STATISTICAL ANALYSIS PLAN

A 4-Week Randomised, Controlled, Examiner-blind, Clinical Study Investigating the efficacy of an Experimental Toothpaste containing Stannous Fluoride in improving gingival health

Protocol Number: 300178

Phase: N/A

This document contains confidentiality statements that are not relevant for this publicly available version

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	04-Dec-2024	Not applicable (N/A)

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Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
BPE	Basic Periodontal Examination
BDM	Biostatistics and Data Management
BDRM	Blinded Data Review Meeting
BI	Bleeding Index
CFU	Colony Forming Unit
CRF	Case Report Form
CRS	Clinical Research Scientist
DMS	Data Management System
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent To Treat
MedDRA	medical Dictionary for Regulatory Activities
MFC	Manufacturing Formulation Code
MGI	Modified Gingival Index
mITT	Modified Intent-To-Treat
Ml	Milliliter
mm	Millimeter
MMRM	Mixed Model with Repeated Measures
N/A	Not Applicable
NBS	Number of Bleeding Sites
OH	Oral Health
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PI	Principal Investigator
PI	Personal Information
PP	Per Protocol

Abbreviation	Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SnF_2	Stannous Fluoride
SS	Safety Statement
TEAE	Treatment Emergent Adverse Event
TPI	Turesky Modification of The Quigley Hein Plaque Index
w/w	Weight For Weight
$ZnCl_2$	Zinc Chloride
CI	Confidence Interval
CS	Compound Symmetry
LS	Least Square
WHODD	World Health Organization Drug Dictionary

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 300178 (Version 3.0, dated 14-Nov-2024).

1 Summary of Key Protocol Information

The purpose of this trial is to evaluate the ability of an experimental toothpaste containing 0.454% Stannous Fluoride (SnF_2), 0.3% Zinc Chloride ($ZnCl_2$) and 1% Alumina, to improve gingival health and plaque accumulation compared to a regular fluoride toothpaste (negative control) after 4 weeks twice daily brushing in subjects with plaque-induced mild to moderate gingivitis. Gingival health and plaque reduction will be evaluated using the Bleeding Index (BI), number of bleeding sites (NBS), Modified Gingival Index (MGI) and Turesky modification of the Quigley Hein Plaque Index (TPI).

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The study will follow a randomized, controlled, single blind (examiner blind), two-treatment arm, parallel study. Study subjects will be healthy adult volunteers, aged 18-70 years (inclusive), with mild to moderate plaque-induced gingivitis and with ≥ 20 natural teeth that meet all study criteria at both the Screening and Baseline visits.

Sufficient subjects will be screened to assess approximately 180 subjects so that at least 160 subjects will be randomized (approximately n=80 per group) to ensure approximately 144 (approximately 72 per group) evaluable subjects complete the entire study (allowing for 10% for drop-outs post-baseline).

1.1 Study Design

This will be a single center, 4 weeks, randomized, controlled, examiner-blind, 2 treatment arms, stratified, parallel group design clinical study, investigating gingival health and supragingival plaque reduction on healthy subjects after using an experimental toothpaste containing 0.454% SnF_2, 0.3% $ZnCl_2$ and 1% Alumina. CCI

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Study subjects will be healthy adult volunteers, aged 18-70 years (inclusive), with mild to moderate plaque-induced gingivitis and with ≥ 20 natural teeth that meet all study criteria at both the Screening and Baseline visits (including ≥ 40 evaluable surfaces for MGI, BI, Basic Periodontal Examination (BPE) and TPI. BI and TPI will be performed at Baseline (Visit 2), as part of the inclusion criteria, and BPE at Screening (Visit 1) as per exclusion criteria. All evaluable teeth (in relation to the inclusion/exclusion general dentition criteria) will be assessed.

Sufficient subjects will be screened to assess approximately 180 subjects so that at least 160 subjects are randomized (approximately n=80 per group) to ensure approximately 144

(approximately 72 per group) evaluable subjects complete the entire study (allowing for 10% drop-outs post-baseline).

This study will consist of 3 study visits: Screening (Visit 1), Baseline (Visit 2) and Week 4 (Visit 3). Gingival health will be assessed using MGI and BI. Plaque will be assessed by TPI, overall and interproximal. CCI [redacted] CCI [redacted]

At the Screening visit (Visit 1), subjects will provide their written informed consent to participate in the study. Demographics, medical history, prior/current medications will be recorded, subject's current oral care product used, and inclusion and exclusion criteria will be checked followed by an oral examination consisting of oral soft tissue (OST), oral hard tissue (OHT) examination, MGI and BPE assessments (as per inclusion/exclusion criteria) to identify subjects likely to meet the qualifying levels of gingivitis at baseline.

Subjects that show signs of periodontitis as assessed by BPE, with a score of 4 or above in one or more sextants will be excluded from the study. In addition, subjects with BPE ≥ 3 will undergo a pocket depth assessment, and those with ≥ 5mm pocket depth in a single tooth will be excluded.

Within approximately 3-5 weeks (21-35 days) of Screening (Visit 1), eligible subjects will return to the site for the Baseline visit (Visit 2), with overnight plaque (subjects will be instructed to abstain from oral hygiene for 12 hours [+3 hours; -2 hours] i.e., overnight immediately before the visit). At the Baseline visit, concomitant medication and inclusion/exclusion criteria will be checked and then subjects will undergo a full OST examination, CCI [redacted], MGI, BI and TPI assessments.

Subjects will be considered eligible with a minimum of 20 natural teeth, at least 40 evaluable surfaces, overall MGI ≥1.75 and ≤ 2.3 and overall TPI ≥ 1.5. Subjects with MGI or TPI score outside the study range will be discontinued from the study at this visit.

After saliva sample collection and all initial clinical assessments, eligible subjects will receive a standardised snack followed by a full mouth dental prophylaxis to remove sub and supragingival calculus, stain, plaque and debris from the teeth. Post-prophylaxis, the subject's teeth will be re-disclosed, and a second clinician will check all plaque and calculus has been removed. Any residual plaque and/or calculus will be removed to bring the subject to zero plaque (TPI = 0) before entering the treatment period.

Subjects will be then stratified based on gender and baseline mean whole mouth MGI score (Low: ≤2.00/High >2.00), to ensure a balance of gingivitis across both treatment groups and will be then randomized to study products. Gender is a known modifier of the initiation and outcome of conditions related to gingival health. Stratifying by MGI will facilitate evaluation of BI and MGI in low and high MGI subgroups.

