STATISTICAL ANALYSIS PLAN

A 12-Week, Randomised, Controlled, Examiner-blind, Clinical Study to Evaluate the Efficacy of a Stannous Fluoride Toothpaste with a Cetylpyridinium Chloride Mouthwash in Improving Gingival Health and Reducing Plaque Accumulation

Protocol Number: 300211

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	06-Jan-2025	Not applicable (N/A)
V2.0	13-Mar-2025	Updated Product labels for the reference and negative control toothpastes by interchanging the label correctly under section '1. Summary of Key Protocol Information' on page #6.

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Abbreviations

Abbreviation	Term
AE	Adverse Event
AngBI	Angulated-bleeding index
BDRM	Blind Data Review Meeting
CI	Confidence Interval
CPC	Cetylpyridinium Chloride
CRF	Case Report Form
CRS	Clinical Research Scientist
EBI	Expanded Bleeding Index
EC	Ethics Committee
eCRF	Electronic Case Report Form
ICF	Informed Consent Form
MedDRA	medical Dictionary for Regulatory Activities
MFC	Manufacturing Formulation Code
MGI	Modified Gingival Index
mITT	Modified Intent-To-Treat
mm	Millimeter
MMRM	Mixed Model with Repeated Measures
N/A	Not Applicable
NBS	Number of Bleeding Sites
NRS	Numeric Rating Scale
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PP	Per Protocol
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
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 300211 (Version 2.0, dated 29-Oct-2024).

1 Summary of Key Protocol Information

The purpose of this trial is to assess the ability of a marketed CPC (Cetylpyridinium Chloride) mouthwash alongside a marketed toothpaste containing 0.454% w/w SnF_2 (Stannous Fluoride) in improving gingival health and reducing plaque accumulation, compared to the use of a regular fluoride toothpaste alone in subjects with clinically measurable plaque-induced gingivitis after 6 and 12 weeks twice-daily tooth brushing. This study will also explore whether a CPC mouthwash used with a SnF_2 toothpaste could provide benefits in plaque accumulation reduction and gingival health improvement over the sole use of SnF_2 toothpaste. This study will thus include three treatment arms, using currently marketed products:

1. Toothpaste/Mouthwash: Parodontax Complete Protection Toothpaste (0.454% w/w SnF_2) + Parodontax Active Gum Health Mouthwash (0.07% w/w CPC).
2. Negative Control: Crest Cavity Protection (0.243% w/w sodium fluoride (NaF))
3. Reference Toothpaste: Parodontax Complete Protection (0.454% w/w SnF_2)

Gingival health and plaque reduction will be evaluated using Number of Bleeding Sites (NBS), Bleeding Index (BI), Modified Gingival Index (MGI) and Turesky modification of the Quigley Hein Plaque Index (TPI).

An exploratory analysis will be conducted to evaluate the efficacy of Toothpaste/Mouthwash (a toothpaste containing 0.454% w/w SnF_2 with a mouthwash containing 0.07% w/w CPC) in reducing gingivitis and plaque accumulation, as measured by NBS, BI, MGI and TPI, Overall and Interproximal, compared to a Reference Toothpaste (containing 0.454% w/w SnF_2), after 6 and 12 weeks twice-daily tooth brushing. Also, subject satisfaction will be investigated with Toothpaste/Mouthwash (a toothpaste containing 0.454% w/w SnF_2 with a mouthwash containing 0.07% w/w CPC) for the Overall liking, as measured by a Numeric Rating Scale (NRS), after 12 weeks treatment.

The study will follow a randomized, controlled, examiner-blind, 3-treatment arm, parallel group, stratified by sex (male/female). Study subjects will be healthy adult volunteers aged 18 and over with generalized clinically measurable plaque-induced gingivitis.

Sufficient subjects will be screened so that at least 198 subjects will be randomized (approximately n=66 per group) to ensure approximately 180 (approximately 60 per group) evaluable subjects complete the entire study (allowing for 10% for dropouts).

1.1 Study Design

This will be a single center, 12-week, randomized, controlled, examiner-blind, 3-treatment arm, parallel group, stratified by sex (male/female) study to evaluate the efficacy of using the

Toothpaste/Mouthwash twice daily in reducing gingivitis and plaque accumulation in a population with clinically measurable levels of gingivitis.

The clinical efficacy of the commercially available Toothpaste/Mouthwash will be compared with that of a commercially available, regular fluoride toothpaste with no known anti-gingivitis nor anti-plaque efficacy properties (Negative Control).

Study subjects will be healthy adult volunteers aged 18 and over with generalized clinically measurable plaque-induced gingivitis. Approximately 198 subjects (approximately 66 per group) will be randomized to ensure approximately 180 evaluable subjects (approximately 60 per group) complete the study (allow up to 10% dropout).

This study will consist of four study visits: Screening, Baseline, Week 6 and 12.

MGI, BI (NBS is derived from BI) and TPI will be used to assess gingival inflammation, bleeding and plaque accumulation. For MGI, instead of measuring 4 sites per eligible tooth, six sites per tooth (total up to 168 sites) will be assessed in order to evaluate gingival inflammation both Overall and Interproximal. EBI (Expanded BI) is an expanded version of the Angulated-bleeding index (AngBI) on the marginal gingiva, which measures all 6 sites surrounding a tooth and emphasizes the Interproximal area where most bleeding occurs.

At Screening visit (Visit 1), subjects will provide their written informed consent to participate in the study. Demographics, medical history, and current medications will be recorded, followed by an oral examination (oral soft tissue (OST), oral hard tissue (OHT) examination) and dentition exclusions, a gross gingival assessment and pocket depth assessment. Eligible subjects will be given a washout toothpaste and toothbrush to use in between the Screening and Baseline Visits.

Within 14-28 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 [+6 hours; -2 hours] i.e., overnight immediately before the visit).

At the Baseline visit, subjects will undergo, in the following order, a full OST examination, assessments of gingival inflammation (MGI), gingival bleeding (EBI), and supra-gingival plaque (TPI). Subjects with % bleeding sites (derived from EBI assessment) and TPI score outside the study range will be discontinued from the study at this visit. Eligible subjects will then receive full mouth dental prophylaxis and be randomized to study product. The dental prophylaxis (followed by flossing) is to remove sub and supra-gingival calculus, stain, plaque and debris from the teeth. All subjects will enter the treatment period with no visible plaque (TPI=0). Subjects will then undergo a supervised product use and will be instructed to use their product twice daily, per instruction, until their next visit.

