PHILIP MORRIS PRODUCTS S.A.

Statistical Analysis Plan

Study Number:	P1-AAA-02-JP
Study Title:	A controlled, open-label, 3-arm parallel group, multi-center study to evaluate the Abdominal Aortic Aneurysm (AAA) growth rate in adult smoking patients randomized to either cigarette smoking or IQOS use and to compare with the AAA growth rate in patients who had stopped smoking.
Product Name:	IQOS (Tobacco Heating System [THS] with Marlboro Heatsticks)
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	1.0, Approved
Date:	20 September 2022

STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

When this page is signed the Statistical Analysis Plan (SAP) is considered final. The signatories agree to the statistical analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs).

CRO Approval:

[redacted]	Date 27 SEP 2022
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1 INTRODUCTION

This plan document stipulates the details of the statistical analysis plan for "A controlled, open-label, 3-arm parallel group, multi-center study to evaluate the Abdominal Aortic Aneurysm (AAA) growth rate in adult smoking patients randomized to either cigarette smoking or IQOS use and to compare with the AAA growth rate in patients who had stopped smoking." (Protocol Number: P1-AAA-02-JP).

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

This SAP and any amendments 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 described in the clinical study report (CSR).

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

- International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" (ICH Guideline E9 1998),
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" (ICH Guideline E3 1995),
- Subject Case Report Forms (eCRF) version 4.0 (dated 12 AUG 2020),
- Biostatistical Addendum – Subject Randomization List version 1.0 (dated 04 DEC 2017),
- Protocol versions and amendments:

Protocol	Version	Date	Amendment
Current protocol	Final Version 9.0	17 September 2021	No. 7; non-substantial changes
Sixth amended protocol	Final Version 8.0	14 January 2020	No. 6; substantial changes
Fifth amended protocol	Final Version 7.0	23 July 2019	No. 5; non-substantial changes
Fourth amended protocol	Final Version 6.0	10 April 2019	No. 4; non-substantial changes
Third amended protocol	Final version 5.0	12 November 2018	No. 3; non-substantial changes
Second amended protocol	Final Version 4.0	25 June 2018	No. 2; non-substantial changes
First amended protocol	Final Version 3.0	26 February 2018	No. 1; non-substantial changes
First updated protocol	Final Version 2.0	10 January 2018	Non-substantial updates
Original protocol	Final Version 1.0	05 October 2017	

1.1 Revision History

Version	Date of Revision	Revision
1.0	20 September 2022	Initial Version

2 ABBREVIATIONS OF TERMS

AAA	Abdominal Aortic Aneurysm
AE	Adverse Event
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BoExp	Biomarker of Exposure
BUN	Blood Urea Nitrogen
CIG	Cigarette
2-CyEMA	2-Cyanoethylmercapturic Acid
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
ECG	Electrocardiogram
FAS	Full Analysis Set
GGT	Gamma-Glutamyl Transferase

HPHC	Harmful and Potentially Harmful Constituents
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IP	Investigational Product (including the comparator product: CIG)
IXRS	Interactive Web and Voice Response System
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Qualification
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
NEQ	Nicotine Equivalents
NNK	Nicotine-derived nitrosamine ketone (= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)
NRT	Nicotine Replacement Therapy
PK	Pharmacokinetics
PMI	Philip Morris International
QC	Quality Control
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Smoking Cessation
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TC	Total Cholesterol
TG	Triglycerides
THS	Tobacco Heating System
Total NNAL	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
Total NNN	Total N-nitrosonornicotine
ULOQ	Upper Limit of Qualification
WBC	White Blood Cell

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives and Endpoints

The primary objective of this study is:

To evaluate the reduction in the AAA annual growth rate in patients who switch from smoking cigarettes (CIG) to using IQOS, as compared to patients who continue to smoke CIG (IQOS arm versus cigarette arm), also as compared to patients who had stopped smoking (IQOS arm

versus Smoking Cessation (SC) arm), and to evaluate the reduction in the AAA annual growth rate in patients who continue to smoke CIG as compared to patients who had stopped smoking (CIG arm versus SC arm).

Endpoints (to be assessed using all available diameter measurements from V3 to V8):

- Measurement of the maximum minor-axis AAA diameter in mm
- AAA annual growth rate (calculated by annualizing the slope of the linear regression over the available diameter measurements)

3.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

1. To describe the time from diagnosis of the AAA until open surgical AAA treatment or AAA endovascular repair or AAA rupture in patients who switch from smoking CIG to using IQOS, as compared to patients who continue smoking CIG and patients who had stopped smoking.
   Endpoints (over the entire study period):
   - Date of diagnosis
   - Date of decision to perform open surgical AAA treatment or AAA endovascular repair
   - Date of AAA rupture
2. To describe the number of open surgical AAA treatment or AAA endovascular repair and AAA rupture in patients who switch from smoking CIG to using IQOS, as compared to patients who continue to smoke CIG and patients who had stopped smoking.
   Endpoints (number per year across all visits):
   - Number of patients with open surgical AAA treatment or AAA endovascular repair annually (based on date of decision to perform open surgical AAA treatment or AAA endovascular repair)
   - Number of patients with AAA rupture annually (based on date of AAA rupture)
3. To evaluate the number of AAA growth above 5 mm in 6 months and the number of patients with an overall maximum minor-axis AAA diameter >55mm in male patients and >50mm in female patients, in patients who switch from smoking CIG to using IQOS, as compared to patients who continue smoking CIG and patients who had stopped smoking.
   Endpoints (number per year across all visits):
   - Number of patients with an increase in maximum minor-axis AAA diameter of more than 5 mm within 6 months
   - Number of patients with an overall maximum minor-axis AAA diameter >55mm in male patients and >50mm in female patients

4. To monitor the safety profiles associated with IQOS use, CIG smoking and smoking cessation during the study.
   Endpoints (over the entire study period):
   - Incidence of Adverse events (AEs) / serious adverse events (SAEs)
   - Vital signs - change from Baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
   - Electrocardiogram (ECG) - change from Screening Visit (V1) used as Baseline (Heart rate, PR, QRS, QT, QTcB (Bazett's correction) and QTcF (Fridericia's correction) intervals)
   - Clinical chemistry, hematology, and urine analysis safety panel
   - Physical examination - changes from Baseline
   - Concomitant medications
   - Incidence of IQOS adverse incidences, malfunctions and misuses
5. To describe nicotine exposure over time in AAA patients who switch from smoking CIG to using IQOS, patients who continue to smoke CIG, and patients who had stopped smoking.
   Endpoints (over the entire study period):
   - 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)
6. To describe the changes in cardiovascular risk factors and BoExp to selected HPHCs over time in AAA patients who switch from smoking CIG to using IQOS, patients who continue to smoke CIG and patients who had stopped smoking.
   Endpoints (over the entire study period):
   1. Cardiovascular risk factors:
      a. Systolic and diastolic blood pressure
      b. Body weight and waist circumference
   2. BoExp to selected HPHCs (in spot urine, expressed as concentration adjusted to creatinine):
      a. Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL),
      b. Total N-nitrosonornicotine (Total NNN), and
      c. 2-Cyanoethyl Mercapturic Acid N-Acetyl-S-(2-cyanoethyl)-L-cysteine (2-CyEMA)

3.3 Exploratory Endpoints

Not Applicable

3.4 Additional Endpoints

Throughout the course of the study, several amendments to the protocol were issued with updates on some of the objectives or endpoints considered. The following endpoints have been collected up to the issuances of these amendments (note that subjects were enrolled only after protocol version 4 was issued):

Amendments	Endpoint
Protocol version 6	Part of the Selected clinical risk endpoints (CREs) in Secondary Objectives and Endpoints are collected up to the amendments. • Hemoglobin A1c (HbA1c) • Total Antioxidant Capacity (TAC) • Metalloproteinase (MMP) 2 and 9

Protocol version 7	Secondary Objectives and Endpoints below are collected up to the amendments.
	• Co-morbidities
	• CREs
	  o High sensitive C-reactive protein (hs-CRP)
	  o Low density lipoprotein (LDL)
	  o High density lipoprotein (HDL)
	  o Total Cholesterol (TC)*
	  o Triglyceride (TG)*
	  o Fasting blood glucose*
	  o White blood cell (WBC)*
	  o Platelet counts*
	  o D-dimer
	  o Fibrinogen
	  o 11-dehydro-thromboxane B2 (11-DTX-B2)
	  o 8-Epi Prostaglandin F2 Alpha (8-epi-$PGF_{2\alpha}$)
	  o Soluble inter-cellular adhesion molecule-1 (sICAM-1)
	  o Apolipoprotein A1 (Apo A1)
	  o Apolipoprotein B (Apo B)
	  o Homocysteine in the respective body matrix
	• Ankle-brachial index (ABI)
	• Assessment of Transcriptomic, Proteomic, and Lipidomic Profiles
	  o Transcriptomic, proteomic and lipidomic profiles assessment derived from blood samples
	  o Lipidomic profile assessment in urine

The data related to these endpoints will be listed and summarized in AAA patients who switch from smoking CIG to using IQOS, patients who continue to smoke CIG, and patients who had stopped smoking.

