STATISTICAL ANALYSIS PLAN

A RANDOMIZED, CONTROLLED, SINGLE-BLIND CLINICAL STUDY TO INVESTIGATE THE TOOTH STAIN REMOVAL EFFICACY OF TWO EXPERIMENTAL POTASSIUM NITRATE DENTIFRICES IN SUBJECTS WITH EXTRINSIC DENTAL STAIN COMPARED TO A STANDARD DENTIFRICE CONTROL WHEN USED TWICE DAILY FOR 8 WEEKS

Protocol Number: 300024

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	V1.0 04-OCT-2022	Not applicable (N/A)

Table of contents

List of Tables

List of Figures

Abbreviations

Abbreviation	Term
AE	Adverse Event
A × I	Area × Intensity
BDRM	Blinded Data Review Meeting
CH	Consumer Healthcare
CI	Confidence Interval
COVID-19	Coronavirus Disease of 2019
eCRF	Electronic Case Report Form
GSK	GlaxoSmithKline
GSKCH	GlaxoSmithKline Consumer Healthcare
ICF	Informed Consent Form
ITT	Intent-To-Treat
KNO_3	Potassium Nitrate
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intend-To-Treat
MLSI	Total Modified Lobene Stain Index
MMRM	Mixed Model with Repeated Measures
N/A	Not Applicable
NA	Not Applicable
NaF	Sodium Fluoride
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
WHODD	World Health Organization Drug Dictionary

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 300024 (version 3.0, dated 07-Sep-2022).

1 Summary of Key Protocol Information

This will be a single-center, 8-week, randomized, controlled, single-blind (clinical examiner[s] and VITA EasyShade operator), three treatment-arm, parallel design, stratified clinical study in healthy volunteers with a propensity to form dental stain. It has been designed to investigate changes in tooth stain and color, following twice-daily use of two experimental dentifrices, after four- and eight-weeks twice daily use; a regular fluoride dentifrice will be included as reference dentifrice. Sufficient subjects will be screened to randomize approximately 300 subjects to study treatment to ensure approximately 270 subjects complete the study.

At screening (Visit 1, Day 0), subjects will give their written informed consent to participate in the study. Demography, relevant medical history, and current medications/treatments will be recorded, followed by oral soft tissue (OST) and oral hard tissue (OHT) examinations. Subjects meeting the relevant study criteria, will be considered eligible to proceed for baseline assessments on the same day.

At baseline (Visit 2, Day 0) subjects, having refrained from oral hygiene procedures for at least 6 hours, will undergo clinical assessment of the stain on the facial surfaces of their six maxillary anterior teeth and six mandibular anterior teeth (tooth numbers 6-11 and 22-27) and the lingual surfaces of their six mandibular anterior teeth using the MacPherson modification of the Lobene Stain Index (MLSI). The shade (color) of the facial surfaces of the central and lateral maxillary incisors (tooth numbers 7-10) will then be assessed clinically using the VITA Bleachedguide 3D-MASTER and the color of the same surfaces will be evaluated using the VITA EasyShade instrument. Subjects who fulfil all inclusion/exclusion criteria will be enrolled into the study.

Qualifying subjects with a Total MLSI $_{(A \times I)} \geq 15$ for the facial surfaces of the 12 anterior teeth and a mean tooth shade ≥ 11 on the facial surfaces of the 4 maxillary incisors, who meet all other entry criteria, will be stratified according to their baseline Total MLSI (A × I) (low < 45; high ≥ 45) and smoking status (smoker; non-smoker) and randomized to study treatment.

Randomized subjects will brush twice daily (morning and evening) with their assigned study dentifrice for the next 8 weeks and record each brushing in the diary provided; significant changes in diet or smoking status should also be noted in the diary. Subjects, having refrained from oral hygiene procedures for at least 6 hours, will return to the clinic after 4- and 8-weeks treatment (Visits 3 and 4, respectively) for clinical and instrumental assessments of dental stain and tooth shade/color.

The clinical examiner will perform replicate MLSI and tooth shade assessments (as described in Sections 4.6) at Visits 2 to 4. The clinical examiner may brush the subject's anterior teeth with water and/or floss between the anterior teeth prior to MLSI assessments, if required, to remove any debris on the teeth.

Safety and oral tolerability of the study products will be monitored over the 8-week usage period by review of reported Adverse Events (AEs).

1.1 Study Design

This will be a single-center, 8-week, randomized, controlled, single-blind (clinical examiner[s] and VITA EasyShade operator), three treatment-arm, parallel design, stratified clinical study in healthy volunteers with clinically confirmed dental stain (originating from the diet and/or smoking) on the surfaces of their anterior teeth.

Potential subjects will attend a screening visit (Visit 1, Day 0) to determine their suitability to participate. Having obtained their written informed consent, relevant details of their medical history and current medications will be recorded, followed by OST and OHT examinations. Subjects meeting the relevant study criteria, will be considered as eligible to proceed for baseline assessments on the same day.

At the baseline visit (Visit 2, Day 0), eligible subjects will undergo clinical and instrumental assessments of extrinsic dental stain (MLSI: facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth) and tooth color (VITA Bleachedguide 3D-MASTER and VITA EasyShade instrument: facial surfaces of the central and lateral maxillary incisors). Qualifying subjects will be stratified by baseline Total MLSI (A ×I) (calculated for the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth only) and smoking status and randomized to one of the three study treatments. Randomized subjects will be instructed to brush twice daily (for 2 minutes, morning and evening) with their assigned study dentifrice for the next 8 weeks. Extrinsic dental stain and tooth color assessments will be repeated after 4- and 8-weeks treatment. Table 1-1 presents the schedule of activities.

