STATISTICAL ANALYSIS PLAN

A 12-Week, Randomized, Controlled, Examiner-blind, Clinical Study to Evaluate the Efficacy of a Stannous Fluoride Toothpaste for the Relief of Dentine Hypersensitivity in a Chinese Population

Protocol Number: 300026

Phase: N/A

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan (Version 1.0)	05-May-2023	Not applicable (N/A)
Amendment 1 (Version 2.0)	26-Oct-2023	Minor amendment: In Section 4.4.2.2, the Tactile threshold is set to 90 g if it is recorded as >80 g at post baseline.

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Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
BDRM	Blind Data Review Meeting
CI	Confidence Interval
COVID-19	Coronavirus Disease of 2019
CRF	Case Report Form
CSPS	Calcium Sodium Phosphosilicate
DH	Dentine hypersensitivity
EAR	Erosion/Abrasion/Recession
eCRF	Electronic Case Report Form
ES	Effect Size
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Master Formulation Code
MGI	Modified Gingival Index
mITT	Modified Intent-To-Treat
MMRM	Mixed Model with Repeated Measures
MoH	Ministry of Health
N/A	Not Applicable
NaF	Sodium Fluoride
OHT	Oral hard tissue
OST	Oral soft tissue
PP	Per-Protocol
PT	Preferred Term
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SnF_2	Stannous fluoride
SOC	System Organ Class
TEAEs	Treatment Emergent Adverse Events
VAS	Visual Analogue Scale
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 300026 (version 3.0, dated 14-Feb-2023).

1 Summary of Key Protocol Information

Dentine hypersensitivity (DH) has been defined as 'pain derived from exposed dentine in response to chemical, thermal, tactile, or osmotic stimuli which can't be explained as arising from any other dental defect or disease'. The primary aetiological factors associated with the onset of DH include gingival recession and/or enamel loss (e.g., through dental erosion or abrasion), both result in exposure of dentine with patent dentinal tubules The hydrodynamic theory of DH hypothesizes that an external stimulus (e.g., a temperature/osmotic differential) applied to exposed dentine disrupts the movement of fluid within dentinal tubules. This disruption may stimulate nerve processes in the pulpal area of the dentine including irritation of odontoblasts, pulpal neurons, and even subodontoblastic blood vessels, resulting in the characteristic short, sharp pain of DH.

Currently there are two approaches to the management of DH: nerve depolarization or dentine tubule occlusion. Nerve depolarizing agents, typically potassium salts, generally require a period of use (e.g., 14 to 28 days) before their benefit is established. The delivery of potassium ions to the dentine-pulp junction (odontoblastic layer) *via* exposed dentine tubules is believed to result in depolarisation of the afferent nerve membrane thereby interrupting the pain response. The second approach uses occluding agents which act to physically block or narrow the exposed end of dentinal tubules (by the precipitation of insoluble materials onto the dentine surface and/or within dentinal tubules), thus reducing disruption to dentinal fluid movement in response to an external stimulus.

Stannous fluoride (SnF_2) has been incorporated into oral hygiene products indicated for the reduction of DH since the 1990s; it provides relief from DH by the occlusion of the dentine tubules through chemical precipitation of stannous oxides and hydroxides. Proctor and Gamble (P&G), Colgate and the sponsor market 0.454% SnF_2 toothpastes indicated for DH relief, with published evidence demonstrating longitudinal clinical efficacy.

1.1 Study Design

This will be a single center, 12-week, randomized, controlled, examiner-blind, 3 treatment arm, parallel group design, stratified (by maximum Baseline Schiff sensitivity score of the two selected test teeth) clinical study, investigating the clinical efficacy of a 0.454% SnF_2 toothpaste for the relief of DH in a Chinese population. A 5.0% w/w calcium sodium phosphosilicate (CSPS) toothpaste with clinically proven longer term DH efficacy in the Chinese population will be included in the study as a positive control. The clinical efficacy of both antisensitivity toothpastes (test and positive control) will be compared with that of a regular fluoride toothpaste (negative control), with no known anti-sensitivity properties.

Randomized subjects will be requested to brush their teeth twice daily (morning and evening) with their assigned study toothpaste for the duration of the 12-week treatment period. DH will be assessed at Screening, Baseline (Day 1), Week 6 and Week 12 using three clinical measures (an evaporative (air) stimulus with Schiff sensitivity score; a tactile stimulus with tactile threshold [g]; an evaporative (air) stimulus with Visual Analogue Scale (VAS) [mm]). Safety and oral tolerability of the study products will be monitored over the 12-week usage period by review of reported adverse events (AEs).

Table 1-1 presents the schedule of activities.

