STATISTICAL ANALYSIS PLAN

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 Product:	Tobacco Heating Systems [THS]
Sponsor Reference No:	P1-PES-01-JP
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
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1 STATISTICAL ANALYSIS PLAN APPROVAL

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3 INTRODUCTION

The purpose of the study is to assess that impact of passive IQOS exposure in Non-Smokers in a restaurant setting on the urinary levels of Biomarkers of Exposure (BoExp) to selected Harmful and Potentially Harmful Constituents (HPHCs) representative of Enviromental Tobacco Smoke (ETS). And to compare the levels of BoExp in Non-Smokers from passive IQOS exposure with the levels of BoExp caused by background (Non-Exposure). Furthermore the impact of passive IQOS exposure was assessed in IQOS Users and Cigarette Smokers who did not use any nicotine or tobacco products during the Exposure Event.

The addition of IQOS Users who don't use IQOS, and Cigarette Smokers who did not use any nicotine or tobacco products during an Exposure Event, allows for the assessment of individuals with varying levels of BoExp to HPHCs in their personal lives, in order to assess whether there is any measurable additive exposure from IQOS. The study also evaluated Indoor Air Quality (IAQ) through the assessment of concentrations of IAQ markers in the air during the Exposure Events where IQOS was used and also during the Non-Exposure Events where there was no IQOS usage or Cigarette smoking allowed.

This Statistical Analysis Plan (SAP) describes the methodology and considerations of the planned analyses and lists the Tables, Figures and Listings (TFLs) for this study. A detailed description of the TFLs will be provided in a separate TFL shell document. Any changes to the TFL shell numbering or to the title of a TFL will not require an amendment to the SAP.

This SAP will be finalized prior to the lock of the clinical database. Any changes to the analyses described in this document or additional analyses performed to supplement the planned analyses, will be documented and described in the clinical study report (CSR).

4 REVISION HISTORY

Version	Date of Revision	Description
1.0	05 Feb 2018	• Original version
2.0	19 Apr 2018	• Clarified wording for statistical modelling that estimates will be exponentiated to present the results on the original scale. • Updated pseudo code in 11.6.2.1.1. for analysis of carbonyls. • Updated pseudo code in 11.6.2.1.2. for analysis of tobacco specific markers. • Updated algorithm for active exposure group in section 11.6.2.3, removing the wording 'estimate exposures for each product use group' since there were only Active IQOS users. • Updated pseudo code in 11.6.2.3., removing location since it is not part of the model. • Added section on post-hoc analysis describing additional analysis to be performed.
3.0	11 Jul 2018	• Added post-hoc analysis to investigate effects of Heatsticks on Urinary BoExp in Compliant Exposure Set. • Added post-hoc analysis to estimate effect of no HeatSticks use in the Active Exposure Set. • Added post-hoc analysis to estimate pre-event adjusted IAQ parameters during the Events.

5 ABBREVIATION OF TERMS AND DEFINITIONS

5.1 Abbreviations

3-HPMA	3-hydroxypropylmercapturic acid
AE	Adverse Events
ANOVA	Analysis of Variance
BoExp	Biomarker of Exposure
CASI	Computer Assisted Self Interview
CI	Confidence Interval
CRF	Case Report Form
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
EA	Environmental Aerosol
ETS	Environmental Tobacco Smoke
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
IRB	Institutional Review Board
ISO	International Organization for Standardization
NEQ	Nicotine Equivalents
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
PMI	Philip Morris International
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

TSNAs	Tobacco Specific Nitrosamines

5.2 Definition of Special Terms

The following special terms are used in this SAP:

Baseline	Baseline is defined as the observation recorded prior to entering the event room.
Duration of exposure (Actively Exposed)	The duration of exposure for actively exposed participants is defined as the time that a participant is allowed to use IQOS after entering the event room for priming until the time of last urine void.
Duration of exposure (Passively Exposed)	The duration of exposure for passively exposed participants is defined as the time that a participant enters the event room until the time of last urine void.
Product Use Status	For each participant, the product use categories were defined based on the Self-Reported Tobacco and Nicotine-Containing Product Use Questionnaire.

6 STUDY OBJECTIVES

6.1 Primary Objective and Endpoints

The primary objective of this study is:

1) To estimate the mean change in levels of urinary BoExp to selected tobacco specific HPHCs representative of ETS after passive exposure to IQOS in a planned restaurant dinner event ('Exposure Event') where IQOS use, but not cigarette smoking, is allowed. Mean change in BoExp will be estimated for participants passively exposed to IQOS 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)

6.2 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 (no IQOS use or Cigarette smoking allowed during event) 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)[1]
     - 3-Ethenylpyridine (3-EP) [$\mu g/m^3$]
     - Nicotine [$\mu g/m^3$]
   - Carbonyls

[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.

- 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 PM2.5-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 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)

6.3 Study Hypotheses And Evaluation Criteria

6.3.1 Hypotheses

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.

7 INVESTIGATIONAL PLAN

7.1 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. Three

types of participants with the following characteristics will be enrolled in this study: 1) Non-Smokers; 2) Cigarette Smokers and 3) IQOS Users. IQOS Users were further broken into two groups the IQOS Passive Users (not using IQOS during the Exposure or Non-Exposure Events) or IQOS Active Users (using IQOS during the Exposure Events).

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 of BoExp of selected HPHCs representative of ETS in the absence of exposure to IQOS for all participants;
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 Passive Users and Cigarette Smokers. No IQOS, cigarettes or other tobacco or nicotine-containing products were used 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 Passive Users and Cigarette Smokers, not using IQOS, cigarettes or any other tobacco or nicotine-containing product for the duration of the Exposure Event;
- Active Exposure Group (IQOS Use): IQOS Users using IQOS for the duration of the Exposure Event. A minimum of 20% ± 5% of the available seats at the Event location were required to be used by the IQOS Active Users.

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

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%[2]
• Group 2: Cigarette Smokers	25%[1]	25%[1,2]
• Group 3a: IQOS Passive Users	25%[1]	25%[1,2]
Total	**100% participants in Non-Exposure Events**	**100% participant passively exposed in Exposure Events**
• Group 3b: IQOS Active Users	n/a	20% of the total number of available 96 seats in the event location[3]
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 are allocated in these proportions after allowing for 20% of seats in each Exposure Event to Group 3b users.

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

7.1.1 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 Philip Morris International's (PMI) 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 the "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 their 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. Participants will only be compensated for the Non-Exposure or Exposure Events they participated in.

7.1.2 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 Passive 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 will be analyzed.

Urine specimens will also be used to confirm self-reported non-smoking status of the invited participants. Total NNAL values over 75.9 pg/mL will be used to excluded participants in the Non-Smoking Group from the Compliant Use Population.

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.

7.1.3 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 (i.e., location, air ventilation and table setting) that could confound study results. The first of the Exposure Events will occur within 4 weeks of the Non-Exposure Events The Exposure Events will replicate the meal, beverages and restaurant dynamics of the Non-Exposure Event.

Exposure Event participants may or may not have attended a Non-Exposure Event. Participants attend the dinner Event at no cost to themselves. The participants who attend more than one event will represent the same product use phenotypes for both events, except the IQOS Users will be assigned for the Exposure Events to either a) an IQOS Active User, or b) an IQOS Passive User (see Table 1).

