HALEON

STATISTICAL ANALYSIS PLAN

A Randomized, Controlled, Single-Blind Clinical Study Assessing the Effects of an Experimental Dentifrice in Maintaining Tooth Color Following Tooth Bleaching

Protocol Number: 300109

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	16-JAN-2024	Not applicable (N/A)

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Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
A × I	Area × Intensity
BDRM	Blinded Data Review Meeting
CI	Confidence Interval
DH	Dentine Hypersensitivity
eCRF	Electronic Case Report Form
ICF	Informed Consent Form
KNO_3	Potassium Nitrate
LMS	Labelled Magnitude Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intend-To-Treat
MLSI	Total Modified Lobene Stain Index
N/A	Not Applicable
NA	Not Applicable
NaF	Sodium Fluoride
NRS	Numerical Rating Scale
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
STP	Sodium Tripolyphosphate
TEAEs	Treatment Emergent Adverse Events
VAS	Visual Analogue Scale
WHODD	World Health Organization Drug Dictionary

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 300109 (version 2.0, dated 13-Oct-2023).

1 Summary of Key Protocol Information

This will be a randomized, single-blind, single-center, controlled, two arm, stratified (clinically diagnosed DH (Y/N)), parallel group study to evaluate the efficacy of an experimental dentifrice containing 5% potassium nitrate (KNO3), 1% alumina and 5% sodium tripolyphosphate (STP), to maintain tooth color and reduce the accumulation of extrinsic tooth stain following peroxide tooth bleaching compared to a regular fluoride-containing dentifrice. The study will recruit generally healthy subjects who wish to undergo peroxide tooth bleaching.

Approximately 160 subjects (80 per treatment group) will be randomized to study treatment to ensure 128 evaluable subjects complete the study by assuming dropout rate of 20%. Subjects will be stratified according to their clinically diagnosed DH Status (Y/N).

The primary aim of this study is to evaluate whether an experimental dentifrice containing 5% potassium nitrate (KNO_3), 1% alumina and 5% sodium tripolyphosphate (STP) maintains tooth color after peroxide tooth bleaching compared to regular fluoride dentifrice.

1.1 Study Design

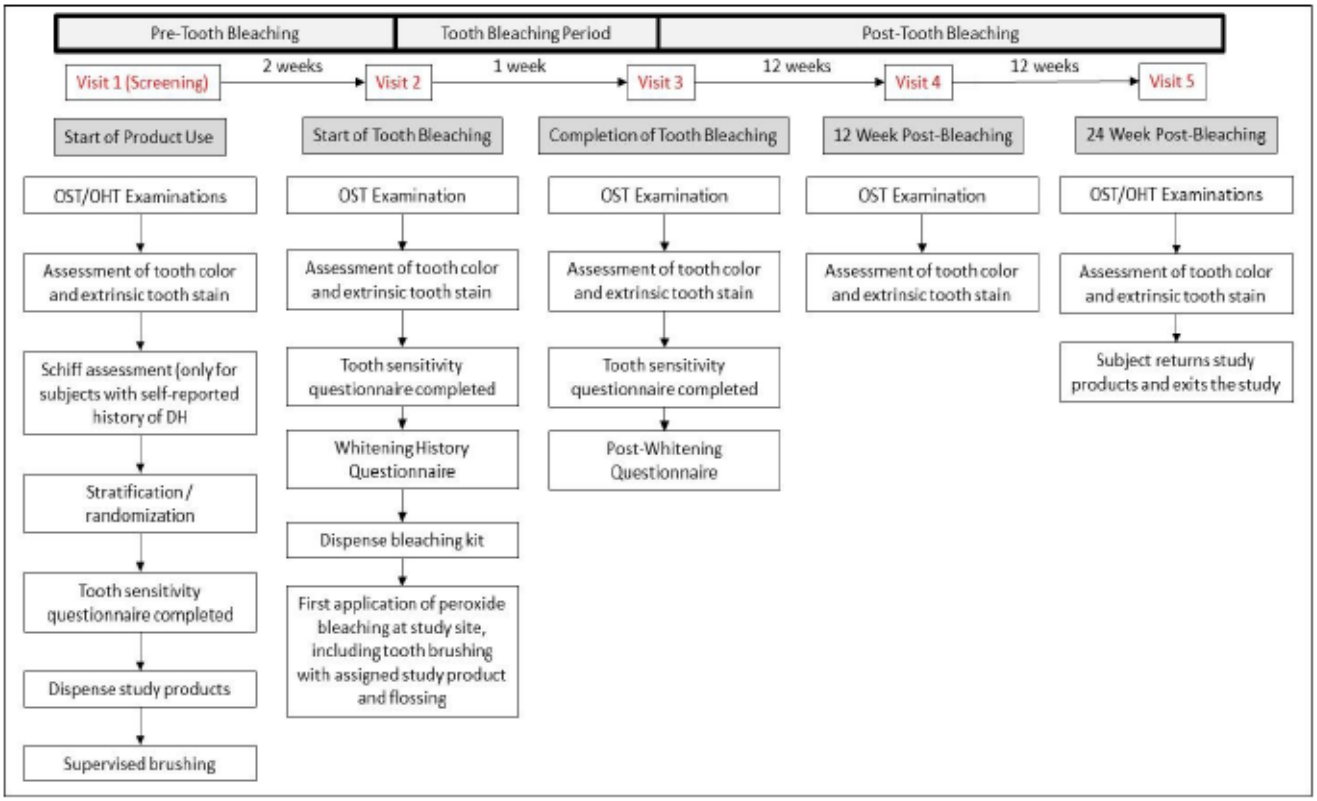
This will be a randomized, single-blind, single-center, controlled, two-arm, stratified (clinically diagnosed DH (Y/N)), parallel group study to evaluate the efficacy of an experimental dentifrice containing 5% potassium nitrate (KNO3), 1% alumina and 5% sodium tripolyphosphate (STP), to maintain tooth color and reduce the accumulation of extrinsic tooth stain following peroxide tooth bleaching compared to a regular fluoride-containing dentifrice. The study will recruit generally healthy subjects of aged 18-65 inclusive who wish to undergo peroxide tooth bleaching.
Potential subjects will attend a screening visit (Visit 1, Day 1) to determine their suitability to participate. Having obtained their written informed consent, relevant details of their demography, medical history and current medications will be recorded, followed by OST and OHT examinations.