Table 1-1 Schedule of Activities

Procedure/Assessment	**Screening**		**Study Visits**		
	Visit 1		**Visit 2 Baseline** (Day 1)	**Visit 3 Week 6** (Day 43±4)	**Visit 4 Week 12** (Day 85±4)
Informed consent[1]	X				
Demographics	X				
Confirm WeChat application available on subject's mobile phone[2]	X				
DH screening questionnaire	X				
Confirm absence of anti-sensitivity ingredients & DH claims from subject's own oral care products	X				
Review subject's normal oral hygiene routine, specifically their rinsing habits	X	**Acclimatization Period** (14-28 Days)			
Medical history and prior/current medication/treatment review	X				
Changes in health and medications/treatments			X	X	X
Compliance checks - Check returned study supplies, review diary & evaluate compliance with twice daily use. - Check compliance with Lifestyle Guidelines/ Medication requirements.			X	X	X
Check brushing videos to confirm compliance with acclimatization toothpaste usage instructions			X		
Oral soft tissue (OST) examination	X		X	X	X
Oral hard tissue (OHT) examination	X				X

Procedure/Assessment	Screening		Study Visits		
	Visit 1		Visit 2 Baseline (Day 1)	Visit 3 Week 6 (Day 43±4)	Visit 4 Week 12 (Day 85±4)
Eligible teeth assessments (dentition exclusions, Erosion/Abrasion/Recession [EAR], Modified Gingival Index [MGI], clinical mobility)	X				
Qualifying tactile sensitivity assessment (tactile threshold (g)) for all eligible teeth [3,4]	X		X		
Qualifying evaporative (air) sensitivity assessments (Schiff sensitivity score, VAS) for all eligible teeth with a tactile threshold ≤ 20g [3,4]	X		X		
Identify all **eligible teeth which qualify for Baseline sensitivity assessments**: - No dentition exclusions - Presence of EAR - MGI = 0 adjacent to the test area only - Clinical mobility = 0 - Tactile threshold ≤ 20g - Schiff sensitivity score ≥ 2	X	**Acclimatization Period** (14-28 Days)			
Select two test teeth [5]			X		
Inclusion/exclusion criteria	X		X		
Subject eligibility	X		X		
Subject continuance				X	X
Dispense acclimatization toothpaste, toothbrush, rinsing cups, timer, and diary	X				
Supervised brushing with acclimatization toothpaste [6]	X				
Return to site with acclimatization toothpaste, toothbrush and completed diary			X		
Stratification and randomization			X		
Dispense study toothpaste, toothbrush, rinsing cups and diary			X		
Dispense toothbrush only				X	

Procedure/Assessment	Screening	Study Visits		
	Visit 1	Visit 2 Baseline (Day 1)	Visit 3 Week 6 (Day 43±4)	Visit 4 Week 12 (Day 85±4)
Supervised brushing with study toothpaste and reminder of product usage instructions [6,7]		X	X	
Return to site with study toothpaste, toothbrush and completed diary			X	X
Tactile sensitivity assessment (tactile threshold): Two test teeth only [5]			X	X
Evaporative (air) sensitivity assessment (Schiff sensitivity score, VAS): Two test teeth only [5]			X	X
Study conclusion				X
Monitor adverse events (AEs) [8]	X	X	X	X

Footnotes:

1. Study information will be communicated to the subjects by the investigator, or designee, and by interactive video. After signing the ICF, subjects will be asked to complete a knowledge check (a quiz).
   Subjects will also be shown a list of the ingredients contained in the test products to confirm they have no known allergies or hypersensitivity to any of the ingredients.
2. Send study information video (at Screening) and brushing instruction video (at Baseline) to subjects using WeChat.
3. Qualifying tactile threshold (g) and Schiff sensitivity scores can be recorded on paper source documents for later transcription into the electronic case report form (eCRF).
4. Prior to clinical examinations and assessments, subjects will be shown or reminded how to complete a VAS. Evaporative (air) assessments follow the tactile assessments, with minimum 5 minutes between last tactile assessment and first evaporative (air) assessment (to allow tooth recovery).

- **Visits 1 and 2:** maximum force for tactile assessments = 20g
- **Visits 3 and 4:** maximum force for tactile assessments = 80g

   The clinical examiner should communicate their Schiff sensitivity score to the scribe (non-verbally) before the subject completes the VAS. Examiner and subject should be blinded to each other's scores.
   VAS is a qualifying assessment at Baseline ONLY.

5. Test teeth must only be selected from eligible teeth (no dentition exclusions, presence of EAR, MGI = 0 adjacent to the test area only, clinical mobility = 0) with a tactile threshold ≤ 20 g and a Schiff sensitivity score ≥ 2 at both Screening and Baseline, and VAS ≥ 40 mm at Baseline.
   Test teeth must have the same Schiff sensitivity score at Screening and Baseline (i.e., Schiff sensitivity score = 2 at Screening and Baseline, **or** Schiff sensitivity score = 3 at Screening and Baseline**)**
6. Return study supplies to subject after supervised brushing.
7. **Subjects randomized to test toothpaste only:** Dispensing staff will show the subject the location of their two test teeth prior to supervised brushing.
8. Record AEs from signing of the informed consent form (ICF) until 5 days after last use of study product (or the last study procedure).

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 determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to an evaporative (air) stimulus (as measured by	Change from Baseline in Schiff sensitivity score at Week 12.