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening	Treatment Period				
	Visit 1 **Screening** (Day 0)[4]	Visit 2 **Baseline** (Day 0)[4]		Visit 3 **Week 4** (Day 28 ±3 days)		Visit 4 **Week 8** Day 56 ±3 days)
Informed consent	X					
Demographics	X					
Medical History / current oral care products / current and prior medication review	X					
Review changes in health and concomitant medications/treatments				X		X
OST Examination	X			X		X
OHT Examination	X					X
Clinical assessment of extrinsic dental stain (MLSI)[2]		X		X		X
Clinical assessment of tooth color (VITA Bleachedguide)		X		X		X
Instrumental assessment of tooth color (VITA EasyShade)		X	4 Weeks	X	4 Weeks	X
Repeatability assessments[3]		X		X		X
Inclusion/exclusion criteria review	X	X				
Subject eligibility	X	X				
Subject continuance				X		X
Randomization and stratification		X				
Dispense study products, diary and sundry items		X		X		
Supervised tooth brushing		X		X		
Return of study dentifrice, toothbrush and completed diary				X		X
Adverse events review[1]		X		X		X
Medical device incidents review[1]		X		X		X
Study conclusion						X

Abbreviations: OST: Oral Soft Tissue, OHT: Oral Hard Tissue, MLSI: Modified Lobene Stain Index

Footnotes:

1. Adverse Events (AEs), Serious Adverse Events (SAEs) and medical device incidents collected immediately after subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF) until 5 days after last use of the study dentifrice (or last procedure). Medical device in this study is the supplied toothbrush.

2. Brushing and/or flossing of the subject's assessment teeth will be performed prior to this assessment by the examiner if required (at the examiner's discretion).

3. Repeatability assessments for VITA Bleachedguide and MLSI assessments will be performed on a subset of subjects
4. Note Visits 1 & 2 will occur on the same day.

1.2 Study Objectives

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

Table 1-2 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To evaluate the change in extrinsic dental stain after 8 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice, a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice and a regular fluoride dentifrice, as measured by Total Modified Lobene Stain Index (Total MLSI [Area × Intensity]).	Change from baseline in mean Total MLSI (Area × Intensity) score at week 8.
Secondary Objectives	**Secondary Endpoints**
Efficacy	
To evaluate the change in extrinsic dental stain after 4 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice, a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice and a regular fluoride dentifrice, as measured by Total Modified Lobene Stain Index (Total MLSI [Area × Intensity]).	Change from baseline in mean Total MLSI (Area × Intensity) score at week 4.
To compare the change in extrinsic dental stain after 4 & 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured by Total MLSI (Area × Intensity).	Change from baseline in mean Total MLSI (Area × Intensity) score at weeks 4 & 8.
To evaluate and compare the change in tooth shade (color) after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride	Change from baseline in mean VITA shade score (examiner assessed) at weeks 4 & 8.

Objectives	Endpoints
dentifrice, as measured by the VITA Bleachedguide 3D-MASTER.	
To evaluate and compare the changes in dental stain at specific tooth sites (along gingival margin, inter-proximally and on the body of the tooth) after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured by Total MLSI (Area × Intensity).	Change from baseline in mean MLSI (Area × Intensity) in: • Gingival sites • Interproximal sites • Body sites
To evaluate and compare change in extrinsic dental stain after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured by MLSI (Area) and MLSI (Intensity).	Change from baseline in mean MLSI (Area) and MLSI (Intensity)
Exploratory Objectives	**Exploratory Endpoints**
To evaluate and compare the change in tooth color co-ordinates after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured using the VITA EasyShade.	Change from baseline in mean tooth shade, L*, a*, b*, WI_D and ΔE* determined using the VITA EasyShade instrument at weeks 4 & 8
Safety	
To assess the safety and tolerability of the two experimental KNO_3 dentifrices.	Treatment emergent adverse events

1.3 Study Products

Table 1-3 presents the study products.

Table 1-3 Study Products

	Experimental Dentifrice 1	Experimental Dentifrice 2	Reference Dentifrice
Product Description	5% KNO_3 dentifrice with 1% alumina and 5% STP	5% KNO_3 dentifrice with 1% alumina, 5% STP and 2% high cleaning silica	Regular Fluoride Dentifrice
Product Name	N/A	N/A	Aquafresh Cavity Protection (US market)
Fluoride Content	0.2542% NaF (1100 ppm fluoride)		
Pack Design	One carton containing 2 tubes of dentifrice		
Dispensing Details	Visit 2 (Baseline): 2 cartons; Visit 3 (Week 4): 2 cartons		
Product Master Formulation Code (MFC)	CCI [redacted]	CCI [redacted]	CCI [redacted]
Dose/Product Application	Subjects will dose the toothbrush provided with a strip of dentifrice (a full brush head) on each brushing occasion		
Route of Administration	Topical oral use		
Usage Instructions	Subjects will brush twice daily (morning and evening) for 2 timed minutes with their allocated product.		
Return Requirements	Used and unused study product to be returned to the sponsor.		

KNO_3: Potassium Nitrate, STP: Sodium Tripolyphosphate, N/A: Not Applicable, NaF: Sodium Fluoride

All dentifrices will be applied in the same manner and will be brushed on to the teeth, twice daily (morning and evening) for 2 timed minutes.

1.4 Sample Size Calculation

The study will be powered sufficiently (>90%) to provide evidence of superiority for an Experimental Dentifrice compared to the Reference Dentifrice for both stain removal and whitening after 8 weeks under the graphical approach method (with initial two-sided alpha allocation of 5% for testing within each Experimental Dentifrice) to adjust for multiple comparisons and preserve a two-sided 10% family wise error rate as described in Figure 4-1.

Table 1-4 Sample Size Power by Endpoint at 5% and 2.5% Significance Levels with 90 Subjects per Arm

Endpoint at Week 8	Assumptions		Independent power from 90 subjects per arm for each endpoint by two-sided significance level[3]		Power from graphical approach to achieve statistical significance at 5% level[4]
	Mean Difference	Standard Deviation (SD)	5%	2.5%	
Within Experimental Dentifrice change from baseline in mean Total MLSI (Area × Intensity)[1]	0.6	0.4	>99.9%	>99.9%	>99.9%
Comparison with Reference Dentifrice in change from baseline in mean Total MLSI (Area × Intensity)[1]	0.3	0.4	99.8%	99.7%	99.8%
Within change from baseline in the mean VITA shade score[2]	2	2	>99.9%	>99.9%	>99.9%
Comparison with Reference Dentifrice in change from baseline in the mean VITA shade score[2]	1	2	91.5%	86.1%	90.2%

1) Estimates of mean difference and SD were based on results from a previous GSKCH study of similar design CCI [redacted]

2) Estimates of mean difference and SD were based on results from previous GSKCH studies of similar design CCI [redacted] Within treatment study reductions in the mean VITA shade score are expected to be greater in this study due to greater baseline VITA shade scores and an 8 week primary assessment instead of 4 weeks. As such, the SD is also assumed to increase, so an effect size (mean difference/SD) of 0.5 is assumed.