Subjects meeting all study criteria, will be considered as eligible to proceed, stratified (based upon their clinically diagnosed DH status [Y/N]) and randomized to treatment group. Randomized subjects will then complete the tooth sensitivity questionnaire. Subjects will be dispensed their study products (including diary and sundry items) and undertake a supervised brushing with their allocated dentifrice at the clinical site and be scheduled to attend Visit 2 (2 weeks ± 2 days after Screening/Randomization). Subjects will continue to use their allocated study products (twice-daily) throughout the study and will record this usage in their study diary.

Detailed information is provided in section 4.1 of Protocol (v2.0 dated 13-Nov-2023).

Figure 1-1 presents the key study assessments.

Figure 1-1 Schematic of Flow of Key Study Assessments/Procedures



1.2 Study Objectives

Study objectives and endpoints are defined in Table 1-2

Table 1-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To compare tooth color after 24 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice following peroxide tooth bleaching as measured by VITA Bleached guide 3D-Master.	Mean VITA shade score at 24 weeks after tooth bleaching.
Secondary Objectives	**Secondary Endpoints**
To compare tooth color after 12 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice following peroxide tooth bleaching as measured by VITA Bleached guide 3D-Master.	Mean VITA shade score at 12 weeks after tooth bleaching.
To compare extrinsic dental stain after 12 and 24 weeks, twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice following peroxide tooth bleaching as measured by Modified Lobene Stain Index.	Mean MLSI at 12 and 24 weeks after tooth bleaching in: • Total MLSI (Area (A) x Intensity (I)) • Gingival sites (AxI) • Interproximal sites (AxI) • Body sites (AxI) • MLSI (A) • MLSI (I)
Exploratory Objectives	**Exploratory Endpoints**
To compare subject-perceived tooth sensitivity during peroxide tooth bleaching with twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice, as measured by subject-completed sensitivity questionnaire overall and within strata (clinically-diagnosed DH [Y/N])	Mean sensitivity questionnaire scores pre and post peroxide tooth bleaching in: • Visual analogue scale (VAS) • Labelled Magnitude scales (Intensity, Duration, Tolerability, Description) – • Bothersomeness score -NRS
To explore subject's experience of peroxide tooth bleaching when simultaneously using either a '5% KNO_3/1% alumina/5% STP' dentifrice or a regular fluoride dentifrice.	Post-whitening questionnaire
To confirm the tooth whitening efficacy of peroxide tooth bleaching with concurrent, twice daily use of '5% KNO3/1% alumina/5% STP' dentifrice and a regular fluoride dentifrice as measured by VITA Bleached guide 3D Master.	Change in mean VITA shade score from pre to post tooth bleaching
Safety	

Objectives	Endpoints
Safety	
To assess the safety and tolerability of a '5% KNO_3/1% alumina/5% STP' dentifrice.	Treatment emergent adverse events

This study will be considered successful if the Test dentifrice containing 5% KNO_3, 1% alumina and 5% STP demonstrates statistically significant whither teeth as measured by VITA Bleached guide Shade in comparison with the reference dentifrice 24 weeks after peroxide tooth bleaching.

1.3 Treatments

The study product will be Test Dentifrice which is Dentifrice containing 5% w/w KNO_3, 1% alumina, 5% STP and 1150ppm fluoride as sodium fluoride and Reference product will be Dentifrice containing 1150ppm fluoride as sodium fluoride. Subjects will brush for two timed minutes twice daily (morning and evening).

