PMI RESEARCH & DEVELOPMENT

Statistical Analysis Plan

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
Product Name:	IQOS (Tobacco Heating System (THS) with Marlboro Heatsticks)
Sponsor:	Philip Morris Products S.A. PMI Reduced Risk Products Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	2.0
Date:	07 Jun 2019

Statistical Analysis Plan Approval Signatures

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

CRO Approval:

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1 INTRODUCTION

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.

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

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

This SAP has been developed to supplement the statistical analysis described in the clinical study protocol ("P1-OHS-01-JP" final version 4.0 dated 09 Jan 2019). In addition, the SAP has been prepared based on the following documents:

- International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials"
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports"
- Case report forms (CRF) final version 3.0.01 (dated 15 August 2018)

1.1 Revision History

Version	Date of Revision	Description
1.0 (Draft for Dry-run)	13 DEC 2018	• Original version
2.0	07 Jun 2019	• As Exposed Set to only include patients with no major protocol deviations affecting safety or evaluability. • Adherent Use Set removed from analysis populations • Analysis of biomarkers of exposure updated to

		include only parameters adjusted for creatinine. • Examples for major protocol deviations added. • Section 9.5.4 was updated to add the percentage of AEs, summary tables for AEs related to study procedure or investigational product and also to clarify the summarization for conmeds/prior medication based on ATC codes.

2 ABBREVIATIONS OF TERMS AND DEFINITION OF SPECIAL TERMS

Abbreviation	Term
AE	Adverse Event
BoExp	Biomarkers of Exposure
BOP	Bleeding on Probing
CAL	Clinical Attachment Level
CC	Cigarettes
CEJ	Cementoenamel junction
CEMA	2-Cyanoethylmercapturic acid
CI	Confidence interval
CMP	Clinical Monitoring Plan
CRO	Contract research organization
CV	Coefficient of variation
DMP	Data Management Plan
EOS	End of study
FAS	Full Analysis Set
GCF	Gingival crevicular fluid
GI	Gingival index
ICF	Informed consent form
KR	Kenward Roger Method
LLOQ	Lower limit of quantification
LS	Least Squares
MAD	Median absolute deviation
MAP	Multiplex assay
MedDRA	Medical dictionary for regulatory activities
NEQ	Nicotine equivalents
NNAL	4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol
PCR	Plaque control record
PD	Pocket depth
PMI	Philip Morris International
PP	Per protocol set
PRM	Parallel reaction monitoring
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SP	Subgingival plaque

Abbreviation	Term
THS	Tobacco Heating System
ULOQ	Upper limit of quantification
WHO	World Health Organization
WHO-DD	World Health Organization drug dictionary

2.1 Definitions for Statistical Analysis

2.1.1 Definition of Special Terms

The following special terms are used in this SAP

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

For the following collection of GCF for cytokine analysis, the baseline will be the assessment taken at Visit 2 (1st SRP and randomization).

Cigarette — The term 'cigarette' refers to commercially available cigarettes (manufactured) or roll-your-own cigarettes and excludes IQOS with *HeatSticks*, other heat not burn, e-cigarettes, smokeless tobacco pipe, smokeless tobacco, cigars/pipes/kiseru/shisha and nicotine replacement therapy products.

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 Advisor	Medical doctor who answers any medical question 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.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives and Endpoints

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.

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 clinical attachment level (CAL) to mechanical periodontal therapy over time.

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

3.3 Exploratory Objectives Endpoints

The exploratory objectives of this study are as indicated below, only objective 1 will be part of the CSR and objectives 2 and 3 are part of a separate SAP

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.

Endpoint (3 months):
- Measurement of pro-inflammatory and immuno-regulatory mediators in the GCF

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

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.

Endpoint (3 and 6 months):

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

3.4 Study Hypotheses and Evaluation Criteria

3.4.1 Primary 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.

3.4.1.1 Primary 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 smokers who continue to smoke cigarettes.

3.4.2 Secondary Study Hypotheses

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

1. 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.

2. 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.

3. 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

4 INVESTIGATIONAL PLAN

4.1 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 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 1). 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.

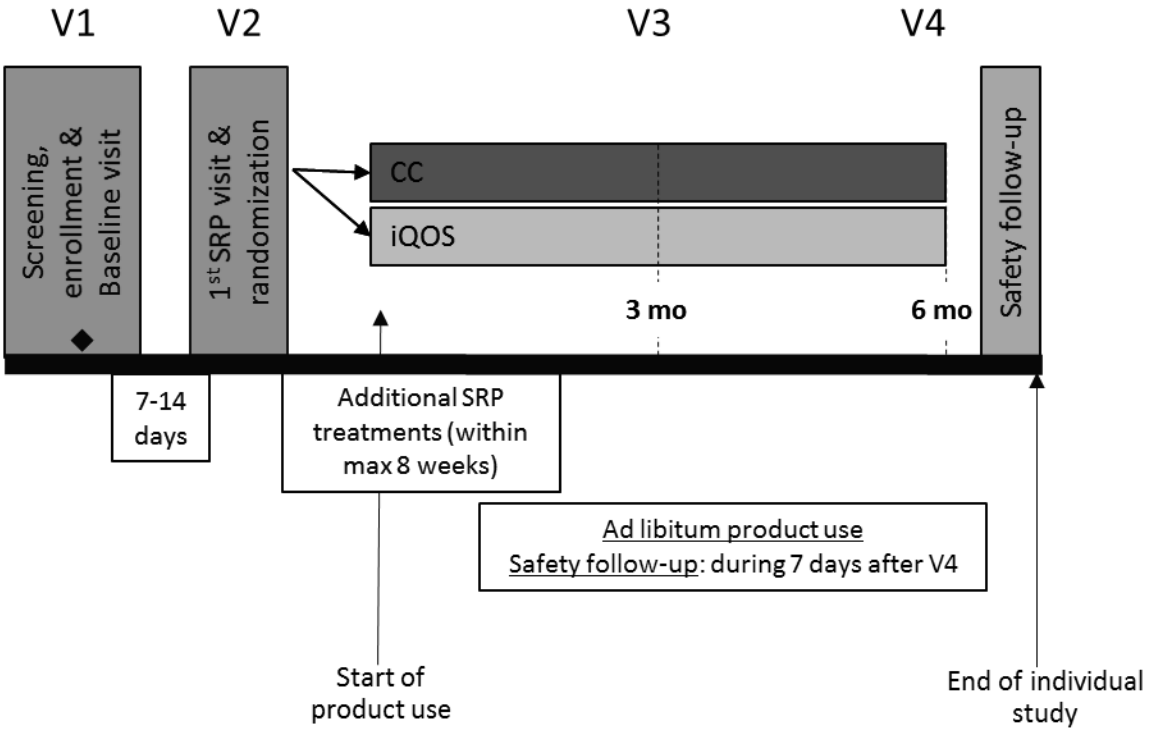
Patients will be randomized using a stratified randomization with a 1:1 ratio into the IQOS or cigarette arms and will be instructed to use their allocated product for 6 month study period. In each arm, a quota should be applied to ensure that patients with PD ≥ 5 mm (based on the most severely diseased tooth) represent at least 50% of the randomized patients. 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

CC = Conventional Cigarette

Figure 1 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, 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 Informed Consent Form (ICF) signature until end of study (EOS) will also be recorded. 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 can be distributed to the patients.

4.2 Selection of Study Population

4.2.1 Inclusion Criteria

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.

4.2.2 Exclusion Criteria

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 planning 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.

4.3 Product Allocation and Blinding

4.3.1 Method of Assigning Patients to Sequence/Product 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. Patients will be randomized in one of the two study arms, IQOS arm: cigarette arm in a 1:1 ratio using a stratified randomization.

Stratification:

- Daily cigarette consumption over the month (30 days) prior to V1 (10-19 cigarettes/day vs. >19 cigarettes/day)
- 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.

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.

4.3.2 Blinding

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. 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.

Unblinded information will not be shared with the blinded study team, until the end of the blinding period. Philip Morris International (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.

The table below shows the blinding scheme.

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

4.3.3 Compliance to Product Allocation

Patients will be allowed to use their allocated products (cigarette or IQOS) according to their needs. However, from Visit 2 onwards, information on the risks of the use of tobacco containing products and advice to quit smoking will be given to patients at every visit. 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.

4.3.4 Adherence

Adherence to randomized product is determined by product use as described in section 5.2. A patient is considered adherent to randomized arm if their product use category matches the randomized arm, i.e., a patient determined to be a cigarette smoker per section 5.2 and was randomized to the cigarette arm is considered adherent.

Patients who were not adherent to the cigarette smoker or IQOS arm are considered not adherent to their randomized arm.

5 DERIVED AND COMPUTED VARIABLES

5.1 Dental/Clinical Assessments

5.1.1 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.

