169 participants in the Exposure and Non-Exposure Events Each is based on the expected exposure of a Non-Smoker when exposed to cigarette smoke as documented in the literature. Variability of exposure levels and method variability were furthermore considered to estimate the sample size needed.

12.3 Analysis Populations

The main population for analysis will be the Compliant Exposure Set.

12.3.1 Compliant Exposure Set

The Compliant Exposure Set will consist of all enrolled participants who have signed the ICF and who have participated in either a Non-exposure Event or an Exposure Event, have provided two urine samples (at minimum, one urine sample prior to the start of the event and one urine sample after a minimum 2h of individual participation in the event) and are compliant with the Event Exposure Groups (Non-Exposure vs. Passive Exposure).

12.3.2 Active Exposure Set

The Active Exposure Set (PP) will consist of all enrolled participants who have signed the ICF and who have participated in an Exposure Event, have provided two urine samples (at minimum, one urine sample prior to the start of the event and one urine sample after a minimum of 2h after start of the Active Exposure) and were in the Active Exposure Group.

12.4 Primary Analysis

The primary endpoints will be the pre-event urinary BoExp and latest post two hour urinary BoExp observation. A linear mixed effects model with event type, IAQ, duration of exposure (time between pre-event collection and last post exposure collection), product use status and product use status and event type interaction will be modelled as fixed effects with a random subject effect. Other covariates or interactions terms may be added as needed. Appropriate contrasts will be constructed to determine the effect of passive exposure to IQOS aerosol during the Exposure Event on the mean change in levels of urinary BoExp to selected tobacco specific HPHCs together with the 95% confidence intervals (CIs). Other contrasts can be constructed to determine the change in urinary BoExp for subjects with other smoking status after passive exposure to IQOS usage

12.5 Secondary Analysis

The same statistical model described in the analysis of the primary endpoint will be used to analyze to evaluate the levels of exposure to additional selected HPHCs representative of ETS during both the Non-Exposure Events and Exposure Events in the study population. The results will also be looked at stratified by incoming smoking status. Additional analysis may be defined in the SAP and performed and reported in the Assessment Study Report.

The IAQ data will be processed at the assessing laboratory (see Appendix B) and the individual results per compound will be summarized and tabulated. An Analysis of variance (ANOVA) design will be applied as the quantitative results of the IAQ sessions will be compared per compound. The mean, standard deviation, relative standard deviation,

minimum and maximum will be computed per compound and the number of observation will be indicated. A significance level set at 0.05 will be used to determine equality between sessions.

12.5.1 Analysis of the Active Exposure Group

The primary endpoints will look at the change between the pre-event urinary BoExp and latest post two-hour urinary BoExp observation. A linear mixed effects model with IAQ, duration of exposure (time between pre-event collection and last post exposure collection) and number of sticks used during the event, will be modelled as fixed effects with a random subject effect. Other covariates or interaction terms may be added as needed. Appropriate contrasts will be constructed to determine the effect of active exposure to IQOS usage during the Exposure Event on the mean change in levels of urinary BoExp to selected tobacco specific HPHCs together with the 95% confidence intervals (CIs).

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Principal Investigator's and Study Administrative Structure

13.1.1 Principal Investigator

Principal Investigator:	Dr. Takao Ohki, MD, PhD Tokyo Jikei University School of Medicine [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] Study Coordinator	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]
[redacted] Study Scientist	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]
[redacted] Study Biostatistician	Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]

13.1.3 Other Responsibilities

[redacted] is the Contract Research Organization designated by PMI to manage and monitor the study: all duties and responsibilities transferred to [redacted] by PMI will be defined in the agreement signed between the two parties.

CRO:	[redacted]
[redacted] Lead Study Scientist	Phone: +1[redacted] E-mail: [redacted]
[redacted] Study Scientist	[redacted]
[redacted] Project Lead	Phone: +34[redacted] E-mail: [redacted]

13.2 Participant Confidentiality

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

The anonymity of participants participating in this study will be maintained. Participants will be identifiable by the Sponsor (or Sponsor's authorized representative) on CRFs and other documents by their participant number/code, sex and date of birth, but not by name, initial, or

any other details relating to identifiable person (e.g., address). The assignment of a participant number/code for participant identification will be based on the appropriate data protection rules.

Any documents that allow full identification of the participant (e.g., the participant's signed ICF) must be maintained in confidence by the Principal Investigator. If any document relating to this study shows a participant's name or any other details relating to an identifiable person (e.g., address), the name or other identifiable details must be obscured before a copy of that document is supplied to the Sponsor. PRX staff will have access to email, geographical data and phone number as well as other personal data (i.e. passport check).

In the exceptional case where a participant a) is recruited into the study through PMP's Product Registration Database, and b) communicates in any way their intention to quit smoking or stop using IQOS, their email address will be shared with PMP so that this participant no longer receives any commercial communication from the Sponsor moving forward. No other identifiers will be shared with the Sponsor so that no study data will be linked to that email address.

