STATISTICAL ANALYSIS PLAN

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

Haleon Protocol Number:	300268
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)
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Abbreviations

Abbreviation	Term
AE	Adverse Event
AngBI	Angulated-bleeding index
BDRM	Blind Data Review Meeting
BI	Bleeding Index
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
IRT	Interactive Response Technology
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
OHT	Oral Hard Tissue
OM	Observed Margin
OST	Oral Soft Tissue
PBS	Phosphate-Buffered Saline
PD	Protocol Deviation
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

Abbreviation	Term
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

1 Document Purpose and Status

The purpose of this Statistical Analysis Plan is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 300268 Version 3.0, dated 07-Apr-2025.

This version of the SAP was approved prior to any unblinding in the study.

2 Summary of Key Protocol Information

2.1 Background

Dental plaque is a structured, resilient biofilm composed of microbial communities that adhere to the tooth surface, it is primarily composed of bacteria, extracellular polysaccharides, proteins, and lipids. It is a causative agent of gingivitis and periodontitis.

Many people are unable to achieve adequate plaque control by toothbrushing alone. Antimicrobial agents (such as metal salts, Cetylpyridinium Chloride (CPC) and chlorhexidine) have been included in daily use dentifrice and mouthwash formulations for many years, with a view to delivering improved plaque control and gum health benefits. They complement mechanical plaque removal by inhibiting the growth of bacteria (via bacteriostatic and/or bactericidal activity) in areas of the mouth less accessible to the toothbrush and by interfering with the re-colonization of plaque bacteria.

Antimicrobial mouthwashes play a crucial role in maintaining oral health by reducing the microbial load in the oral cavity and inhibiting plaque formation. Various formulations, including those containing chlorhexidine, essential oils, and cetylpyridinium chloride, have been shown to be effective in controlling plaque and gingivitis.

The use of antimicrobial mouthwash as adjunct to mechanical oral hygiene routine is considered a means to enhance plaque removal and recommended by dental professionals. The mouthwash format complements brushing and flossing as a means of enhancing plaque removal and allows the antimicrobial active ingredient to contact the area of the mouth where brushing access could be an issue, such as between teeth, and the back of the mouth, and areas that would not be easily accessible for consumers with reduced manual dexterity.

2.2 Study Design

This will be a single-center, 12-week, randomized, controlled, single blind (examiner only), 2-treatment arms, parallel group, stratified (by sex (male/female)) study, investigating gingival health and CCI reduction on healthy subjects after twice daily using of an experimental mouthwash containing CCI CPC in combination with a commercially available regular toothpaste containing 0.243% w/w NaF compared to a commercially available regular toothpaste containing 0.243% w/w NaF with no known anti-gingivitis nor anti plaque efficacy properties as control group.

Study subjects will be healthy adult volunteers, aged 18 and over with generalized clinically measurable plaque-induced gingivitis.

Approximately 132 subjects (approximately 66 per group) will be randomized to ensure approximately 120 evaluable subjects (approximately 60 per group) complete the study (allow up to 10% dropout).

This study will consist of 4 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.

CCI

All evaluable teeth (in relation to the inclusion/ exclusion general dentition criteria) will be assessed.

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), CCI , 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 supragingival 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. Subjects 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 toothbrushing 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 inspected visually to determine treatment compliance. During visits 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, CCI CCI 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. At least 3 repeatability examinations for each clinical measure will be obtained over the duration of each of visit 2, 3 and 4. This will give a total of at least 9 repeatability assessments for each endpoint collected across the 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. 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 2-1 presents the schedule of activities.

Table 2-1 Schedule of Activities

Procedure/Assessment	Screening				
	Visit 1		Visit 2 **Baseline**[1] Day 1	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		
Subject Eligibility	X		X		
Subject continuance				X	X

Procedure/Assessment	Screening Visit 1		Visit 2 **Baseline**[1] Day 1	Visit 3 **Week 6**[1] Day 42 (±4)	Visit 4 **Week 12**[1] Day 84 (±4)
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
CCI [redacted]			X		X
Expanding Bleeding Index (EBI) assessment[5]			X	X	X
Disclose dental plaque			X	X	X
Turesky Plaque Index (TPI) assessment			X	X	X
Repeat TPI assessment[6]			X	X	X
Dental prophylaxis			X		
2nd clinician check to confirm TPI=0 (additional dental cleaning will be performed as required)			X		
Stratification/Randomisation			X		
Dispense study product, toothbrush and dosing cups for Mouthwash[7], timer			X		
Dispense additional study supplies[7]				X	
Supervised study product use			X	X	
Subject returns study product(s) and toothbrush to site for compliance checks				X	X
Subjects returns study product to site					X
Adverse Events (AEs) Review[8]	X		X	X	X
End of study dental prophylaxis (optional)					X
Study Conclusion/Subject Exit from Study					X

