PMI RESEARCH & DEVELOPMENT

Clinical Study Protocol

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.
Short name:	Comparison AAA growth in adult smoking patients who either switch to IQOS, continue smoking, or had stopped smoking.
Product name:	IQOS (Tobacco Heating System [THS] with Marlboro Heatsticks)
Registration number:	Not assigned
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version number:	Final 9.0
Date :	17 of September 2021
Author:	[redacted], PhD, Clinical Scientist [redacted], MD, MSc, Medical Safety Officer [redacted], PhD, Study Biostatistician

SUMMARY OF CHANGES

Clinical Study Protocol
P1-AAA-02-JP

	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	

INTRODUCTION

The main purpose of this summary of changes is:

To summarize

- the non-substantial updates between the clinical study protocol P1-AAA-02-JP (Final Version 1.0) dated 05 October 2017 and its first updated version (Final Version 2.0) dated 10 January 2018.

- the non-substantial changes between the Final Version 2.0 study protocol and the first amended protocol (Final Version 3.0) dated 26 February 2018 which is to be referred to as Amendment No. 1.
- the non-substantial changes between the Final Version 3.0 study protocol (Amendment No. 1) and the second amended protocol (Final Version 4.0) dated 25 June 2018 which is to be referred to as Amendment No. 2.
- the non-substantial changes between the Final Version 4.0 study protocol (Amendment No. 2) and the third amended protocol (Final Version 5.0) dated 12 November 2018 which is to be referred to as Amendment No. 3.
- the non-substantial changes between the Final Version 5.0 study protocol (Amendment No. 3) and the fourth amended protocol (Final Version 6.0) dated 10 April 2019 which is to be referred to as Amendment No. 4.
- the non-substantial changes between the Final Version 6.0 study protocol (Amendment No. 4) and the fifth amended protocol (Final Version 7.0) dated 23 July 2019 which is to be referred to as Amendment No. 5.
- the substantial changes between the Final Version 7.0 study protocol (Amendment No. 5) and the sixth amended protocol (Final Version 8.0) dated 14 January 2020 which is to be referred to as Amendment No. 6.
- The non-substantial changes between the Final Version 8.0 study protocol (Amendment No. 6) and the seventh amended protocol (Final version 9.0) dated 17 of September 2021 which is to be referred to as Amendment No. 7.

More precise details on the protocol sections changed are provided below.

Section		Changes
From Final 8.0 to Final 9.0		
	General	The version number and the revision date were updated accordingly to the most current version and date.
First Page	**Authors**	Changes of roles were done. Laura Rio has become the Clinical Scientist, Cam Tuan Tran has replaced Nicolas Blanc as the Medical Safety Officer and Grégory Vuillaume has replaced Guillaume de La Bourdonnaye as Study Biostatistician.
Sections 8.3 and 8.5	**Reporting and follow-up of serious adverse**	The safety section has been updated to reflect current safety management, which is within PMI and no longer with UBC.

Section		Changes
From Final 8.0 to Final 9.0		
	events and Reporting and follow-up of pregnancies	

SYNOPSIS

Sponsor:

Philip Morris Products S.A.

Name of Product:

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

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.

Study Number:

P1-AAA-02-JP

Patient recruitment:

In spite of significant efforts undertaken to improve the recruitment of patients into this study, the recruitment rate remains low. Indeed, after over a year of recruitment only 32 patients were enrolled out of 114 planned. Furthermore, the forecast until June 2020 shows only 15 new patients potentially eligible to participate in the study. In addition, the recruiting sites are reaching the limits of available patients (recruitment is limited to existing patients only), and new sites joining the study have more limited pool of patients as compared to the originally selected sites. The pool of the new sites to be potentially suitable for patients recruitment has also now reached the limits - during the site selection/qualification process most promising sites were already contacted. In such a situation, it is not possible to predict the length of the recruitment needed to reach 114 patients, if at all possible. Therefore, rather than terminating the study, which would result in loss of site's and patient's efforts and 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. This would still allow an evaluation of already collected data to gather evidence of the impact of switching to IQOS on the evolution of the disease in patients suffering from abdominal aortic aneurysm.

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.

Objectives and Endpoints

Primary Objective 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 (CC) to using IQOS, as compared to patients who continue to smoke CC (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 CC as compared to patients who had stopped smoking (CC 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)

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 CC to using IQOS, as compared to patients who continue smoking CC 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 CC to using IQOS, as compared to patients who continue to smoke CC 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 CC to using IQOS, as compared to patients who continue smoking CC 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, CC 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 CC to using IQOS, patients who continue to smoke CC, 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 CC to using IQOS, patients who continue to smoke CC 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-cyanoethylmercapturic acid (CEMA)

Study evaluation criterion:

This is a descriptive study, designed to gain an understanding on the effect of complete switching from cigarettes to IQOS use compared to continued CC smoking on AAA growth rate and disease progression. Dual use of IQOS on top of CC will be also investigated. There are no formal statistical hypotheses to be tested.

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 2.

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 CC 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 [1], 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 advices 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.

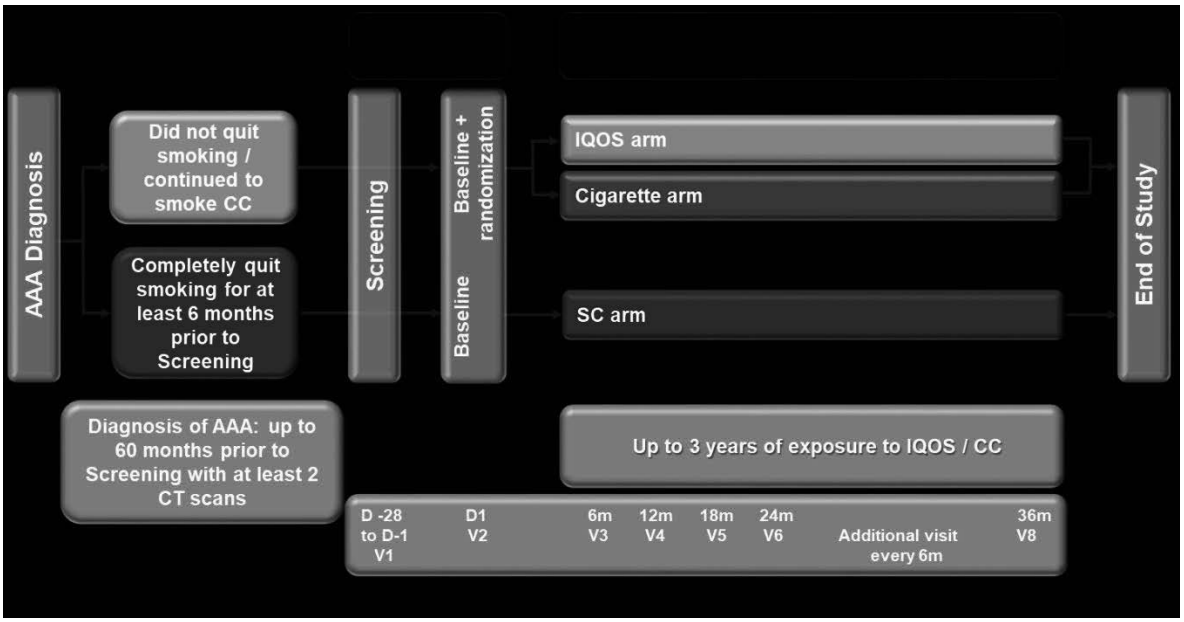

Figure 1 Study Flow Chart

Study Population and Main Criteria for Inclusion:

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

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 CC 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 CC 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 CC and IQOS arms of the study:

6. Patient has smoked on average > 5 commercially available and/or roll-your-own CC per day (no CC 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).

Criteria for Exclusion:

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).

Investigational Products; Dose and Mode of Use:

***Test product*:** The product tested in this study is the THS with *Marlboro Heatsticks*, marketed in Japan under the brand name IQOS and generally referred to as IQOS in this protocol. All versions of IQOS (including Tobacco Heating Devices (THD) with two elements: Charger and Holder, and THD with one single element (holder only: e.g., IQOS 3 Multi)) and *Marlboro Heatsticks* available for sale in Japan at the time of study start or becoming available during the course of the study are allowed to be used in the context of this study.

Two IQOS devices and one selection of *HeatStick* flavor variants available on the Japanese market will be supplied either by the site or by a third party courier service to the patients randomized to IQOS arm after randomization. The second IQOS device is to be used as backup, in case the first one does not work properly. Following this supply, patients allocated to IQOS arm will be asked to buy *HeatSticks* for their own use during the entire Investigational Period. *HeatSticks* will not be provided (except for the first distribution) or reimbursed by the Sponsor. Patients will use IQOS *ad libitum* with no flavor variant restrictions.

***Comparator and Baseline product*:** The patients' own preferred brand of commercially available and/or roll-your-own CC will not be provided by the Sponsor but purchased by the patients for their own use for the full duration of the study. Patients will use *ad libitum* their CC with no brand restrictions including no restriction to change preferred brand during the study.

Smoking Cessation (Reference):
Patients who had completely quitted smoking will continue to remain abstinent from smoking cigarettes or use any tobacco or nicotine containing products, except nicotine replacement therapy (NRT), from the Screening Visit onwards and during the Investigational Period.

Study Duration:

The study duration for each patient will be up to 3 years and 1 month. This includes the Screening Period of up to 28 days prior to Visit 2 (Baseline Visit), followed by an Investigational Period up to 3 years.

The end of the study for an individual patient will be defined as V8 or the date of early termination. The end of the entire study is the latest date that an individual patient reaches the end of the study.

Independent Data Monitoring Committee (IDMC):

An Independent Data Monitoring Committee (IDMC) will be established prior to starting the recruitment of patients and will meet periodically throughout the study to monitor the patients' safety, to review and evaluate the study data such as disease characteristics, the quality of the study conduct, e.g., feasibility, robustness and integrity, and the study progress. Members of the IDMC with expertise in the field of the disease and statistics, independent of both the sites and the Sponsor, are defined in a separate document, the IDMC Charter. The IDMC will organize meetings accordingly to review these study-specific data taking into consideration the relevant background knowledge about the disease and the patient population being studied. The IDMC Charter will define further details such as the review cycles, number of planned IDMC data reviews as well as stopping rules for the study, if considered by the IDMC as needed.

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.

The Role of IDMC

1. The IDMC will monitor the **safety of the patients** and disease progression based on clinical parameters listed in the IDMC charter. They will evaluate the risks/benefits for the patients based on clear and consistent evidence of higher harm (without formal boundaries) in patients randomized to IQOS relative to CC.
2. The IDMC will also evaluate the **quality of study conduct** and implication for further study course based on parameters described in the IDMC charter.

3. The IDMC will not monitor or make any recommendations in regards to effectiveness or futility in the study.

The IDMC may provide recommendations to the Sponsor regarding any identified study-conduct issues (e.g., protocol deviations), and may make recommendations to the Sponsor concerning the continuation or termination of the study based on their evaluation of safety (risk /benefit for the patient) and the quality of the study conduct.

Statistical Methods:

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

The Safety Set will consist of all enrolled patients who have signed the ICF and who have at least one valid value for a safety assessment during the course of the study. Descriptive statistics for continuous variables will include the number of patients, number and percent of patients with missing data, the mean and standard deviation, median, first and third quartiles, minimum and maximum, and 95% confidence interval (CI) across all patients by enrollment arm. In addition, the results may be presented as a stratified summary as defined in the Statistical Analysis Plan (SAP).

Adverse events data will serve as the primary assessment of safety and will be analyzed by tabulating the number and percentage of patients in the Safety Set with AEs and SAEs using MedDRA®. Concomitant medications, incidence of IQOS malfunction and misuse, laboratory parameters, ECG, vital signs, and physical examination, will also be analyzed as the safety endpoints.

Sample Size:

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 CC on the progression of disease.

Safety Assessments:

AEs (including SAEs) and product events will be captured. Any AEs (including SAEs) will be assessed by the Investigator(s) or designee(s) in order to establish relationship to Investigational Products (IPs) and study procedures. AEs and product events will be collected from the time when the patients have signed their ICFs until the end of the study.

The Investigator must notify the Sponsor of all SAEs and pregnancies within 24 hours of the first awareness.

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LIST OF ABBREVIATIONS AND DEFINITIONS 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
CC	Cigarette
CDISC	Clinical Data Interchange Standards Consortium
CEMA	2-Cyanoethylmercapturic Acid
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
DICOM	Digital Imaging and Communications in Medicine
DMP	Data Management Plan
ECG	Electrocardiogram
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HPHC	Harmful and Potentially Harmful Constituents
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

IP	Investigational Product
IRB	Institutional Review Board
IXRS	Interactive Web and Voice Response System
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Qualification
LOCF	Last Observation Carried Forward
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
SHM	Sample Handling Manual
SMP	Safety Management Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SPI	Summary of Product Information
TC	Total Cholesterol
TG	Triglycerides
THD	Tobacco Heating Device
THS	Tobacco Heating System

Total NNAL	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
Total NNN	Total N-nitrosonornicotine
ULOQ	Upper Limit of Qualification
USB	Universal Serial Bus
WBC	White Blood Cell
WPI	Whole Person Impairment

Explanation of terms

The following special terms are used in this protocol:

Cigarette	The term 'cigarette' refers to commercially available cigarettes (manufactured) and roll-your-own cigarettes. Cigarettes are tobacco rolled in paper that is lighted on fire to produce smoke.
End of study	The end of the study for an individual patient will be defined as Visit 8, or the date of early termination of the patient. The end of the entire study is defined as the last individual patients' end of the study.
Enrollment	For the SC Arm: at Visit 2 (V2) for eligible patients after all applicable entry criteria have been satisfactorily met. For the IQOS and CC Arm: at Visit 2 (V2) for eligible patients after all applicable entry criteria have been satisfactorily met.
HeatSticks	The *HeatStick* is designed to be used with IQOS only. The *HeatStick* is made up of: tobacco plug, hollow acetate tube, polymer-film filter, mouth piece filter, outer and mouth-end papers.
IQOS	Unless otherwise specified, IQOS in this document refers to PMI's Tobacco Heating System (THS) with *HeatSticks* as available for purchase in the Japanese market. No other tobacco sticks should be used with the IQOS device.
Investigator	Investigator or sub-Investigator.
Randomization	Assignment to IQOS or cigarette arm. Patients will be randomized and informed of their randomized study arm by the study site at Visit 2 (V2,

	Baseline Visit). All patients will be instructed to continue to solely use their assigned product until they complete the study.
Screen failure	Patient who signs ICF but was not enrolled. Re-screening of patients who did not meet any entry criteria will not be permitted.

