# STATISTICAL ANALYSIS PLAN

## A Randomized, Single-Blind Clinical Study Assessing the Effects of an Experimental Dentifrice Compared to a Regular Fluoride Dentifrice on Breath Odor When Used Twice Daily for 3 Weeks in a Population with Clinically Diagnosed Gingivitis

**Protocol Number:** 300025

**Phase:** N/A

This document contains confidentiality statements that are not relevant for this publicly available version

## Document History

| Document | Version Date | Summary of Changes (New analysis or Change in planned analysis) |
|---|---|---|
| Original Analysis Plan | 06-OCT-2022 | Not applicable (N/A) |

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# Abbreviations

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| BDRM | Blinded Data Review Meeting |
| CIs | Confidence Intervals |
| COVID-19 | Coronavirus Disease of 2019 |
| CRF | Case Report Form |
| CV | Coefficient of Variation |
| GSKCH | GlaxoSmithKline Consumer Healthcare |
| ICF | Informed Consent Form |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MFC | Master Formulation Code |
| mITT | Modified Intent-To-Treat |
| N/A | Not Applicable |
| OHT | Oral Hard Tissue |
| OST | Oral Soft Tissue |
| PP | Per-Protocol |
| ppb | parts per billion |
| PT | Preferred Term |
| SAEs | Serious Adverse Events |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SE | Standard Error |
| SOC | System Organ Class |
| TEAEs | Treatment Emergent Adverse Events |
| VSC | Volatile Sulphur Compound |
| WHODD | World Health Organization Drug Dictionary |

The purpose of this Statistical Analysis Plan is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 300025 (Version 2.0, dated 17-Sep-2022).

# 1 Summary of Key Protocol Information

This will be a single center, single blind (to the examiners undertaking the oral malodor assessments), randomized (stratified by the subject's sex), controlled, two arm parallel study in volunteers with clinically diagnosed gingivitis and oral malodor. The study will evaluate the clinical efficacy of an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride to reduce oral malodor after 3 weeks of twice-daily use compared to a regular reference dentifrice.

Potential subjects will attend a screening visit to determine their suitability to participate having abstained from oral hygiene procedures and food consumption for at least 8 hours. Having obtained their written informed consent, relevant details of their medical history and current medications will be recorded, followed by the screening assessment of their oral malodor.

Subjects will then undergo oral soft tissue (OST) and oral hard tissue (OHT) examinations, and a gingivitis assessment (bleeding on probing examination). Subjects with sufficient gingivitis and sufficient concentration of hydrogen sulfide in their breath as per the inclusion criteria, as well as meeting all other study criteria, will be considered as eligible to proceed, appointed for baseline assessments and dispensed a washout dentifrice and toothbrush to use instead of their regular oral hygiene products until they return for Visit 2 (1-3 weeks after screening). A washout diary will also be dispensed for the subjects to record their washout product usage.

At the Baseline visit (Visit 2) subjects, having abstained from oral hygiene procedures and food consumption for at least 8 hours, will undergo baseline breath Volatile Sulphur Compound (VSC) (using the OralChroma instrument) and organoleptic assessments (judged by a panel of 3 assessors using the hedonic scale of Rosenberg. The organoleptic panel will have been recently calibrated and standardized (within the past year) with a kappa statistic of ≥0.6 per the American Dental Association guidelines.

Qualifying subjects, having a hedonic score ≥2 and a mean concentration of hydrogen sulfide (a major contributor to oral malodor) in their breath of at least 150ppb, will be stratified by the subject's sex and randomized to one of the 2 study treatments. Subjects will be instructed on the use of their study products and subject diary and will brush their teeth, under supervision, for 1 timed minute with their assigned dentifrice. One hour (±5 minutes) post brushing, subjects will have their post-brushing breath VSC and organoleptic assessments, followed by an OST examination. Subjects will be instructed to brush twice daily (for 1 minute, morning and evening) with their assigned study dentifrice for the next 3 weeks (+ 2 days) until their next visit (Visit 3).

At Visit 3, subjects, having abstained from oral hygiene procedures and food consumption for at least 8 hours will undergo pre- and post-brushing evaluation of breath VSCs and hedonic

scores in the same manner as performed at the Baseline visit. Following all breath odor assessments subjects will undergo OST and OHT examinations and exit the study.

Safety and oral tolerability of the study products will be monitored over the 3-week usage period by review of reported AEs.

## 1.1 Study Design

This will be a single center, single blind (to the examiners undertaking the oral malodor assessments), randomized (stratified by subject's sex), controlled, two arm parallel study in volunteers with clinically diagnosed gingivitis. The study will evaluate the clinical efficacy of an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride to reduce oral malodor after 3 weeks of twice-daily use compared to a regular reference dentifrice.