The MGI and the BI are established clinical measures of gingival inflammation and gingival bleeding, respectively (i.e. gingival health); the TPI is an established clinical measure of

supragingival plaque accumulation. To avoid inter-examiner variability, a single examiner will be responsible for the conduct of each of the clinical indices (MGI, BI, TPI).

Randomized subjects will then receive their assigned study product, a toothbrush, rinsing cups and instructions on product usage. Subjects will be instructed to brush twice daily (morning and evening) with their allocated study product, in their usual manner, for 1-timed minute for the next 4 weeks. They will complete the first brushing at the study site, under supervision. CCI

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After using the study products for 4 weeks, subjects will return to the study site (Visit 3) with overnight plaque (subjects will be instructed to abstain from overnight tooth brushing for 12 hours [+3 hours; -2 hours] immediately before the assessment visit), at approximately the same time of day as the Baseline visit. Changes in health/concomitant medications will be recorded and compliance check will be performed by visual inspection of study products by study stuff to ensure adequate brushing. Subjects will then have a full OST examination followed by a saliva sample collection, MGI, BI and TPI assessments.

To assess examiner reproducibility across the treatment period, repeat MGI and TPI assessments will be performed on selected subjects at Visits 2-3. (Replicate BI examinations cannot be performed due to the inherent invasiveness of this measure). At least 3 subjects will be selected for repeatability examinations for each of the 2 clinical measures over the duration of each of visits 2 and 3. This will give a total of at least 6 subjects with repeatability examinations for each of the MGI and TPI assessments across the entire study. Repeatability examinations should be separated by a minimum of 10 minutes and, where possible, separated by another subject. MGI and TPI repeat assessments should be performed on different subjects.

All assessments will be carried out on the facial and lingual/palatal surfaces of each incisor, canine, pre-molar and molar, excluding third molars. To control inter-examiner variability, the same examiner will be used throughout the study for each clinical index.

Subjects will not be able to eat or drink, except for small sips of water used to alleviate thirst or to aid with medication, following supervised brushing at Visit 2 and Visit 3 CCI

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Table 1-1 presents the schedule of activities.

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening Visit 1		Visit 2 Baseline Day 1	Visit 3 Week 4 Day 28 (± 2)
Informed Consent	X	Lead in period [approximately 3-5 weeks (21-35 days)]		
Demographics	X			
Medical History	X			
Current/Prior Medication Review	X			
Review subject's current oral care products	X			
Oral soft tissue (OST) examination	X		X	X
Oral hard tissue (OHT) examination	X			X
Inclusion/exclusion criteria	X		X	
Modified Gingival Index (MGI)	X[1]		X[1]	X
Basic Periodontal Examination (BPE)	X[1]			
BI (Bleeding index)			X	X
CCI			X	X
Disclose dental plaque			X	X
Turesky Plaque Index (TPI) assessment			X	X
Subject eligibility	X		X	
Repeat MGI assessment[3]			X	X
Repeat TPI assessment[4]			X	X
Compliance Checks			X	X
Concomitant medications and treatments			X	X
Subject Continuance				X
Dental prophylaxis			X	
2nd clinician check to confirm TPI=0 (additional dental cleaning will be performed as required)			X	
Randomization			X	
Dispense study product, toothbrush, rinsing cups and oral hygiene instructions			X	
Supervised brushing with study product			X	X
CCI			X	X

Procedure/Assessment	Screening Visit 1		Visit 2 Baseline Day 1	Visit 3 Week 4 Day 28 (± 2)
Subject brings study product, toothbrush for brushing on site				X
Visual inspection of study product to check compliance				X
Adverse Events (AEs) Review[5]	X		X	X
Optional dental prophylaxis at the end of Visit 3				X
Study Conclusion/Subject Exit from Study				X

Footnotes:

1. In relation to the general dentition inclusion/exclusion criteria.
2. Subjects will abstain from overnight tooth brushing for a minimum of 12hrs (+3hr, -2hr) immediately prior to the assessment visits (Visits 2-3).
3. At least 3 subjects at each of visits 2&3 will be selected for repeat MGI assessments.
4. At least 3 subjects at each of visits 2&3 will be selected for repeat TPI assessments.
5. Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF).

The site may contact subjects prior to study visits, either as part of pre-screening activities or as a reminder of the approaching scheduled visit. Further details included in the ICF.

1.2 Study Objectives

Study objectives and endpoints are defined in Table 1-2.

Table 1-2 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To evaluate gingival health, as measured by the Bleeding Index (BI), of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control following 4 weeks twice daily use	Mean BI at Week 4.
Secondary Objectives	**Secondary Endpoints**
To evaluate gingival health, as measured by the Number of Bleeding Sites (NBS) of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control following 4 weeks twice daily use	Mean NBS at Week 4.
To evaluate gingival health, as measured by Modified Gingival Index (MGI) of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control following 4 weeks twice daily use	Mean MGI at Week 4.
To evaluate supragingival plaque levels, as measured by the Turesky Plaque Index (TPI), of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control for following 4 weeks twice daily use	• Mean overall TPI at Week 4. • Mean interproximal TPI at Week 4.
Exploratory Objectives	**Exploratory Endpoints**
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Safety	

Objectives	Endpoints
To evaluate the safety and oral tolerability of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina following 4 weeks twice daily use	Treatment emergent adverse events (TEAEs) over 4 weeks.

This study will be considered successful if there is a statistically significant difference in mean BI after 4 weeks of twice daily brushing with the experimental toothpaste containing 0.454% SnF_2, 0.3% $ZnCl_2$ and 1% Alumina compared to the control toothpaste.

1.3 Treatments

Table 1-3 presents the study products.

Table 1-3 Investigational/Study Product Supplies

	Test Product	**Reference Product (Negative Control)**
Product Name	Experimental toothpaste containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride,1% Alumina	Colgate Cavity Protection (UK Marketplace)
Pack Design	Carton of 2 over-wrapped tubes	
Dispensing Details	One carton – baseline visit	
Product Master Formulation Code (MFC)	CCI [redacted]	Commercial Product
Fluoride concentration	1100ppm	1450ppm
Dose/Application	Full ribbon of toothpaste on head of toothbrush provided	
Route of Administration	Oral	
Usage Instructions	Subjects will brush their teeth for one timed minute twice a day (morning and evening) Rinsing is not a study requirement. Subjects who wish to rinse after brushing will be provided with a measuring cup to rinse once with 10mL water.	
Return Requirements	All used/unused samples to be returned	

Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction which will be provided by Haleon during the study in time for study close out visit.

