PMI RESEARCH & DEVELOPMENT

Clinical Study Protocol

P1-OHS-01-JP

Study title:	A 6-month randomized, controlled, open-label, 2-arm parallel group, multicenter study to evaluate the effect of switching from cigarette smoking to the use of IQOS in smokers with generalized chronic periodontitis on the response to mechanical periodontal treatment and oral health status.
Short name:	Effect of switching from cigarette smoking to the use of IQOS on periodontitis treatment outcome
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 version 4.0
Date :	09 January 2019
Author:	[redacted], PhD, Clinical Scientist [redacted] MD, Medical Safety Officer [redacted] PhD, Statistician

SUMMARY OF CHANGES

Clinical Study Protocol

P1-OHS-01-JP

	Version	Date	Amendment
Second updated protocol	4.0	09 January 2019	Non-substantial changes
First updated protocol	3.0	06 April 2018	Non-substantial changes
Original protocol	2.0	05 September 2017	

The main purpose of this above table is to summarize the updates between original clinical study protocol P1-OHS-01-JP (Final Version 2.0) dated 05 September 2017, its first updated version (Final Version 3.0) dated 06 April 2018, and its second updated version (Final version 4.0 dated 09 January 2019.

More precise details on the protocol sections changed are provided in the Appendix 5, with the list of changes, including the previous and the amended texts, as well as the reasons to change. The new text has been highlighted in bold (e.g. **new text**) and deleted text has been crossed out (e.g. ~~deleted text~~).

SYNOPSIS

Sponsor:

Philip Morris Products S.A.

Name of Product:

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

Study Title:

A 6-month randomized, controlled, open-label, 2-arm parallel group, multicenter study to evaluate the effect of switching from cigarette smoking to the use of IQOS in smokers with generalized chronic periodontitis on the response to mechanical periodontal treatment and oral health status.

Study Number:

P1-OHS-01-JP

Objectives and Endpoints

Primary Objective and Endpoint:

The primary objective of this study is:

To demonstrate the effect of switching to IQOS use compared to continued cigarette smoking on the response of pocket depth (PD) to mechanical periodontal therapy.

Endpoint (6 months):

Mean PD reduction in all sites with initial PD ≥ 4 mm after mechanical periodontal therapy.

Secondary Objectives and Endpoints:

The secondary objectives of this study are:

1. To evaluate the effect of switching to IQOS use compared to continued cigarette smoking on the response of PD and CAL to mechanical periodontal therapy over time.

   Endpoint:
   - Mean PD change in sites with initial PD ≥ 4 mm after mechanical periodontal therapy (3 months only).
   - Mean CAL change in sites with initial PD ≥ 4 mm after mechanical periodontal therapy (3 and 6 months).

2. To evaluate the differences of periodontal parameters in the response to periodontal therapy in patients who switch to IQOS use compared to those who continue to smoke cigarettes.

   Endpoints (3 and 6 months):
   - Change in mean full-mouth CAL
   - Change in mean full-mouth PD
   - Mean PD change in sites with initial PD < 4 mm, and with initial PD of 4 mm to < 5mm, 5 mm to < 6 mm, 6 mm to < 7 mm and ≥ 7 mm
   - Mean CAL change in sites with initial PD < 4 mm, and with initial PD of 4 mm to < 5mm, 5 mm to < 6 mm, 6 mm to < 7 mm and ≥ 7 mm
   - Change in the number of sites with PD < 4 mm, with PD 4 mm to < 5mm, with PD 5 mm to < 6 mm , with PD 6 mm to < 7 mm and with PD ≥ 7 mm
   - Change in gingival index (GI) score
   - Change in tooth mobility (grade)
   - Change in plaque control record (PCR)
   - Change in bleeding on probing (BOP) scores

3. To evaluate the levels of biomarkers of exposure (BoExp) over the exposure period in patients who switch to IQOS use and patients who continue to smoke cigarettes.

   Endpoint (3 and 6 months):
   - Urinary nicotine equivalents (NEQ), total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol (NNAL) and 2-cyanoethylmercapturic acid (CEMA).

4. To describe self-reported tobacco or nicotine containing product use over the duration of the study in patients switching to IQOS use and patients who continue to smoke cigarettes.

   Endpoint:
   - Number of self-reported tobacco or nicotine containing product use.

5. To monitor safety.

   Endpoint:
   - Incidence of adverse events (AEs)/serious adverse events (SAEs), including AEs related to device events, and device events, including device malfunction/misuse, over the duration of the study.

Exploratory objectives and Endpoints:

1. To determine quantitative changes in the inflammatory response by measuring pro-inflammatory and immuno-regulatory mediators in the gingival crevicular fluid (GCF) in patients switching to IQOS use compared to those continuing to smoke cigarettes.

   Endpoints (3 months):
   - Measurement of pro-inflammatory and immuno-regulatory mediators in the GCF [1]

2. To evaluate the microbiological status in patients switching to IQOS use compared to those continuing to smoke cigarettes. [2]

   Endpoint (6 months) :
   - Microbiological status from subgingival plaque (SP) samples.

3. To evaluate the transcriptomics profile of buccal swabs in patients switching to IQOS use compared to those continuing to smoke cigarettes. [2]

   Endpoint (3 and 6 months) :
   - Full transcriptomics profile assessment of buccal swabs derived from the right and left buccal mucosa.

Study Hypotheses:

The primary study hypothesis is that there will be a favorable difference in the mean PD at 6 months in IQOS users as compared to smokers who continue to smoke cigarettes in patients with generalized chronic periodontitis.

Evaluation criteria:

The study will substantiate that IQOS improves periodontitis if there is a statistically significant improvement in primary endpoint for smokers who switch to IQOS use as compared to smoker who continue to smoke cigarettes.

The secondary study hypotheses that will be tested in IQOS users and smokers are:

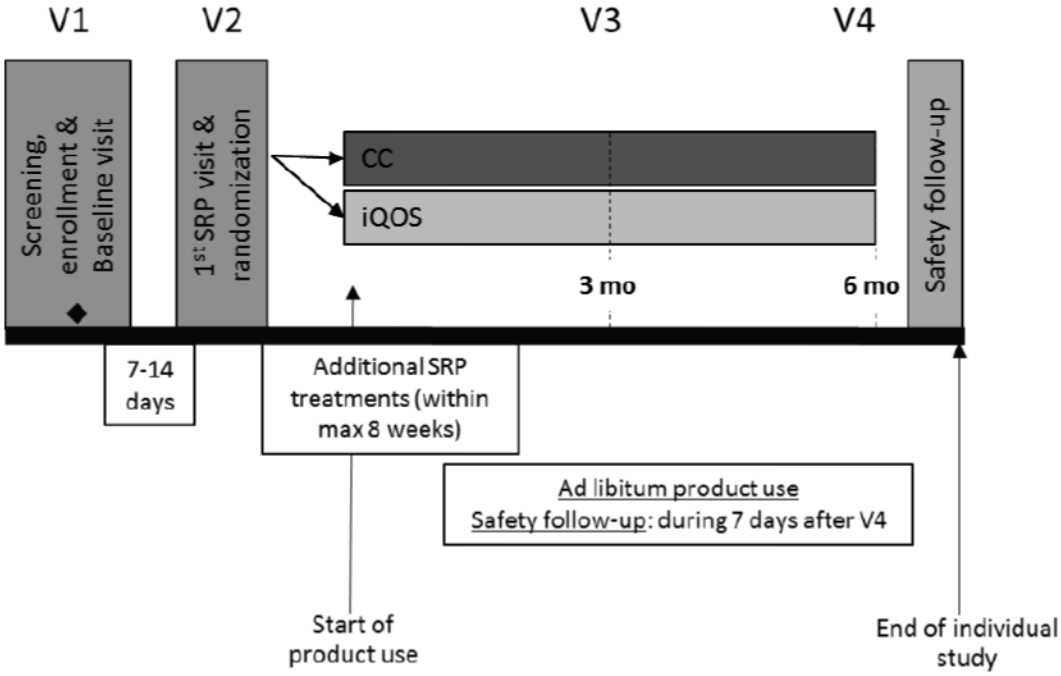
[1] sCD40L, CRP, EGF, Eotaxin/CCL11, Flt3 ligand, GM-CSF, GRO, IFNα2, IL-1α, IL-1β, IL-1Ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8/CXCL8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A/CTLA8, IP-10/CXCL10, MCP-1/CCL2, MCP-3/CCL7, MDC/CCL22, MIP-1α/CCL3, MIP-1β/CCL4, MMP-1, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13, osteoprotegerin, PDGF-AA, PDGF-AB/BB, RANKL, RANTES/CCL5, TGFα, TIMP-1, TNFα, TNFβ / LT-α, (please refer to the Abbreviations for full spelling).

[2] Results of these exploratory objectives will be reported in separate reports, and will not be part of the main clinical study report (CSR).

- That there will be favorable changes of PD at 3 months in IQOS users as compared to smokers who continue to smoke cigarettes in patients with generalized chronic periodontitis.
- That there will be favorable changes of CAL at 3 and 6 months in IQOS users as compared to smokers who continue to smoke cigarettes in patients with generalized chronic periodontitis.
- That there will be favorable changes at 3 and 6 months in total NNAL and CEMA levels in IQOS users as compared to smokers who continue to smoke cigarettes

Study Design:

This is a randomized, controlled, open-label, 2-arm, parallel group ambulatory study with the randomization stratified by daily cigarette consumption over the month (30 days) prior to Visit 1 (V1) (10-19 cigarettes/day vs. > 19 cigarettes/day) and disease severity recorded at Visit 1 (< 5 mm PD vs. ≥ 5 mm PD) based on the most severely diseased tooth, in smokers with generalized chronic periodontitis who are randomized to either switch from smoking cigarettes to IQOS use or continuing smoking cigarettes.



Abbreviations: SRP = Scaling and root planing

Figure 1 Study Flow Chart

All patients included in the study will be first advised that the best way of preventing further periodontal disease progression is to stop smoking as defined in the Japanese guidelines for periodontitis. Only patients who are not willing to quit smoking cigarettes are eligible for the study.

A sufficient number of patients with generalized chronic periodontitis will be screened and enrolled in order to randomize at least 172 patients. Enrollment occurs after checking that all eligibility criteria have been met.

Patients will be randomized using a stratified randomization with a 1:1 ratio into the IQOS or cigarette arms, and will be instructed to use their allocated product for 6 months study period. In each arm, a quota should be applied to ensure that patients with PD ≥ 5 mm represent at least 50% of the randomized patients. When 172 randomized patients are reached, further enrollment will be stopped. Patients already enrolled in the study may still be randomized. Arm assignment for patients with PD < 5 mm will be capped at n = 80, after which patients with PD < 5 mm will be considered as screen failure, while enrollment for PD ≥ 5 mm will continue until 172 patients are randomized and PD ≥ 5 mm represent at least 50% of the randomized patients. At this stage, patients' enrollment will be stopped and patients already

enrolled but not randomized may be discontinued.

- IQOS arm: ~86 patients, switching from cigarette smoking to IQOS use
- Cigarette arm: ~86 patients, continuing cigarette smoking

For each patient, standard of care procedures as defined by the Japanese guidelines on periodontal disease will be applied, and supplemented by additional assessments as per this study protocol. Patients will be encouraged to follow the recommended standard of care treatment as advised by the Investigator.

Study Population and Main Criteria for Inclusion:

Criteria for Inclusion:

A sufficient number of patients will be enrolled in order to randomize at least 172 patients meeting the following main inclusion criteria.

1. Patient is Japanese.
2. Informed consent form (ICF) has been signed.
3. Patient is aged ≥ 30 years old.
4. Patient has smoked on average at least 10 commercially available cigarettes per day (no brand restriction) for at least 5 years prior to Visit 1, based on self-reporting. Smoking status will be verified based on a urinary cotinine test (*i.e.*, cotinine ≥ 200 ng/mL).
5. Patient has at least 15 natural teeth (refer to Definition of Terms), excluding the teeth which need to be extracted or whose mobility grade is ≥ 3.
6. Patient has generalized chronic periodontitis *(i.e.*, more than 30% of diseased teeth with a PD ≥ 4 mm), considering only teeth that do not need to be extracted or whose mobility grade is < 3.
7. Patient does not intend to quit smoking during the study.
8. Patient is ready to comply with study procedures and to use the product he/she is allocated to for the duration of the study.

Criteria for Exclusion:

1. Patient has self-reported history of diagnosed systemic diseases (*e.g.*, stroke or acute cardiovascular event within the last 5 years, diabetes, active cancer), or any other conditions that in the opinion of the Investigator would jeopardize the safety of the participant or affect the validity of the study results.

2. Patient is legally incompetent, physically or mentally incapable of giving consent (*e.g.*, emergency situation, under guardianship, in a social or psychiatric institution, prisoner or involuntarily incarcerated).
3. As per the Investigator's judgment, patient cannot participate in the study for any reason (*e.g.*, medical, psychiatric and/or social reason).
4. As per the Investigator's or designee's judgment, patient has medical conditions which require or will require in the course of the study, a medical intervention (*e.g.*, start of treatment, surgery, hospitalization) which may interfere with the study participation and/or study results.
5. Patient has orthodontic appliances.
6. Patient received root planing therapy within the 6 months prior to V1.
7. Patient received surgical periodontal therapy within 3 years prior to V1.
8. Patient has identifiable premalignant changes of the oral mucosa at V1.
9. Patient was treated within the 3 months prior to V1 with systemic antibiotics or was treated with topical antibiotics applied in the mouth.
10. Continuous systemic use of steroidal or non-steroidal anti-inflammatory drugs for more than 20 days during the past 30-day period (except for low dose aspirin, *i.e.*, ≤ 300 mg, *e.g.*, for prevention of thrombus/embolus in angina pectoris, myocardial infarction, transient ischemic cerebrovascular accidents, bypass operations).
11. Patient has been previously screened or enrolled in this study
12. Female patients who are pregnant, breast-feeding, or planning a pregnancy within the course of the study.
13. Patient is a current or former employee of the tobacco industry or their first-degree relatives (parent and child).
14. Patient is an employee of the investigational site or any other parties involved in the study or their first-degree relatives (parent and child).
15. Patient has participated in a clinical study within 3 months prior V1.

Investigational Products; Dose and Mode of Use:

Test product: IQOS with *HeatSticks*. An IQOS starter kit (IQOS device and a selection of *HeatStick* flavor variants available on the Japanese market) will be supplied to the patient randomized to IQOS arm at the end of V2. Patient allocated to IQOS arm will be asked to buy his/her *HeatSticks* for his/her own use during the entire investigational period as *HeatSticks* will not be provided by the Sponsor. Patients will use IQOS *ad libitum* with no flavor restrictions.

Reference product: The patient's own preferred brand of commercially available cigarettes will not be provided by the Sponsor but purchased by the patients for their own use for the duration of the study. Patients will use *ad libitum* their preferred brand of commercially available cigarettes with no brand restrictions.

Study Duration:

The study duration per patient will be of maximum of up to 31 weeks, including a 1-day visit (V1), up to 2 weeks interval between V1 and V2, followed by a 6-month investigational exposure period, with 1-day visits after 3 and 6 months (V3, ± 7 days, V4, ± 14 days at each visit), and a 1-week safety follow-up period. The end of the study for an individual patient will be defined as V4 or the date of early termination plus the 7 days for the safety follow-up period. The end of the entire study is the latest date that an individual patient reaches the end of the study.

Statistical Methods:

The Full Analysis Set (FAS) will consist of all randomized patients (who have signed the ICF) who have at least post-randomization product use experience, and who have at least one valid non-safety assessment after randomization/enrollment.

The Per Protocol Set (PP) is the subset of the FAS who fulfill key compliance criteria of the protocol, and have no major protocol deviation that influences the evaluability of the study data.

As Exposed Set is the FAS analyzed by actual exposure.

The Safety Set will consist of all enrolled patients with at least one valid value for safety assessment analyzed by actual exposure.

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) for each product exposure, and summary across all patients. In addition, the results may be presented as a stratified summary as defined in the Statistical Analysis Plan (SAP).

The primary analysis will be performed on the As Exposed Set using a mixed model for repeated measures. The treatment by visit interaction term will be included in the model from which the p-values at each time point will be taken.

Sample Size:

The sample size needed to attain 80% power to show at least a 0.25 mm gain of PD in IQOS compared to the cigarette arm, using a one-sided test with 2.5% type I error probability, assuming a dropout rate of 15% and a 10% rate of patients not-adherent to product allocation. A total of 172 patients (86 in each arm) are required to be randomized.

Safety Assessments:

AEs (including SAEs) and device 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 device events will be collected from the time 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

Abbreviations

AE	Adverse event
BoExp	Biomarkers of exposure
BOP	Bleeding on probing
CAL	Clinical attachment level
CCL11	Chemokine (C-C motif) ligand 11
CEJ	Cementoenamel junction
CEMA	2-Cyanoethylmercapturic acid
CI	Confidence interval
CPI	Community Periodontal Index
CRF	Case report from
CRP	C-reactive protein
CV	Coefficient of variation
CRO	Contract research organization
CSF	Colony stimulating factor
CSF-2	Colony stimulating factor-2
CSR	Clinical study report
CTMS	Clinical Trial Management System
CXCL8	Chemokine (C-X-C motif) ligand 8
CXCL10	Chemokine (C-X-C motif) ligand 10
DMP	Data Management Plan
EGF	Epidermal growth factor
EOS	End of study
FAS	Full Analysis Set
FDA	Food and Drug Administration
Flt3 ligand	Fms-related tyrosine kinase 3 ligand
GCF	Gingival crevicular fluid
GCP	Good clinical practice
GI	Gingival index

GM-CSF	Granulocyte-macrophage colony-stimulating factor
GR	Gingival recession
GRO	Growth-regulated oncogene
HPHC	Harmful and potentially harmful constituents
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IFNα2	Interferon alpha-2
IL-1α	Interleukin-1 alpha
IL-1β	Interleukin-1 beta
IL-1Ra	Interleukin-1 receptor antagonist
IL-2	Interleukin-2
IL-3	Interleukin-3
IL-4	Interleukin-4
IL-5	Interleukin-5
IL-6	Interleukin-6
IL-7	Interleukin-7
IL-8/CXCL8	Interleukin-8/Chemokine (C-X-C motif) ligand 8
IL-9	Interleukin-9
IL-10	Interleukin-10
IL-12 (p40)	Interleukin-12 subunit p40
IL-12 (p70)	Interleukin-12 subunit p70
IL-13	Interleukin-13
IL-15	Interleukin-15
IL-17A/CTLA8	Interleukin-17A/Cytotoxic T lymphocyte associated antigen 8
IP	Investigational Product (*i.e.*, IQOS or cigarette)
IP-10/CXCL10	Interferon gamma-induced protein 10/Chemokine (C-X-C motif) ligand 10
IRB	Institutional review board
IXRS	Interactive Web and Voice Response System
LLOQ	Lower limit of quantification

LT-α	Lymphotoxin alpha
MAD	Median absolute deviation
MAP	Multiplex assay
MCP-1/CCL2	Monocyte chemoattractant protein 1/Chemokine (C-C motif) ligand 2
MCP-3/CCL7	Monocyte chemotactic protein 3/Chemokine (C-C motif) ligand 7
MDC/CCL22	Macrophage-derived chemokine/Chemokine (C-C motif) ligand 22
MIP-1α/CCL3	Macrophage inflammatory protein-1 alpha/Chemokine (C-C motif) ligand 3
MIP-1β/CCL4	Macrophage inflammatory protein-1 beta/Chemokine (C-C motif) ligand 4
MedDRA	Medical dictionary for regulatory activities
MMP-1	Matrix metalloproteinase-1
MMP-8	Matrix metalloproteinase-8
MMP-9	Matrix metalloproteinase-9
MMP-10	Matrix metalloproteinase-10
MMP-12	Matrix metalloproteinase-12
MMP-13	Matrix metalloproteinase-13
MMRM	Mixed model for repeated measurements
MRTP	Modified risk tobacco product
NEQ	Nicotine equivalents
NNAL	4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol
NNK	Nicotine-derived nitrosamine ketone
NRT	Nicotine replacement therapy
PCR	Plaque control record
PD	Pocket depth
PDGF-AA	Platelet-derived growth factor-AA
PDGF-AB/BB	Platelet-derived growth factor-AB/BB
PK	Pharmacokinetics
PMI	Philip Morris International
PP	Per protocol set
PRM	Parallel reaction monitoring

RANKL	Receptor activator for nuclear factor kappa B ligand
RANTES/CCL5	Regulated upon activation, normal T-cell expressed and secreted/C-C motif chemokine ligand 5
sCD40L	Soluble CD40 ligand
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SHM	Sample handling manual
SMP	Safety management plan
SOC	System organ class
SP	Subgingival plaque
SPI	Summary of product information
SRP	Scaling and root planing
TBI	Tooth brush instructions
TGFα	Transforming growth factor alpha
THS	Tobacco Heating System
TNFα	Tumor necrosis factor alpha
TIMP-1	Tissue inhibitor of metalloproteinases 1
TNFβ/LT-α	Tumor necrosis factor beta/Lymphotoxin-alpha
ULOQ	Upper limit of quantification
VEGF-A	Vascular endothelial growth factor-A
WHO	World Health Organization

Explanation of terms

The following special terms are used in this protocol:

Cigarette	The term 'cigarette' refers to commercially available cigarettes (manufactured) and excludes IQOS with *HeatSticks*, cigars, cigarillos, e-cigarettes, hand-rolled cigarettes pipes, hookah, bidis, and other tobacco- or nicotine-containing products.
Dental medical monitors	Co-primary contacts (dentists) for dental medical questions
End of study	The end of the study for an individual patient will be defined as Visit 4, or the date of early termination of the patient, plus the 7 days for the safety follow-up period. The end of the entire study is defined as the last individual patients' end of the study.
Enrollment	At V1 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* of Marlboro brands. No other tobacco sticks should be used with the IQOS device.
Investigator	Principal Investigator or sub-Investigator (dentist).
Maintenance treatment	Scaling, plaque control and occlusal adjustment as needed.
Medical expert	Dentist who is the primary contact for dental medical questions
Medical monitor	Medical doctor who answers any medical and safety questions from the Investigators.
Natural tooth	In this study, a natural tooth is defined as a tooth with its natural root, including a tooth with a crown. In the case of a dental bridge, the two teeth with the crowns holding the pontic are considered as natural teeth, while the pontic is not.