* Note that TC, TG, fasting blood glucose, WBC, and platelet counts are still part of the objective related to safety monitoring. These will be analyzed as part of that objective and not considered here as additional endpoints.

3.5 Study Hypotheses and Evaluation Criteria

3.5.1 Hypotheses

Given the exploratory nature of the study, no confirmatory statistical hypotheses will be tested.

3.5.2 Evaluation Criteria

This is a descriptive study, designed to gain an understanding on the effect of complete switching from cigarettes to IQOS use compared to continued CIG smoking on AAA growth rate and disease progression. Dual use of IQOS on top of CIG will be also investigated.

4 INVESTIGATIONAL PLAN

4.1 Study Design

This is a controlled, open-label, 3-arm parallel group, multi-center study in patients diagnosed with Abdominal Aortic Aneurysm (AAA).

The overall study design is depicted in Figure 1.

1. Adult patients currently smoking and not willing to quit smoking at study entry will be enrolled to be randomized at V2 with a 1:1 ratio in the CIG and IQOS arms.

Using the CT scan made according to the CT Scan Manual at V1 and assessed by the central reading site, patients considered eligible will be randomized according to the following stratification criteria:

i. Aortic maximum minor-axis diameter (male patients: < 40 mm and ≥ 40 mm; female patients: < 35 mm and ≥ 35 mm)
ii. Sex (male vs. female)

2. Additionally, adult patients who had completely stopped smoking at study entry will be enrolled as a non-randomized control SC arm.

In general, standard of care, as defined by the Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection, will be provided to all patients and will be supplemented by additional assessments as per this study protocol. As per standard of care, all AAA patients eligible for the screening for this study should have already been provided with smoking cessation advice at their AAA diagnosis (within the past 60 months). If smoking cessation advice was not provided during the last 6 months before the Screening Visit, based on the investigator's judgment, then the respective AAA patient must not be screened for this study.

Based on standard of care, all patients included in the study will be informed about the risks of smoking and provided with SC advice by the Investigator at the Screening Visit and all following study visits. Both standard of care procedures and procedures related to the study will be recorded.

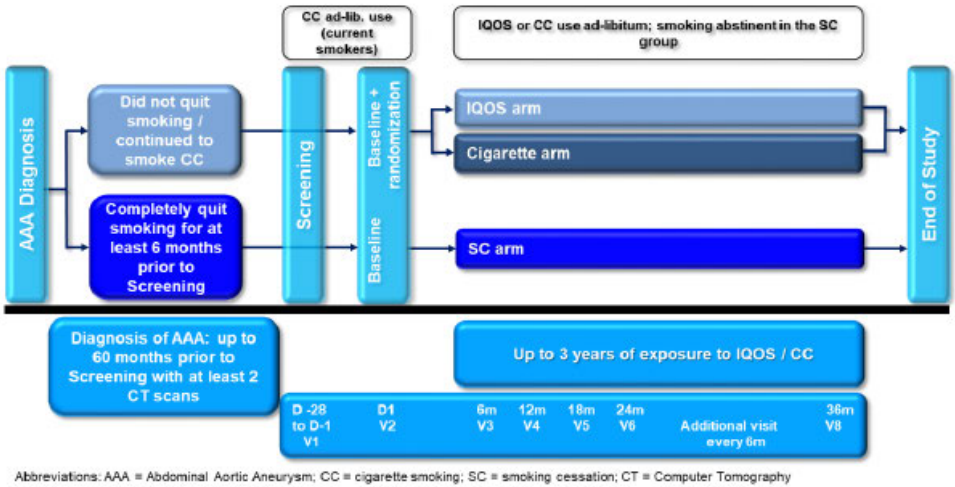

Figure 1: Overall Study Design and Flow Chart

4.2 Selection of Study Population

Female or male Japanese patients diagnosed with AAA and meeting the following main inclusion criteria will be enrolled in the study.

4.2.1 Inclusion Criteria

Main Criteria for Inclusion (all study arms):

1. Patient is aged ≥ 50 years (to be checked at V1).
2. Patient is Japanese (to be checked at V1).
3. Patient diagnosed with AAA (infrarenal, fusiform type) with a current aortic maximum minor-axis diameter of 30 to ≤ 49 mm (in male patient) and 30 to ≤ 44 mm (in female patient).
   a) Diagnosis of AAA within the past 60 months with at least two computerized tomography (CT) assessments since diagnosis. The two CT scans must have been done within the last 30 months before the Screening Visit (V1) with a time difference of at least 20 weeks and must show an increase of the aortic maximum minor-axis diameter between the first and the latter of these 2 CT scans (to be checked at V1).
   b) The maximum minor-axis AAA diameter to be used for assessment of eligibility is the maximum minor-axis AAA diameter available at the time of enrollment (based on the CT scan made according to the CT Scan Manual at V1 and assessed by central reading site (to be checked at V2)).
4. Patient has smoked commercially available and/or roll-your-own CIG on a daily basis for at least 5 years prior to AAA diagnosis, based on self-reporting (to be checked at V1).
5. Patient is ready to comply with the study protocol (e.g., to use their assigned product/regimen during the course of the study) (to be checked at V1 and V2).

Specific to patients screened for enrollment and randomization to the CIG or IQOS arm:
Female or male Japanese adult smokers with diagnosed AAA meeting the following additional main inclusion criteria will be enrolled and randomized in the CIG and IQOS arms of the study:

6. Patient has smoked on average > 5 commercially available and/or roll-your-own CIG per day (no CIG brand restriction) for the last 12 months, based on self-reporting (to be checked at V1). Intermittent attempts to quit smoking, with or without NRT use during these attempts, not exceeding 2 months or short-term interruption of smoking, with or without NRT use during the short-term interruption, up to 10 days within the last 12 months will be allowed. Smoking status will be verified based on a urinary cotinine test (i.e., cotinine ≥ 200 ng/mL) (to be checked at V1 and V2).
7. Not intending to quit smoking within the next 6 months after having been advised to quit smoking (to be checked at V1 and V2).

Specific to patients screened for enrollment into the SC arm:
Female or male Japanese adult patients with diagnosed AAA meeting the following additional main inclusion criteria will be enrolled in the SC arm of the study:

8. Patient had completely quitted smoking and stopped the use of any other tobacco or nicotine-containing products for at least 6 months prior to the Screening and is still abstinent at Screening (V1) and at Baseline (V2). Smoking status will be verified based on a urinary cotinine test (i.e., cotinine < 100 ng/mL) (to be checked at V1 and V2).

4.2.2 Exclusion Criteria

1. Patient is legally incompetent, physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, patient in a social or psychiatric institution, prisoner or patient involuntarily incarcerated) (to be checked at V1).
2. Patient with acute severe cardiovascular events or respiratory diseases (e.g., stroke, acute coronary syndrome, cardiovascular-surgical procedures, pulmonary embolism as judged by the Investigator), within the last 3 months (to be checked at V1 and V2).
3. Patient with currently active cancer or history of cancer within the last 5 years (to be checked at V1).
4. Patient is ineligible as judged by the Investigator to participate in the study for any reason (e.g., medical, psychiatric and/or social reason) (to be checked at V1).
5. Patient with dissecting aneurysm(s) of the aorta (to be checked at V1).
6. Patient with infrarenal pseudo-AAA (false AAA) (to be checked at V1).
7. Patient with a diagnosis of COPD Stage 3 and 4 in the medical history (to be checked at V1).
8. Patient has used any heat-not-burn tobacco product(s), and/or tobacco vapor product(s) on a daily basis for the last 12 months, based on self-reporting (to be checked at V1).
9. Patient with a recent (within 1 year) or current history of alcohol or other substance abuse based on self-reporting (to be checked at V1).
10. Female patient who is pregnant or breast-feeding (to be checked at V1 and V2).
11. Patient with a diagnosis of concomitant genetic diseases such as but not limited to Marfan syndrome, Loeys-Dietz syndrome, Vascular Ehlers-Danlos syndrome, Turner syndrome, Polycystic kidney disease, Noonan syndrome, Alagile syndrome, Arterial tortuosity syndrome and Cutis laxa (to be checked at V1).
12. Patient is a current or former employee of the tobacco industry or their first-degree relatives (parent and child) (to be checked at V1).
13. Patient is an employee of the investigational site or any other parties involved in the study or their first-degree relatives (parent and child) (to be checked at V1).
14. Patient has been previously screened or enrolled in this study (to be checked at V1).
15. Patient was enrolled in any clinical study within 3 months prior to V1 (to be checked at V1).

