Colgate-Palmolive CRO-2020-CAR-ARG-ED

A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anticaries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children

STATISTICAL ANALYSIS PLAN

Version 2.0: November 26, 2024

Prepared by:

[redacted]

Colgate-Palmolive CRO-2020-CAR-ARG-ED

Statistical Analysis Plan
Version 2.0

November 26, 2024

Prepared by: [redacted] Date: 04-Dec-2024

Upon review of this document, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the production of tables, listings, and figures can proceed as described.

Reviewer: [redacted] Date: _____

Reviewer: [redacted] Date: 04-Dec-2024

Reviewer: Maria Ryan, DDS, PhD Date: 04-Dec-2024

Maria Ryan, DDS, PhD
EVP, Clinical Research, KM & Sci Comm
GTech R&D Global Clinical
Colgate-Palmolive Co.

Version Control

V1.0: Original Document
V2.0: Two listed conditions removed from Section 15.2.1., in regards to the calculation of individual surface scores (sScored). This change was made in order to more accurately calculate the DMFS values by not automatically excluding surfaces with sealants and/or restorations that were not due to caries.

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LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
CPI	Community Periodontal Index
CSR	Clinical Study Report
DMFS	Decayed Missing Filled Surfaces
DMFT	Decayed Missing Filled Teeth
eCRF	electronic Case Report Form
F	Fluoride
GAC	Global Assessment of Change
ICDAS	International Caries Detection and Assessment System
ITT	Intent to Treat
OHRQoL	Oral Health Related Quality of Life
PI	Principal Investigator
PP	Per-Protocol
ppm	Parts per million
PSR	Periodontal Screening and Recording
SAP	Statistical Analysis Plan
WHO	World Health Organization

1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods to be used in the summary and analysis of the final data from Colgate-Palmolive Protocol Number CRO-2020-CAR-ARG-ED (Version 3.0), "A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anticaries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children".

2.0 PURPOSE OF THE SAP

This document describes and expands upon the analytical plan presented in the study protocol. It contains all planned analyses, and is accompanied by lists of the tables and listings that will be populated after data closure. This plan is to be reviewed by the sponsor and study team periodically, and may be updated prior to breaking the blind in the trial or database lock, whichever is applicable.

This SAP also supports the completion of the final Clinical Study Report (CSR) for Colgate-Palmolive protocol CRO-2020-CAR-ARG-ED. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts and publications. Additional, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. However, if any post-hoc or unplanned analyses that were not identified in this SAP are reported in the CSR, they will be clearly identified as such that document.

3.0 STUDY OBJECTIVE

The objective of this one-year study is to assess the safety and to evaluate the anti-caries efficacy of non-fluoride dentifrices containing 1.5%, 4.0% or 8.0% arginine. each compared to a 0.24% sodium fluoride dentifrice in 10- to 14-year-old children.

4.0 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the incremental subject-wise DMFS score after one year of product use.

4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will include:

- Incremental subject-wise DMFS score after 6-months of product use;
- Incremental subject-wise DMFS score between 6-months and one year of product use;

- Incremental subject-wise DMFT scores after 6-months and after one year of product use.
- Clinically significant change in ICDAS severity scores between the baseline and the six-months and one-year examinations, and between the six-months and one-year.
    - Clinically significant changes indicating caries progression are changes in ICDAS severity values from 0 to 2 or higher, from 1 or 2 to 3 or higher, or from 3 or 4 to 5 or 6. Clinically significant changes indicating caries regression are changes in ICDAS severity values from 2 or higher to 0 or 1.

4.4 Safety Endpoints

Safety will be assessed by an evaluation of all reported/observed adverse events during the course of the study and by hard and soft-oral tissue examinations conducted at Baseline, 3 months, 6 months, 9 months, and at 1 year.

5.0 INVESTIGATIONAL PLAN

5.1 Design Summary

This is a Phase 2, randomized, parallel groups, multi-center, active-controlled, double-blind study to investigate the safety and efficacy of three non-fluoride dentifrices containing different levels of arginine (1.5% arginine, 4.0% arginine, and 8.0% arginine) relative to each other, and to a dentifrice containing 0.24% sodium fluoride dentifrice with no arginine (active control).

5.2 Study Schedule

Individual subjects will participate in the study for approximately one year. An outline of the study schedule for each individual subject is as follows:

Timepoint	Study Event(s)
Screening Visit	Informed Consent and determination of eligibility for participation.
Baseline Visit	Randomization to study product, baseline caries, and hard and soft tissue assessments.
3 Month Visit	Assessments of safety and product use compliance.
6 Month Visit	Assessments of efficacy, safety, and product use compliance.
9 Month Visit	Assessments of safety and product use compliance.
12 Month Visit	Assessments of efficacy, safety, and product use compliance.