Periodontal assessment	Full mouth assessment of PD, CAL, BOP, tooth mobility, PCR, and assessment of gingival inflammation of the target teeth.
Randomization	After all assessments of V1 have been completed, patients will be randomized to IQOS or cigarette arm. Patients will be informed of their randomized study arm by the study site during V2. All patients will be instructed to continue to solely use their assigned product until they complete the study.
Safety follow-up	After the day of Discharge at V4, patients will enter into a 7-day safety follow-up for the recording of spontaneously reported new AEs/SAEs and the follow-up of ongoing AEs/SAEs by the study site.
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.
Target site	The site of a target tooth, preferably the deepest of the tooth, from which the GCF will be collected.
Target tooth	At V1, for all eligible patients, the Investigator or designee will designate 4 target teeth, *i.e.*, preferably one per quadrant. Teeth with PD ≥ 5 mm but < 7 mm will be preferably selected. If their location does not correspond to one per quadrant, the Investigator or designee will designate the target teeth preferably as single-rooted, and distributed as evenly as possible. Target teeth identification will be reported in the CRF.

1 ETHICS AND REGULATIONS

1.1 Institutional Review Board (IRB) Approval

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent forms [ICFs] including both patient information sheet and consent form, patient recruitment procedures [*e.g.*, advertisements], written information to be provided to the patients, Summary of Product Information [SPI] [1], available safety information, the Principal Investigator's curriculum vitae and/or other evidence of qualifications, the list of sub-Investigators and any other documents requested by the Institutional Review Board [IRB]), will be submitted for review and approval to the relevant IRB. The IRB 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) 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 approval should be provided to the Sponsor and the Investigator. This should identify the study (Principal Investigator's name, study number and title) and the documents that have been approved by the IRB, with dates and version numbers, as well as the date of approval. The composition of the IRB, 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 will be filed in the Investigator Site File and 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.

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

These requirements for approval should in no way prevent any action from being taken by the Principal 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 should be informed immediately.

Relevant safety information will be submitted to the IRB 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 [2], 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) [3], in the Declaration of Helsinki [4] and other applicable regulation. Prior to the initiation of any study procedures, the protocol will be approved by an IRB 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, 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. 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 Principal 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 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 Principal 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

Based on the most recent classification system developed by the American Academy of Periodontology, there are at least eight categories of periodontal diseases and conditions [5]. Of these, the two most common are gingivitis and chronic periodontitis. Periodontal disease is characterized by a non-resolving inflammatory response of the human host to a lasting bacterial infection of the gingiva leading first to gingivitis, followed by connective tissue damage, destruction of the periodontal ligament and alveolar bone loss surrounding the teeth, ultimately leading to tooth loss [6, 7]. The involvement of dental plaque in the development of gingivitis and periodontal diseases is well-recognized as evidenced by several epidemiological studies [8, 9]. Furthermore, periodontal disease is associated with an increased risk in systemic diseases such as cardiovascular disease, diabetes, respiratory disease as well as various types of cancer (neck and head, breast, pancreas, colorectal and lung cancer) and cancer risk overall [8, 10-16]. The prevalence of severe periodontal disease (i.e., when a patient had at least one site with a pocket depth (PD) ≥ 6 mm) was up to 10% in Japan, China, Brazil, Denmark, Poland, Norway and more than 20% in the populations of Bangladesh, Canada, Germany, India, Belarus and Chile as reported by the World Health Organization (WHO) [17].

Gingivitis is the first, reversible stage of periodontal diseases, and is characterized by symptoms such as red, swollen and painful gums, gums that bleed easily while brushing and flossing and a receding gum line. The modified gingival index (GI) developed by Lobene et al. [18], is a good indicator of gingival health, and reducing it would eventually lead to reduced risk of developing periodontal disease. This index is robust, and can change upon short period of times. When the gingival inflammation process is not stopped, gingivitis usually progresses to periodontitis. The assessment of periodontitis is determined through a complete clinical examination, and the measurement of clinical attachment level (CAL). CAL is calculated by adding the periodontal PD and the gingival recession (GR) from the cementoenamel junction (CEJ) as a fixed reference point. During full periodontal assessment, CAL and PD are recorded at 6 sites per tooth, using graduated periodontal probes. Bleeding after probing is noted after recording the PD for each site. Tooth mobility is graded from 0 to III following the method described by Miller [19] and plaque control record (PCR) is often assessed following the method described by O'Leary et al. [20].

The oral cavity is the first part of the human anatomy to be exposed to mainstream smoke in active smokers and consequently smoking has been shown to be a significant risk factor for periodontal disease and tooth loss [21-24]. The association is robust across a wide range of case definitions, populations, and study designs [8]. There is also evidence of a dose-response relationship between smoking intensity and the risk for periodontitis [24, 25]. Both, the number of cigarettes smoked and the duration of smoking are positively associated with disease risk. The magnitude of the relative risk estimates for periodontal disease associated with smoking

varies from 1.4 to 5.0 in different studies [24]. In Japan, based on data from the Survey of Dental Diseases and the National Nutrition Survey in 1999, the prevalence of periodontal disease was shown to vary significantly by smoking status with 39.3%, 49.5% and 47.3% with a Community Periodontal Index (CPI) > 3 (moderate periodontal disease) and 7.9%, 11.7% and 12.4% with a CPI > 4 (severe periodontal disease), for non-smokers, former smokers and current smokers, respectively [22]. The lack of difference between former and current smokers in this study can likely be explained by the lack of data on time since cessation. A study in Korea has indeed shown that the prevalence in former smokers becomes similar to never smokers only if cessation occurred since more than 10 years [26]. In a Japanese study, the odds ratio of having periodontitis, among current smokers compared with those whom had never smoked was 1.74 [27]. A cross-sectional study in Brazil showed a significant dose-response relationship between pack-years of smoking and periodontitis prevalence, as well as a significant decrease in the risk of periodontitis as years of smoking cessation increased [28]. Periodontal disease affects not only the gums, but also the connective tissues and bone that surround and support the teeth, thus chronic periodontitis affects tooth mobility, and eventually tooth loss. Tooth mobility, as assessed by the method of Miller [19] is a good predictor of tooth loss. Tooth loss has been shown to be associated in a dose-dependent manner with smoking [24]. It may take up to 20 years of smoking cessation to decrease the excess risk of tooth loss to the levels of never smokers. Plaque has been shown to be more present in smokers than non-smokers, however, after mechanical treatment, plaque control record, as assessed by the method of O'Leary et al. [20], is often sufficient to decrease the plaque of smokers to levels of non-smokers or quitters.

The likely mechanism for the increase in periodontal disease prevalence in active smokers is that smoking alters the inflammatory host response, with increasing cytokine and inflammatory mediator release and therefore negatively impacts the reparative and regenerative potential of the periodontium and the cell lining of the oral cavity in general [21, 29]. Pro-inflammatory cytokines can be assessed from the gingival crevicular fluid (GCF) of diseased teeth, as described by Tymkiw et al. [29], and serve as markers for inflammation [29]. In periodontitis, clinical parameters, including PD and CAL, were found to be increased in smokers compared to non-smokers (reviewed in [30]). On the other hand, it has been shown that bleeding on probing (BOP) and inflammatory response associated with plaque accumulation are reduced or delayed in smokers compared to never smokers [31-33] . The volumes of gingival cervicular fluid [34] are also less in smokers, like the gingival blood flow [35]. Furthermore, in smokers, signs and symptoms of gingivitis, such as bleeding, erythema and edema, are often less pronounced than in non-smokers [34, 35]. Gingival inflammation, as evaluated by the GI of Löe and Silness [36], is also lower in smokers than non-smokers [37].

Additionally, smokers are more likely to incur dose-dependent quantitative and qualitative differences in the subgingival microflora (*i.e.*, infection with *Porphyromonas gingivalis* and *Tannerella forsythia*, formerly called *Bacteroides forsythus*) compared to former and non-

smokers [38]. The presence of the three "red complex species" (*i.e.*, *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola*), which are recognized as the most important pathogens in adult periodontal disease [39], was shown to be a predictor of higher attachment loss [40]. A study on subgingival microbiome showed that smokers have a highly diverse, pathogen-rich and commensal-poor, anaerobic microbiome, and that the smoking status supersedes the influence of genotypic factors such as ethnicity on the microbiome [41].

Only a few longitudinal studies have assessed the outcome of periodontal disease after smoking cessation, but they indicate that the recovery in PD, and to a lesser extent in CAL, after non-surgical treatment is more successful in those who quit smoking [42-46]. Studies in smokers, non-smokers and former smokers indicate that smoking cessation has a beneficial effect on the outcome of periodontal treatment and thus that the negative impact of tobacco use on periodontal disease is reversible, within a time frame of a few weeks to a few years, depending on the clinical endpoint assessed [32, 33, 42, 47-49]. Volumes of GCF and gingival blood flow are increased within two months of smoking cessation [35]. Such findings can likely be explained by the effect of nicotine or its metabolites, that acts as a peripheral constrictive action on gingival vessels, but also potentially because of an increase of oral mucosa epithelium thickness in smokers [50, 51].

The first line of treatment in periodontal diseases is to restore a healthy periodontium, by instructing the patients on how to increase their oral hygiene, and by mechanically removing supra and subgingival plaque (SP) and calculus deposits (also called scaling and root planing, SRP), with or without antibiotic treatment [52]. In more severe cases, or cases that do not resolve after non-surgical intervention, surgery will be performed. In addition, dental and healthcare associations, such as the World Health Organization [53] and Japanese Society of Periodontology , all support professional education related to the importance of primary prevention of tobacco use and recommend cessation as an intervention for oral health diseases [54, 55]. Nicotine replacement therapy (NRT) is proposed to patients who are willing to quit smoking to reduce the withdrawal effects [56-59].

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 cigarettes and (2) are accepted by smokers as substitutes for cigarettes.

More than 6000 smoke constituents have been identified when the tobacco is burned or combusted [60], and more than 100 of them have been categorized as harmful and potentially harmful constituents (HPHCs) [61]. 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 (*HeatSticks* of Marlboro brand) within a precisely

controlled temperature range (far lower temperatures than cigarette) rather than burning it. IQOS replicates the ritual of smoking but without combustion. [60, 61].

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. A Charger allows to recharge the Holder after each use. Unlike cigarettes, 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 cigarette, 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 [3]. 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 cigarette smoke. Results from pre-clinical *in vivo* studies comparing cigarette 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 cigarette smoking [62, 63]. Furthermore, exposure to IQOS aerosol in mice does not enhance cardiovascular disease or emphysema, as cigarette smoke does, and switching from cigarette smoke to IQOS aerosol exposure halts of *e.g.*, aortic plaque growth in a similar manner as smoking cessation [64, 65]. Recent non-clinical data on human organotypic buccal epithelial cultures demonstrated that acute exposure to IQOS aerosols, when compared to cigarette smoke, had overall a significantly lower impact on buccal epithelial physiology [66]. Unlike cultures exposed to cigarette smoke, IQOS aerosol-exposed cultures showed no cytotoxicity, regardless of exposure, concentration, or time, and tissue damage was minimal, with no apical keratinization, intracellular granular structure, or loss of structural integrity. Furthermore, levels of pro-inflammatory mediators were significantly modulated in cigarette smoke-exposed cultures (*e.g.*, increased VEGF-A, TGFα, MMP-1, IL1β and decreased Chemokine [C-X-C motif] ligand 10 [CXCL10], Chemokine [C-X-C motif] ligand 8 [CXCL8], CSF-2, and IL-6) and to a much lesser extent in IQOS.

Several clinical studies have been conducted with IQOS, in Europe, Asia and the United States, in order to evaluate the nicotine pharmacokinetics (PK) profile [67-70], to demonstrate reduced exposure [71-74], and to determine functional and biological changes when adult smokers

[3] 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

switch from cigarettes to IQOS use compared to smokers continuing smoking cigarettes [73, 74]. The PK studies demonstrated similar nicotine absorption in subjects using IQOS and subjects smoking cigarettes. The Reduced Exposure studies showed reductions in the levels of biomarkers of exposure (BoExp) to selected HPHCs, in subjects using IQOS compared to subjects continuing smoking cigarettes 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.

A 6-month exposure study [75], followed by a 6-month extension study [76], with the specific aim to demonstrate favorable changes in clinical risk endpoints in smokers switching from cigarettes to IQOS compared to smokers continuing smoking cigarettes is ongoing. Post-marketing studies are ongoing, in order to have a better understanding of the product use behaviors and first insights in health outcomes [77]. Safety data available to date show a similar short-term safety profile for IQOS than for cigarettes. PMI is now launching a series of new clinical studies to better understand whether switching to IQOS can have beneficial effects on health outcomes. Because of the effects of smoking on oral diseases (such as periodontitis), this study is part of this program.

Further product information can be found in the SPI [1].

2.2 Purpose of the Study

The purpose of this study is to demonstrate in patients with generalized chronic periodontitis that switching from smoking cigarette to using IQOS improves the response to periodontal therapy and the overall oral health status compared to continuing cigarette smoking.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

Advice on health risk associated with tobacco smoking and smoking cessation advice will be provided at V1 and then at each visit from V2 to V4 as per Japanese guideline for treatment of periodontal disease [78]. The advice will follow the recommendations of the Japanese Circulation Society [79] and of the Ministry of Health, Labour and Welfare [80]. Patients who are motivated to quit using tobacco-containing products (*e.g.*, IQOS and cigarette) are to be referred for additional smoking cessation counselling by their General Practitioner. Patients who participate in this study will also benefit from repeated, detailed oral check-ups, which may help to increase efficacy of periodontal therapy.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures

The risk of procedures (*e.g.*, periodontal examination, standard of care, GCF, buccal swabs and SP collection) are deemed to be on par with procedures routinely performed during normal or extended buccal examinations by the patient's dentist.

2.3.3 Anticipated Foreseeable Risks due to Investigational Products

A substantial body of evidence already exists on IQOS and its development product, Tobacco Heating System (THS) (please refer to SPI [81]). Adverse events (AEs) reported so far seem to be mostly in line with the side effects that can be observed while using 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 cigarettes. Mitigation will include close monitoring and medical supervision to detect any unforeseeable risks or safety signals at the earliest time possible.

3 STUDY OBJECTIVES

3.1 Primary Objective and Endpoint

The primary objective of this study is:

To demonstrate the effect of switching to IQOS use compared to continued cigarette smoking on the response of PD to mechanical periodontal therapy.

Endpoint (6 months):

- Mean PD reduction in all sites with initial PD ≥ 4 mm after mechanical periodontal therapy.

3.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

1. To evaluate the effect of switching to IQOS use compared to continued cigarette smoking on the response of PD and CAL to mechanical periodontal therapy over time.

   Endpoint (3 and 6 months):

   - Mean PD change in sites with initial PD ≥ 4 mm after mechanical periodontal therapy (3 months only).
   - Mean CAL change in sites with initial PD ≥ 4 mm after mechanical periodontal therapy (3 and 6 months).

2. To evaluate the differences of periodontal parameters in the response to periodontal therapy in patients who switch to IQOS use compared to those who continue to smoke cigarette.

   Endpoints (3 and 6 months):

   - Change in mean full-mouth CAL
   - Change in mean full-mouth PD
   - Mean PD change in sites with initial PD < 4 mm, and with initial PD of 4 mm to < 5 mm, 5 mm to < 6 mm, 6 mm to < 7 mm and ≥ 7 mm
   - Mean CAL change in sites with initial PD < 4 mm, and with initial PD of 4 mm to < 5 mm, 5 mm to < 6 mm, 6 mm to < 7 mm and ≥ 7 mm
   - Change in the number of sites with PD < 4 mm, with PD 4 mm to < 5 mm, with PD 5 mm to < 6 mm , with PD 6 mm to < 7 mm and with PD ≥ 7 mm
   - Change in GI score
   - Change in tooth mobility (grade)
   - Change in PCR
   - Change in BOP scores

3. To evaluate the levels of BoExp over the exposure period in patients who switch to IQOS use and patients who continue to smoke cigarettes.

   Endpoint (3 and 6 months):
   - Urinary nicotine equivalents (NEQ), total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol (NNAL), and 2-cyanoethylmercapturic acid (CEMA).

4. To describe self-reported tobacco or nicotine containing product use over the duration of the study in patients switching to IQOS use and patients who continue to smoke cigarettes.

   Endpoint:
   - Number of self-reported tobacco or nicotine containing product used.

5. To monitor safety

   Endpoint:
   - Incidence of AEs/serious adverse events (SAEs), including AEs related to device events, and device events, including device malfunction/misuse, over the duration of the study.

3.3 Exploratory Objectives and Endpoints

1. To determine quantitative changes in the inflammatory response by measuring pro-inflammatory and immuno-regulatory mediators in the GCF in patients switching to IQOS use compared to those continuing to smoke cigarettes.