3) Based on carrying out a two tailed one-sample (within Experimental Dentifrice) or two-sample (Comparison with Reference Dentifrice) t-test at the 5% significance level using PASS software version 19.0.1.

4) Simulation using SAS9.4 software based on stated assumptions for all endpoints and graphical approach analysis as described in Figure 4-1

As detailed in the independent sample size calculations in Table 1-4, the minimum required sample size assessment depends almost entirely on the mean VITA shade score reduction comparison between Experimental and Reference Dentifrices. Simulation shows that under the graphical approach methodology and the above underlying assumptions for an Experimental Dentifrice, the power to show statistical significance in all 4 comparisons for that Experimental Dentifrice (reduction from baseline and superior reduction compared to Reference Dentifrice in both mean Total MLSI [A×I] and mean VITA shade score) is > 90%.

Approximately 100 subjects per group (approximately 300 in total) will be randomized to account for a drop-out rate of up to 10% prior to Week 8.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned.

2.2 Final Analyses

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

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

3 Considerations for data analyses and Data Handling Conventions

3.1 Baseline Definition

For all endpoints, the baseline value will be the Day 0 (Visit 2) pre-brushing assessment with a non-missing value.

3.2 Subgroups/Stratifications

Subjects who satisfy the study selection criteria will be stratified according to their baseline Total MLSI (A × I) (low < 45; high ≥ 45) and smoking status (smoker; non-smoker) and randomized to study treatment.

For stratification purposes, the Total MLSI (A × I) will be derived as the sum of the MLSI (A × I) scores for each of evaluated regions (gingival and body) of the facial surfaces of each anterior tooth (4 values per assessed tooth surface).

The two stratification factors will give rise to four strata.

- Stratum 1: Baseline Total MLSI (A × I) < 45, Smoker
- Stratum 2: Baseline Total MLSI (A × I) < 45, Non-smoker
- Stratum 3: Baseline Total MLSI (A × I) ≥ 45, Smoker
- Stratum 4: Baseline Total MLSI (A × I) ≥ 45, Non-smoker

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 centres is not applicable.

3.4 Timepoints and Visit Windows

The timepoints and visits for this study are defined in the Table 1-1 "Schedule of Activities". 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 GSK CH. The statistical analysis software used will be SAS version 9.4 or higher. For the implementation of graphical approach as described in Section 4.4, SAS IML or gMCP package in R will be used.

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 BDRM is the assessment of the number of subjects who have dropped or discontinued from the study due to pandemic related events (e.g., Coronavirus Disease of 2019 [COVID-19]) 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

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 subjects will be presented in Table 14.1.1.

The number and percentage of screen failure subjects (subjects not randomized) with reasons why subjects are not randomized including percentage of subjects not randomized due to COVID-19 pandemic 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 including percentage of subjects discontinued/withdrew from study due to COVID-19 pandemic, 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.

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 due to COVID-19 pandemic.

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
- Non-compliance with product administration
- Inadmissible concomitant medication

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

Four analysis populations are defined.

Population	Definition / Criteria	Analyses Evaluated
Safety	Comprise of all randomized subjects who complete at least one use of study product. Any subject who receives a randomization number will be considered to have been randomized. This population will be based on the treatment the subject actually received.	Safety
Modified Intent-To-Treat (mITT)	Comprise all randomized subjects who complete at least one use of study product and have at least one post-baseline efficacy assessment. Any subject who receives a randomization number will be considered to have been randomized. This population will be based on the study product to which the subject was randomized.	Demographic Baseline Characteristics Efficacy Analysis
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 would 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 Assessment	Comprise of all subjects who have a repeat clinical assessment of efficacy at any visit. There will be a separate population for repeat MLSI assessment and repeat tooth shade assessment: MLSI Repeatability population: Subjects with at least one initial and repeat assessment of MLSI at any visit. VITA Shade Repeatability population: Subjects with at least one initial and repeat assessment of Tooth shade at any visit.	Repeatability analyses

NOTES :
Please refer to Appendix 1: List of Data Displays which details the population to be used for each displays 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 change from baseline for Mean Total MLSI (A×I) and Mean VITA shade score endpoints only if more than 10% 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

4.2.1 Demographic and Baseline 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, 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.

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 by cumulative visit.

Number of brushings is defined as: [(date of Visit N – date of Visit 2) 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 2) 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.

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

4.3.2 Prior and Concomitant Medication

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 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, frequency, start date and end date both relative to study product start date (Listing 16.2.4.3) for all screened 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 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.

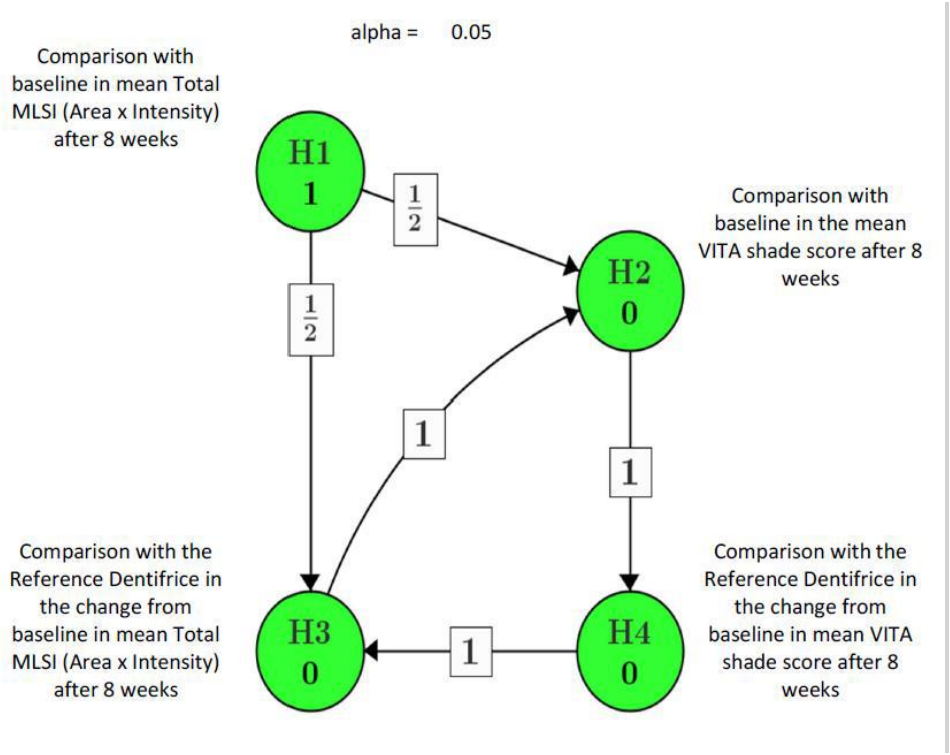
4.4 Analysis of Efficacy

The primary population for assessment of efficacy will be the mITT Population.