For each patient, Full mouth PD for a visit is calculated by the following formula which estimates the mean PD per tooth and then averages this for all teeth,

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

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 $s_i \geq 4$.

5.1.2 Clinical Attachment Level (CAL)

CAL is the measured distance from an invariable reference point such as cementoenamel junction (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.

For each patient, 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 $s_i \geq 4$.

5.1.3 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 patient, 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 $j = 1, \dots, s_i$.

5.1.4 Gingival Index (GI)

The degree of gingival inflammation of the target teeth is assessed by calculating the GI of each target tooth during visits V1, V3 and V4. Six surfaces of each tooth of the target teeth 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 patient, GI of target teeth is calculated by averaging the score for each target tooth, then averaging over the target teeth using the following formula (Löe, 1967),

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

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

5.1.5 Plaque Control Record (PCR)

Presence of the plaque on individual tooth surfaces in full mouth is assessed and PCR (%) is calculated. PCR will be recorded as YES or NO 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 patient, 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 , $i = 1, \dots, t$ at the surface j where $j = 1, \dots, s_i$.

5.2 Product Use

The number of Cigarettes, Heatsticks, and other nicotine/tobacco containing product used daily, as reported by the patient and collected in the electronic diary, will be used to monitor product use and evaluate adherence to product allocation.

Patients will be classified according to their monthly actual product use pattern into four categories: cigarette users; IQOS user, dual user, or other as described in Figure 2. "Other" will include the following products: Other heat not burn products, e-cigarettes, Smokeless Tobacco Pipe, Smokeless Tobacco, Cigars/Pipes/Kiseru/Shisha, and Nicotine Replacement Therapy.

The calculation of the monthly product use to classify patients into the four categories is described in section 5.2.3

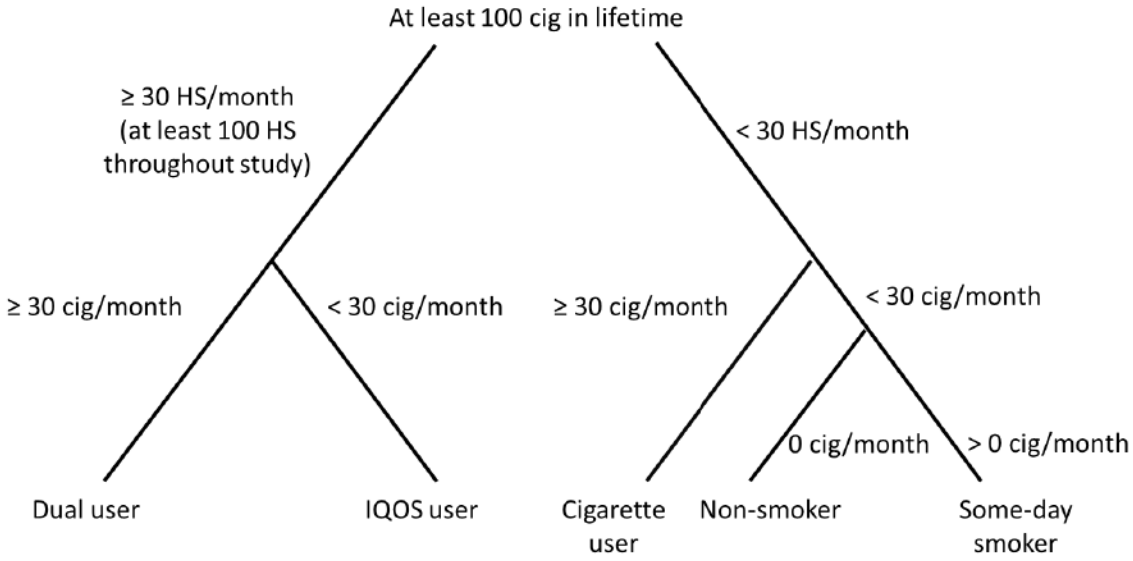


Figure 2: Product Use Categories

Abbreviations: HS, Marlboro HeatSticks; cig, cigarette

5.2.1 Total product consumption

The total number of products (HeatSticks, cigarette, other heat not burn products, e-cigarettes, smokeless tobacco pipe, smokeless tobacco, cigars/pipes/kiseru/shisha and nicotine replacement therapy) consumed will be defined as a sum of product consumption recorded on patient's self-reporting from their monthly product use questionnaires post randomization.

$$\left[\text{Total product consumption} = \sum_{i} (\text{Product consumption recorded at monthly self reporting})\right]$$

where i is the month where product use was recorded.

5.2.2 Daily product consumption

Number of daily product (HeatSticks, cigarette, other heat not burn products, e-cigarettes, smokeless tobacco pipe, smokeless tobacco, cigars/pipes/kiseru/shisha and nicotine replacement therapy) usage will be defined as an average of total consumption of each product (see 5.2.1) divided by the number of days from randomization until last reported monthly product use.

$$\left[\text{Daily product consumption} = \frac{\text{Total product consumption}}{\text{Total number of days}}\right]$$

where *i* is the month where product use was recorded.

5.2.3 Monthly product consumption

Number of monthly product (HeatSticks, cigarette, other heat not burn products, e-cigarettes, smokeless tobacco pipe, smokeless tobacco, cigars/pipes/kiseru/shisha and nicotine replacement therapy) usage will be defined the daily average (see 5.2.2) multiplied by 30.

$$\left[\text{Monthly product consumption} = 30 * \frac{\text{Total product consumption}}{\text{Total number of days}}\right]$$

5.2.4 Percentage for specific product consumption for dual-users

Percentage for specific product consumption (HeatSticks and cigarettes) will be defined as total consumption of the specific product divided by all product consumption (excluding all other products) from post randomization until date of last self-reported product use.

$$\left[\text{Percentage for specific product consumption to all product consumption (\%)} = \frac{\text{Total consumption of a given product}}{\text{Total consumption of Heatsticks and cigarettes}}\right]$$

5.2.5 Average cigarette consumption at V3 and V4.

For each patient regardless of randomized arm, the average daily cigarette consumption at V3 and V4 will be calculated. This will be done as described in section 5.2.2 except that total consumption up to each visit and days elapsed since randomization will be used.

$$\left[\text{Daily product consumption at } V_i = \frac{\text{Total product consumption until } V_i}{\text{Total number of days until } V_i}\right], i = 3, 4$$

vhere V_3 is Visit 3 and V_4 is Visit 4.

5.3 Urinary Biomarkers

5.3.1 Nicotine Equivalents

The concentration of Neq in spot urine will be derived according to the formula below, and considering the conversion factors described in Table 1. The concentrations reported for free nicotine and its five major metabolites will not be used individually as analysis variables.

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

Table 1: Conversion factors from ng/ml into µmol/L

	Molecular weight (g/mol)	**Conversion factor from ng/mL to µmol/L**
Free Nicotine	162.232	0.006164
Nicotine glucuronide	338.356	0.002955
Cotinine	176.218	0.005675
Cotinine-glucuronide	352.341	0.002838
Trans-3'hydroxycotinine	192.217	0.005202
Trans-3'hydroxycotinine-glucuronide	368.34	0.002715

5.3.2 Biomarkers of Exposure adjusted for Creatinine

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

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

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

5.3.3 Change from baseline

Mean change from Baseline is the mean of all individual patients' change from Baseline values. Each individual change from Baseline will be calculated by subtracting the individual patient's Baseline value from the value at a given timepoint.

For log-transformed variables, the geometric relative change (RC) from baseline will be calculated,

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

Where ln(x) is the natural logarithm of the observation and ln(base) is the natural logarithm

of the baseline value.

5.3.4 Coefficient of variation

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

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

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

6 SAMPLE SIZE JUSTIFICATION

The sample size needed to attain 80% power to show at least a 0.25 mm gain of PD in IQOS user compared to the cigarette user categories as defined in Figure 2, 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 was172 patients in total (86 randomized in each arm).

7 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

Changes to “As Exposed Set” to exclude patients with major protocol deviations that affect evaluability of the data. The removal of the “Adherent Use Set” from the analysis sets.

8 ANALYSIS SETS

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

As this study was intended to investigate the effects of IQOS and/or cigarettes on periodontitis treatment, therefore patients who are not in the cigarette, IQOS or dual-user product use categories will not be analyzed except in the Safety Set described below. There is no systematic way to quantify product use for patients who were using other products and the effects of these products on periodontitis are not known. Furthermore, this study was not powered to assess the impact of other products on periodontitis.

8.1 As Exposed Set

The As Exposed Set consists of all randomized patients who have at least one post-randomization product use experience, who have at least one valid non-safety assessment after randomization and have no major protocol deviation that influences the evaluability of the study data. The major protocol deviations are described in "12.1 Major Protocol Deviations". The As Exposed Set will be analysed by actual exposure (see "product use pattern").