   Endpoints (3 months):
   - Measurement of pro-inflammatory and immuno-regulatory mediators in the GCF [4].

2. To evaluate the microbiological status in patients switching to IQOS use compared to those continuing to smoke cigarettes. [5]

   Endpoint (6 months):
   - Microbiological status from SP samples.

[4] sCD40L, CRP, EGF, Eotaxin/CCL11, Flt3 ligand, GM-CSF, GRO, IFNα2, IL-1α, IL-1β, IL-1Ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8/CXCL8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A/CTLA8, IP-10/CXCL10, MCP-1/CCL2, MCP-3/CCL7, MDC/CCL22, MIP-1α/CCL3, MIP-1β/CCL4, MMP-1, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13, osteoprotegerin, PDGF-AA, PDGF-AB/BB, RANKL, RANTES/CCL5, TGFα, TIMP-1, TNFα, TNFβ / LT-α, (please refer to the Abbreviations for full spelling).

[5] Results of these exploratory objectives will be reported in separate reports, and will not be part of the main clinical study report.

3. To evaluate the transcriptomics profile of buccal swabs in patients switching to IQOS use compared to those continuing to smoke cigarettes. [6]

   Endpoint (3 and 6 months):

   - Full transcriptomics profile assessment of buccal swabs derived from the right and left buccal mucosa.

[6] Results of these exploratory objectives will be reported in separate reports, and will not be part of the main clinical study report.

4 OVERALL STUDY DESIGN AND PLAN

This is a randomized, controlled, open-label, 2-arm, parallel group ambulatory study with the randomization stratified by daily cigarette consumption over the month (30 days) prior to V1 (10-19 cigarettes/day vs. > 19 cigarettes/day) and disease severity record at V1 (< 5 mm PD vs. ≥ 5 mm PD) based on the most severely diseased tooth, in smokers with generalized chronic periodontitis who are randomized to either switch from smoking cigarettes to IQOS use or continuing smoking cigarettes (Figure 2). Disease severity classification is based on the site having the most severe condition. Patients with a mild disease as per the inclusion criteria will not be eligible for this study.

All patients included in the study will be first advised that the best way of preventing further periodontal disease progression is to stop smoking as defined in the Japanese guidelines for periodontitis. Only patients who are not willing to quit smoking cigarettes will be eligible for the study. The patients who quit smoking or using IQOS or those who quit smoking and start using IQOS will not be discontinued from the study, will receive their financial compensation and will come at all scheduled visits for assessments.

A sufficient number of patients with generalized chronic periodontitis will be screened and enrolled in order to randomize at least 172 patients. Enrollment occurs after checking that all eligibility criteria have been met.

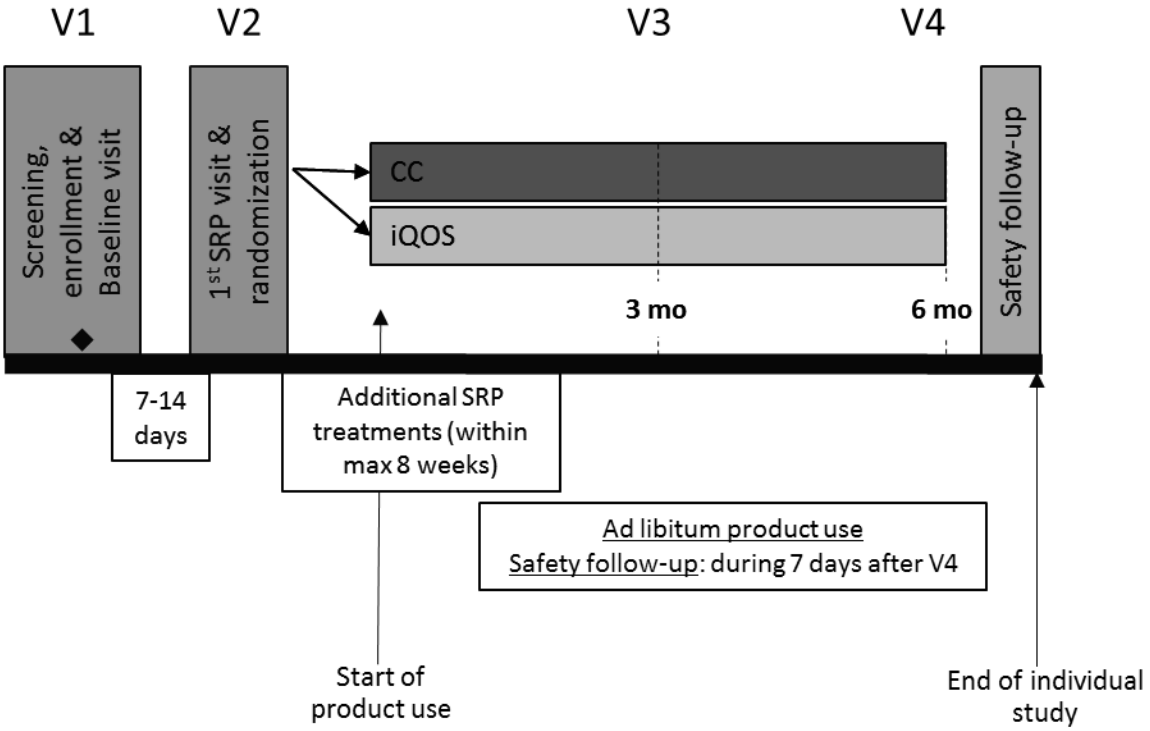
Patients will be randomized using a stratified randomization with a 1:1 ratio into the IQOS or cigarette arms and will be instructed to use their allocated product for 6 month study period. In each arm, a quota should be applied to ensure that patients with PD ≥ 5 mm (based on the most severely diseased tooth) represent at least 50% of the randomized patients (section 6.3). When 172 randomized patients are reached, further enrollment will be stopped. Patients already enrolled in the study may still be randomized. Arm assignment for patients with PD < 5 mm will be capped at n = 80, after which patients with PD < 5 mm will be considered as screen failure, while enrollment for PD ≥ 5 mm will continue until 172 patients are randomized and PD ≥ 5 mm represent at least 50% of the randomized patients. At this stage, patients' enrollment will be stopped and patients already enrolled but not randomized may be discontinued.

- IQOS arm: ~86 patients, switching from cigarette smoking to IQOS use
- Cigarette arm: ~86 patients, continuing cigarette smoking

From V2 onwards, information on the risks of the use of tobacco containing products and advice to quit smoking will be given to the patients at every visit.

Any patient, who is willing to attempt quitting during the study will be encouraged to do so and will be referred to appropriate medical services. The patient will not be discontinued from

the study, but will continue to come for the scheduled visits, and this will not affect his/her financial compensation.



Abbreviations: SRP = Scaling and root planing

Figure 2 Study Flow Chart

From V2 to V4, patients will be asked not to drink, eat, chew gum, or use mouth rinse or brush their teeth for at least 30 minutes before collection of oral samples *(i.e.*, SP, GCF or buccal swabs).

For each patient, standard of care procedures as defined by the Japanese guideline on periodontal disease will be applied [78], including occlusal adjustment or toothbrush instructions, and supplemented by additional assessments as per this study protocol. Patients will be encouraged to follow the recommended standard of care treatment as advised by the Investigator. Any other dental treatments required for the safety of patient which are different from the one required in this protocol during the study will also be performed, as per Investigator's decision. All screen failure and all patients discontinued from the study will be advised by the Investigator to follow-up with their dentist for further dental care.

AEs/SAEs, including AEs related to device events, device events, pregnancies and concomitant medications will be part of the examination and recorded throughout the study. In addition standard of care procedures and procedures related to the assessments throughout the whole study duration, starting from ICF signature until end of study (EOS) will also be recorded. Patients identified by the site as potentially eligible will be provided with the information about the study and if interested, and they will be invited to the screening Visit (V1) by the site. The ICF can be distributed to these potential patients before V1.

Screening, enrollment & baseline, periodontal assessment, and SP collection (V1)

Patients will sign the ICF before the start of any study procedure, and will enter screening. All eligibility criteria will be checked, including periodontal assessment, which will be also used as baseline assessment for enrolled patients (Appendix 1). Patients who meet the eligibility criteria will be enrolled. Patients who do not meet the eligibility criteria will be considered as screen failures, and their urine samples will be discarded at the end of the visit.

After enrollment, the remaining baseline assessments will be conducted (Appendix 1). Target teeth (see Definition of terms) will be designated by the Investigator or designee and will be identified in the source documents and in the case report form (CRF). Sampling of SP for microbiological status on 4 target teeth will be performed (Appendix 1).

At this visit, a first supragingival scaling treatment will be performed, and occlusal adjustment will be implemented as needed. Patient will be provided with toothbrush instructions (TBI) and will be instructed to continue this method throughout the whole study.

After all assessments of V1 have been completed, patients will be randomized to 1 of the 2 study arms; continued cigarette smoking or IQOS use. Patients will be informed about their study arm allocation at V2.

1st SRP visit, GCF and buccal swabs collection (V2/Day 1)

This visit will be scheduled 7 to 14 days after V1. GCF and buccal swabs collection will be conducted before any periodontal assessment. PD, tooth mobility and BOP will be assessed before the SRP treatment as per standard of care, but will not be recorded in the CRF.

The first SRP treatment will be performed on teeth with PD $\geq$ 4 mm and with the most severely diseased tooth. The following SRP treatments will be performed in subsequent visits as agreed and scheduled between the site and the patient. As the number and timing of the visits is flexible, the data will be captured in the CRF as “unscheduled” SRP visits. All SRP treatments must be completed within 8 weeks after V2.

Patients will be informed of their randomized study arm during this visit and can start using their allocated product after the randomization. All patients will be instructed to use their assigned product until they complete the study. Patients randomized to the IQOS arm will

receive an IQOS starter kit which includes an IQOS device and a selection of *HeatStick* flavor variants available on the Japanese market. All patients will purchase their own product during the course of the study (no brand or flavor restrictions). During the study, switching to different cigarette brands or different IQOS devices or *HeatStick* flavor variants will be allowed.

The Investigational period (from V3 to V4)

V3 will be scheduled with a flexibility of ± 7 days, and V4 with a flexibility of ± 14 days. The 3 and 6 months visits (*i.e.*, V3 to V4) will be scheduled according to the randomization visit (V2).

3 months, periodontal assessment & maintenance visit, GCF and buccal swabs collection

Patients will come to the site for periodontal assessment (Appendix 1), including GCF collection from the same 4 target sites than at V1, and collection of buccal swabs. Maintenance treatment will be provided as needed.

6 months, periodontal assessment & maintenance visit, SP and buccal swabs

Patients will come to the site for periodontal assessment (Appendix 1). Sampling of SP for microbiological status from the same 4 target teeth than at V1 will be performed. Buccal samples will also be collected. Maintenance will be provided as needed.

At the end of V4, patients will be discharged from the study. Procedure of discharge will include urine pregnancy test for all females (irrespective of age), as well as recording of AEs/SAEs or device events. For patients who terminate the study earlier, the same procedure of discharge will apply.

Safety Follow-up Period

After the procedures of discharge, patients will enter a 7-day Safety Follow-up Period. Any non-serious AE that is ongoing during the Safety Follow-up Period will be passively followed-up by the Investigator during that period until it has been resolved, stabilized (*i.e.*, no worsening of the condition), or an acceptable explanation has been found (*e.g.*, a chronic condition). At the end of the Safety Follow-up Period, all ongoing non-serious AEs will be documented as "ongoing" and no follow-up information will be sought for on 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 for further follow up. All SAEs will be actively followed up by the Investigator, despite their continuation after the end of the Safety Follow-up 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).

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 even if unscheduled and document the reason for the visit. For the SRP treatments, there is one required visit within the study procedures, and all additional visits that are required to complete the SRP treatment must be recorded as "unscheduled" SRP visits.

4.1 Rationale for Study Design and Control Group(s)

PMI is now launching a series of new clinical studies to better understand whether IQOS can have beneficial effects on health outcomes. Because of the well-known adverse effects of smoking on oral diseases (such as periodontitis), this study is part of this program. The overall objective of the IQOS design is to provide an acceptable alternative to current, adult smokers, with substantial reduction of exposure to HPHCs by its aerosol compared to cigarette smoke.

The purpose of this study is to demonstrate in patients with generalized chronic periodontitis that switching from smoking cigarette to using IQOS improves the response to periodontal therapy and the overall oral health status compared to continuing cigarette smoking. IQOS could then become an alternative to cigarettes for smokers with periodontitis who cannot stop smoking.

Further product information on IQOS can be found in the SPI [81].

The minimum age of 30 years old in the inclusion criteria was selected based on:

- The likelihood to develop chronic periodontal disease, 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 use of IQOS on the healing of periodontal disease after mechanical treatment compared to the use of cigarettes.

The healing of periodontal disease, as measured by the amelioration of different periodontal assessments, such as reduction in PD, has been shown to be influenced by smoking (reviewed in [30]). Other parameters measured, such as GI, tooth mobility, PCR and BOP will further illustrate potential benefits of switching to IQOS on the overall oral health, even though parameters such as CAL or tooth mobility may need more than 6 months to change favorably. Smokers have often reduced gingival inflammation, BOP and decreased volume of GCF [35],

probably due to the vasoconstrictive action of nicotine on gingival vessels. Because IQOS delivers nicotine, but much reduced levels of other HPHCs, this study may help to differentiate the effects of nicotine vs the effects of HPHCs. To investigate this, it is planned to collect 1) GCF samples, to measure inflammatory components of this oral fluid when switching to IQOS compared to continuing using cigarettes, 2) buccal swabs, to perform an RNA profiling of those cells which are directly exposed to cigarette smoke or IQOS aerosol; and 3) SP samples, to assess the change of the oral microbiome when switching to IQOS compared to patients continuing using cigarettes. The analyses of GCF and buccal swabs will help to better understand the underlying mechanism of the diseases related to cigarette smoke.

The study will follow a two parallel arm randomization design with the following strata: 1) daily cigarette consumption over the month prior to V1 and 2) PD in smokers with generalized chronic periodontitis [78]. This selection is based on the fact that: 1) the degree of smoking exposure is related to the severity of periodontal destruction [25, 82] 2) pre-treatment depth of PD and CAL have been shown to affect response of therapy [83, 84].

The choice of the primary and secondary objectives are based as a selection of 1) the most published assessment, *i.e.*, reduction of PD, which has been shown to occur rather rapidly after mechanical therapy (*i.e.*, within 3 to 6 months) and is more representative of the overall inflammation, 2) the most clinically relevant endpoint, *i.e.*, CAL change, which is more representative of tissue destruction, and is thus determinant in the increased risk of tooth loss. Data on CAL change in smokers vs non-smokers or quitters, are, however, sparser than data on PD. The assessment of both parameters as primary and secondary endpoint will thus provide evidence on both the effect of IQOS on inflammation status and on tissue repair and will provide information about the modification of the healing profile related to switching to IQOS.

The limitation of use of antibiotics before and during the study is largely driven by the differential effect that those may have on healing after mechanical periodontal therapy [85], but also, to a slighter extent, because they will affect the microbial oral environment of the patients. Similarly, use of steroidal or non-steroidal anti-inflammatory drugs may affect healing [86, 87], bisphosphonates, which have been shown to be effective in periodontitis management through inhibition of the alveolar bone resorption, should be considered with care during the study because of a potential risk of osteonecrosis of the jaw [88]. Anti-coagulants should also be considered with care because of the risk of bleeding [89].

BoExp to NEQ, nicotine-derived nitrosamine ketone (NNK) (total NNAL) and acrylonitrile (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 cigarettes, levels of NEQ are not expected to be lower in IQOS users than cigarette users, but it will serve as an overall estimate of exposure

to nicotine exposure. Spot-urine collection will be performed, and the BoExp levels will be adjusted to creatinine to adjust urinary excretion rates.

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

All patients will be asked to buy their own cigarettes 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.

4.2 Appropriateness of Measurements

All dental variables to be measured in this study were selected based on the following criteria: 1) commonly assessed by dentists; 2) acceptability by patients; 3) robustness of the method (*i.e.*, index or evaluation criteria are available to assess improvement of periodontal disease); 4) clinical relevance to support the objectives of the study.

Blinding of the examiners is planned to reduce the potential bias of the periodontal assessments that could be introduced by the smell of tobacco on patients using cigarettes, which is not present on patients using IQOS. Blinding was applied in studies by Preber and Bergstrom [90], Liu and Hwan [46], Rosa et al. [44] and Nair et al. [33]. If the examiner gets unblinded, this will be reported by the Investigator, but the patient will not be discontinued. Because mouth wash may influence the collection of samples, the patients will be instructed not to use mouth wash during the study. Blinding will be ensured by asking the patients to wash their hands before the examination, and the examiners will all wear the same mask, that will mask odors. The patients will also be asked not to drink, eat, chew gum, use mouth rinse or brush their teeth for at least 30 minutes before collection of oral samples, because of the influence it may have on the analytes.

The measurement of PD or CAL can be quite variable, as it depends on 1) the extent to which a probe penetrates into a given pocket (can vary because + line, can vary by more than 0.5 mm 2) the diameter of the probe tip (*e.g.*, WHO probe, Florida probe, Williams SE manual probe) 3) the tine (part of the probe with markings) 4) the probing force used, which is a further major factor influencing probe penetration 5) the angulation of the probe tine to the pocket wall 6) the accuracy or otherwise of markings on the tine, which even in the same batch from a production line can vary by more than 0.5 mm 7) the experience of the examiner 8) the presence of (overhanging) restorations [91]. Intra-examiner reproducibility has nevertheless been shown to be high, with calibration and operator training, rather than operator experience being fundamental for reproducibility [92]. In the oral health component of the National Health and Nutrition Examination Survey (NHANES), cycle 1999–2004, intraclass correlation coefficients for mean loss of periodontal attachment varied from 0.72 to 0.93 and for mean PD from 0.55 to 0.87 [93]. Another study where 3 periodontists were trained and calibrated showed inter-examiner variance from the "reference examiner" for the other 2 of 0.32 and 0.50 mm for PD measurement and 0.56 and 0.52 mm for CAL measurement [32]. In a study involving 18 clinical centers, clinicians were

trained and calibrated to measure PD: interexaminer reliability was high, with intraclass coefficients and percent agreement (within 1 mm) values ranging from 0.81 to 0.98 and 87.5% to 98.5%, respectively [94]. To decrease variability in the present study, the same dental probe will be used by all examiners, and a calibration session of all examiners will be organized.

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 smoking cessation/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).

4.3 Study Duration

The study duration per patient will be of maximum of up to 31 weeks, including a 1-day visit (V1), up to 2 weeks interval between V1 and V2, followed by a 6-month (the month means 30 days) investigational exposure period, with 1-day visits after 3 and 6 months (V3, ± 7 days, V4, ± 14 days at each visit), and a 1-week safety follow-up period. The end of the study for an individual patient will be defined as V4 or the date of early termination plus the 7 days for the safety follow-up period. The end of the entire study is the latest date that an individual patient reaches the end of the study.