The Exposure Events will include a minimum of 169 passively exposed participants. During each Exposure Event a total of 20% ± 5% of the available seats at the Event location will be allocated to IQOS Active Users (who use IQOS during the event). The remaining seats will consist of passively exposed participants with the following product use phenotypes: 50% (±5%) Non-Smokers, 25% (±5%) IQOS Passive Users who refrain from using any nicotine or tobacco product, and 25% (±5%) Cigarette Smokers who refrain from using any nicotine or tobacco products.

IQOS Active Users 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 will be analyzed.

7.2 Selection of Study Population

7.2.1 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 IQOS User, Cigarette 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	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	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	Abstinent for at least 12 month from the use of any tobacco or nicotine -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.).

7.2.2 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.

7.3 Product Allocation and Blinding

7.3.1 Method of Grouping Participants According to Self Reported Product Use

In the Non-Exposure Events, participants will be either be in the IQOS Passive 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 allowed during the enrollment process to be in either the IQOS Active User Group, or the IQOS Passive User Group. The assignment to either of the two groups will be automatically done by the system with the IQOS Active User Group being filled first, to ensure the necessary sample size for the events.

7.3.2 Blinding

There is no blinding in this study.

8 DERIVED AND COMPUTED VARIABLES

For each timepoint (baseline urine void and last void), the change from Baseline will be calculated by subtracting the individual subject's Baseline value from the value at the end of the study. Mean change from Baseline is the mean of all individual subjects' change from Baseline values.

The percent change from Baseline will be calculated by subtracting the individual subject's Baseline value from the value at the end of the study and then dividing by the individual's Baseline value and multiplying by 100. Mean percent change from Baseline is the mean of all individual participant' percent change from Baseline values.

When the Baseline value is 0, the percent change from baseline will not be calculated and the number of such cases will be tabulated as "Not Calculated" in the descriptive summaries.

The geometric coefficient of variation (CV) will be calculated using the following formula:

$$\mathrm{CV} = 100\sqrt{e^{\mathrm{var}} - 1}$$

where var = the variance from the log transformed data.
The geometric percent Relative Change (RC) from baseline will be calculated using the following formula:

$$\mathrm{RC} = 100 * (\exp(\mathrm{mean}(\ln(\mathrm{x}) - \ln(\mathrm{base}))) - 1)$$

where ln(x) are the natural logarithm of the individual values at the end of the study and ln(base) are the natural logarithm of the individual baseline values.

8.1 Biomarkers of Exposure in Urine

The adjustment for creatinine for the urinary BoExp will be calculated as:

$$\text{BoExp (creatinine adjusted)} = \frac{\text{BoExp}}{\text{Creatinine}}$$

where the [ ] indicated concentrations measured from the spot urine collection.

8.2 Indoor Air Quality Measurements

This section describes how the IAQ variables are derived (Section 8.2.1) when used as covariates for the primary and secondary analysis of urinary BoExp. In addition, we describe the derivations (Section 8.2.2) for the IAQ variables when they are treated as endpoints.

8.2.1 Primary and Secondary Analysis of Urinary Biomarkers of Exposure

- Carbonyls: Acetaldehyde, Acrolein, Crotonaldehyde and Formaldehyde
    - At each event there are 3 machines where each collects 1 sample at 1 hour intervals over a 3 hour period.
    - All readings will be averaged over the 3 hour interval of an event and taken as one observation for all participants of the particular event.
- ISO measurement standards for ETS: 3-Ethenylpyridine (3-EP)
    - At each event there are 3 machines where each collects 2 samples at 3 hour intervals.
    - All readings from the 3 machines will be averaged and taken as one observation for all participants of the particular event.
- Real-time measurements of PM2.5 and PM10 suspended particles in air.
    - At each event there are 2 dedicated sensors measuring suspensed particulate matter with a 1 minute interval monitoring.
    - For passively exposed participants we define the start time of exposure as the time of entry to the event room and end time of exposure as the time of collection of last urine sample. The exposure duration is defined as the start to end time of exposure for a participant. For each type of particulate matter (PM2.5 and PM10), the reading associated with a particular participant will be the average of all the readings from the 2 sensors depending on the participant's exposure duration.
    - For actively exposed participants we define the start time of exposure as the start time of first IQOS use and end time of exposure as the time of collection of last urine sample. The exposure duration is defined as the start to end time of exposure for a participant. For each type of particulate matter (PM2.5 and PM10), the reading associated with a particular participant will be the average of all the readings from the 2 sensors depending on the participant's exposure duration.

8.2.2 Secondary Analysis of Indoor Air Quality Measurements

- Carbonyls: Acetaldehyde, Acrolein, Crotonaldehyde and Formaldehyde
    - At each event there are 3 suitcases sampling each sample at 1 hour intervals over 3 hours.
    - Each of the 9 observations will be used as the observations for the associated event.
- ISO measurement standards for ETS: 3-Ethenylpyridine (3-EP) and Nicotine
    - At each event there are 3 suitcases sampling 2 replicate samples at the end of the 3 hour interval.
    - Each of the 6 observations will be used as the observations for the associated event.
- Tobacco Specific Nitrosamines: NNN and NNK
    - At each event there are 3 suitcases sampling 2 replicate samples at the end of the 3 hour interval.
    - Each of the 6 observations will be used as the observations for the associated event.

- Real-time measurements of PM2.5 and PM10 suspended particles in air.
    - At each event there are 2 sensors measuring the suspended particulate matter a 1 minute interval monitoring.
    - For each sensors, the average of all readings will be calculated from the start till end of the event. These averages will be used as observations for that particular event.

8.3 Questionnaires

All questionnaire data will be listed.

8.3.1 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.

The questions on Smoking History/Habits are self-administrated, to be answered by participants. No imputation for missing data will be performed.

The questions on product use are shown in Table 3.

Table 3. Self-Reported Tobacco and Nicotine Containing Tobacco Product Use

	Question	Answer
1.1*	Have you smoked at least 100 cigarettes in your ENTIRE LIFE?	Yes / No
1.2	In the past 12 months, did you smoke cigarettes?	Yes / No
1.3	In the past 30 days, did you smoke cigarettes…	Every day/Some days/Not at all
1.4	On how many of the past 30 days did you smoke cigarettes?	Numeric response, 2 digits
1.5	On average, on those days you smoked, how many cigarettes did you usually smoke each day?	Numeric response, 3 digits
2.1*	Have you used at least 100 IQOS *HeatSticks* in your ENTIRE LIFE?	Yes / No

Table 3. Self-Reported Tobacco and Nicotine Containing Tobacco Product Use

	Question	Answer
2.2	In the past 12 months, did you use IQOS with *HeatSticks*?	Yes / No
2.3	In the past 30 days, did you use IQOS with *HeatSticks*?	Every day/Some days/Not at all
2.4	On how many of the past 30 days did you use IQOS with *HeatSticks*?	Numeric response, 2 digits
2.5	On average, on those days you smoked, how many cigarettes did you use IQOS with *HeatSticks*?	Numeric response, 3 digits
2.6	In the past 12 months, did you use a Heat-not-burn product other than IQOS with *HeatSticks*?	Yes / No
2.7	In the past 30 days, did you use a Heat-not-burn product other than IQOS with *HeatSticks*?	Every day/Some days/Not at all
2.8	On how many of the past 30 days did you use a Heat-not-burn product other than IQOS with *HeatSticks*?	Numeric response, 2 digits
2.9	On average, on those days you smoked, how many cigarettes did you use a Heat-not-burn product other than IQOS with *HeatSticks*?	Numeric response, 3 digits
3.1	In the past 12 months, did you use an e-cigarette?	Yes / No
3.2	In the past 30 days, did you use an e-cigarette?	Every day/Some days/Not at all
3.3	On how many of the past 30 days did you use an e-cigarette?	Numeric response, 2 digits
3.4	On average, on days you used, how many times did you usually use an e-cigarette each day?	Numeric response, 3 digits