8.2 Full Analysis Set

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 analysed by randomized study product.

8.3 Per Protocol Set

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. The major protocol deviations are described in "12.1 Major Protocol Deviations". The Per Protocol will be analyzed by randomized study product.

8.4 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 (see "product use pattern").

8.5 **Protocol Deviations**

All protocol deviations will be entered into the Electronic Data Capture (EDC), Rave, by the CRAs.

Information from the source documents will represent the primary source of protocol deviations. Information following manual reviews after the event will be documented in follow-up letters, audit documentation and will be recorded and tracked in Rave. 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 Rave, following site monitoring and other manual reviews will be reviewed against the individual data points in the Case Report Form (CRF) database by PMI 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, Data Management Plan (DMP) and Clinical Monitoring Plan of the CRO. All deviations will be reviewed periodically by PMI, as determined at study start, to identify trends to improve monitoring and/or potential impact on the statistical analysis.

8.5.1 Major Protocol Deviations

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

Patients with major PDs below will be identified to determine whether they will be excluded from any of the analysis sets.

The following general rules will be applied to determine if a deviation was major:

1. If more than 2 out of 6 sites at a measured tooth were not evaluated, then it will be considered major, evaluable.
2. Protocol violations pertaining to inclusion/exclusion criteria will considered major deviations, evaluable if no results or safety is impacted.
3. Protocol violations pertaining to ICF will be considered major deviations, evaluable if no results or safety is impacted. If the ICF was not signed then the patient will be major, non-evaluable.
4. Samples that were destroyed in error were considered major, evaluable.

8.5.2 Minor Protocol Deviations

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

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Data analysis will be performed using SAS® Version 9.2 or higher.

9.1.1 Stratified Presentation

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).

9.1.2 Sub-group Analyses

The following factors will be used for the sub group analysis.

- Sex (Male/Female)
- Age (30≤ <40, 40≤ <50, 50≤ <60, 60≥)

9.1.3 Descriptive Statistics

9.1.3.1 Descriptive Statistics in general

For continuous data, summary statistics will include the number of patients [n], number and percentage of patients with missing data, the mean and standard deviation (SD), median, first and third quartiles, minimum and maximum, and 95% confidence interval (CI). The change from baseline will be presented as well. For confidence intervals calculated for bounded endpoints, for example, percentages which should be only between 0 and 100%, the CI's will be truncated to 0 if it is negative and 100% if it is greater than 100%.

Log-normally distributed data (*e.g.*, BoExp data) will also include the geometric mean, 95% CI of geometric mean, and coefficient of variation (CV) will be presented in addition to the mean and SD. The geometric relative change from baseline will be presented.

For categorical data, frequency counts and percentages will be presented.

Descriptive statistics will be presented by product exposure for As Exposed and Safety sets, by randomization arm for all other sets, and overall (across the entire study population) at each time point, where applicable.

9.1.3.2 Descriptive Statistics for Exploratory Analysis

Descriptive statistics will be reported by product exposure 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.

9.1.3.3 Median Absolute Deviation (MAD)

Calculate median absolute deviation with the following equation.

$$[\text{MAD} = \text{median}\ (|X_i - \text{median}(X)|)]$$

where X_i is a sequence of observations $(i = 1, \dots, n)$ for the variable X.

9.1.3.4 Rounding

For the calculation of summary statistics and statistical analysis, unrounded data will be used.

In listings, data will be presented with the same precision as the original data at the time of creating the output, unless otherwise specified. Derived data will be rounded for presentation purposes.

For all summaries, mean, standard deviation, percentage, quartiles, median absolute deviation (MAD) and median will be presented to one decimal place greater than the original data and the minimum and maximum will be presented to the same number of decimal places as the original data.

9.1.3.5 Sort Order for Listings

Data will be presented in listings, sorted by patient, day and study visit, unless otherwise specified. All unscheduled assessments will be included in the listings.

9.1.4 Definitions for Statistical Data Analysis

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 all periodontal assessments for that tooth will be excluded from the calculation of the means over all teeth (see Section 5.1.1).

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 calculation of creatinine adjusted BoExp if the denominator is below LLOQ then the ratio will not be calculated and will be tabulated as "Not Calculated" in descriptive summaries and excluded from the main analysis.

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.

9.1.5 Handling of Dropouts or Missing Data

9.1.5.1 Drop Out (withdrawal)

Subjects who dropped out from the study in any way will have their data analyzed up to the point of last contact.

9.1.5.2 For Missing or Partial Dates

Missing dates for Visits after randomization will be imputed by adding nominal days to the date of randomization. If the imputed date falls after EOS date (e.g. for early terminated subjects), then the end of study date will be used.

Partial dates will not be imputed for Adverse Events (AEs), for medical history, and for concomitant medications, but assumptions will be made as follows to assign them to specific analysis categories:

Date information	AE data	Medical History/Concomitant Disease data	Prior and Concomitant Medication data
Missing or Partial date (e.g., --May2012, or ----2011). If month/year is the same as, or later than the month and/or year of Screening.	Included in summaries	Concomitant disease (included in summaries)	Concomitant Medication (included in summaries)
Partial date, (e.g., --May2012, or ----2011). If month and/or	Listings	Medical history	Prior medication

year is earlier than the month and/or year of Screening.	only	(included in summaries)	(included in summaries)

9.1.6 Handling of Unplanned Data

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

9.1.7 Multicenter Studies

The study will be conducted at multiple centers. In order to consider the effects on the endpoint analysis caused by site, site will be included as a random effect in statistical model. Detail will be described in 9.5.1.

9.1.8 Multiple Comparison/Multiplicity

There will be an adjustment for multiplicity for the secondary testing of CAL and PD within the As Exposed Set, as well as for BoExp. PD at 3 months and CAL at 6 and 3 months will be tested in a hierarchical manner, depending on the outcome of the test at previously specified endpoint in hierarchical testing order. The order of testing is as follows,

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 secondary analysis of 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%.

9.2 Disposition of Subjects

Summary Table of Subject Disposition		
Population	:	All subjects screened
Contents	:	• All subjects screened • All screen failure subjects (include subjects who were enrolled but not randomized) ➢ Primary reason for screen failure • All subjects randomized ➢ Randomized (IQOS/Cigarettes) ➢ Completed subject ➢ Discontinued subject • Reason of discontinuation
Remarks	:	Percentage will be presented for disposition events after randomization and the denominator will be the number of subjects randomized into each arm.
Output		15.2.1.1 Summary Table of Subject Disposition - All Subjects Screened - 15.3.1.1 Listing of Subject Disposition - All Subjects Screened - 15.3.1.2 Listing of Screen Failed Subjects and Reason - All Subjects Screened - 15.3.1.3 Listing of Informed Consent - All Subjects Screened -

9.3 Demographic and Other Baseline Characteristics

Summary Table of Analysis Sets		
Population	:	All subjects randomized ➢ Randomization arm ➢ Product use pattern categories
Contents	:	The number and percentage of subjects of analysis set defined in "population" will be presented.

Output		15.2.2.1 Summary Table of Analysis Sets by Randomization Arm - Randomized Subjects - 15.2.2.2 Summary Table of Analysis Sets by Product Use Categories - Randomized Subjects - 15.3.2.1 Listing of Analysis Sets - Randomized Subjects -

Summary Table of Demographics		
Population	:	• As Exposed Set ➢ Product use pattern categories • Full Analysis Set ➢ Randomization arm • Per Protocol Set ➢ Randomization arm • Safety Set ➢ Product use pattern categories
Contents	:	Refer to Descriptive statistics
Analysis variables	:	• Age [years] • Age (30≤ <40, 40≤ <50, 50≤ <60, 60≥) • Sex (Male, Female) • Race (Asian, Black or African American, White, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native) • Nationality (Japanese) • Daily cigarette consumption over the month prior to V1 (10-19 cigarettes/day, > 19 cigarettes/day) • Disease severity in smokers with generalized chronic periodontitis (PD < 5mm, PD ≥ 5mm) • Cotinine (Negative < 200 ng/mL, Positive ≥ 200 ng/mL)
		• Use the value of age from SDTM datasets. • Denominator will be the number of subjects in the target population. For the race, no percentage will be calculated since multiple selections are permitted.
Output		15.2.2.3 Summary Table of Demographics by Product Use Categories - As Exposed Set -

		15.2.2.4 Summary Table of Demographics by Randomization Arm - Full Analysis Set, Per Protocol Set, Safety Set - 15.3.2.2 Listing of Demographics - As Exposed Set -