Footnotes:

1: Subjects will abstain from overnight toothbrushing 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 3 MGI repeatability assessments will be obtained over the duration of each of visits 2, 3 and 4; MGI repeatability assessment at Baseline visit will be conducted on an eligible subject. If the repeat exam is performed on a subject that was deemed non-eligible, another repeatability exam will be performed until it is completed on a subject that was deemed eligible.

4: CCI [redacted]

5: NBS and bleeding sites% are derived from EBI assessment.

6: Minimum 3 TPI repeatability assessments will be obtained over the duration of each of visits 2, 3 and 4; TPI repeatability assessment at Baseline visit will be conducted after the subject's eligibility has been confirmed.

7: Toothpaste/mouthwash treatment arm only

8: 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).

2.3 Study Objectives

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

Table 2-2 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To evaluate the efficacy of toothpaste/mouthwash (toothpaste containing 0.243% w/w NaF with a mouthwash containing CCI [redacted] CPC) in reducing gingivitis, as measured by NBS (overall), compared to a regular toothpaste alone (containing 0.243% w/w NaF), after 12 weeks twice daily use	At Week 12, overall: • Number (no.) of bleeding sites
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of toothpaste/mouthwash (toothpaste containing 0.243% w/w NaF with a mouthwash containing CCI [redacted] CPC) in reducing gingivitis, as measured by NBS (interproximal), compared to a regular toothpaste alone (containing 0.243% w/w NaF), after 12 weeks twice daily use	At Week 12, interproximal: • Number (no.) of bleeding sites (NBS)
To evaluate the efficacy of toothpaste/mouthwash (toothpaste containing 0.243% w/w NaF with a Mouthwash containing CCI [redacted] CPC) in reducing gingivitis, as measured by NBS (overall and interproximal), compared to a regular toothpaste alone (containing 0.243% w/w NaF), after 6 weeks twice daily use	At Week 6, overall and interproximal: • Number (no.) of bleeding sites (NBS)
To evaluate the efficacy of toothpaste/mouthwash (toothpaste containing 0.243% w/w NaF with a Mouthwash containing CCI [redacted] CPC) in reducing gingivitis, as measured by bleeding index (EBI), Modified Gingival Index (MGI) and Turesky Plaque Index (TPI), overall and interproximal, compared to a regular toothpaste alone (containing 0.243% w/w NaF), after 6 and 12 weeks twice daily use	At Week 6 and 12, overall and interproximal: • Mean EBI • Mean MGI • Mean TPI

CCI	CCI
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 NBS (overall) after 12 weeks of twice daily use of the toothpaste/mouthwash (a toothpaste containing 0.243% w/w NaF with a Mouthwash containing CCI CPC) compared to a regular fluoride toothpaste (containing 0.243% w/w NaF), and the difference is in the favor of the toothpaste/mouthwash group.

2.4 Treatments and Randomization

2.4.1 Treatments

Table 2-3 presents the study products.

Table 2-3 Investigational/Study Product Supplies

	Product Name	MFC #	Route of Administration and Dosage	Usage Instructions
Test Products (Toothpaste/Mouthwash)	Crest Cavity Plus Protection (0.243% w/w sodium fluoride) + Experimental Mouthwash (CCI CPC)	Toothpaste: US Commercial Product + Mouthwash CCI	Toothpaste: Full ribbon of toothpaste on head of toothbrush provided Mouthwash: 20 milliliters of mouthwash	Brush teeth for at least one minute twice daily (morning and evening). After each brushing, Swish 20 ml of mouthwash for 30 seconds without rinsing with water after use of mouthwash.
Reference product (control group, toothpaste)	Crest Cavity Plus Protection (0.243% w/w sodium fluoride)	US Commercial Product	Full ribbon of toothpaste on head of toothbrush provided	Brush teeth for at least one minute twice daily (morning and evening)
Washout/Acclimatization	Colgate Cavity Protection (0.76% w/w sodium monofluorophosphate)	US Commercial Product		

Toothbrush	Sensodyne Sensitive Care soft-bristled Toothbrushes (US marketplace)	Commercial Product	Topical oral use	As above for Test, Reference and washout

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.