Table 3. Self-Reported Tobacco and Nicotine Containing Tobacco Product Use

	Question	Answer
4.1	In the past 12 months, did you use a Smokeless Tobacco Pipe?	Yes / No
4.2	In the past 30 days, did you use a Smokeless Tobacco Pipe?	Every day/Some days/Not at all
4.3	On how many of the past 30 days did you use a Smokeless Tobacco Pipe?	Numeric response, 2 digits
4.4	On average, on days you used, how many tobacco cartridges did you usually use each day?	Numeric response, 3 digits
5.1	In the past 12 months, did you use Smokeless Tobacco products?	Yes / No
5.2	In the past 30 days, did you use Smokeless Tobacco products?	Every day/Some days/Not at all
5.3	On how many of the past 30 days did you use Smokeless Tobacco products?	Numeric response, 2 digits
5.4	On average, on days you used, how many Smokeless Tobacco products did you use each day?	Numeric response, 3 digits
6.1	In the past 12 months, did you smoke Cigars/Pipes/Kiseru/Shisha?	Yes / No
6.2	In the past 30 days, did you smoke Cigars/Pipes/Kiseru/Shisha?	Every day/Some days/Not at all
6.3	On how many of the past 30 days did you smoke Cigars/Pipes/Kiseru/Shisha?	Numeric response, 2 digits
6.4	On average, on days you used, how many did you smoke Cigars/Pipes/Kiseru/Shisha?	Numeric response, 3 digits
7.1	In the past 12 months, did you use Nicotine Replacement Therapy?	Yes / No

Table 3. Self-Reported Tobacco and Nicotine Containing Tobacco Product Use

	Question	Answer
7.2	In the past 30 days, did you use Nicotine Replacement Therapy?	Every day/Some days/Not at all
7.3	On how many of the past 30 days did you use Nicotine Replacement Therapy?	Numeric response, 2 digits
7.4	On average, on days you used, how many Nicotine Replacement Therapy did you usually use each day?	Numeric response, 3 digits

*Only for CASI

8.3.2 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.

The questions on health outcomes are self-administrated, to be answered by participants. No imputation for missing data will be performed.

The questions on health outcomes in CASI are shown in Table 3.

Table 4. Self-Reported Health Outcomes and Events Questionnaire

Question		Answer
*Question 1. Are you currently pregnant or breastfeeding?	1	Yes
	2	No
	3	Don't know/Not Sure
Question 2. In the last 4 weeks, how has your overall physical health been?	1	Excellent
	2	Very good
	3	Good
	4	Fair
	5	Poor
	6	I prefer not to say

Table 4. Self-Reported Health Outcomes and Events Questionnaire

Question		Answer
Question 3. Have you ever been told by a medical professional that you have any of the following cardiovascular conditions or diseases?	1	Heart attack
	2	Stroke
	3	Angina (chest pain that happens suddenly and becomes worse over time)
	4	Unstable angina (chest pain that occurs seemingly without cause and has a sudden onset, sudden worsening)
	5	High blood pressure / hypertension
	6	Any other condition involving your heart or circulatory system
	7	None of the above
Question 3a Were any of the conditions you refer to above, diagnosed in the last 12 months?	1	Yes
	2	No
Question 4. Have you ever been told by a medical professional that you have any of the following respiratory conditions or diseases?	1	Chronic bronchitis
	2	Emphysema
	3	Chronic obstructive pulmonary disease (COPD)
	4	Apnoea (pauses in breathing during sleep)
	5	High blood pressure / hypertension
	6	Any other condition involving your lungs or respiratory system
	7	None of the above
Question 4a Were any of the conditions you refer to above, diagnosed in the last 12 months?	1	Yes
	2	No
Question 5 Have you ever been told by a medical professional that you have cancer in some parts of your body?	1	Yes
	2	No
Question 5a Was the cancer you refer to above, diagnosed in the last 5 years?	1	Yes
	2	No
	3	Don’t know/Not sure

Table 4. Self-Reported Health Outcomes and Events Questionnaire

Question		Answer
Question 6 Have you ever been told by a medical professional that you have any of the following mental health disorders?	1	Anxiety disorder (including obsessive compulsive disorder)
	2	Depression
	3	Bipolar disorder
	4	Mood disorders (mood swings)
	5	Personality disorders (such as borderline personality or antisocial personality disorders)
	6	Other
	7	None of the above
Question 6a Were any of the conditions you refer to above, diagnosed in the last 12 months?	1	Yes
	2	No
	2	Don't know/Not sure

*For female participants only

8.4 Recording of IQOS Use

At each Exposure Event, the IQOS Active Users, will be provided with a personalized ashtray. IQOS *HeatSticks* that are used during the event will be collected in the ashtray and will be collected at approximately 1 hour intervals and recorded by the study personnel to evaluate the total number of *HeatSticks* used per participant during the Exposure Event.

For the analysis of the IQOS Active User Group, the number of *HeatSticks* used by a participant is defined as all *HeatSticks* used from the start of first use during priming until the end of the event.

8.5 Recording of Food and Alcohol Consumption

Overall Event-level consumption of beverages both alcoholic and non-alcoholic will be recorded hourly at each Event. The overall food consumption per food type will be recorded at each Event.

9 SAMPLE SIZE JUSTIFICATION

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

10 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

For the primary and secondary analysis, the random subject effect is removed as there are no repeated measures.

11 ANALYSIS POPULATIONS

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

11.1 Enrolled Participant Set

The Enrolled Participant Set will consist of all enrolled participants who signed the ICF.

11.2 Compliant Exposure Set

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

11.3 Active Exposure Set

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

11.4 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 manual reviews after the event will be documented in follow-up letters, audit documentation 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 Case Report Form (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.

11.4.1 Major Protocol Deviations

Major protocol deviations are protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

11.4.2 Minor Protocol Deviations

Minor protocol deviations are defined as deviation that does not impact any of the following: (1) the safety of a subject participating the study; (2) the integrity of the data collected for the evaluation of the study; or (3) the overall evaluation and/or interpretation of the outcome of the study, specifically with respect to the primary objective(s).

12 PLANNED STATISTICAL ANALYSIS

12.1 General Considerations

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

12.1.1 Stratified Presentation

For the primary analysis, the following stratification criteria will be used:

1. Product Use Status.
2. Event Type.
3. Sex.

12.1.2 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 CV (for log-transformed variables), median, first and third quartiles, minimum and maximum, and 95% confidence interval (CI) for each product exposure, and summary across all participants.

12.1.3 Definitions for Statistical Data Analysis

12.1.3.1 Categorical Variables

Categorical variables used in this study are shown in Table 5 below.

