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.

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.

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.

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.

7.3.4 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 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.

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

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.

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

- 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)

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

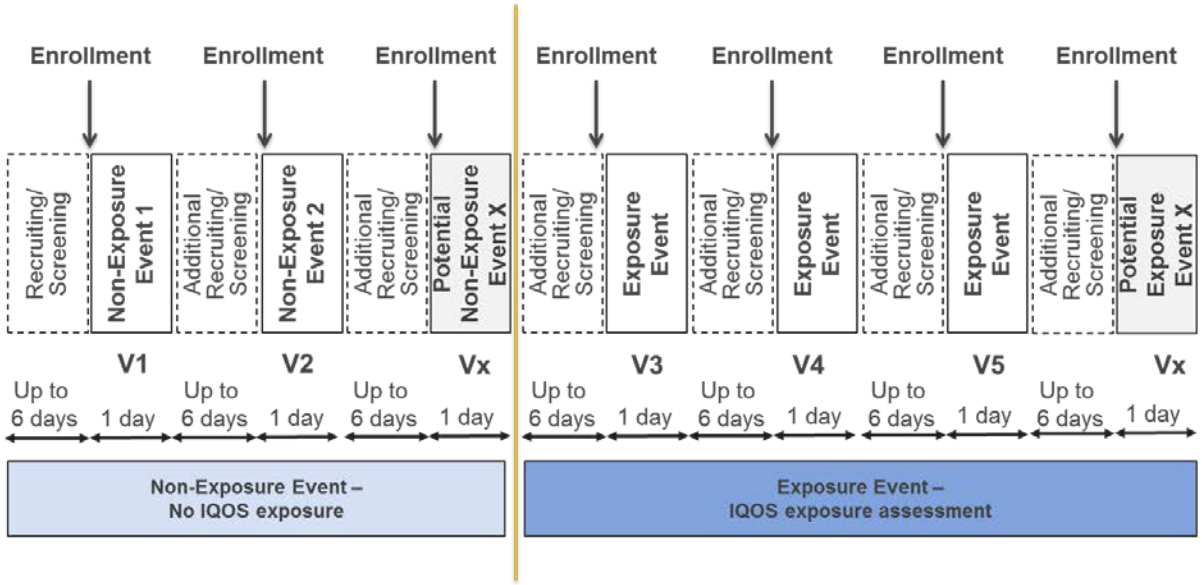

Figure 2 - Study Design

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

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.

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.

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.

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	

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.

12.3 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,

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]