After using the study product(s) for 6, and 12 weeks, subjects will return to the study site (Visits 3 and 4, respectively) with overnight plaque (subjects will be instructed to abstain from overnight tooth brushing for 12 hours [+6 hours; -2 hours] immediately before each assessment visit), at approximately the same time of day as the Baseline visit. The study product use will be reviewed to determine treatment compliance. During the visit 3 and 4, the investigator will

ask subjects about product usage compliance and remind them to follow product usage instructions (visit 3 only). The investigator will also ask subjects if there are any changes in their health and medical occurrences since the last visit. Subjects will have a full OST examination and then undergo, in the following order, MGI, EBI, and TPI assessments. At Visit 4, subjects will also have a full OHT examination, return all study supplies if required and have a dental prophylaxis if deemed appropriate by the investigator or examiner.

At Visits 2, 3, and 4, repeatability data will be generated for MGI and TPI assessments from replicate examinations on the same subject (the subject for the MGI repeat assessment and the subject for the TPI assessment can be different). Depending on subject visit scheduling, every effort will be made to complete one repeatability examination for each clinical measure during each clinical assessment day, that is, at least one MGI and one TPI repeat assessment on each assessment day. Repeatability examinations will be separated by a minimum of 10 minutes and, where possible, separated by another subject. Due to the invasive nature of the EBI assessment, it is not feasible to conduct an accurate repeatability assessment for this index. Adverse events (AEs) and incidents will be recorded from informed consent and at the end of each study visit.

Table 1-1 presents the schedule of activities.

Table 1-1 Schedule of Activities

Procedure/Assessment	**Study Visits**				
	Visit 1 **Screening**		Visit 2 **Baseline**[1] Day 0	Visit 3 **Week 6**[1] Day 42 (± 4)	Visit 4 **Week 12**[1] Day 84 (± 4)
Informed Consent	X	**Washout period (14 - 28 days)**			
Medical History	X				
Demographics	X				
Current/Prior/Concomitant Medication Review	X		X	X	X
Oral Soft Tissue (OST) examination	X		X	X	X
Oral Hard Tissue (OHT) examination	X				X
Gross Visual Assessment of Gingival Health	X				
Pocket Depth Assessment[2]	X				
Inclusion/Exclusion Criteria	X		X		

Procedure/Assessment	Study Visits				
	Visit 1 **Screening**		Visit 2 **Baseline**[1] Day 0	Visit 3 **Week 6**[1] Day 42 (± 4)	Visit 4 **Week 12**[1] Day 84 (± 4)
Subject Eligibility	X		X		
Subject Continuance				X	X
Dispense Washout Toothpaste and Toothbrush	X				
Return Washout Toothpaste and Toothbrush			X		
Modified Gingival Index (MGI) Assessment			X	X	X
Repeat MGI Assessment[3]			X	X	X
Expanded Bleeding Index (EBI) Assessment[4]			X	X	X
Disclose Dental Plaque			X	X	X
Turesky Plaque Index (TPI) Assessment			X	X	X
Repeat TPI Assessment[5]			X	X	X
Dental Prophylaxis			X		
2nd Clinician Check to Confirm TPI=0 (Additional Dental Cleaning Will Be Performed if Required)			X		
Stratification/Randomization			X		
Dispense Study Product(s), Toothbrush and Dosing Cups for Mouthwash[6], Timer			X		
Dispense Additional Mouthwash and Dosing Cups[6]				X[6]	
Supervised Study Product Use			X	X	

Procedure/Assessment	Study Visits				
	Visit 1 **Screening**		Visit 2 **Baseline**[1] Day 0	Visit 3 **Week 6**[1] Day 42 (± 4)	Visit 4 **Week 12**[1] Day 84 (± 4)
Subject Brings Study Product(s) and Toothbrush to Site for Compliance Checks				X	X
Subject Returns Study Product to Site					X
Adverse Events (AEs) Review [7]	X		X	X	X
End of Study Dental Prophylaxis (Optional)					X
Satisfaction Survey: Subject-Completed NRS and Questionnaire[6]					X[6]
Study Conclusion/Subject Exit from Study					X

Footnotes:

1) Subjects will abstain from overnight tooth brushing for a minimum of 12hrs (+6hr, -2hr) immediately prior to the assessment visits (Visits 2, 3 and 4).
2) In relation to the general dentition inclusion/ exclusion criteria.
3) Minimum one MGI repeatability assessments during each clinical assessment day; MGI repeatability assessment at Baseline visit will be conducted after the subject's eligibility has been confirmed.
4) NBS and bleeding sites % are derived from EBI assessment.
5) Minimum one TPI repeatability assessments during each clinical assessment day; TPI repeatability assessment at Baseline visit will be conducted after the subject's eligibility has been confirmed.
6) Toothpaste/mouthwash treatment arm only.
7) Adverse Events (AEs), Serious Adverse Events (SAEs) and medical device incidents collected immediately after subject provides consent participate in the study by the completion of the Informed Consent Form (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 the efficacy of toothpaste/mouthwash (a toothpaste containing 0.454% w/w SnF_2 with a mouthwash containing 0.07% w/w CPC) in reducing gingivitis, as measured by NBS (Overall), compared to a Negative Control (containing 0.243% w/w NaF), after 12 weeks twice daily tooth brushing	At Week 12, Overall: • Number (no.) of bleeding sites (NBS)
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of toothpaste/mouthwash (a toothpaste containing 0.454% w/w SnF_2 with a mouthwash containing 0.07% w/w CPC) in reducing gingivitis, as measured by NBS (Interproximal), compared to a Negative Control (containing 0.243% w/w NaF), after 12 weeks twice daily tooth brushing	At Week 12, Interproximal: • Number (no.) of bleeding sites (NBS)
To evaluate the efficacy of toothpaste/mouthwash (a toothpaste containing 0.454% w/w SnF_2 with a mouthwash containing 0.07% w/w CPC) in reducing gingivitis, as measured by NBS (Overall and Interproximal), compared to a Negative Control (containing 0.243% w/w NaF), after 6 weeks twice daily tooth brushing	At Week 6, Overall and Interproximal: • Number (no.) of bleeding sites (NBS)
To evaluate the efficacy of toothpaste/mouthwash (a toothpaste containing 0.454% w/w SnF_2 with a mouthwash containing 0.07% w/w CPC) in reducing gingivitis and plaque accumulation, as measured by bleeding index (BI), Modified Gingival Index (MGI) and Turesky Plaque Index (TPI), Overall and Interproximal, compared to a Negative Control (containing 0.243% w/w NaF), after 6 and 12 weeks twice daily tooth brushing	At Weeks 6 & 12, Overall and Interproximal: • Mean BI • Mean MGI • Mean TPI
To evaluate the efficacy of a reference toothpaste (containing 0.454% w/w SnF_2) in reducing gingivitis and plaque accumulation, as measured by NBS, BI, MGI and TPI, Overall and Interproximal, compared to a Negative Control toothpaste (containing 0.243% w/w NaF), after 6 and 12 weeks twice daily tooth brushing	At Weeks 6 & 12, Overall and Interproximal: • Number (no.) of bleeding sites (NBS) • Mean BI • Mean MGI • Mean TPI