1.4 Sample Size Calculation

Sufficient subjects will be screened to assess approximately 180 subjects so that at least 160 subjects are randomized (approximately 80 per group) to ensure approximately 144 (approximately 72 per group) evaluable subjects complete the entire study (allowing for 10% drop-outs post-baseline).

The study will be sufficiently powered to demonstrate statistically significant differences between Test Product compared to the Reference Product (negative control) for mean BI at Week 4 (primary objective). A sample size of 72 evaluable subjects per treatment group will provide at least 90% power to detect a mean difference of 0.07 units (SD = 0.128) in mean BI score after 4 weeks of treatment, using a 2-tailed 2-sample t-test with a 5% significance level. The sample size calculation was performed using PASS software version 23.0.1.

The assumed treatment efficacy estimates come from a review of sponsor clinical studies CCI and 212537, sponsor data held on file and available on request) where the mean difference (SD) between the test and reference product reported a mean difference in BI of 0.07 between groups with standard deviation ranging from 0.04 to 0.128 at 12 weeks. The higher SD of 0.128 was used to calculate the sample size for this study.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned.

2.2 Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities including any external data reconciliation have been completed and database has been locked.
3. All criteria for unblinding the randomization codes have been met and the randomization codes have been distributed.

3 Considerations for Data Analyses and Data Handling Conventions

3.1 Baseline Definition

For all endpoints, the baseline value will be the Day 1 (Visit 2) pre-brushing assessment with a non-missing value.

Unless otherwise stated, if baseline data is missing no derivation will be performed and the baseline value will be set to missing.

3.2 Subgroups/Stratifications

Subjects who satisfy the study selection criteria will be stratified by their gender and Baseline Mean MGI resulting in the following strata:

- Male, baseline Mean MGI ≤2.00 (low)
- Male, baseline Mean MGI >2.00 (high)
- Female, baseline Mean MGI ≤2.00 (low)
- Female, baseline Mean MGI >2.00 (high)

3.3 Centers Pools

Since this is a single center study, pooling of centers is not applicable.

3.4 Timepoints and Visit Windows

The timepoints and visits for this study are defined in Table 1-1 "Schedule of Activities". Any deviation from the study schedule may be reviewed on a case-by-case basis at the Blind Data Review Meeting (BDRM) to determine whether the data should be excluded from the Per Protocol (PP) population.

4 Data Analysis

Data analysis will be performed by CCI [redacted] with oversight from Haleon. The statistical analysis software used will be SAS version 9.4 or higher.

Prior to database closure a BDRM will be conducted in which various aspects of the trial will be discussed and agreed.

Except as described below, all listings will be produced for all randomized subjects.

4.1 Populations for Analysis

4.1.1 Subject Disposition

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. An enrolled subject is a subject who has signed informed consent and is eligible to proceed beyond the screening visit.

The number of subjects screened, enrolled, and randomized will be presented in Table 14.1.1.

The number and percentage of screen failure subjects (subjects not randomized) with reasons why subjects are not randomized will be displayed. Percentages for screen failure subjects will be based on the total number of subjects screened.

The number and percentage of randomized subjects who complete and discontinue the study, broken down by reason for discontinuation, will be presented by study product and overall, in Table 14.1.1. The percentages will be based on the number of subjects randomized.

Table 14.1.1 will also present the number and percentage of randomized subjects in each of the defined analysis populations (as defined in Section 4.1.3) by study product and overall. Percentages will be based on the number of subjects randomized.

Subject disposition including demographic data (age, sex, race and ethnicity), screening date, study product start date/time, subject status (completer, Yes/No), study completion or withdrawal date, duration (in days) in the study (defined as [(date of completion or withdrawal – study product start date) + 1], and the primary reason for withdrawal and further details for withdrawal will be listed (Listing 16.2.1.1) by study product.

Subject disposition information will be listed for non-randomized subjects (Listing 16.2.1.2), including demographic information (age, sex, race and ethnicity), enrolled (Yes/No), screening date, reason for screen failure and any further details of reason for screen failure.

4.1.2 Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to unblinding and closure of the database to ensure all important deviations are captured and categorized. Subjects with important protocol deviations liable to influence the efficacy outcomes will be excluded from the PP population. Subjects may also be identified as having important protocol deviations not leading to exclusion from the PP population.

Important deviations of the protocol procedures may include, but will not necessarily be limited to the following:

- Consent procedures
- Inclusion or exclusion criteria
- Concomitant medication/therapy
- Laboratory Assessments
- Study procedures
- Randomization procedures
- Study drug dosing/study product administration/study product compliance
- Visit schedule/interval
- Other

The specific details of the important protocol deviations will be listed in the Protocol Deviation Management Plan, and the assessment process will be specified in the Blind Data Review Plan. Subjects with important protocol deviations will be identified at the BDRM.

The number and percentage of subjects with at least one important protocol deviation, subjects with important protocol deviations not leading to exclusion from PP population with reasons for deviations and subjects with important protocol deviations leading to exclusion from the PP population with reasons for deviations will be presented by study product and overall, for all randomized subjects (Table 14.1.2) and listed in Listing 16.2.2.1.

All protocol deviations collected on the protocol deviation case report form (CRF) will be listed in Listing 16.2.2.2. The listing will present date of deviation, type of deviation and deviation description.

4.1.3 Analysis Populations

Five analysis populations are defined.

Population	Definition / Criteria	Analyses Evaluated
Safety	Comprise of all randomized subjects who receive at least one dose of investigational product. Summaries and analyses of this population will be based on the investigational product the subject received.	• Demographics • Safety
Modified Intent-To-Treat (mITT)	Comprise of all randomized subjects who receive at least one dose of investigational product and complete at least one-post Baseline BI assessment. This population will be based on the investigational product the subject was randomized to. All subjects who receive a randomization number will be considered randomized.	• Demographics • Compliance • Efficacy
Per-Protocol (PP)	Comprise of all subjects in the mITT population who have at least one non-missing BI assessment considered to be unaffected by protocol deviations. Protocol deviations that may exclude subjects from the PP population are defined in Section 4.1.2 (Protocol Deviations).	• Efficacy
MGI Repeatability	Comprise of all subjects who have at least one repeat MGI clinical assessment at any visit.	• Repeatability for MGI
TPI Repeatability	Comprise of all subjects who have at least one repeat TPI clinical assessment at any visit.	• Repeatability for TPI

NOTE:

Please refer to Appendix 1: List of Data Displays, which details the population to be used for each display being generated.