Table 5. Categorical Variables Definitions

Variable	Categories
Sex	Male
	Female
Event Type	Exposure Event
	Non-Exposure Event
Product Use Status	IQOS Active User
	IQOS Passive User
	Non-Smoker
	Cigarette Smoker

12.1.4 Handling of Dropouts or Missing Data (Including Outside the Limits of Quantification)

For BoExp parameters and creatinine:

- Values below the lower limit of quantification (LLOQ) will be imputed using LLOQ/2. For values above the upper limit of quantification (ULOQ), the value will be imputed using the ULOQ.
- The number of values below LLOQ or above ULOQ will be presented in each summary table.

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

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

For calculation of parameters derived as a ratio of two components (creatinine-adjusted endpoints) if the denominator is below LLOQ then the ratio will not be calculated and will be tabulated as “Not Calculated” in descriptive summaries and excluded from the main analysis. A sensitivity analysis will be produced by including derived values using LLOQ/2 values for the denominator of the impacted endpoint for the Compliant Exposure Set and Active Exposure Set.

For Duration of Exposure:

If the collection time of a urine sample is missing and the duration of exposure cannot be calculated, and therefore 2 hours of participation cannot be confirmed, the participant’s samples will not be analyzed and they will be excluded from the analysis set. These participants may be included in other descriptive analyses.

Participants enrolled in the study who did not participate for at least 2 hours of the planned Event (discontinued subjects), they will be included in data summaries for demographics, disposition, and self-reported questionnaires using the Enrolled Participant Set.

For participants with missing CASI data, they will be analyzed in the Study Population(s) when data are available, without imputation of the missing data.

12.2 Disposition of Participants

The disposition of participants will be listed and summarized.

12.3 Demographic and Other Baseline Characteristics

Demographic data collected from CASI will be summarized for each Study Population by event type (Exposure vs. Non-Exposure), product use status and sex.

12.4 Extent of Exposure (Product Consumption)

The number of *HeatSticks* used for each IQOS Active User will be listed by event. Summary statistics of *HeatSticks* usage will be presented by hour and over the entire event. IQOS exposure will also be presented as total per hour, total for the event, and average usage per hour for each Exposure Event and across all Exposure Events.

12.5 Food and Alcohol Consumption

The overall amount of food and alcohol consumed will be summarized by food and beverage type for each event.

12.6 Planned Statistical Analyses

12.6.1 Primary Analysis

12.6.1.1 Statistical Analysis of Primary Endpoints

For each urinary BoExp in the primary analysis NEQ, Total NNAL, Total NNN, the change between pre-event and end of study levels adjusted for creatinine will be modeled using a linear model in the Compliant Exposure Set.

The SAS procedure PROC MIXED will be used with the restricted maximum likelihood method for estimation of the parameters. The mixed model will have the change from baseline as dependent variable and the following covariates will be included in the model: Baseline, Sex, Event Type (Exposure or Non-Exposure), Duration of Exposure, Product Use Status, Product Use Status by Event Type interaction for all BoExp. In addition, an air quality covariate related to each BoExp is included in the model depending on the endpoint and is described in Appendix 15.2. This table also specifies the various IAQ covariates that are assessed using a step-wise regression approach for each BoExp. The algorithm is described below,

1. Fit a full model with all covariates

2. Drop one IAQ covariate and re-fit the model.
3. Perform a likelihood ratio test and drop the IAQ covariate with the largest p-value for the likelihood ratio statistic if it is more than 0.05.
4. Repeat steps 2 and 3 until no more IAQ covariates can be dropped.
5. Refit the final model with the IAQ covariates remaining in the model and estimate exposures for each product use group.

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 together with the 95% CIs for non-smokers during an Exposure Event. Other contrasts can be constructed to determine the change in urinary BoExp for participants with other smoking status (Cigarette Smoker and IQOS Passive Users) after passive exposure to IQOS usage.

An example of SAS code for the final model is provided below,

```
Proc mixed data=_data_ method=reml;
Class event_type sex product_use;
Model endpoint = baseline sex event_type product_use event_type*product_use
duration <IAQ covariates> / ddfm=kr;
estimate 'Cigarette Smoker' intercept 1 baseline xx sex .5 .5 product_use 1 0 0
event type 1 event_type*product_use 1 0 0 0 0 0 duration  xx IAQ1 xx … IAQn xx /
alpha=0.05 cl;
Run;
```

We define xx are the mean of a continuous covariate for participants in the product use group across all Exposure Events. For air quality covariates, they will be the mean calculated over all Exposure Events since they were the same regardless of product use group.

The LSmeans and corresponding confidence intervals will be exponentiated, back-transformed to the original scale and reported as geometric means with its confidence intervals.

12.6.1.2 Descriptive Analysis and Listing of Primary Endpoints

The level of BoExp parameters (NEQ, Total NNAL, Total NNN) and their change from Baseline will be summarized by Product Use Status (Non-Smoker, IQOS Passive User, Cigarette User), Event Type (Exposure vs Non-Exposure) and sex for the Compliant Exposure Set. All BoExp values will be log-transformed ($base_e$) prior to the analysis.

For each BoExp parameter, the quantity excreted at baseline and from last urine void together with the change from baseline (both relative change and absolute change) will be summarized according to descriptive statistics listed in Section 12.1.2. In addition, the concentrations adjusted for creatinine and also its change from baseline will the summarized in a similar fashion.

Line graphs with the geometric means for each parameter and 95% CI over time (baseline and last void) will be produced. In each graph, the values of both Exposure and Non-Exposure Events for each Product Use Status will be plotted. The same graph will be repeated stratified further using sex.

12.6.2 Secondary Analysis

12.6.2.1 Indoor Air Quality Assessment

The assessment of the various IAQ compounds between Exposure and Non-Exposure Events will be analysed using a mixed model approach. The precise definition of each endpoint is detailed in Section 8.2.2.

12.6.2.1.1 Carbonyls

During each Exposure and Non-Exposure Event, there are 3 sampling cases that collects air for the assessment of carbonyls at 1 hour intervals. Each sampling case was placed at the same location during an Event.

The SAS procedure PROC MIXED will be used with the restricted maximum likelihood method for estimation of the parameters. The mixed model will have the carbonyl reading as dependent variable and the following covariates will be included in the model: Location, Event Number (Exposure Events 1-4 and Non-Exposure Event 1 and 2) and Event Type (Exposure and Non-Exposure Event). A repeated statement will be used to model repeated measures for the time variable.

The denominator degrees of freedom will be determined using the method of Kenward and Roger (1997). In case of non-convergence of the preferred model or memory space issues, the Kenward-Roger method will be replaced by Satterthwaite approximation.

The SAS code for the mixed model to be used is shown below:

```
Proc mixed data=_data_ method=reml;
Class location time event_type;
Model endpoint = location event type event num/  ddfm=kr;
Repeated time/subject=location(event num) type=cs;
Lsmeans event_type / diff alpha=0.05 cl;
Lsmeans location / diff alpha=0.05 cl;
Run;
```

The Geometric LS means and estimate of the ratio of geometric means between Exposure and Non-Exposure Events along with its 95% CI will be presented in tables for Formaldehyde, Acetaldehyde, Acrolein and Crotonaldehyde. The geometric LS means and ratio of geometric means together with their respective CIs are calculated by exponentiating the LSmeans and differences between exposures groups.