1.4 Sample Size Calculation

There were no previous directly comparable studies that have evaluated the effect of dentifrice on maintaining tooth whiteness after peroxide bleaching upon which to base an estimate of sample size. However, based on a previous study evaluating the tooth whitening abilities of the test dentifrice (Haleon Clinical Study 300024, 2023), a mean change (SD) of VITA scores of 1 (±2) was assumed. Sufficient individuals will be screened to enroll approximately 160 subjects (approximately 80 per group) assuming an estimated 20% dropout rate; approximately 128 completed subjects (approximately 64 per group) are deemed sufficient to detect a difference between the Test and Reference Dentifrices at 24 weeks with 80% power.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned for this study.

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

There will be no change-from-baseline assessments done for this study.

3.2 Subgroups/Stratifications

Subjects who satisfy all selection criteria will be randomized into the study. Randomization numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible.

Subjects will be stratified based on clinically diagnosed DH status (Yes/No). The stratification factor will give rise to two strata.

- **Stratum 1**: Dentine Hypersensitivity Present
- **Stratum 2**: Dentine Hypersensitivity Not Present

With each stratum, subject will be randomized to Test Dentifrice and Reference Dentifrice with 1:1 allocation ratio.

In the event of mis-stratification, the correct strata according to CRF information will be used in the analysis (i.e., derived stratification variable from ADSL will be used for analysis).

3.3 Centers Pools

Since this is 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 "Schedule of Activities" defined in section 1.2 of study Protocol (v2.0 dated 13-Nov-2023). Any deviation from the study schedule may be reviewed on case-by-case basis at the Blinded Data Review Meeting (BDRM) to determine whether the data should be excluded from the Per-Protocol (PP) analyses.

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.

One aspect that will be considered prior to or during the BDRM is the assessment of the number of subjects who have dropped or discontinued from the study due to pandemic related events

and the potential need of a sensitivity analysis. Any major changes to planned analyses will need an amendment to SAP.

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

4.1 Populations for Analysis

Tables described in this section will be produced for all randomized subjects.

4.1.1 Subject Disposition

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

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

The number and percentage of screen failure subjects (subjects not randomized) with reasons why subjects are not 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 by study product and overall will also be displayed. The percentages will be based on the number of subjects randomized.

Table 14.1.1 will also present the number and percentage of 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 and time, subject status (completer, Yes/No), study completion /withdrawal date, duration (in days) in the study (defined as [(date of completion or withdrawal – start date of study product) + 1], and the primary reason for withdrawal will be listed (Listing 16.2.1.1) by study product for all randomized subjects.

Subject disposition information will be listed for non-randomized subjects (Listing 16.2.1.2), displaying subject number, demographic information (age, sex, race and ethnicity), screening date, reason for screen failure and any further details of reason for screen failure and discontinuation status.

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 categorised. Subjects with important protocol deviations liable to influence the efficacy outcomes will have affected data excluded from the PP analyses. Subjects may also be identified as having important protocol deviations not leading to exclusion of data from the PP analyses.

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

- Consent procedures
- Inclusion/Exclusion criteria
- Study procedures
- Randomization procedures
- Non-compliance with product administration
- Inadmissible concomitant medication
- Visit schedule/interval
- Other

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

The number and percentage of subjects with at least one important protocol deviation, at least one important protocol deviation not leading to exclusion of data from PP analyses (overall and by each deviation reason) and at least one important protocol deviation leading to exclusion of data from the PP analyses (overall and by each deviation reason) will be presented by study product (Table 14.1.2) and listed in Listing 16.2.2.1.

All protocol deviations collected on the protocol deviation case report form page 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

Analysis populations are defined as

Population	Definition / Criteria	Analyses Evaluated
Safety	Comprise of all randomized subjects who complete at least one use of study product. This population will be based on the product the subject actually received*. Any subject who receives a randomization number will be considered to have been randomized.	Demographics Safety
Modified Intent-To-Treat (mITT)	Comprise all randomized subjects who complete at least one use of study product and have at least one assessment of tooth color after the bleaching period.	Demographics Compliance Efficacy Analysis Exploratory Analysis

Population	Definition / Criteria	Analyses Evaluated
	This population will be based on the study product to which the subject was randomized. Any subject who receives a randomization number will be considered to have been randomized.	
Per-Protocol	Comprise all subjects in the mITT population who have at least one assessment of efficacy considered unaffected by protocol violations. Protocol deviations that may exclude subjects from the PP population are defined in Section 4.1.2 (Protocol Deviations). This population will be based on the study product to which the subject was randomized.	Efficacy Analysis
Repeatability Population	Tooth Color Repeatability Population: subjects who have at least one repeat tooth color clinical assessment at any visit. MLSI Repeatability Population: Subjects who have at least one repeat MLSI clinical assessment at any visit.	Repeatability Assessment Analysis

NOTES:

* The treatment actually received will be assumed to be the same as the randomized treatment unless a protocol deviation is recorded to indicate that incorrect treatment was dispensed to the subject.

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

The numbers of subjects included in each of the analysis populations, will be summarized (Table 14.1.1). Subjects excluded from any of the analysis populations will be listed in Listing 16.2.3.1.

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

4.2 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for Safety and mITT Population.

4.2.1 Demographic Characteristics

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

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

4.2.2 General Medical History

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

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

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

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

4.3.1 Study Product Compliance and Exposure

Compliance data will also be summarized for the mITT population and will be assessed by number of brushings.