Summary Table of Smoking History		
Population	:	• As Exposed Set ➢ Product use pattern categories • Full Analysis Set ➢ Randomization arm • Per Protocol Set ➢ Randomization arm
Contents	:	Refer to Descriptive statistics
Analysis variables	:	• Smoked for at least the past 5 consecutive years • Number of cigarettes smoked per day over the last 5 years [cig/day] • Number of menthol cigarettes per day [cg/day] • Number of years of smoking history [years] • Number of cigarettes smoked per day after starting smoking [cig/day]
Output		15.2.2.5 Summary Table of Smoking History by Product Use Categories - As Exposed Set - 15.2.2.6 Summary Table of Smoking History by Randomization Arm - Full Analysis Set, Per Protocol Set - 15.3.2.3 Listing of Smoking History - As Exposed Set - 15.3.2.4 Listing of Starter Kit Information - As Exposed Set -

Summary Table of Baseline Characteristics of Periodontal Disease		
Population	:	• As Exposed Set ➢ Product use pattern categories
Contents	:	Refer to Descriptive statistics. Calculate the descriptive statistics by

Summary Table of Baseline Characteristics of Periodontal Disease		
		Cigarette Consumption Prior to V1, Pocket Depth at V1, and overall for each analysis item.
Analysis variables	:	• Teeth Count • Pocket Depth (mm) • Clinical Attachment Loss (mm) • Bleeding on Probing (%) • Gingival Index • Plaque Control Record (%)
Output		15.2.2.7 Baseline Characteristics of Periodontal Disease - As Exposed Set -

Summary Table of Medical History		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	The number and percentage of patients experiencing medical history and the number of medical history will be counted by Medical Dictionary for Regulatory Activities (MedDRA, Version 20.0 or higher) System Organ Class (SOC) term and Preferred Term (PT). All cases collected on the form for medical history of CRF (MHCAT=" MEDICAL HISTORY") will be tabulated.
Definition	:	Medical history is defined as any condition that started and ended prior to ICF signature.
Remark	:	SOC and PT will be sorted by alphabetical order.
Output		15.2.3.1 Summary Table of Medical History - Safety Set - 15.3.3.1 Listing of Medical History/ Concomitant disease and Periodontal Disease - Safety Set -

Summary Table of Periodontal Disease History

Summary Table of Periodontal Disease History		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	The number and percentage of patients experiencing periodontal disease and the number of periodontal disease history will be counted by Medical Dictionary for Regulatory Activities (MedDRA, Version 20.0 or higher) SOC and PT. All cases collected on the form for periodontal disease history (MHCAT=" PERIODONTAL DISEASE HISTORY") will be tabulated.
Definition	:	Periodontal disease history is defined as any condition that started and ended prior to ICF signature.
Remark	:	SOC and PT will be sorted by alphabetical order.
Output		15.2.3.3 Summary Table of Periodontal Disease History - Safety Set -

Summary Table of Concomitant Disease		
Population	:	• **Safety Sets** ➢ **Product use pattern**
Contents	:	The number and percentage of patients experiencing concomitant disease and the number of concomitant disease will be counted by Medical Dictionary for Regulatory Activities (MedDRA, Version 20.0 or higher) SOC and PT. All cases collected on the form for concomitant disease (MHCAT=" CONCOMITANT DISEASE") will be tabulated.
Definition	:	A concomitant disease is defined as any condition that started prior to ICF signature and is still ongoing at the end of V1.
Remark	:	SOC and PT will be sorted by alphabetical order.
Output		15.2.3.2 Summary Table of Concomitant Disease - Safety Set -

9.4 Product Use Pattern Categories/Product Adherence

Summary Table of Product Use		
Population	:	• As Exposed Set ➢ Product use pattern categories • Per Protocol Set
Contents	:	Refer to Descriptive statistics
Analysis variables	:	• For cigarettes ➢ Days of exposure to cigarettes [days] ➢ Daily product consumption (cigarettes)[/day] • For IQOS ➢ Days of exposure to IQOS [days] ➢ Daily product consumption (IQOS) [heatsticks/day] • For heat-not-burn other than IQOS ➢ Days of exposure to heat-not-burn other than IQOS [days] ➢ Daily product consumption (heat-not-burn other than IQOS) [/day] • For e-cigarettes ➢ Days of exposure to e-cigarettes [days] ➢ Daily product consumption(e-cigarettes) [/day] • For smokeless tobacco pipe ➢ Days of exposure to smokeless tobacco pipe [days] ➢ Daily product consumption smokeless tobacco pipe [/day] • For smokeless tobacco product ➢ Days of exposure to smokeless tobacco pipe [days] ➢ Daily product consumption smokeless tobacco pipe [/day] • For cigar/ pipe/ kiseru/ shisha ➢ Days of exposure to cigar/ pipe/ kiseru/ shisha [days] ➢ Daily product consumption (cigar/ pipe/ kiseru/ shisha) [/day] • For nicotine replacement therapy ➢ Days of exposure to nicotine replacement therapy [days]

Summary Table of Product Use		
		➢ Daily product consumption (nicotine replacement therapy) [/day]
Target visit		Overall for the summary table, month 1 to 6 and overall for listing.
Output		15.2.4.1 Summary Table of Product Use Categories - As Exposed Set, Per Protocol Set - 15.3.4.1 Listing of Product Use Categories - As Exposed Set -

9.5 Endpoint Evaluation

9.5.1 Primary Analyses

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.

9.5.1.1 Primary Analyses

Primary Analysis of Change from Baseline in PD at V4		
Population	:	• As Exposed Set For this analysis, subjects categorized in IQOS user, cigarette user or dual user will be included with initial PD ≥ 4mm will be included.
	:	The primary analysis will be performed on the As Exposed Set using a mixed model for repeated measurements (MMRM). Estimates of difference in PD will be calculated for Cigarette User against IQOS User categories and Cigarette User against Dual User categories. The model will include the PD change from baseline as the dependent variable, adjusting for the following covariates; 1. Daily cigarette consumption at V1 2. Disease severity at V1 3. Full mouth PD at V1 4. Visit 5. Product use pattern (IQOS user, cigarette smoker or dual user) 6. Interaction between visit and product use

Primary Analysis of Change from Baseline in PD at V4		
		7. Average daily cigarette use at each visit 8. Interaction between Daily cigarette consumption at V1 and product use 9. Interaction between Disease severity at V1 and product use 10. Time since last SRP 11. Number of target tooth/teeth extracted 12. Number of non-measured target tooth/teeth extracted 13. Baseline tooth mobility Site will be included as a random effect. The degrees of freedom will be adjusted by using Kenward Roger (KR) method. A Toeplitz structure ("type=toep") will be specified as the covariance matrix. However, other covariance structures may be used in case of non-convergence. Covariates 8-12 will be assessed for adequacy in the model using a step-wise (backward) approach through the following algorithm. 1. Fit a full model using maximum likelihood with all covariates 2. Perform a likelihood ratio test for the full model and drop the covariate with the largest p-value for the likelihood ratio statistic if it is more than 0.05. 3. Drop one covariate (only covariates 7-14) and re-fit the model. 4. Perform a likelihood ratio test and drop the covariate with the largest p-value for the likelihood ratio statistic if it is more than 0.05. 5. Repeat steps 2 and 3 until no more covariates can be dropped. 6. Refit the final model with the covariates remaining in the model and estimate PD for each product use group using the restricted likelihood method. Note that other covariates may be added if deemed necessary. Number of subjects included in analysis, regression coefficients, 95% CI for regression coefficient, p-value for regression coefficient, Least Squares (LS) means (Cigarette User, IQOS User and Dual-User categories), Difference in LS Means (Cigarette User vs IQOS User/Dual-User) and 95% CI for Difference in LS Means will be presented. The model fit will be assessed by the analysis of the residual (diagnostics) and by comparing the values predicted vs. the observed values (calibration).