Potential subjects will attend a screening visit to determine their suitability to participate. Having obtained their written informed consent, relevant details of their medical history and current medications will be recorded. Subjects will then undergo the screening assessment of their oral malodor followed by OST and OHT examinations and assessments of gingivitis (Bleeding on probing examination). Subjects with gingivitis and oral malodor per the inclusion criteria, as well as meeting all other study criteria, will be considered as eligible to proceed, appointed for baseline assessments and dispensed a washout dentifrice and toothbrush to use instead of their regular oral hygiene products until they return for Visit 2 (1-3 weeks after screening).

At the Baseline visit (Visit 2), subjects, having abstained from oral hygiene procedures and food consumption for at least 8 hours, will undergo baseline breath VSC and organoleptic assessments. Qualifying subjects will be stratified by the subject's sex and randomized to one of the two study treatments. Subjects will then be instructed on the use of their study products and will brush their teeth, under supervision, for 1 timed minute with their assigned dentifrice. One hour (±5 minutes) post brushing, subjects will have their post-brushing breath VSC and organoleptic assessments. Subjects will then undergo an OST examination and instructed to brush twice daily (for 1 minute, morning and evening) with their assigned study dentifrice for the next 3 weeks until their next visit (Visit 3).

At Visit 3, subjects, having abstained from oral hygiene procedures and food consumption for at least 8 hours will undergo pre- and post-brushing evaluation of breath VSCs and organoleptic scores in the same manner as performed at the Baseline visit. Subjects will then undergo OST and OHT examinations and exit the study.

Table 1-1 presents the schedule of activities.

**Table 1-1 Schedule of Activities**

| Procedure/Assessment | Screening | Wash-out period of at least 7 days (maximum 21 days) | Study Period | 3 Weeks (+2 days) | |
|---|---|---|---|---|---|
| | Visit 1 | | Visit 2 Baseline | | Visit 3 Week 3 |
| Informed consent | X | | | | |
| Demographics | X | | | | |
| Medical history | X | | | | |
| Current/prior/concomitant medication review | x | | x | | x |
| Screening assessment of oral malodor | x | | | | |
| OST examination | x | | x | | x |
| OHT examination | x | | | | x |
| Bleeding on probing assessment | x | | | | |
| Review of inclusion/exclusion criteria | x | | x | | |
| Subject eligibility | x | | x | | |
| Dispense wash-out dentifrice, toothbrush and diary | x | | | | |
| Subject returns wash-out dentifrice and toothbrush | | | x | | |
| Pre-brushing assessment of oral malodor[2] | | | x | | x |
| Subject continuance | | | | | x |
| Stratification and randomization | | | x | | |
| Dispense study products, and sundry items with instruction in proper use | | | x | | |
| Supervised brushing | | | x | | x |
| Post-brushing assessment of oral malodor[3] | | | x | | x |
| Return study products and diary | | | | | x |
| Adverse events review[1] | x | | x | | x |
| Medical device incidents review[1] | | | x | | x |
| Study conclusion | | | | | x |

Abbreviations: OST: Oral Soft Tissue, OHT: Oral Hard Tissue, VSC: Volatile Sulfur Compound

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). Medical device in this study is the supplied toothbrush.
2. At Visits 2&3, pre-brushing breath VSC-determination (by OralChroma) and organoleptic assessments will be performed with subjects having not brushed their teeth and not eaten for at least 8 hours.
3. Post-brushing breath VSC-determination (by OralChroma) and organoleptic assessments will be performed 1 hour (±5 minutes) after supervised brushing.

## 1.2 Study Objectives

| Objectives | Endpoints |
|---|---|
| **Primary Objective** | **Primary Endpoint** |
| To evaluate and compare the change in morning oral malodor by an organoleptic assessment following 3 weeks of twice-daily tooth brushing using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice. | Change in mean organoleptic score from Baseline (pre-brushing) to 3 weeks (pre-brushing) |
| **Secondary Objectives** | **Secondary Endpoints** |
| **Efficacy** | |
| To evaluate and compare the change in morning oral malodor by VSC determination following 3 weeks of twice-daily tooth brushing using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice. | Change from Baseline (pre-brushing) to 3 weeks (pre-brushing) in:<br>• Mean total VSC concentration in breath.<br>• Mean hydrogen sulfide, methanethiol and<br>• dimethyl sulfide concentration in breath. |
| To evaluate and compare the change in oral malodor post brushing following 3 weeks of twice-daily tooth brushing using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice. | Change from Baseline (pre-brushing) to 3 weeks (1 hour post-brushing) in:<br>• Mean total VSC concentration in breath.<br>• Mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath<br>• Mean breath organoleptic scores. |
| To evaluate and compare the change in oral malodor 1 hour post brushing at Baseline, and 1 hour post brushing following 3 weeks twice-daily use using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice. | Change from pre-brushing to 1 hour post brushing at Baseline and after 3 weeks in:<br>• Mean total VSC concentration in breath.<br>• Mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath.<br>• Mean breath organoleptic scores. |
| **Safety** | |
| To assess the tolerability of an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride | • Treatment emergent adverse events |