13.3 Access to Source Documentation

Participants enrolled in the study will be informed that, during the course of the study, the Sponsor, any authorized representatives of the Sponsor, IRB, or regulatory authorities may inspect the information collected, and ensure that all personal information made available for inspection is handled in the strictest confidence and in accordance with national and local data protection and privacy legislation.

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

13.4 Record Retention

All records of data, source data and source documents (original records or certified copies), in any form (including, but not limited to, written, electronic, magnetic, optical records and test results) that describe or record the methods, conduct, and/or results of the study, the factors affecting the study, and the actions taken will be maintained by the Principal Investigator for the study. After the finalization of the study the Principal Investigator can request that all study related files (Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced) are transferred to the Sponsor. The Sponsor will perform a quality control check for completeness of the data prior to accepting the request. Ones the request is accepted and the transfer is complete, essential study documents/records, which individually and collectively

permit evaluation of the conduct of a study and the quality of the data produced must be retained by the Sponsor for a minimum of:

- At least 15 years after completion or discontinuation of the study, or
- At least 2 years depending on, for example, the circumstances, or
- After formal discontinuation of clinical development of the IP.

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 participants and master ICF
- Participant identification code list, enrollment log (if applicable)
- Record of all communications between the Principal Investigator and the IRB, composition of the IRB
- Record of all communications/contact between the Principal Investigator, Sponsor, and its authorized representatives
- Study specific questionnaires (and associated data/scoring), CASI data
- All other source documents (e.g., laboratory records) or any electronically captured study source data
- Record of any body fluids or tissue samples collected and retained
- Information regarding participants' discontinuation.

The Principal Investigator (until transfer to the Sponsor is complete) and the Sponsor (after completion of the transfer) must take measures to prevent accidental or premature destruction of these documents.

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

The Principal Investigator must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the Principal Investigator's archives. If the Principal 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. In case the Principal Investigator has agreed with the Sponsor to transfer the files to the Sponsor it is the obligation of the Sponsor to document the destruction of the records according to local law and regulations.

The Sponsor or Sponsor's authorized representative will maintain documentation relating to the study for 15 years after the Study Report has been finalized.

13.5 Assessment Study Report

The Sponsor must ensure that an assessment study report for this study is prepared regardless of whether the study is completed or prematurely terminated. In certain circumstances, an abbreviated assessment study report may be acceptable. Submission of the assessment study report to the IRB 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 assessment study report.

13.6 Financial Disclosure

Principal Investigator is required to provide financial disclosure information to the Sponsor. In addition, the Principal Investigator 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 one year following the completion of the study.

13.7 Publication and Disclosure Policy

This document contains data, information and trade secrets that are confidential and proprietary to the Sponsor. This document is being provided solely for the purpose of evaluation and/or conducting this study for the Sponsor. Disclosure of the content of this document is allowed only to study personnel, IRB, 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 study, 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 to the participants that are associated with the IQOS use or with study procedures which are used during this study, except for AEs and health damage to the participants caused by a negligent or an intentional misconduct and/or significant deviation to the protocol of the Principal Investigator or the Event Site or the participants. 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 A SCHEDULE OF EVENTS

Variable	Screening and Enrollment	Non-Exposure Events	Exposure Events
CASI Questionnaire			
Informed Consent	●		
Inclusion and Exclusion Criteria	●	●[g]	●[g]
Selection of Event Dates	●		
Enrollment in the Study	●		
Demographics	●		
Self-reported tobacco and nicotine-containing product use	●		
Self-Reported Health Outcomes and Events Questionnaire [a]	●		
Exposure and Non-Exposure Events			
Registration and Check In [b]		●	●
Self-Reported Health Outcomes and Events Questionnaire [a]		●	●
Recording of Product Use during Event [c]		●	●
Indoor Air Quality Assessment [d]		●	●
Dinner and Drink		●	●
Self-reported tobacco and nicotine-containing product use		●	●
Spot Urine for Biomarker of Exposure Assessment [e]		●	●
Check Out [f]		●	●

a: Questionnaire to assess if the participants had a medical history of severe cardiovascular or respiratory diseases (e.g., stroke, acute cardiovascular event, pulmonary thrombosis) as self-reported in the last 12 months, has a currently active cancer or history of cancer within the last 5 years or is pregnant or breast-feeding.

b: see **Table 7** and **Table 8**

c: Collection of used IQOS HeatSticks for product use counting purposes and recording by PI.

d: Assessment of IAQ parameters as defined in **section 7.3.8**.

e: Spot urine will be collected before and during the 4-hour Event. A minimum of two spot urine must be collected (one prior to the Event and one after post 2-hour Event. The latest spot urine should be kept from the post-2 hour spot urine collection

f: Check out procedures, i.e. time of departure, confirm that all required urine samples have been provided and collected and registered.

g: Re-check of Self-reported Health Outcomes and Events questionnaire and Self-reported Tobacco and Nicotine-containing product use questionnaire

APPENDIX B LIST OF PARTICIPATING LABORATORIES

The following laboratories will be used in the study:

Laboratory for analysis of urine samples for BoExp assessment:	Celerion Lincoln [redacted] **and/or** Celerion Zurich [redacted]
Laboratory for analysis of IAQ assessment:	ABF GmbH [redacted]