Primary Analysis of Change from Baseline in PD at V4		
		The residuals, predicted vs observed values from the final model will be plotted.
Target visit	:	V4 (6 Months)
Sample code		ODS GRAPHICS ON; PROC MIXED DATA = X METHOD=ML (REML for final model); CLASS *Product_use Subject Visit site*; MODEL *PD reduction (Dependent variable) = avisit avisit*trt01a 3 4 5 6 7 8 9 10 11 12/* ddfm=kr outp=dsn residuals vciry; RANDOM *Site*; REPEATED / subject=visit (subject) type=toep; LSMEANS *Product_use * Visit* / CL ALPHA=0.025 DIFF E UPPER; RUN; Where *1 2 3 4 5 6 7 8 9 10 11 12 refers to the covariates.* ODS GRAPHICS OFF;
Output		15.4.5.1 Primary Analysis of Change from Baseline in Pocket Depth (mm) at V4 with Initial Pocket Depth ≥ 4 mm - As Exposed Set - 15.4.5.2 Regression Coefficients and Graphical Diagnostics of Primary Analysis of Change from Baseline in Pocket Depth (mm) at V4 - As Exposed Set - 15.4.5.3 Primary Analysis of Change from Baseline in Pocket Depth (mm) at V4: Variables Dropped - As Exposed Set -

Summary Table of Mean full-mouth PD		
Population	:	• As Exposed Set ➢ Product use pattern categories
Contents	:	Refer to Descriptive statistics
Analysis	:	• Mean in full-mouth PD

variables		• Change in mean full-mouth PD from baseline
Target visit		• Baseline • V3 (3 months) • V4 (6 months)
Output		15.2.5.1 Descriptive Statistics of Mean Full-mouth Pocket Depth (mm) and 95% CI - As Exposed Set - 15.2.5.2 Descriptive Statistics of Mean Pocket Depth (mm) in Subjects with Initial Pocket Depth ≥ 4 mm - As Exposed Set - 15.1.5.1 Plot of Full-Mouth Pocket Depth (mm) and 95% CI vs Visit by Product Use Categories - As Exposed Set - 15.1.7.1 Plot of Full-Mouth Pocket Depth (mm) and 95% CI vs Visit by Product Use Categories and Disease Severity - As Exposed Set - 15.1.7.2 Plot of Full-Mouth Pocket Depth (mm) and 95% CI vs Visit by Product Use Categories and Daily Cigarette Consumption - As Exposed Set - 15.1.7.3 Plot of Full-Mouth Pocket Depth (mm) and 95% CI vs Visit by Product Use Categories, Disease Severity and daily Cigarette Consumption - As Exposed Set - 15.1.7.4 Plot of Full-Mouth Pocket Depth (mm) and 95% CI vs Visit by Product Use Categories for Subjects with Initial Pocket Depth ≥ 4 mm - As Exposed Set - 15.3.5.1 Listing for Pocket Depth (mm) Value - As Exposed Set – 15.1.9.4 Plot of Mean Pocket Depth (mm) for Initials Sites with Pocket Depth ≥ 4 mm - As Exposed Set -

9.5.1.2 Supportive Analysis for Primary Objective

Supportive/Sensitivity Analyses of Change from Baseline in PD		
Population	:	• Full Analysis Set • Per Protocol Set
Contents	:	Refer to "Primary Analysis"
Target visit	:	• V3 (3 months) • V4 (6 months)

Supportive/Sensitivity Analyses of Change from Baseline in PD		
Sample code		Refer to "Primary Analysis"
Output		15.4.6.1 Analysis of Change from Baseline in Pocket Depth (mm) with Initial Pocket Depth ≥ 4 mm - Full Analysis Set, Per Protocol Set - 15.4.6.2 Regression Coefficients and Graphical Diagnostics of Analysis of Change from Baseline in Pocket Depth (mm) - Full Analysis Set , Per Protocol Set -

Summary Table of Mean Full-Mouth PD by (i) Daily Cigarette Consumption, (ii) Disease Severity (iii) Age group		
Population	:	• As Exposed Set • Full Analysis Set • Per Protocol Set
Contents	:	Refer to Descriptive statistics
Analysis variables	:	• Mean full-mouth PD • Change of mean full-mouth PD
Target visit		• Baseline • V3 (3 months) • V4 (6 months)
Remarks		Output titles to be changed depending on target population.
Output		15.2.6.1 Summary Table of Mean Full-Mouth Pocket Depth (mm) by Disease Severity - As Exposed Set, Full Analysis Set, Per Protocol Set - 15.2.6.2 Summary Table of Mean Full-Mouth Pocket Depth (mm) by Daily Cigarette Consumption - As Exposed Set, Full Analysis Set, Per Protocol Set - 15.2.6.3 Summary Table of Mean Full-Mouth Pocket Depth (mm) by Sex - As Exposed Se, Full Analysis Set, Per Protocol Set - 15.2.6.4 Summary Table of Mean Full-Mouth Pocket Depth (mm) by Age Group - As Exposed Set, Full Analysis Set, Per Protocol Set -

9.5.2 Secondary Analyses

9.5.2.1 Secondary Analysis

Analysis of Change from Baseline in PD at V3 and CAL at V4 / V3		
Population	:	• As Exposed Set
Contents	:	The model will include the PD (or CAL) change from baseline as the dependent variable, adjusting for the following covariates; • The statistical model is described in section 9.5.1. Note that "Full mouth PD at V1" will be replaced as "Full mouth CAL at V1"
Target visit	:	• V3 (3 Months) for PD • V3 (3 Months) and V4 (6 Months) for CAL
Remarks	:	• Statistical tests for PD at V3, CAL and V4 and V3 are performed in a sequential manner as detailed in section 9.1.8. • The same model for the primary analysis will be used with both V3 and V4 data included; PD at 3 months will be reported only if the test for PD between Cigarette User and IQOS User categories at 6 months is significant. • If the test between Cigarette User and IQOS Users Categories for PD is significant at V3, then the model with change from baseline CAL will be fitted with both V3 and V4 data and the test between CC and IQOS for CAL at V4 will be reported. • If the test between Cigarette User and IQOS User categories for CAL at V4 is significant, then the test between Cigarette User and IQOS User Categories for CAL at V3 will be reported.
Sample code		Refer to "Primary Analysis"
Output		15.4.7.1 Analysis of Change from Baseline in Pocket Depth (mm) at V3 with Initial Pocket Depth ≥ 4 mm - As Exposed Set - 15.4.7.2 Regression Coefficients and Graphical Diagnostics of Analysis of Change from Baseline in Pocket Depth (mm) at V3- As Exposed Set - 15.4.7.3 Analysis of Change from Baseline in Clinical Attachment Level (mm) with Initial Pocket Depth ≥ 4 mm - As Exposed Set -

Analysis of Change from Baseline in PD at V3 and CAL at V4 / V3		
		15.4.7.4 Regression Coefficients and Graphical Diagnostics of Analysis of Change from Baseline in Clinical Attachment Level (mm) - As Exposed Set - 15.4.7.17 Analysis of Change from Baseline in Pocket Depth (mm) at V3: Variables Dropped - As Exposed Set - 15.4.7.18 Analysis of Change from Baseline in Clinical Attachment Level (mm): Variables Dropped - As Exposed Set -

Summary Table of Analysis for BoExp Geometric mean value		
Population	:	• As Exposed Set
Contents	:	The analysis will be performed on the As Exposed Set using a mixed model for repeated measurements (MMRM). The model will include the change from baseline of log transformed BoExp adjusted for creatinine as the dependent variable, adjusting for the following covariates; 1. Daily cigarette consumption 2. Sex 3. Visit 4. Baseline level of BoExp 5. Product use 6. Interaction between visit and product use 7. Interaction between Daily cigarette consumption at V1 and product use 8. Average daily cigarette use at each visit Site will be included as a random effect. For analysis, PROC MIXED will be used. Site will be included as RANDOM effect. Degree of freedom will be adjusted by using KR. Number of patients included in analysis, regression coefficient, 95% CI for regression coefficient, p-value for regression coefficient,

Summary Table of Analysis for BoExp Geometric mean value		
		Geometric LS means (IQOS-cigarette), Ratio of Geometric LS Means and 95% CI for Ratio of Geometric LS means at 3 and 6 month for each product use will be presented. The modelling 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). • Predicted value and observed value will be plotted.
Analysis Variables	:	• NEQ adjusted for creatinine • Total NNAL adjusted for creatinine • CEMA adjusted for creatinine
Target visit	:	• Baseline • V3 (3 months) • V4 (6 months)
Remarks	:	• Statistical tests for each BoExp at V3 and V4 performed in a sequential manner as detailed in section 9.1.8. • The same model for the analysis will be used with both V3 and V4 data included, if the test between CC and IQOS is significant at V4 then the test between CC and IQOS for V3 will be reported in the same table.
Sample code		Refer to "Primary Analysis"
Output		15.4.7.5 Analysis of Relative Change from Baseline in NEQ (mg/g) (Biomarkers of Exposure) (Geometric LS means, Ratio of Geometric Means and p-value) - As Exposed Set - 15.4.7.6 Regression Coefficients and Graphical Diagnostics of Analysis of Relative Change from Baseline in NEQ (mg/g) (BoExp) Geometric Mean Value - As Exposed Set - 15.4.7.7 Analysis of Relative Change from Baseline in Total NNAL (pg/mL) (Biomarkers of Exposure) (Geometric LS means, Ratio of Geometric Means and p-value) - As Exposed Set - 15.4.7.8 Regression Coefficients and Graphical Diagnostics of Analysis of Relative Change from Baseline in Total NNAL (pg/mL) (Biomarkers of Exposure) Geometric Mean Value - As Exposed Set -