4.3 Product Allocation and Blinding

4.3.1 Method of Assigning Subjects to Study Arms

4.3.1.1 IQOS and CIG arms

At V2, randomization will be done through the Interactive Web and Voice Response System (IXRS). Patients eligible for randomization, will be randomized in one of the two randomized

study arms (IQOS arm and CIG arm), in a 1:1 ratio within the corresponding stratum using the following strata:

- Aortic maximum-minor-axis diameter (male patients: < 40 mm and ≥ 40 mm; female patients: < 35 mm and ≥ 35 mm)
- Sex (male vs. female)

Patients will be informed of their randomized study arm by the study site at V2.

4.3.1.2 SC Arm

Patients who had stopped smoking will be enrolled in the SC arm at Baseline Visit (V2) through the Interactive Web and Voice Response System (IXRS) without being randomized.

4.3.2 Blinding

4.3.2.1 Blinding of the CT-Overreaders

This is an open-label study, however, in order to avoid potential involuntary bias of the CT-overreaders by the product use status, he/she will be kept blinded to all study arms (CIG, IQOS and SC arms). If the CT-overreaders should become unblinded for any reason, including accidental disclosure, the unblinding event will be documented. A patient-specific unblinding event will not prevent the use of the patient's data, including those recorded after disclosure.

4.3.2.2 Blinding of data

There will be an additional, though limited, degree of blinding during the conduct of the study, including the data review and data analysis process. In particular, PMI and the contract research organization (CRO) personnel involved in this study will be blinded as summarized in Table 1.

Table 1 Blinding Scheme

Blinded Study Personnel	Blinded Data	End of Blinding Period
PMI and CMIC study statisticians	Actual values of primary endpoints after enrollment / randomization [a]	After the SAP finalization or database lock, whichever comes last.
PMI clinical scientist	Actual values of primary endpoints after enrollment / randomization [b]	After the finalization of PMI blind database review. Can

		be actively un-blinded when appropriate.

SAP: Statistical Analysis Plan

a. To avoid indirect unblinding of the "actual values of primary endpoints" additional data were blinded in the CRF (e.g., adverse event terms).

b. As part of the PMI Quality Control (QC) activity, data listings will be reviewed by CMIC and PMI before database lock. Full details will be available in the data review plan.

Any PMI and CRO personnel who are not listed in Table 1 will be unblinded by default including the statistician(s) from CMIC specifically assigned to provide all the data needed for reviews by the IDMC members.

All IDMC members are unblinded by default.

Unblinded information will not be shared with the blinded study team, until the end of the blinding period (Table 1). PMI will receive blinded and unblinded data for the data review prior to database lock or any other analysis as planned in the data review plan. Blinded data will be accessible by the blinded study personnel in a masked format or presented independent of the patient identifier so to ensure that data cannot be associated within or to a patient. Unblinded data will only be reviewed by the unblinded study team.

4.3.3 Adherence to Product Allocation

Based on the numbers of the used *Marlboro HeatSticks* or the smoked CIG as self-reported in the diary, and further determinants such as the total duration of use of the respective products and the percentages of the respective products over a predefined period, the adherence to the respective randomized products will be calculated. During the scheduled visits, the Investigator will ask the patient whether he/she has been using the assigned product (CIG and IQOS arms only) and will remind him/her to use exclusively the product he/she was randomized to, unless he/she wants to stop using any tobacco or nicotine containing products. The investigator should also check and make sure that the product use diary is completed by the patient as required.

Although patients are being requested to use solely the product allocated to their respective study arm, it is considered that not all patients randomized to the IQOS arm or to continue smoking CIG will exclusively use the randomized product at all times during the study. For instance, patients may concomitantly use IQOS and CIG (dual use). Similarly, it is expected that some patients in the SC arm who had stopped smoking after AAA diagnosis may relapse to the use of tobacco or nicotine-containing products (e.g., CIG or IQOS). Those patients who might change their smoking habits after randomization to an arm (e.g., who have been allocated to the IQOS arm but restart smoking CIG) will remain for the statistical analysis in the arm they have been randomized to. Nevertheless, additional analyses will be conducted using the subjects classified according to their smoking pattern (see section 5.7).

4.4 Summary of Changes in Study Design

Throughout the course of the study, several amendments to the protocol were issued with updates to the study design. In spite of significant efforts undertaken to improve the recruitment of patients into this study, the recruitment rate remained low. Therefore, rather than terminating the study, which would've resulted in the loss of a site's and/or patient's efforts and due to the lack of any new scientific knowledge for the broader community, it was decided to stop recruitment early and to continue the follow up of patients already recruited.

In addition, to ease the burden for the patients and to avoid potential issues with retention rate and missing data, it was also decided to decrease the number of procedures, such as those related to co-morbidities, and to shorten the duration of the follow-up from five to three years.

Due to the low numbers in recruitment and shortened study period, the planned interim analysis was cancelled.

5 DERIVED AND COMPUTED VARIABLES

5.1 Urinary Biomarkers

The concentration of NEQ in spot urine will be derived according to the formula below and considering the conversion factors described in Table 2. The concentrations reported for free nicotine and its five major metabolites will not be used individually as analysis variables.

NEQ [mg/L] = (free nicotine [µmol/L] + nicotine-glucuronide [µmol/L]
+ free cotinine [µmol/L] + cotinine-glucuronide [µmol/L]
+ free *trans*-3'-hydroxycotinine [µmol/L]
+ *trans*-3'-hydroxycotinine-glucuronide [µmol/L])
*162.2[µg/µmol] / 1000 [µg/mg]

Table 2 Conversion factors from ng/mL into µmol/L

	Conversion factor from ng/mL to µmol/L
Nicotine	0.006164
Nicotine glucuronide	0.002955
Cotinine	0.005675
Cotinine-glucuronide	0.002838

Trans-3'hydroxycotinine	0.005202
Trans-3'hydroxycotinine-glucuronide	0.002715

Example: Free Nicotine [μmol/L]= Free Nicotine [ng/mL]×0.006164

5.1.1 Biomarkers of Exposure adjusted for Creatinine

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

$$\left[\text{BoExp (creatinine adjusted)} = \frac{\text{BoExp}}{\text{Creatinine}}\right]$$

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

5.1.2 Change from baseline

For a given subject, change from Baseline will be calculated by subtracting the individual patient's Baseline value from the value at a given timepoint. In case of log-normally distributed values, the change from Baseline for a given subject will be replaced by the percent change from Baseline. Each individual percent change from Baseline will be calculated by subtracting the individual subject's Baseline value from the value at the desired timepoint and then dividing this calculated value by the individual subject's Baseline value and multiplying by 100.

5.1.3 Coefficient of variation

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

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

where var = the variance from the log-transformed data.

5.2 Laboratory Evaluations

5.2.1 Clinical Chemistry

Items	**Units**
Albumin	μg/mL

Items	Units
Total protein	g/L
Alkaline phosphatase (AP)	nkat/L
Alanine aminotransferase (ALT)	µkat/L
Aspartate aminotransferase (AST)	µkat/L
Blood urea nitrogen (BUN)	mmol/L
Creatinine	umol/L
Gamma-glutamyl transferase (GGT)	U/L
Fasting Glucose	mmol/L
Lactate dehydrogenase (LDH)	µkat/L
Potassium	mmol/L
Sodium	mmol/L
Total bilirubin	µmol/L
Direct bilirubin	µmol/L
Total cholesterol	mmol/L
Triglycerides	mmol/L

5.2.2 Hematology

Items	Units
Hematocrit	-
Hemoglobin	g/L
Mean corpuscular hemoglobin (MCH)	pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	g/L
Mean corpuscular volume (MCV)	fL
Platelet count	10^9/L

Items	Units
Red blood cell (RBC) count	10^12/L
White blood cell (WBC) count	10^9/L
Differential WBC count: Neutrophils Basophils Eosinophils Lymphocytes Monocytes	-

5.2.3 Urine Analysis

Items	Units
pH	-
Bilirubin	-
Glucose	-
Nitrite	-
Occult blood	-
Protein	-
Specific gravity	-

5.2.4 Clinical Risk Endpoints (CREs)

Items	Units
Apolipoprotein A1 **	g/L
Apolipoprotein B **	g/L
Hemoglobin A1C/Hemoglobin *	mmol/mol