The number of subjects included in each of the analysis populations will be presented (Table 14.1.1). Subjects excluded from any of the analysis populations will be listed in Listing 16.2.3.1, with the reason for exclusion.

The primary population for assessment of efficacy will be the mITT population. A PP analysis will be performed on the primary endpoint only if more than 10% of mITT subjects are excluded from the PP population. A decision on whether a PP analysis will be performed will be made prior to study unblinding (release of the randomization codes).

Any repeat clinical data collected for the repeatability assessment will only be used to assess repeatability. The main assessment of efficacy will be based on the initial assessment.

4.2 Subject Demographics and Other Baseline Characteristics

4.2.1 Demographic Characteristics

Descriptive statistics [number of subjects (n), mean, standard deviation (SD), median, minimum and maximum for continuous variables, and frequency count (n) and percentage (%) of subjects for categorical variables] will be presented for demographic characteristics by study product and overall. These variables include age (years), sex, race, ethnicity and baseline MGI subgroup, and will be presented for the Safety population (Table 14.1.3.1) and the mITT population (Table 14.1.3.2) and if applicable, for the PP population (Table 14.1.3.3).

Demographic information will be listed for all randomized subjects in Listing 16.2.4.1.

4.2.2 General Medical History

Medical and surgical history (in the last year) including allergies or drug sensitivity will be listed in Listing 16.2.4.2, with start date and end date or ongoing at the start of study product.

4.3 Treatments (Study Product, Rescue Medication, other Concomitant Therapies, Compliance)

Randomization details will be listed, including the randomization number, stratification group, the planned study product, the actual study product the subject was randomized to and the randomization date (Listing 16.1.7.1).

The study product kit allocations will be listed (Listing 16.1.7.2), including kit number and study product information.

4.3.1 Study Product Compliance and Exposure

Compliance data will be summarized for the mITT population.

A table (Table 14.2.1) with frequency count (n) and percentage (%) of subjects with each compliance response (Yes/No) will be presented by study product and Time period ‘Baseline to Week 4’.

Study product compliance (compliance response [Yes/No]) will be listed in Listing 16.2.5.1 for all randomized subjects by study product.

Supervised study product application (subject number, visit, and time of the supervised procedure) will be listed (Listing 16.2.5.2) for all randomized subjects.

4.3.2 Prior and Concomitant Medication

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days and prior to signing the informed consent form, will be documented in the CRF. The prior and concomitant medications will be coded using a validated medication dictionary, World Health Organization Drug Dictionary (WHODD).

Prior medications and prior non-drug therapies will be listed by subject, with drug name, WHODD drug synonym, reason for medication, route, dose, frequency, start date, start day relative to the study product start date, and end date and end day relative to the study product start date (Listing 16.2.4.3) for all randomized subjects. Prior medications are defined as those which stopped before the study product start date.

Concomitant medications and concomitant non-drug therapies taken during treatment will be listed similarly (Listing 16.2.4.4) for all randomized subjects with either ongoing or end date displayed. Concomitant medications are defined as medications that started or stopped on or after the study product start date or are ongoing.

Unknown dates will not be imputed. However, if the start or stop date is unknown, then it will be assumed to be concomitant medication unless the partial start date or stop date indicates differently.

4.4 Analysis of Efficacy

The primary population for assessment of efficacy will be the mITT population. No repeat assessment data is to be used in any efficacy analyses.

Descriptive summary statistics will be presented for the observed values and change from baseline at each time point for primary and secondary endpoints.

All p-values presented will be two-sided and assessed at the 5% significance level. No adjustments will be made for multiple comparisons in this study.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary endpoint for the study is the Mean BI at Week 4. The BI score for each subject at each visit will be calculated as the average index value over all evaluable tooth sites scored as follows:

- BI Score = Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites.

The BI score has a range of 0 to 2.

BI will be assessed for all evaluable surfaces of the facial and lingual/palatal gingiva, six sites per tooth (mesiobuccal, buccal and distobuccal; mesiolingual/palatal, lingual/palatal and distolingual/palatal).

The BI scoring system is described in Table 4-1.

Table 4-1 Bleeding Index Scoring System

Score	Description
0	Absence of bleeding on probing
1	Bleeding observed within 30 seconds of probing
2	Bleeding observed immediately on probing
9	Missing tooth or not qualified tooth

Descriptive statistics (n, mean, SD, standard error [SE], median, minimum, and maximum) will be presented for the BI score at each time point (observed value and change from baseline) in Table 14.2.2.1.1 for all subjects in the mITT population by study product.

Raw means (± SE) of the BI score at each time point will be presented graphically by study product in Figure 14.2.2.1.3 for all subjects in the mITT population.

Individual data for the BI assessment at each individual tooth site will be listed for each subject by study product group and visit in Listing 16.2.6.1.1, and individual data for the derived BI score will be listed for each subject in Listing 16.2.6.1.2, by study product group and visit for all randomized subjects.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in mean BI score at 4 weeks between the Test product and Reference product.
- H_1: There is a difference in mean BI score at 4 weeks between the Test product and Reference product.

Mean BI at Week 4 will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and Baseline Mean BI and Baseline Mean MGI as covariates. Gender will also be included as a stratification factor. The MGI stratification factor is not included in the model as the actual value is included as a covariate. The adjusted mean treatment difference will be presented in Table 14.2.2.2.1 for the mITT population, along with the two-sided p-value and 95% CIs. The observed margin (OM) option in SAS will be used when estimating least square means. The % adjusted mean difference will also be presented.

The assumptions of normality and homogeneity of variance in the model will be investigated. In case of violation of these assumptions, a data transformation, or a suitable non-parametric test (van Elteren test adjusting for gender and baseline MGI stratification) will be performed; the results will be provided to support the ANCOVA results.

4.4.1.3 Supportive Analyses

If there is a difference of 10% or more in the overall number of subjects between the PP and mITT populations, a summary of the primary efficacy variable will be presented for all subjects in the PP population (Table 14.2.2.1.2), mean and SE will be presented graphically over time (Figure 14.2.2.1.4) and the same ANCOVA model applied to the primary analysis will be performed on the PP population (Table 14.2.2.2.2).

4.4.2 Secondary Efficacy Endpoints

All secondary endpoint analyses will be performed on the mITT population.