1 ETHICS AND REGULATIONS

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

Prior to the start of the study, the clinical study protocol, together with its associated documents (as applicable, informed consent forms [ICFs] including both patient information sheet and consent form, patient recruitment procedures [e.g., advertisements] if applicable, written information to be provided to the patients, Summary of Product Information [SPI] [2], the Investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the Institutional Review Board [IRB] / Independent Ethics Committee [IEC]), will be submitted for review and approval to the relevant IRB / IEC. The IRB / IEC shall be appropriately constituted and perform its functions in accordance with the International Council for Harmonization of Technical Requirements for pharmaceuticals for Human Use (ICH) Tripartite Guidance for Good Clinical Practice (GCP), and Ministerial Ordinance on Good Clinical Practice for Drugs and local requirements, as applicable.

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

The written approval from the IRB / IEC will be filed in the Investigator Site File and a copy will be filed in the Study Master File at the Sponsor or designated organization. The study must not start before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IRB / IEC.

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

These requirements for approval should in no way prevent any action from being taken by the Investigator or sub-Investigator (Investigator) or by the Sponsor in order to eliminate immediate hazards to the patients. If such a change to the protocol is considered necessary by the Investigator, and is implemented for safety reasons, the Sponsor and the IRB / IEC should be informed immediately.

Relevant safety information will be submitted to the IRB / IEC during the course of the study in accordance with national regulations and requirements.

1.2 Ethical Conduct of the Study

The study will follow the principles as defined in the ICH GCP [3], in the Ministerial Ordinance on Good Clinical Practice for Drugs (Ministry of Health and Welfare, 1997 (as last amended by the Ordinance of Ministry of Health, Labor and Welfare No. 9 of January 22, 2016) [4], in the Declaration of Helsinki [5] and other applicable local regulations and guidelines such as Japanese-GCP [4]. Prior to the initiation of any study procedures, the protocol will be approved by an IRB / IEC and the patient will have received information on the study, as well as signed the study ICF.

1.3 Patient Information and Consent

1.3.1 Informed Study Consent Form/Patient Information Sheet for Participation to the Study

Before or at the Screening Visit (V1), the Investigator will ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study, and the Investigator will answer all questions the patient might have to his/her full satisfaction. The patient will have sufficient time for consideration of his/her participation in the study and will be notified that he/she is free to discontinue his/her participation at any time. Once the patient has received all necessary information, and if he/she agrees to participate, this will be documented in the ICF by the date, time and signature of both the patient and the person who conducted the inform consent discussion. No study-specific procedures will be performed before the ICF has been signed.

The original, dated and signed ICF must be kept in the Investigator file at the site, and a copy must be given to the patient.

The patient will be informed that if he/she withdraws from the study, the data collected until the point of withdrawal will be maintained as part of the study data and the samples collected prior to withdrawal will be analyzed, unless he/she refuses in writing.

Furthermore, the patient will be informed that additional data analyses not mentioned in the protocol or the statistical analysis plan might be performed with the collected data at a later time. If any additional analyses will be performed, they will fully be covered by data confidentiality, as for the main analyses described in this protocol.

1.3.2 Amendment Informed Consent Forms/ Patient Information Sheet for Participation to the Study

If a protocol amendment is required, an amendment may be required to the ICF. If revision of the ICF is necessary, the Investigator or designee will, with the support of the Sponsor or

authorized representative, ensure that the documents have been reviewed and approved by the IRB / IEC before study participants are required to re-sign and time and date the ICF.

1.4 Good Clinical Practice and Regulatory Requirements

The procedures set out in this clinical study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by the principles of the current version of the ICH guidelines on GCP and will carry out the clinical study in accordance with these principles. Although these guidelines were written specifically to set a standard for pharmaceutical development, they nevertheless provide a robust and ethical framework for conducting clinical studies of tobacco products.

2 INTRODUCTION

2.1 Background

Aortic Abdominal Aneurysm (AAA) is a permanent localized dilatation of the abdominal aorta. It is usually asymptomatic, almost exclusively occurs in the infrarenal part of the abdominal aorta and is incidentally discovered by ultrasound imaging. AAA and aortic rupture/dissections are responsible for at least 15,000 deaths annually, and was the 10th leading cause of death in white men with 65 to 74 years of age in the U.S. in the year 2000 [6]. Deaths due to aortic aneurysm/dissection are increasing every year in Japan. It was the 9th leading cause of death in Japan in 2014 (Statistics of Ministry of Health, Labour and Welfare). The limited regional investigational data in Japan indicate that the incidence rate of aortic aneurysm/dissection per year to be about 3 per 100,000 in the population [1].

The Japanese Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection defines AAA as follows: "Aortic aneurysm is a circumferential or local enlargement (increased diameter) or protrusion of a part of the aortic wall. Normal diameter in the abdominal region is generally 20 mm. When a part of the aortic wall is dilated and thereby forms a bump, or when the diameter is increased to a degree at least 1.5-fold greater than normal (exceeding 30 mm in the abdominal region) in a fusiform manner, the condition is called aneurysm"[1]. The development of AAA can be observed in 3 steps:

(1) formation/development,

(2) expansion, and

(3) rupture.

The strongest predictors of developing a AAA are cigarette (CC) smoking, sex, age, family history of AAA, hypertension, coronary artery disease, hypercholesterolemia, lower extremity peripheral arterial disease, carotid disease, history of cerebrovascular event, overweight or obesity, and low high-density lipoprotein cholesterol [7]. Cigarette smoking represents an independent risk factor for AAA, as it has been shown that there is a 10.1 and 7.5 times higher relative risk in male and female smokers, respectively, when compared to never smokers [8]. Furthermore, the relative risk of an AAA in individuals who have ever smoked is 2.5 times greater than that of coronary heart disease in the same patient group. There is a direct dose-response relationship between AAA and CC smoking (i.e., the risk of AAA rises with the increasing exposure to CC smoke and it has been shown that the risk of developing AAA gradually decreases with the years of Smoking Cessation (SC) [9-12].

Besides its role as the most important risk factor for developing AAA, smoking also significantly accelerates the growth of an AAA. The growth rate observed in CC smokers is higher than it is in former CC smokers (an increase of approximately 0.4 mm/year) [12,13]. Through the impact on growth rate, CC smoking also increases the risk of an AAA rupture and decreases the time to AAA open surgical/endovascular repair intervention [13,14]. Furthermore, a larger aneurysm size at diagnosis indicates a more rapid expansion of the aneurysm further on and therefore a faster disease progression [10]. Abdominal Aortic Aneurysms that reach a diameter of ≥ 55 mm in males or ≥ 50 mm in females, as well as AAA that have a growth rate of ≥ 5 mm within 6 months are common indicators for open surgical interventional treatment or AAA endovascular repair of the AAA [1].

Philip Morris International (PMI) develops, assesses and commercializes a portfolio of innovative products intended to (1) significantly reduce the risk of smoking-related disease compared to continued smoking of CC and (2) are accepted by smokers as substitutes for CC.

More than 6000 smoke constituents have been identified when the tobacco is burned or combusted [15], and more than 100 of them have been categorized as harmful and potentially harmful constituents (HPHCs) [16]. Lowering the temperature and heating the tobacco instead of burning it can substantially reduce levels of HPHCs. PMI's Tobacco Heating System (THS, marketed under the brand name of IQOS) is a novel tobacco heating system that heats a specifically designed tobacco stick (*HeatStick*) within a precisely controlled temperature range (far lower temperatures than CC) rather than burning it. IQOS replicates the ritual of smoking but without combustion. [15,16].

The Tobacco Heating Device (THD) consists of either two elements (charger and holder) or one single element (holder only: e.g., IQOS 3 Multi). IQOS is composed of the Holder and of dedicated *HeatSticks*. In this document, unless otherwise specified, IQOS refers to the device with *HeatSticks*. No other tobacco sticks should be used with the device. The Charger of the THD with two elements allows to recharge the Holder after each use. The Holder of the THD with one single element must be recharged after approximatively 10 inhalation experiences and can be recharged from household power. Unlike CC, the *HeatSticks* do not burn down during their consumption and their lengths remain constant after use. IQOS has been commercialized in Japan since November 2014. With this product, the heating of the tobacco is maintained below 350°C, a temperature much lower than what is observed for CC, which can reach 900°C.

PMI has undertaken a comprehensive assessment program on IQOS, including pre-clinical and clinical studies, aiming to demonstrate that IQOS is a reduced risk product[1]. The non-clinical assessment of IQOS, consisting of the aerosol chemistry analysis, *in vitro* and *in vivo* studies, supported the initiation of clinical studies, as no new or increased toxicological hazard in the product's aerosol was detected when compared with CC smoke. Results from pre-clinical *in*

vivo studies comparing CC smoke with IQOS aerosol in continuous inhalation show that exposure to IQOS aerosol, at multiple concentrations, results in a dramatically lower systemic toxicity, extensively reduced lung inflammation and reduced histopathological changes in the nasal epithelium as well as lung tissue compared to CC smoking [17,18]. Furthermore, exposure to IQOS aerosol in mice does not enhance cardiovascular disease or emphysema, as CC smoke does, and switching from CC smoke to IQOS aerosol exposure halts, e.g., aortic plaque growth in a similar manner as SC [19,20].

Several clinical studies have been conducted with IQOS, in Europe, Asia and the United States, in order to evaluate the nicotine pharmacokinetics (PK) profile [21-24], to demonstrate reduced exposure [25-28], and to determine functional and biological changes when adult smokers switch from CC to IQOS use compared to smokers continuing smoking CC [27,28]. The PK studies demonstrated similar nicotine absorption in subjects using IQOS and subjects smoking CC. The Reduced Exposure studies showed reductions in the levels of biomarkers of exposure (BoExp) to selected HPHCs in subjects using IQOS, when compared to subjects continuing smoking CC, close to levels observed when subjects stopped smoking for the duration of the study, both in controlled and ambulatory settings, for a duration of up to 3 months. These studies also indicated favorable biological and functional changes in clinical risk endpoints linked to smoking-related diseases, such as cardiovascular diseases. The number of tobacco sticks (= *Marlboro Heatsticks*) daily used over the entire study period in these studies was not increased, when compared to Baseline [29].

A 6-month exposure study [30], followed by a 6-month extension study [31], with the specific aim to demonstrate favorable changes in clinical risk endpoints in smokers switching from CC to IQOS compared to smokers continuing smoking CC has been completed and data analysis is on-going. Post-marketing studies are initiated, in order to have a better understanding of the product use behaviors and first insights in health outcomes [32]. Safety data available to date show a similar short-term safety profile for IQOS as for CC. PMI is now launching a series of new clinical studies to better understand whether switching to IQOS can have beneficial effects on health outcomes. Due to the known adverse effects of CC smoking and the benefits of SC on cardiovascular diseases (such as AAA), this study is part of this program. Further product information such as the nicotine content of each *Marlboro HeatStick* tested in this study can be found in Table 1 (section 6.1) and in the SPI [2].

[1] Reduced risk products ("RRPs") is the term used by PMI to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

2.2 Purpose of the Study

The data available in the literature for AAA growth rates in Japanese patients who continue to smoke CC and patients who had stopped smoking are scarce. In consequence, a well-informed estimate of the expected effect size in the different study groups as well as an evaluation of the operational feasibility, in particular the IQOS study group, is difficult.
Therefore, the purpose of this study is to evaluate the reduction of the AAA annual growth rate in patients who switch from smoking CC to using IQOS as compared to patients who continue to smoke CC. The study also aims to provide context to the scale of reduction in the growth rate, by comparing the AAA annual growth rates for continuing to smoke and switching to IQOS with the AAA annual growth rate in smokers who had stopped smoking.
The data derived from this study will help to close the existing gaps in the literature and inform on the appropriate design for further research studies in this field.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

Advice on health risk associated with tobacco smoking and SC advice will be provided at V1 and then at each visit from V2 to V8. The advice will follow the recommendations of the Japanese Circulation Society [33] and of the Ministry of Health, Labour and Welfare [34]. Patients who are motivated to quit using tobacco or nicotine-containing products (e.g., CC, IQOS or any other product) will be provided with SC support as per standard of care in Japan and will be referred for additional SC counselling to their General Practitioner. Patients who participate in this study will be compensated for their time and any inconvenience and will also benefit from repeated, detailed check-ups during the entire study period, which may help to increase efficacy of AAA therapy. The exact compensation amount and the schedule of payments will be listed in the site specific ICF.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures

The risk of study procedures (e.g., computerized tomography [CT] measurement, blood draw, etc.) are deemed to be on par with procedures routinely performed during normal or extended examinations by the patient's doctor.

2.3.3 Anticipated Foreseeable Risks due to Investigational Products

A substantial body of evidence already exists on IQOS [2]. Adverse events (AEs) reported so far seem to be mostly in line with the safety profile of SC pharmacotherapies such as nicotine replacement therapy (NRT).

2.3.4 Unforeseeable Risks

The possibility of unforeseeable events/risks will be explained at V1. Non-expected malfunction of IQOS may lead to unforeseeable risks. Patients will be informed that IQOS is not demonstrated yet to be less harmful than CC. Mitigation will include close monitoring and medical supervision to detect any unforeseeable risks or safety signals at the earliest time possible. In case of any disadvantages, the Investigator will take the decision to act accordingly.

3 STUDY OBJECTIVES

3.1 Primary Objective 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 (CC) to using IQOS, as compared to patients who continue to smoke CC (IQOS arm versus CC 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 CC as compared to patients who had stopped smoking (CC arm versus SC arm).

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

- Measurement of 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 CC to using IQOS, as compared to patients who continue smoking CC 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 CC to using IQOS, as compared to patients who continue to smoke CC 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 CC to using IQOS, as compared to patients who continue smoking CC 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, CC smoking, and SC 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 CC to using IQOS, patients who continue to smoke CC, 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 CC to using IQOS, patients who continue to smoke CC 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-cyanoethylmercapturic acid (CEMA)

3.3 Exploratory Objectives and Endpoints

Not Applicable.