The hypothesis testing of the change from baseline in the mean Total MLSI (A×I) and mean VITA shade score at week 8 for each Experimental Dentifrice will employ the graphical approach shown in Figure 4-1 (as per Bretz et al., 2009) in order to maintain an overall two-sided familywise error rate at 5% within each Experimental Dentifrice (10% overall).

Therefore, the final p-values presented for all these endpoints (primary efficacy endpoint and secondary efficacy endpoints 1-3) may be adjusted depending on results of the other endpoints and the completion of the graphical approach testing.

Figure 4-1 Graphical Approach Showing Allocation and Propagation of Alpha Between Hypotheses Within Each Experimental Dentifrice



For all other secondary and exploratory endpoints, there will be no adjustments for multiplicity and unadjusted p-values will be presented.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary endpoints for this study are the change from baseline in the mean Total MLSI (A×I) at Week 8 within each study product.

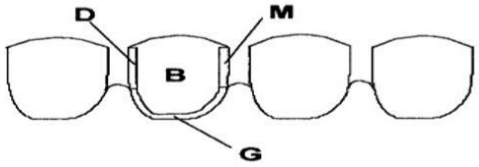
Extrinsic dental stain will be assessed on the facial surfaces of the 6 maxillary and 6 mandibular anterior teeth (6-11 and 22-27), and the lingual surfaces of the 6 mandibular anterior teeth (22-27) at baseline, Week 4, and Week 8 (Visits 2-4) using MLSI.

The facial and lingual surfaces of each assessable tooth will be divided into 2 regions, with a total of 4 sites per tooth surface (Figure 4-2).

- **Gingival Region:** Defined as a crescent-shaped band (~ 2 mm wide) adjacent to the free margin of the gingiva and extending to the crest of the inter-dental papillae of the adjacent teeth (1 site).

- **Body Region:** The remainder of the tooth surface (the body) is further sub-divided into 3 sites.
  - Distal facial, body facial, mesial facial sites
  - Distal lingual, body lingual, mesial lingual sites

Figure 4-2 MLSI Assessment Sites: Body (B), Gingival (G), Mesial (M), Distal (D)



Area (A) and intensity (I) of extrinsic dental stain is scored separately for the four 'gingival' and 'body' sites, as follows.

Score	Area	Intensity
0	No stain	No stain
1	Stain covering up to one third of region	Light stain
2	Stain covering up to two thirds of region	Moderate stain
3	Stain covering more than two thirds of region	Heavy stain

The mean Total MLSI (A×I) score for each subject at each visit is calculated as the mean of all MLSI (A×I) scores over all non-missing gingival, body, mesial and distal sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.

Descriptive statistics (n, mean, SD, SE, median, minimum, and maximum) will be presented for the mean Total MLSI at each time point (absolute and change from baseline) in Table 14.2.2.1.1 for all subjects in mITT population by study product. Raw means (± SE) of the mean Total MLSI scores at each time point will be plotted by study product in Figure 14.2.1.1 for all subjects in mITT population.

Individual and derived MLSI (A×I) score data will be listed for each subject by visit and study product group in Listing 16.2.6.1.1 and Listing 16.2.6.1.2 respectively for all randomized subjects.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- H_0: There is no difference between baseline and week 8
- H_1: There is a difference between baseline and week 8

The following study product comparisons will be analyzed:

- For Experimental Dentifrice 1, baseline versus week 8

- For Experimental Dentifrice 2, baseline versus week 8

The change from baseline in the mean Total MLSI (A×I) score will be analysed using a Mixed Model with Repeated Measures (MMRM). Fixed effects will be included for smoking status, study product, visit and study product x visit interaction. The baseline mean Total MLSI (A×I) score will be included as a covariate. Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied. The least square means for each study product at week 8 will be presented based on observed margins and used to test for a non-zero change from baseline. If unstructured covariance matrix does not converge, compound symmetry covariance matrix will be used.

Using the above model, the adjusted mean change from baseline in the mean Total MLSI (A × I) score will be reported by study product group along with 95% confidence intervals (CIs) and adjusted p-values testing for a non-zero change from baseline will be provided in Table 14.2.2.2.1. For each Experimental Dentifrice, only adjusted p-values following the graphical approach (see Figure 4-1) will be presented. Significance testing will be conducted at the two-sided 5% significance level.

The assumption of normality and homogeneity of variance in the MMRM 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 8 and results will be provided to support the MMRM results.

4.4.1.3 Supportive Analyses

A PP analysis will be performed on the change from baseline in the mean Total MLSI (A×I) score if there is more than 10% difference in the number of subjects between the PP and mITT populations. A decision on whether a PP analysis will be performed will be made prior to study unblinding (release of the randomization codes).

A summary of the mean Total MLSI (A×I) will be presented for the PP Population in Table 14.2.2.1.2. Statistical analysis of the mean Total MLSI score will be presented for the PP population in Table 14.2.2.2.2. In addition, the mean profiles of the mean Total MLSI (A×I) (Figure 14.2.1.2) at each time point will be plotted by study product for all subjects in the PP Population.

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Secondary Efficacy Endpoint 1

The Secondary Efficacy Endpoint 1 will be the change from baseline in the mean VITA shade score at week 8 within each study product.

Tooth shade (color) of the facial surfaces of the four central and lateral maxillary incisors (tooth numbers 7-10) will be assessed by a single, trained clinical examiner using the VITA Bleachedguide 3D-MASTER. The VITA Bleachedguide 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 Bleachedguide.

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 the four central and lateral maxillary incisors.