5 STUDY POPULATION

5.1 Selection of Study Population

5.1.1 Inclusion Criteria

At the screening visit (V1), each patient to be enrolled must meet the following criteria:

Study Population and Main Criteria for Inclusion:

A sufficient number of patients will be enrolled in order to randomize at least 172 patients meeting the following main inclusion criteria:

1. Patient is Japanese.
2. ICF has been signed.
3. Patient is aged ≥ 30 years old.
4. Patient has smoked on average at least 10 commercially available cigarettes per day (no brand restriction) for at least 5 years prior to V1, based on self-reporting. Smoking status will be verified based on a urinary cotinine test (*i.e.*, cotinine ≥ 200 ng/mL).
5. Patient has at least 15 natural teeth (refer to Definition of Terms), excluding the teeth which need to be extracted or whose mobility grade is ≥ 3.
6. Patient has generalized chronic periodontitis (*i.e.*, more than 30% of diseased teeth with a PD ≥ 4 mm), considering only teeth that do not need to be extracted or whose mobility grade is < 3.
7. Patient does not intend to quit smoking during the study.
8. Patient is ready to comply with study procedures and to use the product he/she is allocated to for the duration of the study.

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 has self-reported history of diagnosed systemic diseases (*e.g.*, stroke or acute cardiovascular event within the last 5 years, diabetes, active cancer), or any other conditions that in the opinion of the Investigator would jeopardize the safety of the participant or affect the validity of the study results.

2. Patient is legally incompetent, physically or mentally incapable of giving consent (*e.g.*, emergency situation, under guardianship, in a social or psychiatric institution, prisoner or involuntarily incarcerated).
3. As per the Investigator's judgment, patient cannot participate in the study for any reason (*e.g.*, medical, psychiatric and/or social reason).
4. As per the Investigator's or designee's judgment, patient has medical conditions which require or will require in the course of the study, a medical intervention (*e.g.*, start of treatment, surgery, hospitalization) which may interfere with the study participation and/or study results.
5. Patient has orthodontic appliances.
6. Patient received root planing therapy within the 6 months prior to V1.
7. Patient received surgical periodontal therapy within 3 years prior to V1.
8. Patient has identifiable premalignant changes of the oral mucosa at V1.
9. Patient was treated within the 3 months prior to V1 with systemic antibiotics or was treated with topical antibiotics applied in the mouth.
10. Continuous systemic use of steroidal or non-steroidal anti-inflammatory drugs for more than 20 days during the past 30-day period (except for low dose aspirin, *i.e.*, ≤ 300 mg *e.g.*, for prevention of thrombus/embolus in angina pectoris, myocardial infarction, transient ischemic cerebrovascular accidents, bypass operations).
11. Patient has been previously screened or enrolled in this study.
12. Female patients who are pregnant, breast-feeding, or planning a pregnancy within the course of the study.
13. Patient is a current or former employee of the tobacco industry or their first-degree relatives (parent and child).
14. Patient is an employee of the investigational site or any other parties involved in the study or their first-degree relatives (parent and child).
15. Patient has participated in a clinical study within 3 months prior V1.

5.2 Discontinuation of Patients from the Study

Discontinued patients will include both, 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 questioned 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 9.6) as soon as possible after the time of withdrawal unless the patient refuses to do it in writing.

If a patient expressed his/her wish to quit the study during a visit planned for clinical assessment, he/she will be asked whether he/she would agree to still do the dental/clinical assessments planned for this visit, but with no obligation.

After the time of withdrawal, the patient will enter into the 7-day period of safety follow-up.

Discontinuation from the study

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

1. Withdrawal of informed consent.
2. Discontinuation is considered to be in the interest of the patient from a safety perspective as judged by the Investigator
3. Positive or unclear pregnancy test.
4. 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 head of the medical institution should report the fact and the reason in writing to the IRB.
5. Patient has to undergo periodontal surgery (as per dentist's decision).
6. Patient becomes an employee of the investigational site or any other parties involved in the study.
7. Lost to follow-up.

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

1. Non-compliance to the study procedures based on the judgment of the Investigator.
2. Patient needs to take systemic antibiotic treatment for any medical condition other than periodontitis, for more than 2 consecutive weeks, during the course of the study.
3. Patient needs to take systemic or topical (in the mouth) antibiotic for more than 5 consecutive days for acute inflammation of periodontitis.

4. Patient needs to take systemic steroidal or non-steroidal anti-inflammatory drugs for more than 6 consecutive days
5. Patient needs to take bisphosphonates or anti-coagulants.
6. The number of patients in each randomization stratum has been reached before patient reached V2.

5.2.1 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. 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.

5.2.2 Other Reasons for Discontinuation of Patients from the Study

<NA>

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, reasonable number of attempts to contact the patient (including written correspondence and phone calls) should be done 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 weeks (*i.e.*, 31 weeks), then the Investigator(s) or designee(s) will discontinue the patient with reason as lost to follow-up.

6 INVESTIGATIONAL PRODUCT(S)

6.1 Description of Investigational Product(s)

6.1.1 Test Product(s)

The product tested in this study is the Tobacco Heating System with Marlboro Heatsticks, marketed in Japan under the brand name IQOS and referred to as IQOS in this protocol. All versions of IQOS and Marlboro Heatsticks 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. The IQOS is composed of the following components: a tobacco *HeatStick*, a Holder and a Charger (Table 1), as well as a cleaning tool, a power supply, and a USB cable (see information on the user guide in Appendix 3):

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/stick per *HeatStick*.
Holder:	The Holder is a slim electrical heating unit that heats the *HeatStick* in a controlled manner by using a heater blade. The Holder stores enough energy for a single experience, delivering puffs over a period of about 6 minutes or 14 puffs (whichever comes first). A Light Emitting Diode indicates the end of the experience. Once this cycle is complete, the Holder must be recharged before a new *HeatStick* can be used.
Charger:	The power supply for the Holder is the Charger. The Charger holds enough energy for approximately 20 uses of the Holder and can be recharged from household power. The Charger stores the Holder when not in use, and provides a secure environment for the cleaning process of the heater blade.

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

cigarette [95, 96]. A summary of description of the product, pre-clinical and clinical data available on IQOS is provided in the SPI [81].

6.1.2 Reference and Baseline Product(s)

Cigarette arm (reference product): patient's own preferred brand of commercially available cigarettes will not be provided by the Sponsor but purchased by the patients for their own use for the duration of the study.

6.1.3 Packaging and Labeling

An IQOS starter kit (*i.e.*, IQOS device and a selection of *HeatSticks* flavor variants available on the Japanese market) will be supplied to the site by the Sponsor or authorized representative in packages that protect against deterioration during transport and storage.

The Sponsor or authorized representative will label in local language the IQOS starter kit 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)
- IQOS device serial number

6.2 Administration of Investigational Product(s)

The study is designed as an *ad libitum* use study. The patients will be allowed to use their allocated products (cigarette or IQOS) according to their need. Patients should be advised that when smoking cigarette 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.

Any patient who wish to stop smoking during the study will be encouraged to do so and referred to their General Practitioner for a smoking cessation program. This will not lead to discontinuation.

6.2.1 From Enrollment to Randomization

From screening visit (V1) to randomization (V2), all patients will be allowed to continue smoking *ad libitum* their preferred usual brand of cigarettes. After randomization all patients will purchase their product, as it will not be provided by the Sponsor.

At randomization, patients allocated to the IQOS arm will be supplied with an IQOS starter kit (*i.e.*, IQOS device and a selection of *HeatStick* flavor variants available on the Japanese market) but thereafter they will have purchase their own *HeatSticks* for use during the study.

6.2.2 Investigational Period

6.2.2.1 IQOS Arm

IQOS arm: patients randomized to the IQOS arm will be instructed to use exclusively IQOS *ad libitum*. The switch to different flavors of *HeatSticks* as well as the use of other tobacco- or nicotine-containing products will not lead to discontinuation.

6.2.2.2 Cigarette Arm

Cigarette arm: patients randomized to the cigarettes arm will be instructed to continue smoking their cigarettes *ad libitum*. The switch to different cigarette brands and the use of other tobacco- or nicotine-containing products will not lead to discontinuation.

6.2.3 Safety Follow-up Period

During the safety follow-up period (*i.e.*, after the time of V4 or prematurely discontinued), all patients will be free to smoke their own cigarettes, or any other product of their choice.

6.3 Method for Assigning Patients to Study Arms

After all assessments of V1 have been completed, patients will be randomized to 1 of the 2 study arms; continued cigarette smoking or IQOS use. Patients will be informed about their study arm allocation at V2. Randomization will be done through the Interactive Web and Voice Response System (IXRS) at any time during the visit. Patients will be randomized in one of the two study arms, IQOS arm:cigarette arm in a 1:1 ratio using a stratified randomization (based on daily cigarette consumption over the month (30 days) prior to V1 (10-19 cigarettes/day vs. >19 cigarettes/day), and disease severity (< 5 mm PD vs. ≥ 5 mm PD) in smokers with generalized chronic periodontitis. Disease severity is based on the tooth site having the most severe condition of PD [78]. In each arm, a quota will be applied to ensure that patients with PD ≥ 5 mm represent at least 50% of the randomized patients. Arm assignment for patients with PD < 5 mm will be capped at n = 80, after which enrollment of patients with PD < 5 mm will be stopped. Patients with PD < 5 mm already enrolled but not randomized may be discontinued in order to ensure that randomization quota are met. Enrollment of patients with PD ≥ 5 mm will continue until 172 patients are randomized. At this stage, patients' enrollment will be stopped and patients already enrolled but not randomized may be discontinued. In case patients are discontinued after V1, they will be referred to their dentist/general practitioner and will receive financial compensation for the

visit. Patients will be informed of their randomized study arm by the study site during V2. All patients will be instructed to use their assigned product until they complete the study.

6.4 Blinding

6.4.1 Blinding of the Examiner

This is an open-label study, however, in order to avoid potential involuntary bias of the examiner by the smoking status, he/she will be kept blinded to the patient arm after randomization. In order to enforce the blinding, the examiner will wear a prescribed mask to avoid noticing the odor, during the full periodontal examination at 3 and 6 months. The blinded examiner should avoid contact with the patient outside of the required full periodontal examinations. In addition, the patients will be asked to wash their hands. If the examiner should become unblinded for any reason, including accidental disclosure, the unblinding event will be documented by the Investigator in a specific log kept in the Site Investigator File. A patient-specific unblinding event will not lead to discontinuation of the patient and will not prevent the use of the patient's data, including those recorded after disclosure.

If a designee needs to perform the periodontal assessments, he/she needs to have been trained on the PD and CAL probing before doing it, *i.e.*, by an examiner who attended the calibration session (section 10.2.1). This needs to be described in the back-up plan that will be provided by the sites (section 10.2.1). The blinding status of the designee will be described in the specific log for blinding.

6.4.2 Blinding of Data

There will be additional, even though limited, degree of blinding during the conduct of the study, including the data review and data analysis process. In particular, PMI and contract research organization (CRO) personnel will be as summarized in Table 2:

Table 2 Blinding Scheme

Blinded Study Personnel	Blinded Data	End of Blinding Period
PMI and CRO study statisticians	Patient randomization arm and actual values of CAL and PD values after randomization	After the SAP finalization or database lock, whichever comes last.
PMI clinical scientist	Patient randomization arm and actual values of CAL and PD values after randomization	After the finalization of PMI blind database review. Can be actively un-blinded when appropriate.

Any PMI and CRO personnel who are not listed in the above Table 2 will be 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 pre-analysis data review 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.

6.5 Investigational Product Accountability and Adherence

6.5.1 Dispensing Investigational Product

Patients allocated to IQOS arm will be supplied with an IQOS starter kit (IQOS device and a selection of *HeatStick* flavor variants available on the Japanese market) at the randomization visit (V2), 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. In case the device needs replacement due to a device malfunction or in case of loss/theft of the device, the patient will need to contact his/her site. In case a patient decides to purchase their own device, these will not be replaced by the site.

Patients allocated to cigarette arm will buy cigarettes for their own use for the entire duration of the study.

6.5.2 Storage and Accountability

The study collaborator (the investigational product (IP) storage manager) designated by the head of the investigational site will be responsible for the storage and accountability of the IQOS devices and *HeatSticks* to be distributed only once at V2, together with the device. The IQOS devices (charger and holder) as well as *HeatSticks* (to be distributed only once at V2, together with the device) will be stored in a secured storage site with access limited to authorized personnel only. Because cigarettes will be bought by the patients, cigarettes will not be stored at site. As for *HeatSticks*, a sufficient number of packs will be stored at site, to be delivered with the initial hand out of the IQOS device to patients allocated to the IQOS arm only. A few additional devices will be stored in case a patient needs to have his/her IQOS device replaced. Full accountability of the distributed IQOS starter kit and replacement devices, if any, will be ensured by the designated IP storage manager and recorded in IP accountability logs. This includes but is not limited to the record of the device serial number, *HeatSticks* batch number, the quantity of devices and *HeatStick* packs delivered per patient, date of delivery, total quantity available at site, the quantity of devices returned to the site at the end of the study.

Except for the initial packs of *HeatSticks* delivered together with the IQOS device at V2, neither *HeatSticks* nor cigarettes will be stored at site during the study as they will be bought by the patients throughout the study.

6.5.3 Investigational Product Retention

The patients will return the IQOS device, including replacement devices to the study site upon early discontinuation or at V4. The study site will return to the Sponsor or authorized representative the IQOS product components upon study completion. This does not apply to devices purchased by the patients.

6.5.4 Adherence to Investigational Product(s)

Adherence to the allocated product will be monitored using a questionnaire on self-reported current tobacco and nicotine containing tobacco product consumption (including frequency and quantity of product use) over the past month (section 7.5.7).

6.5.5 Product Use Restrictions

There will be no restriction on allocated product use.

6.5.6 Dietary Restrictions

From V2 to V4, patients will be asked not to drink, eat, chew gum, use mouth rinse or brush their teeth for at least 30 minutes before collection of oral samples (*i.e.*, SP, GCF or buccal swabs).

6.6 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 medical care including medication of the patients during their participation in the study. Any use of concomitant medication must be fully documented in the source document and transcribed into the CRF.

Records of medication taken 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.

Treatment of periodontitis with antibiotics or bisphosphonates should be avoided as much as possible during the study. If required for the periodontal treatment, systemic or topical (in the mouth) antibiotics should not be given for more than 5 consecutive days and will be recorded

as concomitant medication, but this will not necessarily be a reason to discontinue the patient from the study (section 5.2). If required, systemic antibiotics for other medical conditions should ideally not be taken for more than 2 consecutive weeks. Systemic steroidal or non-steroidal anti-inflammatory drugs should not be given for more than 6 consecutive days. Anti-coagulants for any medical condition should also be avoided as much as possible. However all treatment needed must be in the best interest of the patient and would not lead to discontinuation.

6.7 Concomitant Therapeutic Procedures

Any concomitant therapeutic procedure (e.g. tooth extraction due to cavity or due to worsening of periodontitis, appendicectomy), which is not part of study procedures (as described in Section 7), will be fully documented in the source document and transcribed into the CRF. All medications used during these concomitant procedures will also be captured in the source document and reported as concomitant medication 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 (Appendix 1 – Schedule of Events).

In this section, only the expected/planned time points for the various measurements are given. Considering that not all study participants can have a procedure at the same time point, adequate time windows are given for each study procedure and each time point in section 9. Site personnel will adhere to the site's standard operating procedures (SOPs) for all activities relevant to the quality of the study. Appropriate dental/medical advice will be provided to the patients in case of any dental/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 to the study (ICF) section 1.3. 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/Smoking Cessation Advice and Debriefing on IQOS

All patients included in the study will be first advised that the best ways of preventing further periodontal disease progression is to stop smoking as defined in the Japanese guidelines for periodontitis [78]. Only patients who are not willing to quit smoking cigarettes will be eligible for the study.

From V1 onwards, information on the risks of smoking and advice to quit smoking will be given to all patients at every Visit. This will take the form of a brief interview according to WHO recommendations [97].

In addition to the information of the risk of use of tobacco-containing products on smoking products/smoking cessation advice, a debriefing of patients will be done at each visit to address any intended or unintended beliefs participants have about IQOS. The goal of the debriefing is to ensure that patients have an accurate understanding of product risks including an understanding that IQOS has not been demonstrated to be less harmful than cigarettes.

Any enrolled patient, who is willing to attempt quitting during the study will be encouraged to do so and will be referred to appropriate medical services. The patients who quit smoking or using IQOS or those who quit smoking and start using IQOS will not be discontinued from the study, will receive their financial compensation and will come at all scheduled visits for assessments.

7.3 Dental/Clinical Assessments

As per medical responsibility plan, a medical expert (dentist) will be the primary contact for dental medical questions that Investigators might have. Dental medical monitors will be the co-primary contacts for dental medical questions. Other roles for medical expert and dental medical monitors are defined in the medical responsibility plan.

7.3.1 Demographic Data

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

7.3.2 Questions on Smoking History/Habits and Intention to Quit Smoking

Patients will be questioned for their smoking history and self-reported current tobacco and nicotine containing tobacco product use over the past month at V1. The patient will also be asked if he/she is planning to quit smoking during the study. This information will be used to assess their eligibility for the study.

7.3.3 Presentation of IQOS

IQOS including *HeatSticks* will be presented to all male patients by the Investigator or study collaborator at V1. With respect to female patients, it will be presented to the patients whose pregnancy test was negative.

7.3.4 Dental/Medical History and Previous and Ongoing Medications

Relevant dental/medical history and any concomitant disease will be documented at V1. Dental/medical history is defined as any condition that started and ended prior to ICF signature. A concomitant disease is defined as any condition that started prior to ICF signature and is still ongoing at the end of V1.

Prior 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.

If the use of a concomitant medication cannot be avoided for the patient's safety, it must be fully documented in the Source Document and CRF. Therapy changes (including changes of regimen) during the study have to be documented.

7.3.5 Dental Assessments

In the investigational sites with two or more dentists, a dentist will measure each periodontal disease parameter. In the investigational sites with one dentist only, a dentist will preferably measure these parameters, however, a trained hygienist could also do it.

From the moment the examiner meets the patient, blinding of the smoking status should be ensured, as described in section 6.4.1.

A single examiner at each site will perform all measurements throughout the whole study duration, if possible. A calibration session between examiners from different sites must be organized before V1.

Each site will need to develop a plan on how to ensure that they have properly qualified personnel, including back-up personnel necessary to conduct the required dental assessments. This will be documented in the delegation of authority log.

Unified periodontal probes will be used to ensure that all examiners will apply the same pressure when probing. The probe in this study will be PCPUNC15 (#30) by Hu-Friedy. Measurements will be rounded to the nearest millimeter (mm), based on visual judgement.

The dental assessments listed in the sections 7.3.5.1 to 7.3.5.8 below will be recorded on the prescribed periodontal charts.

7.3.5.1 Target Tooth

At V1, for all eligible patients, the Investigator or designee will designate 4 target teeth, *i.e.*, preferably one per quadrant. Teeth with PD ≥ 5 mm but < 7 mm will be preferably selected. If their location does not correspond to one per quadrant, the Investigator or designee will designate the target teeth preferably as single-rooted, and distributed as evenly as possible. Target teeth identification will be reported in the CRF.

7.3.5.2 Target site

The Investigator or designee will designate one site on each target tooth (section 7.3.5.1), which will be the target sites for GCF collection (section 7.5.3). These four target sites should preferably be the deepest of the target teeth. Target site identification will be reported in the CRF.

7.3.5.3 Pocket Depth (PD)

PD is the distance from the gingival margin to which a probe penetrates into the pocket. Full mouth PD is measured based on 6 sites per tooth (6-site measurement method) at a pressure of approximately 20g using the intended probe at V1, V3 and V4. PD is recorded in 1 mm increments. If PD is not measurable on more than 2 sites, the whole tooth should be skipped and any periodontal parameters will not be measured for the tooth.

The site must differentiate within their documentation when PD is not measured from when PD cannot be measured as there is no longer a pocket to measure.