2.4.2 Randomization

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

All subjects will be centrally randomized using an Interactive Response Technology (IRT).

The investigator's knowledge of the product allocation should not influence the decision to enroll a subject or affect the order in which subjects are enrolled.

This study is described as examiner-blind only (the examiner(s) will be blinded to the product received). Study subjects may be unblinded due to the presence of mouthwash in the Test Group. To ensure the examiner remains blinded throughout the study, staff involved in the preparation, dispensing of study products will work in a separate area.

Subjects will be instructed not to remove study products from the opaque bags provided/cartons outside of the dispensing room, while at the study site. Dispensing staff will not be involved in any efficacy/safety assessment procedures during the study.

Eligible subjects will be stratified according to their sex (male or female) to ensure a balance of sex across both treatment groups and then randomized to study product. This will give rise to two strata:

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

Site staff will be instructed to not enter any information into the clinical database that could potentially unblind study personnel.

The project is described as examiner-blind, and the blinding of site staff to the Protocol Deviations eCRFs is controlled by pre-defined access roles as detailed in the Data Management Plan.

No blinding will be applied to the study data extracts provided to the CCI Biostatisticians and Statistical Programmers. The Lead Clinical Data Manager will place the full data extract (including the Protocol Deviations datasets) in the SAS Azure access-controlled project folder per the standard process.

As an additional precaution, no data extracts will be provided to the CCI Biostatisticians or Statistical Programmers until after the Statistical Analysis Plan has been approved as Final.

2.5 Sample Size Calculation

Sufficient subjects will be screened so that approximately 132 subjects are randomized (approximately 66 per group) to ensure approximately 120 (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 0.243% w/w sodium fluoride with a mouthwash containing CCI CPC) compared to the control group (a toothpaste containing 0.243% w/w sodium fluoride) for mean NBS (overall) at Week 12 (primary objective). CCI [redacted] CCI [redacted] CCI [redacted] The sample size calculation was performed using PASS software version 23.0.1.

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

3 Planned Analyses

Prior to database lock and any unblinded analyses, a Blind Data Review (BDR) will be conducted in which the following aspects of the analysis will be discussed and the SAP may be updated as required:

- Classify protocol deviations as Important or Not Important
- Determine any Important protocol deviations which lead to subject exclusions from an analysis population and/or data exclusions from an analysis
- Determine any incorrect use of study product to which the subject was not randomized to and how this affects the 'as treated' study product group for safety analyses. Details and discussions will be based on blinded data only. As such, it will not be possible to definitively define the 'as treated' group, but all possibilities will be assessed, with defined actions to take following unblinding.
- Appropriateness of current planned analyses based on blinded data review

3.1 Interim Analysis

No interim analyses are planned in this study.

3.2 Final Analyses

The final planned 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:

- Blind data review (BDR) meeting has been completed and documented.
- Protocol deviations (PDs) have been documented as Important or Not Important and whether they have any impact on efficacy data.
- Analysis population exclusions and data exclusions from analyses have been documented.
- This SAP has been finalized and approved, capturing any actions (if applicable) from the BDR meeting (e.g., Baseline derivations, strata/subgroup pooling, pooling of centers, visit remapping).

4. Randomization schedule has been released and the study is unblinded.

4 Considerations for Data Analyses and Data Handling Conventions

4.1 Baseline Definition

For all efficacy endpoints, the value collected at the planned Visit 2 (Day 1) is intended to be the latest non-missing result collected prior to randomization and/or first exposure to study product and represent the Baseline result for all endpoint derivations and analyses. In the case of a later unscheduled non-missing result collected prior to the first exposure to study product, or a protocol deviation resulting in the planned Baseline result being missed or recorded following the first exposure to study product, the potential impact on the analyses and subsequent actions will be discussed and the SAP will be updated accordingly, prior to unblinding, detailing how this will be handled.

Unless otherwise stated, if baseline data is missing, no imputation will be performed and the value will be treated as missing data.

4.2 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

In the case of stratification errors at randomization, the corrected stratum will be derived based on the collected data and used for stratification variables or subgroup analyses across all analyses (instead of the randomized stratum).

4.3 Pooling of Centers

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

4.4 Timepoints and Visit Windows

'Study Day' will be based on the relative number of days from the date of first exposure of study product which will be termed 'Day 1'.