For all the secondary efficacy variables described in subsections below, the comparison of interest will be the test product versus reference product. Secondary efficacy variables will be analyzed using the same ANCOVA model described above for the primary endpoint, but with Baseline Mean BI replaced with the Baseline of the respective endpoint (Baseline Mean overall TPI for Mean overall TPI at Week 4; Baseline Mean interproximal TPI for Mean interproximal TPI at Week 4; Baseline NBS for NBS at Week 4. For Mean MGI at Week 4, no additional term will be added as Baseline Mean MGI is already included in the model as a covariate). Adjusted mean product differences will be provided, along with 95% CIs. The % adjusted mean difference will also be presented.

The assumption of residual normality and variance homogeneity in the ANCOVA analysis used to analyze secondary endpoints will be investigated through residual plots. If violated, data transformation or a nonparametric method (van Elteren test adjusting for gender and baseline MGI stratification) will be used and the results will be provided to support the ANCOVA results.

4.4.2.1 Number of Bleeding Sites (NBS) at Week 4

The NBS for each subject at each visit is calculated as the number of evaluable tooth sites with a BI score of 1 or 2. The BI scoring system is described in Section 4.4.1.1.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of NBS at each time point will be provided by study product group for the mITT population (Table 14.2.3.1.1).

The raw mean and SE of the NBS will be presented graphically over time for each study product group in Figure 14.2.3.1.2 for the mITT population.

Individual data for the NBS will be listed for each subject by study product group and visit in Listing 16.2.6.2 for all randomized subjects.

4.4.2.1.1 Statistical Hypothesis, Model and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the NBS at 4 weeks between the Test product and Reference product.
- H_1: There is a difference in the NBS at 4 weeks between the Test product and Reference product.

NBS will be analyzed as described for the primary analysis (Section 4.4.1.2), using the Baseline NBS value as covariate. The adjusted means and SEs of the two product groups together with the product difference, SE, 95% CI of the difference and p-value will be provided in Table 14.2.3.2.1 for the mITT population. The % adjusted mean difference will also be presented.

4.4.2.2 Mean Modified Gingival Index (MGI) at Week 4

The MGI score for each subject at each visit will be calculated as the average index value over all evaluable tooth sites scored as follows:

- MGI Score = Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites.

The MGI score has a range of 0 to 4.

MGI will be assessed for all evaluable surfaces of the facial and lingual/palatal gingiva, four sites per tooth (facial gingiva: papilla and margin; lingual/palatal gingiva: papilla and margin) and scored as follows.

The MGI scoring system is described in Table 4-2.

Table 4-2 Modified Gingival Index

Score	Description
0	Absence of inflammation
1	Mild inflammation; slight change in colour, little change in colour; little change in texture of any portion of the marginal or papillary gingival unit
2	Mild inflammation; criteria as above but involving the entire marginal or papillary gingival unit
3	Moderate inflammation; glazing, redness, oedema, and/or hypertrophy of the marginal or papillary gingival unit
4	Severe inflammation; marked redness, oedema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration
9	Missing tooth or not qualified tooth

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) will be presented for the Mean MGI score at each time point (observed value and change from baseline) by study product group for the mITT population (Table 14.2.4.1.1).

Raw means (± SE) of the Mean MGI score at each time point will be presented graphically by study product group in Figure 14.2.4.1.2 for the mITT population.

Individual data for the MGI assessment at each individual tooth site will be listed for each subject by study product group in Listing 16.2.6.3.1, and individual data for the derived MGI score will be listed for each subject in Listing 16.2.6.3.2, by study product group for all randomized subjects.

4.4.2.2.1 Statistical Hypothesis, Model and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the mean MGI score at 4 weeks between the Test product and Reference product.
- H_1: There is a difference in the mean MGI score at 4 weeks between the Test product and Reference product.

Mean MGI at Week 4 will be analyzed as described for the primary analysis (Section 4.4.1.2), using the Baseline MGI value as covariate. The adjusted means and SEs of the two product groups together with the product difference, SE, 95% CI of the difference and p-value will be provided in Table 14.2.4.2.1 for the mITT population. The % adjusted mean difference will also be presented.

4.4.2.3 Mean Turesky Plaque Index (TPI) [Overall and Interproximal] at Week 4

The Overall TPI score for each subject at each visit will be calculated as the average index value over all evaluable tooth sites scored as follows:

- Overall TPI Score = Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites.

The Interproximal TPI score for each subject at each visit will be calculated as the average index value over all interproximal tooth sites (distal and mesial) scored as follows:

- Interproximal TPI Score = Sum of index values over all evaluable interproximal tooth sites (distal and mesial) /Number of evaluable interproximal tooth sites (distal and mesial).

The evaluable tooth sites are those scored as 0, 1, 2, 3, 4 or 5.

The Overall TPI score and Interproximal TPI score have a range of 0 to 5.

TPI will be assessed for all evaluable surfaces of the facial and lingual surfaces of the teeth (7-7 in each arch). Each tooth surface is divided into 3 areas; three scores are recorded facially (mesiofacial, facial, distofacial) and three scores lingually (mesiolingual, lingual and distolingual), generating six scores per tooth.

The TPI scoring system is described in Table 4-3.

Table 4-3 Turesky Plaque Index

Score	Description
0	No plaque
1	Separate flecks of plaque at the cervical margin of the tooth
2	Thin continuous band of plaque (1 millimitre (mm) or smaller) at the cervical margin of the tooth
3	Band of plaque wider than 1mm but covering less than 1/3 of the area
4	Plaque covering at least 1/3 but less than 2/3 of the area
5	Plaque covering 2/3 or more of the crown of the tooth
9	Missing tooth or not qualified tooth

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) will be presented for the Mean Overall TPI score and Mean Interproximal TPI score at each time point (observed value and change from baseline) by study product group for the mITT population in Table 14.2.5.1.1 and Table 14.2.6.1.1, respectively.

Raw means (± SE) of the Mean Overall TPI score and Mean Interproximal TPI score at each time point will be presented graphically by study product group in Figure 14.2.5.1.2 and Figure 14.2.6.1.2 respectively, for the mITT population.

Individual data for the TPI assessment at each evaluable tooth site will be listed for each subject by study product group in Listing 16.2.6.4.1, and individual data for the derived TPI score (overall and interproximal, respectively), will be listed for each subject in Listing 16.2.6.4.2, by study product group for all randomized subjects.