For each subject, full mouth PD is calculated by the following formula:

$$\text{Full Mouth PD (mm)} = \frac{1}{t}\sum_{i=1}^{t}\sum_{j=1}^{s_i}\frac{PD_{ij}}{s_i}$$

where PD_{ij} is the PD measurement of tooth i , $i = 1, \dots, t$ at the site j where $j = 1, \dots, s_i$. Note that s_i is the number of measurable sites per tooth and $s_i \geq 4$.

7.3.5.4 Clinical Attachment Level (CAL)

CAL is the measured distance from an invariable reference point such as CEJ to the bottom of pocket using the intended probe based on 6 sites per tooth (6-site measurement method) in full mouth at V1, V3 and V4. CAL is recorded in 1 mm increments. If CAL is not measurable on 1 or 2 of 6 sites on V1, the site(s) should be skipped but the tooth can be included in the assessment. If CAL is not measurable on more than 2 sites, the whole tooth should be skipped. If the CEJ is unclear on site(s), the fixed point (e.g. margin of the crown) will be chosen if possible and distance from the chosen fixed point to the bottom of pocket will be measured, and the same position will be measured throughout the study period. The site must differentiate within their documentation when CAL is not measured from when CAL cannot be measured as there is no longer attachment loss to be measured.

For each subject, the mean Full mouth CAL is calculated by the following formula:

$$\text{Full Mouth CAL (mm)} = \frac{1}{t}\sum_{i=1}^{t}\sum_{j=1}^{s_i}\frac{CAL_{ij}}{s_i}$$

Where CAL_{ij} is the CAL measurement of tooth i , $i = 1, \dots, t$ at the site j where $j = 1, \dots, s_i$. Note that s_i is the number of measurable sites per tooth and $s_i \geq 4$.

7.3.5.5 Bleeding on Probing (BOP)

BOP in full mouth is determined to assess inflammatory status in the pocket and is assessed as YES or NO of bleeding at 6 sites per tooth at V1, V3 and V4. Gently probing (approximately 20g pressure), the bleeding site within 30 seconds is assessed as YES. For each subject, BOP is calculated by the following formula:

$$\text{Full Mouth BOP (\%)} = 100 * \frac{1}{t}\sum_{i=1}^{t}\sum_{j=1}^{s_i}\frac{BOP_{ij}}{s_i}$$

Where BOP_{ij} is a binary response (Yes = 1, No = 0) of bleeding of tooth i , $i = 1, \dots, t$ at the site j where $j = 1, \dots, s_i$.

7.3.5.6 Tooth Mobility

Tooth mobility will be assessed by Miller's classification [19] below to observe periodontal severity in full mouth at V1, V3 and V4:

Grade 0: Physiologic movement within 0.2 mm

Grade 1: Slight mobility, tooth can be moved 0.2 – 1 mm labiolingually

Grade 2: Moderate mobility, tooth can be moved 1 – 2 mm labiolingually or mesiodistally

Grade 3: Severe mobility, tooth can be moved more than 2 mm labiolingually or mesiodistally, or ability to depress the tooth in a vertical direction

7.3.5.7 Gingival Index (GI)

The degree of gingival inflammation of the target teeth is assessed by calculating the GI of each target tooth. Six surfaces of each tooth of the target teeth are rated according to the score by Löe and Silness [36]. The surfaces are rated according to the following criteria:

Score Criteria:

0: Normal gingiva.

1: Mild inflammation – slight change in color, slight edema, no bleeding on probing.

2: Moderate inflammation – redness, edema and glazing, bleeding on probing.

3: Severe inflammation – marked redness and edema, ulceration, tendency to spontaneous bleeding.

For each subject, GI of target teeth is calculated by the following formula:

$$\mathrm{GI} = \frac{1}{t}\sum_{i=1}^{t}\sum_{j=1}^{s_i}\frac{GI_{ij}}{s_i}$$

where GI_{ij} is the GI of target tooth i , $i = 1, \ldots, t$ at surface j where $j = 1, \ldots, s_i$.

7.3.5.8 Plaque Control Record (PCR)

Presence of the plaque on individual tooth surfaces in full mouth is assessed and PCR (%) is calculated.

According to the PCR of O'Leary et al. [20], plaque retention in the dentogingival areas of mesial, distal, facial and lingual tooth surfaces is determined to be YES or NO and recorded at V1, V3 and V4.

Usual plaque disclosing agent is used in each site and the product name of the plaque disclosing agent will be recorded.

For each subject, PCR (%) is calculated by the following formula:

$$Full\ Mouth\ PCR\ (\%) = 100 * \frac{1}{t}\sum_{i=1}^{t}\sum_{j=1}^{s_i}\frac{PCR_{ij}}{s_i}$$

Where PCR_{ij} is a binary response (Yes = 1, No = 0) of PCR at tooth i , $i = 1, \ldots, t$ at the surface j where $j = 1, \ldots, s_i$.

7.4 Biomarker Assessments

7.4.1 Assessments in Urine

All bioanalytical assays will be carried out using validated methods (section 7.5.6). The bioanalytical methods used will be documented in the Bioanalytical Plans/Reports. A list of laboratories is provided in Appendix 2.

7.4.1.1 NEQ, total NNAL, CEMA, Creatinine Analysis

Spot urine will be collected at V1, V3 and V4 for analysis of NEQ, total NNAL, a biomarker for NNK (*i.e.*, nicotine-derived nitrosamine ketone, also known as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), CEMA, a biomarker for acrylonitrile, and creatinine. Creatinine will be measured for normalization of urinary BoExp, *i.e.*, NEQ, total NNAL and CEMA.

7.5 Other Clinical Assessments and Sampling

Sample collection of GCF, SP and buccal swabs will be performed prior to periodontal assessment, scaling/maintenance or scaling and root planing (SRP).

From V2 to V4, patients will be asked not to drink, eat, chew gum, use mouth rinse or brush their teeth for at least 30 minutes before collection of oral samples (*i.e.*, SP, GCF or buccal swabs).

7.5.1 Urine Pregnancy Testing

All female patients will undergo urine pregnancy testing at all Visits.

Female patients with a urine positive pregnancy test at the 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.

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

7.5.2 Cotinine Test

A urine cotinine test will be performed at V1 in order to confirm the patient's smoking status. The test must detect cotinine with a cotinine of ≥ 200 ng/mL (*e.g.*, One-Step Cotinine Test 008A086, Ultimed, Belgium).

7.5.3 Assessments in GCF

GCF will be collected from 4 target sites at V2 and V3. The sampling should be performed before periodontal assessments. The selection of the target sites is described in section 7.3.5.2).

At the time of the analysis, in order to characterize the inflammatory response, immuno-regulatory mediators in GCF [7] will be measured with two types of technologies, i.e., bead-based multiplex assays (MAP) using the Luminex technology or targeted mass spectrometry.

Targeted mass spectrometry analysis will be performed using the quantitative parallel reaction monitoring (PRM) where the unique peptides of the selected protein targets will be analyzed for absolute quantitation in reference to a synthetic unique peptide of the selected protein

[7] sCD40L, CRP, EGF, Eotaxin/CCL11, Flt3 ligand, GM-CSF, GRO, IFNα2IL-1α, IL-1β, IL-1Ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8/CXCL8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A/CTLA8, IP-10/CXCL10, MCP-1/CCL2, MCP-3/CCL7, MDC/CCL22, MIP-1α/CCL3, MIP-1β/CCL4, MMP-1, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13, osteoprotegerin, PDGF-AA, PDGF-AB/BB, RANKL, RANTES/CCL5, TGFα, TIMP-1, TNFα, TNFβ / LT-α (please refer to the Abbreviations for full spelling)

targets using mass spectrometry. Absolute quantitation will be performed using a heavy labeled synthetic peptide of the selected unique peptide of the target. The targets that will be analyzed by mass spectrometry are: MMP-8, MMP-12, MMP-13, CRP, RANKL, TIMP-1 and osteoprotegerin (please refer to the Abbreviations for full spelling).

7.5.4 Assessments in Subgingival Plaque

SP will be collected from 4 target teeth, at V1 and V4 in order to evaluate the microbiological status. The sampling should be performed before periodontal assessments, except at V1, when it will be performed after periodontal assessments and designation of target teeth. If plaque sample is too small, additional collection can be performed on mesiobuccal SP of second molars, which needs to be recorded by the examiner. These teeth are the same than those selected for GCF collection (section 7.5.3). DNA isolation from these samples will enable the evaluation of the bacterial diversity and the detection of the abundance of bacteria in these samples. Some human host DNA (*i.e.*, of the patient) will also be isolated, however, the host DNA sequences obtained during the DNA sequencing will be filtered out of the raw sequencing data before analysis, and no formal analysis of the patient DNA will be performed.

7.5.5 Assessments in Buccal Swabs

Buccal swabs will be derived from the right and left cheeks (intraoral) to conduct transcriptomics analysis at V2, V3 and V4. These samples will be analyzed for whole human genome expression profiles, also known as transcriptome. No analysis of the patient DNA will be performed.

7.5.6 Sample Handling, Storage, and Shipment

The urine dip-stick for 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 that were planned for analysis will be destroyed post database lock or post finalization of the bioanalytical reports depending on which one is coming the latest.

7.5.7 Self-reported Tobacco- or Nicotine-Containing Product Use

Patients will be questioned for their smoking history at V1. At V1, patients will also answer a questionnaire on self-reported current tobacco- and nicotine-containing product, with instructions from study staff so that they can then answer the questionnaire on their own on a monthly basis. After randomization, patients will be asked to complete a monthly diary, 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 sites will call the patients to remind them to fill the questionnaire. The Investigator or study collaborator will collect the completed diaries at V3 for Month 1 and Month 2 and for Month 3 only if the questionnaire completion date was before or on the day of the Visit. If the completion date of Month 3 questionnaire is after the V3 date, the Month 3 questionnaire will be brought to the next visit. All remaining questionnaires will be collected at V4, even if the 30-day period for completion of Month 6 questionnaire is after the date of V4. The diary data will be transcribed into the CRF by study staff.

7.6 Periodontal Treatment/Maintenance

For each patient, standard of care procedures as defined by the Japanese guideline on periodontal disease will be applied [78]. All medications/treatments provided to patients must be documented in source documentation. However, medication commonly used during SRP and maintenance treatment procedure will not be recorded as concomitant medication in the CRF, except if it is identified as causally related to an AE.

This section describes more specifically the mechanical treatment which is targeted for this study.

7.6.1 Scaling

Supragingival scaling will be performed at V1, and at further visits if required, including at unscheduled visits, based on PI's judgement. Maintenance treatment will be provided in the order of supragingival scaling and plaque control at all other visits. Ultrasonic scaler usually used at each site will be used for scaling.

7.6.2 Scaling and Root Planing (SRP)

First SRP will be performed on teeth with PD ≥ 4 mm by using Gracey Hand Curettes at V2. The following SRP treatments will be performed and recorded as "unscheduled" SRP visits. SRP treatments of teeth with PD < 4 mm will be performed based on PI's judgment, at the time he/she finds it necessary. All SRP treatments must be completed within 8 weeks after V2. If additional SRP visits need to be performed because of periodontitis worsening, based on Investigator's judgement, they will be recorded as unscheduled visits, including the reason for this unplanned SRP.

PD, mobility and BOP before SRP will be measured as per the standard of care treatments at V2. These data will, however, not be reported in the CRF.

The order of SRP should be determined for individual patients. The identification of each tooth treated and the respective time of treatment should be recorded.

8 ADVERSE EVENTS

A medically qualified monitor(s) (*i.e.*, medical monitor) will be available during the study to address any safety question an Investigator may have.

8.1 Definitions

8.1.1 Adverse Events

According to ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [98], an AE is defined as any untoward medical occurrence in a patient administered an IP or reference product, which does not necessarily have a causal relationship with the IP or reference product. 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 or reference product, whether or not it is considered related to the IP or reference product.

Any dental condition identified after signature of the ICF, caused by factors other than periodontitis (e.g. cavity, broken tooth) and requiring future treatment/s, will be identified as an AE. Treatment of this condition (e.g. cavity filling, tooth extraction) will be captured in the CRF.

Worsening of the periodontitis parameters after baseline assessments will not be considered as an AE, as dental assessments will capture any worsening of the periodontal condition. Patients experiencing unexpected worsening of the disease, will be treated based on 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, or,
- Is a congenital anomaly/birth defect.

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 definitions.

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 study participation ICF onwards until the end of the safety follow-up 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 withdrawal from the study), and outcome (*e.g.*, resolved, withdrawal 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).

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 Investigational Products and study procedures. AEs will be collected from the time the patients have signed their ICFs until the end of the safety follow-up period.

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

8.2.2.1 Screening Visit (V1)

All existing health conditions identified during the screening visit and judged by the Investigator as preexisting condition will be recorded as concomitant disease and the patient's eligibility for admission to the study will be reviewed.

8.2.2.2 From End of V1 until the End of Study

From V1 onwards until the EOS, all AEs will be documented.

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. During the safety follow-up period AEs and/or SAEs will be recorded only if reported spontaneously by the patient.

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

At the end of the safety follow-up period, all ongoing non-serious AEs will be documented as "ongoing" and no follow-up information will be sought for on 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 actively followed up by the Investigator, despite their continuation after the end of the safety follow-up 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 (*i.e.*, IQOS or cigarette) 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 dental or 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 dental or 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 [81].

8.2.6 Medical Monitor

All Investigator of this study are dentists. A medical monitor will be designated by Sponsor or authorized representative to answer any medical question that a dentist may have on any medical condition besides dental conditions, as well as on any question related to the safety of the patient (*i.e.*, AE/SAE).

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, or any SAE related to the product and spontaneously reported after the safety follow-up period must be reported by the Investigator **within 24 hours after first awareness by any party involved in the study** to [redacted] and to the Sponsor.
An SAE report form must be e-mailed or faxed as an attachment to:

[redacted]:	**Phone number:**	[redacted]
	E-mail:	[redacted]
	Fax:	[redacted]
	Address:	[redacted]

Sponsor:	**Phone number:**	[redacted]
	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) 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 [redacted] and 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 actively 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.

8.4 Reporting of other events critical to safety evaluations

An ongoing medical condition, clinically relevant finding detected during the screening visit (V1), will be considered a concomitant disease and the patient's eligibility for participating to the study will be reviewed.

Any new, clinically relevant, abnormal finding or worsening of a pre-existing condition detected during the study after the screening visit until the end of the study will be documented as an AE.

Any new onset of symptoms or worsening of pre-existing symptoms identified through the study questionnaires may be documented as AEs at the discretion of the Investigator.

In order to avoid duplicate reports, the patients will be instructed to report AEs, SAEs and occurrences of malfunction of the IQOS device only to a member of the study staff and not to the IQOS hotline.

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 V2 prior to randomization, 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 randomization, must be reported by the Investigator to the Sponsor within 24 hours of the first awareness and must be followed-up 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 Investigator will complete a pregnancy form (provided as a separate document) for all pregnancies diagnosed (including positive urine pregnancy tests) after randomization.

The procedure to report a pregnancy and provide any additional/follow-up information to [redacted] and 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. [redacted] will follow up pregnancies only if they were detected after first product use (*i.e.*, IQOS or cigarettes after V2). 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 Principal Investigator/head of the investigational site is responsible for informing the IRB 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 procedures, as described in section 9.6, as soon as possible and will enter the safety follow-up period. The Investigator will follow up these AEs as described in section 8.2.2.

8.7 Device Events / Investigational Product Malfunction and Misuse

Any occurrences of device events, including IQOS malfunction (*e.g.*, holder does not charge when inserted into the charger) or misuse (use not in accordance with its label and instruction) by a patient, will be documented by a site collaborator in a device 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 the 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 assessment can be found in Appendix 1.

If no start time for the procedures is provided, then the procedure can be performed at any time during the visit. Assessments will be conducted only by qualified and trained site personnel. Toothbrush instructions will be provided throughout the study as per standard of care.

From V2 to V4, patients will be asked not to drink, eat, chew gum, use mouth rinse or brush their teeth for at least 30 minutes before collection of oral samples (*i.e.*, SP, GCF or buccal swabs).

9.1 Screening, Enrollment and Baseline Visit: V1

The screening, enrollment and baseline visit (V1) will be scheduled within 2 weeks (Day -14 to -7) prior to randomization visit (V2).

Patient will sign the study participation ICF before the start of any procedure, and will enter Screening. All eligibility criteria will be checked, including periodontal assessment, which will be also used as baseline assessment for enrolled patients.

Table 3 shows the assessments that will be performed at the screening, enrollment and baseline visit:

Table 3 Schedule - Screening, Enrollment and Baseline Visit: V1

Time	Sample collection	Procedures	Additional information
Start of procedure		**Screening, Enrollment and Baseline**	
Start of the visit [1]		ICF signature	
During the visit Before enrollment		Advice on the risks of smoking/smoking cessation advice and debriefing on IQOS	
		Demographics data	Sex, date of birth, ethnicity
		Dental/medical history, including history of alcohol or drug abuse, concomitant diseases,	
		Prior medication and/or concomitant medication / Procedures	
	U	Spot urine collection for pregnancy (all females) and cotinine tests, and collection	Pregnancy test (all females): at the study site

[1] The informed consent process can be started as soon as the patient is invited to participate in the study, but the ICF must be signed no later than before the first assessment at V1.

Time	Sample collection	Procedures	Additional information
Start of procedure		**Screening, Enrollment and Baseline**	
		for NEQ, total NNAL, CEMA and creatinine samples.	Cotinine test: at the study site. Cotinine ≥ 200 ng/mL Process samples for NEQ, total NNAL, CEMA, creatinine analysis according to laboratory manual/SHM.
		IQOS presentation	To all males. For females, only those who presented negative pregnancy test.
		Smoking history	Patients will be questioned on their smoking history.
		Tobacco or nicotine containing product use self-reporting	Patients will answer this questionnaire on site, with instructions from study staff so that they can then fill it alone on a monthly basis [1]. Distribution of the diaries for the next Visit.
		Readiness to comply to study procedures, and to use the product he/she has been allocated to for the duration of the study	
		Patient is not planning to quit smoking during the study	
		Periodontal assessment: Full mouth PD Full mouth CAL Full mouth BOP Full mouth tooth mobility Full mouth PCR [2]	Last assessment performed as part of the eligibility criteria, to avoid unnecessary examination for those patients who are in any case not eligible.
		Judgment on eligibility	All eligibility criteria must be checked.

[1] For the questionnaire, "monthly" can be considered as 30 days, or as a calendar month. A flexibility of ± 2 day is allowed to fill it.

[2] PCR can be performed after enrollment based on PI's decision.

Time	Sample collection	Procedures	Additional information
Start of procedure		**Screening, Enrollment and Baseline**	
		Enrollment	If all eligibility criteria are met.
		Designation of 4 target teeth and 4 target sites	Target teeth: preferably 4 teeth with ≥ 5 mm initial PD, from which SP and GCF will be collected at their respective visits indicated in the Appendix 1. Target sites: preferably the deepest sites of the target teeth.
After enrollment		Gingival inflammation of target teeth	Part of periodontal assessment, to be performed after designation of 4 target teeth
	SP	Collect from 4 target teeth	For microbiological status. Store the sample according to laboratory manual/SHM.
		Supragingival scaling	
		AE/SAE recording	
For screen failures		Discard any urine samples that might have been collected for patients who are not enrolled.	
End of the visit			

Abbreviations: AE = Adverse event; BOP = Bleeding on probing; CAL = Clinical attachment level; CEMA = 2-cyanoethylmercapturic acid; GCF = Gingival crevicular fluid; 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; PCR = Plaque control record; PD = Pocket depth; SAE = Serious adverse event; SHM = Sample handling manual; SP = Subgingival plaque; U = Urine

9.2 1st SRP and Randomization Visit: V2

The first SRP visit (V2) will be scheduled 7 to 14 days after V1.