Summary Table of Analysis for BoExp Geometric mean value		
		15.4.7.9 Analysis of CEMA (ng/mL) (Biomarkers of Exposure) Geometric Mean Value - As Exposed Set - 15.4.7.10 Regression Coefficients and Graphical Diagnostics of Analysis of Relative Change from Baseline in CEMA (ng/mL) (Biomarkers of Exposure) - As Exposed Set - 15.4.7.11 Analysis of NEQ Adjusted for Creatinine (mg/dL) (Biomarkers of Exposure) Geometric Mean Value - As Exposed Set - 15.4.7.12 Regression Coefficients and Graphical Diagnostics of Analysis of Relative Change from Baseline in NEQ Adjusted for Creatinine (mg/g creat) (Biomarkers of Exposure) - As Exposed Set - 15.4.7.13 Analysis of Total NNAL Adjusted for Creatinine (pg/mL creat) (Biomarkers of Exposure) Geometric Mean Value - As Exposed Set - 15.4.7.14 Regression Coefficients and Graphical Diagnostics of Analysis of Change from Baseline in Total NNAL Adjusted for Creatinine (pg/mL creat) (Biomarkers of Exposure) - As Exposed Set - 15.4.7.15 Analysis of CEMA Adjusted for Creatinine (ng/mL creat) (Biomarkers of Exposure) Geometric Mean Value - As Exposed Set - 15.4.7.16 Regression Coefficients and Graphical Diagnostics of Analysis of Change from Baseline in CEMA Adjusted for Creatinine (ng/mL creat) (Biomarkers of Exposure) - As Exposed Set -

Summary Table of Mean Full-Mouth CAL		
Population	:	• As Exposed Set ➢ Product use pattern categories
Contents	:	Refer to Descriptive statistics
Analysis variables	:	• Mean full-mouth CAL • Change of mean full-mouth CAL

Summary Table of Mean Full-Mouth CAL		
Target visit		• Baseline • V3 (3 months) • V4 (6 months)
Output		15.1.7.5 Plot of Full-Mouth Clinical Attachment Level (mm) and 95% CI vs Visit by Product Use Categories - As Exposed Set - 15.1.7.6 Plot of Full-Mouth Clinical Attachment Level (mm) and 95% CI vs Visit by Product Use Categories and Disease Severity - As Exposed Set - 15.1.7.7 Plot of Full-Mouth Clinical Attachment Level (mm) and 95% CI vs Visit by Product Use Categories and Daily Cigarette Consumption - As Exposed Set - 15.1.7.8 Plot of Full-Mouth Clinical Attachment Level (mm) and 95% CI vs Visit by Product Use Categories, Disease Severity and daily Cigarette Consumption - As Exposed Set - 15.1.7.9 Plot of Full-Mouth Clinical Attachment Level (mm) and 95% CI vs Visit in Patients with Initial Pocket Depth ≥ 4 mm - As Exposed Set - 15.2.7.1 Descriptive Statistics of Mean Full-Mouth Clinical Attachment Level (mm) and 95% CI- As Exposed Set - 15.3.7.1 Listing for Clinical Attachment Level (mm) Value - As Exposed Set – 15.1.9.5 Plot of Clinical Attachment Loss (mm) for initials sites with Pocket Depth ≥ 4 mm - As Exposed Set -

Summary Table of Change in PD in Sites Based on Baseline PD Level		
Population	:	• As Exposed Set
Contents	:	Refer to Descriptive statistics In addition, a bar graph representing the mean PD in sites with different Initial PD, and a heatmap of PD against time by product use category will be created.
Analysis variables	:	• PD • Change of mean PD

Summary Table of Change in PD in Sites Based on Baseline PD Level		
Category		Initial PD of • PD < 4 mm • 4 mm ≤ PD < 5mm • 5 mm ≤ PD < 6 mm • 6 mm ≤ PD < 7 mm • PD ≥ 7 mm
Target visit		• Baseline • V3 (3 months) • V4 (6 months)
Output		15.2.7.2 Summary Table of Change in Pocket Depth (mm) in Sites based on Initial Pocket Depth (mm) Level - As Exposed Set - 15.1.7.14 Mean Pocket Depth (mm) in Sites with Different Initial Pocket Depth (mm) - As Exposed Set - 15.1.9.3 Heatmap of Pocket Depth (mm) Level Count by Time and Product Use Categories - As Exposed Set -

Summary Table of Change in CAL in Sites Based on Baseline PD Level		
Population	:	• As Exposed Set
Contents	:	Refer to Descriptive statistics
Analysis variables	:	• CAL • Change of mean CAL
Category		Initial PD of • PD < 4 mm • 4 mm to ≤ PD < 5mm • 5 mm to ≤ PD < 6 mm • 6 mm to ≤ PD < 7 mm • PD ≥ 7 mm
Target visit		• Baseline • V3 (3 months)

Summary Table of Change in CAL in Sites Based on Baseline PD Level		
		• V4 (6 months)
Output		15.2.7.3 Summary Table of Change in Clinical Attachment Level (mm) in Sites based on Initial Pocket Depth Level (mm) - As Exposed Set -

Shift Table of Change in Number of Sites with PD Level		
Population	:	• As Exposed Set
Contents	:	Provide shift table with percentage based on PD level by product use pattern
Category		PD level at baseline • < 4 mm • 4 mm ≤ PD < 5mm • 5 mm ≤ PD < 6 mm • 6 mm ≤ PD < 7 mm • PD ≥ 7 mm
Target visit		• V3 (3 months) • V4 (6 months)
Output		15.2.7.4 Shift Table in Number of Sites with Pocket Depth Level (mm) - As Exposed Set -

Summary Table of BoExp Parameters		
Population	:	• As Exposed Set ➢ Product use pattern categories
Contents	:	In addition to the contents defined in "Descriptive statistics", 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. In addition, the geometric means, CV and geometric relative change will be presented.

Summary Table of BoExp Parameters		
		Figures of NEQ, total NNAL, CEMA against product use category will be plotted. In addition, scatter plot of CEMA against time and a box plot of CEMA against time by product use will also be prepared.
Analysis variables	:	• NEQ adjusted for creatinine • Total NNAL adjusted for creatinine • CEMA adjusted for creatinine
Target visit		• Baseline • V3 (3 months) • V4 (6 months)
Output		15.2.7.5 Summary Table of Biomarkers of Exposure Parameters (NEQ (mg/g)) - As Exposed Set - 15.2.7.6 Summary Table of Biomarkers of Exposure Parameters (Total NNAL (pg/mL)) - As Exposed Set - 15.2.7.7 Summary Table of Biomarkers of Exposure Parameters (CEMA (ng/mL)) - As Exposed Set - 15.2.7.8 Summary Table of Biomarkers of Exposure Parameters (NEQ adjusted for creatinine (mg/g creat)) - As Exposed Set - 15.2.7.9 Summary Table of Biomarkers of Exposure Parameters (Total NNAL adjusted for creatinine (pg/mg creat)) - As Exposed Set - 15.2.7.10 Summary Table of Biomarkers of Exposure Parameters (CEMA adjusted for creatinine (ng/mg creat)) - As Exposed Set - 15.3.7.2 Listing for Biomarkers of Exposure - As Exposed Set - 15.1.4.1 Plot of NEQ adjusted for creatinine (mg/g creat) vs Visit by Product Use Categories - As Exposed Set - 15.1.4.2 Plot of Total NNAL adjusted for creatinine (pg/mg creat) vs Visit by Product Use Categories - As Exposed Set - 15.1.4.3 Plot of CEMA adjusted for creatinine (ng/mg creat) vs Visit by Product Use Categories - As Exposed Set - 15.1.7.15 Scatter Plot of CEMA adjusted for creatinine (ng/mg creat) vs Time - As Exposed Set - 15.1.7.16 Box Plot of CEMA adjusted for creatinine (ng/mg creat) vs Time by Product Use Categories - As Exposed Set -

Summary Table of Periodontal Examination (BOP, GI, Tooth mobility and PCR)		
Population	:	• As Exposed Set ➢ Product use pattern categories
Contents	:	Refer to Descriptive statistics For GI and Tooth Mobility, in addition to the descriptive statistics shift tables will be constructed based on the individual (discrete) values. Scatter plots of GI and Tooth Mobility vs Visit by Product Use, Initial PD level will be plotted as well.
Analysis variables	:	• BOP (%) • GI • Tooth Mobility • PCR (%)
Target visit		• Baseline • V3 (3 months) • V4 (6 months)
Output		15.2.7.11 Descriptive Statistics of Periodontal Examination (Bleeding On Probing (%)) - As Exposed Set - 15.2.7.12 Descriptive Statistics of Periodontal Examination (Gingival Index) - As Exposed Set - 15.2.7.13 Descriptive Statistics of Periodontal Examination (Tooth Mobility) - As Exposed Set - 15.2.7.14 Descriptive Statistics of Periodontal Examination (Plaque Control Record (%)) - As Exposed Set - 15.2.7.15 Shift Table in Number of Each Category for Gingival Index - As Exposed Set - 15.2.7.16 Shift Table in Number of Each Category for Tooth Mobility - As Exposed Set - 15.3.7.3 Listing for Bleeding On Probing (%) Assessment - As Exposed Set - 15.3.7.4 Listing for Plaque Control Record (%) Assessment - As Exposed Set - 15.3.7.5 Listing for Gingival Index Assessment - As Exposed Set - 15.3.7.6 Listing for Calculated Bleeding On probing (%) and Plaque Control Record (%) - As Exposed Set -