This study will be considered successful if the experimental dentifrice containing stannous fluoride and zinc chloride demonstrates statistically significant greater reduction in total breath VSC compared to the reference dentifrice following 3 weeks of twice daily brushing.

## 1.3 Treatments

Table 1-2 presents the study products.

**Table 1-2 Investigational/Study Product Supplies**

| Product Description | Experimental Dentifrice | Reference Dentifrice |
|---|---|---|
| | 0.454% Stannous Fluoride dentifrice with 0.3% Zinc Chloride | Regular Fluoride Dentifrice |
| **Product Name** | N/A | Crest Cavity Protection (US Market Product) |
| **Pack Design** | One carton containing 2 overwrapped tubes of dentifrice | |
| **Dispensing Details** | Visit 2 (Baseline): 1 carton | |
| **Product Master Formulation Code (MFC)** | CCI [redacted] | N/A |
| **Dose/Product Application** | Subjects will dose the toothbrush provided with a ribbon of paste to cover the brush head (a full brush head) on each brushing occasion | |
| **Route of Administration** | Oral topical use | |
| **Usage Instructions** | Subjects will brush twice daily (morning and evening) for 1 timed minute with their allocated product. | |
| **Return Requirements** | Used and unused study product to be returned to the sponsor. | |

Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction which will be provided by the sponsor during the study in time for study close out visit.

## 1.4 Sample Size Calculation

Sufficient subjects will be enrolled to randomize approximately 106 subjects to have at least 100 complete the study (at least 50 subjects per treatment arm). It is considered sufficient to have 100 subjects complete in this study to meet the study's objectives. The subjects will be stratified by their sex prior to randomization. Existing GSKCH studies were referred to for information and data to enable calculation of an appropriate power and sample size however no relevant information was observed for a 3-week study in a gingivitis population as planned for this study.

Data from a published study that evaluated halitosis in subjects with gingivitis and periodontitis was taken into consideration to provide information regarding the variability and sample size for this endpoint. The sample size in this literature was N=116 for the gingivitis population and the variability estimate was observed to be 0.46 for the organoleptic score. The scoring was on a 5-point scale with very similar descriptors to those to be used in this study however only one assessor was used for organoleptic score assessment (as opposed to 3 assessors which will be used in this study). Considering the number of assessors in this study, the standard deviation (SD) was estimated to be 0.265 (0.46/sqrt(3)).

Using the SD of 0.265, for 50 subjects per arm (100 subjects completing the study) the detectable mean difference is estimated to be 0.15 for 80% power and alpha=0.05.

# 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.

For secondary endpoints VSC and Organoleptic score, analysis is based on two baselines. One is as mentioned above Day 0 (Pre-brushing) and other is Week 3 (Pre-brushing).

## 3.2 Subgroups/Stratifications

Qualifying subjects will be stratified by the subject's sex and randomized to one of the two study treatments.

Two factors will be:

- Male
- Female

## 3.3 Centers Pools

Since this is a 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) population.

# 4 Data Analysis

Data analysis will be performed by PPD 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 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 also 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 use) + 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), enrolled [Yes or No], 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 be excluded from the PP population. Subjects may also be identified as having important protocol deviations not leading to exclusion from the PP population.

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

- Consent procedures
- Inclusion/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, important protocol deviations not leading to exclusion from PP population with reasons for deviations and subjects with important protocol deviations leading to exclusion from the PP population with reasons for deviations will be presented by study product and overall (Table 14.1.2) and listed in Listing 16.2.2.1.