The duration between visits will be assessed against the visit windows presented in section 2.2 and any deviations will be recorded as protocol deviations (PD) as per section 5.1.2.

The timepoints and visits for this study are defined in Table 2-1 "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.

In the case of visits performed out-of-window that require any changes to the above mapping, identified either prior to or during the BDR process, the SAP will be updated prior to unblinding.

5 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 in a Windows environment.

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

Unless stated otherwise, all listings will be produced for all randomized subjects and listed by study product group (as-randomized and as-treated groups in case of misallocation).

5.1 Populations/Data for Analysis

Tables described in this section will be produced for all randomized subjects and summarized by study product group and overall, unless otherwise specified.

5.1.1 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 defined as a subject who has agreed to participate in the study following completion of the informed consent process directly or via their legally authorized representative and successfully met the study eligibility criteria to proceed beyond the Screening visit.

A subject who receives a randomization number will be considered to be randomized.

Subject disposition will be presented in Table 14.1.1.

The number of subjects screened, enrolled and randomized, and the number and percentage of screened subjects who were randomized and not randomized (including reason) will be presented overall.

The number and percentage of subjects who:

- complete the study
- prematurely withdraw from the study (by reason)
- complete the planned duration of the study product
- discontinue use of study product early (by reason)
- are included in each analysis population

will be presented.

The following will be listed in 16.2.1.1:

- demographic data (age, sex, race and ethnicity)

- screening date
- study product use start date and time
- study completion status (Yes/No, Primary reason for withdrawal and Further details of reasons for withdrawal)
- study completion/withdrawal date
- duration (in days) in the study, defined as [date of completion/withdrawal – start date of study product use + 1]

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.

5.1.2 Protocol Deviations

Important protocol deviations are defined as protocol deviations which might significantly affect the completeness, accuracy, and/or reliability of the study data or significantly affect a subject's rights, safety, or well-being.

Potential important protocol deviations will be identified in the protocol and/or a separate Protocol Deviation Management Plan, with the assessment process specified in the BDR Plan. Data will be reviewed on an ongoing basis and as part of the BDR prior to unblinding and database lock to ensure all important deviations are captured and categorized as important or not.

In addition, as part of the BDR, each important deviation will also be assessed as to whether it may impact any data related to the PP analyses.

The following (list not exhaustive) important protocol deviations will be considered for exclusion of the subject or subject data from the per-protocol population analyses if they are deemed to potentially influence the efficacy outcome (See Section 5.1.3):

- Use of prohibited medication
- Subject not eligible for the study
- Poor study product compliance

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.

5.1.3 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 5.1.2 (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.

5.2 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the mITT, Safety populations and if applicable, for the PP population and summarized by study product group and overall, unless otherwise specified.

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Statistical Analysis Plan Template, CCI , v8.0. Parent SOP: CCI

5.2.1 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.

5.2.2 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.

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

5.3.1 Study Product Compliance and Exposure

Randomization details will be listed in Listing 16.1.7.1, including randomization number, randomization date, stratification group, planned randomized study product group and actual study product group 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.

Compliance data will be summarized for the mITT population by study product group and overall. In case of incorrect allocation of study product, this will be repeated for the safety population.

For the derivation of study product compliance overall for a subject, Visit 4 (Week 12) will be the latest visit for the subject with study product compliance data recorded.

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.

5.3.2 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 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.

5.3.3 Medical Device Incidents and Malfunctions

Medical devices provided by Haleon for use in this study are the supplied toothbrushes.

Any incidents with medical devices will be listed in Listing 16.2.7.3.

5.4 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 observed values 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 was used to adjust for the comparisons between the Toothpaste/Mouthwash combination and Control Group for overall and interproximal NBS at each time point, starting at Week 12.

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 Control Group. 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 Control Group 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 and performing MMRM analysis.

5.4.1 Primary Efficacy Endpoint

5.4.1.1 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 5-1.

Table 5-1 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 2-1) .

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 at each time point (Observed value and change from baseline) 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.

5.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The primary hypothesis test will be the comparison between the Toothpaste/Mouthwash and the Control Group 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 Control Group.
- H_1: There is a difference in the Overall NBS at 12 weeks between the Toothpaste/Mouthwash and Control Group.

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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 Control Group) 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.

5.4.1.3 Supportive / Sensitivity 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).

5.4.2 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 5.4), 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 Control Group'. 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. For the secondary endpoints of overall NBS at week 6, Baseline overall NBS will remain in the model.