Items	Units
C Reactive Protein **	mg/L
HDL Cholesterol **	mmol/L
Homocysteine **	µmol/L
LDL Cholesterol **	mmol/L
Matrix Metalloproteinase 2 *	pg/mL
Matrix Metalloproteinase 9 *	pg/mL
11-dehydro-thromboxane B2 (11-DTX-B2) **	pg/mL
8-Epi Prostaglandin F2 Alpha (8-epi-$PGF_{2\alpha}$) **	pg/mg creat
soluble inter-cellular adhesion molecule-1 (sICAM-1) **	ng/mL
Total Antioxidant Capacity *	umol/L
Fibrinogen **	umol/L
D-Dimer **	mg/L

* Measured up to protocol version 6

** Measured up to protocol version 7

5.3 Vital Signs

Items	Units
Systolic blood pressure	mmHg
Diastolic blood pressure	mmHg
Pulse Rate	beats/min
Respiratory Rate	breaths/min
Waist Circumference	cm
Body Weight	Kg
BMI*	-

* BMI = Body Weight (kg) / [Baseline Height (m)] ^{2}

5.4 Physical Examinations

Items	Units
General appearance	-
HEENT (Head, eyes, ears, nose, throat)	-
Thyroid gland	-
Chest	-
Lungs	-
Gastrointestinal	-
Cardiovascular system	-
Neurologic	-
Skin	-
Musculoskeletal	-
Abdomen	-
Dentition	-

5.5 ECG

Items	Units
Heart rate	beats/min
PR interval	msec
QRS interval	msec
QT interval	msec
QTcB interval	msec
QTcF interval	msec

5.6 ABI (Ankle-Brachial Index)

Items (left and right)	Units
Calculated ABI	-
Systolic pressure at the dorsalis pedis artery	mmHg
Systolic pressure at the posterior tibial artery	mmHg
Brachial arterial systolic pressure	mmHg

5.7 Product Use Categories

In addition to enrolled arms, subjects will be classified by product use categories. These will be defined based on the monthly average number of nicotine-containing products as self-reported in the diary.

More specifically, monthly for each subject, the average number over the entire month of cigarettes per day, IQOS per day, heat-not-burn products other than IQOS per day, e-cigarettes per day, smokeless tobacco pipe per day, smokeless tobacco per day, cigars/pipes/kiseru/shisha per day, and nicotine replacement therapy per day, will be determined as follows:

- If the subject answers ‘every day’ to the initial question related to a nicotine-containing product type, the number of days of use is set to 30. If the subject answers ‘not at all’ to this question, then the number of days of use is set to 0. If the subject answers ‘some days’, the number of days of use is set to the answer provided by the subject to the subsequent question on how many of the past 30 days the subject has used the product.
- The number of days of use is then multiplied by the number provided as answer to the question on the average number of products used per day by the subject (if the subject has 0 day of use, the subject does not need to answer that question and the average number of products used can be set to 0). The result of this multiplication is then divided by 30 to get an estimate of the average number of products used per day over the entire month.
- If the number of days is missing, or if it is not equal to 0 but the average number of products per day is missing, then the average number of products used per day over the entire month is set to missing.

Once the average number of products used per day over the entire month will be determined, all the available (out of 6) monthly averages collected between V2 and V3 will be summed up and divided by the number of non-missing monthly averages, and the result of this calculation

will be assigned to V3 and represent the average number of products used per day over the previous 6 months. Similarly, all the available (out of 6) monthly averages collected between V3 and V4 will be summed up and divided by the number of non-missing monthly averages , and the result of this calculation will be assigned to V4. The process is repeated to obtain estimates of average number of products used per day over the previous 6 months for V5, V6, V7, and V8. If none of the 6 previous monthly averages is available, the average number of products used per day over the previous 6 months will be set to missing.

If a subject terminates the study early between V_i and V_{i+1} (where i represents any number between 2 and 7), the average number of products used per day over the previous 6 months will be set to missing at V_{i+1}.

For each subject, the following table will be filled, where each cell represents an average number of products used per day over the previous 6 months:

Product	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Cigarettes/Roll-your-own cigarettes	Cig3	Cig4	Cig5	Cig6	Cig7	Cig8
IQOS	IQ3	IQ4	IQ5	IQ6	IQ7	IQ8
Heat-not-burn other than IQOS	HnB3	HnB4	HnB5	HnB6	HnB7	HnB8
E-cigarettes	EC3	EC4	EC5	EC6	EC7	EC8
Smokeless tobacco pipes	Stp3	Stp4	Stp5	Stp6	Stp7	Stp8
Smokeless tobacco	St3	St4	St5	St6	St7	St8
Cigars/Pipes/Kiseru/Shisha	Cpk3	Cpk4	Cpk5	Cpk6	Cpk7	Cpk8
Nicotine replacement therapy	Nrt3	Nrt4	Nrt5	Nrt6	Nrt7	Nr8

Using this table, the product use category for any subject will be determined as follows:

- A subject will be classified in the smoking abstinence product use category if all Cigx < 1, IQx < 1, HnBx < 1, ECx $= 0$, Stpx $= 0$, Stx $= 0$, Cpk3 $= 0$ for all x = 3, 4, 5, 6, 7, and 8.
- A subject will be classified in the IQOS product use category if all Cigx < 1, IQx ≥ 1, HnBx < 1, ECx $= 0$, Stpx $= 0$, Stx $= 0$, Cpk3 $= 0$ for all x = 3, 4, 5, 6, 7, and 8.
- A subject will be classified in the CIG product use category if all Cigx ≥ 1, IQx < 1, HnBx < 1, ECx $= 0$, Stpx $= 0$, Stx $= 0$, Cpk3 $= 0$ for all x = 3, 4, 5, 6, 7, and 8.
- A subject will be classified in the dual-use product use category if all Cigx ≥ 1, IQx ≥ 1, HnBx < 1, ECx $= 0$, Stpx $= 0$, Stx $= 0$, Cpk3 $= 0$ for all x = 3, 4, 5, 6, 7, and 8.

- A subject will be classified in the 'other' product use category in all other cases not mentioned above.

6 SAMPLE SIZE JUSTIFICATION

The sample size of patients is not based on a statistical hypothesis, as this is a descriptive study, designed to characterize the growth rate of AAA and the progression of disease, to better understand the impact of IQOS relative to CIG on the progression of disease. Patients will be enrolled/randomized per study arm.

7 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

Stratified analyses were planned in the protocol. However, after taking into account the sample size, the expected number of subjects in each stratum will be too small to draw any conclusion. Thus, stratified analyses will not be conducted.

Transcriptomic, proteomic and lipidomic profiles will not be evaluated and only some of those data which are collected with other laboratory parameters will be provided in the listings.

Table 3 of the Clinical Study Protocol (CSP) contains a footnote stating that 'the albumin to creatinine ratio will be used to evaluate potential microalbuminuria'. This ratio will not be evaluated since albumin is not measured in urine, but only in blood; and computing the ratio based on blood measurements cannot be used to evaluate potential microalbuminuria.

8 ANALYSIS SETS

The main population for non-safety analyses will be the Full Analysis Set.

Safety will be analyzed using the Safety Set.

8.1 Full Analysis Set

The Full Analysis Set (FAS) will consist of all enrolled patients in the SC arm who have signed the ICF and who have at least one valid non-safety assessment after enrollment as well as all patients randomized to the CIG or IQOS arm who have signed the ICF, have at least one valid non-safety assessment after randomization and have at least one post-randomization product (IQOS or CIG) use experience. The FAS will be analyzed by enrolled arm (randomization arm for CIG or IQOS, or SC arm) and by product use category (see section 5.7).

8.2 Safety Set

Safety Set consists of all the patients enrolled with signed ICF who have at least one valid value for a safety assessment during the course of the study. The Safety Set will be analyzed by enrollment arm and in patients exposed but not randomized.

8.3 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.

Classification of the protocol deviation will be decided before the database lock during the pre-analysis data review meeting. Protocol deviations will be summarized and listed. All protocol deviations will be reviewed to determine their severity/impact when subjects are assigned to analysis sets. Each deviation will be classified as major or minor. All major deviations will be further reviewed to determine whether or not the deviation impacts the evaluability of the results and therefore should result in the subject being excluded from an analysis set.

The categories for the major protocol deviations will include, but are not limited to, the deviations presented in Table 3.

Table 3 Definition of Major Protocol Deviations

Category	Description
Mis-randomization	Being administered the wrong product according to the randomization schedule
Violation	Violation of inclusion/exclusion criteria
Product adherence	Non-adherence in the IQOS and SC arms will be defined per subject. It will be based on product use reported in the diaries. Product use categories will be defined on top of the randomization arm (see section 5.7).