Objectives	Endpoints
Schiff sensitivity score), compared to a negative control toothpaste, after 12 weeks twice daily use.	
Secondary Objectives	**Secondary Endpoints**
Efficacy	
To determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to a tactile stimulus (as measured by tactile threshold), compared to a negative control toothpaste, after 12 weeks twice daily use.	Change from Baseline in tactile threshold (grams [g]) at Week 12.
To determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to an evaporative (air) stimulus (as measured by Visual Analogue Scale [VAS]), compared to a negative control toothpaste, after 12 weeks twice daily use.	Change from Baseline in VAS (millimeters [mm]) at Week 12.
To determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to evaporative (air) and tactile stimuli (as measured by Schiff sensitivity score/VAS and tactile threshold, respectively), compared to a negative control toothpaste, after 6 weeks twice daily use.	Change from Baseline in Schiff sensitivity score, tactile threshold (g) and VAS (mm) at Week 6.
To determine the clinical efficacy of a 5.0% w/w calcium sodium phosphosilicate (CSPS) toothpaste (positive control) in reducing DH to evaporative (air) and tactile stimuli (as measured by Schiff sensitivity score/VAS and tactile threshold, respectively), compared to a negative control toothpaste, after 6 and 12 weeks twice daily use.	Change from Baseline in Schiff sensitivity score and tactile threshold (g) and VAS (mm) at Week 6 and Week 12.
Safety	
To evaluate the safety and oral tolerability of the study toothpastes when used twice daily for 12 weeks.	Treatment emergent adverse events (TEAEs)

This study will be considered successful if there is a statistically significant difference between 0.454% SnF_2 and negative control by the primary efficacy variable, change from Baseline in Schiff sensitivity score at week 12.

1.3 Study Products

Table 1-3 presents the study products.

Table 1-3 Study Products

Product Description	Test Toothpaste	Reference Toothpaste (Positive Control)	Reference Toothpaste (Negative Control)
Product Name	0.454% w/w SnF_2 toothpaste (Sensodyne Sensitivity & Gum*)	5.0% w/w CSPS toothpaste (Sensodyne Repair & Protect*)	Regular Fluoride toothpaste (Crest Cavity Protection Fresh Lime*)
Fluoride Content	1100 ppm fluoride as SnF_2	1150 ppm fluoride as sodium fluoride (NaF)	1150 ppm fluoride as NaF
Pack Design	One carton containing 6 over-wrapped tubes of toothpaste		
Dispensing Details	Baseline (Visit 2): One carton		
Product Master Formulation Code (MFC)	CCI [redacted]	CCI [redacted]	N/A
Product Application	Dose the toothbrush with a strip of toothpaste (a ribbon of toothpaste across the full brush head) on each brushing occasion		
Route of Administration	Topical oral use		
Usage Instructions[#]	Brush the two test teeth first, then the whole mouth (all teeth) for 1-timed minute, twice daily (morning and evening). After brushing, rinse once with 10 ml water using the measuring cup provided.	Brush the whole mouth (all teeth) for 1-timed minute. After brushing, rinse once with 10 ml water using the measuring cup provided.	
Return Requirements	All used/unused samples to be returned.		

*Chinese commercial product
[#] After completing each toothbrushing, subjects will be permitted to clean their tongue using the toothbrush provided (but this is not a study requirement). Tongue brushing must be completed after toothbrushing but before rinsing with 10 ml water.

1.4 Sample Size Calculation

Sufficient subjects will be screened to randomize approximately 240 subjects to study treatment to ensure approximately 235 complete the study (approximately 94 subjects each for test toothpaste and negative control, and 47 subjects for positive control), allowing for 2% dropouts after randomization, as observed in previous clinical studies conducted in China.

The study will be powered sufficiently to demonstrate statistical superiority of the test toothpaste compared to the negative control for the change from Baseline in the Schiff sensitivity score after 12 weeks of treatment.

The true effect size is expected to be 0.5 (effect size (ES) = mean difference [test toothpaste – negative control] / pooled standard deviation [SD]; mean difference = 0.3, SD = 0.6). Such assumptions would also infer at least a 15% superior relative mean change from Baseline for the test toothpaste compared to the negative control (assuming mean change from a Baseline Schiff sensitivity score for negative control less than 2), a requirement of the Chinese MoH guidelines for the testing of functional (desensitising) toothpastes for at least one clinical DH measure (Ministry of Health (China), 2010).

With 94 subjects per group (for test toothpaste and negative control arms), there is 92.65% power to detect an effect size of 0.5 at the two-sided 5% significance level based on a two-sample t-test (using PASS software version 19.0.1).

Estimates of the above dropout rate and SD are based on results from three similar clinical studies (sponsor clinical studies: 205794, 208153, 216954).

The positive control has clinically proven longer-term DH efficacy in two clinical studies conducted in China on Chinese populations (sponsor clinical studies: CCI [redacted]) which satisfied the China MoH requirements (Ministry of Health (China), 2010). As such, it has been included in this study as a benchmark of performance in the Chinese population for 'study validation'; 47 subjects in the positive control group are deemed sufficient to demonstrate statistical superiority for positive vs. negative controls.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned.

2.2 Final Analyses

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

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

3 Considerations for data analyses and Data Handling Conventions

3.1 Baseline Definition

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

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

3.2 Subgroups/Stratifications

Subjects who satisfy 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 by the maximum Baseline Schiff sensitivity score of their two selected test teeth. The stratification factor will give rise to two strata.

- **Stratum 1:** Maximum Schiff sensitivity score = 2
- **Stratum 2:** Maximum Schiff sensitivity score = 3

Within each stratum, subjects will be randomized to test toothpaste, negative control, or positive control with 2:2:1 allocation ratio using permuted randomized blocks.

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 the Table 1-1 "Schedule of Activities". Any deviation from the study schedule may be reviewed on case-by-case basis at the Blind Data Review Meeting (BDRM) to determine whether the data should be excluded from the Per-Protocol (PP) population.