All protocol deviations collected on the protocol deviation case report form (CRF) 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. | Safety |

| Population | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| | Any subject who receives a randomization number will be considered to have been randomized.<br>This population will be based on the treatment the subject actually received. | |
| Modified Intent-To-Treat (mITT) | Comprise all randomized subjects who complete at least one use of study product and have at least one post treatment efficacy assessment.<br>Any subject who receives a randomization number will be considered to have been randomized.<br>This population will be based on the study product to which the subject was randomized. | Demographic<br>Baseline Characteristics<br>Efficacy Analysis |
| Per-Protocol | Comprise all subjects in the mITT population who have at least one assessment of efficacy considered unaffected by protocol violations.<br>Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1.2 (Protocol Deviations).<br>This population will be based on the study product to which the subject was randomized. | Efficacy Analysis |

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 primary endpoint 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).

## 4.2 Subject Demographics and Other Baseline Characteristics

### 4.2.1 Demographic Characteristics

Descriptive statistics (number of subjects [n], mean, SD, median, minimum, and maximum for continuous variables and frequency count [n] and percentage [%] of subjects for categorical variables) will be presented for demographic variables by study product and overall. These variables include age, gender, race, and ethnicity 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 over 3 weeks.

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 3 – 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 3 – 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, supervised brushing completed? [Yes or No] and, date and start time of the supervised procedure/brushing) will be listed (Listing16.2.5.2) 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.

### 4.4.1 Primary Efficacy Endpoint

#### 4.4.1.1 Primary Efficacy Endpoint Definition

The primary endpoint for the study is the change in mean breath organoleptic score from Baseline (pre-brushing) to 3 weeks (pre-brushing) and the comparison between the Experimental and Reference Dentifrices in the mITT population.

Descriptive statistics (n, mean, SD, standard error [SE], median, minimum, and maximum) will be presented for mean breath organoleptic score at each assessment time point in Table 14.2.2.1.1 for all subjects in mITT population by study product. Raw means (± SE) of the mean breath organoleptic score at each time point will be plotted by study product in Figure 14.2.1.1 for all subjects in mITT population.

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

#### 4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

Study product differences will be tested under the null hypothesis:

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

The following study product comparisons will be analyzed:

- Experimental Dentifrice versus Reference Dentifrice

An Analysis of Covariance (ANCOVA) model will be used to analyze the change in mean breath organoleptic score from baseline (pre-brushing) to week 3 (pre-brushing) with study product and gender as fixed effects and the mean baseline (pre-brushing) breath organoleptic score as a covariate. The least square means for each study product will be presented based on observed margins and used to test for < 0 change from baseline. The difference between least square means for the Experimental Dentifrice compared to the Reference Dentifrice will be presented and used to test for a difference between products. The two-sided p-values and 95%

confidence intervals (CIs) will be provided. This will be assessed at the two-sided 5% significance level.

Using the above model, adjusted mean change from baseline, along with 95% CIs will be reported by study product group and will be provided for mean breath organoleptic score in Table 14.2.2.2.1. Also, p-values testing for negative 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 mean breath organoleptic score in Table 14.2.2.2.1. This will be assessed at the two-sided 5% significance level.

The assumption of normality and homogeneity of variance in the ANCOVA will be investigated. In case of violation of these assumptions, a suitable nonparametric test (the Van Elteren test, adjusted for gender) will be performed, and results will be provided to support the ANCOVA results. If the inferences from the two analyses are similar, then both sets of results will be reported and emphasis will be made on the ANCOVA results. In case of discrepancies between inferences of the ANCOVA and non-parametric analysis, results will be drawn from the non-parametric analysis.

#### 4.4.1.3 Supportive Analyses

A PP analysis will be performed on the Change in mean organoleptic score from Baseline (pre-brushing) to 3 weeks (pre-brushing) 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 breath organoleptic score endpoints will be presented for the PP Population in Table 14.2.2.1.2. Statistical analysis of mean breath organoleptic score will be presented for the PP population in Table 14.2.2.2.2. In addition, the mean breath organoleptic score (Figure 14.2.1.2) at each time point will be plotted by study product for all subjects in PP Population.

### 4.4.2 Secondary Efficacy Variables

All secondary endpoint analyses will be performed on the mITT population. There will be no adjustment for multiplicity in the analyses described in this section.

Secondary efficacy endpoints are:

- Mean total VSC concentration in breath.
- Mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath.
- Mean breath organoleptic scores.

Secondary efficacy variables are defined as:

- Change from baseline (pre-brushing) to 3 weeks (pre-brushing) in mean total VSC concentration in breath.

- Change from baseline (pre-brushing) to 3 weeks (pre-brushing) in mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath.
- Change from baseline (pre-brushing) to 3 weeks (1 hour post-brushing) in mean total VSC concentration in breath.
- Change from baseline (pre-brushing) to 3 weeks (1 hour post-brushing) in mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath.
- Change from baseline (pre-brushing) to 3 weeks (1 hour post-brushing) in mean breath organoleptic scores.
- Change from pre-brushing to 1 hour post brushing at Baseline and after 3 weeks in mean total VSC concentration in breath.
- Change from pre-brushing to 1 hour post brushing at Baseline and after 3 weeks in mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath.
- Change from pre-brushing to 1 hour post brushing at Baseline and after 3 weeks in mean breath organoleptic scores.