4.4.2.3.1 Statistical Hypothesis, Model and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- **Overall TPI:**

- H_0: There is no difference in the mean Overall TPI score at 4 weeks between the Test product and Reference product.
- H_1: There is a difference in the mean Overall TPI score at 4 weeks between the Test product and Reference product.

- **Interproximal TPI:**

- H_0: There is no difference in the mean Interproximal TPI score at 4 weeks between the Test product and Reference product.
- H_1: There is a difference in the mean Interproximal TPI score at 4 weeks between the Test product and Reference product.

Mean Overall and Interproximal TPI will be analyzed as described for the primary analysis (Section 4.4.1.2), using the Baseline mean Overall/Interproximal TPI value as covariate, respectively. The adjusted means and SEs of the two product groups together with the product difference, SE, 95% CI of the difference and p-value will be provided in Table 14.2.5.2.1 and

Table 14.2.6.2.1 for the mITT population, respectively for Overall TPI and Interproximal TPI. The % adjusted mean difference will also be presented.

4.4.3 Exploratory Efficacy Variables

4.4.3.1 CCI

CCI

- Day 1 post-brushing compared to Day 1 pre-brushing
- Week 4 post-brushing compared to Week 4 pre-brushing
- Week 4 pre-brushing compared to Day 1 pre-brushing
- Week 4 post-brushing compared to Day 1 pre-brushing

Note: post-brushing is 3 hours post-brushing on site.

CCI

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of CCI CCI values at both the visits pre-brushing & post-brushing will be provided by study product group for the mITT population in Table 14.2.7.1.1.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) CCI CCI values at all the comparison of interest timepoints will be provided by study product group for the mITT population in Table 14.2.7.1.2.

Individual data CCI will be listed for each subject by visit with pre-brushing & post-brushing timepoint in Listing 16.2.6.5.

4.4.3.1.1 Statistical Hypothesis, Model and Method of Analysis

For comparisons within each treatment group, the following null and alternative hypotheses will be evaluated:

- CCI

- CCI

For comparisons to negative control, the following null and alternative hypotheses will be evaluated:

- CCI

CCI

For within treatment differences, the above time points will be analyzed using a paired t-test in Table 14.2.7.2.1.

CCI

CCI . Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied (Kenward and Roger 1997). The difference between the least square mean changes from timepoint x to timepoint y (where x represents the later timepoint and y represents the earlier timepoint in each comparison) for the Test Product compared to Reference Product (Negative Control) from the MMRM will be presented, along with the two-sided p-value and 95% CIs in table 14.2.7.2.2. The % adjusted mean difference will also be presented.

The assumptions of normality and homogeneity of variance in the MMRM will be investigated. Similarly, the assumptions for the paired t-test will be investigated. In case of violation of these assumptions, a van Elteren test adjusting for gender and baseline MGI stratification (between products comparisons) and Wilcoxon Signed Rank Test (within product comparisons with baseline) will be performed to support the parametric results.

4.4.4 Handling of Missing Values/Censoring/Discontinuations

Primary and Secondary Analysis:

Subjects who withdraw from the study early will be included in the statistical analysis up to the point at which they withdraw. There will be no imputation for missing data (i.e. analyses will be conducted on an observed case basis).

Exploratory Analysis:

CCI

4.5 Analysis of Safety

The safety profile of the study products will be assessed with respect to adverse events (AEs), and OST/OHT abnormalities in this oral health study.

4.5.1 Adverse Events and Serious Adverse Events

All AEs will be reviewed by the Clinical Research Scientist or designee prior to database lock and unblinding, and will be coded to a system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be classified as oral and non-oral on the AE page of eCRF.

Treatment emergent adverse events (TEAEs) are defined as new AEs that occur on or after the first study product use (if this date is missing, a suitable alternative will be used e.g. date of randomization). AEs with an onset date/time prior to the first study product use at the baseline visit will be considered as non-treatment emergent.

The following summary tables and listings will be presented by study product group.

- Table of TEAEs overall summary (Table 14.3.1.1)
- Table of TEAEs by SOC and PT (Table 14.3.1.2)
- Table of TEAEs by Oral/Non-Oral and PT (Table 14.3.1.3)
- Table of treatment related TEAEs by SOC and PT (Table 14.3.1.4)
- Table of treatment related TEAEs by Oral/Non-Oral and PT (Table 14.3.1.5)
- Listing of all AEs (Listing 16.2.7.1 for all randomized subjects; Listing 16.2.7.2 for non-randomized subjects)
- Listing of deaths (Listing 14.3.2.1)
- Listing of non-fatal SAEs (Listing 14.3.2.2)
- Listing of TEAEs leading to study or product withdrawal (Listing 14.3.2.3)
- Listing of TEAEs classified as Oral (Listing 14.3.2.4)

In the event that there is nothing to report, a null table or listing will be produced.

4.5.2 Other Safety Variables

Other safety variables are listed below:

- OST examination
- OHT examination

4.5.2.1 OST Examination

The OST examination will be accomplished by direct observation and palpation, using retraction aids as appropriate. It will include examination of the labial mucosa (including lips), buccal mucosa, mucogingival folds, gingival mucosa, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands. Any abnormal findings from the OST examination will be recorded in the eCRF with details of the abnormalities.

Where possible, this procedure should be conducted by a single clinical examiner.

OST will be summarized (number of subjects and percentages with abnormalities) by visit and study product in Table 14.3.4.1 for all subjects in the Safety Population. Abnormal findings from the OST examination will be listed (Listing 16.2.8.1) for all randomized subjects.

4.5.2.2 OHT Examination

The OHT examination will be accomplished by direct observation, using retraction aids as appropriate. It will identify enamel irregularities, tooth fractures, grossly carious lesions/gross decay, defective/faulty restorations, direct & indirect restorations including fixed/removal prostheses, non-carious tooth surface loss (abrasion, attrition, abfraction and erosion), any other hard tissue irregularities (e.g., hypo/hypermineralisation, decalcification) and significant tooth staining. Any conditions noted as 'Present' from the OHT examination will be described in the eCRF with details of the 'Present' condition.

The presence of implants, fixed or removable dentures, fixed or removable orthodontic braces/bands, fixed orthodontic retainers, full crowns or veneers will be recorded, along with evidence of gross intra-oral neglect or the need for extensive dental therapy. Where possible, this procedure should be conducted by a single clinical examiner.