4 Data Analysis

Data analysis will be performed by CCI with oversight from GlaxoSmithKline Consumer Healthcare (GSK CH). 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 (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

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 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, and race), 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, and race), 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 categorized. Subjects with important protocol deviations liable to influence the efficacy outcomes will have affected data excluded from the PP population. Subjects may also be identified as having important protocol deviations not leading to exclusion of data from the PP population.

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

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

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

The number and percentage of subjects with at least one important protocol deviation, with at least one important protocol deviation not leading to exclusion from PP population (overall and by each deviation reason) and at least one important protocol deviation leading to exclusion from the PP population (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

Three 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*.	Demographics Safety

Population	Definition / Criteria	Analyses Evaluated
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.	Demographics Compliance 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 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.	Demographics Efficacy 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, with the reason for exclusion.

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

4.2 Subject Demographics and Other Baseline Characteristics

4.2.1 Demographic Characteristics

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

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

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

Number of expected brushings at visit X = 2 × Number of days between Visit 2 and Visit X.

Number of actual brushings = (Number of expected brushings) – (Number of missed brushings) + (Number of additional brushings).

% Compliance at 'Visit X' = (Number of actual brushings prior to Visit X / Number of expected brushings prior to Visit X) × 100.

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

Supervised study product brushings will also be summarized for the mITT population in Table 14.2.1.2 by visit. Supervised acclimatization product brushings at the Screening visit will be summarized for the mITT population in Table 14.2.1.3. 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. Supervised acclimatization product application (subject number, date of visit and time of supervised procedure) will be listed (Listing 16.2.5.3) for all randomized subjects.

4.3.2 Prior and Concomitant Medication

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

Prior medications and prior non-drug 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 safety population 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 safety population 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.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary efficacy variable is the change from Baseline in Schiff sensitivity score at 12 weeks, derived as the average score of the 2 test teeth (identified at Baseline). The change from Baseline is derived from the individual teeth first before calculating the average change of the 2 test teeth.

Descriptive statistics (n, missing, mean, SD, standard error [SE], median, minimum, and maximum) will be presented for Schiff sensitivity score calculated as the average score of the 2 test teeth at each assessment time point together with the change from Baseline in Table 14.2.2.1.1 for all subjects in the mITT population by study product. Raw means (± SE) of the Schiff sensitivity score at each time point will be plotted by study product in Figure 14.2.2.1.4 for all subjects in the mITT population.

Individual data for Schiff sensitivity 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 toothpaste and the negative control 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 Week 12:

- H_0: there is no difference between test product and negative control;
- H_1: there is a difference between test product and negative control;

Change from Baseline in Schiff sensitivity score will be analyzed using a Mixed Model with Repeated Measures (MMRM), with study product, visit and study product by visit interaction as fixed effects, and Baseline Schiff sensitivity score as a covariate. Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied (Kenward and Roger, 1997). If the model with unstructured covariance matrix does not converge then compound symmetry covariance matrix will be used.

Using the above model, adjusted mean change from Baseline, along with 95% confidence intervals (CIs) will be reported by study product. P-values testing for non-zero change from Baseline will be presented for all study products. Mean difference between study products at Week 12 (test toothpaste compared to negative control), 95% CIs and p-values will be provided for Schiff sensitivity score in Table 14.2.2.1.2. 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 non-parametric test (the Van Elteren test, adjusted for the randomization stratification) will be performed to assess change from Baseline comparisons (test toothpaste vs. negative control at Week 12) and the results will be provided to support the MMRM results. The non-parametric results will be considered confirmatory under the observation of strong violations of the assumptions.

4.4.1.3 Supportive Analyses

As a sensitivity analysis, the change from Baseline in Schiff sensitivity score at Week 12 will be compared between study products (test toothpaste vs. negative control) using an Analysis of Covariance (ANCOVA) model with study product as a fixed effect and Baseline Schiff sensitivity score as a covariate.

Using the above model, adjusted mean change from Baseline, along with 95% CIs will be reported by study product. P-values testing for non-zero change from Baseline will be presented for all study products. Mean difference between study products (test toothpaste vs. negative control), 95% CIs and p-values will be provided for Schiff sensitivity score in Table 14.2.2.1.3. Significance testing will be conducted at the two-sided 5% significance level.

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 (MMRM and ANCOVA) will be presented for the PP population in Table 14.2.2.2.1, Table 14.2.2.2.2 and Table 14.2.2.2.3, respectively.

4.4.2 Secondary Efficacy Endpoints

The mITT population will be considered as the primary population for efficacy analyses.

4.4.2.1 Change from Baseline in Schiff Sensitivity Score

The secondary efficacy variable is the change from Baseline in Schiff sensitivity score at Week 6 (for the comparisons between test product and negative control and between positive control and negative control) and Week 12 (for the comparison between positive control and negative control only), derived as the average score of the 2 test teeth (identified at Baseline). The change from Baseline is derived from the individual teeth first before calculating the average change of the 2 test teeth.

Individual data for Schiff sensitivity score will be listed for each subject by study product group and visit in Listing 16.2.6.1 for all randomized subjects.