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the efficacy of toothpaste/mouthwash (a toothpaste containing 0.454% w/w SnF_2 with a mouthwash containing 0.07% w/w CPC) in reducing gingivitis and plaque accumulation, as measured by NBS, BI, MGI and TPI, Overall and Interproximal, compared to a reference toothpaste (containing 0.454% w/w SnF_2), after 6 and 12 weeks twice daily tooth brushing	At weeks 6 and 12, Overall and Interproximal: • Number (no.) of bleeding sites (NBS) • Mean BI • Mean MGI • Mean TPI
To investigate subject satisfaction with toothpaste/mouthwash (a toothpaste containing 0.454% w/w SnF_2 with a mouthwash containing 0.07% w/w CPC) for the Overall liking, as measured by a Numeric Rating Scale (NRS), after 12 weeks treatment.	At Week 12: • Satisfaction NRS score
Safety	
To evaluate the safety and oral tolerability of the study products when used twice daily for 12 weeks	Treatment emergent adverse events (TEAEs) over 12 weeks

This study will be considered successful if there is a statistically significant difference in Overall NBS after 12 weeks of twice daily use of the Toothpaste/Mouthwash (a toothpaste containing 0.454% w/w SnF_2 with a mouthwash containing 0.07% w/w CPC) compared to the Negative Control toothpaste (containing 0.243% w/w NaF), and the difference is in favor of the Toothpaste/Mouthwash group.

1.3 Treatments

Table 1-3 presents the study products.

Table 1-3 Investigational/Study Product Supplies

Product Description	Test Products (Toothpaste/Mouthwash)	Reference Product (Negative Control, Toothpaste)	Reference Product (Toothpaste)
Product Name	Parodontax Complete Protection Toothpaste (0.454% w/w SnF_2) + Parodontax Active Gum Health Mouthwash (0.07% w/w CPC)	Crest Cavity Protection (0.243% w/w sodium fluoride)	Parodontax Complete Protection (0.454% w/w SnF_2)
Pack Design	Carton of 6 overwrapped tubes (toothpaste) + 12 blinded bottles (mouthwash)	Carton of 6 overwrapped tubes	Carton of 6 overwrapped tubes

Product Description	Test Products (Toothpaste/Mouthwash)	Reference Product (Negative Control, Toothpaste)	Reference Product (Toothpaste)
Dispensing Details	One carton (toothpaste) – baseline visit + 6 blinded bottles (mouthwash) – baseline visit 6 blinded bottles (mouthwash) – week 6 visit	One carton – baseline visit	One carton – baseline visit
Product Master Formulation Code (MFC)	Toothpaste CCI (US Commercial Product) Mouthwash CCI (US Commercial Product)	US Commercial Product	CCI (US Commercial Product)
Dose/Application	Toothpaste: Full ribbon of toothpaste on head of toothbrush provided Mouthwash: 20 milliliters of mouthwash	Full ribbon of toothpaste on head of toothbrush provided	Full ribbon of toothpaste on head of toothbrush provided
Route of Administration	Oral, Topical	Oral, Topical	Oral, Topical
Usage Instructions	Subjects will brush their teeth for at least one (timed) minute twice a day (morning and evening). After each brushing (morning and evening), subject will swish 20 milliliters of the mouthwash vigorously between teeth for 30 seconds. No further rinsing with water is permitted.	Subjects will brush their teeth for at least one (timed) minute twice a day (morning and evening)	Subjects will brush their teeth for at least one (timed) minute twice a day (morning and evening)
Return Requirements	All used/unused samples to be returned	All used/unused samples to be returned	All used/unused samples to be returned

Detailed instructions for the return of study product/study supplies will be provided by Haleon during the study in time for study close out. Investigational products can only be destroyed at site in agreement with and after approval from the Sponsor.

1.4 Sample Size Calculation

Sufficient subjects will be screened so that approximately 198 subjects are randomized (approximately 66 per group) to ensure approximately 180 (approximately 60 per group) evaluable subjects complete the entire study (allowing for 10% for drop-outs post-baseline).

The study will be sufficiently powered to demonstrate statistically significant differences between group Toothpaste/Mouthwash (a toothpaste containing 0.454% w/w SnF_2 with a mouthwash containing 0.07% w/w CPC) compared to the Negative Control (a toothpaste containing 0.243% w/w sodium fluoride) for Mean NBS (Overall) at Week 12 (primary objective). CCI

CCI

The dropout rate and SD estimates are based on the review of the sponsor clinical study evaluating 0.454% SnF_2 toothpastes. As the estimate was based on only one study, the sample size was inflated from the initial calculation to account for this.

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 0 (Visit 2) 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 resulting in the following stratum:

- Stratum 1: Sex = Male
- Stratum 2: Sex = Female

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 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 one who has agreed to participate in the clinical study following completion of the informed consent process directly or via their legally authorized representative and successfully met eligibility criteria 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
- 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 efficacy 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 efficacy 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 for the primary endpoint if ≥ 10% subjects in the mITT population are excluded from the PP population. Efficacy data determined to have been potentially impacted by a protocol deviation will be excluded from the PP analysis. The decisions as to whether or

not a protocol deviation impacts efficacy data and whether to perform a PP analysis will be made during BDR, prior to database lock.

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, SD, median, minimum and maximum for continuous variables, 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 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 for all randomized subjects, 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) for all randomized subjects.

The study product kit allocations will be listed (Listing 16.1.7.2) for all randomized subjects, 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 for compliance response (Yes/No) will be presented by study product and Time period ‘Baseline to Week 6’ and ‘Week 6 to Week 12’.

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, CCI CCI

Prior medications and prior non-drug therapies will be listed by subject, with drug name, CCI 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 safety population. 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 safety population 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 both 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. A sequential testing strategy will be used to adjust for the comparisons between the Toothpaste/Mouthwash combination and the Negative Control in Overall NBS and Interproximal NBS at each assessment time point.

At each time point, the Interproximal NBS will only be assessed for confirmatory evidence if the Overall NBS achieves a statistically significant greater reduction for the Toothpaste/Mouthwash combination compared to the Negative Control. This strategy will begin at Week 12, and then move to Week 6, only moving to the earlier time point for confirmatory evidence if the 'Week 12' time point achieves statistically significant greater reductions for the Toothpaste/Mouthwash compared to the Negative Control for both Overall NBS and Interproximal NBS. There will be no further adjustments for multiplicity for the other secondary endpoints.

The observed margin (OM) option in SAS will be used when estimating least square means/ performing MMRM analysis.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary endpoint of this study is Overall NBS at Week 12.