The categories for the minor deviations will include, but are not limited to, the deviations presented in Table 4.

Table 4 Definition of Minor Protocol Deviations

Category	Description
Procedural violation	Violation of planned procedure
Visit window deviation	Visits outside of visit window
Time missing	Assessment date or time is missing
Assessment missing	Assessment is missing
Visit missing	Scheduled visit not done

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

9.1.1 Stratified Presentation

As described in Section 7, stratified analyses will not be conducted as part of this SAP.

9.1.2 Sub-group Analyses

Not applicable.

9.1.3 Descriptive Statistics

Data will be presented in listings, enrollment arm, patient, and study visit, unless otherwise specified.

For continuous data, summary statistics will include the number of patients with non-missing values [n], number and percent of patients with missing data, the mean and standard deviation (SD), median, first and third quartiles, minimum and maximum, and 95% confidence interval (CI). Log-normally distributed data (e.g., BoExp data) will also include the geometric mean and coefficient of variation (CV) in addition to the mean and SD. Post-baseline summaries will include change from baseline apart from log-normal variables which will present % change from baseline (see Section 5.1.2).

For categorical data, frequency counts and percentages will be presented. Percentages of missing values will be computed using the number of patients [N] included in the corresponding group in the denominator, while percentages related to 'non-missing' categories will be computed using the number of patients with non-missing values in the denominator.

9.1.4 Definitions for Statistical Data Analysis

In general, baseline value for any given variable will be the last assessment prior to randomization for the patients randomized to either IQOS or CIG smoking. For the patients in the SC arm, baseline value for any given variable will be the assessment of any given variable performed at V2 (e.g., CT scan made at V1 and assessed by the central reading site and available at V2).

9.1.5 Handling of Dropouts or Missing Data

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 and percentage of values below LLOQ or above ULOQ will be presented in each summary table (the percentage of values below LLOQ/ULOQ will use the number of patients with non-missing values in the denominator). 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 self-reported tobacco or nicotine-containing product use:

- Only available data will be included in the product use summaries.

9.1.5.1 Insufficient Data for Analysis/Presentation

If no data is available for presentation for a TFL, then a blank TFL will be displayed with "No applicable data for this summary." displayed.

9.1.6 Handling of Unplanned Data

All data collected on scheduled visits will be used for tables. Therefore, data collected on unscheduled visit will be excluded from tables, however included in listings (no time window will be considered).

9.1.7 Multiple Comparison/Multiplicity

This is a descriptive study, designed to characterize the growth rate of AAA and the progression of disease. Thus, this section is not applicable.

9.1.8 Confidence Interval

All confidence intervals will be 95% CIs.

9.2 Disposition of Subjects

Summary of Subject Disposition		
Population	:	All subjects screened
Contents	:	• All subjects screened • All screen failure subjects (include subjects who were enrolled but not randomized) ➢ Primary reason for screen failure • All subjects randomized ➢ Randomized to IQOS/CIG or enrolled in SC ➢ Completed subject ➢ Discontinued subject • Reason of discontinuation
Remarks	:	Percentage will be presented. Percentage of screen failure will be calculated using the number of all screened subjects in the denominator. For disposition events after randomization, the denominator will be the number of subjects randomized to IQOS/CIG groups or enrolled in SC.
Output		Summary of Subject Disposition (Study Termination) -All Subjects Screened- Listing of Screen Failed Subjects and Reason Listing of Subject Disposition (Study Termination)

Summary of Protocol Deviations		
Population	:	All subjects screened
Contents	:	The number and percentage of both major and minor protocol deviations by category will be summarized.
Output		Summary of Protocol Deviation -All Subjects Screened- Listing of Protocol Deviation

Summary of Analysis Sets and Reasons for Exclusions from Analyses		
Population	:	All subjects screened
Group	:	• Study Arm • Product Use Category
Contents	:	The number and percentage of subjects (included/not included/ reasons for not included) of analysis set defined in "Analysis Sets" will be presented.
Remarks	:	• Denominator will be the number of subjects enrolled into each arm for the table displaying enrollement arms. • Denominator will be the number of subjects in each product use category for the table displaying product use categories.
Output	:	Summary of Analysis Sets and Reasons for Exclusions from Analyses -All Subjects Screened- Summary of Analysis Sets and Reasons for Exclusions from Analyses by Product Use Category -All Subjects Screened- Listing of Analysis Sets

9.3 Demographic and Other Baseline Characteristics

Summary of Demographics and Other Baseline Characteristics		
Population	:	FAS and Safety Set
Group	:	• Study Arm • Product Use Category (for FAS only)

Contents		Refer to Descriptive statistics
Analysis variables	:	• Age [years] • Age (50≤ <75, 75≥) • Sex (Male, Female) • Race (Asian, Black or African American, White, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native) • Nationality (Japanese, Non-Japanese) • Baseline Waist Circumference [cm] • Baseline Waist Circumference (<50, 50≤ <60, 60≤ <70, 70≤ <80, 80≤ <90, 90≥) • Baseline Weight [kg] • Baseline Height [cm] • BMI [kg/m^2] • BMI (<18.5, 18.5≤ <25, 25≤ <30, 30≤ <35, 35≥) • Recent (within 1 year) History of Alcohol Addiction? • Recent (within 1 year) History of Substance Addiction? • Smoking Status • Maximum minor-axis diameter (mm) • Maximum minor-axis diameter (mm) ➢ Male (<40 mm, >=40 mm) ➢ Female (<35 mm, >=35 mm)
Definition	:	• Use the value of age from SDTM datasets. • For the race, subjects can have multiple races. The percentages may not sum to 100.
Outputs	:	Summary of Demographics and Other Baseline Characteristics -FAS- Summary of Demographics and Other Baseline Characteristics -Safety Set- Summary of Demographics and Other Baseline Characteristics by Product Use Category -FAS- Listing of Demographics

Summary of Smoking History		
Population	:	FAS and Safety Set
Group	:	• Study Arm • Product Use Category (for FAS only)
Contents		Refer to Descriptive statistics
Analysis variables	:	• Have you smoked for at least the past 5 years prior to AAA diagnosis? • How many cigarettes per day have you smoked over the past 5 years prior to AAA diagnosis? [cig/day] • Have you been smoking in the last 12 months? • How many cigarettes per day have you smoked over the last 12 months? [cig/day] • Have you quit smoking within 2 months after AAA diagnosis? • Are you still abstinent now? Those questions below are only answered by those enrolled in a protocol version equal or after 6. • Have you been using any heat-not-burn tobacco product(s), for example IQOS or GLO, in the last 12 months? • How many tobacco HeatSticks / tobacco sticks per day have you used over the last 12 months? • Have you been using any tobacco vapor product(s), for example PLOOM Tech, in the last 12 months? • How many tobacco capsules per day have you used over the last 12 months? • Have you completely quit smoking cigarettes or completely stopped using any other tobacco or nicotine-containing products 6 months ago or even longer? • Are you still abstinent now?
Output	:	Summary of Smoking History -FAS- Summary of Smoking History -Safety Set- Summary of Smoking History by Product Use Category -FAS- Listing of Smoking History

9.4 Measurement of Product Adherence

Summary of Product Use		
Population	:	FAS and Safety Set
Group	:	• Study Arm • Product Use Category (for FAS only)
Contents	:	Refer to Descriptive statistics
Analysis variables	:	• For cigarettes ➢ Days of exposure to cigarettes [days] ➢ Daily product consumption (cigarettes)[/day] • For IQOS ➢ Days of exposure to IQOS [days] ➢ Daily product consumption (IQOS) [heatsticks/day] • For heat-not-burn other than IQOS ➢ Days of exposure to heat-not-burn other than IQOS [days] ➢ Daily product consumption (heat-not-burn other than IQOS) [/day] • For e-cigarettes ➢ Days of exposure to e-cigarettes [days] ➢ Daily product consumption(e-cigarettes) [/day] • For smokeless tobacco pipe ➢ Days of exposure to smokeless tobacco pipe [days] ➢ Daily product consumption smokeless tobacco pipe [/day] • For smokeless tobacco product ➢ Days of exposure to smokeless tobacco pipe [days] ➢ Daily product consumption smokeless tobacco pipe [/day] • For cigar/ pipe/ kiseru/ shisha ➢ Days of exposure to cigar/ pipe/ kiseru/ shisha [days] ➢ Daily product consumption (cigar/ pipe/ kiseru/ shisha) [/day] • For nicotine replacement therapy ➢ Days of exposure to nicotine replacement therapy [days] ➢ Daily product consumption (nicotine replacement therapy) [/day]