12.6.2.1.2 Tobacco-specific markers and Tobacco-specific nitrosamines

During each Exposure and Non-Exposure Event, there are 3 sampling cases that collects air for the assessment of Tobacco-specific markers (3-Ethenylpyridine (3-EP) and Nicotine) and Tobacco-specific nitrosamines (NNN and NNK) at 3 hour intervals. For each sampling case it was placed at the same location during an event, each sampling case provides two replicates.

The SAS procedure PROC MIXED will be used with the restricted maximum likelihood method for estimation of the parameters. The mixed model will have the value of the exposure as dependent variable and the following covariates will be included in the model: Location, Event Number (Exposure Events 1-4 and Non-Exposure Event 1 and 2) and Event Type (Exposure and Non-Exposure Event). Replicate will be modelled as a repeated variable.

The denominator degrees will be the same as describe for the Carbonyls (Section 11.6.2.1.1).

The SAS code for the mixed model to be used is shown below:

```
Proc mixed data=_data_ method=reml;
Class location replicate event_type;
Model endpoint = location event_type/  ddfm=kr;
repeated replicate /subject=location(event_type) type=cs;
Lsmeans event_type / diff alpha=0.05 cl;
Lsmeans location / diff alpha=0.05 cl;
Run;
```

The Geometric LS means and ratio of geometric means between Exposure and Non-Exposure Group along with its 95% CI will be presented in tables for Nicotine, 3-ethenylpyridine, NNN and NNK. The geometric LS means and ratio of geometric means together with their respective CIs are calculated by exponentiating the LSmeans and differences between exposures groups.

12.6.2.1.3 Particles Suspended in Air

During each Exposure and Non-Exposure Event, there are 2 Dust Trak sensors that measure in real-time suspended particulate matter in air (PM1, PM2.5, PM4 and PM10) every minute. Each sensor was placed at different locations during an event. To assess the change in particulate matter suspended in air between an Exposure and Non-Exposure Event, this will be modelled using a linear model.

The SAS procedure PROC MIXED will be used with the restricted maximum likelihood method for estimation of the parameters. The dependent variable will be the average of the 1 minute readings from the start till end of each event for each sensor. The mixed model will use the mean as dependent variable and the following covariates will be included in the model: location and event type.

The denominator degrees will be the same as describe for the Carbonyls (Section 11.6.2.1.1).

The SAS code for the mixed model to be used is shown below:

```
Proc mixed data=_data_ method=reml;
Class location event_type;
Model endpoint = location event_type/  ddfm=kr;
Lsmeans event_type / diff alpha=0.05 cl;
Lsmeans location/ diff alpha=0.05 cl;
Run;
```

12.6.2.1.4 Descriptive Analysis of Indoor Air Quality parameters

In addition to the statistical analysis of the indoor air quality parameters described in Sections 12.6.2.1.1 to 12.6.2.1.3. The IAQ parameters (formaldehyde, acetaldehyde, acrolein and crotonaldehyde, 3-Ethenylpyridine (3-EP), Nicotine, NNN, NNK, PM1, PM2.5, PM4 and PM10) and will be summarized by time (where applicable), event number and type of event (Exposure vs Non-Exposure). All IAQ values will be log-transformed ($base_e$) prior to the analysis except the particulate matter values PM1, PM2.5, PM4 and PM10.

All raw IAQ values except particulate matter variables PM1, PM2.5, PM4 and PM10 generated during an event will be listed. For particulate matter parameters only the mean for each sensor during an event will be listed.

Summary statistics (Section 12.1.2) of the IAQ endpoints will also include the percent change between Exposure and Non-Exposure Event, together with 95% CI for IAQ values having at least 50% of the measured values above the limit of quantification (LOQ).

For each IAQ parameter, a plot will be generated by location and exposure type (Exposure vs Non-Exposure) to assess whether differences exist in exposures at different locations.

For carbonyls, exposure vs time will be plotted with separate colors for location and type of Exposure Event. For TSNAs and tobacco specific markers, exposure vs location will be plotted with separate colors for the event type. Lastly, for particles suspended in air, the mean exposure (averaged over the duration of an event) vs location will be plotted with separate colors for each event type.

12.6.2.2 Assessment of levels of exposure to additional selected HPHCs

Similar to the primary analysis described in 12.6.1.1, for each urinary biomarker of exposure listed in the secondary objective HMPMA, 3-HPMA, S-PMA and HEMA, the change between pre-event and latest post two hour urinary BoExp adjusted for creatinine will be modeled using a linear model in the Compliant Exposure Set. The effect of passive exposure to IQOS aerosol during the Exposure Event on the mean change in levels of urinary BoExp together with the 95% confidence intervals (CIs). Other contrasts can be constructed to determine the change in urinary BoExp for participants with other smoking status after passive exposure to IQOS usage.

A descriptive analysis of these same biomarkers will be performed as well as detailed in Section 12.6.1.2.

12.6.2.3 Analysis of the Active Exposure Group

To quantify the change between the pre-event and end of study urinary BoExp levels in IQOS Active Users. The change from baseline adjusted for creatine is the dependent variable with baseline, Sex, number of *HeatSticks*, duration of exposure and IAQ parameters (Section 8.2.1) as the covariates. Similar to Section 12.6.1.1, an air quality covariate related to each BoExp is included in the model depending on the endpoint and is described in Appendix 15.2. The same IAQ covariates listed for the

various BoExp is also assesed using a step-down regression approach in the following algorithm. Fit a full model with all covariates

1. Drop one IAQ covariate and re-fit the model.
2. Perform a likelihood ratio test and drop the IAQ covariate with the largest p-value for the likelihood ratio statistic if it is more than 0.05.
3. Repeat steps 2 and 3 until no more IAQ covariates can be dropped.
4. Refit the final model with the IAQ covariates remaining in the model and estimate exposures for the Active IQOS group

An example of the SAS code is shown below,

```
Proc mixed data=_data_ method=reml;
Class sex heatsticks;
Model endpoint = baseline sex heatsticks duration <IAQ covariates> / ddfm=kr;
estimate 'Active' intercept 1 baseline xx sex 0.5 0.5  heatsticks xx duration xx
IAQ1 xx … IAQn xx / alpha=0.05 cl;
Run;
```

We define xx are the mean of a continuous covariate for participants in the active Exposure Group across all Exposure Events. For air quality covariates, xx is the mean calculated over all Exposure Events.

The LSmeans and corresponding confidence intervals will be exponentiated, back-transformed to the original scale and reported as geometric means with its confidence intervals.

Descriptive statistics and figures of each BoExp for the actively exposed participants will summarized in the same way as described in Section 12.6.1.2. However, the results will only be stratified by Sex.

12.6.3 Safety Evaluation

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. Adverse events that may occur during the study will not be collected.

13 ANALYSES AND REPORTING

13.1 Interim Analyses and Data Monitoring

This analysis may be conducted and reported in steps over time. Although these analyses will only be performed after database lock. Any interim reports will be incorporated into the final complete study report (Section 12.3).

13.2 Safety Reporting

Not applicable within this study.

13.3 Final Analyses

The final analysis will be performed after database lock and finalization of this SAP. A data review meeting will be held prior to database lock and analysis of the study data.

Any post-hoc, additional exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported as applicable. Any unplanned analyses conducted prior to the finalization of the CSR will be clearly documented in the CSR, any additional analysis performed after the finalization of the CSR will either be included in an amendment of the CSR or be created as an addendum to the CSR.

14 POST-HOC ANALYSIS

This section describes additional analyses to be performed to further support the interpretation of the results from the study.