4 OVERALL STUDY DESIGN AND PLAN

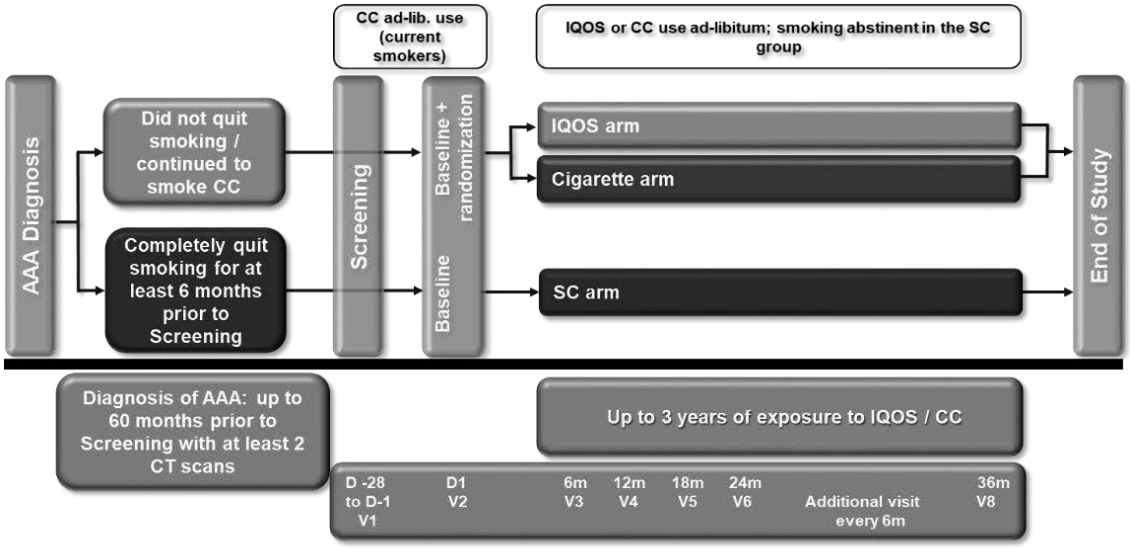
This is a controlled, open-label, 3-arm parallel group, multi-center study in patients diagnosed with Abdominal Aortic Aneurysm (AAA).

Adult patients with diagnosis of AAA currently smoking will be enrolled to be randomized in the CC and IQOS arms, and patients who had completely stopped smoking will be enrolled in the SC arm.

In general, standard of care, as defined by the Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection [1], 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 advices 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.

The overall study design is depicted in Figure 2.



Abbreviations: AAA = Abdominal Aortic Aneurysm; CC = cigarette smoking; SC = smoking cessation; CT = Computer Tomography

Figure 2 Study Flow Chart

The Screening Period (Screening Visit [V1]): covers a period of up-to 4 weeks prior to Baseline Visit (V2) (from Day -28 until on Day -1):

Patients with AAA diagnosis within the past 60 months with at least two existing CT scans will be invited for screening. Prior to the start of any procedure, patients will sign the ICF, and screening procedures will be conducted thereafter according to the schedule of events (Appendix 1).

A CT scan will be made at V1 according to the CT Scan Manual and assessed by the central reading site at V2 to provide the current the maximum minor-axis AAA diameter for assessment of eligibility.

It is recommended to complete all of the screening procedures in a one-day Screening Visit (V1), however it is permissible to complete the procedures over multiple days prior to the Baseline Visit (V2), if required.

The Baseline Visit (V2, Day 1):

Some eligibility criteria including smoking status will be re-confirmed. Enrollment into the SC, IQOS and CC arm occurs at V2 after checking that all eligibility criteria are met. Patients who do not meet the eligibility criteria prior to enrollment will be considered as screen failures.

Spot urine and blood samples will be collected, and further assessments will be performed according to the schedule of events (Appendix 1).

Patients who are current CC smokers and not willing to quit smoking after having been advised to quit smoking will be randomized at V2 with a 1:1 ratio within the corresponding stratum (as per stratification criteria) into the following study arms:

- IQOS arm: patients, switching to using IQOS
- CC arm: patients, continuing smoking CC

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

- 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 at V2.

All patients will be advised to use their assigned product until they complete the study.

The Investigational Period: the *ad libitum* exposure period from the check-out from V2 until the end of V8:
The Investigational Period will last up to 3 years following V2 and will include up to 61 months of retrospective (prior to V2) data collection for all enrolled/randomized patients.

Each month during the Investigational Period, patients will complete a questionnaire on self-reported current tobacco and nicotine-containing product consumption (including frequency and quantity of product use) over the past month.

At every visit during the Investigational Period, spot urine and blood samples will be collected. CT scans and further assessments will be performed according to the schedule of events (Appendix 1). Following the end of their Investigational Period, the patients will be discharged from the study.

At V8, any non-serious AE that is ongoing after completion of discharge procedures at Visit 8 will be documented as "ongoing". At that point, the Investigator will assess whether the patient should be referred to his/her General Practitioner for further follow-up on their ongoing AEs. All SAEs will be followed up by the Investigator until resolution, stabilization (i.e., no worsening of the condition), or until an acceptable explanation has been found (e.g., a chronic condition).

Unscheduled visits:

As a general rule, procedures requested in the protocol should be performed according to the visit schedule. However, as this study is focused on treating patients, there may be a number of reasons that the patient may visit the investigational site outside of the visit schedule during the course of the study. The site should record any site visit and document the reason for the visit and the assessments performed during the unscheduled site visit.

4.1 Rationale for Study Design and Control Group(s)

IQOS is designed to provide an acceptable alternative to current adult smokers, with substantial reduction of exposure to HPHCs found in CC smoke, considered to cause smoking related diseases. PMI has launched a series of studies to demonstrate reduced risk potential of IQOS in healthy adult smokers relative to CC smoking. To evaluate the adverse health effects of smoking on health outcomes in diseased populations switching from CC to IQOS is the next step for assessment. As it is reported that CC smoking represents an independent risk factor

for AAA, and as it has been shown that there is a 10.1 and 7.5 times higher relative risk in male and female smokers, respectively, when compared to never smokers [8], the study will enroll patients with AAA diagnosis.

The minimum age of 50 years old in the inclusion criteria was selected based on:

- The likelihood to develop AAA, which increases with age and smoking history.

The rationale for having a minimum of 5 years of smoking history is to not discard long-term smokers who might have stopped smoking for some time in their life.

This study will:

- Provide a perspective of the effect of switching to IQOS on the reduction of AAA growth compared to the continued use of CC as well as SC.

The study will be a three arm parallel group design with one observational and two randomized arms with the following strata:

- Aortic maximum-minor-axis diameter (male patients: < 40 mm and ≥ 40 mm; female patients: < 35 mm and ≥ 35 mm, using the assessment of the CT scan made according to the CT Scan Manual at V1 and assessed by the central reading site
- Sex (male vs. female)

This selection of stratification criteria is based on: 1) the size and AAA growth rate prior to stopping smoking have been shown to affect incidence of open surgical AAA treatment or AAA endovascular repair or AAA rupture and 2) sex differences in terms of growth rate and indication for open surgical AAA treatment or AAA endovascular repair as well as for the risk of rupture exist.

The choice of the primary and secondary objectives are based on 1) the standard of care procedures with regards to AAA diagnosis and follow-up as described in the Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection [1], 2) the most clinically relevant endpoints, i.e., AAA diameter and AAA growth within 6 - 12 months' time periods.

Although there is evidence that SC alters the growth rate of AAA and therefore seems to delay the time to open surgical AAA treatment or AAA endovascular repair and AAA rupture, the data available in the literature for AAA growth rates in Japanese patients who continue to smoke CC and patients who had stopped smoking are still scarce. Therefore, the assessment of these parameters as primary and secondary endpoints will thus provide insight on the effect of IQOS on these endpoints in comparison to continued smoking as well as on the effect of SC.

Cardiovascular risk factors will serve to support understanding of the respective effects of continued smoking, stopping smoking or switching to IQOS on the clinically relevant endpoint of AAA growth.

BoExp to nicotine NEQ, Total NNAL, Total NNN, and CEMA will serve as indicators of overall exposure of the patients throughout the study. These markers have relatively long half-lives, and should provide a good estimate of the exposure, even if the patient comes early in the morning for his/her visit. Because nicotine is expected to be delivered with IQOS at levels comparable to CC, levels of NEQ are not expected to be lower in IQOS users than CC users, but it will serve as an overall estimate of exposure to nicotine exposure. Levels of Total NNAL and Total NNN as tobacco-specific nitrosamines are expected to be significantly reduced in IQOS users compared to CC smokers, close to what is expected when patients stop smoking. Urinary excretion of CEMA, a biomarker of acrylonitrile which is generated as an incomplete combustion product in CC, is expected to be higher in smokers than in non-smokers and IQOS users. Additionally, CEMA levels in smokers are significantly correlated with ISO tar yield, daily CC consumption, and other urinary BoExp. Spot-urine collection will be performed, and the BoExp levels will be adjusted to creatinine to adjust urinary excretion rates.

The exclusion of patients with a diagnosis of concomitant genetic diseases such as Marfan syndrome, Loeys-Dietz syndrome, Vascular Ehlers-Danlos syndrome, Turner syndrome, Polycystic kidney disease, Noonan syndrome, Alagile syndrome, Arterial tortuosity syndrome and Cutis laxa is based on the fact that these diseases significantly affect occurrence, location and clinical course of AAA development and progression and would therefore not allow a clear assessment of the effect of smoking, SC or switching to IQOS on AAA growth rate.

This study is designed as an *ad libitum* study without product use restriction in order to mimic as closely as possible “real life” conditions.

All patients will be asked to buy their own CC or *HeatSticks*, according to their needs for the study, in order to minimize any changes in their smoking behavior, and to not promote one product over the other. As different brands of commercially available and/or roll-your-own CC will be used, neither the nicotine content of each CC is predefined nor the maximum as well as the minimum of the CC nicotine content is limited.

4.2 Appropriateness of Measurements

All clinical variables to be measured in this study were selected based on the following criteria:

1) commonly accepted measures used for AAA diagnosis and monitoring as per standard of care as per Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection [1];

2) acceptability by patients;
3) robustness of the method (i.e., index or evaluation criteria are available to assess reduction of AAA growth);
4) clinical relevance to support the objectives of the study.

The BoExp measured in this study were selected based on the following criteria:

1) the availability of a validated analytical method;
2) the measure is known to be directly or indirectly affected by the use of tobacco product;
3) the measure is readily reversible after SC/abstinence;
4) the timeframe of reversibility of measure in the perspective of the study duration;
5) the practicality/acceptability by patients;
6) the robustness of the method (rapid, simple, accurate).

Variability of CT scans:
Various studies have shown that significant variability of maximal aortic aneurysm diameter measurements on CT scan exist, especially when the measurement is conducted by different observers and without standardized protocol to measure the largest diameter perpendicular to the estimated aneurysm centerline from outer aneurysm wall to outer wall. A study by Cayne et al. [35] reported a difference in maximal diameter measurements between each observer of 4.0-5.1 mm (range, 0.0-35.0 mm) on average using an unstandardized method and a mean measurement difference with the standardized protocol of on average 2.8-4.4 mm (range, 0.0-26.0 mm; $P < .05$). The authors concluded that routine CT maximal diameter measurement of AAAs can have substantial inter-observer variability and that a standardized measurement protocol can decrease, but not eliminate, this measurement variability. Thus apparent size changes based on CT measurements may represent measurement artifact rather than actual aneurysm growth or shrinkage, particularly when a standardized system is not used.

In order to minimize the inter-observer variability on the reading of the CT scans, both the Lead CT over-reader and the CT over-reader Delegate will evaluate/assess, independently from each other, the maximum minor-axis AAA diameter in mm delivered by each study site.

The Lead CT over-reader checks the difference between the two readings on the worksheet. If the difference between the two readings is less than 5mm, the final reading of the maximum minor-axis AAA diameter in mm to be sent to the site is the recorded reading of the Lead CT over-reader. This final reading result to be used has to be clearly notified as the final result.

If the difference between the two readings is equal or more than 5 mm, the backup over-reader will, independently from the Lead CT over-reader and CT over-reader Delegate, repeat the process of reading of the maximum minor-axis AAA diameter in mm. The final reading result of the AAA diameter in mm to be sent to the site is the one evaluated/assessed by the backup over-reader. This final reading result to be used has to be clearly notified as the final result.

In order to further limit the variability of AAA maximum diameter measurements, all AAA diameters used for analysis in this study will be assessed by a single central reading site.

4.3 Study Duration

The study duration for each patient will be up to 3 years and 1 month. This includes the Screening Period of up to 28 days prior to Visit 2 (Baseline Visit), followed by an Investigational Period up to 3 years.

The end of the study for an individual patient will be defined as V8 or the date of early termination. The end of the entire study is the latest date that an individual patient reaches the end of the study.

4.4 Patient recruitment

In spite of significant efforts undertaken to improve the recruitment of patients into this study, the recruitment rate remains low. Indeed, after over a year of recruitment only 32 patients were enrolled out of 114 planned. Furthermore, the forecast until June 2020 shows only 15 new patients potentially eligible to participate in the study. In addition, the recruiting sites are reaching the limits of available patients (recruitment is limited to existing patients only), and new sites joining the study have more limited pool of patients as compared to the originally selected sites. The pool of the new sites to be potentially suitable for patients recruitment has also now reached the limits - during the site selection/qualification process most promising sites were already contacted. In such a situation, it is not possible to predict the length of the recruitment needed to reach 114 patients, if at all possible. Therefore, rather than terminating the study, which would result in loss of site's and patient's efforts and 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. This would still allow an evaluation of already collected data to gather evidence of the impact of switching to IQOS on the evolution of the disease in patients suffering from abdominal aortic aneurysm.
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.

4.5 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established prior to starting the recruitment of patients and will meet periodically throughout the study to monitor the patients' safety, to review and evaluate the study data such as disease characteristics, the quality of the study conduct, e.g., feasibility, robustness and integrity, and the study progress. Members of the IDMC with expertise in the field of the disease and statistics, independent of both the sites and the Sponsor, are defined in a separate document, the IDMC Charter. The IDMC will organize meetings accordingly to review these study-specific data taking into consideration the relevant background knowledge about the disease and the patient population being studied. The IDMC Charter will define further details such as the review cycles, number of planned IDMC data reviews as well as stopping rules for the study, if considered by the IDMC as needed.

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.

The Role of IDMC

1. The IDMC will monitor the **safety of the patients** and disease progression based on clinical parameters listed in the IDMC charter. They will evaluate the risks/benefits for the patients based on clear and consistent evidence of higher harm (without formal boundaries) in patients randomized to IQOS relative to CC.
2. The IDMC will also evaluate the **quality of study conduct** and implication for further study course based on parameters described in the IDMC charter.
3. The IDMC will not monitor or make any recommendations in regards to effectiveness or futility in the study.