Summary Table of Periodontal Examination (BOP, GI, Tooth mobility and PCR)		
		15.3.7.7 Listing for Tooth Mobility - As Exposed Set - 15.3.7.8 Listing for Periodontal Treatment/Maintenance - As Exposed Set - 15.1.7.10 Scatter Plot of Gingival Index vs Visit by Product Use Categories - As Exposed Set - 15.1.7.11 Scatter Plot of Gingival Index vs Visit by Initial Full-Mouth Pocket Depth (mm) - As Exposed Set - 15.1.7.12 Scatter Plot of Tooth Mobility vs Visit by Product Use Categories - As Exposed Set - 15.1.7.13 Scatter Plot of Tooth Mobility vs Visit by Initial Full-Mouth Pocket Depth (mm) - As Exposed Set -

9.5.2.2 Supportive Analysis for Secondary Objectives

Summary Table of Supportive/Sensitivity Analyses to Evaluate the Change from Baseline in PD at V3 / CAL at V3 and V4		
Population	:	• Full Analysis Set • Per Protocol Set
Contents	:	The model will include the either PD or CAL change from baseline as the dependent variable, adjusting for the following covariates; • The same model described in "Primary Analysis" will be used.
Target visit	:	• V3 (3 Months) for PD • V3 (3 Months)/ V4 (6 Months) for CAL
Remarks	:	• Statistical tests for PD at V3, CAL and V4 and V3 are performed in a sequential manner as detailed in section 9.1.8. • The same model for the primary analysis will be used with both V3 and V4 data included, PD at 3 months will be reported only if the test for PD between CC and IQOS at 6 months is significant. • If the test between Cigarette User and IQOS User categories for PD is significant at V3, then the model with change from baseline CAL will be fitted with both V3 and V4 data and the test between Cigarette User and IQOS User categories for CAL

Summary Table of Supportive/Sensitivity Analyses to Evaluate the Change from Baseline in PD at V3 / CAL at V3 and V4		
		at V4 will be reported. • If the test between Cigarette User and IQOS User categories for CAL at V4 is significant, then the test between Cigarette User and IQOS User categories for CAL at V3 will be reported.
Sample code		Refer to "Primary Analysis"
Output		15.4.8.1 Analyses of Change from Baseline in Clinical Attachment Level (mm) with Initial Pocket Depth ≥ 4 mm - Full Analysis Set, Per Protocol Set - 15.4.8.2 Regression Coefficients and Graphical Diagnostics of Analysis of Change from Baseline in Clinical Attachment Level (mm) - Full Analysis Set, Per Protocol Set -

Summary Table of Supportive/Sensitivity Analyses for BoExp Geometric Mean Value		
Population	:	• Full Analysis Set • Per Protocol Set
Contents	:	Refer to "Summary Table of Analysis for BoExp Geometric mean value".
Sample code		Refer to "Primary Analysis"
Output		15.4.8.3 Analysis of NEQ Adjusted for Creatinine (mg/g creat) (Biomarkers of Exposure) Geometric Mean Value -Full Analysis Set, Per Protocol Set - 15.4.8.4 Regression Coefficients and Graphical Diagnostics of Analysis of Change from Baseline in NEQ Adjusted for Creatinine (mg/g creat) (Biomarkers of Exposure) - Full Analysis Set, Per Protocol Set - 15.4.8.5 Analysis of Total NNAL Adjusted for Creatinine (pg/mL creat) (Biomarkers of Exposure) Geometric Mean Value - Full Analysis Set, Per Protocol Set - 15.4.8.6 Regression Coefficients and Graphical Diagnostics of

Summary Table of Supportive/Sensitivity Analyses for BoExp Geometric Mean Value		
		Analysis of Change from Baseline in Total NNAL Adjusted for Creatinine (pg/mL creat) (Biomarkers of Exposure) - Full Analysis Set, Per Protocol Set - 15.4.8.7 Analysis of CEMA Adjusted for Creatinine (ng/mL creat) (Biomarkers of Exposure) Geometric Mean Value - Full Analysis Set, Per Protocol Set - 15.4.8.8 Regression Coefficients and Graphical Diagnostics of Analysis of Change from Baseline in CEMA Adjusted for Creatinine (ng/mL creat) (Biomarkers of Exposure) - Full Analysis Set, Per Protocol Set -

9.5.3 Exploratory Analyses

Summary Table of Exploratory Analysis to Evaluate the Change in (i) Multiplex assay (MAP) (ii) Parallel Reaction Monitoring (PRM)		
Population	:	• As Exposed Set
Contents	:	The analysis will be performed on the As Exposed Set using a mixed model for repeated measurements (MMRM). The model will include the log change from baseline as the dependent variable, adjusting for the following covariates; 1.Daily cigarette consumption 2.Disease severity at V1 3.MAP/ PRM at V2 4.Visit 5. Product use 6. Interaction between visit and product use 7. Interaction between Daily cigarette consumption at V1 and product use 8. Average daily cigarette use at each visit 9. Interaction between Disease severity at V1 and product use 10. Time since last SRP 11. Number of target tooth/teeth extracted 12.Number of non-measured target tooth/teeth extracted 13. Baseline tooth mobility Site will be included as a random effect. The degrees of freedom will be adjusted by using Kenward Roger (KR) method. A Toeplitz structure ("type=toep") will be specified as the covariance matrix. However, other covariance structures may be used in case of non-convergence. Covariates 7-12 will be assessed for adequacy in the model using a step-wise (backward) approach through the following algorithm. 1. Fit a full model using maximum likelihood with all covariates 2. Perform a likelihood ratio test for the full model and drop the

		covariate with the largest p-value for the likelihood ratio statistic if it is more than 0.05. 3. Drop one covariate (only covariates 7-12) and re-fit the model. 4. Perform a likelihood ratio test and drop the covariate with the largest p-value for the likelihood ratio statistic if it is more than 0.05. 5. Repeat steps 2 and 3 until no more covariates can be dropped. 6. Refit the final model with the covariates remaining in the model and estimate PD for each product use group using the restricted likelihood method. Note that other covariates may be added if deemed necessary. Number of subjects included in analysis, regression coefficients, 95% CI for regression coefficient, p-value for regression coefficient, Least Squares (LS) means (Cigarette, IQOS and Dual-Users), Difference in LS Means (Cigarette vs IQOS/Dual-user) and 95% CI for Difference in LS Means will be presented. • Predicted value and observed value will be plotted.
Target visit	:	• V3 (3 months) • V4 (6 months)
Sample code		Refer to "Primary Analysis"
Output		15.4.9.1 Exploratory Analysis of Change in Multiplex Assay - As Exposed Set - 15.4.9.2 Regression Coefficients and Graphical Diagnostics of Exploratory Analysis of Change in Multiplex Assay - As Exposed Set - 15.4.9.3 Exploratory Analysis of Change in Parallel Reaction Monitoring - As Exposed Set - 15.4.9.4 Regression Coefficients and Graphical Diagnostics of Exploratory Analysis of Change in Parallel Reaction Monitoring - As Exposed Set -

Summary Table of (i) MAP (ii)PRM		
Population	:	• As Exposed Set

Summary Table of (i) MAP (ii)PRM		
		➢ Product use pattern categories
Contents	:	In addition to the contents defined in "Descriptive statistics", robust measures for the center (median) and the dispersion (median absolute deviation, MAD), geometric means and CV will be presented as well.
Analysis variables	:	• Observed value of MAP and PRM • Change from baseline
Target visit		• Baseline • V3 (3 months) • V4 (6 months)
Output		15.2.9.1 Summary Table of Multiplex Assay - As Exposed Set - 15.2.9.2 Summary Table of Parallel Reaction Monitoring - As Exposed Set - 15.3.9.1 Listing of Multiplex Assay - As Exposed Set - 15.3.9.2 Listing of Parallel Reaction Monitoring - As Exposed Set - 15.1.9.1 Heatmap of Change in Multiplex Assay by Visit and Product Use Categories - As Exposed Set - 15.1.9.2 Heatmap of Change in Parallel Reaction Monitoring by Visit and Product Use Categories - As Exposed Set -

9.5.4 Safety Evaluation

9.5.4.1 Safety Reporting

9.5.4.2 Adverse Events

For AE tables, tabulations will be performed for both the number and percentage of patients experiencing an event and the number of events experienced during the study period by Medical Dictionary for Regulatory Activities (MedDRA, Version 20.0 or higher) System Organ Class (SOC) - sorted by alphabetical order, Preferred Terms (PT) - sorted by alphabetical order. If there is a change in severity for an AE for a subject, that event is counted once at the worst severity. If a subject has AEs that occurs and resolves on multiple occasions, each AE is counted once at the highest severity. Unless otherwise noted, target population will be used as denominator for frequency table.