#### 4.4.2.1 Secondary Efficacy Variable 1

Mouth air VSC determination will be performed pre- and 1 hour (±5 minutes) post-brushing at Visits 2&3. The mouth air sample will be evaluated using the OralChroma Halitosis Measuring instrument (Model CHM-2 [Nissha FIS, Inc.; Osaka, Japan]) in agreement with the manufacturer's instructions. The OralChroma is a portable gas chromatograph with a highly sensitive semiconductor gas detector which can determine the concentration of the 3 main VSCs in breath (hydrogen sulfide, methane thiol and dimethyl sulfide).

There will be individual evaluations of hydrogen sulfide, methanethiol and dimethyl sulfide concentrations in breath taken at each visit (Baseline and Week 3) at each time point (pre-brushing /1-hour post-brushing).

The Total VSC at a visit/time point will have two samples and will be derived as the sum of the hydrogen sulfide, methanethiol and dimethyl sulfide concentrations in breath and then the mean over two samples to derive one value used for analysis per visit/timepoint. The sum and the average will be performed on the raw scale and final value will be transformed.

For each concentration (hydrogen sulfide, methanethiol, dimethyl sulfide, Total VSC), there will be two samples and will be considered as average of two samples before the result are log (base 10) transformed for analysis purpose.

The raw and logged concentration descriptive statistics (n, mean, SD, SE, Geometric mean, Geometric SD, Geometric coefficient of variation(CV), median, minimum, and maximum) will be presented for change from baseline (for each type of baseline detailed below) in each concentration (hydrogen sulfide, methanethiol, dimethyl sulfide, Total VSC) at each assessment time point in, respectively, (Table 14.2.3.1.1, Table 14.2.3.1.2, Table 14.2.3.1.3, Table 14.2.3.1.4 respectively). for all subjects in mITT Population by study product. Raw means (±

SE) of each concentration (hydrogen sulfide, methanethiol, dimethyl sulfide, Total VSC) at each time point will be plotted by study product respectively in Figure 14.2.2.1 for all subjects in mITT population.

Individual concentration data for each concentration parameter (hydrogen sulfide, methanethiol, dimethyl sulfide, Total VSC) will be listed for each subject by visit and study product group in Listing 16.2.6.2 for all randomized subjects.

#### 4.4.2.1.1 Statistical Hypothesis, Model and Method of Analysis

Study product differences will be tested under the null hypothesis:

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

The following study product comparisons will be analyzed:

- Experimental Dentifrice versus Reference Dentifrice

The ANCOVA models described below will be applied for each of the mean concentrations using a different definition of Baseline and post-baseline as follows:

- Baseline = Baseline (pre-brushing), Post-baseline = Week 3 (pre-brushing)
- Baseline = Baseline (pre-brushing), Post-baseline = Week 3 (1-hour post-brushing)
- Baseline = Baseline (pre-brushing), Post-baseline = Baseline (1-hour post-brushing)
- Baseline = Week 3 (pre-brushing), Post-baseline = Week 3 (1-hour post-brushing)

All concentration values will be log (base 10) transformed including baseline for each parameter. The corresponding change from baseline in the logged value will be analyzed for each postbaseline concentration (hydrogen sulfide, methanethiol, dimethyl sulfide, Total VSC) using an ANCOVA model with study product and gender as fixed effects and the respective logged mean Baseline concentration as a covariate. The least square means for each study product will be based on observed margins to test for < 0 change (on the logged scale) from baseline. The difference between least square means for the Experimental Dentifrice compared to the Reference Dentifrice will be used to test for a difference between products. As well as presenting the least square means and differences on the log scale, the corresponding back transformed values (antilog base 10) will be presented to represent percent reduction from baseline and percent difference from control relative to baseline. The two-sided p-values and 95% CIs (logged and back-transformed) will be provided.