The IDMC may provide recommendations to the Sponsor regarding any identified study-conduct issues (e.g., protocol deviations), and may make recommendations to the Sponsor concerning the continuation or termination of the study based on their evaluation of safety (risk /benefit for the patient) and the quality of the study conduct.

At a minimum, the following characteristics will be reviewed by the IDMC to evaluate safety of the patients and quality of the study (see IDMC charter for further details):

1) Safety of Patients:

- Change in the slope of the maximum minor-axis AAA diameter growth rate, following change in product use behavior (size of change, and timing of detection of the change)
- Maximum minor-axis AAA diameter growth rate (mm/year)
- Maximum minor-axis AAA diameter growth of more than 5 mm within 6 months
- Adverse events (AE)s and SAEs
- Confounders
- Number of patients annually undergoing AAA rupture
- Number of patients annually undergoing an open surgical AAA treatment or AAA endovascular repair
- Product use exposure

2) Quality of study conduct:

- Protocol deviations
- Patient recruitment rate in the current study
- Patient retention within each study arm, and switching between study arms

5 STUDY POPULATION

5.1 Selection of Study Population

5.1.1 Inclusion Criteria

Each patient to be enrolled must meet the following criteria:

Study Population and Main Criteria for Inclusion (all study arms):

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

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 CC 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 CC or IQOS arms:

Female or male Japanese adult smokers with diagnosed AAA meeting the following additional main inclusion criteria will be enrolled and randomized in the CC and IQOS arm of the study:

6. Patient has smoked on average > 5 commercially available and/or roll-your-own CC per day (no CC 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 Visit 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).

5.1.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria must not be enrolled into the study.

Criteria for Exclusion:

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).

5.2 Discontinuation of Patients from the Study

Discontinued patients will include patients who withdraw from the study (patient's decision) and patients who are discontinued from the study by the decision of the Investigator. A patient can only be discontinued from the study after enrollment.

Patients will be informed that they are free to withdraw from the study at any time. Patients should be asked for the reason of withdrawal from the study, although they are not obliged to disclose it.

If the patient withdraws from the study, he/she will be asked to perform the early termination procedures (section 9.4) as soon as possible after the time of withdrawal unless the patient refuses to do it in writing.

The patient will be reminded that the data collected until the point of withdrawal will be maintained as part of the study data, and the samples collected prior to withdrawal or during the early termination visit will be analyzed after his withdrawal, unless he/she refuses in writing.

All discontinued patients cannot re-enter the study.

5.2.1 Discontinuation from the study

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

- Withdrawal of informed consent.
- Discontinuation is considered to be in the interest of the patient from a safety perspective as judged by the Investigator.
- Positive or unclear pregnancy test.
- The Sponsor or Investigator terminates the study or the study terminates at a particular investigational site. If the Sponsor or the Investigator decides to prematurely terminate the study, the patient will be promptly informed. The investigational site/head of the medical institution should report the fact and the reason in writing to the IRB / IEC.
- Patient has to undergo open surgical AAA treatment or AAA endovascular repair (as per the treating physician's decision based on the standard of care as documented in the Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection [1]).
- The patient experiences a rupture of his/her AAA.
- Patient becomes an employee of the investigational site, a tobacco company or any other parties involved in the study.
- Lost to follow-up.

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

- Non-compliance to the study procedures based on the judgment of the Investigator.

If a violation of selection criteria is detected after enrollment, patients might be discontinued from the study based on a case-by-case decision of the Investigator.

Patients will not be discontinued from the study for the use of tobacco or nicotine-containing products other than their assigned product/regimen unless judged by Investigator.

5.2.2 Violation of Selection Criteria

Patients who violate the entry criteria prior to enrollment will be considered as screen failures. Re-screening of patients will not be permitted.

5.3 Lost to Follow-up

The date of the last contact with the patient (e.g., last visit, last phone call) should be recorded in the source document. After the last contact, a reasonable number of attempts to contact the patient (including written correspondence and phone calls) should be made and documented in the source documents by the site. Following the contact attempts, if the Investigator(s) or designee(s) decides to discontinue the patient with the reason of lost to follow-up, the discontinuation date will be recorded. The discontinuation date for the patient will be the date the patient was determined to be lost to follow-up and will correspond to the date of the EOS of the patient.

If the site has lost track of the patient, the discontinuation date cannot exceed the maximum number of study months (37), then the Investigator(s) or designee(s) will discontinue the patient with reason as lost to follow-up.

6 INVESTIGATIONAL PRODUCT(S)/REFERENCE

6.1 Description of Investigational Product(s)

Test product (IQOS): The product tested in this study is the Tobacco Heating System with *Marlboro Heatsticks*, marketed in Japan under the brand name IQOS and generally referred to as IQOS in this protocol. All versions of IQOS (including THD with two elements (Charger and Holder), and THD with one single element (holder only: e.g., IQOS 3 Multi)) and *Marlboro Heatsticks* available for sale in Japan at the time of study start or becoming available during the course of the study are allowed to be used in the context of this study. IQOS is composed of the following components: a tobacco *HeatStick*, a Holder and a Charger (THD with two elements), or a tobacco *HeatStick* and a holder (THD with one single element) (Table 1), as well as a cleaning tool, a power supply, and a USB cable.

Table 1 Test Product (IQOS)

HeatStick:	The *HeatStick* is designed to function with the Holder. The *HeatStick* is made up of: tobacco plug, hollow acetate tube, polymer-film filter, mouth piece filter, outer and mouth-end papers. All materials have been evaluated with regards to their toxicological potential and have been approved for use. The tobacco plug is made from tobacco, glycerin, water, guar gum, cellulose, propylene glycol, natural and artificial flavorings. The average amount of nicotine in the tobacco plug is 5-6 mg per *HeatStick*. The average amount of nicotine in the aerosol is 1.02-1.50 mg per *HeatStick* under the Health Canada Intense (HCI) machine-smoking regimen [36].
Holder:	The Holder of the THD with two elements is a slim electrical heating unit that heats the *HeatStick* in a controlled manner by using a heater blade. The Holder stores enough energy for a single experience, delivering puffs over a period of about 6 minutes or 14 puffs (whichever comes first). A Light Emitting Diode indicates the end of the experience. Once this cycle is complete, the Holder must be recharged before a new *HeatStick* can be used. The holder of the THD with one single element stores enough energy for approximatively 10 inhalation experiences, delivering puffs over a period of about 6 minutes or 14 puffs (whichever comes first) for each inhalation experience. A LED indicates when the experience can start and when the experience ends. The Holder of the THD with one single element must be recharged after approximatively 10 inhalation experiences and can be recharged from household power.
Charger:	The power supply for the Holder of the THD with two elements is the Charger. The Charger holds enough energy for approximately 20 uses of the Holder and can be recharged from household power. The Charger stores the Holder when not in use, and provides a secure environment for the cleaning process of the heater blade.

The overall objective of the product design is to provide an acceptable experience in which the HPHCs levels in the aerosol are substantially reduced in comparison with the smoke of a CC

[37,38]. A summary of description of the product, pre-clinical and clinical data available on IQOS is provided in the SPI [2].

6.1.1 Comparator and Baseline Product(s)

The comparator and baseline product will be the patient's own preferred brand of commercially available and/or roll-your-own CC.

6.1.2 Packaging and Labeling

The Sponsor or authorized representative will label the IQOS devices in local language ensuring adherence to local regulatory and requirements. This will include at least the following information:

- Statement 'For investigational use only'
- Name and address of the Sponsor (if the sponsor resides outside Japan, name of the sponsor and name of the country where the sponsor is located, and name and address of the clinical trial in-country representative)

6.2 Administration of Investigational Product(s) (for CC and IQOS arms)

The study is designed as an *ad libitum* use study. The patients will be allowed to use their allocated products (CC or IQOS) according to their need. Patients should be advised that when smoking CC or using IQOS, they should temporarily stop using the products in the event of any signs suggesting nicotine overexposure, (e.g., gastrointestinal disturbance [nausea, vomiting, diarrhea, stomach or abdominal pain], cold sweats, headache, dizziness, breathing problems) or any reasons at the discretion of the Investigator.

6.2.1 From Screening (V1) to Baseline (V2)

All adult current CC smokers who do not intend to quit smoking within the next 6 months after having been advised to quit smoking will be allowed to continue smoking *ad libitum* their preferred usual brand of CC.

6.2.2 Investigational Period

IQOS Arm
Patients will be instructed to use exclusively IQOS *ad libitum* according to their need with no flavor variant restrictions on *HeatSticks*.

CC Arm
Patients will continue to smoke *ad libitum* their CC with no brand restrictions including no restriction to change preferred brand during the study.

6.3 SC Arm (Reference)

NRT potentially used from the Screening Visit onwards and during the Investigational Period will not be provided or reimbursed by the Sponsor.

6.3.1 From Screening (V1) to Baseline (V2)

Patients who had completely quitted smoking will continue to remain abstinent from smoking CC or use any tobacco or nicotine containing products, except NRTs.

6.3.2 Investigational Period

Patients who had completely quitted smoking and are allocated to the SC arm are instructed to refrain entirely from the use of any tobacco or nicotine-containing product (except NRTs).

6.4 Method for Assigning Patients to Study Arms

6.4.1 IQOS and CC 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 CC 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.

6.4.2 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.

6.5 Blinding

6.5.1 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 the all study arms (CC, 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.

6.5.2 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 2.

Table 2 Blinding Scheme

Blinded Study Personnel	Blinded Data	End of Blinding Period
PMI and [redacted] 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 [redacted] 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 2 will be unblinded by default including the statistician(s) from [redacted] 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 2). 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.

6.6 Investigational Product Accountability and Adherence

6.6.1 Dispensing Investigational Product

Patients allocated to the IQOS arm will be supplied either by the site or by third party courier service with two IQOS devices and one selection of *HeatSticks* flavor variants available on the Japanese market, after randomization has occurred, but will be asked to buy his/her flavor of choice of *HeatSticks* for his/her own use for the entire duration of the study. The second IQOS device is to be used as backup, in case the first one does not work properly. In case the device needs replacement due to a device malfunction, the patient will need to follow the instructions provided by the site in order to have the device replaced. In case a patient decides to purchase their own device during the study duration, this will not be replaced in case of failure as part of the study requirements.

Patients allocated to the CC arm will be asked to buy CC for their own use for the entire duration of the study.

6.6.2 Storage and Accountability

Proper storage and accountability of the IQOS devices and *HeatSticks* should be ensured, either in case they are stored at and distributed by the sites or by a third party courier service. After first distribution, the patients will store the device and *HeatSticks* according to the IQOS manual unless instructed otherwise by the site.

Because CC will be bought by the patients, CC will not be stored at site or at the third party courier service.

6.6.3 Investigational Product Retention

The return of IQOS devices, including replacement devices, upon early discontinuation or at V8 will take place according to the instructions in the Investigational Product Handling Manual. This does not apply to the devices purchased by the patients.

6.6.4 Product Use Restrictions

There will be no restriction on allocated product use.

6.6.5 Dietary Restrictions

There will be no dietary restrictions for this study.

6.6.6 Adherence

Based on the numbers of the used *Marlboro HeatSticks* or the smoked CC 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, that will be defined in the SAP, 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 (CC 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.

Those patients who might change their smoking habits after randomization to an arm or do not use their products according to the arm they have been randomized to, will remain during the entire study conduct in the arm they have been randomized to. No change of randomization arm is allowed for all of the randomized patients after randomization, independent of their actual product use. Section 12.3 provides further details on the statistical analysis according to randomization arm.

6.7 Concomitant Medication

Medications will be allowed and carefully monitored during the study by the Investigator or designee. The Investigator or designee is responsible for the overall safety and well-being of the patient including the overall medical care and medication of the patients during their participation in the study. Any decisions regarding the prescribed medications will be made in the best interest of the patient. Maintenance or changes in treatment of any pre-existing concomitant diseases should be discussed by the Investigator with the treating physician or the patients General Practitioner. Any use of concomitant medication must be fully documented in the source document and transcribed into the Case Report Form (CRF).

Records of medication taken including NRT include the drug name (preferably both generic and trade name), route of administration (e.g., oral, intravenous), total daily dose/unit (e.g., expressed in mg, mL or IU), indication, the start and if applicable, the stop date (day, month and year). Any therapy changes (including changes of regimen) during the study have to be documented. Any concomitant medication that is still being taken by the patient at the EOS will be recorded in the CRF.

7 STUDY PROCEDURES

Personnel performing or recording study measurements must have appropriate and fully documented training. Quality control (QC) measures must be defined, implemented and documented. All study procedures are provided as an overview in the schedule of events (Section 15.1, Appendix 1 – Schedule of Events).

Site personnel will adhere to the site's standard operating procedures (SOPs) or other applicable SOPs and study-specific manuals for all activities relevant to the quality of the study. Appropriate medical advice will be provided to the patients in case of any medical findings requiring health care.

7.1 Informed Consent and Guidance

Prior to any study assessment being performed, the patient will be asked to provide his/her written consent to participate in the study and for the collection, storage and subsequent analysis of samples (ICF). All the assessments must start after the time of ICF signature by the patient before study participation. During the consent process, the Investigator or designee obtaining consent must inform each patient of the nature, risks and benefits of, and alternatives to study participation. In addition, each patient must review the ICF and must have sufficient time to understand and have adequate opportunity to ask questions. The ICF must be signed and dated (date and time) prior to undertaking any study-specific procedures. A copy of the signed ICF must be given to the patient.

7.2 Advice on the Risks of Smoking/SC Advice

All patients, screened for the study will be first advised that the best way of preventing further AAA disease progression is to stop smoking and will be given advice on risk of smoking and SC advice at V1.

From V1 onwards, all patients screened to be enrolled into CC, IQOS and SC arms will receive information on the risks of smoking, and the advice to quit smoking or to be abstinent from smoking will be given to all patients as described in Appendix 1 – Schedule of Events. This will take the form of a brief interview according to WHO recommendations [39].

Any patient who is willing to attempt quitting CC or IQOS or use of any tobacco or nicotine-containing products at any time during the study will be encouraged to do so. He/She will be referred to appropriate medical services, and the standard of care to support SC will be applied.