Gingival bleeding will be assessed according to the EBI, by inserting a periodontal probe into the gingival crevice and sweeping from distal to mesial around the tooth at an approximate angle of 60°, while in contact with the sulcular epithelium. Each of six gingival areas (distobuccal, midbuccal, mesiobuccal, distolingual, midlingual, and mesiolingual) around each tooth will be assessed. All scorable teeth in one quadrant should be probed first (approximately 30 seconds) before recording the number of gingival units which bleed.

The BI/EBI score has a range of 0 to 2 as described in Table 4-1.

Table 4-1 Bleeding Index Scoring System

Score	Description
0	No bleeding after 30 seconds
1	Bleeding observed within 30 seconds of probing
2	Bleeding observed immediately on probing
9	Missing tooth or not qualified tooth

The EBI will be assessed by the same examiner on all evaluable teeth from Baseline onwards as indicated in the Schedule of Activities (Table 1.1) .

The Overall NBS score for each subject will be calculated as the number of evaluable tooth sites with an EBI score of either 1 or 2.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of Overall NBS will be provided by study product for the mITT population (Table 14.2.2.1.1).

The raw mean and SE of the Overall NBS will be presented graphically over time for each study product in Figure 14.2.2.1.3 for the mITT population.

Individual data for the NBS will be listed for each subject by study product and visit in Listing 16.2.6.1 for all randomized subjects.

4.4.1.2 Statistical Hypothesis, Model and Method of Analysis

The primary hypothesis test will be the comparison between the Toothpaste/Mouthwash and the Negative Control in the mITT population.

The following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the Overall NBS at 12 weeks between the Toothpaste/Mouthwash and Negative Control.

- H_1: There is a difference in the Overall NBS at 12 weeks between the Toothpaste/Mouthwash and Negative Control.

A Mixed Model for Repeated Measures (MMRM) will be used, with Overall NBS values as the dependent/response variable, the categorical time point Week 12, treatment group (Toothpaste/Mouthwash and Negative Control) and treatment group by time point interaction as fixed effects and baseline Overall NBS as a covariate. Gender will also be included as stratification factor. Subject will be included as a repeated measure with an unstructured covariance matrix. The Kenward Roger degrees of freedom approach will be applied. If unstructured covariance matrix does not converge, the following covariance structures will be applied in order until convergence is achieved: 1) Toeplitz, 2) compound symmetry (CS).

Using the above model, the least squares differences at Week 12 from the MMRM will be presented, along with the two-sided p-value and 95% CI in Table 14.2.2.2.1. The % adjusted mean difference will also be presented.

The assumption of normality and homogeneity of variance in the MMRM will be investigated. In case of violation of these assumptions, a suitable non-parametric test (van Elteren test adjusting for gender stratification) will be performed for between product comparison to support the MMRM results.

4.4.1.3 Supportive Analyses

If there is a difference of 10% or more in the Overall number of subjects between 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 MMRM 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. Other than the sequential testing strategy for comparing the Overall NBS between products (see Section 4.4), there will be no adjustment for multiplicity performed for any other secondary endpoints detailed in this section.

For all the secondary efficacy variables described in subsections below, the comparisons of interest will be the 'Toothpaste/Mouthwash versus Negative Control' and 'Reference Toothpaste versus Negative Control'. Secondary efficacy variables will be analyzed using the same MMRM model described above for the primary endpoint, but with Baseline Overall NBS replaced with the Baseline of the respective endpoint:

Toothpaste/Mouthwash versus Negative Control:

- Baseline Overall NBS for Overall NBS at Week 6; Baseline Interproximal NBS for Interproximal NBS at Week 6 and Week 12.

- Baseline Mean Overall EBI for Mean Overall EBI at Week 6 and Week 12; Baseline Mean Interproximal EBI for Mean Interproximal EBI at Week 6 and Week 12.
- Baseline Mean Overall MGI for Mean Overall MGI at Week 6 and Week 12; Baseline Mean Interproximal MGI for Mean Interproximal MGI at Week 6 and Week 12.
- Baseline Mean Overall TPI for Mean Overall TPI at Week 6 and Week 12; Baseline Mean Interproximal TPI for Mean Interproximal TPI at Week 6 and Week 12.

Reference Toothpaste versus Negative Control:

- Baseline Overall NBS for Overall NBS at Week 6 and Week 12; Baseline Interproximal NBS for Interproximal NBS at Week 6 and Week 12.
- Baseline Mean Overall EBI for Mean Overall EBI at Week 6 and Week 12; Baseline Mean Interproximal EBI for Mean Interproximal EBI at Week 6 and Week 12.
- Baseline Mean Overall MGI for Mean Overall MGI at Week 6 and Week 12; Baseline Mean Interproximal MGI for Mean Interproximal MGI at Week 6 and Week 12.
- Baseline Mean Overall TPI for Mean Overall TPI at Week 6 and Week 12; Baseline Mean Interproximal TPI for Mean Interproximal TPI at Week 6 and Week 12.

Adjusted mean product differences will be provided, along with 95% CIs.

The assumption of residual normality and variance homogeneity in the MMRM 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 stratification) will be used and the results will be provided to support the MMRM results.

4.4.2.1 Number of Bleeding Sites at Week 6 and 12

The Interproximal NBS score for each subject will be calculated as the number of evaluable Interproximal tooth sites (distal and mesial) with an EBI score of either 1 or 2.
The EBI score as described in Table 4-1.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of Overall NBS at Week 6 will also be provided by study product for the mITT population (Table 14.2.2.1.1).

The raw mean and SE of the Overall NBS at Week 6 will also be presented graphically over time for each study product in Figure 14.2.2.1.3 for the mITT population

Similarly, the descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of Interproximal NBS will be provided by study product for the mITT population (Table 14.2.3.1.1).

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

4.4.2.1.1 Statistical Hypothesis, Model and Method of Analysis

The secondary hypothesis test will be the comparison between the 'Toothpaste/Mouthwash vs. Negative Control' and the 'Reference Toothpaste vs. Negative Control' in the mITT population.

For comparison between 'Toothpaste/Mouthwash and Negative Control', the following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the Overall NBS at Week 6 between the Toothpaste/Mouthwash and Negative Control.
- H_1: There is a difference in the Overall NBS at Week 6 between the Toothpaste/Mouthwash and Negative Control.

- H_0: There is no difference in the Interproximal NBS at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.
- H_1: There is a difference in the Interproximal NBS at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.

For comparison between 'Reference Toothpaste and Negative Control', the following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the Overall NBS at Week 6 and 12 between the Reference Toothpaste and Negative Control.
- H_1: There is a difference in the Overall NBS at Week 6 and 12between the Reference Toothpaste and Negative Control.