Summary of Product Use		
Target visit		V3 to V8 Overall for the summary table and listing.
Output		Summary of Product Use -FAS- Summary of Product Use -Safety Set- Summary of Product Use by Product Use Category -FAS- Listing of Product Use Listing of Product Use Categories

9.5 Planned Statistical Analyses

9.5.1 Primary Analyses

9.5.1.1 Mean Growth Rates

Summary of the Annualized Mean Growth Rates in Patients Diagnosed with AAA		
Population	:	FAS
Group		• Study arm • Product Use Category
Contents	:	The primary endpoint is the comparison of the annualized mean growth rates of AAA diameter between patients who were randomized to IQOS use and patients who continue to smoke CIG. The growth rate is calculated as the slope of the linear regression fit to the maximum minor-axis AAA diameter values over the time by randomization arm. Descriptive statistics for the annualized mean growth rates of AAA will be presented.
Target visit	:	V3 to V8
Sample code		Linear regression $Study\ Day = Measured\ date\ of\ visit - measured\ date\ of\ Baseline + 1$

Summary of the Annualized Mean Growth Rates in Patients Diagnosed with AAA		
		proc reg data = TargDs outest=outds ; by subject; model AAA diameter = Study day ; ods output ParameterEstimates = out1; run ;
Output		Summary of the Annualized Mean Growth Rates in Patients Diagnosed with AAA -FAS- Summary of the Annualized Mean Growth Rates in Patients Diagnosed with AAA by Product Use Category -FAS- Figure of the Annualized Mean Growth Rates in Patients Diagnosed with AAA -FAS- Figure of the Annualized Mean Growth Rates in Patients Diagnosed with AAA by Product Use Category -FAS- Listing of Maximum minor-axis AAA Diameter Growth Listing of Statistical Output (REG procedure) Listing of Statistical Output (REG procedure) by Product Use Category

9.5.1.2 Abdominal Aortic Aneurysm (AAA)

Summary of the maximum minor-axis AAA Diameter		
Population	:	FAS
Group		• Study Arm • Product Use Category
Contents	:	Descriptive statistics for the maximum minor-axis AAA diameter and change from baseline at each visit will be presented.
Target visit	:	V1, V3 to V8
Output		Summary of the maximum minor-axis AAA Diameter -FAS-

Summary of the maximum minor-axis AAA Diameter		
		Summary of the maximum minor-axis AAA Diameter by Product Use Category -FAS- Figure of the maximum minor-axis AAA Diameter -FAS- Figure of the maximum minor-axis AAA Diameter by Product Use Category -FAS- Listing of Maximum minor-axis AAA Diameter Growth

9.5.2 Secondary Analyses

9.5.2.1.1 Time to Event

Time from Diagnosis of the AAA until Open Surgical AAA Treatment or AAA Endovascular Repair		
Population	:	FAS
Group	:	• Study Arm • Product Use Category
Contents		• Create a Kaplan Meier curve for the following events ➢ Open surgical or endovascular repair of AAA ➢ Rupture of AAA • Calculate the number of subjects at risk for each of the group.
Definitions		• Calculate the time to the event by the following equation. ➢ Open surgical or endovascular repair Date of decision to perform surgery – date of diagnosis + 1 = time to the event ➢ Rupture of AAA Date of AAA rupture – date of diagnosis + 1 = time to the event • Censor: if a subject does not experience the event, then treat the subject event as censor. Use the last subject visit date.

Time from Diagnosis of the AAA until Open Surgical AAA Treatment or AAA Endovascular Repair		
Remarks	:	The date of actual performance of surgery is not determined from the CRF. Instead, the date of decision to perform the surgery will be used for open surgical or endovascular repair of AAA.

Program		Time (months) = (Date of Event – date of diagnosis + 1) / 30.4375
		
		proc lifetest data=BMT plots=survival (atrisk=0 to 18 by 6);
		time time*status(0);
		strata group;
		run;
		Output Kaplan-Meier estimates at each fixed time point (6, 12, 18, 24, 30, 36 months) along with their 95% CIs.
		95% confidence limits are calculated by log-log transformation using standard error (SE) derived by Greenwood's Formula.
		Also, 25th percentile, median, and 75th percentile of Survival time with their respective 95% confidence intervals

Output	:	Time from Diagnosis of the AAA until Open Surgical AAA Treatment or AAA Endovascular Repair -FAS- Time from Diagnosis of the AAA until Open Surgical AAA Treatment or AAA Endovascular Repair by Product Use Category -FAS- Summary of Time from Diagnosis of the AAA until Open Surgical AAA Treatment or AAA Endovascular Repair -FAS- Summary of Time from Diagnosis of the AAA until Open Surgical AAA Treatment or AAA Endovascular Repair by Product Use Category -FAS- Time from diagnosis of the AAA until time to rupture AAA -FAS- Time from diagnosis of the AAA until time to rupture AAA by Product Use Category -FAS- Summary of Time from diagnosis of the AAA until time to rupture AAA -FAS- Summary of Time from diagnosis of the AAA until time to rupture AAA by Product Use Category -FAS- Listing of Statistical Output (LIFETEST procedure)

Time from Diagnosis of the AAA until Open Surgical AAA Treatment or AAA Endovascular Repair		
		Listing of Statistical Output (LIFETEST procedure) by Product Use Category

9.5.2.1.2 Rupture or Surgical Treatment of AAA

Annual Incidence Rate of AAA Rupture, Open Surgical Treatment, Endovascular Repair		
Population	:	FAS
Group	:	• Study Arm • Product Use Category
Contents		• Count the number of patients for the following variables ➢ Open surgical AAA treatment or AAA endovascular repair ➢ AAA rupture
Definitions		Number of patients were calculated by person-year-method: number of patients event occurred / (sum of days until event occurred / 365.25). Days until event occurred is as follows: Date of decision to perform open surgical AAA treatment or AAA endovascular repair - randomization date + 1. Date of AAA rupture - randomization date + 1. For those without experiencing the event. Subject Reference End Date - randomization date + 1.
Output	:	Annual Incidence Rate of AAA Rupture, Open Surgical Treatment, Endovascular Repair -FAS- Annual Incidence Rate of AAA Rupture, Open Surgical Treatment or Endovascular Repair by Product Use Category -FAS- Listing of Patients Annually Undergoing AAA Rupture, Open Surgical Treatment, Endovascular Repair

9.5.2.1.3 Growth of maximum minor-axis AAA

Growth of maximum minor-axis AAA		
Population	:	FAS
Group	:	• Study Arm • Product Use Category
Contents		• Count the number of patients and percentage, and 95% confidence interval for the following variables ➢ Increase in Maximum minor-axis AAA diameter of more than 5 mm within 6 months ➢ Overall maximum minor-axis AAA diameter >55mm in male patients ➢ Overall maximum minor-axis AAA diameter >50mm in female patients
Sample code		Confidence interval will be calculated based on the Clopper-Pearson exact confidence interval method. $P = X / N$ $P_U = \frac{\nu_1 F_{\nu_1,\nu_2}(\alpha/2)}{\nu_2 + \nu_1 F_{\nu_1,\nu_2}(\alpha/2)}, \quad \nu_1 = 2(X+1), \quad \nu_2 = 2(N-X)$ $P_L = \frac{\nu_2}{\nu_2 + \nu_1 F_{\nu_1,\nu_2}(\alpha/2)}, \quad \nu_1 = 2(N-X+1), \quad \nu_2 = 2X$ proc freq data = INPUT ; weight VAR1 / zeros ; table VAR2 / binomial alpha = 0.05 ; output out = OUTPUT binomial ; run ;
Output	:	Summary of Growth of maximum minor-axis AAA -FAS- Summary of Growth of maximum minor-axis AAA by Product Use Category -FAS-

9.5.2.2 Cardiovascular Risk Factors Biomarker of Exposure

Summary of Cardiovascular Risk Factors		
Population	:	FAS
Group	:	• Study Arm • Product Use Category
Contents	:	• Refer to Descriptive statistics • Calculate the value of Cardiovascular Risk Factors for each visit. Also, calculate the change from baseline.
Analysis variables	:	• Systolic blood pressure • Diastolic blood pressure • Body weight • Waist circumference
Target visit		Baseline (V2) to V8
Output		Summary of Cardiovascular Risk Factors -FAS- Summary of Cardiovascular Risk Factors by Product Use Category -FAS- Series plot of Cardiovascular Risk Factors -FAS- Series plot of Cardiovascular Risk Factors by Product Use Category -FAS- Listing of Cardiovascular Risk Factors

Summary Table of Analysis for BoExp Geometric Mean Value		
Population	:	FAS
Group	:	• Study Arm • Product Use Category
	:	• The analysis will be performed on the FAS using a mixed model for repeated measurements (MMRM). • The model will include the log transformed BoExp adjusted for creatinine as the dependent variable, adjusting for the following covariates;