The schedule of events for this study, as presented in the study protocol, is provided in Appendix 1.

5.3 Study Procedures

Subjects will be enrolled according to the criteria detailed in the study protocol. At each study site, each enrolled subject will be randomized into one of four parallel study groups, and will brush their teeth twice daily at home (unsupervised use) with their assigned dentifrice over the course of the study.

- Assessments of safety will include monitoring of all reported or observed adverse events, and examinations of hard and soft oral tissue.
- Assessments of efficacy will include examinations for dental caries based on visual, ICDAS, and WHO/CPI/PSR criteria.
- Additional assessments will include the administration of the oral health-related quality of life (OHRQoL) and the global assessment of change (GAC) questionnaires.

All subjects will be monitored for adverse events throughout the course of the study.

5.4 Study Sample

Approximately 2,000 children will be enrolled. At each study site, enrolled subjects will be randomized into one of four parallel study groups (1.5% arginine dentifrice, 4.0% arginine

dentifrice, 8.0% arginine dentifrice, and 0.24% sodium fluoride dentifrice with no arginine) in a 1:1:1:1 ratio.

5.4.1 Inclusion Criteria Synopsis

Eligible participants for the study are children between 10-14 years old who have given their assent and whose parents or guardians have provided informed consent. They must be willing to use the assigned products correctly and be available for all study visits, with a high likelihood of completing the trial. Only children with good general health, as confirmed by medical history, who have permanent second molars present or erupting, and at least two active caries lesions (ICDAS scores ≥2) along with a previous caries experience (DMFT >1) will be included.

5.4.2 Exclusion Criteria Synopsis

Children will be excluded from participation if they have more than four permanent teeth with fixed or removable prosthetic appliances or are undergoing orthodontic treatment. Those on medications that increase caries risk, such as those reducing saliva flow or containing sugar, or on long-term antibiotics, will be excluded. Additional exclusion criteria include a confirmed diagnosis of cognitive/motor impairment, severe malocclusion, severe caries (ICDAS 5 or 6) on five or more permanent teeth, moderate to severe periodontal disease, participation in another clinical study within the past 30 days, known allergies to arginine or oral care product ingredients, and those who are pregnant, intending to become pregnant, or breastfeeding.

5.5 Treatment Assignment and Treatment Groups

5.5.1 Randomization

An unblinded biostatistician will generate a separate randomization listing for each study site. Within each randomization, subjects will be assigned to each of the 8.0% arginine/0 ppm F dentifrice, 4.0% arginine/0 ppm F dentifrice, the 1.5% arginine/0ppm F dentifrice and the 0% arginine/ sodium fluoride 0.24% (1100 ppm F), in a 1:1:1:1 ratio.

5.5.2 Blinding

The randomization listings produced by the unblinded statistician will be transferred to a designated un-blinded individual at each study site, who will manage randomized assignment, product dispensing and resupply. Enrolled subjects at each study site will be assigned subject numbers specific to that site. Subjects living in the same household will be assigned the same product code.

The primary study biostatistician will remain blinded to the treatment assignments until after the study has been concluded, all data cleaning and statistical analyses have been programmed and completed (based on the blinded study data), and the investigator at each study site indicates that un-blinding can proceed. Unblinded study data will not be made

available to the primary study statistician until this indication has been received from all study sites.

5.5.3 Unmasking Procedures

Each study site will maintain a list of all individuals who are privy to the randomization listing. Should a situation arise in which it becomes necessary to provide emergency unblinding information for an individual subject, this will be provided by one of the designated unblinded individuals at the study site.

5.6 Withdrawal and Replacement of Subjects

A genuine effort will be made to determine the reason(s) why a subject fails to report to the scheduled examinations or has been dropped from the study. A subject will be dropped from the study if any of the following occurs:

1. Subject fails to report for the examinations.
2. Subject elects to terminate participation in the study.
3. Sponsor elects to terminate the study.
4. Subject experiences a serious adverse reaction to the test products.
5. Subject is determined to be non-compliant by the Site PI in consultation with the Sponsor.

Subjects discontinued from the study for any reason will not be allowed to re-enter the study and will not be replaced.

6.0 SEQUENCE OF PLANNED ANALYSES

6.1 Interim Analyses

No interim analysis is planned for this study.

6.2 Final Analyses and Reporting

Final analyses will be completed on the unblinded study data after the database has been locked and all analysis programs have been validated. At the conclusion of the study, after all data cleaning and statistical analyses have been programmed and completed (based on the blinded study data), the investigator at each study site will indicate that unblinding can proceed. Unblinding of the study data will not take place until this indication has been received from all study sites.