Table 4 shows the assessments that will be performed at V2:

Table 4 Time Schedule – 1st SRP Visit and Randomization: V2

Time	Sample collection	Procedures	Additional information
Start of procedure		**1st SRP and Randomization**	
Start of the visit		Advice on the risks of smoking/smoking cessation advice and debriefing on IQOS	
During the visit		Concomitant medication / Procedures	
	U	Spot urine collection for pregnancy (all females).	Pregnancy test (all females): at the study site
	BS	Derived from the right and left cheek	Store the sample according to SHM for transcriptomics evaluation.
	GCF	Collect from 4 target sites.	Same teeth as SP collection at V1. Store the sample according to SHM.
		PD BOP Tooth mobility	As per standard of care (optional, as per PI's judgment). Will not be recorded in the CRF.
		SRP treatment	Start treatment on teeth with PD ≥ 4 mm.
		AE/SAE recording	
		Randomization	
		Patients are informed of their randomized study arm.	
		Distribution of IQOS starter kit to the patient allocated to the IQOS arm	A selection of *HeatStick* flavor variants available on the Japanese market is included.
			Patients are instructed to report AEs, SAEs and for IQOS arms, occurrences of malfunction of the IQOS device only to a member of the study staff and not to the IQOS hotline.
End of the visit		Patients start using their allocated product	

Abbreviations: AE = Adverse event; BOP = Bleeding on probing; BS = Buccal swabs; CEMA = 2-cyanoethylmercapturic acid; CRF = Case Report Form; GCF = Gingival crevicular fluid; 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; PD = Pocket depth; SAE = Serious adverse event; SHM = Sample handling manual; SP= Subgingival plaque; SRP=Scaling and root planing; U = Urine

9.3 Investigational Period Visit: V3

V3 will be scheduled 3 months after V2 with a flexibility of ± 7 days.

Table 5 shows the assessments that will be performed at V3:

Table 5 Time Schedule – 3 Months Visit: V3

Time	Sample collection	Procedures	Additional information
Start of procedure			
Start of the visit		Advice on the risks of smoking/smoking cessation advice and debriefing on IQOS.	
During the visit		Tobacco or nicotine containing product use self-reporting	Collection of the diaries from the previous Visit, and distribution of the diaries for the next Visit
		Concomitant medication / Procedures	
	U	Spot urine collection for pregnancy (all females), and collection for NEQ, total NNAL, CEMA and creatinine samples.	Test at the study site. Store the sample according to SHM
	BS	Derived from the right and left cheek	Store the sample according to SHM for transcriptomics evaluation.
	GCF	Collect from 4 target sites	Same teeth as SP collection at V1. Store the sample according to SHM
		Periodontal assessment	Same examiner as V1
		Full mouth PD Full mouth CAL Full mouth BOP Full mouth tooth mobility Gingival inflammation of the target teeth Full mouth PCR	Examiner wears mask. Patients wash hands.
		Maintenance treatment	

Time	Sample collection	Procedures	Additional information
Start of procedure			
		AE/SAE/device event recording	
End of the visit			

Abbreviations: AE = Adverse event; BOP = Bleeding on probing; CAL = Clinical attachment level; CEMA = 2-cyanoethylmercapturic acid; GCF = Gingival crevicular fluid ; 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; PCR = Plaque control record; PD = Pocket depth; SAE = Serious adverse event; SHM = Sample handling manual; SP = Subgingival plaque ; U = Urine

9.4 End of Study Assessments Visit: V4

V4 will be scheduled 6 months after V2 with a flexibility of ± 14 days.

At the end of V4, patients will be discharged from the study.

Table 6 shows the assessments that will be performed at V4. The procedure of discharge in case of early termination, i.e., before V4, is described in section 9.6.

Table 6 Time Schedule – 6 Months Visit: V4

Time	Sample collection	Procedures	Additional information
Start of procedure			
Start of the visit		Advice on the risks of smoking/smoking cessation advice and debriefing on IQOS	
During the visit		Tobacco or nicotine containing product use self-reporting	Collection of the diaries from the previous Visit, including questionnaire of Month 6.
		Concomitant medication / Procedures	
	U	Spot urine collection for pregnancy (all females), and collection for NEQ, total NNAL, CEMA and creatinine	Test at the study site. Store the sample according to SHM. The pregnancy test is part of the procedures of discharge.
	SP	Collect from 4 target teeth.	For microbiological status: Same teeth than for SP collection at V1. Store the sample according

Time	Sample collection	Procedures	Additional information
Start of procedure			
			to SHM.
	BS	Derived from the right and left cheeks.	Store the sample according to SHM for transcriptomics evaluation:
		Periodontal assessment: Full mouth PD Full mouth CAL Full mouth BOP Full mouth tooth mobility Gingival inflammation of the target teeth Full mouth PCR	Same examiner as V1 Examiner wears mask. Patients wash hands.
		Maintenance treatment	
		AE/SAE/device event recording	The AE/SAE/device event recording is part of the procedures of discharge.
End of the visit		Discharge	

Abbreviations: AE = Adverse event; BOP = Bleeding on probing; BS = Buccal swab; CAL = Clinical attachment level; CEMA = 2-cyanoethylmercapturic acid; GCF = Gingival crevicular fluid ; 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; PCR = Plaque control record; PD = Pocket depth; SAE = Serious adverse event; SHM = Sample handling manual; SP = Subgingival plaque; U = Urine

9.5 Safety Follow-up Period

After the procedures of discharge, patients will enter a 7-day Safety Follow-up Period. Any non-serious AE that is ongoing during the Safety Follow-up Period will be followed-up by the Investigator during that period until it has been resolved, stabilized (*i.e.*, no worsening of the condition), or an acceptable explanation has been found (*e.g.*, a chronic condition). At the end of the follow-up, all ongoing non-serious AEs will be documented as "ongoing" and no follow-up information will be sought for on 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 actively followed up by the Investigator, despite their continuation after the end of the safety follow-up 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).

9.6 Early Termination Procedures

For patients who terminate the study earlier, i.e., before V4, the procedure of discharge planned for V4 will be performed as early termination procedures (see Section 9.4). AE recording will be done for each patient.

If the patient withdraws from the study or is discontinued based on PI judgment, he/she will be asked to perform the early termination procedures as soon as possible after the time of withdrawal unless the patient has withdrawn their informed consent to do so (section 5.2). He/she will be asked whether he/she would agree to still do the dental/clinical assessments planned for this visit, but with no obligation.

These early termination procedures consist in:

- AE/SAE/device event recording
- Pregnancy test (for all females).

Safety follow-up period will be applicable for these patients.

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 Principal 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 their responsibilities, 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, the general training of the study procedures and specific training on selected procedures will be done and documented.

Subsequent to the Investigator's meeting, and before the first patient is screened into the study, 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 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 meeting will be described in the monitoring plan.

In addition to the Investigator 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 to the study collaborator involved in a timely manner. The record of all individuals involved in the study will be maintained in the Site Investigator File.

10.2.1 Calibration of Examiners

Sites will provide a plan on how to ensure that they have properly qualified personnel, including back-up personnel necessary to conduct the required dental assessments (section 7.3.5).

10.3 Audits and Inspections

Good Clinical Practice regulations 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 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 Principal 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 collaborator 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 / Procedures:	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 CDISC Study Data Tabulation Model (SDTM).

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

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

12.1.1 Stratification Criteria

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

1. Daily cigarette consumption over the month (30 days) prior to V1 (10-19 cigarettes/day vs. >19 cigarettes/day)
2. Disease severity in smokers with generalized chronic periodontitis (< 5 mm vs. ≥ 5 mm PD).

In each arm, a quota should be applied to ensure that patients with PD ≥ 5 mm represent at least 50% of the randomized patients (section 6.3).

12.1.2 Definitions for Statistical Data Analysis

In general, baseline value for any given variable will be the last assessment prior to randomization.

12.1.3 Descriptive Statistics

Data will be presented in listings, sorted by product exposure, 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) will be presented in addition to the mean and SD. For categorical data, frequency counts and percentages will be presented.

Descriptive statistics will be presented by product exposure and overall (across the entire study population) at each time point, where applicable.

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

For periodontal parameters:

- Six sites per tooth are to be evaluated. At least 4 of the 6 sites per tooth must be evaluated and have the measurements recorded for the tooth to be included in the

assessment. If the site is evaluated and there is no PD to measure, the site must be recorded as 0 to indicate that there was no PD at the site (and to distinguish it from a site that was not evaluated). When less than 4 sites are recorded, the assessment of the tooth will be considered as missing, and the values will be excluded from the calculation of the means.

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 tobacco product use over the duration of the study data:

- Only available data will be included in the product use summaries.
- Overall product exposure groups will be defined based on the data collected from randomization until EOS.

Further details will be provided in the SAP.

12.1.5 Significance Level for Inferential Analysis

The primary analysis, of PD at 6 months will be tested using a one-sided alpha level of 2.5%.

1. PD at 6 months will be tested.

The secondary analysis of PD at 3 months and CAL at 6 and 3 months will be tested in a hierarchical manner, using a one-sided alpha level of 2.5%, depending on the outcome of the test at previously specified endpoint in hierarchical testing order.

1. PD at 3 months will be tested only if the test for PD at 6 months is significant.
2. CAL at 6 months will be tested only if the test for PD at 3 months is significant
3. CAL at 3 months will be tested only if the test for CAL at 6 months is significant.

Additional analysis of the secondary endpoint, the BoExp will be tested, in a hierarchical manner within each BoExp (independent of the other statistical tests being performed), using a one-sided alpha level of 2.5%. The hierarchical order will be:

1. BoExp at 6 months will be tested.

2. BoExp at 3 months will be tested only if the test for BoExp at 6 months is significant.

Total NNAL and CEMA levels (concentration data adjusted for creatinine), analyzed on a logarithmic scale, will be tested at 6 and then 3 months, in that order, so that the testing of each BoExp will stop if the test is not significant.

Unless stated otherwise, all statistical tests will be one-sided and conducted at the 2.5% level, and all CIs will be two-sided 95%.

12.2 Determination of Sample Size and Power Consideration

The patients will be randomized into 1 of 2 study groups: IQOS or cigarettes. Patients will be analyzed by their actual exposure throughout the course of the study. Therefore, there will be patients who predominantly use IQOS or patients who predominantly use cigarettes, however, there will also be patients who predominantly use other tobacco and nicotine containing tobacco products, or have a pattern of mixed tobacco product use. All patients will continue in the study but will be analyzed based on their exposure pattern during the study. Depending on the patterns of product use observed in the study, sensitivity analyses and descriptive summaries will be implemented.

The statistical hypothesis that will be tested for PD at 6 months is:

- H_0: $X_{IQOS} - X_{cigarette} \leq 0$.
- H_A: $X_{IQOS} - X_{cigarette} > 0$.

Where X_{IQOS} and $X_{cigarette}$ are the adjusted mean changes from baseline values (baseline minus endline) of PD for IQOS and cigarettes, respectively. The H_0 is rejected with a one-sided alpha level of 2.5%.

In the literature reviewed, the papers of Rosa [44] and Preshaw [43] are similar to the study described in this protocol, in that they include:

- Some requirements on minimum PD for inclusion
- Comparison of smokers with former smokers
- Means and SDs (or standard errors of the mean and sample size)

Therefore it is assumed that the cigarette arm will have similar results to what is described in the literature for current smokers and that the results in the IQOS arm will be similar to what is observed in former smokers.

Based on the published data and recommendations from the American clinical practice guidelines [85], the following estimates with PD differences and standard deviations between smokers and non-smokers Table 7) are based on data assessed at 3, 9 and 12 months:

Table 7 Sample sizes for PD differences between smokers and non-smokers and standard deviations based on the literature

SD \ difference (mm)	0.2	0.25	0.3	0.35
0.4	64	42	29	22
0.45	81	52	37	27
0.5	100	64	45	33

Abbreviation: SD = Standard deviation

Thus, the sample size selected above gives sufficient power for testing PD.

With alpha of 2.5%, power of 80%, SD of 0.5, and effect difference of 0.25 mm, then sample size needed in each arm is 64 patients. By considering 25% of drop out and product switching, 86 patients per arm, i.e., 172 patients in total, are needed.

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 cigarettes will exclusively use the randomized product at all times during the study. Patients may concomitantly use IQOS and cigarettes (dual-use). To assess dual use of IOQS and cigarettes, PMI has defined categories of pattern of product use.

Product use pattern categories will be specified based on the average number of product used per month of each category (i.e., Marlboro HeatSticks or smoked cigarettes) as self-reported in the product use questionnaire over the study duration. Further determinants, such as percentages of the respective products, or numbers of other nicotine-containing products may be used, and will be provided in the SAP.

Actual product use pattern categorization is described in Figure 3. Primary analysis will consider only those patients who used only HeatSticks and/or cigarettes. Those who used other nicotine-containing products (e.g., e-cigarettes) will be considered in a separate category, "Other" (not represented in Figure 3). More granular product exposure categories may be used for the detailed description of the product use patterns observed in the study. Full details of the product use categories will be reported in the SAP.

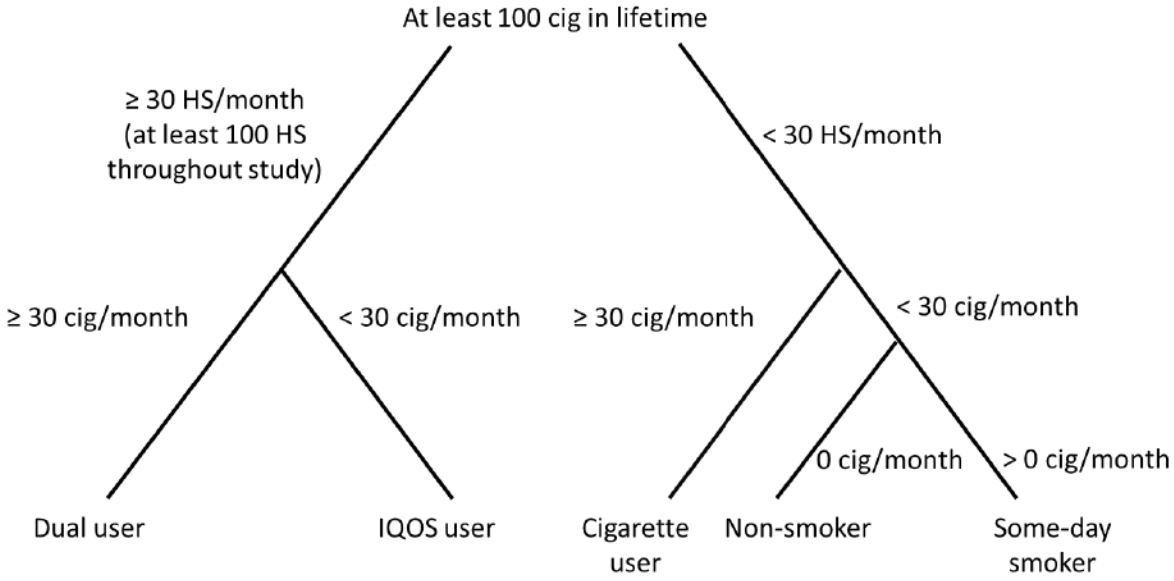


Figure 3 Product Use Categorization

Abbreviations: HS = Marlboro HeatSticks; cig = cigarette
Details of the product use categories will be reported in the SAP.

12.4 Analysis Populations

The main population for non-safety analysis will be the As Exposed Set.

Safety will be analyzed using the Safety Set.

12.4.1 As Exposed Set

The As Exposed Set consists of all randomized patients who have at least one post-randomization product use experience, and who have at least one valid non-safety assessment after randomization. The As Exposed Set will be analyzed by actual exposure (product use pattern).

12.4.2 Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all randomized patients who have at least one post-randomization product use experience, and who have at least one valid non-safety assessment after randomization. The FAS will be analyzed by randomized study product.

12.4.3 Per Protocol Set (PP)

The Per Protocol Set (PP) is the subset of the FAS who fulfill key compliance criteria of the protocol and have no major protocol deviation that influences the evaluability of the study data (to be further described in the SAP).

12.4.4 Adherent Use Set

The Adherent Use Set is the subset of the FAS who are adherent to their randomized study product.

12.4.5 Safety Set

The Safety Set consists of all patients enrolled with signed ICF who have at least one valid safety assessment during the course of the study. The Safety Set will be analyzed by actual exposure (product use pattern).

12.5 Demographics and Baseline Characteristics

The demographic variables will be summarized by product use pattern categories and by the randomization strata (daily cigarette consumption and disease severity) for the As Exposed Set. In addition, they will be summarized by randomization arm for the FAS and PP Sets. Data will be listed by randomization arm. No inferential analyses will be presented for the demographics and baseline characteristics.

12.6 Primary Analysis

The primary analysis evaluates the change from baseline in PD, which will be calculated for each patient across all sites with a baseline PD $\geq$ 4 mm, resulting in one value per patient per endpoint for each visit (baseline, Month 3 and 6).

The primary analysis will be performed on the As Exposed Set using a mixed model for repeated measurements (MMRM) for only subjects who have used cigarettes and/or Heatsticks. The model will include the PD change from baseline as the dependent variable, adjusting for daily cigarette consumption and disease severity at V1, full mouth PD at V1, exposure group and its interaction with visit. Site will be included as a random effect. The modeling assumptions will be evaluated and the model fit will be assessed by the analysis of the residual (diagnostics) and by comparing the values predicted vs. the observed values (calibration).

Additionally, the analysis will be performed on the FAS, PP and Adherent Use populations as a supportive sensitivity analysis. Additional sub group analyses such as for “Other” product use groups may be analyzed and will be defined in the SAP.

Descriptive statistics for PD will be summarized at each visit by exposure group, and overall (across all patients). The primary endpoint will also be summarized by strata (daily cigarette consumption and disease severity).

Study Hypothesis:

The primary study hypothesis is that there will be a favorable difference in the mean PD at 6 months in IQOS users as compared to smokers who continue to smoke cigarettes in patients with generalized chronic periodontitis.

Evaluation Criteria:

The study will substantiate that IQOS improves periodontitis if there is a statistically significant improvement in primary endpoint for smokers who switch to IQOS use (as defined in Figure 3) as compared to smoker who continue to smoke cigarettes.

12.7 Secondary Analysis

The analysis of PD at 3 months, CAL at 3 and 6 months will be also performed, as a secondary endpoint.

There will be an adjustment for multiplicity for the secondary testing of CAL and PD within the As Exposed Set as defined in section 12.1.5.

Urinary NEQ, total NNAL and CEMA levels (concentration data adjusted for creatinine will be analyzed on a logarithmic scale) using an MMRM with the BoExp geometric mean value as the dependent variable, adjusting for daily cigarette consumption at baseline and sex, visit, baseline BoExp level, exposure group and its interaction with visit. Site will be included as a random effect. The modeling assumptions will be evaluated similar to that in the primary analysis.

Descriptive statistics for the BoExp will be summarized at each visit by exposure group and overall (across all patients). The primary endpoint will also be summarized by strata (daily cigarette consumption and sex).

The other secondary endpoints will be summarized descriptively at each visit by exposure group and overall (across all patients) in the As Exposed Set (unless otherwise defined):

- Change in mean full-mouth PD.
- Change in mean full-mouth CAL.
- Mean PD change in sites with initial PD < 4 mm, and with initial PD of 4 mm to $<$ 5mm, 5 mm to < 6 mm, 6 mm to < 7 mm and ≥ 7 mm.