4.4.2.1.1 Statistical Hypothesis, Model and Method of Analysis

Two comparisons will be considered for this secondary endpoint. Firstly, the comparison between the test toothpaste and the negative control at Week 6 in the mITT population. Secondly, the comparison between the positive control and the negative control at Week 6 and Week 12 in the mITT population.

1. Study product differences will be tested under the null hypothesis at Week 6:

- H_0: there is no difference between test product and negative control;
- H_1: there is a difference between test product and negative control;

2. Study product differences will be tested under the null hypothesis at Week 6 and Week 12:

- H_0: there is no difference between positive control and negative control;
- H_1: there is a difference between positive control and negative control;

The results for this endpoint will be obtained from the MMRM detailed in Section 4.4.1.2. The same statistics as presented for the Week 12 analysis for test toothpaste compared to negative control (see Section 4.4.1.2) will also be presented for the Week 6 analysis for test toothpaste compared to negative control, and for the Week 6 and Week 12 analysis for positive control compared to negative control in Table 14.2.2.1.2.

4.4.2.1.2 Supportive Analyses

As a sensitivity analysis, the change from Baseline in Schiff sensitivity score at Week 6 and Week 12 will be compared between study products (test toothpaste vs. negative control [Week 6] and positive control vs. negative control [Week 6 and 12]) using a separate ANCOVA model for each week with study product as fixed effect and Baseline Schiff sensitivity score as a covariate. The comparison for positive control vs. negative control at Week 12 will be obtained from the results of the same ANCOVA detailed in section 4.4.1.3.

Using the above model, adjusted mean change from Baseline, along with 95% CIs will be reported by study product. P-values testing for non-zero change from Baseline will be presented for all study products. Mean difference between study products (test toothpaste vs. negative control and positive control vs. negative control), 95% CIs and p-values will be provided for Schiff sensitivity score in Table 14.2.2.1.3. Significance testing will be conducted at the two-sided 5% significance level.

4.4.2.2 Change from Baseline in Tactile Threshold

The secondary efficacy variable is the change from Baseline in Tactile Threshold (g) at Week 6 and Week 12, derived as the average value of the 2 test teeth (identified at Baseline). The change from Baseline is derived from the individual teeth first before calculating the average change of the 2 test teeth. The teeth recorded as >80 g (for post baseline) will be set to 90g, in calculation of average tactile threshold (g) and change from Baseline.

Descriptive statistics (n, missing, mean, SD, SE, median, minimum, and maximum) will be presented for Tactile Threshold (g) calculated as the average score of the 2 test teeth at each assessment time point together with the change from Baseline in Table 14.2.3.1.1 for all subjects in the mITT population by study product. Raw means (± SE) of the Tactile Threshold (g) at each time point will be plotted by study product in Figure 14.2.3.1.4 for all subjects in the mITT population.

Individual data for Tactile Threshold (g) will be listed for each subject by study product group and visit in Listing 16.2.6.2 for all randomized subjects.

4.4.2.2.1 Statistical Hypothesis, Model and Method of Analysis

Two comparisons will be considered for this secondary endpoint. Firstly, the comparison between the test toothpaste and the negative control in the mITT population. Secondly, the comparison between the positive control and the negative control in the mITT population.

1. Study product differences will be tested under the null hypothesis at Week 6 and Week 12:

- H_0: there is no difference between test product and negative control;
- H_1: there is a difference between test product and negative control;

2. Study product differences will be tested under the null hypothesis at Week 6 and Week 12:

- H_0: there is no difference between positive control and negative control;
- H_1: there is a difference between positive control and negative control;

Change from Baseline in tactile threshold (g) will be analyzed using the same MMRM as the primary endpoint but with Baseline tactile threshold (g) as a covariate, rather than Baseline Schiff sensitivity score. In addition, the maximum Baseline Schiff sensitivity score of the two test teeth (2 or 3) will be fitted as a fixed effect.

Using the above model, adjusted mean change from Baseline, along with 95% CIs will be reported by study product. P-values testing for non-zero change from Baseline will be presented for both study products. Mean difference between study products, 95% CIs and p-values will be provided for Tactile Threshold (g) score in Table 14.2.3.1.2. 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 non-parametric test (the Van Elteren test, adjusted for the randomization stratification) will be performed to assess change from Baseline comparisons (test toothpaste vs. negative control and positive control vs. negative control at Weeks 6 and 12) and the results will be provided to support the MMRM results; the non-parametric results will be considered to supersede the MMRM results under the observation of strong violations of the assumptions.

4.4.2.2.2 Supportive Analyses

As a sensitivity analysis, the change from Baseline in tactile threshold (g) at Week 6 and Week 12 will be compared between study products (test toothpaste vs. negative control and positive control vs. negative control) using a separate ANCOVA model for each week with study product and the maximum Baseline Schiff sensitivity score of the two test teeth (2 or 3) as fixed effects and the Baseline tactile threshold (g) as a covariate.

Using the above models, adjusted mean change from Baseline, along with 95% CIs will be reported by study product. P-values testing for non-zero change from Baseline will be presented for all study products. Mean difference between study products, 95% CIs and p-values will be provided for Tactile Threshold (g) score in 14.2.3.1.3. Significance testing will be conducted at the two-sided 5% significance level.

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 (MMRM and ANCOVA) will be presented for the PP population in Table 14.2.3.2.1, Table 14.2.3.2.2 and Table 14.2.3.2.3, respectively.