- H_0: There is no difference in the Interproximal NBS at Week 6 and 12between the Reference Toothpaste and Negative Control.
- H_1: There is a difference in the Interproximal NBS at Week 6 and 12between the Reference Toothpaste and Negative Control.

Overall and Interproximal NBS will be analyzed as described for primary analysis (Section 4.4.1.2), using the Baseline Overall/Interproximal NBS value as covariate respectively. The adjusted means and SEs of the two study products together with the product difference, SE, 95% CI of the difference and p-value will be provided in Table 14.2.2.2.1 (Overall NBS) and in Table 14.2.3.2.1 (Interproximal NBS) for the mITT population. The % adjusted mean difference will also be presented.

4.4.2.2 Expanded Bleeding Index at Week 6 and 12

The EBI will be assessed at each evaluable tooth site for each subject at each visit as described in Section 4.4.1.1, according to the scoring system in Table 4-1.

EBI score has a range of 0 to 2.

The Mean Overall EBI score for each subject will be calculated as the average index value over all tooth sites scored as follows:

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

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

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

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) will be presented at each time point (Observed value and change from baseline) in Table 14.2.4.1.1 (Overall EBI) and in Table 14.2.5.1.1 (Interproximal EBI) for all subjects in the mITT population by study product.

Raw means (± SE) at each time point will be plotted by study product in Figure 14.2.4.1.2 (Overall EBI) and in Figure 14.2.5.1.2 (Interproximal EBI) for all subjects in the mITT population.

Individual data for the EBI Score will be listed for each subject by study product and visit in Listing 16.2.6.2.1, and individual data for the derived EBI score (Overall and Interproximal, respectively), will be listed for each randomized subject in Listing 16.2.6.2.2, by study product and visit for all randomized subjects. The % adjusted mean difference will also be presented.

4.4.2.3 Statistical Hypothesis, Model, and Method of Analysis

For comparison between 'Toothpaste/Mouthwash and Negative Control', the following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in Mean Overall EBI score at Week 6 and 12 weeks between the Toothpaste/Mouthwash and Negative Control.
- H_1: There is a difference in Mean Overall EBI score at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.

- H_0: There is no difference in Mean Interproximal EBI score at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.
- H_1: There is a difference in Mean Interproximal EBI score at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.

For comparison between 'Reference Toothpaste and Negative Control', the following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the Mean Overall EBI at Week 6 and 12 between the Reference Toothpaste and Negative Control.
- H_1: There is a difference in the Mean Overall EBI at Week 6 and 12 between the Reference Toothpaste and Negative Control.

- H_0: There is no difference in the Mean Interproximal EBI at Week 6 and 12 between the Reference Toothpaste and Negative Control.
- H_1: There is a difference in the Mean Interproximal EBI at Week 6 and 12 between the Reference Toothpaste and Negative Control.

Overall and Interproximal EBI will be analyzed as described for primary analysis (Section 4.4.1.2), using the Baseline Mean Overall and Interproximal EBI value respectively as covariate. The adjusted means and SEs of the two study products together with the product difference, SE, 95% CI of the difference and p-value will be provided in Table 14.2.4.2.1 (Overall EBI) and in Table 14.2.5.2.1 (Interproximal EBI) for the mITT population. The % adjusted mean difference will also be presented.

4.4.2.4 Mean Modified Gingival Index at Week 6 and 12

The MGI assessment is a non-invasive evaluation which focuses on the visual symptoms of gingivitis (for example, redness, texture, edema). The MGI will be assessed on the buccal and lingual marginal gingiva and interdental papillae of all scorable teeth (second permanent molar to second permanent molar in each arch) by an appropriately qualified examiner. Three scores will be recorded buccally/labially (papilla and margin) and three scores lingually/palatally papilla and margin). The scoring of the MGI will be performed under dental office conditions using a standard dental light for illuminating the oral cavity.

The MGI score has a range of 0 to 4.
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 papillar gingival unit.
3	Moderate inflammation; glazing, redness, edema, and/or hypertrophy of the marginal or papillary gingival unit.
4	Severe inflammation; marked redness, edema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.
9	Missing tooth or not qualified tooth

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

- Mean Overall MGI Score = Sum of Index values over all evaluable tooth sites/Number of evaluable tooth sites.

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

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

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) will be presented at each time point (Observed value and change from baseline) in Table 14.2.6.1.1 (Overall MGI) and in Table 14.2.7.1.1 (Interproximal MGI) for all subjects in the mITT population by study product.

The raw mean and SE of the MGI will be presented graphically over time for each study product in Figure 14.2.6.1.2 (Overall MGI) and in Figure 14.2.7.1.2 (Interproximal MGI) for the mITT population.

Individual data for the MGI will be listed for each subject by study product and visit in Listing 16.2.6.3.1 for all randomized subjects and individual data for the derived MGI score (Overall and Interproximal) will be listed for each subject in Listing 16.2.6.3.2, by study product and visit for all randomized subjects. The % adjusted mean difference will also be presented.

4.4.2.5 Statistical Hypothesis, Model and Method of Analysis

For comparison between 'Toothpaste/Mouthwash and Negative Control', the following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in Mean Overall MGI score at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.
- H_1: There is a difference in Mean Overall MGI score at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.

- H_0: There is no difference in Mean Interproximal MGI score at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.
- H_1: There is a difference in Mean Interproximal MGI score at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.

For comparison between 'Reference Toothpaste and Negative Control', the following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the Mean Overall MGI at Week 6 and 12 between the Reference Toothpaste and Negative Control.
- H_1: There is a difference in the Mean Overall MGI at Week 6 and 12 between the Reference Toothpaste and Negative Control.

- H_0: There is no difference in the Mean Interproximal MGI at Week 6 and 12 between the Reference Toothpaste and Negative Control.
- H_1: There is a difference in the Mean Interproximal MGI at Week 6 and 12 between the Reference Toothpaste and Negative Control.

MGI (Overall and Interproximal) will be analyzed as described for primary analysis (Section 4.4.1.2), using the Baseline Mean Overall and Interproximal MGI value respectively 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 14.2.6.2.1 (Overall MGI) and in Table 14.2.7.2.1 (Interproximal Mean MGI) for the mITT population. The % adjusted mean difference will also be presented.

4.4.2.6 Mean Turesky Plaque Index at Week 6 and 12

TPI will be used to assess plaque on all gradable teeth meeting the inclusion/ exclusion criteria and will be performed by an appropriately qualified examiner. Only natural teeth can be assessed. This means no crowns, bridges, and teeth with fillings (surface that has 50% of the surface gradable or no more than 50% of the surface filled) which, in the examiner's judgment, would prevent an accurate grading should be assessed. Third molars should not be assessed.

The plaque will first be disclosed using a plaque disclosing dye solution, in agreement with the manufacturer's instructions. The TPI will be assessed on the facial and lingual surfaces of each scorable tooth (second molar to second molar). Three scores should be recorded buccally/ labially (distal, body, mesial sites) and three scores lingually / palatally (distal, body, mesial sites).