7.3 Debriefing on IQOS

Smokers screened to be enrolled in the IQOS arm and CC arms only will receive a debriefing on IQOS at V1, and if they are randomized to IQOS or CC arm, at each visit from V1 onwards

as described in Appendix 1 – Schedule of Events - to address any intended or unintended beliefs participants may have about IQOS. The goal of the debriefing is to ensure that patients have an accurate understanding of the current scientific knowledge about IQOS and the risks related to using IQOS. Any updates to the IQOS debriefing script will be submitted and approved by an IRB / IEC prior to be used in the study.

No information on IQOS will be given to patients eligible to the SC arm.

7.4 Clinical Assessments

7.4.1 Demographic Data

Demographic data (sex, date of birth, ethnicity) will be recorded at V1 (all patients).

7.4.2 Questions on Smoking History/Habits

All patients will be asked by the Investigator questions about their smoking history/habits (based on self-reporting) at V1, and the answers will be recorded:

1. Have you smoked cigarettes for at least the past 5 years prior to AAA diagnosis? (Yes/No)

    1a. On average, how many cigarettes per day have you smoked over the past 5 years prior to AAA diagnosis? (numeric response, 2 digits)

2. Have you been smoking cigarettes in the last 12 months? (Yes/No)

    2a. On average, how many cigarettes per day have you smoked over the last 12 months? (numeric response, 2 digits)

3. Have you been using any heat-not-burn tobacco product(s), for example IQOS or GLO, in the last 12 months? (Yes/No)

    3a. On average, how many tobacco *HeatSticks* / tobacco sticks per day have you used over the last 12 months? (numeric response, 2 digits)

4. Have you been using any tobacco vapor product(s), for example PLOOM Tech, in the last 12 months? (Yes/No)

    4a. On average, how many tobacco capsules per day have you used over the last 12 months? (numeric response, 2 digits)

5. Have you completely quit smoking cigarettes or completely stopped using any other tobacco or nicotine-containing products 6 months ago or even longer? (Yes/No)

3a. Are you still abstinent now? (Yes/No)

This information will be used to assess the patients' eligibility for inclusion in the different study arms.

7.4.3 Intention to Quit Smoking

The investigator must also ensure that as according to standard of care, smoking cessation advice had been provided to the patients at and after his/her AAA diagnosis and that he/she had had an adequate time period of approximately 6 months to attempt to stop smoking before coming to the Screening Visit.

In addition, smokers who are screened for enrollment and randomization to the IQOS and CC arms will be provided with SC advice at the Screening and Baseline Visit before being enrolled into the study, and will be asked about their intention to quit smoking within the next 6 months after having been advised to quit smoking. This must be clearly documented by the Investigator at V1 and V2.

7.4.4 Demonstration of IQOS using a video

IQOS demonstration using a video will only be made to smokers screened for enrollment and randomization to the IQOS and CC arms only at the time of V1. A video presenting IQOS including *HeatSticks* will be shown to currently smoking male patients by the Investigator or study collaborator. With respect to female patients, the video presenting IQOS will be shown to these patients whose pregnancy test was negative or where post-menopausal status is confirmed (see section 7.7.2).

No demonstration of IQOS will be given to AAA patients screened for the SC arm.

7.4.5 Medical History/Concomitant Disease(s)/Previous and Ongoing Medications

Relevant medical history, any concomitant disease, and previous and ongoing medications will be documented at V1 for all patients. It will be responsibility of the Investigator or designee to collect the relevant medical records for each patient necessary for the purposes of this study.

Medical history is defined as any condition that started and ended prior to Screening. A concomitant disease is defined as any condition that started prior to ICF signature and is still ongoing at the end of V1. After V1, each concomitant disease will be followed-up at each visit to check if it is still ongoing or not.

Previous medication taken within 3 months prior to screening and any ongoing medication at screening needs to be documented. 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. This applies to both prescription and over-the-counter products.

Any use of a concomitant medication must be fully documented in the Source Document and CRF. Therapy changes (including changes of regimen) during the study have to be documented. If a concomitant medication is still being taken by the patient at the end of the study, this will be recorded in the CRF.

7.4.6 Physical Examination

Physical examinations including palpation on abdomen will be conducted at V1 to V8 (all patients).

7.4.7 Body Height, Body Weight and Waist Circumference

Body height will be measured only at V1. Body weight will be recorded at V1 to V8. Waist circumference will be measured at V1 to V8. Appropriate medical advice will be provided to the patient in case of any medical findings requiring health care (all patients).

Body mass index (BMI) will be calculated at V2 to V8 from the body weight and height using the following formula:

$$BMI = \frac{\text{weight in kilograms}}{\text{height in meters}^2} \quad (\text{kg/m}^2)$$

Body weight and waist circumference will also be analyzed as cardiovascular risk factors.

7.4.8 Vital signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate will be measured at V1 to V8 (all patients). All measurements will be made after the patient has rested for at least 5 minutes. For every measurement in patients in the CC or IQOS arms, it will be documented, if applicable, that the last CC smoked or the last IQOS used was at least 15 minutes prior to the measurement.

Systolic and diastolic blood pressures will also be analyzed as cardiovascular risk factors.

7.4.9 Assessments of maximum minor-axis AAA Diameter

The assessment of the current maximum minor-axis AAA diameter on the CT scan which is made according to the CT Scan Manual at V1 at individual study sites will be performed at a single specifically assigned central clinical site (further referred to central reading site) following a standard protocol to assess the maximum minor-axis AAA diameter from the CT scan (Appendix 4) in all patients. All digital imaging data (DICOM files) of the CT scans performed during the up to 30 month period prior to V1 (minimum 2 CT scans) will be sent to the central reading site for assessment. The maximum minor-axis AAA diameter measurements used to assess patient eligibility for enrollment in the study (V1-CT scan) and all AAA diameter measurements used for the calculation of the AAA growth rate and related analysis in this study will be the measurements as assessed by the central reading site.

Although the determination for clinical treatment of a patient and therefore also the decision to perform open surgical AAA treatment or AAA endovascular repair will be based on the site's assessment of the CT scan, the maximum minor-axis AAA diameter recorded in the CRF at the time point of the decision to perform open surgical AAA treatment or AAA endovascular repair will be the maximum minor-axis AAA diameter as assessed by the over-reader at the central reading site.

Further details with regards to the assessment and handling of CT scans and the associated measurements will be described in the CT scan manual.

7.5 Other Clinical Assessments

7.5.1 Electrocardiogram

An Electrocardiogram (ECG) will be recorded in a supine position at V1, V4, V6, and V8 (all patients). ECG testing will be performed as per the site's local practice. A standard 12-lead ECG will be recorded after the patient has rested for at least 5 minutes in a supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QT interval corrected according to Bazett's formula and Fridericia's formula. Every ECG has to be assessed as normal, abnormal – clinically not relevant, or abnormal – clinically relevant. A diagnosis has to be provided on the CRF for all ECGs assessed as abnormal – clinically relevant. All ECG print-outs will be interpreted by a qualified physician. Any print-outs of ECGs on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents and signed by the Investigator or designee(s).

7.5.2 Chest X ray

At V1, a chest X-ray (upright position with anterior-posterior and left lateral views) will be assessed to exclude patients with relevant pulmonary diseases. No new examination is required if the patient can present at V1, a chest X-ray not older than 6 months with upright position with anterior-posterior and left lateral views.

7.6 Bioanalytical Assessments

All bioanalytical assessment assays will be carried out using validated methods (Section 7.8). The bioanalytical methods used will be documented in the Bioanalytical Plans/Reports. A list of laboratories is provided in Appendix 2.

7.6.1 Biomarker of Exposure

7.6.1.1 Total NNAL, Total NNN, CEMA, and NEQ in Urine

At V2 to V8: spot urine collection to measure biomarkers of exposure (expressed as concentration adjusted to creatinine):

- total NNAL, a biomarker for NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone),
- total NNN, a biomarker for NNN (N-nitrosonornicotine),
- CEMA, a biomarker for acrylonitrile, and
- NEQ, a biomarker to nicotine.

7.6.2 Creatinine Analysis

At V2 to V8: Creatinine will be measured for normalization of urinary BoExp.

7.7 Laboratory Assessments

Laboratory analyses will conducted according to Good Clinical Practice (GCP).

7.7.1 Clinical Chemistry, Hematology, and Urine analysis for the Safety Panel

Hematology, clinical chemistry and urine analysis for the safety panel will be measured at V1 to V8. The urine test will be performed semi-quantitatively as a urine test. Parameters to be measured are listed in the following Table 3.

Table 3 Clinical Laboratory Parameters for Safety Panel

Hematology	Clinical Chemistry	Urine analysis

- Hematocrit
- Hemoglobin
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count
- Differential WBC count:
  • Neutrophils
  • Basophils
  • Eosinophils
  • Lymphocytes
  • Monocytes
	- Albumin*
	- Total protein
	- Alkaline phosphatase (AP)
	- Alanine aminotransferase (ALT)
	- Aspartate aminotransferase (AST)
	- Blood urea nitrogen (BUN)
	- Creatinine*
	- Gamma-glutamyl transferase (GGT)
	- Fasting Glucose
	- Lactate dehydrogenase (LDH)
	- Potassium
	- Sodium
	- Total bilirubin
	- Direct bilirubin
	- Total cholesterol
	- Triglycerides
		- pH
		- Bilirubin
		- Glucose
		- Nitrite
		- Red blood cell traces
		- Protein
		- Specific gravity

* The albumin to creatinine ratio will be used to evaluate potential microalbuminuria.

7.7.2 Urine Pregnancy Testing

All female patients (with the exception of women in post-menopausal status, see below) will undergo urine pregnancy testing at all Visits.

Female patients with a urine positive pregnancy test at V1 cannot be enrolled and will be considered a screening failure. In any case of a positive urine pregnancy test, the Investigator will inform the patient about the risks associated with smoking during pregnancy. In case, the urine pregnancy test at screening is unclear, the patient cannot be enrolled. After enrollment, an unclear pregnancy test would lead to discontinuation of the patient.

The post-menopause is formally defined as the time after which a woman has experienced 12 consecutive months of amenorrhea (lack of menstruation) without a period. If a woman claims she is post-menopausal, but has had her menses within 12 months, a follicle stimulating hormone test must be performed and must be within acceptable limits of the post-menopausal status. Once post-menopause is confirmed no further pregnancy test needs to be conducted during the course of this study.

All pregnancies detected during the study must be reported and handled as described in Section 8.5.

7.7.3 Cotinine Test

A urine cotinine test will be performed at V1 and V2 in all patients considered for enrollment in order to confirm the patient's smoking status. The test must be able to detect cotinine with a cotinine level of ≥ 200 ng/mL (e.g., One-Step Cotinine Test 008A086, Ultimed, Belgium) in current smokers, and < 100 ng/mL (e.g., NicAlert ™ Urine, JAN, California, USA) in the former smokers group.

7.8 Sample Handling, Storage, and Shipment

The urine pregnancy tests and urine cotinine tests will be done by personnel at the study sites. Participating laboratories for the analyses of clinical samples are listed in Appendix 2. Detailed procedures for handling of samples are described in a separate Laboratory Manual / Sample Handling Manual (SHM). All samples will be destroyed post database lock or post finalization of the bioanalytical reports depending on which one is coming the latest or when the stability end date of the sample has been reached.

7.8.1 Blood Samples

Arterial blood sampling should be avoided in any case. Venous blood samples will be collected by qualified and trained site personnel. Patients should be in a seated position (if feasible; otherwise supine) during blood collection. The maximal total volume of blood drawn from each patient during the full study duration will be around 80 mL (From V1 to V8: 10 mL at every single visit, i.e. not more than a blood donation every 3 months.

7.8.2 Urine Samples

Spot urine will be collected for analysis of BoExp, creatinine, safety analysis, cotinine test, and pregnancy test.

7.9 Self-reported Tobacco or Nicotine-Containing Product Use

At V2, a diary on current tobacco and nicotine-containing product use will be distributed to the patients, and patients will be provided with instructions from study staff so that they can then fill the diary. Each diary contains 6 questionnaires for 6 months between the visits. The sites will call the patients to remind them to fill the questionnaires in the diary monthly to record their self-reported tobacco and nicotine-containing product consumption (including frequency and quantity of product use) over the past month. In this case, a "month" is to be

considered as 30 days, however a “calendar month” window is acceptable. A flexibility of ± 2 day is allowed, whichever definition of the month is used. The first questionnaire in the diary will be completed one month after V2. The Investigator or study collaborator will collect the completed diaries at every visit from V3 onwards, and the diary data will be transcribed into the CRF by the site staff.

8 ADVERSE EVENTS/PREGNANCIES/PRODUCT EVENTS

8.1 Definitions

8.1.1 Adverse Events

According to ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [40], an adverse event (AE) is defined as any untoward medical occurrence in a patient administered an IP (including the comparator product: CC), which does not necessarily have a causal relationship with the IP (including the comparator product: CC). An AE can therefore be 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.

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, as clinical assessments will capture any worsening of the condition. Patients experiencing unexpected worsening of the disease will be treated according to Investigator's judgement, which will be recorded.

8.1.2 Serious Adverse Event

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.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the patient or the patient may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Any pre-planned hospitalizations that are known at the time of signing the study participation ICF will not be recorded as SAEs (they will be recorded only as AEs). However, any AE that occurs during this pre-planned hospitalization will be considered according to the above definitions.

8.2 Assessment of Adverse Events

The Investigator is responsible for obtaining, assessing and documenting all AEs during the study.

8.2.1 Assessment of Adverse Events

Adverse event information will be collected from the time of signature of the ICF onwards until the end of Investigational Period either by the Investigator via spontaneous reporting or by the use of consistent, open, non-directive questions from study site collaborators (e.g., "Have you had any health problems since the previous visit/How have you been feeling since you were last asked?"). The main source for AE collection will be face-to-face interview(s) with the patient.

Information recorded will include: verbatim description of the AE, start and stop dates and times, seriousness, severity (intensity), action taken (e.g., whether or not the AE led to the patient's discontinuation from the study), and outcome (e.g., resolved, discontinuation due to AE).

For each AE, the intensity (severity) will be graded on a 3-point intensity scale (mild, moderate, severe) using the definitions provided in Section 8.2.3.

Any exacerbation/worsening of an AE or pre-existing condition shall be evaluated and recorded.

Correct medical terminology/concepts are preferred when recording AE terms, and abbreviations must be avoided. Wherever possible, a diagnosis is to be used to describe an AE rather than individual signs and symptoms (e.g., record 'pneumonia' rather than 'fever,' 'cough,' 'pulmonary infiltrate,' or 'septicemia,' rather than 'fever' and 'hypotension' following blood sample).