Using the above model for each of the definition mentioned above, adjusted mean change [log (base 10)-based] from each baseline and percent reduction (back-transformed) from each baseline, along with corresponding 95% CIs will be reported by study product group will be provided for each concentration parameters (hydrogen sulfide, methanethiol, dimethyl sulfide, Total VSC) respectively in Table 14.2.3.2.1, Table 14.2.3.2.2, Table 14.2.3.2.3, Table 14.2.3.2.4 (with baseline as Day 0 pre-brushing) and respectively in Table 14.2.3.3.1, Table 14.2.3.3.2, Table 14.2.3.3.3, Table 14.2.3.3.4 (with baseline as Week 3 pre-brushing). Also, p-

values testing for negative change from baseline will be presented for study product groups. Mean difference between study product groups [Log (base 10) based], percent difference (back-transformed) from control relative to each baseline, corresponding 95% CIs and p-values will be provided for each concentration parameters (hydrogen sulfide, methanethiol, dimethyl sulfide, Total VSC) respectively in Table 14.2.3.2.1, Table 14.2.3.2.2, Table 14.2.3.2.3, Table 14.2.3.2.4 (with baseline as Day 0 pre-brushing) and respectively in Table 14.2.3.3.1, Table 14.2.3.3.2, Table 14.2.3.3.3, Table 14.2.3.3.4 (with baseline as Week 3 pre-brushing). This will be assessed at the two-sided 5% significance level.

The assumption of normality and homogeneity of variance in the above described ANCOVA analyses will not be investigated, because the analysis will be performed on log (base 10) transformed data.

#### 4.4.2.2 Secondary Efficacy Variable 2

Secondary endpoint is the change in mean breath organoleptic score:

At following Baseline and post-baseline definitions:

- Baseline = Baseline (pre-brushing), Post-baseline = Week 3 (1-hour post-brushing)
- Baseline = Baseline (pre-brushing), Post-baseline = Baseline (1-hour post-brushing)
- Baseline = Week 3 (pre-brushing), Post-baseline = Week 3 (1-hour post-brushing)

Descriptive statistics (n, mean, SD, SE, median, minimum, and maximum) will be presented for mean breath organoleptic score at each assessment time point in Table 14.2.2.1.1 for all subjects in mITT population by study product. Raw means (± SE) of the mean breath organoleptic score at each time point will be plotted by study product in Figure 14.2.1.1 for all subjects in mITT population.

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

##### 4.4.2.2.1 Statistical Hypothesis, Model and Method of Analysis

Study product differences will be tested under the null hypothesis:

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

The following study product comparisons will be analyzed:

- Experimental Dentifrice versus Reference Dentifrice

A similar ANCOVA model as used for the primary analysis (as described in Section 4.4.1.2) will be used but with the appropriate pre-brushing and post-baseline result used accordingly.

Using the above model for each of the definition mentioned above, adjusted mean change from each baseline, along with 95% CIs will be reported by study product group will be provided for mean breath organoleptic score in Table 14.2.4.1 (with baseline as Day 0 pre-brushing) and

Table 14.2.4.2 (with baseline as Week 3 pre-brushing). Also, p-values testing for negative 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 mean breath organoleptic score in Table 14.2.4.1 (with baseline as Day 0 pre-brushing) and Table 14.2.4.2 (with baseline as Week 3 pre-brushing). This will be assessed at the two-sided 5% significance level.

The assumption of normality and homogeneity of variance in the ANCOVA will be investigated. In case of violation of these assumptions, a suitable nonparametric test (the Van Elteren test, adjusted for gender) will be performed, and results will be provided to support the ANCOVA results. If the inferences from the two analyses are similar, then both sets of results will be reported and emphasis will be made on the ANCOVA results. In case of discrepancies between inferences of the ANCOVA and non-parametric analysis, results will be drawn from the non-parametric analysis.

### 4.4.3 Handling of Missing Values/Censoring/Discontinuations

All missing data for primary and secondary endpoints will be treated as missing data and not imputed. In the event that one of the hydrogen sulfide, methanethiol or dimethyl sulfide concentrations are missing then the Total VSC will also be treated as missing.

For analysis of VSC, if there is case when any individual concentration value is 0, it will be imputed as 0.01 for log (base 10) transformed analysis. For summary of raw data, 0 values will be considered as is.

## 4.5 Analysis of Safety

The safety profile of the study treatments will be assessed with respect to AEs, incidents and 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, prior to unblinding and will be coded to a system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

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

Treatment emergent adverse events (TEAEs) are defined as new AEs that occur on or after the first study product use (if this date is missing a suitable alternative will be used e.g., date of randomization). Adverse events 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.

#### 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 CRF. 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.

### 4.6 Analysis of Other Variables

Not applicable.