Descriptive statistics (n, mean, SD, Standard Error [SE], median, minimum, and maximum) will be presented for the mean VITA shade score at each assessment time point (absolute and change from baseline) in Table 14.2.3.1.1 for all subjects in mITT Population by study product. Raw means (± SE) of mean VITA shade scores at each time point will be plotted by study product in Figure 14.2.2.1 respectively for all subjects in mITT population.

4.4.2.1.1 Statistical Hypothesis, Model and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- H_0: There is no difference between baseline and week 8
- H_1: There is a difference between baseline and week 8

The following study product comparisons will be analyzed:

- For Experimental Dentifrice 1, baseline versus week 8
- For Experimental Dentifrice 2, baseline versus week 8

The change from baseline in the mean VITA shade score will be analysed using a MMRM. Fixed effects will be included for smoking status, baseline Total MLSI (AxI) stratification (< 45 or ≥ 45), study product, visit and study product x visit interaction. The baseline mean VITA shade score will be included as a covariate. Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied. The least square means for each study product at week 8 will be presented based on observed margins and used to test for a non-zero change from baseline. If unstructured covariance matrix does not converge, compound symmetry covariance matrix will be used.

Using the above model, the adjusted mean change from baseline in the mean VITA shade score will be reported by study product group along with 95% CIs and p-values testing for a non-zero change from baseline will be provided in Table 14.2.3.2.1. For each Experimental Dentifrice, only adjusted p-values following the graphical approach (see Figure 4-1) will be presented. Significance testing will be conducted at the two-sided 5% significance level.

The assumption of normality and homogeneity of variance in the MMRM 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 8 and results will be provided to support the MMRM results.

4.4.2.1.2 Supportive Analyses

A PP analysis will be performed on the change from baseline in the mean VITA shade score if there is more than 10% difference in the number of subjects between the PP and mITT

populations. A decision on whether a PP analysis will be performed will be made prior to study unblinding (release of the randomization codes).

A summary of the mean VITA shade will be presented for the PP Population in Table 14.2.3.1.2. Statistical analysis of the mean VITA shade score will be presented for the PP population in Table 14.2.3.2.2. In addition, the mean profiles of the mean VITA shade score (Figure 14.2.2.2) at each time point will be plotted by study product for all subjects in the PP Population.

4.4.2.2 Secondary Efficacy Endpoint 2

The Secondary Efficacy Endpoint 2 will be the change from baseline in mean Total MLSI (A×I) score at week 8 and the comparison of each Experimental Dentifrice to the Reference Dentifrice.

4.4.2.2.1 Statistical Hypothesis, Model and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- H_0: There is no treatment difference
- H_1: There is a treatment difference

The following study product comparisons will be analyzed:

- Experimental Dentifrice 1 versus Reference Dentifrice at week 8
- Experimental Dentifrice 2 versus Reference Dentifrice at week 8

The results for this endpoint will be obtained from the MMRM detailed in Section 4.4.1.1. Mean differences between each Experimental Dentifrice compared to the Reference Dentifrice in the change from baseline in mean Total MLSI (A×I) score at week 8 will be presented along with 95% CIs and adjusted p-values (following the graphical approach in Figure 4-1) in Table 14.2.2.2.1. Significance testing will be conducted at the two-sided 5% significance level.

The assumption of normality and homogeneity of variance in the MMRM 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 8 and results will be provided to support the MMRM results.

4.4.2.3 Secondary Efficacy Endpoint 3

The Secondary Efficacy Endpoint 3 will be the change from baseline in mean VITA shade score at week 8 and the comparison of each Experimental Dentifrice to the Reference Dentifrice.

4.4.2.3.1 Statistical Hypothesis, Model and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- H_0: There is no treatment difference

- H_1: There is a treatment difference

The following study product comparisons will be analyzed:

- Experimental Dentifrice 1 versus Reference Dentifrice at week 8
- Experimental Dentifrice 2 versus Reference Dentifrice at week 8

The results for this endpoint will be obtained from the MMRM detailed in Section 4.4.2.1.1. Mean differences between each Experimental Dentifrice compared to the Reference Dentifrice in the change from baseline in mean VITA shade score at week 8 will be presented along with 95% CIs and adjusted p-values (following the graphical approach in Figure 4-1) in Table 14.2.3.2.1. Significance testing will be conducted at the two-sided 5% significance level.

The assumption of normality and homogeneity of variance in the MMRM 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 8 and results will be provided to support the MMRM results.

4.4.2.4 Secondary Efficacy Endpoint 4

The Secondary Efficacy Endpoint 4 will be the change from baseline in mean Total MLSI (A×I) score at week 4 for each study product and the comparison of each Experimental Dentifrice to the Reference Dentifrice.

4.4.2.4.1 Statistical Hypothesis, Model and Method of Analysis

The results for this endpoint will be obtained from the MMRM detailed in Section 4.4.1.1. The same results as presented for the week 8 analysis (see Sections 4.4.1.1 and Section 4.4.2.2) will also be presented for week 4, however only unadjusted p-values will be presented.

4.4.2.5 Secondary Efficacy Endpoint 5

The Secondary Efficacy Endpoint 5 will be the change from baseline in mean VITA shade score at week 4 for each study product and the comparison of each Experimental Dentifrice to the Reference Dentifrice.

4.4.2.5.1 Statistical Hypothesis, Model and Method of Analysis

The results for this endpoint will be obtained from the MMRM detailed in Section 4.4.2.1.1. The same results as presented for the week 8 analysis (see Section 4.4.2.1 and Section 4.4.2.3) will also be presented for week 4, however only unadjusted p-values will be presented.

4.4.2.6 Secondary Efficacy Endpoint 6

The Secondary Efficacy Endpoint 6 will be the change from baseline in the mean site MLSI (A×I) score at weeks 4 and 8 (Gingival sites, Interproximal sites, and Body sites).

The mean Interproximal MLSI (A×I) score for each subject at each visit is calculated as the mean MLSI (A×I) score over all interproximal (Mesial + Distal) sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.

The mean Gingival MLSI (A×I) and mean Body MLSI (A×I) score for each subject at each visit is calculated as the respective mean MLSI (A×I) score over Gingival or Body sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.

Descriptive statistics (n, mean, SD, Standard Error [SE], median, minimum, and maximum) will be presented for each site MLSI (A×I) score at each assessment time point (absolute and change from baseline) in Table 14.2.4.1 for all subjects in mITT Population by study product.