All AEs will be summarized by product use group, SOC and PT. The adverse events that occurred during the study will be broken down and reported in the following ways,

- Occurrence of serious adverse events
- Severity of adverse events
- Relatedness of adverse event to study procedure and investigational product
- Adverse events leading to discontinuation

The tables below show the various ways in which adverse events will be reported for the study.

Summary Table of Adverse Events		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	The number and percentage of patients experiencing an adverse event and the number of adverse events during the study period. The overview table 15.2.10.1 includes a summary of overall number of AEs, SAEs, severity and relation to study procedure or investigational product and response to adverse events. The summary table 15.2.10.2 shows a tabulation of adverse events by SOC/PT.
Output		15.2.10.1 Overview Table of Adverse Events - Safety Set - 15.2.10.2 Summary Table of Adverse Events - Safety Set - 15.3.10.1 Listing of Adverse Events - Safety Set -

Summary Table of Adverse Events by Severity		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	The number and percentage of patients experiencing an adverse event and the number of adverse events during the study period by severity. If a subject experiences the same adverse event at more than one

		severity then the AE will be counted only once (in the Table) with the worst severity. Any missing severity will be accounted as "severe".
Output		15.2.10.4 Summary Table of Adverse Events by Severity - Safety Set -

Summary Table of Adverse Events Related to Product Exposure		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	The number and percentage of patients experiencing an adverse event related to product exposure and the number of adverse events related to product exposure during the study period.
Output		15.2.10.3 Summary Table of Adverse Events Related to Product Exposure - Safety Set -

Summary Table for Expectedness of Adverse Events Related to Investigational Product		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	The number and percentage of patients experiencing an adverse event related to an investigational product and its expectedness (Yes/No).
Output		15.2.10.8 Summary Table for Expectedness of Adverse Events Related to Investigational Product - Safety Set -

Summary Table for Relatedness of Adverse Events to Study Procedure		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	The number and percentage of patients experiencing an adverse event related to study procedures.
Output		15.2.10.9 Summary Table for Relatedness of Adverse Events Related to Study Procedure. - Safety Set -

9.5.4.2.1 Serious Adverse Events (Including Deaths)

Summary Table of Serious Adverse Events		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	The number and percentage of patients experiencing a serious adverse event and the number of serious adverse events during the study period.
Output		15.2.10.5 Summary Table of Serious Adverse Events - Safety Set - 15.3.10.2 Listing of Serious Adverse Events - Safety Set -

Summary Table of Adverse Events Leading to Death		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	The number and percentage of patients experiencing an adverse event leading to death during the study period and the number of adverse events leading to death during the study period.
Output		15.2.10.6 Summary Table of Adverse Events Leading to Death - Safety Set - 15.3.10.3 Listing of Adverse Events Leading to Death - Safety Set -

9.5.4.2.2 Adverse Events Leading to Discontinuation

Summary Table of Adverse Events Leading to Discontinuation from the Study		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	The number and percentage of patients experiencing an adverse event leading to discontinuation from the study and the number of adverse events leading to discontinuation from the study.
Output		15.2.10.7 Summary Table of Adverse Events Leading to Discontinuation from the Study - Safety Set -

		15.3.10.4 Listing of Adverse Events Leading to Discontinuation - Safety Set -

9.5.4.3 Device Events

Summary Table of Device Events		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	The number and percentage of patients experiencing device events and the number of device events will be counted by related parts of device and device event term. In addition the number and percentage of patients and the number of events will be counted by related to AE/not related to AE and by device events severity (major and minor).
Remarks	:	Device event term will be sorted by the order shown in CRF
Output		15.2.11.1 Summary Table of Device Events - Safety Set - 15.2.11.2 Summary of Device Events and Relatedness to Adverse Events - Safety Set - 15.3.11.1 Listing of Device Events - Safety Set -

9.5.4.4 Prior and Concomitant Medication/Therapy

Summary Table of Prior Medication/Therapy		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	Following contents will be summarized by using the level 1 and 2 ATC codes. • The number of subject who use prior medication/therapy • Denominator will be the target population All cases collected on the form for prior medication of CRF (CMCAT=”PRIOR MEDICATION”) will be tabulated.
Remark	:	Sorted by ATC1 then ATC2.
Definition	:	Any medication taken within 3 months prior to screening will be

Summary Table of Prior Medication/Therapy		
		considered as prior medication.
Output	:	15.2.12.1 Summary Table of Prior Medication/Therapy - Safety Set - 15.3.12.1 Listing of Prior Medication/Therapy - Safety Set -

Summary Table of Concomitant Medication/Therapy		
Population	:	• Safety Sets ➢ Product use pattern
Contents	:	Following contents will be summarized by using ATC level 1 and 2 codes. • The number of subject who use concomitant medication/therapy • Denominator will be the target population All cases collected on the form for prior medication of CRF (CMCAT="CONCOMITANT MEDICATION") will be tabulated.
Remark	:	Generic name will be sorted by alphabetical order.
Definition	:	Any medication which is started prior to screening and is still being taken by the patient at screening or thereafter will be considered as concomitant medication.
Output	:	15.2.12.2 Summary Table of Concomitant Medication/Therapy - Safety Set - 15.3.12.2 Listing of Concomitant Medication/Therapy - Safety Set -

9.5.4.5 Protocol Deviation

Summary Table of Protocol Deviations		
Population	:	Safety population
Contents	:	The number and percentage of protocol deviations defined in "Protocol Deviation" by category and severity (minor or major) will be summarized.
Output		15.2.13.1 Summary Table of Protocol Deviation - Safety Set -

		15.3.13.1 Listing of Protocol Deviation - Safety Set -

10 ANALYSES AND REPORTING

10.1 Interim Analyses and Data Monitoring

No interim analysis is planned.

11 REFERENCES

Clinical Study Protocol P1-OHS-01-JP Final version 3.0

Chemical Information Specialized Information Services. Nicotine [CAS No. 54-11-5]. Availble from: http://chemsisnlmnihgov/chemidplus/rn/54-11-5 (Accessed on 3 April 2014).

Chemical Information Specialized Information Services. Nicotine N-glucuronide [CAS No. 152306-59-7]. Available from: http://chemsisnlmnihgov/chemidplus/rn/152306-59-7 (Accessed on 3 April 2014).

Chemical Information Specialized Information Services. Cotinine [CAS No. 486-56-6]. Available from: http://chemsisnlmnihgov/chemidplus/rn/486-56-6 (Accessed on 3 April 2014).

Chemical Information Specialized Information Services. Cotinine N-glucuronide [CAS No. 139427-57-9]. Available from: http://chemsisnlmnihgov/chemidplus/rn/139427-57-9 (Accessed on 4 April 2014).

Chemical Information Specialized Information Services. Hydroxycotinine [CAS No. 34834-67-8]. Available from: http://chemsisnlmnihgov/chemidplus/rn/34834-67-8 (Accessed on 4 April 2014).

Chemical Information Specialized Information Services. Trans-3'-Hydroxycotinine-O-glucuronide [CAS No. 132929-88-5]. Availble from http://chemsisnlmnihgov/chemidplus/rn/132929-88-5 (Accessed on 4 April 2014).

Löe H. The gingival index, the plaque index and the retention index systems. J Periodontol. 1967; 38(6 Part II):610-6.

12 APPENDICES

12.1 Study Assessments

Refer to Appendix 1 Schedule of Events of Clinical Study Protocol

12.2 Tables, Figures, Listings & In-Text Tables

13 DATA PRESENTATION

The TFLs will be presented per the PMI TABLES, LISTINGS, AND FIGURES STYLE Style Guide.

13.1.1 Tables

15.2.1.1	Summary Table of Subject Disposition - All Subjects Screened -
15.2.2.1	Summary Table of Analysis Sets by Randomization Arm - Randomized Subjects -
15.2.2.2	Summary Table of Analysis Sets by Product Use Categories - Randomized Subjects -
15.2.2.3	Summary Table of Demographics by Product Use Categories - As Exposed Set -
15.2.2.4	Summary Table of Demographics by Randomization Arm - Full Analysis Set, Per Protocol Set, Safety Set -
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