- Mean CAL change in sites with initial PD < 4 mm, and with initial PD of 4 mm to < 5mm, 5 mm to < 6 mm, 6 mm to < 7 mm and ≥ 7 mm.
- Change in the number of sites with PD < 4 mm, with PD 4 mm to < 5mm, with PD 5 mm to < 6 mm , with PD 6 mm to < 7 mm and with PD ≥ 7 mm. The number of sites will be treated as a continuous variable.
- Change in BOP scores, GI score, tooth mobility (grade) and PCR.
- Number of tobacco or nicotine containing products used, (including cigarettes and *HeatSticks*) based on self-reporting.
- Incidence of AEs/SAEs and device events will be presented as frequencies and percentages of the number of patients per group in the Safety Set.

Additionally, the analyses will be performed on the FAS; PP and Adherent Use populations as a supportive sensitivity analysis. Any sub group analyses will be defined in the SAP.

Study Hypotheses:

The secondary study hypotheses that will be tested in IQOS users and smokers (as defined in Figure 3) are:

- That there will be favorable changes of PD at 3 months in IQOS users as compared to smokers who continue to smoke cigarettes in patients with generalized chronic periodontitis.
- That there will be favorable changes of CAL at 3 and 6 months in IQOS users as compared to smokers who continue to smoke cigarettes in patients with generalized chronic periodontitis.
- That there will be favorable changes at 3 and 6 months in total NNAL and CEMA levels in IQOS users as compared to smokers who continue to smoke cigarettes.

12.8 Safety Analysis

In general, safety data will be provided in listings by exposure group, site, and patient. The data will be tabulated on the Safety Set by exposure group, using the approach described in section 12.1.3.

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

The number and percentage of patients with AEs and SAEs will be tabulated by using the MedDRA® system organ class (SOC) and preferred term (PT), summarized for the Safety Set. Summaries will also be presented for AEs leading to discontinuation, AEs leading to death, AEs by relatedness to product exposure, and AEs by severity. Tabulations will be performed

for both the number of patients experiencing an event and the number of events experienced during the study period.

The number and percentage of patients with clinical findings will be summarized for the Safety Set.

Incidence and frequency of concomitant medications and device events will be tabulated by exposure group.

12.8.1 Vital Signs

Not Applicable.

12.8.2 Laboratory Safety Parameters

Not Applicable.

12.8.3 Other Safety Endpoints

Not Applicable.

12.9 Exploratory Analysis

12.9.1 Exploratory Endpoint Analysis

See section 3.3.

12.9.2 Descriptive Analysis

The analysis for the exploratory endpoints of cytokine/chemokine (MAP) and targeted unique peptides (PRM) will follow the statistical approach described for the secondary endpoints and include descriptive and inferential statistics. Descriptive statistics will be reported by treatment group and strata, and will include basic descriptive statistics such as the sample size, the sample mean, standard deviation, standard error of the mean, and CV. Robust measures for the center (median) and the dispersion (median absolute deviation, MAD) of the data will be also included. Inferential statistics will focus on treatment group differences and will take into account stratification criteria as well as repeated measurements. The general statistical linear mixed model developed for the primary endpoint may be used if necessary for the exploratory endpoints in order to test treatment differences and to adjust for stratification factors and repeated measurements. For the exploratory endpoints, a two-sided alternative for the differences between groups will be tested on the 5% type I error rate, while no adjustment for multiplicity will take place. The null hypothesis tested will be that all means of groups tested for a given variable are equal. The alternative hypothesis is that at least one of the means is different from the others. Further details will be specified in the SAP.

After DNA extraction for the iSWAB-Microbiome Collection Kit, Illumina HiSeq sequencing libraries will be prepared and sequenced. The resulting raw data will be filtered to remove patient sequences based on the human reference genome. Filtered data from each sample will be mapped individually to a reference database consisting of all available bacterial genomes. These mapped reads constitute the analysis set and will be free from human sequences to the best of our ability.

The composition of the microbiome in the SP will be determined by counting high quality mapped sequencing reads at the highest possible taxonomic resolution. The reported microbiome compositions will consist of these counts aggregated at the genus and phylum level percentages.

To assess whether or not the microbiome compositions in the SP differ between continued smoking and switching to IQOS, the relative abundance of each detected genus or phylum will be analyzed as a function of time.

Descriptive analysis of buccal swabs RNA profiles will be performed to compare patients switching to IQOS to patients continuing to smoke cigarettes.

12.10 Interim Analysis

Not Applicable

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Sites, Principal Investigators and Study Administrative Structure

13.1.1 Sites and Principal Investigators

See the Protocol Appendix 4.

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], Clinical Scientist Phone: +41 [redacted] Fax: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]
Statistician	[redacted], PhD, Statistician Phone: +41 [redacted] Fax: +41 [redacted] E-mail: [redacted]
Medical Safety Officer	[redacted], MD, Medical Safety Officer Phone: +41 [redacted] Mobile: +41 [redacted] E-mail: [redacted]

13.1.3 Other Responsibilities

[redacted]

[redacted] is the local CRO designated by PMI to manage and monitor the study; all duties and responsibilities transferred to [redacted] by PMI will be defined in the agreement signed between the two parties.

[redacted]

[redacted]

[redacted]

[redacted]

Responsible person ([redacted]): [redacted]

[redacted]

[redacted]

13.2 Patient Confidentiality

All information obtained during the conduct of the study with respect to the patients, state of health will be regarded as confidential. A statement to this effect will be written 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 da ta 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 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, 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 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 Principal 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 Principal 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 Principal Investigator and the IRB, composition of the IRB.
- 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 Principal Investigator/head of investigational site as to when these documents no longer need to be retained.

The Principal 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 or Sponsor's authorized representative will maintain documentation relating to the study as long as the IP is on the market, and/or for 15 years after the CSR has been finalized.

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.

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 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 trades secretes 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, 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 plans to disclose details of the study protocol on a web-based, publicly available, clinical trial register database (*e.g.*, ClinicalTrials.gov).

13.8 Insurance

The Sponsor is responsible for AEs and health damage of the patients who are associated with the IQOS product which are used during the study, except for AEs and health damage of 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 cried out by the insured.

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Appendix 1 Schedule of Events

Visit	V1 Screening, Enrollment & Baseline	V2 1st SRP and randomization	V3	V4 Last visit	Follow-up 7 days
Study Day or Month	**Day -14 to -7** From Day 1	**Day 1**	**Month 3** **(± 7 days)** From Day 1	**Month 6** **(± 14 days)** From Day 1	**Visit 4 + 7 days**
ICF signature [a]	●				
Advice on the risks of smoking/smoking cessation advice and debriefing on IQOS	●	●	●	●	
IQOS presentation	●				
Inclusion/exclusion criteria	●				
Distribution of IQOS and *HeatSticks*		● [b]			
Enrollment	●				
Randomization		●			
Smoking history	●				
Tobacco- or nicotine-containing product use self-reporting	●		● [c]	● [c]	
Readiness to comply to study procedures, including	●				

Visit	**V1** Screening, Enrollment & Baseline	**V2** 1st SRP and randomization	**V3**	**V4** Last visit	**Follow-up** 7 days
Study Day or Month	**Day -14 to -7** From Day 1	**Day 1**	**Month 3** **(± 7 days)** From Day 1	**Month 6** **(± 14 days)** From Day 1	**Visit 4 + 7 days**
switching to IQOS if randomized in the IQOS arm					
Patient is not planning to quit smoking during the study	●				
Demographics [d], dental/medical history, including history of alcohol or drug abuse, concomitant diseases	●				
Prior medication and/or concomitant medication / procedure	● [e]	●	●	●	
U: spot urine collection for pregnancy test (all females)	● [f]	●	●	●	
U: spot urine collection for NEQ, total NNAL, CEMA, creatinine analysis	● [f, g]		●	●	
U: cotinine test	● [f]				
Full periodontal examination [h]	●		●	●	

Visit	**V1** Screening, Enrollment & Baseline	**V2** 1st SRP and randomization	**V3**	**V4** Last visit	**Follow-up** 7 days
Study Day or Month	**Day -14 to -7** From Day 1	**Day 1**	**Month 3** **(± 7 days)** From Day 1	**Month 6** **(± 14 days)** From Day 1	**Visit 4 + 7 days**
Supragingival Scaling (or maintenance)	●		●	●	
PD, BOP and tooth mobility as per standard of care for SRP (optional, as per PI's judgment)		● [i]			
1st SRP treatment		● [j]			
SP collection for microbiological status [k, l]	●			●	
Collection of GCF for cytokine analysis [k, m]		●	●		
Buccal swabs [k, n]		●	●	●	
AE/SAE/device event recording [o]	●	●	●	●	●
Discharge				●	

The month means 30 days.

Abbreviations: AE = adverse event; BOP = bleeding on probing; CEMA = 2-cyanoethylmercapturic acid; GCF = gingival crevicular fluid; ICF = informed consent form; 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; SAE = serious adverse event; SP = subgingival plaque; SRP = scaling and root planing; U = urine sample required.

a. The informed consent process can be started as soon as the patient is invited to participate in the study, but the ICF must be signed no later than before the first assessment at V1.

b. IQOS starter kit (*i.e.*, device and a selection of *HeatStick* flavor variants available on the Japanese market) will be delivered to all patients randomized to the IQOS arm. They will start using it as soon as possible.

c. The Investigator or study collaborator will collect the completed diaries at V3 and V4, and the diary data will be transcribed into the CRF. The questionnaire can be filled before or after V3, but because V4 is the last Visit, the questionnaire for Month 6 must be filled before or at V4, regardless of the time when the previous questionnaire was filled.

d. Sex, date of birth, ethnicity.

e. Prior medication taken within 3 months prior to V1.

f. The same spot urine collection will be used for pregnancy (all females) and cotinine tests, and for NEQ, CEMA, total NNAL and creatinine measurements (BoExp). Sampling for BoExp should be performed as soon as possible, and samples frozen immediately.

g. These tubes will be discarded at the end of the visit if the patient is not enrolled.

h. Full periodontal examination consists in the measurement of PD, CAL and BOP on 6 sites per tooth, tooth mobility, plaque control record and gingival inflammation of the target teeth. At V1, full periodontal examination should be the last assessment performed as part of the eligibility criteria, to avoid unnecessary examination for those patients who are in any case not eligible.

i. Will not be recorded in the case report form.

j. Additional SRP treatments will be performed during “unscheduled” visits and will be completed within 8 weeks after initial treatment.

k. From V2 to V4, patients will be asked not to drink, eat, chew gum, use mouth rinse or brush their teeth for at least 30 minutes before collection of oral samples (i.e., SP, GCF or buccal swabs).

l. SP collection will be collected from 4 target teeth (the largest PD will be selected). These teeth are the same than those selected for GCF collection [m].

m. GCF will be collected from 4 target sites. These sites are located on the same teeth than those selected for SP collection [l].

n. Two buccal samples will be taken (left and right) for transcriptomics evaluation.

o. Spontaneous reporting of new AEs/SAEs & AEs related to device events by the patient, and active follow-up of ongoing SAEs by the site.

Appendix 2 Participating Laboratories

The following laboratories will be used in the study:

Lab logistics, storage, shipment:	[redacted]
Lab for analyses of GCF, buccal swabs and SP:	Philip Morris Products S.A. c/o [redacted] Quai Jeanrenaud 3 R&D Innovation Cube T1532 2000 Neuchatel Switzerland
Lab for analysis of urine samples (NEQ, CEMA, total NNAL and creatinine):	[redacted] and/or [redacted]

Appendix 3 Investigational Product and Instructions for Use

The product user guide will be provided as part of the IQOS starter kit.

Appendix 4 List of Sites and Principal Investigators

The list of investigators and sites will be provided as a separate document.

Appendix 5 Changes in Protocol Amendments

The changes made in the different protocol versions are listed in the below table, including previous and amended texts, as well as the reasons to change. The new text has been highlighted in bold (e.g. **new text**) and deleted text has been crossed out (e.g. ~~old text~~).

Changes from Version 3.0 to Version 4.0		
Section Number	**Section Name**	**Changes**
	General	The version number and the revision date were updated accordingly to the most current version and date.
- - Section 3.3 Section 7.5.3	Synopsis List of abbreviations Exploratory objectives and endpoints Assessments in GCF	Amended text sCD40L, CRP, EGF, Eotaxin/CCL11, ~~FGF-2/FGF basic~~, Flt3 ligand, ~~Fractalkine /CX3CL1~~, ~~G-CSF~~, GM-CSF, GRO, IFNα2, ~~IFNγ~~, IL-1α, IL-1β, IL-1Ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8/CXCL8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A/CTLA8, IP-10/CXCL10, MCP-1/CCL2, MCP-3/CCL7, MDC/CCL22, MIP-1α/CCL3, MIP-1β/CCL4, MMP-1, ~~MMP-2~~, ~~MMP-7~~, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13, osteoprotegerin, PDGF-AA, PDGF-AB/BB, RANKL, RANTES/CCL5, TGFα, **TIMP-1**, TNFα, TNFβ / LT-α, ~~VEGF-A~~ (please refer to the Abbreviations for full spelling). Reason to change: The number of analytes to be analyzed in the GCF was decreased, as method development showed that some analytes had low sensitivity, thus their results would not be accurate. Another analyte, TIMP-1, was added, because the method development showed that it can be detected. List of abbreviations was updated accordingly.
-	List of Abbreviations and Definitions of Terms	Amended text **Dental medical monitors: co-primary contacts (dentists) for dental medical questions** **Medical expert: dentist who is the primary contact for dental medical questions** Medical **monitor** ~~Advisor~~: medical doctor who answers any medical and **safety** questions from the Investigators. Reason to change: The role of Medical Advisor was not well defined, and did not correspond to the definitions of the

		medical responsibility plan. The above definitions were added, as per medical responsibility plan.
Section 7.3	Dental/Clinical Assessments	Amended text **As per medical responsibility plan, a medical expert (dentist) will be the primary contact for dental medical questions that Investigators might have. Dental medical monitors will be the co-primary contacts for dental medical questions. Other roles for medical expert and dental medical monitors are defined in the medical responsibility plan.** Reason to change: The roles of medical expert and dental medical monitors as defined in the medical responsibility plan were not defined in the protocol, thus the definitions were added at the beginning of the section on dental assessments.
Section 8	Adverse Events	Amended text A medically qualified ~~advisor~~**monitor**(s) (*i.e.*, medical ~~advisor~~**monitor**) will be available during the study to address any safety question an Investigator may have. Reason to change: "advisor" in the medical responsibility plan is called "monitor"
Section 6.1.1	Test Product(s)	Amended text The average amount of nicotine in the tobacco plug is ~~4.3-5.4~~ **5-6** mg/stick per *HeatStick*. Reason to change: Aligned with current version of Summary of Product Information.
Section 6.4.2	Blinding of data	Amended text **Patient randomization arm and** actual values of CAL and PD values after randomization Reason to change: In Table 2, for all blinded personnel, the "patient randomization arm" was added. It was implied, but not clearly stated.

Section 7.3.5	Dental assessments	Amended text The ~~following~~ dental assessments **listed in the sections 7.3.5.1 to 7.3.5.8 below** will be recorded on the prescribed periodontal charts. Reason to change: The sentence about dental assessments was moved to the end of the paragraph, and the sections referring to these assessments were added.
Section 7.3.5.3	Dental Assessments – Pocket Depth (PD)	Amended text **For each subject, f**ull mouth PD is calculated by the following formula: ~~Full mouth PD = $\frac{\text{Sum of all PD measurements (in mm)}}{\text{Total number of examined sites}}$~~ $$\textbf{Full Mouth PD (mm)} = \frac{1}{t}\sum_{i=1}^{t}\sum_{j=1}^{s_i}\frac{PD_{ij}}{s_i}$$ **where PD_{ij} is the PD measurement of tooth i, $i = 1, \dots, t$ at the site j where $j = 1, \dots, s_i$. Note that s_i is the number of measurable sites per tooth and $s_i \geq 4$.** Reason to change: while developing the statistical analysis plan, the way of calculating mean values was modified.
Section 7.3.5.4	Dental Assessments – Clinical Attachment Level (CAL)	Amended text ~~Full mouth CAL is calculated by the following formula:~~ ~~Full mouth CAL = $\frac{\text{Sum of all CAL measurements (in mm)}}{\text{Total number of examined sites}}$~~ **For each subject, the mean Full mouth CAL is calculated by the following formula:** $$\textbf{Full Mouth CAL (mm)} = \frac{1}{t}\sum_{i=1}^{t}\sum_{j=1}^{s_i}\frac{CAL_{ij}}{s_i}$$

		Where CAL_{ij} is the CAL measurement of tooth $i, i = 1, \dots, t$ at the site j where $j = 1, \dots, s_i$. Note that s_i is the number of measurable sites per tooth and $s_i \geq 4$. Reason to change: while developing the statistical analysis plan, the way of calculating mean values was modified.
Section 7.3.5.5	Dental Assessments – Bleeding on Probing (BOP)	Amended text ~~The BOP percentage is the percentage of the total number of YES sites to the total number of sites being examined. BOP is calculated by the following formula.~~ ~~$\text{BOP percentage (\%)} = \frac{\text{Total number of YES sites}}{\text{Total number of examined sites}} \times 100$~~ **For each subject, BOP is calculated by the following formula:** $$\textbf{Full Mouth BOP } (\%) = 100 * \frac{1}{t}\sum_{i=1}^{t}\sum_{j=1}^{s_i}\frac{BOP_{ij}}{s_i}$$ **Where BOP_{ij} is a binary response (Yes = 1, No = 0) of bleeding of tooth $i, i = 1, \dots, t$ at the site j where $j = 1, \dots, s_i$.** Reason to change: while developing the statistical analysis plan, the way of calculating mean values was modified
Section 7.3.5.7	Dental Assessments – Gingival Index (GI)	Amended text ~~GI of target teeth is calculated by the following formula.~~ ~~$\text{GI} = \frac{\text{Total scores of 24 surfaces of target teeth}}{24}$~~ **For each subject, GI of target teeth is calculated by the following formula:** $$\text{GI} = \frac{1}{t}\sum_{i=1}^{t}\sum_{j=1}^{s_i}\frac{GI_{ij}}{s_i}$$ **where GI_{ij} is the GI of target tooth $i, i = 1, \dots, t$ at surface j where $j = 1, \dots, s_i$.**

		Reason to change: while developing the statistical analysis plan, the way of calculating mean values was modified
Section 7.3.5.8	Dental Assessments – Plaque Control Record	Amended text ~~PCR (%) is calculated by the following formula.~~ ~~$\text{PCR (\%)} = \frac{\text{Total number of YES surfaces}}{\text{Total number of examined surfaces}} \times 100$~~ **For each subject, PCR (%) is calculated by the following formula:** $$\boldsymbol{Full\ Mouth\ PCR}\ (\%) = \mathbf{100} * \frac{\mathbf{1}}{\boldsymbol{t}} \sum_{\boldsymbol{i=1}}^{\boldsymbol{t}} \sum_{\boldsymbol{j=1}}^{\boldsymbol{s_i}} \frac{\boldsymbol{PCR_{ij}}}{\boldsymbol{s_i}}$$ **Where PCR_{ij} is a binary response (Yes = 1, No = 0) of PCR at tooth $i, i = 1, \dots, t$ at the surface j where $j = 1, \dots, s_i$.** Reason to change: while developing the statistical analysis plan, the way of calculating mean values was modified
Section 12.3	Product Use	Amended text Product use pattern categories ~~within an analysis period~~ will be ~~categorized~~ **specified** based on the **average** ~~percentage of all product use that is the randomized product~~**number of product used per month of each category (i.e., Marlboro HeatSticks or smoked cigarettes) as self-reported in the product use** questionnaire over the study duration. Further determinants, such as percentages of the respective products, or numbers of other nicotine-containing products may be used, and will be provided in the SAP. Actual product use ~~general~~ pattern ~~categories~~ **categorization** ~~are~~ **is described**~~defined~~ in **Figure 3**~~Table 8~~. Primary analysis will consider only those patients who used only HeatStick and/or cigarettes. Those who used other nicotine-containing products (e.g., e-cigarettes) will be considered in a separate category, "Other" (not represented in Figure 3). More granular product exposure categories ~~will~~ **may** be used for the detailed description of the product use patterns observed in the study.