Any conditions noted as 'Present' from the OHT examination will be listed (Listing 16.2.8.2) for all randomized subjects.

4.6 Analysis of Other Variables

4.6.1 Repeatability of the Examiner

Repeat MGI and TPI assessments will be performed by the clinical examiners at Visits 2 and 3. At least 3 subjects will be selected for repeat assessments over the duration of each of visits 2 and 3. Thus a total of at least 6 subjects repeat assessments for each endpoint will be collected during this study. 'Repeat' subjects will be selected at random from those in attendance on any given assessment day. Different subjects should be used for repeat MGI and TPI assessments.

There should be a delay of at least 10 minutes between the original and the repeat assessment for a given subject; ideally, repeat assessments should be separated by another subject. No other clinical procedure should be carried out on the selected subject between repeat assessments.

Scores from the first assessment must not be visible to the examiner/scribe when the repeat assessment is carried out.

The repeat MGI and TPI assessments will be compared to the respective original assessments (excluding any tooth surfaces assessed as missing or not qualified). The repeat assessments will not be used in any efficacy analysis.

The first and second assessments of each index will be analyzed with a Fleiss-Cohen weighted kappa coefficient (κ), along with the 95% CI, to assess the intra-examiner reliability. Reliability will be deemed:

- Excellent if $\kappa > 0.75$

- Fair to good if $0.4 \leq \kappa \leq 0.75$
- Poor if $\kappa < 0.4$

This analysis will be conducted on each respective index repeatability population (MGI population and TPI population).

4.6.1.1 MGI Repeatability

The first and repeat values of the MGI for each tooth site will be combined and cross-tabulated for the MGI Repeatability population (Table 14.2.8.1). Only subjects with both first and repeat MGI assessments available for a given tooth site at the same visit will be presented and analyzed.

4.6.1.2 TPI Repeatability

The first and repeat values of the TPI for each tooth site will be combined and cross-tabulated for the TPI Repeatability population (Table 14.2.9.1). Only subjects with both first and repeat TPI assessments available for a given tooth site at the same visit will be presented and analyzed.

5 Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 5-1 below.

Table 5-1 Changes to the Protocol Defined Statistical Analysis Plan

Protocol	Statistical Analysis Plan	
Statistical Analysis Section	**Statistical Analysis Plan**	**Rationale for Changes**
Section 6.3.1 of the Protocol states that 'The results of the examination will be recorded in the eCRF as either 'normal' or 'abnormal'.	Section 4.5.2.1 of the SAP has revised the Protocol text to state that 'Any abnormal findings from the OST examination will be recorded in the eCRF with details of the abnormalities.'	This study uses a redesigned standard eCRF, where only abnormal results will be captured in the eCRF for OST examination.
Section 6.3.2 of the Protocol states that 'Conditions will be listed as 'absent' or 'present'; those noted as 'present' will be described in the eCRF'.	Section 4.5.2.2 of the SAP has revised the Protocol text to state that 'Any conditions noted as 'Present' from the OHT examination will be described in the eCRF along with the details of the 'Present' condition.'	This study uses a redesigned standard eCRF, where only 'Present' conditions will be captured in the eCRF for OHT examination.

Appendix 1: List of Data Displays

CSR Section	TLF	Number	Title	Population	Template	Topline
14.1 Demographic Data Summary Tables and Figures						
	Table	14.1.1	Subject Disposition	All Screened Subjects	14.1.1	Yes
	Table	14.1.2	Incidence of Important Protocol Deviations	All Randomized Subjects	14.1.2	
	Table	14.1.3.1	Demographic and Baseline Characteristics	Safety Population	14.1.3.1	
	Table	14.1.3.2	Demographic and Baseline Characteristics	mITT Population	14.1.3.1	Yes
	Table	14.1.3.3	Demographic and Baseline Characteristics	PP Population	14.1.3.1	
14.2 Efficacy Data Summary Tables and Figures						
	Table	14.2.1	Summary of Brushing Compliance	mITT Population	14.2.1	
	Table	14.2.2.1.1	Summary of Bleeding Index (BI)	mITT Population	14.2.2.1.1	Yes
	Table	14.2.2.1.2	Summary of Bleeding Index (BI)	PP Population	14.2.2.1.1	
	Figure	14.2.2.1.3	Bleeding Index (BI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3	
	Figure	14.2.2.1.4	Bleeding Index (BI) (± SE) Plot Over Time by Study Product	PP Population	14.2.2.1.3	
	Table	14.2.2.2.1	Statistical Analysis of Bleeding Index (BI)	mITT Population	14.2.2.2.1	Yes
	Table	14.2.2.2.2	Statistical Analysis of Bleeding Index (BI)	PP Population	14.2.2.2.1	
	Table	14.2.3.1.1	Summary of Number of Bleeding Sites	mITT population	14.2.2.1.1	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Figure	14.2.3.1.2	Number of Bleeding Sites (± SE) Plot over Time by Study Product	mITT Population	14.2.2.1.3	
	Table	14.2.3.2.1	Statistical Analysis of Number of Bleeding Sites	mITT Population	14.2.2.2.1	
	Table	14.2.4.1.1	Summary of Modified Gingival Index (MGI)	mITT Population	14.2.2.1.1	Yes
	Figure	14.2.4.1.2	Modified Gingival Index (MGI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3	
	Table	14.2.4.2.1	Statistical Analysis of Modified Gingival Index (MGI)	mITT Population	14.2.2.2.1	Yes
	Table	14.2.5.1.1	Summary of Overall Turesky Plaque Index (TPI)	mITT Population	14.2.2.1.1	
	Figure	14.2.5.1.2	Overall Turesky Plaque Index (MGI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3	
	Table	14.2.5.2.1	Statistical Analysis of Overall Turesky Plaque Index (TPI)	mITT Population	14.2.2.2.1	Yes
	Table	14.2.6.1.1	Summary of Interproximal Turesky Plaque Index (TPI)	mITT Population	14.2.2.1.1	
	Figure	14.2.6.1.2	Interproximal Turesky Plaque Index (TPI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3	
	Table	14.2.6.2.1	Statistical Analysis of Interproximal Turesky Plaque Index (TPI)	mITT Population	14.2.2.2.1	
	CCI					