Summary Table of Analysis for BoExp Geometric Mean Value		
		➢ Study Arm or Product Use Category ➢ log(BoExp value at V2) ➢ Visit ➢ Interaction between visit and Study Arm or Product Use Category • Degree of freedom will be adjusted by using KR. • Number of patients included in analysis, Geometric LS means (IQOS-CIG), Ratio of Geometric LS Means and 95% CI for Ratio of Geometric LS means at each visit for each product use will be presented. • Select Unstructured (UN) specified for the correlation structure. If the model fails to converge try following option in order; a first order autoregressive (AR(1)), Compound Symmetry (CS), and uncorrelated (IND).
Analysis variables	:	• NEQ adjusted for creatinine • Total NNAL adjusted for creatinine • Total NNN adjusted for creatinine • 2-CyEMA adjusted for creatinine
Target visit	:	V3 to V8
Sample code		proc mixed data=test ; class ARM VISIT ; model Log(AVAL) = ARM Log(Base) VISIT ARM * VISIT / s cl ddfm=kr; repeated VISIT / type=un subject=USUBJID ; lsmeans ARM * VISIT / diff=control("CIG" "1") cl ; ods output diffs=diff ; ods output lsmeans=lsmean ; ods output convergencestatus=check ; run;
Output		Summary of Analysis for BoExp Geometric Mean Value -FAS- Summary of Analysis for BoExp Geometric Mean Value by Product Use Category -FAS-

Summary Table of Analysis for BoExp Geometric Mean Value		
		Time Series Plot of Geometric LS Mean Biomarkers of Exposure Parameters -FAS- Time Series Plot of Geometric LS Mean Biomarkers of Exposure Parameters by Product Use Category -FAS- Listing of Statistical Output (MIXED procedure) Listing of Statistical Output (MIXED procedure) by Product Use Category

Summary Table of BoExp Parameters		
Population	:	FAS
Group	:	• Study Arm • Product Use Category
Contents	:	In addition to the descriptive statistics of value and change from baseline for each visit, the number and percentage of values below LLOQ or above ULOQ will be presented. 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. In addition, the geometric means, CV and geometric relative change will be presented.
Analysis variables	:	• NEQ adjusted for creatinine • Total NNAL adjusted for creatinine • Total NNN adjusted for creatinine • 2-CyEMA adjusted for creatinine • Creatinine (Only on listing)
Target visit		Baseline (V2) to V8
Output		Summary of Biomarkers of Exposure Parameters -FAS- Summary of Biomarkers of Exposure Parameters by Product Use Category -FAS- Listing of Biomarkers of Exposure Parameters

9.5.3 Additional Analyses

Summary of ABI (Ankle-Brachial Index)		
Population	:	FAS
Group	:	• Study Arm • Product Use Category
Analysis variable	:	For Left Ankle-Brachial Index and Right Ankle-Brachial Index, count the number of subjects by visits in the category shown. <0.9 0.9<= <1.0 1.0<=
Output	:	Summary of Ankle-brachial Index -Safety Set- Summary of Ankle-brachial Index by Product Use Category -Safety Set- Listing of Ankle-brachial Index

Summary of CREs (Clinical Risk Endpoints)		
Population	:	FAS
Group	:	• Study Arm • Product Use Category
Analysis variable	:	• Refer to Descriptive statistics • Calculate the value of CREs for each visit. Also, calculate the change from baseline. TC, TG, fasting blood glucose, WBC, and platelet counts are summarized in "9.5.4.3 Clinical Laboratory Evaluation"
Output	:	Summary of CREs -FAS- Summary of CREs by Product Use Category -FAS- Listing of CREs

Summary of Co-morbidities		
Population	:	FAS
Group	:	• Study Arm • Product Use Category
Contents		• The number and percentage of patients with co-morbidity and the terms of co-morbidity will be calculated. • Co-morbidity terms: ➢ Ischemic Heart Disease (IHD) ➢ Progression of IHD ✧ Progression of IHD: Myocardial infarction ✧ Progression of IHD: Stroke ➢ Chronic Obstructive Pulmonary Disease (COPD) ➢ Progression of COPD ➢ Hypertension ➢ Progression of hypertension ➢ Peripheral Arterial Disease (PAD) ➢ Progression of PAD
Output	:	Summary of Co-morbidities -FAS- Summary of Co-morbidities by Product Use Category -FAS- Listing of Co-morbidities

9.5.4 Safety Evaluation

In general, safety data will be provided in listings by study arm, site, patient, visit and time-point if applicable. The data will be tabulated on the Safety Set by study arms and in patients exposed but not randomized.

Item name	Definitions
Adverse Event (AE)	Adverse event is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not it is considered related to the IP.

Item name	Definitions
	Worsening of the AAA parameters (maximum minor-axis AAA diameter in mm, AAA annual growth rate, maximum minor-axis AAA diameter growth of above 5 mm in 6 months) will not be considered as an AE.
Serious Adverse Event (SAE)	An SAE is defined as, but not limited to, any untoward medical occurrence that: • Results in death. • Is life-threatening. • Requires inpatient hospitalization or prolongation of existing hospitalization. • Results in persistent or significant disability/incapacity, • Is a congenital anomaly/birth defect, or • Is an important medical event.

9.5.4.1 Adverse Events

AEs will be summarized by both the number and percentage of patients experiencing an event and the number of events experienced during the study period by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) - sorted by alphabetical order, Preferred Terms (PT) - sorted by alphabetical order.

If a subject has AEs that occurs and resolves on multiple occasions, each AE is counted once at each severity. Unless otherwise noted, target population will be used as denominator for frequency table.

AEs will be summarized by study arm, SOC and PT.

<table>
<tr><td colspan="3">Adverse Events</td></tr>
<tr><td>Population</td><td>:</td><td>Safety Set</td></tr>
<tr><td>Group</td><td>:</td><td>Study Arm</td></tr>
<tr><td>Contents</td><td></td><td>

The number and percentage of patients experiencing an adverse event and the number of adverse events during the study period.
The “Overview of Adverse Events” includes a summary of the following items

Subjects with at least one AE and number of AEs
Subjects with at least one SAE and number of SAE. And criteria of seriousness.
AE severity
Relation to study procedure or investigational product
Smoking related disease
Co-morbidity
Action taken with the investigational product
Action taken in response to AE
Relation to SARS-Cov2

The “Summary of Adverse Events” shows a tabulation of adverse events by SOC/PT.
Common Adverse Events are defined as AE that occurred at least 5% of the subjects in any of the study arms.
The “Annual summary of Adverse Events” shows a tabulation of adverse events by SOC/PT in each year after the enrollment. AE will be summarized based on the study day.
Study Day= Date of AE occurred - randomization date + 1

<table>
<tr><th>Year</th><th>Study Day</th></tr>
<tr><td>Before Randomization</td><td>< 0</td></tr>
<tr><td>0< ≤1</td><td>1≤ ≤365</td></tr>
<tr><td>1< ≤2</td><td>365< ≤730</td></tr>
<tr><td>2< ≤3</td><td>730< ≤1095</td></tr>
<tr><td>3<</td><td>1095<</td></tr>
</table>
</td></tr>
<tr><td>Output</td><td>:</td><td>Overview of Adverse Events -Safety Set-
Summary of Adverse Events -Safety Set-</td></tr>
</table>

		Summary of Common Adverse Events -Safety Set- Summary of Non-serious Common Adverse Events -Safety Set- Annual Summary of Adverse Events -Safety Set- Listing of Adverse Events

Adverse Events by Severity		
Population	:	Safety Set
Group		Study Arm
Contents	:	• The number and percentage of patients experiencing an adverse event and the number of adverse events during the study period by severity. If a subject experiences the same adverse event at more than one severity, then the AE will be counted (in the Table) at each severity where it appears. • Any missing severity will be accounted as “severe”.
Output		Summary of Adverse Events by Severity -Safety Set-

Expectedness of Adverse Events Related to Investigational Product		
Population	:	Safety Set
Group		Study Arm (Only IQOS and CIG)
Contents	:	The number and percentage of patients experiencing an adverse event related to an investigational product and its expectedness (Yes/No). Yes=expected, No=unexpected.
Output		Summary for Expectedness of Adverse Events Related to Investigational Product -Safety Set-

Relatedness of Adverse Events to Study Procedure		
Population	:	Safety Set
Group		Study Arm
Contents	:	The number and percentage of patients experiencing an adverse event related to study procedures.
Output		Summary for Relatedness of Adverse Events Related to Study Procedure -Safety Set-