4.4.2.6.1 Statistical Hypothesis, Model and Method of Analysis

The same MMRM model detailed in Section 4.4.1.1 for the mean Total MLSI (A×I) will be fitted separately for each mean site MLSI (A×I) score (Gingival sites, Interproximal sites, Body sites) but instead using the respective baseline mean site MLSI (A×I) score as a covariate. The same results as presented for the mean Total MLSI (A×I) score (see Section 4.4.1.1, Section 4.4.2.2 and Section 4.4.2.4) will be presented for each mean site MLSI (A×I) score in Table 14.2.4.2.

The assumption of normality and homogeneity of variance in the MMRM 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 weeks 4 and 8 and results will be provided to support the MMRM results.

4.4.2.7 Secondary Efficacy Endpoint 7

The Secondary Efficacy Endpoint 7 will be the change from baseline in the mean Total MLSI (A) and the mean Total MLSI (I) at 4 and 8 weeks.

The mean Total MLSI (A) and mean Total MLSI (I) score for each subject at each visit is calculated as the respective mean MLSI (A) or mean MLSI (I) score over all gingival, body, mesial and distal sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.

Descriptive statistics (n, mean, SD, Standard Error [SE], median, minimum, and maximum) will be presented for the mean Total MLSI (A) and the mean Total MLSI (I) scores at each assessment time point (absolute and change from baseline) in Table 14.2.5.1 for all subjects in mITT Population by study product.

4.4.2.7.1 Statistical Hypothesis, Model and Method of Analysis

The same MMRM model detailed in Section 4.4.1.1 for the mean Total MLSI (A×I) will be fitted separately for mean Total MLSI (A) score and mean Total MLSI (I) score but instead

using the baseline mean Total MLSI (A) and baseline mean Total MLSI (I) score as respective covariates. The same results as presented for the mean Total MLSI (A×I) score (see Section 4.4.1.1, Section 4.4.2.2 and Section 4.4.2.4) will be presented in Table 14.2.5.2.

The assumption of normality and homogeneity of variance in the MMRM 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 weeks 4 and 8 and results will be provided to support the MMRM 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

Exploratory variables are Change from baseline in Mean VITA EasyShade color co-ordinates (L*, a*, b*, WI_D) and ΔE* determined using the VITA EasyShade instrument at weeks 4 and 8.

VITA EasyShade color coordinates (L*, a*, b*) will be measured instrumentally for the facial surfaces of the four central and lateral maxillary incisors (tooth numbers 7-10) using the VITA EasyShade instrument.

The collected data will be used to calculate the ΔE* and WI_D values as:

ΔE^* = Square root ($\Delta L^{*2} + \Delta a^{*2} + \Delta b^{*2}$), where ΔL^*, Δ a*, Δ b* are respective change from baseline values. Since ΔE^* is calculated as change from baseline. There will be no change from baseline separately for analysis.

$WI_D = 0.511L^* - 2.324a^* - 1.100b^*$

The mean VITA EasyShade color co-ordinate for L*/a*/b*/WI_D score for each subject at each visit is calculated as the respective mean L*/a*/b*/WI_D score over all facial surfaces of the four central and lateral maxillary incisors (tooth numbers 7-10). Change from baseline values will be used for analysis.

The mean VITA EasyShade color co-ordinate for ΔE* score for each subject at each visit is calculated as the mean ΔE* score over all facial surfaces of the four central and lateral maxillary incisors (tooth numbers 7-10). Derived ΔE* values will be used for analysis directly since ΔE* is calculated as change from baseline already and only derived at post-baseline visits.

Descriptive statistics (n, mean, SD, SE, median, minimum, and maximum) will be presented for each mean VITA EasyShade color co-ordinates (L*, a*, b*, and WI_D) (absolute and change from baseline) and post-baseline ΔE* score at each assessment time point in Table 14.2.6.1 for all subjects in mITT Population by study product. Raw means (± SE) of Mean VITA EasyShade color co-ordinates (L*, a*, b*, WI_D and ΔE*) scores at each time point will be plotted by study product in Figure 14.2.3 respectively for all subjects in mITT population.

Individual Mean VITA EasyShade color co-ordinates (L*, a*, b*, WI_D and derived ΔE*) score data will be listed for each subject by visit and study product group in Listing 16.2.6.3 for all randomized subjects.

4.4.3.1.1 Statistical Hypothesis, Model and Method of Analysis

Using the same MMRM model mentioned in Section 4.4.2.1.1 (replaced with the respective baseline covariate for all apart from ΔE* for which baseline L*, a*, and b* covariates will be used) for each color co-ordinates (change from baseline in each of L*/ a*/ b*/ WI_D and derived ΔE*), adjusted mean change from baseline, along with 95% CIs will be reported by study product group will be provided for each Mean VITA EasyShade color co-ordinates (L*, a*, b*, WI_D and ΔE*) in Table 14.2.6.2. Also, P-values testing for non-zero change from baseline will be presented for study product groups. Mean difference between study product groups, 95% CIs and p-values will be provided for each of Mean VITA EasyShade color co-ordinates (L*, a*, b*, WI_D and ΔE*) in Table 14.2.6.2. Significance testing will be conducted at the two-sided 5% significance level.

The assumption of normality and homogeneity of variance in the MMRM 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 weeks 4 and 8 and results will be provided to support the MMRM 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 MMRM analyses account 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 the same smoking status and similar non-missing results at other timepoints (baseline and post-baseline). 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.

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 TEAEs by SOC and PT (Table 14.3.1.1).
- Table of TEAEs by Oral/Non-Oral and PT (Table 14.3.1.2)
- Table of treatment related TEAEs by SOC and PT (Table 14.3.1.3)
- Table of treatment related TEAEs by Oral/Non-Oral and PT (Table 14.3.1.4)
- Table of AEs related to COVID-19 by SOC 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 drug withdrawal (Listing 14.3.2.3)
- Listing of TEAEs classified as Oral (Listing 14.3.2.4)
- Listing of all AEs related to COVID-19 (Listing 16.2.7.3 for all screened subjects)

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

All Incidents will be listed in Listing 16.2.7.4. In the event that there is nothing to report, a null listing will be produced.