Toothpaste/Mouthwash versus Control Group:

- 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.

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- 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.

5.4.2.1 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 5-1.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of Overall NBS at Week 6 will also be provided by study product (Observed value and change from baseline) 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 at each time point (Observed value and change from baseline) 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.

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

For comparison between 'Toothpaste/Mouthwash and Control Group', 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 Control Group.
- H_1: There is a difference in the Overall NBS at Week 6 between the Toothpaste/Mouthwash and Control Group.

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

Overall and Interproximal NBS will be analyzed as described for primary analysis (Section 5.4.1.2), 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.

5.4.2.2 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 5.4.1.1),according to the scoring system in Table 5-1.

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.

For comparison between 'Toothpaste/Mouthwash and Control Group', 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 Control Group.
- H_1: There is a difference in Mean Overall EBI score at Week 6 and 12 between the Toothpaste/Mouthwash and Control Group.

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

Overall and Interproximal EBI will be analyzed as described for primary analysis (Section 5.4.1.2), 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.

5.4.2.3 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 5-2.

Table 5-2 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.

For comparison between 'Toothpaste/Mouthwash and Control Group', 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 Control Group.
- H_1: There is a difference in Mean Overall MGI score at Week 6 and 12 between the Toothpaste/Mouthwash and Control Group.

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

MGI (Overall and Interproximal) will be analyzed as described for primary analysis (Section 5.4.1.2), 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.

5.4.2.4 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 5-3.

Table 5-3 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.

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

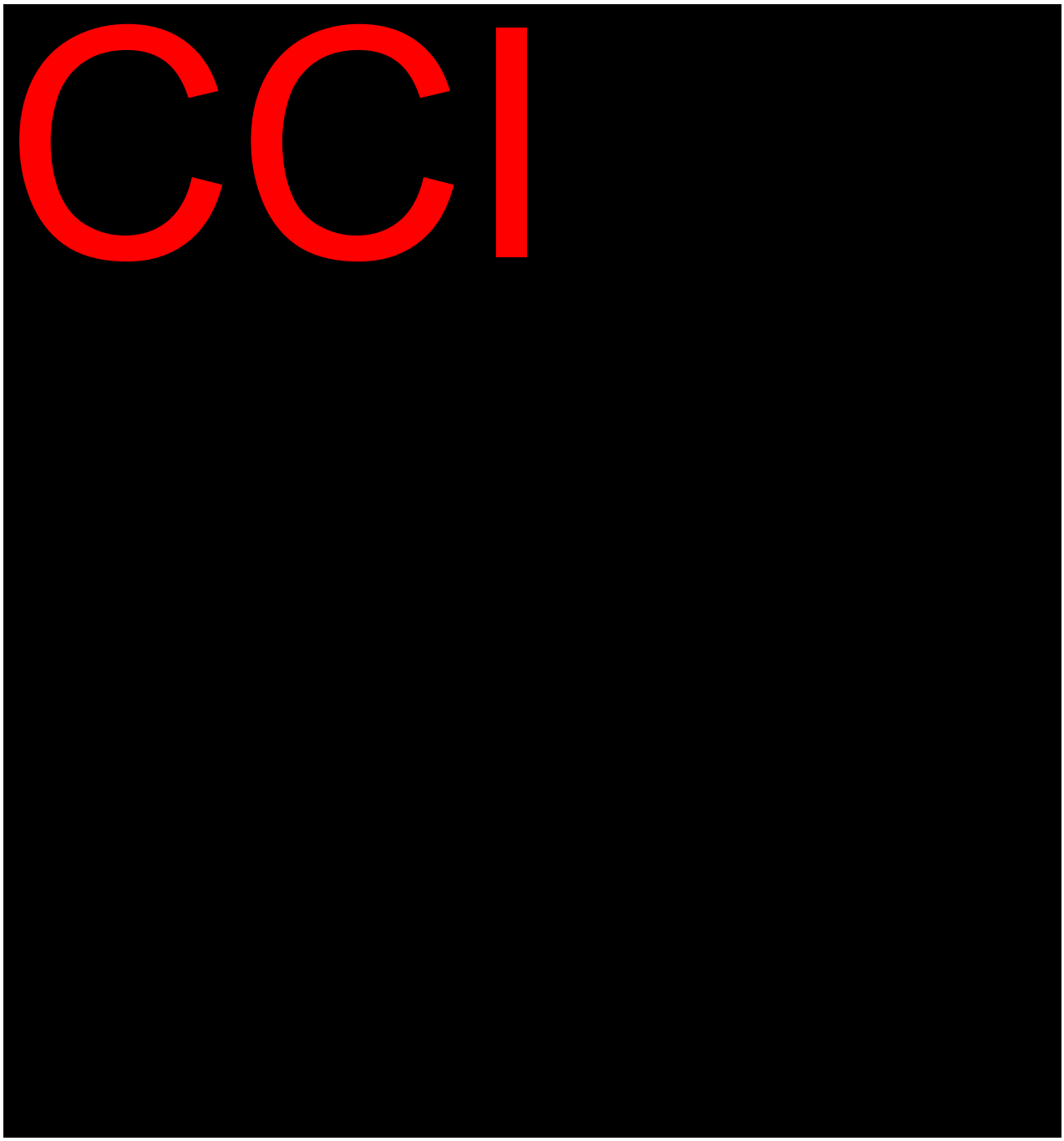
- H_0: There is no difference in Mean Overall TPI score at Week 6 and 12 between the Toothpaste/Mouthwash and Control Group.
- H_1: There is a difference in Mean Overall TPI score at Week 6 and 12 between the Toothpaste/Mouthwash and Control Group.
- H_0: There is no difference in Mean Interproximal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