## 5 Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 17/SEP/2022).

## 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 | Yes |
| | Table | 14.1.3.2 | Demographic and Baseline Characteristics | mITT 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 Breath Organoleptic Score | mITT Population | 14.2.2.1.1 | Yes |
| | Table | 14.2.2.1.2 | Summary of Mean Breath Organoleptic Score | PP Population | 14.2.2.1.1 | |
| | Table | 14.2.2.2.1 | Statistical Analysis of Change from Day 0 (pre-brushing) to Week 3 (pre-brushing) in Mean Breath Organoleptic Score | mITT Population | 14.2.2.2.1 | Yes |
| | Table | 14.2.2.2.2 | Statistical Analysis of Change from Day 0 (pre-brushing) to Week 3 (pre-brushing) in Mean Breath Organoleptic Score | PP Population | 14.2.2.2.1 | |
| | Table | 14.2.3.1.1 | Summary of Hydrogen Sulfide (ppb) Concentration | mITT Population | 14.2.3.1.1 | |
| | Table | 14.2.3.1.2 | Summary of Methanethiol (ppb) Concentration | mITT Population | 14.2.3.1.1 | |
| | Table | 14.2.3.1.3 | Summary of Dimethyl Sulfide (ppb) Concentration | mITT Population | 14.2.3.1.1 | |

| CSR Section | TLF | Number | Title | Population | Template | Topline |
|---|---|---|---|---|---|---|
| | Table | 14.2.3.1.4 | Summary of Total VSC (ppb) Concentration | mITT Population | 14.2.3.1.1 | |
| | Table | 14.2.3.2.1 | Statistical Analysis of Change from Day 0 (pre-brushing) in Hydrogen Sulfide (ppb) Concentration | mITT Population | 14.2.3.2.1 | Yes |
| | Table | 14.2.3.2.2 | Statistical Analysis of Change from Day 0 (pre-brushing) in Methanethiol (ppb) Concentration | mITT Population | 14.2.3.2.1 | Yes |
| | Table | 14.2.3.2.3 | Statistical Analysis of Change from Day 0 (pre-brushing) in Dimethyl Sulfide (ppb) Concentration | mITT Population | 14.2.3.2.1 | Yes |
| | Table | 14.2.3.2.4 | Statistical Analysis of Change from Day 0 (pre-brushing) in Total VSC (ppb) Concentration | mITT Population | 14.2.3.2.1 | Yes |
| | Table | 14.2.3.3.1 | Statistical Analysis of Change from Week 3 (pre-brushing) in Hydrogen Sulfide (ppb) Concentration | mITT Population | 14.2.3.3.1 | Yes |
| | Table | 14.2.3.3.2 | Statistical Analysis of Change from Week 3 (pre-brushing) in Methanethiol (ppb) Concentration | mITT Population | 14.2.3.3.1 | Yes |
| | Table | 14.2.3.3.3 | Statistical Analysis of Change from Week 3 (pre-brushing) in Dimethyl Sulfide (ppb) Concentration | mITT Population | 14.2.3.3.1 | Yes |
| | Table | 14.2.3.3.4 | Statistical Analysis of Change from Week 3 (pre-brushing) in Total VSC (ppb) Concentration | mITT Population | 14.2.3.3.1 | Yes |
| | Table | 14.2.4.1 | Statistical Analysis of Change from Day 0 (pre-brushing) in Mean Breath Organoleptic Score | mITT Population | 14.2.4.1 | Yes |
| | Table | 14.2.4.2 | Statistical Analysis of Change from Week 3 (pre-brushing) in Mean Breath Organoleptic Score | mITT Population | 14.2.4.2 | Yes |

| CSR Section | TLF | Number | Title | Population | Template | Topline |
|---|---|---|---|---|---|---|
| | Figure | 14.2.1.1 | Mean Breath Organoleptic Score (±SE) Plot Over Time by Study Product | mITT Population | 14.2.1.1 | Yes |
| | Figure | 14.2.1.2 | Mean Breath Organoleptic Score (±SE) Plot Over Time by Study Product | PP Population | 14.2.1.1 | |
| | Figure | 14.2.2.1 | Mean VSC Concentration (±SE) Plot Over Time by Study Product and Compound | mITT Population | 14.2.2.1 | |
| 14.3 Safety Data Summary Tables and Figures | | | | | | |
| 14.3.1 Displays of Adverse Events | | | | | | |
| | Table | 14.3.1.1 | 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 | Death | All randomized subjects | 16.2.7.1 | |