Number of brushings, brushing compliance (%), number of missed brushings, number of additional brushings will be summarized using descriptive statistics as separate categories by study product in Table 14.2.1.1 by cumulative visit.

Number of brushings is defined as: [(date of Visit N – date of Visit 1) multiplied by 2 – number of missing brushings + number of additional brushings].

Brushing compliance (%) is defined as: [100 x (Number of brushings / Expected number of brushings)], where expected number of brushings is defined as: [(date of Visit N – date of Visit 1) multiplied by 2].

Study product compliance (number of brushings / brushing compliance [%] / number of missed brushings / numbers of additional brushings) will be listed in Listing 16.2.5.1 for all randomized subjects by study product.

4.3.2 Bleaching Compliance and Exposure

Bleaching Compliance will be summarized for mITT Population where number of bleaching, bleaching compliance (%) and missed/additional bleaching occurrence will be summarized using descriptive statistics as separate categories by study product in Table 14.2.1.2 by cumulative visit.

Number of bleaching is defined as: [(date of Visit 3 – date of Visit 2) – number of missing bleaching + number of additional bleaching].

Bleaching compliance (%) is defined as: [100 x (Number of bleaching / Expected number of bleaching)], where expected number of bleaching is defined as: (date of Visit 3 – date of Visit 2).

Bleaching compliance (number of bleaching / bleaching compliance [%] / number of missed bleaching / numbers of additional bleaching) will be listed in Listing 16.2.5.2 for all randomized subjects by study product.

4.3.3 Prior and Concomitant Medication

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 28 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 treatments will be listed by subject, with drug name, WHODD Drug Synonym, reason, route, dose, unit, frequency, start date and end date both relative to study product start date (Listing 16.2.4.3) for all randomized subjects. Prior medications are defined as those which stopped before the first use of the study product.
Concomitant medications and concomitant non-drug treatments/significant non-drug therapies taken during treatment will be listed similarly (Listing 16.2.4.4) for all randomized subjects with either ongoing or end date displayed.
Concomitant medications that have been taken to alleviate tooth sensitivity/pain will be summarized in Table 14.3.4.2 for all randomized population and will be listed in Listing 16.2.4.5.
Concomitant medications are defined as medications that started or stopped on or after the first use of the study product 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.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary efficacy variable is mean Vita Bleached guide shade at 24 weeks after tooth bleaching has completed, calculated at the subject level as the average Vita Bleached guide shade over all sites assessed.

Tooth color of the facial surfaces of the six anterior maxillary teeth (tooth numbers 6-11) [Universal tooth numbering system] will be assessed by a single, trained clinical examiner using the VITA Bleached guide 3D-MASTER. The VITA Bleached guide 3D-MASTER uses a value-ranked ordered scale from 1 (the lightest) to 29 (the darkest). The shade level of each tooth surface is scored visually by the clinical examiner with reference to the Bleached guide.

The mean VITA shade score for each subject at each visit is calculated as the mean VITA shade score over all non-missing facial surfaces of six anterior maxillary teeth (tooth numbers 6-11).

Descriptive statistics (n, missing, mean, SD, standard error [SE], median, minimum, and maximum) will be presented for mean VITA shade score at each assessment time point in Table 14.2.2.1.1 for all subjects in the mITT population by study product.

Raw means (± SE) of the mean VITA shade score at each time point will be plotted by study product in Figure 14.2.1.1 for all subjects in the mITT population.

Individual data for mean VITA shade score will be listed for each subject by study product group 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 comparison is between the Test Dentifrice and the Reference Dentifrice in the mITT population. As there is only a single primary objective, no adjustment for multiple comparisons is required.

Study product differences will be tested under the null hypothesis at 24 weeks after tooth bleaching has completed:

- H_0: there is no difference in mean VITA shade score between Test Dentifrice and Reference Dentifrice
- H_1: there is a difference in mean VITA shade score between Test Dentifrice and Reference Dentifrice

Mean VITA Bleached guide shade will be analyzed using a repeated measures ANOVA model with treatment group and study time points (Visit 2 to 5) as factor and treatment group by time point (Visit 2 to 5) as interaction. Subject will be included as a repeated measure with unstructured covariance matrix; the Kenward Rogers degrees of freedom approach will be

applied (Kenward and Roger, 1997). If the model with unstructured covariance matrix does not converge then compound symmetry covariance matrix will be used.

Using the above model, mean differences between Test Dentifrice compared to Reference Dentifrice in Mean VITA shade score will be reported by study product group along with 95% CIs and p-values will be provided in Table 14.2.2.2.1. All p-values presented will be two-sided and assessed at the 5% significance level.

The assumption of normality and homogeneity of variance in repeated measures ANOVA will be investigated. In case of violation of these assumptions, a suitable nonparametric test (Van Elteren Test adjusted for randomization stratification) will be performed, and the results will be provided to support the repeated measures ANOVA results. The non-parametric results will be considered confirmatory under the observation of strong violations of the assumptions.