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
2	Thin continuous band of plaque (up to 1 mm) at the cervical margin
3	Band of plaque wider than 1 mm but covering < 1/3 of the tooth surface
4	Plaque covering ≥ 1/3 but < 2/3 of the tooth surface
5	Plaque covering ≥ 2/3 of the tooth surface
9	Missing tooth or not qualified tooth

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

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

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

- Mean 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 Mean Interproximal TPI score have a range of 0 to 5.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) will be presented at each time point (Observed value and change from baseline) in Table 14.2.8.1.1 (Overall TPI) and in Table 14.2.9.1.1 (Interproximal TPI) for all subjects in the mITT population by study product.

The raw mean and SE of the TPI will be presented graphically over time for each study product in Figure 14.2.8.1.2 (Overall TPI) and in Figure 14.2.9.1.2 (Interproximal TPI) for the mITT population.

Individual data for the TPI assessment at each evaluable tooth site will be listed for each subject 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 and visit for all randomized subjects. The % adjusted mean difference will also be presented.

4.4.2.7 Statistical Hypothesis, Model and Method of Analysis

For comparison between 'Toothpaste/Mouthwash and Negative Control', the following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in Mean Overall TPI score at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.
- H_1: There is a difference in Mean Overall TPI score at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.

- H_0: There is no difference in Mean Interproximal TPI score at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.
- H_1: There is a difference in Mean Interproximal TPI score at Week 6 and 12 between the Toothpaste/Mouthwash and Negative Control.

For comparison between 'Reference Toothpaste and Negative Control', the following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the Mean Overall TPI at Week 6 and 12 between the Reference Toothpaste and Negative Control.
- H_1: There is a difference in the Mean Overall TPI at Week 6 and 12 between the Reference Toothpaste and Negative Control.

- H_0: There is no difference in the Mean Interproximal TPI at Week 6 and 12 between the Reference Toothpaste and Negative Control.
- H_1: There is a difference in the Mean Interproximal TPI at Week 6 and 12 between the Reference Toothpaste and Negative Control.

TPI (Overall and Interproximal) will be analyzed as described for primary analysis (Section 4.4.1.2), using the Baseline Mean Overall and Interproximal TPI value respectively 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 14.2.8.2.1 (Overall TPI) and in Table 14.2.9.2.1 (Interproximal TPI) for the mITT population. The % adjusted mean difference will also be presented.

4.4.3 Exploratory Efficacy Variables

The exploratory endpoints comparing the Toothpaste/Mouthwash versus Reference Toothpaste will be analyzed using the same MMRM model described above for the primary and secondary endpoints.

4.4.3.1 Number of Bleeding Sites at Week 6 and Week 12

The key exploratory hypothesis test will be the comparison between the 'Toothpaste/Mouthwash' versus 'Reference Toothpaste' in the mITT population.

The following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the Overall NBS at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.
- H_1: There is a difference in the Overall NBS at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.

- H_0: There is no difference in the Interproximal NBS at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.
- H_1: There is a difference in the Interproximal NBS at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.

NBS (Overall and Interproximal) will be analyzed as described for primary analysis (Section 4.4.1.2), using the Baseline Interproximal/Overall NBS 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 14.2.2.2.1 (Overall NBS) and in Table 14.2.3.2.1 (Interproximal NBS) for the mITT population. The % adjusted mean difference will also be presented.

4.4.3.2 Expanded Bleeding Index at Week 6 and Week 12

For comparison between 'Toothpaste/Mouthwash and Reference Toothpaste', the following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the Mean Overall EBI at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.
- H_1: There is a difference in the Mean Overall EBI at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.

- H_0: There is no difference in the Mean Interproximal EBI at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.
- H_1: There is a difference in the Mean Interproximal EBI at Week 6 and 12 between Toothpaste/Mouthwash and Reference Toothpaste.

EBI (Overall and Interproximal) will be analyzed as described for primary analysis (Section 4.4.1.2), using the Baseline Mean Interproximal/Overall EBI 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 14.2.4.2.1 (Overall EBI) and in Table 14.2.5.2.1 (Interproximal EBI) for the mITT population. The % adjusted mean difference will also be presented.

4.4.3.3 Mean Modified Gingival Index at Week 6 and Week 12

For comparison between 'Toothpaste/Mouthwash and Reference Toothpaste', the following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the Mean Overall MGI at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.
- H_1: There is a difference in the Mean Overall MGI at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.

- H_0: There is no difference in the Mean Interproximal MGI at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.
- H_1: There is a difference in the Mean Interproximal MGI at Week 6 and 12 between Toothpaste/Mouthwash and Reference Toothpaste.

MGI (Overall and Interproximal) will be analyzed as described for primary analysis (Section 4.4.1.2), using the Baseline Mean Interproximal/Overall EBI 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 14.2.6.2.1 (Overall MGI) and in Table 14.2.7.2.1 (Interproximal MGI) for the mITT population. The % adjusted mean difference will also be presented.

4.4.3.4 Mean Turesky Plaque Index at Week 6 and Week 12

For comparison between 'Toothpaste/Mouthwash and Reference Toothpaste', the following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the Mean Overall TPI at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.
- H_1: There is a difference in the Mean Overall TPI at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.

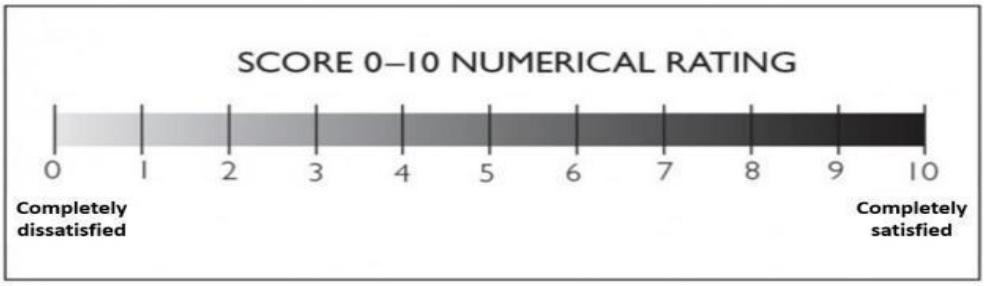
- H_0: There is no difference in the Mean Interproximal TPI at Week 6 and 12 between the Toothpaste/Mouthwash and Reference Toothpaste.
- H_1: There is a difference in the Mean Interproximal TPI at Week 6 and 12 between Toothpaste/Mouthwash and Reference Toothpaste.