| CSR Section | TLF | Number | Title | Population | Template | Topline |
|---|---|---|---|---|---|---|
| | Listing | 14.3.2.2 | Non-fatal Serious Adverse Events | All randomized subjects | 16.2.7.1 | |
| | Listing | 14.3.2.3 | Treatment Emergent Adverse Events leading to study or product discontinuation | All randomized subjects | 16.2.7.1 | |
| | Listing | 14.3.2.4 | Treatment Emergent Adverse Events Classified as Oral | All randomized subjects | 16.2.7.1 | |
| 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events | | | | | | |
| 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 Day 0 (pre-brushing) to Week 3 (pre-brushing) in Mean Breath Organoleptic Score (Reference: Table 14.2.2.2.1) | mITT Population | SAS Output | |
| | Raw output | 16.1.9.1.2 | Statistical Analysis of Change from Day 0 (pre-brushing) to Week 3 (pre-brushing) in Mean Breath Organoleptic Score (Reference: Table 14.2.2.2.2) | PP Population | SAS Output | |

| CSR Section | TLF | Number | Title | Population | Template | Topline |
|---|---|---|---|---|---|---|
| | Raw output | 16.1.9.2.1.1 | Statistical Analysis of Change from Day 0 (pre-brushing) in Hydrogen Sulfide (ppb) Concentration (Reference: Table 14.2.3.2.1) | mITT Population | SAS Output | |
| | Raw output | 16.1.9.2.1.2 | Statistical Analysis of Change from Day 0 (pre-brushing in Methanethiol (ppb) Concentration (Reference: Table 14.2.3.2.2) | mITT Population | SAS Output | |
| | Raw output | 16.1.9.2.1.3 | Statistical Analysis of Change from Day 0 (pre-brushing in Dimethyl Sulfide (ppb) Concentration (Reference: Table 14.2.3.2.3) | mITT Population | SAS Output | |
| | Raw output | 16.1.9.2.1.4 | Statistical Analysis of Change from Day 0 (pre-brushing) in Total VSC (ppb) Concentration (Reference: Table 14.2.3.2.4) | mITT Population | SAS Output | |
| | Raw output | 16.1.9.2.2.1 | Statistical Analysis of Change from Week 3 (pre-brushing) in Hydrogen Sulfide (ppb) Concentration (Reference: Table 14.2.3.3.1) | mITT Population | SAS Output | |
| | Raw output | 16.1.9.2.2.2 | Statistical Analysis of Change from Week 3 (pre-brushing) in Methanethiol (ppb) Concentration (Reference: Table 14.2.3.3.2) | mITT Population | SAS Output | |
| | Raw output | 16.1.9.2.2.3 | Statistical Analysis of Change from Week 3 (pre-brushing) in Dimethyl Sulfide (ppb) Concentration (Reference: Table 14.2.3.3.3) | mITT Population | SAS Output | |
| | Raw output | 16.1.9.2.2.4 | Statistical Analysis of Change from Week 3 (pre-brushing) in Total VSC (ppb) Concentration (Reference: Table 14.2.3.3.4) | mITT Population | SAS Output | |

| CSR Section | TLF | Number | Title | Population | Template | Topline |
|---|---|---|---|---|---|---|
| | Raw output | 16.1.9.3.1 | Statistical Analysis of Change from Day 0 (pre-brushing) in Mean Breath Organoleptic Score (Reference: Table 14.2.4.1) | mITT Population | SAS Output | |
| | Raw output | 16.1.9.3.2 | Statistical Analysis of Change from Week 3 (pre-brushing) in Mean Breath Organoleptic Score (Reference: Table 14.2.4.2) | 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 | | | | | | |

| CSR Section | TLF | Number | Title | Population | Template | Topline |
|---|---|---|---|---|---|---|
| | Listing | 16.2.4.1 | Demographic and Baseline Characteristics | All randomized subjects | 16.2.4.1 | |
| | Listing | 16.2.4.2 | Medical History and Current Medical Conditions | All randomized subjects | 16.2.4.2 | |
| | Listing | 16.2.4.3 | Prior medications | All Screened 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 | Breath Organoleptic Score Data | All randomized subjects | 16.2.6.1 | |
| | Listing | 16.2.6.2 | VSC Concentration Data | All randomized subjects | 16.2.6.2 | |
| 16.2.7 Adverse Event Listings | | | | | | |
| | Listing | 16.2.7.1 | Adverse Events | All randomized subjects | 16.2.7.1 | Yes |

| CSR Section | TLF | Number | Title | Population | Template | Topline |
|---|---|---|---|---|---|---|
| | Listing | 16.2.7.2 | Adverse Events | Non-randomized subjects | 16.2.7.1 | |
| | Listing | 16.2.7.3 | All Adverse Events Related to COVID-19 | All Screened subjects | 16.2.7.1 | |
| | Listing | 16.2.7.4 | Incidents | All Randomized Subjects | 16.2.7.4 | |
| 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 | | | | | |