Any AE that meets the serious criteria must be recorded both on the AE report form of the CRF and on a separate SAE report form (Section 8.3).

Information regarding AEs related to product events should be actively collected during the study visits.

8.2.2 Period of Collection

Any AEs (including SAEs) will be captured by the study site collaborators and assessed by the Investigator(s) or designee(s) in order to establish relationship to IP and study procedures. AEs (including SAEs) will be collected from the time the patients have signed their ICFs until the end of the Investigational Period.

All collected AEs will be reported in the clinical study report (CSR) as described below and in accordance with the respective local regulatory guidelines.

8.2.2.1 Screening Period

All existing health conditions identified during the Screening Visit and judged by the Investigator as a preexisting condition will be recorded as concomitant disease and the patient's eligibility for admission to the study will be reviewed. Any AEs which occur during the Screening period will be captured by the study site staff and assessed by the Investigator(s) or designee(s) in order to establish relationship or relatedness in respect to study procedures. For screen failure patients, only the study procedure-related AEs will be reported in the CRF and in accordance with respective regulatory guidelines.

8.2.2.2 From ICF signature until the End of Study

Any new, clinically relevant, abnormal finding or worsening of a pre-existing condition/concomitant disease detected during the study will be documented as an AE and/or SAE and assessed by the Investigator or designee.

SAEs will be reported by the Investigator as described in this document and the safety management plan (SMP).

At the end of the Investigational Period, all ongoing non-serious AEs will be documented as "ongoing" and no follow-up information will be sought for them anymore by the Investigator or designee. At that point, the Investigator will assess whether the patient should be referred to his/her General Practitioner to have their ongoing AEs addressed accordingly.

All SAEs will be followed-up by the Investigator, despite their continuation after the end of the Investigational Period, until their resolution, stabilization (i.e., no worsening of the condition), or until an acceptable explanation has been found (e.g., a chronic condition).

8.2.3 Intensity of Adverse Event

For each AE, the intensity will be graded by the Investigator on a 3-point intensity scale (mild, moderate, severe) using the following definitions:

Mild: The AE is easily tolerated and does not interfere with daily activity.

Moderate: The AE interferes with daily activity, but the patient is still able to function.

Severe: The AE is incapacitating and requires medical intervention.

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

In general, all AEs and/or SAEs will be assessed by the Investigator as either 'related' or 'not related' to IP or comparator product as described below. In addition to the assessment of the relationship of the clinical event to the IP, the Investigator shall document a potential relationship of the clinical event to any particular study procedure.

Not related: The temporal relationship of the clinical event to IP administration or to a study procedure makes a causal relationship unlikely, or, concomitant medication, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Related: The temporal relationship of the clinical event to study IP administration or to a certain study procedure makes a causal relationship possible, and concomitant medication, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

8.2.5 Expectedness

Any AE assessed as related to the IP will be assessed for its expectedness. An AE will be regarded as 'unexpected' if its nature or severity is not consistent with information already known about the IP, and is not listed in the current SPI [2].

8.3 Reporting and Follow-Up of Serious Adverse Events

Any SAEs reported or observed during the study, whether or not attributable to the IP, or to any study procedures must be reported by the Investigator **within 24 hours after first awareness by any party involved in the study** to the Sponsor via email, having the SAE form attached as detailed in the Safety Management Plan (SMP).

An SAE report form must be e-mailed as an attachment to:

Sponsor:

E-mail: [redacted]
Address: Philip Morris Products S.A.
R&D Innovation Cube
5 Quai Jeanrenaud
2000 Neuchâtel
Switzerland

The Investigator/head of the investigational site is responsible for local reporting (i.e., to the IRB / IEC) of SAEs that occur during the study, according to local regulations.

Any additional/follow-up information that becomes available after the initial SAE report form

has been completed will be forwarded to the Sponsor **within 24 hours after first awareness** by any person at the site using a new SAE report form and indicating that this is a follow-up report.

The follow-up SAE report form must include the minimum information required for form completion and only changed/new information needs to be specified. Information provided in the follow-up SAE report form supersedes any information that was initially reported.

All SAEs will be followed up by the Investigator until their resolution or until the Investigator considers the event to be stabilized (i.e., no worsening of condition), or until an acceptable explanation has been found (e.g., a chronic condition). The details of the SAE management will be provided in a separate document, namely the safety management plan (SMP) for this study.

The SAE report form to be used in this study is provided as a separate document. All SAEs will be recorded on the relevant CRF page, in addition to the SAE report form.

The Investigator or designee is responsible for submitting the relevant reports of SAEs that occur during the study to the IRB, according to local regulations and in accordance with the respective safety management plan (SMP).

8.4 Reporting of other events critical to safety evaluations

8.4.1 Abnormal Results of Laboratory Tests

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the Investigator and assessed for clinical significance.

In addition, any clinical safety laboratory test result that is outside of the normal reference range will be assessed for severity by the Investigator using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grading system. Whenever that grading scheme is not available for the laboratory result of concern, the Investigator should assess the severity of that result using his/her medical judgment.

Abnormal laboratory test results detected at the Screening Visit and deemed clinically significant are usually concomitant disease or a manifestation of one and must be recorded accordingly.

Abnormal laboratory test results detected after the Screening Visit and deemed clinically significant must be either recorded as AEs or linked to a concomitant disease or to an already reported AE.

If there is no diagnosis available to record an AE or a concomitant disease corresponding to a

clinically significant abnormal laboratory test result, it will be recorded as “increased <lab parameter>” or “decreased <lab parameter>” to ensure consistency of recording/coding.

8.4.2 Reporting other abnormal findings

The other abnormal findings discovered during different clinical assessments (e.g., ECG, physical examination, vital signs) should be evaluated for the clinical significance by the Investigator/designee based on his/her medical judgement. All abnormal clinical significant test results or clinical examination findings can, at the discretion of the Investigator, be reported as AEs.

8.5 Reporting and Follow-Up of Pregnancies

For pregnancies detected between the time of signature of the study participation ICF and the enrollment of the patient, the patient will be considered as a screen failure. In that situation, the pregnancy will not be reported to the Sponsor, however, the identified pregnancy(ies) must be captured in the screen failure CRF. No pregnancy form will be filled.

For pregnancies detected between enrollment and prior to randomization (IQOS and CC arm only), patients will be discontinued, and reported as “enrolled but not randomized” patients. Early termination procedures shall apply. No pregnancy form will be filled.

Any pregnancy detected after enrollment for the SC arm and after randomization for CC and IQOS arm, must be reported by the Investigator to the Sponsor within 24 hours of the first awareness and must be followed-up for up to 8 weeks after the pregnancy outcome is reached. This also includes pregnancies spontaneously reported to the Investigator after the end of the study for a patient.

The pregnancy form to be used in this study is provided as a separate document.

The procedure to report a pregnancy and provide any additional/follow-up information to the Sponsor must be followed in the same manner and within the same timelines as described for an SAE (Section 8.3). No invasive procedures must be done in such patients after the discovery of pregnancy. If pregnancies are to be followed-up, they will be followed-up until an outcome is reached (e.g., normal delivery, spontaneous abortion, or voluntary termination) and also until 8 weeks after delivery.

Any pregnancy complication, adverse pregnancy outcome, or maternal complications will be recorded as an AE (or SAE).

The Investigator/head of the investigational site is responsible for informing the IRB / IEC of any pregnancy that occurs during the study and its outcome, according to local regulations.

8.6 Adverse Events Leading to Discontinuation

Patients who are discontinued from the study because of an AE will undergo the early termination procedure, as described in Section 9.4, as soon as possible. The Investigator will follow-up these AEs as described in Section 8.2.2.

8.7 Product Events / Investigational Product Malfunction and Misuse

Any occurrences of product events, including IQOS malfunction (e.g., holder does not charge when inserted into the charger), misuse by a patient (use not in accordance with its label and instruction) or events related to *HeatSticks*, will be documented by the Investigator or his/her designated collaborator using a product issue log developed by the site.

Investigational product misuse may result in use-related hazards (Section 2.3.4).

Furthermore, any misuse or malfunction of IQOS that leads to an AE/SAE will follow the same processes as described above for the reporting of the AE/SAE.

9 STUDY ACTIVITIES

A detailed schedule of assessments can be found in Appendix 1.

Measurements not conducted at the exact time point, but conducted within the given time window (if applicable) do not constitute a protocol deviation but an accepted variability for the given time point. In general, if no start time for the procedures is provided, then the procedure can be performed at any time during the day. Assessment during the study visits will be performed by qualified and trained personnel.

9.1 Screening Visit: V1

The Screening Visit (V1) will be scheduled within 4 weeks (Day -28 to -1) prior to the Baseline Visit (V2).

Patient will sign the study participation ICF before the start of any study procedure, and will enter Screening. When/if the ICF is signed (date and time), screening procedures can be performed in the order deemed most practical. While it is recommended to complete as many screening procedures as possible in one day, it is permissible to complete those over more than one day. Smoking is allowed at V1 unless otherwise instructed by the site.

Table 4 shows the assessments that will be performed at the Screening Visit: all the assessments described below have to be conducted in all patients unless specified otherwise. All the samples will be collected, stored, and shipped according to the laboratory/sample handling manual.

Table 4 Schedule - Screening Visit: V1

Time	Sample collection	Procedures	Additional information
Start of procedure		**Screening**	
Start of the visit		ICF procedure and signature	Informed consent for study participation
After ICF signature, during the visit		Advice on the risks of smoking/SC advice	
		Check of eligibility criteria	
		Demographics data	Sex, date of birth, ethnicity
		Medical history, including history of recent and current alcohol and substance abuse (only history of recent and current alcohol and substance abuse is based on self-reporting)	

Time	Sample collection	Procedures	Additional information
Start of procedure		**Screening**	
		Concomitant diseases	
		Previous medication and/or concomitant medication	
		Retrospective CT scan evaluation within the last 30 months prior to V1	2 CT scans to be sent to central reading for evaluation
		Intention to quit smoking in the next 6 months after having been advised to quit smoking	Smoking patients only
During the visit			
	U	Spot urine collection for pregnancy and cotinine tests	Pregnancy test (all females, except when menopause is confirmed): at the study site.
			Cotinine test: test at the study site. The cut-off value of urine cotinine Screening test in smoking patients: ≥ 200 ng/ml, in all former CC smokers: < 100 ng/ml.
		IQOS demonstration and debriefing	For smoking patients only. For female smoking patients, only after pregnancy test was tested negative.
		Smoking history/habits questions	
		Readiness to comply to study procedures	
		Clinical assessments: Vital signs Physical examinations Electrocardiogram Chest X ray Body height and weight	Vital signs: at least 15 min after having smoked CC or used IQOS

Time	Sample collection	Procedures	Additional information
Start of procedure		**Screening**	
		Waist circumference	
	B/U	Hematology, clinical chemistry, urine analysis	
		Judgment on eligibility	All eligibility criteria must be checked.
		AE/SAE recording	
		CT scan for abdominal aorta	Recommended as last assessment once all other assessments are done, and all of other eligibility criteria are checked. To be made at V1 and to be sent to the central reading site (can also be organized after V1).
End of the visit			

Abbreviations: AAA = Abdominal Aortic Aneurysm; AE = Adverse event; B = Blood/Plasma; CT = Computed Tomography; SAE = Serious adverse event; SC = Smoking Cessation; U = Urine.

9.2 Baseline Visit: V2

Table 5 shows the assessments that will be performed at Baseline Visit (V2): all the assessments described below have to be conducted in all patients unless specified otherwise. All the samples will be collected, stored, and shipped according to the laboratory/sample handling manual.

Table 5 Time Schedule – Baseline Visit: V2

Time	Sample collection	Procedures	Additional information
Start of procedure			
Start of the visit		Advice on the risks of smoking/SC advice	
Prior to enrollment		Re-check of applicable eligibility criteria	
		CT scan assessment for eligibility	Made at V1, sent to the central reading site for assessment, to be checked at V2 for eligibility.

Time	Sample collection	Procedures	Additional information
Start of procedure			
		Spot urine for pregnancy and cotinine tests	Pregnancy test (all females, except when menopause is confirmed): at the study site. Cotinine test: test at the study site. The cut-off value of urine cotinine test in all smoking patients: ≥ 200 ng/ml, in all former smokers: < 100 ng/ml.
		Intention to quit smoking in the next 6 months after having been advised to quit smoking	Smoking patients only
		Concomitant medication	
		Follow-up on concomitant diseases (ongoing or not)	
		Assessment of concomitant diseases	
		Readiness to comply to study procedures	
		Judgment on eligibility	
Enrollment		Enrollment of eligible patients for the IQOS and CC arm in IXRS	Smoking patients only.
		Enrollment of eligible patients into the SC arm in IXRS	Former smoker patients only.
After enrollment		Distribution of the diary for tobacco or nicotine-containing product use self-reporting	Patients will be provided with information on how to fill the diary
	U	Spot urine collection for collection of samples for total NNN, total NNAL, CEMA, NEQ, creatinine	
	B/U	Blood/Urine: Hematology, clinical chemistry, urine analysis	Blood samples have to be taken after at least 10 hours of fasting.

Time	Sample collection	Procedures	Additional information
Start of procedure			
		Clinical assessments:	
		Vital signs	Vital signs: at least 15 min after having smoked CC or used IQOS. Systolic and diastolic blood pressure also assessed as cardiovascular risk factors
		Physical examinations	
		Body weight	Assessed as cardiovascular risk factor
		Waist circumference	Assessed as cardiovascular risk factor
		AE/SAE recording	
		Debriefing on IQOS	Smoking patients only.
		Randomization	Smoking patients only
		Patients are informed of their randomized study arm.	Smoking patients only
		Distribution of the IQOS supplies as per site process	Smoking patients randomized to IQOS arm only
		Any other assessment as per standard of care for AAA patients and deemed necessary by the Investigator	
End of the visit			
After check out		Patients start using their allocated product	**IQOS and CC arm only**

Abbreviations: AAA = Abdominal Aortic Aneurysm; AE = Adverse event; ; B = Blood/Plasma; CEMA = 2-Cyanoethylmercapturic Acid; CT = Computed Tomography; NEQ = nicotine equivalents, consisting of the molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine and trans-3'-hydroxycotinineglucuronide; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; NNN = N-nitrosonornicotine; SAE = Serious adverse event; SC = Smoking Cessation; U = Urine; .

9.3 Investigational Period (from V3 to V8)

All the assessments described in the tables have to be conducted in all patients unless specified otherwise. All the samples will be collected, stored, and shipped according to the laboratory/sample handling manual.