CSR Section	TLF	Number	Title	Population	Template	Topline
	CCI					
	Table	14.2.8.1	Intra-Examiner Repeatability Analysis of Modified Gingival Index (MGI)	MGI Repeatability	14.2.8.1	
	Table	14.2.9.1	Intra-Examiner Repeatability Analysis of Turesky Plaque Index (TPI)	TPI Repeatability	14.2.9.1	
14.3 Safety Data Summary Tables and Figures						
14.3.1 Displays of Adverse Events						
	Table	14.3.1.1	Treatment Emergent Adverse Events Overall Summary	Safety Population	14.3.1.1	Yes
	Table	14.3.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	14.3.1.2	
	Table	14.3.1.3	Treatment Emergent Adverse Events by Oral/Non-Oral and Preferred Term	Safety Population	14.3.1.3	
	Table	14.3.1.4	Treatment Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	14.3.1.2	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Table	14.3.1.5	Treatment Related Serious Treatment Emergent Adverse Events by Oral/Non-Oral and Preferred Term	Safety Population	14.3.1.3	
14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events						
	Listing	14.3.2.1	Deaths	All Randomized Subjects	16.2.7.1	
	Listing	14.3.2.2	Non-Fatal Serious Adverse Events	All Randomized Subjects	16.2.7.1	
	Listing	14.3.2.3	Treatment Emergent Adverse Events Leading to Study or Product Discontinuation	All Randomized Subjects	16.2.7.1	
	Listing	14.3.2.4	Treatment Emergent Adverse Events Classified as Oral	All Randomized Subjects	16.2.7.1	
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events						
	NA					
14.3.4 Other Observations Related to Safety and Abnormal Laboratory Values						
	Table	14.3.4.1	Summary of Oral Soft Tissue Examination Abnormalities	Safety Population	14.3.4.1	
APPENDIX						
16.1.6 Listing of Subjects Receiving Test Drug(s)/Investigational Product(s) from Specific Batches, where more than one batch was used						
	NA					
16.1.7 Randomization Scheme and Codes (Subject identification and treatment assigned)						

CSR Section	TLF	Number	Title	Population	Template	Topline
	Listing	16.1.7.1	Randomization Information	All Randomized Subjects	16.1.7.1	
	Listing	16.1.7.2	Kit List Allocation	All Randomized Subjects	16.1.7.2	
16.1.9 Documentation of Statistical Methods						
	Raw output	16.1.9.1.1	Statistical Analysis of Bleeding Index (BI) (Reference: Table 14.2.2.2.1)	mITT Population	SAS Output	Yes
	Raw output	16.1.9.1.2	Statistical Analysis of Bleeding Index (BI) (Reference: Table 14.2.2.2.2)	PP Population	SAS Output	
	Raw output	16.1.9.2	Statistical Analysis of Number of Bleeding Sites (Reference: Table 14.2.3.2.1)	mITT Population	SAS Output	
	Raw output	16.1.9.3	Statistical Analysis of Modified Gingival Index (MGI) (Reference: Table 14.2.4.2.1)	mITT Population	SAS Output	Yes
	Raw output	16.1.9.4	Statistical Analysis of Overall Turesky Plaque Index (TPI) (Reference: Table 14.2.5.2.1)	mITT Population	SAS Output	Yes
	Raw output	16.1.9.5	Statistical Analysis of Interproximal Turesky Plaque Index (TPI) (Reference: Table 14.2.6.2.1)	mITT Population	SAS Output	
	CCI					

CSR Section	TLF	Number	Title	Population	Template	Topline
	CCI					
16.2 Subject Data Listings						
16.2.1 Discontinued Subjects						
	Listing	16.2.1.1	Subject Disposition	All Randomized Subjects	16.2.1.1	
	Listing	16.2.1.2	Subject Disposition	Non-Randomized Subjects	16.2.1.2	
16.2.2 Protocol Deviations						
	Listing	16.2.2.1	Important Protocol Deviations	All Randomized Subjects	16.2.2.1	
	Listing	16.2.2.2	All Protocol Deviations	All Randomized Subjects	16.2.2.2	
16.2.3 Patients Excluded from the Efficacy Analysis						
	Listing	16.2.3.1	Exclusions from Analysis Populations	All Randomized Subjects	16.2.3.1	
16.2.4 Demographic Data						
	Listing	16.2.4.1	Demographic and Baseline Characteristics	All Randomized Subjects	16.2.4.1	
	Listing	16.2.4.2	Medical History and Current Medical Conditions	All Randomized Subjects	16.2.4.2	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Listing	16.2.4.3	Prior Medications	All Randomized Subjects	16.2.4.3	
	Listing	16.2.4.4	Concomitant Medications and Concomitant Non-Drug Therapies	All Randomized Subjects	16.2.4.4	
16.2.5 Compliance and/or Drug Concentration Data (if available)						
	Listing	16.2.5.1	Brushing Compliance	All Randomized Subjects	16.2.5.1	
	Listing	16.2.5.2	Supervised Brushing	All Randomized Subjects	16.2.5.2	
16.2.6 Individual Efficacy Response Data						
	Listing	16.2.6.1.1	Bleeding Index (BI) Individual Scores	All Randomized Subjects	16.2.6.1.1	
	Listing	16.2.6.1.2	Bleeding Index (BI) Derived Scores	All Randomized Subjects	16.2.6.1.2	
	Listing	16.2.6.2	Number of Bleeding Sites	All Randomized Subjects	16.2.6.2	
	Listing	16.2.6.3.1	Modified Gingival Index (MGI) Individual Scores	All Randomized Subjects	16.2.6.3.1	
	Listing	16.2.6.3.2	Modified Gingival Index (MGI) Derived Scores	All Randomized Subjects	16.2.6.3.2	
	Listing	16.2.6.4.1	Turesky Plaque Index (TPI) Individual Scores	All Randomized Subjects	16.2.6.4.1	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Listing	16.2.6.4.2	Turesky Plaque Index (TPI) Derived Scores	All Randomized Subjects	16.2.6.4.2	
	CCI					
16.2.7 Adverse Event Listings						
	Listing	16.2.7.1	All Adverse Events	All Randomized Subjects	16.2.7.1	Yes
	Listing	16.2.7.2	All Adverse Events	Non-Randomized Subjects	16.2.7.1	
16.2.8 Other Listings and Listing of Laboratory Measurements, when required by regulatory authorities (if applicable)						
	Listing	16.2.8.1	Oral Soft Tissue Examination Abnormalities	All Randomized Subjects	16.2.8.1	
	Listing	16.2.8.2	Oral Hard Tissue Examination Findings	All Randomized Subjects	16.2.8.2	
16.4 Individual Subject Data Listings						
	NA					