14.1 Additional Analysis to Explore Outcome of Primary Analysis

During the review of results from the primary analyis of the urinary biomarkers of exposure (BoExp) for both the Non-Exposure and Exposure Events it was identified that we could expand the predefined model to add more context and systematically evaluate the difference between the event types. The planned model, provided the estimates of the average levels of each BoExp during an exposure or Non-Exposure Event for each product use group, but did not compare between the events.

However for the indoor air quality compounds we defined the model to also compare across Exposure and Non-Exposure Events. When looking at the results and trying to understand the link between the indoor air quality compounds and the BoExp, we decided that it would be beneficial to have the similar comparison (across Exposure and Non-Exposure Events) for the BoExp. Since these values could be estimated by expanding the predefined model, it was decided to implement this change as a post hoc analysis.

To perform this analysis, an 'estimate' statement was added to the code to calculate the ratio of geometric means between the exposure and non-exposure group for each product use group. An example of the modified pseudo code from section 12.6.1.1 is presented below.

```
Proc mixed data=_data_ method=reml;
Class event_type sex product_use;
Model endpoint = baseline sex event_type product_use event_type*product_use
duration <IAQ covariates> / ddfm=kr;
estimate 'Cigarette Smoker' intercept 1 baseline xx sex .5 .5 product_use 1 0 0
event_type 1 event_type*product_use 1 0 0 0 0 0 duration  xx IAQ1 xx … IAQn xx /
alpha=0.05 cl;
estimate 'Cigarette Smoker Exp vs Non-exp' intercept 0 baseline yy sex 0 0
product_use 0 0 0 event_type 0 0 event_type*product_use 1 0 0 -1 0 0 duration
yy IAQ1 yy … IAQn yy / alpha=0.05 cl;
Run;
```

Note that yy is the change in a covariate between the exposure vs the non-exposure groups. For example, the value for the covariate baseline is the change for baseline values in the exposure group minus baseline values in the non-exposure group for a product use group.

All estimates and respective 95% confidence intervals will be exponentiated and back-transformed to the original scale. This additional analysis will be presented and integrated with Table 15.2.2.1.1.

14.2 Additional Analysis to Explore Effect of Heatstick Consumption, Alcoholic Beverages and Food Consumption on Concentrations of HPHCs in Air

During the internal review period of the End of Trial Report for study P1-PES-01-JP and following a request of [redacted] after presentation of the preliminary results to the [redacted] it was identified that we should further examine the source of the increases of concentrations of Harmful or Potentially Harmful Constituents (HPHCs) in indoor air during a restaurant setting where the Non-Exposure and Exposure events took place by looking at the relationship between HeatStick consumption and its impact on HPHC concentrations including the IAQ markers acetaldehyde, formaldehyde, crotonaldehyde and acrolein. The statistical analysis defined in SAP version 1 did not allow an interpretation of these results directly, as it only included descriptive statistics.

To further explore the impact of potential impact of other covariates that may affect the concentrations of these HPHCs in air, we will use a linear regression model to assess the effects of beverage and food consumption on acetaldehyde, acrolein, crotonaldehyde and formaldehyde in addition to Heatsticks consumption. For acetaldehyde, we use a mixed effects repeated measures model representation to model the cumulative effects of these covariates over time as the covariates were measured on an hourly basis. A summary of the covariates used in the models are listed in Table 6.

Table 6. Covariates for Analysis of HPHCs in air

Model	Time Points Used	Endpoint	Covariates
1	Average	Acetaldehyde	Baseline, Event Type, Cumulative Heatstick Consumption at 3rd Hour
1	Average	Acrolein	Baseline, Event Type, Cumulative Heatstick Consumption at 3rd Hour
1	Average	Crotonaldehyde	Baseline, Event Type, Cumulative Heatstick Consumption at 3rd Hour
1	Average	Formaldehyde	Baseline, Event Type, Cumulative Heatstick Consumption at 3rd Hour
2	All timepoints	Acetaldehyde	Baseline, Event Type, Heatstick Consumption, Alcoholic Beverages Consumption, Heatstick and Alcoholic Beverages interaction
3	Average	Acrolein	Baseline, Event Type, Cumulative Food Consumption during event
3	Average	Crotonaldehyde	Baseline, Event Type, Cumulative Food Consumption during event

Model 1 in Table 6 above describes a basic model relating the average levels of carbonyls to HeatSticks consumption. In this model the dependent variable is the change from baseline of the average reading of the carbonyls. Note that the average reading is taken as the mean of all readings from the three suitcases that were used to collect the carbonyls data. Baseline is the mean reading of all pre-event readings that were taken during a specific event. The endpoint change from baseline will be log-transformed prior to analysis. Baseline, Event type (Exposure or Non-Exposure), cumulative Heatstick usage will be fitted as fixed effects. Estimates of the carbonyl readings at mean levels of the covariates will be calculated for each event type. The estimates will be exponentiated and presented on the original scale. In addition to the estimates at an event level, the relative change in the carbonyls between and Exposure and Non-Exposure Event will be estimated as well. These estimates also be exponentiated and presented as a ratio of geometric means of an Exposure Event relative to a Non-Exposure Event. An example of the SAS code for model 1 is as given below.

```
proc mixed data=data;
class event exposure;
model ch=baseline exposure cumu_heatsticks /ddfm=kr solution;
estimate 'Non-exp 3rd hr' intercept 1 baseline xx exposure 1 0 cumu_heatsticks 0
/e cl alpha=.05;
```

```
estimate 'Exp 3hr hr' intercept 1 baseline yy exposure 0 1 cumu_heatsticks yy/e
cl alpha=.05;
estimate 'Change in carbonyl 3hr hr' intercept 0 baseline xy exposure 1 -1
cumu_heatsticks xy /e cl alpha=.05;
run;
```

Note that xx is the average of the observations of the associated covariate in the Non-Exposure Event and yy is the average of the observations of the associated covariates in the Exposure Event. The value for the covariates to estimate the relative change between events denoted by xy is the average difference between Exposure and Non-Exposure events.

For acetaldehyde in Model 2, all 3 timepoints will be used in the analysis and a repeated measures analysis will be used to model the effects over time. Due to the equally spaced observations, a toeplitz structure will be fitted to the covariance structure to allow for variance components to be estimated at each timepoint. Heatstick and alcohol consumption will be fitted as fixed effects and their interaction terms will be added to the model as well.

```
proc mixed data=data;
class event exposure time;
model change=baseline exposure cumu_alcohol cumu_heatsticks
cumu_alcohol*cumu_heatsticks /ddfm=kr solution;
repeated time/type=toep subject=event;
estimate 'Non-exp 3rd hr' intercept 1 baseline xx exposure 1 0 cumu_alcohol xx
cumu_heatsticks 0 cumu_alcohol*cumu_heatsticks 0 /e cl alpha=.05;
estimate 'Exp 3hr hr' intercept 1 baseline yy exposure 0 1 cumu_alcohol yy
cumu heatsticks yy cumu alcohol*cumu heatsticks  yy/e cl alpha=.05;
estimate 'Change in carbonyl 3hr hr' intercept 0 baseline xy exposure 1 -1
cumu_alcohol xy cumu_heatsticks xy cumu_alcohol*cumu_heatsticks  xy/e cl
alpha=.05;
run;
```

Note that xx is the average of the observations of the associated covariate in the Non-Exposure Event and yy is the average of the observations of the associated covariates in the Exposure Event. The value for the covariates to estimate the relative change between event types denoted by xy is the average difference between Exposure and Non-Exposure events.