4.5.2 Other Safety Variables

Other safety variables are listed below:

- OST examination
- OHT examination

4.5.2.1 OST Examination

This procedure will be conducted by a qualified, experienced clinical examiner. The OST examination will be accomplished by direct observation and palpation with 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. Findings from the examination will be recorded in the CRF as either normal or abnormal, with details of any abnormalities. The results of the OST examination performed at screening will be used to determine subject eligibility. Any new OST abnormality or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject after the screening examination will be recorded as an AE. Where possible, this procedure should be conducted by a single clinical examiner.

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 Safety Population. OST examination will be listed (Listing 16.2.8.1) for all randomized subjects.

4.5.2.2 OHT Examination

This procedure should be conducted by a qualified, experienced clinical examiner. The OHT examination will be accomplished by direct observation, using retraction aids as appropriate and will identify any 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 either absent or present, and conditions noted as present will be described in the eCRF. Any change observed by the clinical examiner or reported by the subject after the screening examination will be recorded as an AE. The results of the OHT examination performed at Screening will be used to determine subject eligibility. Where possible, this procedure should be conducted by a single clinical examiner.

OHT examination will be listed (Listing 16.2.8.2) for all randomized subjects.

4.6 Analysis of Other Variables

Repeat individual MLSI and tooth shade assessments will be performed by the clinical examiner at Baseline-Day 0 (Visit 2), Week 4 (Visit 3), and Week 8 (Visit 4). To assess the repeatability of the MLSI and tooth shade assessments, replicate examinations will be performed by the same clinical examiner.

Ten subjects will be randomly selected for repeat MLSI and tooth shade assessments at each assessment time point (Visits 2, 3, and 4), a total of 30 repeat assessments (for both MLSI and tooth shade assessments) over the duration of the study. Replicate assessments will be separated by a minimum of 10 minutes (maximum 60 minutes) from the original assessment for a given subject and, where possible, separated by at least one subject.

The scores of the initial assessment will not be visible to the examiner or scribe when the repeat assessment is carried out.

The repeat dental assessments (MLSI and tooth shade assessments) will be compared to the respective original assessments and will be used to investigate intra-examiner variability. The repeat assessments will not be used in any efficacy analyses.

The first and repeat assessments for each tooth site will be cross tabulated for MLSI (by Area and Intensity) (Table 14.2.7.1) and for tooth shade assessments (Table 14.2.7.2).

A weighted Kappa coefficient (κ), along with the 95% CIs will be calculated to assess the intra-examiner repeatability across all initial versus repeat assessments performed. Fleiss-Cohen weighted kappa using the raw scores will be calculated for the repeatability analysis. Repeatability 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 for MLSI using the MLSI Repeatability population and for tooth shade assessments using the VITA Shade Repeatability population. Only results with non-missing initial and repeat assessments of the same value (MLSI area, MLSI intensity or tooth shade) at the same tooth site/surface will be presented and analyzed.

5 Changes to the Protocol Defined Statistical Analysis Plan

There were below changes to the originally planned statistical analysis specified from the protocol version 3.0 (Dated: 07-SEP-2022).

Initially it was planned for primary analysis of Mean Total MLSI (A × I) to provide adjusted mean difference between study product groups, adjusted 95% CIs and adjusted p-values (following graphical testing approach) in Table 14.2.2.2.1. However, adjusted 95% CIs will no longer be provided in the table. In place of adjusted CIs, we will provide standard 95% CIs.

Similarly in secondary endpoint 1 (Mean VITA shade score) related Table 14.2.3.2.1, we will provide standard CIs in place of adjusted CIs.

For secondary and exploratory endpoints not related to MLSI, an additional fixed effect for the Total MLSI (AxI) strata (< 45 or ≥ 45) will be included in the MMRMs.

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	mITT Population	14.1.3.1	Yes
	Table	14.1.3.2	Demographic and Baseline Characteristics	Safety Population	14.1.3.1	
14.2 Efficacy Data Summary Tables and Figures						
	Table	14.2.1	Summary of Brushing Compliance	mITT Population	14.2.1	
	Table	14.2.2.1.1	Summary of Mean Total MLSI (A×I) Score	mITT Population	14.2.2.1.1	Yes
	Table	14.2.2.1.2	Summary of Mean Total MLSI (A×I) Score	PP Population	14.2.2.1.1	
	Table	14.2.2.2.1	Statistical Analysis of Change from Baseline in Mean Total MLSI (A×I) Score	mITT Population	14.2.2.2.1	Yes
	Table	14.2.2.2.2	Statistical Analysis of Change from Baseline in Mean Total MLSI (A×I) Score	PP Population	14.2.2.2.1	
	Table	14.2.3.1.1	Summary of Mean VITA Shade Score	mITT Population	14.2.3.1.1	Yes
	Table	14.2.3.1.2	Summary of Mean VITA Shade Score	PP Population	14.2.3.1.1	
	Table	14.2.3.2.1	Statistical Analysis of Change from Baseline in Mean VITA shade score	mITT Population	14.2.3.2.1	Yes