9.5.4.1.1 Serious Adverse Events (Including Deaths)

Summary of Serious Adverse Events		
Population	:	Safety Set
Group		Study Arm
Contents	:	The number and percentage of patients experiencing a serious adverse event and the number of serious adverse events during the study period.
Output		Summary of Serious Adverse Events -Safety Set- Listing of Serious Adverse Events

Summary of Adverse Events Leading to Death		
Population	:	Safety Set
Group		Study Arm
Contents	:	The number and percentage of patients experiencing an adverse event leading to death during the study period and the number of adverse events leading to death during the study period.
Output		Summary of Adverse Events Leading to Death -Safety Set- Listing of Adverse Events Leading to Death

9.5.4.1.2 Adverse Events Leading to Discontinuation

Summary of Adverse Events Leading to Discontinuation from the Study		
Population	:	Safety Set
Group		Study Arm
Contents	:	The number and percentage of patients experiencing an adverse event leading to discontinuation from the study and the number of adverse events leading to discontinuation from the study.
Output		Summary of Adverse Events Leading to Discontinuation from the Study -Safety Set- Listing of Adverse Events Leading to Discontinuation

9.5.4.2 Device Events

Summary of Device Events		
Population	:	Safety Set
Group		Study Arm (Only IQOS)
Contents	:	• The "Overview of Device Events" includes a summary of the following items ➢ Subjects with at least one Device event ➢ Device Event severity ➢ Relation to AE ➢ Action taken with the device The number and percentage of patients experiencing device events and the number of device events will be summarized by severity and overall, by related parts of device, and by device event term. In addition, the number and percentage of patients and the number of events will be counted by related to AE/not related to AE and by device events severity (major and minor).

Summary of Device Events		
Remarks	:	Use data from CRF form “Device Events” and “Device Malfunction and product complaints”. Device event term will be sorted by the order shown in CRF
Output		Overview of Device Events -Safety Set- Summary of Device Events -Safety Set- Listing of Device Events

9.5.4.3 Clinical Laboratory Evaluation

Laboratory Evaluation		
Population	:	Safety Set
Group	:	Study Arm
Contents		• Refer to Descriptive statistics • Calculate the value of laboratory parameters for each visit. Also, calculate the change from baseline. ➢ Clinical chemistry ➢ Hematology • Also create a graph displaying mean ± standard deviation. • For parameters with the reference range, calculate the number and percentage of subjects in low, normal, or high compared to the reference range. • For urine analysis, calculate the number of subjects in each visit and the number of subjects in each result category by visits.
Analysis variable	:	Create for the following categories • Clinical chemistry • Hematology • Urine analysis
Output	:	Summary of Laboratory Parameters -Safety Set- Summary of Abnormal Laboratory Parameters -Safety Set-

		Series plot of Laboratory Parameters -Safety Set- Summary of Qualitative Urine Parameters -Safety Set- Listing of Laboratory

9.5.4.4 Medications, Physical Findings, Vital Signs and Other Observations Related to Safety

9.5.4.4.1 Medical History and Concomitant Disease

Summary of Medical History		
Population	:	Safety Set
Group	:	Study Arm
Contents		The number and percentage of patients experiencing medical history and the number of medical histories will be counted by MedDRA SOC and PT.
Definitions		Medical history is defined as any condition that started and ended prior to Screening (i.e., ended before signing the Informed consent).
Remarks	:	All cases collected on the form for medical history of CRF (MHCAT=" MEDICAL HISTORY") will be tabulated.
Output	:	Summary of Medical History -Safety Set- Listing of Medical History/ Concomitant Disease

Summary of Concomitant Disease		
Population	:	Safety Set
Group	:	Study Arm
Contents		The number and percentage of patients experiencing concomitant disease and the number of concomitant diseases will be counted by MedDRA SOC and PT.
Definitions		A concomitant disease is defined as any condition that started prior to ICF signature and is still ongoing at the end of V1.

Summary of Concomitant Disease		
Remarks	:	All cases collected on the form for medical history of CRF (MHCAT=" CONCOMITANT DISEASE") will be tabulated.
Output	:	Summary of Concomitant Disease -Safety Set- Listing of Medical History/ Concomitant Disease

9.5.4.4.2 Prior and Concomitant Medication

Summary of Prior Medication		
Population	:	Safety Set
Group	:	Study Arm
Contents	:	The number and percentage of patients with prior medication/therapy, using the level 1 and 2 ATC codes.
Definition	:	Any medication taken within 3 months prior to screening will be considered as prior medication.
Remarks		All cases collected on the form for "Prior and Concomitant Medication" of CRF (CMCAT="PRIOR MEDICATION") will be tabulated.
Output	:	Summary of Prior Medication -Safety Set- Listing of Prior and Concomitant Medication

Summary of Concomitant Medication		
Population	:	Safety Set
Group	:	Study Arm
Contents	:	The number and percentage of patients with concomitant medication/therapy, using the level 1 and 2 ATC codes.
Definition	:	Any medication which is started prior to screening and is still being taken by the patient at screening or thereafter will be considered as concomitant medication.

Summary of Concomitant Medication		
Remarks		All cases collected on the form for "Prior and Concomitant Medication" of CRF (CMCAT="CONCOMITANT MEDICATION") will be tabulated.
Output	:	Summary of Concomitant Medication -Safety Set- Listing of Prior and Concomitant Medication

Prior and Concomitant Surgical or Therapeutic Procedures		
Population	:	Safety Set
Group	:	Study Arm
Remarks		All cases collected on the form for "Prior and Concomitant Procedures" of CRF (PRCAT=" CONCOMITANT THERAPEUTIC PROCEDURE") will be listed.
Definition	:	Any Surgical or Therapeutic Procedures taken within 3 months prior to screening will be considered as prior procedures. Any Surgical or Therapeutic Procedures which is started prior to screening and is still being taken by the patient at screening or thereafter will be considered as concomitant procedures.
Output	:	Summary of Prior Surgical or Therapeutic Procedures -Safety Set- Summary of Concomitant Surgical or Therapeutic Procedures -Safety Set- Listing of Prior and Concomitant Surgical or Therapeutic Procedures

9.5.4.4.3 Physical Examination

Summary of Physical Examination		
Population	:	Safety Set
Group	:	Study Arm
Contents		Calculate the number of subjects in each visit and the number of subjects in each result category by visits.

Output	:	Summary of Physical Examination -Safety Set- Listing of Physical Examination

9.5.4.4.4 Vital Signs

Vital Signs		
Population	:	Safety Set
Group	:	Study Arm
Contents		• Refer to Descriptive statistics • Calculate the value of vital sign parameters for each visit. Also, calculate the change from baseline. ➢ Systolic blood pressure ➢ Diastolic blood pressure ➢ Pulse rate ➢ Respiratory rate • Also create a graph displaying mean ± standard deviation.
Output	:	Summary of Vital Signs -Safety Set- Series plot of Vital Signs -Safety Set- Listing of Vital Signs

9.5.4.4.5 Electrocardiogram

Summary of ECG		
Population	:	Safety Set
Group	:	Study Arm
Contents		• Refer to Descriptive statistics • Calculate the value of ECG parameters for each visit. Also, calculate the change from baseline.

		• Calculate the number of subjects within each visit and the number of subjects in each result category by visits.
Output	:	Summary of Electrocardiogram -Safety Set- Summary of Qualitative Electrocardiogram -Safety Set- Series plot of Electrocardiogram -Safety Set- Listing of Electrocardiogram

9.5.4.4.6 Other Safety Assessments

Listing of Chest X-Ray		
Population	:	Safety Set
Group	:	Study Arm
Output	:	Listing of Chest X-Ray

10 ANALYSES AND REPORTING

10.1 Interim Analyses and Data Monitoring

For this study, data reviews by IDMC members will be performed one year and two years after the first patient has been randomized. Sponsor will be informed at least with meeting minutes.

All data reviews by IDMC members will focus on safety, study quality, product use exposure, and disease characteristics and progression.

10.2 Safety Reporting

Not applicable

10.3 Topline Results

Not applicable

10.4 Final Analyses

Not applicable

10.5 ClinicalTrials.Gov Reporting

The planned TFLs contain the necessary information for reporting to ClinicalTrials.gov.

11 DATA PRESENTATION

Data presentation details are provided in a separate TFL mock shell document, based on the PMI style guide provided by PMI.

12 REFERENCES

1. JCS Joint Working Group. Guidelines for diagnosis and treatment of aortic aneurysm and aortic dissection (JCS 2011). *Circulation Journal* 2013; **77**: 789-828.

13 APPENDICES

13.1 Study Assessments

Not applicable

13.2 Tables, Figures & Listings

The list of TFLs is provided in a separate TFL mock shell document.