Model 3 will be similar to Model 1 but with cumulative Heatstick consumption replaced by cumulative food consumption. The estimates from this model will be calculated at the mean levels calculated for each event type.

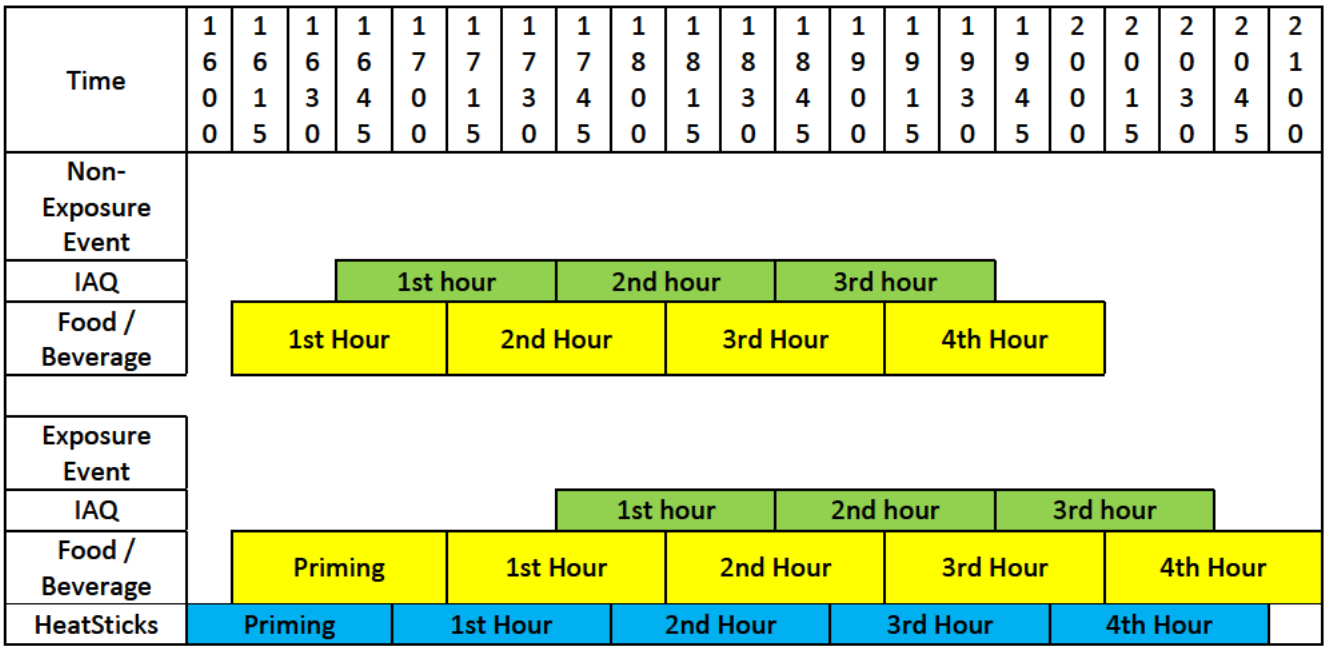
Due to the irregular nominal times of the carbonyls, food/beverages and HeatStick consumption collection as shown in Table 7, we will pro-rate the values of the covariates against the time of carbonyl collection. For example, during a Non-Exposure Event at the end of the 1st hour for the carbonyls taken at 1730 the corresponding value for food or alcoholic beverages will be the sum of the 1st hour plus half of the 2nd hour. Similarly for an Exposure event, for the 2nd hour carbonyl reading the corresponding observation for food/beverages will be the cumulative sum until 2.5 hours and Heatsticks consumption will be the sum up to the 2nd hour plus a quarter of the 3rd hour observation.

From this model we will estimate the cumulative effects of the covariates on carbonyls at the end of 3 hours and also estimate the average concentrations of carbonyls in air over 3 hours.

For each type of carbonyl, boxplots of observations at each timepoint will be plotted against time and grouped by Event in the same figure.

A sensitivity analysis will also be performed matching the endpoints by the nominal timepoints, this approach is more conservative as the cumulative effects of food/beverage or HeatStick consumption is lower than what it actually was during time of the carbonyls reading.

Table 7. Nominal Sampling Times of Food/Beverages, IAQ parameters (Carbonyls) and HeatSticks consumption during Exposure and Non-Exposure Events



14.3 Additional Descriptive Analysis on IAQ Parameters

During the review and finalization of results from the analysis of the IAQ parameters, it was identified that pre-event data was available but not analyzed. For each of the IAQ parameters that were collected in the study, we will calculate descriptive statistics for the parameters to obtain information about background levels of the various analytes.

14.4 Additional Secondary Analysis on IAQ Parameters Performed by CRO ([redacted])

During the review and finalization of the results from the secondary analysis of the IAQ parameters it was identified that there was a discepancy between the SAP specified model and the results provided by the CRO ([redacted] The planned model, uses observations collected at each timepoint for each events in the model however [redacted] used a model with endpoints averaging observations from each event.

This was due to an incorrect model specification in section 11.6.2.1.1. which did not allow the specified model to converge. Results from this additional analysis will be kept and presented in the Appendix of the study report.

14.5 Additional Analysis to Explore Effect of Heatstick Consumption on Urinary BoExp

14.5.1 Effect of HeatStick Consumptions on Urinary BoExp in Compliant Exposure Set

During the review of the Clinical Study Report questions were raised about the relationship between HeatStick consumption and the levels of BoExp in the Compliant Exposure Set. A prior post-hoc analysis (14.2) investigated the effect of HeatSticks consumption and other covariates such as food consumption and consumption of alcoholic beverages on carbonyls in air. To corroborate the results from that analysis and impact of HeatSticks on the urinary BoExp, we will use the models developed for the BoExp (12.6.1.1, 12.6.2.2) and include a covariate for total HeatSticks consumption used during an Event. As with the existing models for the BoExp, the estimates for each product use group will be exponentiated and reported as geometric means and the ratio of geometric lsmeans between Exposure and Non-Exposure Events will be calculated and reported together with its 95% confidence intervals.

A sample of the code is presented below,

```
Proc mixed data=_data_ method=reml;
Class event_type sex product_use;
Model endpoint = baseline sex event_type product_use event_type*product_use
duration cumulative_heatsticks product_use*cumulative_heatsticks<IAQ covariates>
/ ddfm=kr;
estimate 'Cigarette Smoker Exposure event' intercept 1 baseline xx sex .5 .5
product_use 1 0 0 event_type 1 event_type*product_use 1 0 0 0 0 0 duration xx
cumulative_heatsticks xx IAQ1 xx … IAQn xx / alpha=0.05 cl;
estimate 'Cigarette Smoker Non-Exposure event' intercept 1 baseline yy sex .5 .5
product_use 1 0 0 event_type 0 event_type*product_use 0 0 0 1 0 0 duration yy
cumulative_heatsticks 0 IAQ1 yy … IAQn yy / alpha=0.05 cl;
estimate 'Cigarette Smoker Exposure vs Non-Exposure event' intercept 0 baseline
xx-yy sex 0 0 product_use 0 0 0 event_type 0 event_type*product_use 1 0 0 -1 0 0
duration xx-yy cumulative_heatsticks xx IAQ1 xx-yy … IAQn xx-yy / alpha=0.05 cl;
Run;
```

We define xx as the average values of a covariate for a participant belonging to the product use group of interest during an Exposure Event and yy as the corresponding average during a Non-Exposure Event. If the model fails to converge, then the individual exposure to HeatSticks based on the duration a participant was in the Exposure Event will be calculated and this will be used in place of an overall cumulative exposure to HeatSticks during the entire Exposure Event. The value of xx in this case would be the average of all the individual exposures to HeatSticks for each participant.