V3 will be scheduled 6 months after V2 with a flexibility of ± 14 days. All subsequent visits until Visit 8 will be conducted every 6 months with a flexibility of ± 14 days since the previous visit.

Table 6 shows the assessments that will be performed at:

- 6 month Visit: V3
- 12 month Visit: V4
- 18 month Visit: V5
- 24 month Visit: V6
- 30 month Visit: V7
- 36 Month Visit: V8

Electrocardiogram is to be performed at V4, V6, and V8 only.

Table 6 Time Schedule – V3 to V8

Time	Sample collection	Procedures	Additional information
Start of procedure			
Start of the visit		Advice on the risks of smoking/SC advice	
		Debriefing on IQOS	IQOS and CC arm only.
During the visit		Tobacco or nicotine-containing product use self-reporting diary	Collection of the Diaries from the previous visit, and distribution of the diaries for the next visit
		Concomitant medication Follow-up on concomitant diseases (ongoing or not)	
	U	Spot urine collection for pregnancy, and collection of samples for NEQ, total NNN, total NNAL, CEMA, creatinine	Pregnancy test (all females, except when menopause is confirmed): at the study site
	B/U	Blood/Urine: Hematology, clinical chemistry, urine analysis	Blood samples have to be taken after at least 10 hours

Time	Sample collection	Procedures	Additional information
Start of procedure			
			of fasting.
		Clinical assessments:	
		Vital signs	Vital signs: at least 15 min after having smoked CC or used IQOS. Systolic and diastolic blood pressure also assessed as cardiovascular risk factor
		Physical examinations	
		Body weight	Assessed as cardiovascular risk factor
		Waist circumference	Assessed as cardiovascular risk factor
		CT scan	CT scan to be made at site and to be sent to the central reading site for assessment by the central reading site following standardized protocol.
		Assessment of concomitant diseases	
		Any other assessment as per standard of care for AAA patients and deemed necessary by the Investigator	
		Record of the date of open surgical AAA treatment or AAA endovascular repair if applicable	
		Electrocardiogram	At V4, V6, and V8 only
		Return of IQOS device, replacement of devices as appropriate	For IQOS arm only: at V8 or when the device needs replacement due to a device malfunction according to the instructions in the

Time	Sample collection	Procedures	Additional information
Start of procedure			
			Investigational Product Handling Manual
End of the visit		AE/SAE/product event recording	
		Discharge	At V8 only

Abbreviations: AAA = Abdominal Aortic Aneurysm; AE = Adverse event; B = Blood/Plasma; CEMA = 2-Cyanoethylmercapturic Acid; CT = Computed Tomography; NEQ = nicotine equivalents, consisting of the molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine and trans-3'-hydroxycotinineglucuronide; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; NNN = N-nitrosonornicotine; SAE = Serious adverse event; SC = Smoking Cessation; U = Urine; .

At the end of V8, patients will be discharged from the study. The procedures prior to discharge of the patient will also apply in case of early termination of the patient.

9.4 Early Termination Procedures

For patients who terminate the study early, the procedure of discharge planned for V8 will be performed as an early termination (Table 7).

Table 7 Time Schedule – Early Termination Procedures

Time	Sample collection	Procedures	Additional Information
Start of Procedure			
During the visit		Advice on the risks of smoking/SC advice	
		Follow-up on concomitant diseases (ongoing or not)	
During the visit	U	Spot urine collection for pregnancy	Pregnancy test (all females, except when menopause is confirmed): at the study site
	B/U	Blood/Urine: Hematology, clinical chemistry, urine analysis	Blood samples have to be taken after at least 10 hours of fasting.
		Clinical assessments:	
		Electrocardiogram	At least 5 minutes in supine position
		Physical examinations	

	Return of IQOS device	For IQOS arm only upon early discontinuation
End of the visit	AE/SAE/product event recording	

Abbreviations: AE = Adverse event; SAE = Serious adverse event.

If the patient withdraws from the study, or is discontinued based on Investigator judgment, he/she will be asked to perform the early termination procedure as soon as possible after the time of discontinuation unless the patient refuses to do so (section 5.2).

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

The Clinical Research Associate ("Monitor") will be responsible for the monitoring of the study. Monitoring will be performed according to CRO's Standard Operating Procedures (SOPs) and as per the agreed monitoring plan with the Sponsor.

The Investigator/head of the investigational site shall permit the Monitor to review study data as frequently as considered necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator shall access medical records for the Monitor in order that entries in the CRFs may be verified. The Investigator, as part of his/her responsibility, is expected to ensure that the study adheres to GCP requirements.

An Investigator's meeting will be held prior to the site initiation visit. During this meeting, a general training on the study procedures and specific training on selected procedures will be done and documented.

After the Investigator's meeting, and before the first patient is screened into the study, a site initiation visit will be conducted by the Monitor and, if necessary, with the Sponsor or its authorized representative. The purpose of the site initiation visit will be detailed in the monitoring plan.

Communication by telephone, mail, and e-mail may be used as needed to supplement site visits. The Investigator and study personnel will cooperate with the Monitor, provide all appropriate documentation, and will be available to discuss the study.

The Monitor and the Sponsor's personnel will be available between visits, should the Investigator or other study collaborator at the sites need information and advice.

Site visits will be made at regular intervals during the study. The frequency of the monitoring visits will be defined in the monitoring plan agreed with the Sponsor.

The Investigator, or a designated member of the Investigator's study collaborator, must be available during the monitoring visit to review the data and resolve any queries, and to allow direct access to the patient's records for source data verification.

10.2 Training of Staff

A formal meeting (Investigator's meeting) will be conducted prior to site initiation. During this meeting, the Sponsor or its authorized representative will discuss the requirements of the clinical study protocol and related documents and will also provide training in the relevant systems and other study-specific procedures. The activities of the Investigator's meeting will be described in the monitoring plan.

In addition to the Investigator's meeting, the Investigator will ensure that appropriate training relevant to the study is provided to all study collaborators involved in the study, and that any new information relevant to the performance of this study is forwarded in a timely manner to the study collaborator. The record of all individuals involved in the study will be maintained in the Site Investigator File.

10.3 Audits and Inspections

Good Clinical Practice guidelines require that there are independent inspections of clinical program activities. Such inspections may be performed at any time before, during and/or after the study.

Authorized representatives of the Sponsor, regulatory agencies and/or the IRB / IEC may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP guidelines, and any applicable regulatory requirements. The Investigator/head of investigational site will contact the Sponsor or the authorized representative immediately, if contacted by a regulatory agency about an inspection at their site.

The Investigator and study collaborators are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its authorized representative, and/or regulatory agencies. In signing this protocol, the Investigator understands and agrees to provide access to the necessary documentation and files.

11 DATA MANAGEMENT ACTIVITIES

All Data Management activities will be described in detail in the Data Management Plan (DMP) and documents specified therein.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

Data Collection Procedures:

The results from the clinical assessments will be recorded in the source data file by the Investigator or their authorized designee and then captured in the CRFs.

Trained study personnel will be responsible for capturing the data from the observations, tests, and assessments specified in the protocol and in the source documents, and transferring the data to the CRF according to the CRF Completion Guidelines.

The Investigator has ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. The CRF must be signed by the Investigator to attest that the data contained on the CRF are true and accurate. Any corrections made to source documents must be clearly recorded, without obscuring the original values and be accompanied by the date of change, reason for change, and identification of the person making the change. The CRF data will be verified against the source documents at the study site by the clinical research associate. Instances of missing or unclear data will be discussed with the Investigator for resolution.

11.1.2 Protocol Deviations

All protocol deviations will be entered into the Clinical Trial Management System (CTMS) or other approved format.

Information from the source documents will represent the primary source of protocol deviations. Information following site monitoring and other manual reviews will be documented in the site visit reports, follow-up letters, audit documentation, or other manual review and will be recorded and tracked in the CTMS or other approved format. Telecommunications and other verbal communications regarding deviations will be considered and handled as important communication, and documented and tracked as protocol deviations, as necessary.

Individual entries for protocol deviations that are recorded in the CTMS, or other approved format, following site monitoring and other manual reviews will be reviewed against the individual data points in the CRF database but will not be formally reconciled with the CRF database (e.g., their description or occurrence date). The overall procedures for managing protocol deviations are described in the SOPs of the CRO Data Management Team. All deviations will be reviewed periodically, as determined at study start, to identify trends to improve monitoring and/or potential impact on the statistical analysis.

11.2 Data Handling

All study data will be managed by the Data Management Team at the CRO. The overall procedures for quality assurance of clinical study data are described in the SOPs of the CRO Data Management Team. The Data Management Team at CRO will prepare a DMP, to be reviewed and approved by the Sponsor, prior to the start of the study. This document will describe, in detail, the Data Management related procedures and processes.

All data of all patients enrolled and screening failures who experience an AE during the study (from time of informed consent) will be captured.

All data collected during the study is property of the Sponsor, irrespective of the location of the database and the Data Management CRO.

11.2.1 Data Validation

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

Data queries will be raised for discrepant or missing data. All changes to data will be captured in the database with a comprehensive audit trail.

11.2.2 Coding

AEs, medical/surgical history, and prior/concomitant medication will be classified according to the terminology of the latest version of the following Dictionaries, at time of coding the first entry:

Medical history:	Medical Dictionary for Regulatory Activities (MedDRA®)
Adverse events:	MedDRA®
Medications:	WHODrug Global
IQOS device issues and/or malfunctions:	C54451/Medical_Device_Problem_Codes_FDA_CDRH

11.2.3 Database Lock

When all outstanding Data Management issues have been resolved and all validation, quality review, and cleaning activities are complete, the database or selected data is/are declared soft locked. Access to change data in the soft-locked database or to change selected data at this time is limited.

After the data is reviewed by the Sponsor, resolution of all raised queries and QC of the changed data, database, or selected data upon Sponsor approval as applicable, is declared locked.

Any changes to the database after that time can only be made by written agreement between the Sponsor and the Data Management and Statistical Teams at the CRO. Any of those changes must be documented in the database log file.

After study completion, the study database will be transferred to the Sponsor in the format specified in the DMP and compliant with Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM).

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

This study is following the International Conference on Harmonization (ICH) guidelines and Good Clinical Practices (GCP) [3] ensuring that there is a complete traceability and auditability of the data from the CRF until final database and statistical analysis. Monitoring ensures that correct data from the CRF are entered in the database, and as soon as the data are entered in the database, that there is a complete audit trail of these data (any update, change, deleting are traced). Any audit or regulatory inspection should be able to retrieve any statistical results from the raw data (CRF data).

The data management, statistical analysis and reporting of the data will be performed according to the international guidelines on clinical studies.

During the study, study statisticians are blinded to data related to the primary endpoints. The Statistical Analysis Plan is written in a blinded manner without seeing the data. The Statistical Analysis Plan has to be signed before the database lock and before receiving the final data for the analysis. As soon as the Statistical Analysis Plan is signed, all analyses described in the Statistical Analysis Plan have to be performed accordingly.

Full details of the statistical analysis will be given in the Statistical Analysis Plan (SAP). Any changes to the planned statistical methods will be documented in the CSR. The statistical evaluation will be performed using SAS®, version 9.2 or later.

12.1.1 Stratification Criteria

For the primary analysis of AAA annual growth rate, the following stratification criteria will be used:

- Aortic maximum-minor-axis diameter (male patients: < 40 mm and ≥ 40 mm; female patients: < 35 mm and ≥ 35 mm, using the CT scan made at V1 and assessed by the central reading site
- Sex (male vs. female)

Although smokers who had stopped smoking will be enrolled in the SC arm without randomization, they will be analyzed based on the defined stratification criteria. Additional stratified presentations (e.g., pack years of history of smoking) may be defined in the SAP.

12.1.2 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 CC 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). Further details will be described in the SAP.

12.1.3 Descriptive Statistics

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

For continuous data, summary statistics will include the number of patients [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. For categorical data, frequency counts and percentages will be presented.

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

For BoExp parameters:

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

For self-reported tobacco or nicotine-containing product use:

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

12.1.5 Significance Level for Inferential Analysis

This study is of exploratory nature and therefore no statistical hypothesis is to be tested.

12.1.6 Confidence Interval

All confidence intervals will be 95% CIs.

12.2 Determination of Sample Size

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 CC on the progression of disease. Patients will be enrolled/randomized per study arm.

12.3 Product Use

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 CC will exclusively use the randomized product at all times during the study. For instance, patients may concomitantly use IQOS and CC (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., CC 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 CC) will remain for the statistical analysis in the arm they have been randomized to.

12.4 Analysis Populations

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

Safety will be analyzed using the Safety Set.

12.4.1 Full Analysis Set (FAS)

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 CC 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 CC) use experience. The FAS will be analyzed by enrolled arm (randomization arm for CC or IQOS, or SC arm).

12.4.2 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.

12.5 Demographics and Baseline Characteristics

The demographic variables will be summarized by enrollment arm for the Full Analysis Set.. No inferential analyses will be presented for the demographics and baseline characteristics.

12.6 Primary Analysis

The primary analysis will be a descriptive analysis of patients who were randomized to IQOS use as compared to patients who were randomized to continue to smoke CC (IQOS arm versus CC arm) in the Full Analysis Set of AAA patients.

The primary endpoint is the comparison of the annualized mean growth rates in patients diagnosed with AAA between patients who were randomized to IQOS use and patients who continue to smoke CC. 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 maximum minor-axis AAA diameter will be summarized at each visit and overall (across all patients). The primary endpoint will also be summarized by strata (maximum-minor-axis AAA diameter, CC consumption, sex).

Study evaluation criterion:

This is a descriptive study, designed to gain an understanding on the effect of complete switching from cigarettes to IQOS use compared to continued CC smoking on the AAA growth rate and disease progression. Dual use of IQOS on top of CC will be also investigated. There are no formal statistical hypotheses to be tested.

Evaluation Criteria:

No formal evaluation criterion is applied since this is a descriptive study.

12.7 Secondary Analysis

Descriptive statistics for the maximum minor-axis AAA diameter will be summarized at each visit and overall (across all patients). The endpoints will also be summarized by strata (maximum-minor-axis AAA diameter, CC consumption, sex).

Urinary NEQ, and Total NNAL, Total NNN, and CEMA levels (concentration data adjusted for creatinine will be analyzed on a logarithmic scale) using an MMRM with the logarithmic transformation.