4.4.2.3 Change from Baseline in Visual Analogue Scale

The secondary efficacy variable is the change from Baseline in VAS (mm) score at Week 6 and Week 12, derived as the average score or value, respectively, of the 2 test teeth (identified at Baseline). The change from Baseline is derived from the individual teeth first before calculating the average change of the 2 test teeth.

Descriptive statistics (n, missing, mean, SD, SE, median, minimum, and maximum) will be presented for VAS (mm) score calculated as the average score of the 2 test teeth at each assessment time point together with the change from Baseline in Table 14.2.4.1.1 for all subjects in the mITT population by study product. Raw means (± SE) of the VAS (mm) score at each time point will be plotted by study product in Figure 14.2.4.1.4 for all subjects in the mITT population.

Individual data for VAS (mm) will be listed for each subject by study product group and visit in Listing 16.2.6.3 for all randomized subjects.

4.4.2.3.1 Statistical Hypothesis, Model and Method of Analysis

Two comparisons will be considered for this secondary endpoint. Firstly, the comparison between the test toothpaste and the negative control in the mITT population. Secondly, the comparison between the positive control and the negative control in the mITT population.

1. Study product differences will be tested under the null hypothesis at Week 6 and Week 12:

- H_0: there is no difference between test product and negative control;
- H_1: there is a difference between test product and negative control;

2. Study product differences will be tested under the null hypothesis at Week 6 and Week 12:

- H_0: there is no difference between positive control and negative control;
- H_1: there is a difference between positive control and negative control;

Change from Baseline in VAS (mm) will be analyzed using the same MMRM as mentioned in Section 4.4.2.2.1 but with Baseline VAS (mm) as a covariate, rather than the Baseline tactile threshold (g).

Using the above model, adjusted mean change from Baseline, along with 95% CIs will be reported by study product. P-values testing for non-zero change from Baseline will be presented for both study products. Mean difference between study products, 95% CIs and p-values will be provided for VAS (mm) score in Table 14.2.4.1.2. 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 non-parametric test (the Van Elteren test, adjusted for the randomization stratification) will be performed to assess change from Baseline comparisons (test toothpaste vs. negative control and positive control vs. negative control at Weeks 6 and 12) and the results will be provided to support the MMRM results; the

non-parametric results will be considered to supersede the MMRM results under the observation of strong violations of the assumptions.

4.4.2.3.2 Supportive Analyses

As a sensitivity analysis, the change from Baseline in VAS (mm) at Week 6 and Week 12 will be compared between study products (test toothpaste vs. negative control and positive control vs. negative control) using the same ANCOVA models as mentioned in Section 4.4.2.2.2 but with Baseline VAS (mm) as a covariate, rather than the Baseline tactile threshold (g).

Using the above models, adjusted mean change from Baseline, along with 95% CIs will be reported by study product. P-values testing for non-zero change from Baseline will be presented for all study products. Mean difference between study products, 95% CIs and p-values will be provided for VAS (mm) score in Table 14.2.4.1.3. Significance testing will be conducted at the two-sided 5% significance level.

4.4.3 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.

MMRM analyses account for missing data using 'a missing at random' assumption, i.e., there is a systematic relationship between the propensity for missing values and the observed data, but not the missing data. Under such assumptions, MMRM is shown to provide unbiased estimates of the treatment effect, whilst the analysis of only complete cases using ANCOVA are biased (Baron et al, 2008; Ashbeck et al, 2016). Such complete case analysis requires a 'missing completely at random' assumption to remain unbiased and this is unlikely to hold, i.e., the fact that the data are missing is independent of the observed and unobserved data.

Using an MMRM, it will therefore be assumed that a subject with missing data at one post-Baseline visit would have obtained a similar efficacy result at that visit 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 will present results from the separate ANCOVA models using only non-missing values at each single time point. Additional sensitivity analyses may be added to the SAP prior to unblinding in case of high drop-out rates and/or exclusion from PP population.

4.4.4 Pharmacokinetic (Secondary)

Not applicable.

4.5 Analysis of Safety

All safety data will be reported for the Safety Population as per actual study product received. No treatment kit list is generated for this study; unblinded site monitors will review the kits dispensed to subjects against the randomized treatment, and protocol deviations will be recorded in the event of a dispensing error. Therefore, the actual study product 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.

4.5.1 Adverse Events and Serious Adverse Events

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

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

Treatment emergent adverse events (TEAEs) are defined as new AEs that occur on or after the first study product use at Baseline (Visit 2; 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 usage will be considered as non-treatment emergent. In case of misallocation, compared to the randomization schedule, TEAEs will be associated with the most recent study product received.

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 all AEs related to COVID-19 subject (Listing 16.2.7.3 for all screened 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 that there is nothing to report, a null table or listing will be produced.

4.5.2 Other Safety Variables

Other safety variables are listed below:

- OST examination

- OHT examination

4.5.2.1 OST Examination

The OST examination will be accomplished by direct observation and palpation, using retraction aids as appropriate, 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.

4.5.2.2 OHT Examination

The OHT examination will be accomplished by direct observation, using retraction aids as appropriate, and will identify enamel irregularities, tooth fractures, grossly carious lesions/gross decay, defective/faulty restorations (all direct & indirect restorations including fixed/removal prostheses), non-carious tooth surface loss (abrasion, attrition, abfraction and erosion), any other hard tissue irregularities (e.g., hypo/hypermineralisation, decalcification) and significant tooth staining. 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.