If there is more than 10% difference in the overall number of subjects between PP and mITT populations, a summary and analysis of the primary efficacy variable will be presented for the PP population in Table 14.2.2.1.2 and Table 14.2.2.2.2 respectively.

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Secondary Efficacy Variable 1

The Secondary Efficacy Endpoint 1 will be mean VITA shade score at 12 weeks after tooth bleaching and the comparison of Test Dentifrice to the Reference Dentifrice.

4.4.2.1.1 Statistical Hypothesis, Model and Method of Analysis

Study product differences will be tested under same hypothesis stated in Section 4.4.1.2. Mean VITA Bleached guide shade will be analyzed using a repeated measures ANOVA model with treatment group and study time points (Visit 2 to 5) as factor and treatment group by time point (Visit 2 to 5) as interaction. Subject will be included as a repeated measure with unstructured covariance matrix; the Kenward Rogers degrees of freedom approach will be applied (Kenward and Roger, 1997). If the model with unstructured covariance matrix does not converge then compound symmetry covariance matrix will be used.

Refer to Section 4.4.1.2. Mean differences between Test Dentifrice compared to Reference Dentifrice in Mean VITA shade score at 12 weeks after tooth bleaching will be presented along with 95% CIs and p-values in Table 14.2.2.2.1. All p-values presented will be two-sided and assessed at the 5% significance level.

The assumption of normality and homogeneity of variance in repeated measures ANOVA will be investigated. In case of violation of these assumptions, a suitable nonparametric test (Van Elteren Test adjusted for randomization stratification) will be performed to assess comparisons (Test Dentifrice vs. Reference Dentifrice at Week 12) and the results will be provided to support

the repeated measures ANOVA results. The non-parametric results will be considered confirmatory under the observation of strong violations of the assumptions.

4.4.2.2 Secondary Efficacy Variable 2

For comparison of extrinsic dental after stain the Secondary Efficacy Endpoint 2 will be mean scores at 12 and 24 weeks after tooth bleaching in:

- Total MLSI (Area (A) x Intensity (I))
- MLSI (AxI) for gingival sites (AxI)
- MLSI (AxI) for interproximal sites (AxI)
- MLSI (AxI) for body sites (AxI)
- Total MLSI Area (A)
- Total MLSI Intensity (I)

Extrinsic dental stain will be assessed on the facial surfaces of the 6 maxillary anterior teeth (6-11) [Universal tooth numbering system] at Visits 1-5), using (MLSI) described in section 9.2.2 of the study Protocol (v2.0, dated 13-Nov-2023).

4.4.2.2.1 Statistical Hypothesis, Model and Method of Analysis

The results for mean total MLSI Area x Intensity (AxI), mean total MLSI (AxI) for gingival sites (AxI), mean total MLSI (AxI) for interproximal sites (AxI), mean total MLSI (AxI) for body sites (AxI), mean total MLSI Area (A), and mean total MLSI Intensity (I) will be obtained from the Repeated Measures ANOVA detailed in Section 4.4.1.2. Mean differences between Test Dentifrice compared to the Reference Dentifrice in mean Total MLSI (A×I) score at 12 and 24 weeks after tooth bleaching will be presented along with 95% CIs and p-values in Table 14.2.3.2 for all subjects in the mITT population. Significance testing will be conducted at the two-sided 5% significance level. Study product differences for each of the aforementioned efficacy variables will be tested under the null hypotheses described below at 12 and 24 Weeks:

- **Total MLSI (Area (A) x Intensity (I))**

  H0: there is no difference in mean total MLSI Area x Intensity (A×I) scores between Test Dentifrice and Reference Dentifrice;

  H1: there is a difference in mean total MLSI Area x Intensity (A×I) scores between Test Dentifrice and Reference Dentifrice;

  Descriptive statistics (n, mean, SD, Standard Error [SE], median, minimum, and maximum) will be presented for Mean Total MLSI (AxI) score at each assessment time point in Table 14.2.3.1 for all subjects in mITT Population by study product. Raw mean ± (SE) of mean Total MLSI (AxI) score at each timepoint will be plotted by study product in Figure 14.2.2.1 for all subjects in the mITT population.

- **Gingival sites (AxI)**

  H0: there is no difference in mean MLSI (A×I) scores for gingival sites between Test Dentifrice and Reference Dentifrice;

  H1: there is a difference in mean MLSI (A×I) scores for gingival sites between Test Dentifrice and Reference Dentifrice;

- **Interproximal sites (AxI)**

  H0: there is no difference in mean MLSI (A×I) scores for interproximal sites between Test Dentifrice and Reference Dentifrice;

  H1: there is a difference in mean MLSI (A×I) scores for interproximal sites between Test Dentifrice and Reference Dentifrice;

- **Body sites (AxI)**

  H0: there is no difference in mean MLSI (A×I) scores for body sites between Test Dentifrice and Reference Dentifrice;

  H1: there is a difference in mean MLSI (A×I) scores for body sites between Test Dentifrice and Reference Dentifrice;

- **MLSI (A)**

  H0: there is no difference in mean total MLSI Area (A) scores between Test Dentifrice and Reference Dentifrice;