TPI (Overall and Interproximal) will be analyzed as described for primary analysis (Section 5.4.1.2), 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.

5.4.3 Other Efficacy Data

5.4.4 CCI





5.4.5 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 assume data is missing at random, meaning there's a systematic relationship between missing values and observed data. This method provides unbiased treatment effect estimates, unlike ANCOVA, which is biased unless data is missing completely at random. MMRM assumes that a subject with missing data at one post-Baseline visit would have similar efficacy results to a subject with similar non-missing results at other timepoints.

5.5 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.

Descriptive summaries of safety will be produced for the Safety population and summarized by study product group (as treated) and overall, unless otherwise specified.

5.5.1 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.

All TEAEs will be coded according to the latest version of MedDRA.

The following AE summaries (number of distinct AEs and frequency/percentage of subjects affected) will be presented:

- 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)

All AEs will be listed for randomized subjects (listing 16.2.7.1) and non- randomized subjects (listing 16.2.7.2) detailing the reporting/ PT/ SOC terms, start/end dates/times (including study day), outcome, frequency/intensity, relationship to study product, action taken with study product, whether serious or not and whether subject withdrawn.

Deaths occurring during treatment (if any) will be listed by study product, including the date and study day of death, and the principal cause of death (listing 14.3.2.1). Non-fatal serious adverse events, TEAEs causing study product discontinuation and TEAEs classified as Oral will also be listed (listing 14.3.2.2, 14.3.2.3 and 14.3.2.4 respectively).

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

5.5.2 Other Safety Data

Other safety variables are listed below:

- OST examination
- OHT examination

5.5.2.1 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.

5.5.2.2 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.

5.6 Analysis of Other Data Type

5.6.1 Repeatability of the Examiner

Repeat MGI and TPI assessments will be performed by the clinical examiners at Visits 2, 3 and 4. At least 3 repeat assessment should be performed for each index over the duration of visits 2, 3 and 4. Thus a total of at least 9 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. 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).

5.6.1.1 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.

5.6.1.2 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.

6 Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol V3.0 (Dated: 07/APR/2025).

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 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	Yes
	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	Yes

CSR Section	TLF	Number	Title	Population	Template	Topline
	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	
	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	Yes
	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	Yes
	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	

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	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	
	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	

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	CCI	CCI	CCI	CCI	CCI	CCI
	CCI	CCI	CCI	CCI	CCI	CCI
	CCI	CCI	CCI	CCI	CCI	CCI
	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	
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	Yes
	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	

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CSR Section	TLF	Number	Title	Population	Template	Topline
	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						
	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 Overall Number of Bleeding Sites (Reference: Table 14.2.2.2.1)	mITT Population	SAS Output	Yes
	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	Yes
	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	

CSR Section	TLF	Number	Title	Population	Template	Topline
	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	
	CCI	CCI	CCI	CCI	CCI	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	

CSR Section	TLF	Number	Title	Population	Template	Topline
	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	
	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	

CSR Section	TLF	Number	Title	Population	Template	Topline
	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	
	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	
	CCI	CCI	CCI	CCI	CCI	
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)						

CSR Section	TLF	Number	Title	Population	Template	Topline
	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					