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, along with evidence of gross intra-oral neglect or the need for extensive dental therapy.

The OHT examination is also used to assess the dentition against the general and specific dentition exclusions.

OHT will be summarized (number of subjects and percentages of 'Absent', 'Present' or 'OST not examined') by visit and study product in Table 14.3.4.2 for all subjects in the Safety Population. OHT examination will be listed (Listing 16.2.8.2) for all randomized subjects.

4.6 Analysis of Other Variables

Not applicable.

5 Changes to the Protocol Defined Statistical Analysis Plan

Any changes from the originally planned statistical analysis specified in the protocol (Version 3.0, Dated: 14-FEB-2023) are outlined in Table 5-1.

Table 5-1 Changes to Protocol Defined Analysis Plan

Protocol	Statistical Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
12.3.3 Safety Analyses A listing of all AEs will be presented for all subjects in the Safety population.	**4.6.1 Adverse Events and Serious Adverse Events** AEs will be listed separately for all randomized subjects for non-randomized subjects.	For consistency with previous protocols, and to ensure that all AEs are listed.

Appendix 1: List of Data Displays

CSR Section	TLF	Number	Title	Population	Template	Topline
14.1 Demographic Data Summary Tables and Figures						
	Table	14.1.1	Subject Disposition	All Screened Subjects	14.1.1	Yes
	Table	14.1.2	Incidence of Important Protocol Deviations	All Randomized Subjects	14.1.2	
	Table	14.1.3.1	Demographic and Baseline Characteristics	Safety Population	14.1.3.1	
	Table	14.1.3.2	Demographic and Baseline Characteristics	mITT Population	14.1.3.1	Yes
	Table	14.1.3.3	Demographic and Baseline Characteristics	PP Population	14.1.3.1	
14.2 Efficacy Data Summary Tables and Figures						
	Table	14.2.1.1	Summary of Compliance	mITT Population	14.2.1.1	
	Table	14.2.1.2	Summary of Supervised Brushing (Investigational Product)	mITT Population	14.2.1.2	
	Table	14.2.1.3	Summary of Supervised Brushing (Acclimatization Product)	mITT Population	14.2.1.3	
	Table	14.2.2.1.1	Summary of Schiff Sensitivity Score of the 2 Test Teeth	mITT Population	14.2.2.1.1	Yes

CSR Section	TLF	Number	Title	Population	Template	Topline
	Table	14.2.2.1.2	Statistical Analysis of Change from Baseline in Schiff Sensitivity Score Over Time (MMRM)	mITT Population	14.2.2.1.2	Yes
	Table	14.2.2.1.3	Statistical Analysis of Change from Baseline in Schiff Sensitivity Score Over Time (ANCOVA Sensitivity Analyses)	mITT Population	14.2.2.1.3	
	Figure	14.2.2.1.4	Schiff Sensitivity Score by Visit and Study Product	mITT Population	14.2.2.1.4	
	Table	14.2.2.2.1	Summary of Schiff Sensitivity Score of the 2 Test Teeth	PP Population	14.2.2.1.1	
	Table	14.2.2.2.2	Statistical Analysis of Change from Baseline in Schiff Sensitivity Score Over Time (MMRM)	PP Population	14.2.2.1.2	
	Table	14.2.2.2.3	Statistical Analysis of Change from Baseline in Schiff Sensitivity Score Over Time (ANCOVA Sensitivity Analyses)	PP Population	14.2.2.1.3	
	Table	14.2.3.1.1	Summary of Tactile Threshold (g) of the 2 Test Teeth	mITT Population	14.2.2.1.1	Yes
	Table	14.2.3.1.2	Statistical Analysis of Change from Baseline in Tactile Threshold (g) Over Time (MMRM)	mITT Population	14.2.3.1.2	Yes

CSR Section	TLF	Number	Title	Population	Template	Topline
	Table	14.2.3.1.3	Statistical Analysis of Change from Baseline in Tactile Threshold (g) Over Time (ANCOVA Sensitivity Analyses)	mITT Population	14.2.3.1.3	
	Figure	14.2.3.1.4	Tactile Threshold (g) by Visit and Study Product	mITT Population	14.2.3.1.4	
	Table	14.2.3.2.1	Summary of Tactile Threshold (g) of the 2 Test Teeth	PP Population	14.2.2.1.1	
	Table	14.2.3.2.2	Statistical Analysis of Change from Baseline in Tactile Threshold (g) Over Time (MMRM)	PP Population	14.2.3.1.2	
	Table	14.2.3.2.3	Statistical Analysis of Change from Baseline in Tactile Threshold (g) Over Time (ANCOVA Sensitivity Analyses)	PP Population	14.2.3.1.3	
	Table	14.2.4.1.1	Summary of VAS (mm) of the 2 Test Teeth	mITT Population	14.2.2.1.1	Yes
	Table	14.2.4.1.2	Statistical Analysis of Change from Baseline in VAS (mm) Over Time (MMRM)	mITT Population	14.2.4.1.2	Yes
	Table	14.2.4.1.3	Statistical Analysis of Change from Baseline in VAS (mm) Over Time (ANCOVA Sensitivity Analyses)	mITT Population	14.2.4.1.3	
	Figure	14.2.4.1.4	VAS (mm) by Visit and Study Product	mITT Population	14.2.4.1.4	
14.3 Safety Data Summary Tables and Figures						