  H1: there is a difference in mean total MLSI Area (A) scores between Test Dentifrice and Reference Dentifrice;

- **MLSI (I)**

  H0: there is no difference in mean total MLSI Intensity (I) scores between Test Dentifrice and Reference Dentifrice;

  H1: there is a difference in mean total MLSI Intensity (I) scores between Test Dentifrice and Reference Dentifrice;

Descriptive statistics (n, mean, SD, Standard Error [SE], median, minimum, and maximum) will be presented for all the aforementioned efficacy variables at each assessment time point in Table 14.2.3.1 for all subjects in mITT Population by study product. Raw mean ± (SE) of mean Total MLSI (AxI) score at each time point will be plotted by study product in Figure 14.2.2.1 for all subjects in the mITT population.

Individual and derived MLSI (A×I) score data will be listed for each subject by visit and study product group in Listing 16.2.6.2.1 and Listing 16.2.6.2.2 respectively for all randomized subjects.

The assumption of normality and homogeneity of variance in the repeated measures ANOVA model will be investigated. In case of violation of these assumptions, a suitable nonparametric test (the Van Elteren test, adjusted for the randomization stratification) will be performed for each comparison at week 12 and 24 and results will be provided to support the repeated measures ANOVA results.

4.4.3 Exploratory Efficacy Variables

There will be no adjustment for multiplicity in the analyses for exploratory efficacy variables.

4.4.3.1 Exploratory Efficacy Variable 1

The Exploratory Endpoint 1 will be Mean sensitivity questionnaire scores pre and post bleaching to access tooth sensitivity of subjects and comparison between Test Dentifrice and Reference Dentifrice. To assess tooth sensitivity below questionnaire will be used:

- Visual Analogue Scale (VAS)
- Labelled Magnitude Scale (Intensity, Duration, Tolerability, Description) - LMS
- Bothersomeness Score (NRS)

Descriptive statistics (n, missing, mean, SD, standard error [SE], median, minimum, and maximum) will be presented for VAS score, NRS Score and LMS (Intensity, Duration, Tolerability, Description) score at each assessment time point in Table 14.2.4.1 for all subjects in the mITT population by study product within Strata.

Additionally, number of subjects who experienced tooth sensitivity will be summarized by study product group and stratum [DH (Y/N)] in Table 14.2.4.1.

Individual data for VAS score, LMS score and NRS score will be listed for each subject by study product group and visit in Listing 16.2.6.3 for all randomized subjects.

4.4.3.2 Exploratory Efficacy Variable 2

The Exploratory Endpoint 2 will be Post Whitening Questionnaire and Whitening History Questionnaire to explore subject's experience of peroxide tooth bleaching when simultaneously using either Test Dentifrice or Reference Dentifrice.

- Whitening History Questionnaire

Individual data from questionnaire will be listed for each subject by study product group in Listing 16.2.6.5 for all randomized subjects.

- Post Whitening Questionnaire

The questionnaire will be summarized [n (%)] for all questions and subject's response in Table 14.2.4.2 for all subjects in the mITT Population by study product group.

Individual data will be listed for each subject by study product group in Listing 16.2.6.4 for all randomized subjects.

4.4.3.3 Exploratory Efficacy Variable 3

The exploratory endpoint 3 will be change in mean VITA shade score from pre to post bleaching Treatment.

Descriptive statistics (n, missing, mean, SD, standard error [SE], median, minimum, and maximum) will be presented for mean VITA shade score at visit 2 (pre bleaching) and visit 3 (post bleaching) together with change from Visit 2 to Visit 3 will be presented in Table 14.2.4.3 for all subjects in the mITT population by study product group.
The results for this endpoint will be analyzed from an ANCOVA model where study product group will be fixed effect and mean VITA shade score prior to the start of tooth bleaching fitted as a covariate.

Using the above model, least squared mean, pairwise difference along with 95% CIs will be reported by study product in Table 14.2.4.4 for all subjects in the mITT population. Significance testing will be conducted at the two-sided 5% significance level.
The assumption of normality and homogeneity of variance in will be investigated. In case of violation of these assumptions, a suitable non-parametric test (Van Elteren) will be performed, and results will be provided to support the parametric results.

4.4.4 Handling of Missing Values/Censoring/Discontinuations

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.

The use of repeated measures analyses accounts for missing data assuming a missing at random assumption, i.e., there is a systematic relationship between the propensity of missing values and the observed data, but not the missing data.

It is therefore assumed that a subject with missing data would have obtained a similar efficacy result compared to a subject using the same study product with similar non-missing results at other timepoints (Baseline and the other post-Baseline visit).

Sensitivity analyses may be added to the SAP prior to unblinding in case of high drop-out rates and/or exclusion from PP analyses.

4.5 Analysis of Safety

The safety profile of the study treatments will be assessed with respect to AEs or incidents or others such as OST/OHT abnormalities in oral health study and incidents related to medical devices.

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 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 will be considered as non-treatment emergent.