CSR Section	TLF	Number	Title	Population	Template	Topline
	Table	14.2.3.2.2	Statistical Analysis of Change from Baseline in Mean VITA shade score	PP Population	14.2.3.2.1	
	Table	14.2.4.1	Summary of Mean MLSI (A×I) Score by Sites (Interproximal/Gingival/Body)	mITT Population	14.2.4.1	
	Table	14.2.4.2	Statistical Analysis of Change from Baseline in Mean MLSI (A×I) Score by Sites (Interproximal/Gingival/Body)	mITT Population	14.2.4.2	
	Table	14.2.5.1	Summary of Mean MLSI Score by Area and Intensity	mITT Population	14.2.5.1	
	Table	14.2.5.2	Statistical Analysis of Change from Baseline in Mean MLSI Score by Area and Intensity	mITT Population	14.2.5.2	
	Table	14.2.6.1	Summary of Mean VITA EasyShade color co-ordinates (L*, a*, b*, WI_D and Delta E*) score	mITT Population	14.2.6.1	Yes
	Table	14.2.6.2	Statistical Analysis of Change from Baseline in Mean VITA EasyShade color co-ordinates (L*, a*, b*, WI_D and Delta E*) score	mITT Population	14.2.6.2	Yes
	Table	14.2.7.1	Intra-examiner Repeatability Analysis of MLSI Score	MLSI Repeatability Population	14.2.7.1	
	Table	14.2.7.2	Intra-examiner Repeatability Analysis of VITA Shade Score	Vita Shade Repeatability Population	14.2.7.2	
	Figure	14.2.1.1	Mean Total MLSI (A*I) Score Mean (±SE) Plot Over Time by Product Group	mITT Population	14.2.1.1	
	Figure	14.2.1.2	Mean Total MLSI (A*I) 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 VITA Shade Score Mean (±SE) Plot Over Time by Product Group	mITT Population	14.2.2.1	
	Figure	14.2.2.2	Mean VITA Shade Score Mean (±SE) Plot Over Time by Product Group	PP Population	14.2.2.1	
	Figure	14.2.3	Mean VITA EasyShade color co-ordinates (L*, a*, b*, WI_D and Delta E*) Score Mean (±SE) Plot Over Time by Product Group	mITT Population	14.2.3.1	
14.3 Safety Data Summary Tables and Figures						
14.3.1 Displays of Adverse Events						
	Table	14.3.1.1	Treatment Emergent Adverse Events by SOC/PT	Safety Population	14.3.1.1	Yes
	Table	14.3.1.2	Treatment Emergent Adverse Events by Oral/Non-oral/PT	Safety Population	14.3.1.2	
	Table	14.3.1.3	Treatment Related Treatment Emergent Adverse Events by SOC/PT	Safety Population	14.3.1.1	
	Table	14.3.1.4	Treatment Related Treatment Emergent Adverse Events by Oral/Non-oral/PT	Safety Population	14.3.1.2	
	Table	14.3.1.5	Adverse Events Related to COVID-19 by System Organ Class and Preferred Term	Safety Population	14.3.1.5	
14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events						
	Listing	14.3.2.1	Death	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	

CSR Section	TLF	Number	Title	Population	Template	Topline
	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						
14.3.4 Other Observations Related to Safety and Abnormal Laboratory Values						
	Table	14.3.4.1	OST examination	Safety Population	14.3.4.1	
APPENDIX						
16.1.6 Listing of Subjects Receiving Test Drug(s)/Investigational Product(s) from Specific Batches, where more than one batch was used						
	NA					
16.1.7 Randomization Scheme and Codes (Subject identification and treatment assigned)						
	Listing	16.1.7.1	Randomization Information	All Randomized Subjects	16.1.7.1	
16.1.9 Documentation of Statistical Methods						
	Raw output	16.1.9.1.1	Statistical Analysis of Change from Baseline in Mean Total MLSI (A×I) Score (Reference: Table 14.2.2.2.1)	mITT Population	SAS Output	
	Raw output	16.1.9.1.2	Statistical Analysis of Change from Baseline in Mean Total MLSI (A×I) Score (Reference: Table 14.2.2.2.2)	PP Population	SAS Output	
	Raw output	16.1.9.2.1	Statistical Analysis of Change from Baseline in Mean VITA shade (Reference: Table 14.2.3.2.1)	mITT Population	SAS Output	
	Raw output	16.1.9.2.2	Statistical Analysis of Change from Baseline in Mean VITA shade (Reference: Table 14.2.3.2.2)	PP Population	SAS Output	
	Raw output	16.1.9.3	Statistical Analysis of Change from Baseline in Mean MLSI (A×I) Score by Sites (Interproximal/Gingival/Body) (Reference: Table 14.2.4.2)	mITT Population	SAS Output	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Raw output	16.1.9.4	Statistical Analysis of Change from Baseline in Mean MLSI Score by Area and Intensity (Reference: Table 14.2.5.2)	mITT Population	SAS Output	
	Raw output	16.1.9.5	Statistical Analysis of Change from Baseline in Mean VITA EasyShade color co-ordinates (L*, a*, b*, WID and Delta E*) score (Reference: Table 14.2.6.2)	mITT Population	SAS Output	
16.2 Subject Data Listings						
16.2.1 Discontinued Subjects						
	Listing	16.2.1.1	Subject Disposition	All randomized subjects	16.2.1.1	
	Listing	16.2.1.2	Subject Disposition	Non-randomized subjects	16.2.1.2	
16.2.2 Protocol Deviations						
	Listing	16.2.2.1	Important Protocol Deviations	All randomized subjects	16.2.2.1	
	Listing	16.2.2.2	All Protocol Deviations	All randomized subjects	16.2.2.2	
16.2.3 Patients Excluded from the Efficacy Analysis						
	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	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Listing	16.2.4.3	Prior medications	All randomized subjects	16.2.4.3	
	Listing	16.2.4.4	Concomitant medications and significant non-drug therapies taken during treatment	All randomized subjects	16.2.4.4	
16.2.5 Compliance and/or Drug Concentration Data (if available)						
	Listing	16.2.5.1	Brushing Compliance	All randomized subjects	16.2.5.1	
	Listing	16.2.5.2	Supervised Brushing	All randomized subjects	16.2.5.2	
16.2.6 Individual Efficacy Response Data						
	Listing	16.2.6.1.1	MLSI (AxI) Score Data	All randomized subjects	16.2.6.1.1	
	Listing	16.2.6.1.2	Derived MLSI (AxI) Score Data	All randomized subjects	16.2.6.1.2	
	Listing	16.2.6.2	VITA Shade Score Data	All randomized subjects	16.2.6.2	
	Listing	16.2.6.3	VITA EasyShade color co-ordinates (L*, a*, b*, WI_D and Delta E*) score Data	All randomized subjects	16.2.6.3	
16.2.7 Adverse Event Listings						
	Listing	16.2.7.1	Adverse Events	All randomized subjects	16.2.7.1	Yes
	Listing	16.2.7.2	Adverse Events	Non-randomized subjects	16.2.7.1	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Listing	16.2.7.3	All Adverse Events Related to COVID-19	All randomized subjects	16.2.7.1	
	Listing	16.2.7.4	Incidents	All Randomized Subjects	16.2.7.4	Yes
16.2.8 Other Listings and Listing of Laboratory Measurements, when required by regulatory authorities (if applicable)						
	Listing	16.2.8.1	Oral Soft Tissue examination	All randomized subjects	16.2.8.1	
	Listing	16.2.8.2	Oral Hard Tissue examination	All randomized subjects	16.2.8.2	
16.4 Individual Subject Data Listings						
	NA					