Full details of the product use categories will be reported in the SAP.

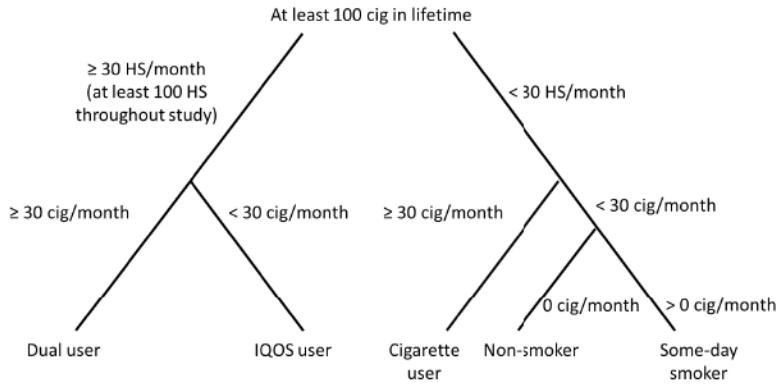

Figure 4 Product Use Categorization

Abbreviations: HS = Marlboro HeatSticks; cig = cigarette

Table 8 Actual Product Use General Pattern Categories

~~Category label~~	~~General description~~
~~IQOS user~~	• ~~Used at least 100 *HeatSticks*~~ • ~~Uses IQOS daily > 1/day~~ • ~~Uses a cigarette less than daily~~ • ~~Uses less than 30 cigarettes/month~~ • ~~IQOS is > 95% of product (all product use) – excluding other products (e-cig/Ploom/etc…)~~
~~Cigarette user~~	• ~~Used at least 100 cigarettes~~ • ~~Uses cigarettes daily > 1/day~~ • ~~Uses IQOS less than daily~~ • ~~Uses less than 30 *HeatSticks*/month~~ • ~~Cigarette is > 95% of product (all product use)~~

		~~Dual user~~ — ~~• Used at least 100 *HeatSticks* and cigarettes • Uses IQOS and cigarettes daily > 1/day • Broken into categories: 70 - 95% IQOS, 30< - > 70% IQOS and 5 - 30% IQOS~~ ~~Other tobacco product user~~ — ~~• Uses 1 or more other tobacco product daily • Not using IQOS or cigarettes • Broken into categories (combustible tobacco product vs. non-combustible)~~ ~~Smoking cessation~~ — ~~• No tobacco product use~~ Details of the product use categories will be reported in the SAP. Reason to change: Product use categorization was revised to reflect not so much the percentage of each product used, but rather to reflect an actual number of products.
Section 12.6	Primary Analysis	Amended text The primary analysis will be performed on the As Exposed Set using a mixed model for repeated measurements (MMRM) for only subjects who have used cigarettes and/**or** Heatsticks. Reason to change: primary analysis will focus on patients who used only cigarettes and/or HeatSticks, not on those who used other nicotine-containing products.
Section 12.6	Primary Analysis	Amended text Additional sub group analyses **such as for "Other" product use groups** may be analyzed and will be defined in the SAP. Reason to change: categories for patients using products other than cigarettes and/or HeatSticks were not mentioned.
Section 13.1.2 and	Sponsor	Amended text [redacted], ~~PhD, Manager Clinical Science, Lead Clinical Scientist~~

Front page		Reason to change: [redacted] role has changed, and is not applicable to this study anymore.
Section 13.1.3	Other responsibilities	Amended text Responsible person ([redacted]): [redacted] Reason to change: change of responsiblity
14	References	Amended text: [1] Philip Morris Products S.A. *Unpublished on file data:* Summary of product information (SPI) - ~~iQOS with HeatSticks~~ **Tobacco Heating System (THS)**. Version **4**~~2~~.0. **2018**~~2017~~. Reason to change: an updated version of the SPI has been made available.

Changes from Version 2.0 to Version 3.0		
Section Number	**Section Name**	**Changes**
	General	The version number and the revision date were updated accordingly to the most current version and date. The statistician has changed. [redacted] has thus replaced [redacted]. A table containing the "**Summary of changes**" has been added, referring to this Appendix 5 for the detailed changes.
4	Overall Study Design	Old text Patients will be invited to the screening Visit (V1) by the Investigator, based on his/her evaluation of the patients examined as part of a standard visit of the patient to the Investigators dentistry practice.

		Information about the study will be provided and the ICF will be distributed to the patients. Amended text Patients **identified by the site as potentially eligible will be provided with the information about the study and if interested, they** will be invited to the screening Visit (V1) by the **site.** ~~Investigator, based on his/her evaluation of the patients examined as part of a standard visit of the patient to the Investigators dentistry practice. Information about the study will be distributed and t~~**T**he ICF ~~will~~ **can** be distributed to the**se potential** patients **before V1.** Reason to change: potential candidates can now be identified by phone or emails, thus the text needed to be updated to reflect this new possibility of patients' identification.
4	Overall Study Design	Old text Patients will sign the ICF before the start of any procedure, and will enter screening. Amended text Patients will sign the ICF before the start of any **study** procedure, and will enter screening. Reason to change: to clarify which procedure.
4	Overall Study Design	Old text Target teeth (see Definition of terms) will be designated by the Investigator or designee and will be identified in the case report form (CRF). Amended text Target teeth (see Definition of terms) will be designated by the Investigator or designee and will be identified **in the source documents and** in the case report form (CRF). Reason to change: to clarify that this needs to be captured in source data.
4	Overall Study Design	Old text As the number and timing of the visits is flexible, the data will be capture as "unscheduled" SRP visits.

		All SRP treatments must be completed within 8 weeks after V2. Amended text As the number and timing of the visits is flexible, the data will be captur**ed in the CRF** as "unscheduled" SRP visits. All SRP treatments must be completed within 8 weeks after V2. Reason to change: to correct typo and clarify that how these visits need to be captured in the CRF.
4	Overall Study Design	Old text: 3 months, periodontal assessment & maintenance visit, GCF and buccal swabs collection Patients will come to the site for periodontal assessment (Appendix 1), including GCF collection from the same 4 target teeth than at V1, and collection of buccal swabs. Maintenance treatment will be provided. 6 months, periodontal assessment & maintenance visit, SP and buccal swabs Patients will come to the site for periodontal assessment (Appendix 1). Sampling of SP for microbiological status from the same 4 target teeth than at V1 will be performed. Buccal samples will also be collected. Maintenance will be provided. Amended text 3 months, periodontal assessment & maintenance visit, GCF and buccal swabs collection Patients will come to the site for periodontal assessment (Appendix 1), including GCF collection from the same 4 target **sites**~~teeth~~ than at V1, and collection of buccal swabs. Maintenance treatment will be provided **as needed**. 6 months, periodontal assessment & maintenance visit, SP and buccal swabs Patients will come to the site for periodontal assessment (Appendix 1). Sampling of SP for microbiological status from the same 4 target teeth than at V1 will be performed. Buccal samples will

		also be collected. Maintenance will be provided **as needed**. Reason to change: as per PI's suggestions.
4	Overall Study Design	Old text The site should record any site visit and document the reason for the visit. Amended text The site should record any site visit **even if unscheduled** and document the reason for the visit. Reason to change: to clarify that all visits should be recorded.
5.2	Discontinuation of Patients from the Study	Old text 2. Patient needs to take antibiotic treatment for any medical condition other than periodontitis, for more than 2 consecutive weeks, during the course of the study. 3. Patient needs to take antibiotic for more than 5 consecutive days for acute inflammation of periodontitis. 4. Patient needs to take steroidal or non-steroidal anti-inflammatory drugs for more than 6 consecutive days Amended text 2. Patient needs to take **systemic** antibiotic treatment for any medical condition other than periodontitis, for more than 2 consecutive weeks, during the course of the study. 3. Patient needs to take **systemic or topical (in the mouth)** antibiotic for more than 5 consecutive days for acute inflammation of periodontitis. 4. Patient needs to take **systemic** steroidal or non-steroidal anti-inflammatory drugs for more than 6 consecutive days Reason to change: to clarify systemic vs topical use of antibiotics anti-inflammatory drugs.

6.5.4	Adherence to Investigational Product(s)	Old text Adherence to the allocated product will be monitored using a questionnaire on self-reported current tobacco and nicotine containing tobacco product consumption (including frequency and quantity of product use) over the past month. Amended text Adherence to the allocated product will be monitored using a questionnaire on self-reported current tobacco and nicotine containing tobacco product consumption (including frequency and quantity of product use) over the past month **(section 7.5.7)**. Reason to change: following a number of questions regarding on when the questionnaire needs to be filled, we provided a more exhaustive explanation in section 7.5.7.
6.6	Concomitant medication	Old text If required for the periodontal treatment, antibiotics should not be given for more than 5 consecutive days and will be recorded as concomitant medication, but this will not necessarily be a reason to discontinue the patient from the study (section 5.2). If required, antibiotics for other medical conditions should ideally not be taken for more than 2 consecutive weeks. Steroidal or non-steroidal anti-inflammatory drugs should not be given for more than 6 consecutive days. Amended text If required for the periodontal treatment, **systemic or topical (in the mouth)** antibiotics should not be given for more than 5 consecutive days and will be recorded as concomitant medication, but this will not necessarily be a reason to discontinue the patient from the study (section 5.2). If required, **systemic** antibiotics for other medical conditions should ideally not be taken for more than 2 consecutive weeks. **Systemic s**~~S~~teroidal or non-steroidal anti-

		inflammatory drugs should not be given for more than 6 consecutive days. Reason to change: The distinction between topical and systemic drug was not clearly made, thus has been clarified.
6.7 **New section**	**Concomitant Therapeutic Procedures**	Amended text **Concomitant Therapeutic Procedures** **Any concomitant therapeutic procedure (e.g. tooth extraction due to cavity or due to worsening of periodontitis, appendicectomy), which is not part of study procedures (as described in Section 7), will be fully documented in the source document and transcribed into the CRF. All medications used during these concomitant procedures will also be captured in the source document and reported as concomitant medication in the CRF.** Reason to change: worsening of periodontitis is not considered as an AE, however, if a tooth is extracted, we need to understand why (e.g. broken tooth or worsening of the disease?). We have thus clarified the fact that the reason for extracting a tooth must be recorded in the CRF.
7	Study procedures	Old text All study procedures are provided as an overview in the schedule of events (section 15.1, Appendix 1 – Schedule of Events) Amended text All study procedures are provided as an overview in the schedule of events (~~section 15.1,~~ Appendix 1 – Schedule of Events) Reason to change: wrong reference
7.2	Advice on the Risks of Smoking/Smoking Cessation Advice and Debriefing on IQOS	Old text will be given to all patients at every visit Amended text will be given to all patients at every ~~v~~**V**isit

		Reason to change: to be consistent throughout the text
7.5.6	Sample Handling, Storage, and Shipment	Old text All samples will be destroyed post database lock or post finalization of the bioanalytical reports depending on which one is coming the latest. Amended text All samples **that were planned for analysis** will be destroyed post database lock or post finalization of the bioanalytical reports depending on which one is coming the latest. Reason to change: to distinguish those that should be discarded during the course of the study, for example, of a discontinued patient who refuses to have his/her samples analyzed.
7.5.7	Self-reported Tobacco- or Nicotine-Containing Product Use	Old text: The sites will call the patients to remind them to fill the questionnaire. The Investigator or study collaborator will collect the completed diaries at every visit and the diary data will be transcribed into the CRF. Amended text: **In this case, a "month" can 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 sites will call the patients to remind them to fill the questionnaire. ~~The Investigator or study collaborator will collect the completed diaries at every visit and the diary data will be transcribed into the CRF.~~ **The Investigator or study collaborator will collect the completed diaries at V3 for Month 1 and Month 2 and for Month 3 only if the questionnaire completion date was before or on the day of the Visit. If the completion date of Month 3 questionnaire is after the V3 date, the Month 3 questionnaire will be brought to the next visit. All remaining questionnaires will be collected at V4, even if the 30-day period for completion of Month 6 questionnaire is after the date of V4.**

		The diary data will be transcribed into the CRF by study staff. Reason to change: It was not clear for the sites when the questionnaire had to be filled exactly, considering that the study is planned for 6 months, but with a flexibility of ± 7 days at V3 and ± 14 days et V4. Also, months don't all have the same number of days. We have thus added flexibility in the definition of "monthly", while explaining that the last questionnaire should be filled for V4, regardless of when the end of the month is.
7.6	Periodontal Treatment/Maintenance	Amended text (new): **All medications/treatments provided to patients must be documented in source documentation. However, medication commonly used during SRP and maintenance treatment procedure will not be recorded as concomitant medication in the CRF, except if it is identified as causally related to an AE.** Reason to change: it was not clear for PIs what had to be recorded in the CRF or not, thus we clarified it with this added text.
7.6.1	Scaling	Old text: Supragingival scaling will be performed at V1. Maintenance treatment will be provided in the order of supragingival scaling and plaque control at all other visits. Ultrasonic scaler usually used at each site will be used for scaling. Amended text: Supragingival scaling will be performed at V1**, and at further visits if required, including at unscheduled visits, based on PI's judgement**. Maintenance treatment will be provided in the order of supragingival scaling and plaque control at all other visits. Ultrasonic scaler usually used at each site will be used for scaling. Reason to change: it was not clear for PIs that scaling could be performed as many times as needed.

7.6.2	Scaling and Root Planing (SRP)	Amended text (new): **SRP treatments of teeth with PD < 4 mm will be performed based on PI's judgment, at the time he/she finds it necessary**. Reason to change: it was not clear for a PI how to treat the teeth with PD < 4mm.
8.1.1	Adverse Events	Amended text (new): **Any dental condition identified after signature of the ICF, caused by factors other than periodontitis (e.g. cavity, broken tooth) and requiring future treatment/s, will be identified as an AE. Treatment of this condition (e.g. cavity filling, tooth extraction) will be captured in the CRF.** Reason to change: it was not clear for PIs what had to be recorded in the CRF or not, thus we clarified it with this added text.
8.1.1	Adverse Events	Old text Worsening of the periodontitis parameters will not be considered as an AE, as dental assessments will capture any worsening of the periodontal condition. Amended text Worsening of the periodontitis parameters **after baseline assessments** will not be considered as an AE, as dental assessments will capture any worsening of the periodontal condition. Reason to change: added to clarify from when "worsening" is meant.
8.4	Reporting of other events critical to safety evaluations	Old text the IQOS device only to the a member of the Amended text the IQOS device only to ~~the~~ a member of the Reason to change: typo
9.1	Table 3	Old text: Start of the visit Amended text (addition of a footnote) [1] The informed consent process can be started as soon as the patient is invited to participate in the study, but the ICF must be signed no later than before the first assessment at V1.

		Reason to change: added to clarify that ICF can be signed before the beginning of assessments.
9.1	Table 3	Old text: Prior medication and/or concomitant medication Amended text: Prior medication and/or concomitant medication / **procedures** Reason to change: "procedures" was added to distinguish from concomitant medication
9.1	Table 3	Old text: Patients will answer this questionnaire on site, with instructions from study staff so that they can then fill it alone on a monthly Amended text (including addition of a footnote): Patients will answer this questionnaire on site, with instructions from study staff so that they can then fill it alone on a monthly basis [1]. **Distribution of the diaries for the next Visit.** **[1] For the questionnaire, "monthly" can be considered as 30 days, or as a calendar month. A flexibility of ± 2 day is allowed to fill it.** Reason to change: it was not clear for the sites when the questionnaire had to be filled exactly.
9.1	Table 3	Old text: Full mouth PCR Amended text (including addition of a footnote): Full mouth PCR [2] **PCR can be performed after enrollment based on PI's decision.** Reason to change: a PI commented that PCR can prevent proper evaluation of gingival inflammation.
9.2	Table 4	Old text: Concomitant medication Amended text: Concomitant medication / **procedures** Reason to change: "procedures" was added to distinguish from concomitant medication
9.2	Table 4	Old text (Next to PD, BOP, Tooth mobility): As per standard of care. Amended text: **(optional, as per PI's judgment).**

		Reason to change: not all sites have the same practices, thus added clarification.
9.3	Table 5	Amended text (added next to Tobacco or nicotine containing product use self-reporting): **Collection of the diaries from the previous Visit, and distribution of the diaries for the next Visit.** Reason to change: to clarify when questionnaires are distributed and collected.
9.3	Table 5	Old text: Concomitant medication Amended text: Concomitant medication / **procedures** Reason to change: "procedures" was added to distinguish from concomitant medication
9.3	Table 5	Moved text (After "gingival inflammation"): **Full mouth PCR** Reason to change: a PI commented that PCR can prevent proper evaluation of gingival inflammation.
9.4	Table 6	Amended text (added next to Tobacco or nicotine containing product use self-reporting): **Collection of the diaries from the previous Visit, including questionnaire of Month 6.** Reason to change: to clarify when questionnaires are collected.
9.4	Table 6	Old text: Concomitant medication Amended text: Concomitant medication / **procedures** Reason to change: "procedures" was added to distinguish from concomitant medication
9.4	Table 6	Moved text (After "gingival inflammation"): **Full mouth PCR** Reason to change: a PI commented that PCR can prevent proper evaluation of gingival inflammation.
11.2.2	Coding	Old text: WHO Drug Dictionary Enhanced and Anatomical Therapeutic and Chemical Classification System

		Amended text: WHO ~~Drug Dictionary Enhanced and Anatomical Therapeutic and Chemical Classification System~~**Drug Global**
11.2.2	Coding	Old text: adverse events Amended text: adverse events **/ Procedures** Reason to change: procedures also need to be coded following MedDRA
13.1.2	Sponsor	Old text: [redacted], PhD, Statistician Phone: +41 [redacted] Mobile: +41 [redacted] Email: [redacted] Replaced with: [redacted] **PhD, Statistician** **Phone: +41** [redacted] **Fax: +41** [redacted] **Email:** [redacted]
Appendix 1	Schedule of events	Two footnotes were added. The other footnotes were "renumbered" accordingly. Added: ICF signature [a] **[a] The informed consent process can be started as soon as the patient is invited to participate in the study, but the ICF must be signed no later than before the first assessment at V1.** Tobacco- or nicotine-containing product use self-reporting [c] **[c] The Investigator or study collaborator will collect the completed diaries at V3 and V4, and the diary data will be transcribed into the CRF. The questionnaire can be filled before or after V3, but because V4 is the last Visit, the questionnaire for Month 6 must be filled before or at V4, regardless of the time when the previous questionnaire was filled.** Reason to change: to clarify, like in the text that ICF can be signed before V1, and to clarify when the questionnaires need to be filled/collected.

Appendix 1	Schedule of events (footnote [h])	Old text: PD CAL on 6 sites per tooth, BOP, tooth mobility New text: PD**,** CAL **and BOP** on 6 sites per tooth, ~~BOP,~~ tooth mobility Reason to change: BOP is also measured on 6 sites per tooth