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

- Table of All AEs (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 discontinuation (Listing 14.3.2.3)
- Listing of TEAEs classified as Oral (Listing 14.3.2.4)

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

4.5.2 Medical Device Incidents

Medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all subjects, including those who discontinue study product or are withdrawn from the study.
All reported incidents including onset date/time, outcome, end date/time, death date/time if any, treatment provided, reason of study withdrawn will be listed in Listing 16.2.7.3 for all Randomized subjects.

4.5.3 Other Safety Variables

Other safety variables are listed below:

- OST examination
- OHT examination

4.5.3.1 OST Examination

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

Any observation that changes from 'normal' to 'abnormal', or worsens, from the OST examination completed at Screening will be recorded as an AE.

OST will be summarized (number of subjects and percentages with abnormalities, without abnormalities, or OST not examined) by visit and study product in Table 14.3.4.1 for all subjects in the Safety Population. OST examination will be listed (Listing 16.2.8.1.1) with all records ('normal', 'abnormal' and 'not examined') for all randomized subjects, and a separate listing will be presented for 'abnormal' records only (Listing 16.2.8.1.2) for all randomized subjects.

4.5.3.2 OHT Examination

The OHT examination will be accomplished by direct observation, using retraction aids as appropriate, and will identify grossly carious lesions, signs of erosive wear, enamel irregularities, tooth fracture, gross generalized dental caries decay, decalcification and faulty restorations. 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. Observations will be listed as 'absent' or 'present'; conditions noted as 'present' will be described in the eCRF. Any observation that changes from 'absent' to 'present', or worsens, from the OHT examination completed at Screening will be recorded as an AE.
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 Tooth Color Assessment

Approximately ten subjects will be randomly selected for repeat shade assessments at each assessment time point (Visits 1-5) to test the consistency of the examiner.

The repeat tooth stain assessments will be compared to the original assessments and will not be used in any efficacy analysis. The first and second assessments on each tooth site will be cross tabulated. A weighted Kappa coefficient (κ), along with the 95% CI will be calculated to assess the intra-examiner reliability in Table 14.2.5.1 for all subject in VITA Shade repeatability population by study Product Group. Fleiss-Cohen weighted kappa will be calculated for the repeatability analysis. Reliability will be deemed-

- Excellent if $\kappa > 0.75$

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

All subjects who have repeatability data will be included in this analysis.
If the same subject is selected at random for repeatability assessments at multiple visits, the pairs of observations will be considered as independent for the purposes of repeatability analysis; that is, any potential with subject correlation will be ignored.

4.6.2 Repeatability of the MLSI Assessment

Approximately ten subjects will be randomly selected for repeat MLSI assessments at each assessment time point (Visits 1-5) to test the consistency of the examiner.

The repeat color assessments will be compared to the original assessments and will not be used in any efficacy analysis. The first and second assessments on each tooth site will be cross tabulated. A weighted Kappa coefficient (κ), along with the 95% CI will be calculated to assess the intra-examiner reliability in Table 14.2.5.2 for all subject in MLSI repeatability population by study Product Group. Fleiss-Cohen weighted kappa will be calculated for the repeatability analysis. Reliability will be deemed-

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

All subjects who have repeatability data will be included in this analysis.
If the same subject is selected at random for repeatability assessments at multiple visits, the pairs of observations will be considered as independent for the purposes of repeatability analysis; that is, any potential with subject correlation will be ignored.

5 Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment (Dated: 13-Nov-2023).

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
14.2 Efficacy Data Summary Tables and Figures						
	Table	14.2.1.1	Summary of Brushing Compliance	mITT Population	14.2.1.1	
	Table	14.2.1.2	Summary of Bleaching Compliance	mITT Population	14.2.1.2	
	Table	14.2.2.1.1	Summary of Mean VITA Shade Score	mITT Population	14.2.2.1.1	Yes
	Table	14.2.2.1.2	Summary of Mean VITA Shade Score	PP Population	14.2.2.1.1	
	Table	14.2.2.2.1	Statistical Analysis of Mean VITA Shade Score (Repeated Measures ANOVA)	mITT Population	14.2.2.2.1	Yes
	Table	14.2.2.2.2	Statistical Analysis of Mean VITA Shade Score (Repeated Measures ANOVA)	PP Population	14.2.2.2.1	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Table	14.2.3.1	Summary of Mean Total MLSI Score	mITT Population	14.2.3.1	Yes
	Table	14.2.3.2	Statistical Analysis of Mean Total MLSI Score (Repeated Measures ANOVA)	mITT Population	14.2.3.2	Yes
	Table	14.2.4.1	Summary of Sensitivity Questionnaire Score	mITT Population	14.2.4.1	Yes
	Table	14.2.4.2	Post Whitening Questionnaire	mITT Population	14.2.4.2	Yes
	Table	14.2.4.3	Summary of Mean VITA Shade Score at Pre to Post Bleaching	mITT Population	14.2.2.1.1	Yes
	Table	14.2.4.4	Statistical Analysis of Change in Mean VITA Shade Score Pre to Post Bleaching	mITT Population	14.2.4.4	Yes
	Table	14.2.5.1	Intra-examiner Repeatability Analysis of VITA Shade Score	VITA Shade Repeatability Population	14.2.5.1	Yes
	Table	14.2.5.2	Intra-examiner Repeatability Analysis of MLSI	MLSI Repeatability Population	14.2.5.2	Yes
	Figure	14.2.1.1	Mean VITA Shade Score Mean (±SE) Plot Over Time by Product Group	mITT Population	14.2.1.1	
	Figure	14.2.1.2	Mean VITA Shade Score Mean (±SE) Plot Over Time by Product Group	PP Population	14.2.1.1	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Figure	14.2.2.1	Mean Total MLSI (A*I) Score Mean (±SE) Plot Over Time by Product Group	mITT Population	14.2.2.1	
14.3 Safety Data Summary Tables and Figures						
14.3.1 Displays of Adverse Events						
	Table	14.3.1.1	Summary of All 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	
	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	