CSR Section	TLF	Number	Title	Population	Template	Topline
14.3.1 Displays of Adverse Events						
	Table	14.3.1.1	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	14.3.1.1	Yes
	Table	14.3.1.2	Treatment Emergent Adverse Events by Oral/Non-Oral and Preferred Term	Safety Population	14.3.1.2	
	Table	14.3.1.3	Treatment Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	14.3.1.1	
	Table	14.3.1.4	Treatment Related Treatment Emergent Adverse Events by Oral/Non-Oral and Preferred Term	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	Deaths	Safety Population	16.2.7.1	
	Listing	14.3.2.2	Non-Fatal Serious Adverse Events	Safety Population	16.2.7.1	
	Listing	14.3.2.3	Treatment Emergent Adverse Events Leading to Study or Product Discontinuation	Safety Population	16.2.7.1	
	Listing	14.3.2.4	Treatment Emergent Adverse Events Classified as Oral	Safety Population	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						
	N/A					
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	Summary of Oral Hard Tissue Examination	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	
16.1.9 Documentation of Statistical Methods						
	Raw Output	16.1.9.1	Statistical Analysis of Change from Baseline in Schiff Sensitivity Score Over Time (Reference Table 14.2.2.1.2)	mITT Population	SAS Output	Yes
	Raw Output	16.1.9.2	Statistical Analysis of Change from Baseline in Schiff Sensitivity Score Over Time (Reference Table 14.2.2.2.2)	PP Population	SAS Output	
	Raw Output	16.1.9.3	Statistical Analysis of Change from Baseline in Schiff Sensitivity Score Over	mITT Population	SAS Output	

CSR Section	TLF	Number	Title	Population	Template	Topline
			Time (Sensitivity Analysis) (Reference Table 14.2.2.1.3)			
	Raw Output	16.1.9.4	Statistical Analysis of Change from Baseline in Schiff Sensitivity Score Over Time (Sensitivity Analysis) (Reference Table 14.2.2.2.3)	PP Population	SAS Output	
	Raw Output	16.1.9.5	Statistical Analysis of Change from Baseline in Tactile Threshold (g) Over Time (Reference Table 14.2.3.1.2)	mITT Population	SAS Output	Yes
	Raw Output	16.1.9.6	Statistical Analysis of Change from Baseline in Tactile Threshold (g) Over Time (Reference Table 14.2.3.2.2)	PP Population	SAS Output	
	Raw Output	16.1.9.7	Statistical Analysis of Change from Baseline in Tactile Threshold (g) Over Time (Sensitivity Analysis) (Reference Table 14.2.3.1.3)	mITT Population	SAS Output	
	Raw Output	16.1.9.8	Statistical Analysis of Change from Baseline in Tactile Threshold (g) Over Time (Sensitivity Analysis) (Reference Table 14.2.3.2.3)	PP Population	SAS Output	
	Raw Output	16.1.9.9	Statistical Analysis of Change from Baseline in VAS (mm) Over Time (Reference Table 14.2.4.1.2)	mITT Population	SAS Output	Yes

CSR Section	TLF	Number	Title	Population	Template	Topline
	Raw Output	16.1.9.10	Statistical Analysis of Change from Baseline in VAS (mm) Over Time (Sensitivity Analysis) (Reference Table 14.2.4.1.3)	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 and Baseline Characteristics	All Randomized Subjects	16.2.4.1	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Listing	16.2.4.2	Medical History and Current Medical Conditions	All Randomized Subjects	16.2.4.2	
	Listing	16.2.4.3	Prior Medications	Safety Population	16.2.4.3	
	Listing	16.2.4.4	Concomitant Medications and Significant Non-Drug Therapies	Safety Population	16.2.4.4	
16.2.5 Compliance and/or Drug Concentration Data (if available)						
	Listing	16.2.5.1	Study Product Compliance	All Randomized Subjects	16.2.5.1	
	Listing	16.2.5.2	Study Product Supervised Brushing	All Randomized Subjects	16.2.5.2	
	Listing	16.2.5.3	Acclimatization Product Supervised Brushing	All Randomized Subjects	16.2.5.3	
16.2.6 Individual Efficacy Response Data						
	Listing	16.2.6.1	Schiff Sensitivity Data for the Two Test Teeth	All Randomized Subjects	16.2.6.1	
	Listing	16.2.6.2	Tactile Threshold (g) Data for the Two Test Teeth	All Randomized Subjects	16.2.6.2	
	Listing	16.2.6.3	VAS (mm) Data for the Two Test Teeth	All Randomized Subjects	16.2.6.3	
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 Subjects	16.2.7.1	
	Listing	16.2.7.3	All Adverse Events Related to COVID-19	All Screened 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 Results)	All Randomized Subjects	16.2.8.1.1	
	Listing	16.2.8.1.2	Oral Soft Tissue Examination (Abnormal Results)	All Randomized Subjects	16.2.8.1.2	
	Listing	16.2.8.2	Oral Hard Tissue Examination	All Randomized Subjects	16.2.8.2	
16.4 Individual Subject Data Listings						
	NA					