Descriptive statistics for the secondary endpoints shown below, will be summarized at each visit, except for vital signs (systolic and diastolic blood pressure) which will be summarized

every 12 months, by exposure group and overall (across all patients) in the FAS (unless otherwise defined):

- Time from diagnosis of AAA until open surgical AAA treatment or endovascular repair
- Time from diagnosis of AAA until AAA rupture
- Annual growth rate of AAA
- 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)
- Systolic and diastolic BP
- Body weight and waist circumference

For the secondary endpoints shown below, the number at each visit and overall (across all patients) will be described:

- Number of patients with open surgical AAA treatment or endovascular repair annually (based on date of decision to perform open surgical AAA treatment or AAA endovascular repair)
- Number of patients with a AAA rupture annually (based on date of AAA rupture)
- 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
-
- Incidence of IQOS malfunctions and misuses
- Number of tobacco products used, (including CC and HeatSticks) based on self-reporting

12.8 Safety Analysis

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. Adverse events data will serve as the primary assessment of safety.

The number and percentage of patients in the Safety Set with AEs and SAEs will be tabulated by using the MedDRA® system organ class (SOC) and preferred term (PT), summarized annually for the Safety Set. Summaries will also be presented for AEs leading to discontinuation of the patients due to AE, AEs leading to death, AEs by relatedness to CC or IQOS, and AEs by severity.

Incidence and frequency of concomitant medications and product events will be tabulated by study arms.

Tabulations will be performed for both the number of patients experiencing an event and the number of events.

The number and percentage of patients in the Safety Set with clinical findings will be tabulated by study arms and exposure group for laboratory safety parameters, ECG, physical examinations and vital signs. Shift tables showing change from Baseline of clinical findings will be provided for ECGs (for ECGs: change from Screening Visit (V1) used as Baseline), physical examinations, and laboratory parameters (both shifts in normal ranges and toxicity grades). Descriptive statistics will be summarized by visit and change from Baseline for laboratory parameters, ECG (for ECGs: change from Screening Visit (V1) used as Baseline), and vital signs (systolic and diastolic blood pressure will be summarized every 12 months).

Abnormal values of laboratory parameters will be shown in the listing. Individual laboratory parameters will be plotted over time.

12.9 Exploratory Analysis

Not Applicable.

12.10 IDMC Analyses

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.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

13.1.1 Investigators

See Appendix 5.

13.1.2 Sponsor

Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland Phone: +41 (58) 242 2111 Fax: +41 (58) 242 2811
Clinical Scientist	[redacted] PhD, Clinical Scientist [redacted]
Study Biostatistician	[redacted], Senior Scientist, Biostatistics, Study Biostatistician [redacted]
Medical Safety Officer	[redacted], MD, MSc, Medical Safety Officer

	[redacted]
Clinical Study Manager	[redacted], PhD, Associate Clinical Study Manager [redacted]

13.1.3 Other Responsibilities

[redacted] is the CRO designated by PMI to perform duties and have responsibilities transferred to [redacted] by PMI as defined in the agreement signed between the two parties. [redacted] does not have any interests in sponsor activities related to the Test Product (IQOS).

[redacted]

13.2 Patient Confidentiality

All information obtained during the conduct of the study with respect to the patients, and their state of health, will be regarded as confidential. A statement to this effect will be included in

the information provided to the patient. An agreement to disclose any such information will be obtained from the patient in writing and signed by the patient, in compliance with all local and national data protection and privacy legislation.

The anonymity of patients participating in this study will be maintained. Patients will be identifiable by the Sponsor (or Sponsor's authorized representative) on CRFs and other documents by their patient (or randomization) number/code, sex and date of birth, but not by name, initial, or any other details relating to an identifiable person (e.g., address, health insurance ID card, medical chart number, etc.). The assignment of a patient number/code for patient identification will be based on the appropriate data protection rules.

Any documents that allow full identification of the patient (e.g., the patient's signed study participation ICF) must be maintained in confidence by the Investigator. If any document relating to this study shows a patient's name or any other details relating to an identifiable person (e.g., address, health insurance ID card, medical chart number, etc.), the name or other identifiable details must be obscured before a copy of that document is supplied to the Sponsor or the Sponsor's authorized representative.

13.3 Access to Source Documentation

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

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

13.4 Record Retention

All records of data, source data and source documents (original records or certified copies), in any form (including, but not limited to, written, electronic, magnetic, optical records and scans) that describe or record the methods, conduct, and/or results of the study, the factors affecting the study, and the actions taken will be maintained by the Investigator/head of investigational site for the study, as required by ICH GCP and any other applicable local or national regulations.

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, are described in Article 41 of

Ministerial Ordinance on GCP (Ordinance of the Ministry of Health and Welfare No. 28 of March 27, 1997 (as last amended by the Ordinance of Ministry of Health, Labour and Welfare No. 161 of December 28, 2012). Essential documents must be retained by the Investigator/head of investigational site for a minimum of:

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

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

Examples of essential records/documents include, but are not limited to:

- Signed informed consent documents for all patients and study participation ICF.
- Patient identification code list, Screening Log and Enrollment Log (if applicable).
- Record of all communications between the Investigator and the IRB / IEC, composition of the IRB / IEC.
- Record of all communications/contact between the Investigator, Sponsor, and its authorized representatives.
- List of sub-Investigators and other appropriately qualified persons to whom the head of the investigational site has delegated significant study-related duties, together with their roles in the study.
- Investigator Logs.
- CRFs, study-specific questionnaires (and associated data/scoring), patient diaries.
- AE reports and details of follow-up investigations, details of concomitant medication.
- All other source documents or any electronically captured study source data.
- Original medical/hospital records, if applicable (the medical files of study patients must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital or study site).
- Record of any body fluids or tissue samples collected and retained.
- Device Issue Log, IP Accountability Logs, dispensing records.
- Information regarding patients' discontinuation and any follow-up.

It is the responsibility of the Sponsor to inform the Investigator/head of investigational site as to when these documents no longer need to be retained.

The Investigator/head of investigational site must take measures to prevent accidental or premature destruction of these documents.

If the head of the investigational site wishes to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

The head of the investigational site must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the Investigator's archives. If the head of the investigational site is unable to meet this obligation, they must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements must be documented.

The Sponsor will maintain documentation relating to the study as long as the IP is on the market and three years after its discontinuation or for 15 years after the CSR has been finalized whichever is longer.

13.5 Assessment Study Report

The Sponsor must ensure that a CSR for this study is prepared regardless of whether the study is completed or prematurely terminated, and whether the study succeeds to evaluate/describe the study objectives or not.

The CSR will be written based on standards of the ICH Guideline for the Structure and Content of Clinical Study Reports. In certain circumstances, an abbreviated CSR may be acceptable. Submission of the CSR to the IRB / IEC will be complied with as requested by local requirements.

The results of the additional variables for analysis will be presented in reports separate from the CSR.

13.6 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

13.7 Publication and Disclosure Policy

This document contains data, information and trade secrets that are confidential and proprietary to the Sponsor. This document is being provided solely for the purpose of evaluation and/or conducting this clinical study for the Sponsor. Disclosure of the content of this document is allowed only to study personnel, IRB / IEC, or duly authorized representatives of regulatory agencies for this purpose under the condition that confidentiality is maintained. The contents of this document may not be used in any other clinical study or disclosed to any other person

or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations; however, prompt notice will be given to the Sponsor prior to any such disclosure.

The Sponsor will disclose details of the study protocol as well as study results, according to applicable local regulations, on a web-based, publicly available, clinical trial register database (e.g., ClinicalTrials.gov).

13.8 Insurance

The Sponsor is responsible for AEs and health damage to the patients who are associated with the IQOS product which are used during the study, except for AEs and health damage to the patients caused by a negligent or an intentional misconduct and/or significant deviation to the protocol of the Investigator or the clinical study site or the patients. The Sponsor has taken out insurance to cover any bodily injury and property damage caused by the operations carried out by the insured.

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Appendix 1 Schedule of Events

	Screening Visit	Baseline	Investigational Period					
Visit (time window)	Visit 1	Visit 2	Visit 3 (± 14 days)	Visit 4 (± 14 days)	Visit 5 (± 14 days)	Visit 6 (± 14 days)	Visit 7 (± 14 days)	Visit 8 (± 14 days)
Study Month	Day -28 to Day -1	Day 1	6 months after Visit 2	12 months after Visit 2	18 months after Visit 2	24 months after Visit 2	30 months after Visit 2	36 months after Visit 2
Informed consent for study participation	●							
Information on the risk of smoking, SC advice [a]	●	●	●	●	●	●	●	●
IQOS demonstration [b]	●							
Debriefing on IQOS for smoking patients only	●	●	●	●	●	●	●	●
Inclusion/exclusion criteria	●	●						
Readiness to comply with study protocol	●	●						
Enrollment [c]		●						
Randomization procedures		●						
Allocation to study arms [d]		●						
Distribution of Diary		●						
Demographics, medical history (including history of recent and current alcohol and substance abuse)	●							
Concomitant diseases at V1, and follow-up of	●	●	●	●	●	●	●	●

	Screening Visit	Baseline	Investigational Period					
Visit (time window)	Visit 1	Visit 2	Visit 3 (± 14 days)	Visit 4 (± 14 days)	Visit 5 (± 14 days)	Visit 6 (± 14 days)	Visit 7 (± 14 days)	Visit 8 (± 14 days)
Study Month	Day -28 to Day -1	Day 1	6 months after Visit 2	12 months after Visit 2	18 months after Visit 2	24 months after Visit 2	30 months after Visit 2	36 months after Visit 2
concomitant diseases after V1								
Previous medication/Concomitant medication	●	●	●	●	●	●	●	●
Questions about smoking history/habits	●							
Intention to quit smoking in the next 6 months	●	●						
Tobacco or nicotine-containing product use self-reporting (1 month retrospective)			●	●	●	●	●	●
Urine: Pregnancy test (all females) [e]	●	●	●	●	●	●	●	●
Urine cotinine screening test in smoking patients [f]	●	●						
Urine cotinine screening test in former smokers [g]	●	●						
Vital signs [h]	●	●	●	●	●	●	●	●
Physical examination	●	●	●	●	●	●	●	●
Body height and weight [i]	●	●	●	●	●	●	●	●
Waist circumference [j]	●	●	●	●	●	●	●	●
Electrocardiogram	●			●		●		●
Chest X-ray [k]	●							
Retrospective CT scan evaluation	●							

	Screening Visit	Baseline	Investigational Period					
Visit (time window)	Visit 1	Visit 2	Visit 3 (± 14 days)	Visit 4 (± 14 days)	Visit 5 (± 14 days)	Visit 6 (± 14 days)	Visit 7 (± 14 days)	Visit 8 (± 14 days)
Study Month	Day -28 to Day -1	Day 1	6 months after Visit 2	12 months after Visit 2	18 months after Visit 2	24 months after Visit 2	30 months after Visit 2	36 months after Visit 2
from the 30 months prior to V1 [l]								
CT for abdominal aorta [m]	●		●	●	●	●	●	●
Record of the date when the decision of an open surgical AAA treatment or AAA endovascular repair is made			●	●	●	●	●	●
Blood/Urine: Hematology, clinical chemistry, urine analysis [n]	●	●	●	●	●	●	●	●
Urine: Total NNAL, Total NNN, NEQ, CEMA, creatinine in spot urine		●	●	●	●	●	●	●
AE/SAE recording [o]	●	●	●	●	●	●	●	●

Abbreviations: AAA = Abdominal Aortic Aneurysm; AE = Adverse event; CEMA = 2-Cyanoethylmercapturic Acid; CT = Computed Tomography; NEQ = nicotine equivalents, consisting of the molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine and trans-3'-hydroxycotinineglucuronide; NNAL = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol; NNN = N-nitrosonornicotine; SAE = Serious adverse event; SC = Smoking Cessation

a: Information on the risk of smoking and SC advice will be provided at every visit.

b: IQOS demonstration will be given to smoking patients only. For females, the demonstration will take place only after negative pregnancy test.

c: SC, IQOS, and CC arm = Enrollment at V2.

d: SC, IQOS and CC arm at V2.

e: Except post-menopausal women. The post-menopause is formally defined as the time after which a woman has experienced 12 consecutive months of amenorrhea (lack of menstruation) without a period. If a woman claims she is post-menopausal, but has had her menses within 12 months, a follicle stimulating hormone test must be performed and must be within acceptable limits of the post-menopausal status.

f: The cut-off value of urine cotinine Screening test in all smoking patients eligible for the CC and IQOS arms: ≥ 200 ng/ml.

g: The cut-off value will be < 100 ng/ml for former smoker patients eligible for the SC arm.

h: Systolic and diastolic blood pressure, pulse rate, and respiratory rate. Systolic and diastolic blood pressure will also be analyzed as cardiovascular risk factors at Visit 2 to Visit 8.

i: Including height (only at the Screening Visit). Body weight will also be analyzed as cardiovascular risk factor at Visit 2 to Visit 8.

j: Waist circumference will also be analyzed as cardiovascular risk factor at Visit 2 to Visit 8.

k: Chest X-ray performed within 6 months prior to V1 will be used for checking eligibility. If chest X-ray has not been performed, then it has to be performed.

l: All patients (SC arm, IQOS and CC arm) at V1.

m: CT scan made at V1 will be send to central reading site to provide the current the maximum minor-axis AAA diameter for assessment of eligibility at V2. The CT scan is recommended to be made as the last assessment at the end of V1 which can also be scheduled after V1.

n: Samples have to be taken after at least 10 hours of fasting, except at V1.

o: Spontaneous reporting of new AEs/SAEs by the patients and follow-up of ongoing AEs/SAEs by the site, as described in section 8.

Appendix 2 Participating Laboratories

The following laboratories will be used in the study:

Laboratory for analysis of NEQ, total NNAL, total NNN, CEMA, and creatinine in urine:	[redacted] Lincoln, NE 68502 USA Switzerland: [redacted] 8320 Fehraltorf Switzerland (referred to as [redacted])
Laboratory for the assessment of clinical chemistry, hematology, and urine analysis in the safety panel	[redacted] Tokyo 101-8517 Japan Telephone +81-[redacted]

Appendix 3 Investigational Product and Instructions for Use

The product user guide will be provided as a separate document.

Appendix 4 Standard protocol to assess the maximum minor-axis AAA diameter from the CT scan

The standard protocol to assess the maximum minor-axis AAA diameter from the CT scan will be provided in a separate document.

Appendix 5 List of Investigators and Study Sites

The list of Investigators and study sites will be provided in a separate document.