CSR Section	TLF	Number	Title	Population	Template	Topline
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events						
14.3.4 Other Observations Related to Safety and Abnormal Laboratory Values						
	Table	14.3.4.1	Summary of Oral Soft Tissue Examination	Safety Population	14.3.4.1	
	Table	14.3.4.2	Concomitant Medication taken to alleviate Tooth Sensitivity	Safety Population	14.3.4.2	
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 in Mean VITA Shade Score (Repeated Measures ANOVA) (Reference: Table 14.2.2.2.1)	mITT Population	SAS Output	Yes
	Raw output	16.1.9.1.2	Statistical Analysis in Mean VITA Shade Score (Repeated Measures ANOVA) (Reference: Table 14.2.2.2.2)	PP Population	SAS Output	
	Raw output	16.1.9.2	Statistical Analysis in Mean Total MLSI Score (Repeated Measures ANOVA)	mITT Population	SAS Output	Yes

CSR Section	TLF	Number	Title	Population	Template	Topline
			(Reference: Table 14.2.3.2)			
	Raw output	16.1.9.3	Statistical Analysis of Change in Mean VITA Shade Score Pre to Post Bleaching (Reference: Table 14.2.4.4)	mITT Population	SAS Output	Yes
16.2 Subject Data Listings						
16.2.1 Discontinued Subjects						
	Listing	16.2.1.1	Subject Disposition	All Randomized Subjects	16.2.1.1	---
	Listing	16.2.1.2	Subject Disposition	Non- Randomized Subjects	16.2.1.2	
16.2.2 Protocol Deviations						
	Listing	16.2.2.1	Important Protocol Deviations	All Randomized Subjects	16.2.2.1	---
	Listing	16.2.2.2	All Protocol Deviations	All Randomized Subjects	16.2.2.2	
16.2.3 Patients Excluded from the Efficacy Analysis						
	Listing	16.2.3.1	Exclusions from Analysis Populations	All Randomized Subjects	16.2.3.1	---
16.2.4 Demographic Data						
	Listing	16.2.4.1	Demographic 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	All Randomized Subjects	16.2.4.3	
	Listing	16.2.4.4	Concomitant Medications and Concomitant Non-Drug Therapies	All Randomized Subjects	16.2.4.4	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Listing	16.2.4.5	Concomitant Medications used to Alleviate Tooth Sensitivity	All Randomized Subjects	16.2.4.5	
16.2.5 Compliance and/or Drug Concentration Data (if available)						
	Listing	16.2.5.1	Brushing Compliance	All Randomized Subjects	16.2.5.1	---
	Listing	16.2.5.2	Peroxide Bleaching Compliance	All Randomized Subjects	16.2.5.2	
	Listing	16.2.5.3	Supervised Brushing	All Randomized Subjects	16.2.5.3	
16.2.6 Individual Efficacy Response Data						
	Listing	16.2.6.1	VITA Shade Score Data	All Randomized Subjects	16.2.6.1	---
	Listing	16.2.6.2.1	MLSI (AxI) Score Data	All Randomized Subjects	16.2.6.2.1	
	Listing	16.2.6.2.2	Derived MLSI (AxI) Score Data	All Randomized Subjects	16.2.6.2.2	
	Listing	16.2.6.3	Tooth Sensitivity Questionnaire	All Randomized Subjects	16.2.6.3	
	Listing	16.2.6.4	Post Whitening Questionnaire	All Randomized Subjects	16.2.6.4	
	Listing	16.2.6.5	Whitening History Questionnaire	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	---

CSR Section	TLF	Number	Title	Population	Template	Topline
	Listing	16.2.7.2	All Adverse Events	Non- Randomized	16.2.7.1	
	Listing	16.2.7.3	Incidents due to medical device	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	16.2.8.1.1	Oral Soft Tissue Examination (All Result)	All Randomized Subjects	16.2.8.1.1	---
	Listing	16.2.8.1.2	Oral Soft Tissue Examination (Abnormal Result)	All Randomized Subjects	16.2.8.1.1	
	Listing	16.2.8.2	Oral Hard Tissue Examination	All Randomized Subjects	16.2.8.2	
16.4 Individual Subject Data Listings						
	NA					