This analysis will be repeated for all endpoints listed in Table 8.

14.5.2 Effect of HeatSticks on the Active Exposure Set

The effects of HeatSticks and other covariates on urinary BoExp is described in the analysis in section 12.6.2.3.. To assess the impact on urinary BoExp with and without adjustment for HeatSticks, the

same model from section 12.6.2.3. will be fitted but without HeatSticks as a covariate. From this model, we will calculate the effect on the endpoints similar to section 12.6.2.3. The estimates will be exponentiated and back-transformed to produce the geometric means and the corresponding 95% confidence intervals. An example of the code is provided below.

```
Proc mixed data=_data_ method=reml;
Class sex;
Model endpoint = baseline sex duration <IAQ covariates> / solution ddfm=kr;
estimate 'Active no HeatSticks' intercept 1 baseline xx sex 0.5 0.5  duration xx
IAQ1 xx … IAQn xx / alpha=0.05 cl;
Run;
```

14.6 Additional Analysis to Account for Pre-Event Levels of IAQ Parameters

The review of the pre-event IAQ data described in section 14.3 suggests that the levels of building background should be taken into account during the statistical analysis of the IAQ parameters. The statistical analysis of IAQ parameters described in sections 12.6.2.1.1, 12.6.2.1.2 and 12.6.2.1.3 will therefore be repeated but the endpoint will be the change from pre-event average instead of the raw values measured during an event. Note that the change from pre-event average will be log-transformed prior to analysis. The estimates from these models will be exponentiated and reported as geometric means for each Event type. Comparisons between Exposure and Non-Exposure Event will be reported as ratio of geometric means. All estimates will be reported together with their corresponding 95% confidence intervals.

15 APPENDICES

15.1 Study Assessments

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		●	●
Self-Reported Health Outcomes and Events Questionnaire [a]		●	●
Recording of IQOS 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.

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

d: Assessment of IAQ parameters as defined in **Section 8.2**.

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

15.2 Covariates used in Analysis of Urinary BoExp

Table 8. Covariates for Analysis of Urinary BoExp

Endpoint	Included Covariates[1]	Included Air Quality Covariates[1]	Evaluated Air Quality Covariates
NEQ	Baseline, Sex, Event Type, Duration of Exposure, Product Use Status, Product Use Status by Event Type	Nicotine	Formaldehyde, Acetaldehyde, Acrolein, Crotonaldehyde, 3-ethenylpyridine, PM2.5, and PM10
Total NNAL	Baseline, Sex, Event Type, Duration of Exposure, Product Use Status, Product Use Status by Event Type	NNK	Formaldehyde, Acetaldehyde, Acrolein, Crotonaldehyde, 3-ethenylpyridine, PM2.5, and PM10
Total NNN	Baseline, Sex, Event Type, Duration of Exposure, Product Use Status, Product Use Status by Event Type	NNN	Formaldehyde, Acetaldehyde, Acrolein, Crotonaldehyde, 3-ethenylpyridine, PM2.5, and PM10
HMPMA	Baseline, Sex, Event Type, Duration of Exposure, Product Use Status, Product Use Status by Event Type	Crotonaldehyde	Formaldehyde, Acetaldehyde, Acrolein, 3-ethenylpyridine, PM2.5, and PM10
3-HPMA	Baseline, Sex, Event Type, Duration of Exposure, Product Use Status, Product Use Status by Event Type	Acrolein	Formaldehyde, Acetaldehyde, Crotonaldehyde, 3-ethenylpyridine, PM2.5, and PM10

Table 8. Covariates for Analysis of Urinary BoExp

Endpoint	Included Covariates[1]	Included Air Quality Covariates[1]	Evaluated Air Quality Covariates
S-PMA	Baseline, Sex, Event Type, Duration of Exposure, Product Use Status, Product Use Status by Event Type	NNK	Formaldehyde, Acetaldehyde, Acrolein, Crotonaldehyde, 3-ethenylpyridine, PM2.5, and PM10
HEMA	Baseline, Sex, Event Type, Duration of Exposure, Product Use Status, Product Use Status by Event Type	NNK	Formaldehyde, Acetaldehyde, Acrolein, Crotonaldehyde, 3-ethenylpyridine, PM2.5, and PM10

1 These covariates will be included in the statistical models for their respective urinary BoExp
2 The covariates pertaining to air quality will be assessed as described in Section 12.6.1.1

15.3 Summary of Biomarkers of Exposure to HPHC

All parameters listed here will be log-transformed.

Table 9. Table of HPHCs measured in spot urine

HPHC	Biomarker	Primary Analysis
Acrolein [gas]	3-Hydroxypropyl-mercapturic acid (3-HPMA)	No
Benzene [gas]	S-Phenyl-mercapturic acid (S-PMA)	No
Crotonaldehyde [gas]	3-Hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA)	No
Ethylene oxide [gas]	2-Hydroxyethyl-mercapturic acid (HEMA)	No
Nicotine [particulate]	Nicotine equivalents (NEQ)	Yes
NNK	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL)	Yes

HPHC	Biomarker	Primary Analysis
NNN [particulate]	Total N-nitrosonornicotine (Total NNN)	Yes

15.4 Tables, Figures and Listings

Tables

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15.2.1.2	Summary of Reasons for Premature Discontinuation
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15.2.1.4.1.1	Summary of Demographics and Other Baseline Characteristics by Event Type – All Participants
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15.2.1.6	Summary of Self-Reported Health Outcomes & Events Questionnaire by Event Type
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15.2.2.1.3	Descriptive Statistics of the Primary Urinary Biomarkers of Exposure by Exposure Type, Product Use & Sex – Compliant Exposure Set
15.2.2.2.1	Analysis of the Secondary Urinary Biomarkers of Exposure – Compliant Exposure Set
15.2.2.2.2	Descriptive Statistics of the Secondary Urinary Biomarkers of Exposure by Exposure Type & Product Use – Compliant Exposure Set

Table No.	Title
15.2.2.2.3	Descriptive Statistics of the Secondary Urinary Biomarkers of Exposure by Exposure Type, Product Use & Sex – Compliant Exposure Set
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15.2.2.5.1	Analysis of Indoor Air Quality Parameters (Particulate Matter)
15.2.2.5.2	Descriptive Statistics of Indoor Air Quality Parameters (Particulate Matter) by Exposure Type & Location
15.2.2.6.1	Analysis of the Urinary Biomarkers of Exposure – Active Exposure Set
15.2.2.6.2	Descriptive Statistics of the Urinary Biomarkers of Exposure by Sex – Active Exposure Set
15.2.2.7.1	Post-Hoc1a: Additional Analysis to Explore Effect of Heatstick Consumption, Alcoholic Beverages and Food Consumption on Concentrations of HPHCs in Air Using Matched Timings

Listings

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Figures