TPI (Overall and Interproximal) will be analyzed as described for primary analysis (Section 4.4.1.2), using the Baseline Mean Interproximal/Overall 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 14.2.8.2.1 (Overall TPI) and in Table 14.2.9.2.1 (Interproximal TPI) for the mITT population. The % adjusted mean difference will also be presented.

4.4.3.5 Exit Satisfaction Survey Questionnaire (Toothpaste/Mouthwash Treatment Arm)

At the end of the study (Visit 4/Week 12), subjects in Toothpaste/Mouthwash treatment arm will be asked to rate their level of satisfaction with the Toothpaste and the Mouthwash using a Numeric Rating Scale (NRS). The NRS is an 11-point ordinal scale used to assess the subject's satisfaction with the Toothpaste and Mouthwash. The scale ranges from 0 (completely dissatisfied) to 10 (completely satisfied), with higher scores indicative of greater satisfaction.

Subjects will be asked to record the numeric value on the segmented scale that best describes their level of satisfaction after 12 weeks twice daily use and indicate why they select a particular score in answer to the question 'Please give more details on why you are satisfied or dissatisfied with the product' (free text response).



A summary of the number and percentage of subjects reporting at each level of the NRS and the cumulative number of subjects reporting at each level or higher at Week 12 will be presented in Table 14.2.10.1.1 and the numeric (integer) NRS score at Week 12 will be summarized

descriptively in Table 14.2.10.1.2 by the test product Toothpaste and the test product Mouthwash.

Subject free text comments will be listed after each NRS rating in listing 16.2.6.5 for all randomized subjects.

In addition to each NRS, subjects will be asked whether they would recommend the products to their family and friends who have gum problems at the end of the study. Responses ("yes" or "no") will be summarized by the number and percentage of subjects in the 'Test Toothpaste/ Mouthwash' treatment in Table 14.2.10.1.3.

4.4.4 Handling of Missing Values/Censoring/Discontinuations

For the primary analyses, missing data will not be replaced or imputed. Subjects who withdraw from the study prematurely will be included in the statistical analyses up to the point of discontinuation. Subjects who withdraw will not be replaced. In the event that a subject has no individual BI, MGI or TPI assessments available at a given visit, the Mean NBS, BI score, MGI score or TPI score will also be considered as missing for that visit.

MMRM analyses account for missing data using 'a missing at random' assumption, i.e., there is a systematic relationship between the propensity for missing values and the observed data, but not the missing data. Under such assumptions, MMRM is shown to provide unbiased estimates of the treatment effect whilst analysis of only complete cases using analysis of covariance (ANCOVA) is biased (Ashbeck, 2016; Baron, 2008).

Such complete case analysis requires a 'missing completely at random' assumption to remain unbiased and this is unlikely to hold, i.e., the fact that the data are missing is independent of the observed and unobserved data. Using an MMRM, it will therefore be assumed that a subject with missing data at one post- Baseline assessment visit would have obtained a similar efficacy result at that visit compared to a subject using the same investigational product with similar non-missing results at other timepoints (Baseline and the other post-Baseline assessment visits).

4.5 Analysis of Safety

The safety profile of the study products will be assessed with respect to adverse events (AEs), incidents 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 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 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)

All incidents will be listed in Listing 16.2.7.3.

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. The examination will cover the oral 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 any grossly carious lesions, signs of erosive wear, enamel

irregularities, tooth fracture, gross generalized dental caries decay, decalcification and faulty restorations. Any conditions noted as 'Present' from the OHT examination will be described in the eCRF with details of the 'Present' condition.

The presence of any implants, fixed or removable dentures, fixed or removable orthodontic braces/bands, fixed orthodontic retainers, full crowns or veneers will be recorded. 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, 3 and 4. At least 1 repeat assessment should be performed for each index on each clinical assessment day '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. Due to the invasive nature of the EBI assessment, it is not feasible to conduct an accurate repeatability assessment for this index.

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 14.2.11.1). 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 14.2.11.2). 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 8.3.4 of the protocol states that “Responses (“yes” or “no”) will be summarized by the number and percentage of subjects in the test product Toothpaste and the test product Mouthwash treatment respectively	Section 4.4.3.5 of the SAP has revised the protocol text to state that “Responses (“yes” or “no”) will be summarized by the number and percentage of subjects in the ‘Test Toothpaste/ Mouthwash’ treatment in Table 14.2.10.3.”	As per eCRF section ‘EXIT SATISFACTION SURVEY (ESQ)’, there is a single ‘Yes/No’ question that combines both Test Toothpaste and Mouthwash together: “Will you recommend the products (Toothpaste and Mouthwash) to your family and friends who have gum problems?”. Therefore, it is not possible to summarize ‘Yes/No’ responses for Test Toothpaste and Mouthwash separately.
Section 6.3.1 of the Protocol states that ‘Findings from the examination will be recorded in the CRF as either normal or abnormal, with details of any abnormalities.’	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 ‘Observations will be listed as either absent or	Section 4.5.2.2 of the SAP has revised the Protocol text to state that ‘Any conditions noted as ‘Present’ from the OHT	This study uses a redesigned standard eCRF, where only ‘Present’ conditions will be

Protocol	Statistical Analysis Plan	
Statistical Analysis Section	**Statistical Analysis Plan**	**Rationale for Changes**
present, and conditions noted as present will be described in the CRF'.	examination will be described in the eCRF along with the details of the 'Present' condition.'	captured in the eCRF for OHT examination.

Appendix 1: List of Data Displays

CSR Section	TLF	Number	Title	Population	Template
14.1 Demographic Data Summary Tables and Figures					
	Table	14.1.1	Subject Disposition	All Screened Subjects	14.1.1
	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
	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 Product Use Compliance	mITT Population	14.2.1
	Table	14.2.2.1.1	Summary of Overall Number of Bleeding Sites	mITT Population	14.2.2.1.1
	Table	14.2.2.1.2	Summary of Overall Number of Bleeding Sites	PP Population	14.2.2.1.1
	Figure	14.2.2.1.3	Overall Number of Bleeding Sites (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3
	Figure	14.2.2.1.4	Overall Number of Bleeding Sites (± SE) Plot Over Time by Study Product	PP Population	14.2.2.1.3
	Table	14.2.2.2.1	Statistical Analysis of Overall Number of Bleeding Sites	mITT Population	14.2.2.2.1
	Table	14.2.2.2.2	Statistical Analysis of Overall Number of Bleeding Sites	PP Population	14.2.2.2.1
	Table	14.2.3.1.1	Summary of Interproximal Number of Bleeding Sites	mITT Population	14.2.2.1.1

CSR Section	TLF	Number	Title	Population	Template
	Figure	14.2.3.1.2	Interproximal 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 Interproximal Number of Bleeding Sites	mITT Population	14.2.2.2.1
	Table	14.2.4.1.1	Summary of Overall Expanded Bleeding Index (EBI)	mITT population	14.2.2.1.1
	Figure	14.2.4.1.2	Overall Expanded Bleeding Index (EBI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3
	Table	14.2.4.2.1	Statistical Analysis of Overall Expanded Bleeding Index (EBI)	mITT Population	14.2.2.2.1
	Table	14.2.5.1.1	Summary of Interproximal Expanded Bleeding Index (EBI)	mITT population	14.2.2.1.1
	Figure	14.2.5.1.2	Interproximal Expanded Bleeding Index (EBI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3
	Table	14.2.5.2.1	Statistical Analysis of Interproximal Expanded Bleeding Index (EBI)	mITT Population	14.2.2.2.1
	Table	14.2.6.1.1	Summary of Overall Modified Gingival Index (MGI)	mITT Population	14.2.2.1.1
	Figure	14.2.6.1.2	Overall Modified Gingival Index (MGI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3
	Table	14.2.6.2.1	Statistical Analysis of Overall Modified Gingival Index (MGI)	mITT Population	14.2.2.2.1
	Table	14.2.7.1.1	Summary of Interproximal Modified Gingival Index (MGI)	mITT Population	14.2.2.1.1

CSR Section	TLF	Number	Title	Population	Template
	Figure	14.2.7.1.2	Interproximal Modified Gingival Index (MGI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3
	Table	14.2.7.2.1	Statistical Analysis of Interproximal Modified Gingival Index (MGI)	mITT Population	14.2.2.2.1
	Table	14.2.8.1.1	Summary of Overall Turesky Plaque Index (TPI)	mITT Population	14.2.2.1.1
	Figure	14.2.8.1.2	Overall Turesky Plaque Index (TPI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3
	Table	14.2.8.2.1	Statistical Analysis of Overall Turesky Plaque Index (TPI)	mITT Population	14.2.2.2.1
	Table	14.2.9.1.1	Summary of Interproximal Turesky Plaque Index (TPI)	mITT Population	14.2.2.1.1
	Figure	14.2.9.1.2	Interproximal Turesky Plaque Index (TPI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3
	Table	14.2.9.2.1	Statistical Analysis of Interproximal Turesky Plaque Index (TPI)	mITT Population	14.2.2.2.1
	Table	14.2.10.1.1	Summary of Exit Satisfaction Survey (Frequency of Responses)	mITT Population	14.2.10.1.1
	Table	14.2.10.1.2	Summary of Exit Satisfaction Survey (Descriptive Statistics)	mITT Population	14.2.10.1.2
	Table	14.2.10.1.3	Summary of Exit Satisfaction Survey Product Recommendations	mITT Population	14.2.10.1.3
	Table	14.2.11.1	Intra-Examiner Repeatability Analysis of Modified Gingival Index (MGI)	MGI Repeatability	14.2.11.1
	Table	14.2.11.2	Intra-Examiner Repeatability Analysis of Turesky Plaque Index (TPI)	TPI Repeatability	14.2.11.2

CSR Section	TLF	Number	Title	Population	Template
14.3 Safety Data Summary Tables and Figures					
14.3.1 Displays of Adverse Events					
	Table	14.3.1.1	Overall Summary of Treatment Emergent Adverse Events	Safety Population	14.3.1.1
	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
	Table	14.3.1.5	Treatment Related 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					

CSR Section	TLF	Number	Title	Population	Template
	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)					
	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 Overall Number of Bleeding Sites (Reference: Table 14.2.2.2.1)	mITT Population	SAS Output
	Raw output	16.1.9.1.2	Statistical Analysis of Overall Number of Bleeding Sites (Reference: Table 14.2.2.2.2)	PP Population	SAS Output
	Raw output	16.1.9.1.3	Statistical Analysis of Interproximal Number of Bleeding Sites (Reference: Table 14.2.3.2.1)	mITT Population	SAS Output
	Raw output	16.1.9.2.1	Statistical Analysis of Overall Expanded Bleeding Index (EBI) (Reference: Table 14.2.4.2.1)	mITT Population	SAS Output

CSR Section	TLF	Number	Title	Population	Template
	Raw output	16.1.9.2.2	Statistical Analysis of Interproximal Expanded Bleeding Index (EBI) (Reference: Table 14.2.5.2.1)	mITT Population	SAS Output
	Raw output	16.1.9.3.1	Statistical Analysis of Overall Modified Gingival Index (MGI) (Reference: Table 14.2.6.2.1)	mITT Population	SAS Output
	Raw output	16.1.9.3.2	Statistical Analysis of Interproximal Modified Gingival Index (MGI) (Reference: Table 14.2.7.2.1)	mITT Population	SAS Output
	Raw output	16.1.9.4.1	Statistical Analysis of Overall Turesky Plaque Index (TPI) (Reference: Table 14.2.8.2.1)	mITT Population	SAS Output
	Raw output	16.1.9.4.2	Statistical Analysis of Interproximal Turesky Plaque Index (TPI) (Reference: Table 14.2.9.2.1)	mITT Population	SAS Output
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					

CSR Section	TLF	Number	Title	Population	Template
	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
	Listing	16.2.4.3	Prior Medications	Safety Population	16.2.4.3
	Listing	16.2.4.4	Concomitant Medications and Concomitant Non-Drug Therapies	Safety Population	16.2.4.4
16.2.5 Compliance and/or Drug Concentration Data (if available)					
	Listing	16.2.5.1	Product Use Compliance	All Randomized Subjects	16.2.5.1
	Listing	16.2.5.2	Supervised Product Application	All Randomized Subjects	16.2.5.2
16.2.6 Individual Efficacy Response Data					
	Listing	16.2.6.1	Number of Bleeding Sites	All Randomized Subjects	16.2.6.1
	Listing	16.2.6.2.1	Expanded Bleeding Index (EBI) Individual Scores	All Randomized Subjects	16.2.6.2.1
	Listing	16.2.6.2.2	Expanded Bleeding Index (EBI) Derived Scores	All Randomized Subjects	16.2.6.2.2
	Listing	16.2.6.3.1	Modified Gingival Index (MGI) Individual Scores	All Randomized Subjects	16.2.6.3.1

CSR Section	TLF	Number	Title	Population	Template
	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
	Listing	16.2.6.4.2	Turesky Plaque Index (TPI) Derived Scores	All Randomized Subjects	16.2.6.4.2
	Listing	16.2.6.5	Exit Satisfaction Survey at Week 12	All Randomized Subjects	16.2.6.5
16.2.7 Adverse Event Listings					
	Listing	16.2.7.1	All Adverse Events	All Randomized Subjects	16.2.7.1
	Listing	16.2.7.2	All Adverse Events	Non-Randomized Subjects	16.2.7.1
	Listing	16.2.7.3	Incidents	All Randomized Subjects	16.2.7.3
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				