7.0 SAMPLE SIZE DETERMINATION / JUSTIFICATION

The sample size determination was based on the expected half width of the 95% confidence interval for the one-year DMFS increment for each treatment group. Based on past data we expect a standard deviation of approximately 3.0. Using the normal

approximation and 450 subjects per group at one year, the confidence interval half-width would be ±0.28. These estimates will provide data to be used in planning the next (pivotal) study.

8.0 ANALYSIS POPULATIONS

8.1 Intent to Treat (ITT) Population

The ITT population will consist of all subjects who were randomized and dispensed study treatment.

8.2 Safety Population

The Safety population will consist of all randomized subjects who received at least one administration of study treatment

8.3 Per-Protocol (PP) Population

The PP population will consist of those subjects in the ITT population who completed all study examinations, and who experienced no serious protocol violations.

For the purpose of this determination, serious protocol violations include:

1. Subject fails to report for examinations.
2. Subject elects to terminate participation in the study.
3. Sponsor elects to terminate the study.
4. Subject is treated with medications that may affect the parameters under investigation during the study.

8.4 Application of Analysis Populations

All analyses performed on the ITT population will be based on treatments as randomized. Analyses performed on both the Safety and PP populations will be based on treatments actually received. Analyses performed to investigate safety and exploratory endpoints will be performed on the Safety population. Analyses to investigate efficacy will be performed on both the ITT and PP populations; however, the primary efficacy analyses will be those based on the PP population.

9.0 GENERAL ISSUES FOR DATA ANALYSES

9.1 Software

All statistical summaries and analyses will be produced using SAS®[1], version 9.4 or higher.

9.2 General Procedure for Statistical Tests of Hypotheses

Unless otherwise specified, all statistical tests performed for the comparison of means or proportions will be two-sided; and all tests performed for any purpose will employ a level of significance of alpha = 0.05.

9.3 General Procedure for Data Summarization

Data summaries for variables measured on a continuous scale will include the number of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. Unless otherwise specified, data summaries for each evaluation time point will be calculated based on the number of subjects in the study population being analyzed who presented non-missing values for the visit.

9.4 Adjustments for Covariates

Although the analyses to be performed are primarily descriptive in nature, comparisons among the study treatments will be performed in order to provide the study sponsor with information useful for the planning of a definitive, Phase 3 study. These analyses will employ baseline values and other covariates as described in section 15 of this document in the statistical model employed for each comparison.

9.5 Handling of Dropouts and Missing Data

Subjects who are discontinued cannot reenter treatment and will not be replaced. All analyses performed on the Safety and PP populations will be based on data as observed.

For the analyses of the primary efficacy endpoint performed on the ITT population, multiple imputation methodology will be employed to impute missing values for subjects who have missed visits, or who have dropped out of the study. Multiple imputation will be implemented using baseline subject characteristics to randomly impute each data point five times. The five complete data sets will be analyzed and then combined to incorporate both the estimated within and between data set error terms.

The SAS code that will perform the multiple imputations is provided in Appendix 3 of this document.

9.6 Procedures for Multicenter Studies

Since the analyses to be performed are primarily descriptive in nature, no adjustments are planned for this study.

9.7 Multiple Comparisons and Multiplicity

No adjustments are planned for this study.

9.8 Subgroup Analyses

No subgroup analyses are planned for this study.

9.9 Repeated Assessments

If there are repeated assessments at the same scheduled visit or measurement time point, the last non-missing assessment will be used as the value for that scheduled visit or time point.

9.10 Handling of Data from Unscheduled Visits

Any data obtained at unscheduled visits will be presented in the listings.

9.11 Baseline Definition(s)

Baseline values for all parameters will be the most recent value prior to the first administration of study treatment.

9.12 Longitudinal Comparisons

As noted above, all the primary and secondary efficacy endpoints consist of longitudinal changes in measured parameters. Additionally, the exploratory endpoints will include selected changes from baseline. Details regarding the analyses of these parameters will be provided in subsequent sections of this document.

9.13 Coding Dictionaries

All adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 26.1. No coding will be employed for data on concomitant medications.

9.14 Changes from the Methodology Described in the Study Protocol

The following changes to the statistical methodology described in the study protocol have been made in this SAP:

- The comparison of the treatment means with respect to the DMFS and DMFT study endpoints will be performed using an analysis of covariance (ANCOVA). This change was made because the ANCOVA methodology is a standard approach for the comparison of means in clinical dental caries studies.
- The methodology for the summarization of the exploratory endpoints has been clarified to indicate that the summaries will be based on the Safety population.
- The methodology for the imputation of missing data for the analyses performed on the ITT population has been clarified to indicate that such imputations will be employed only for the analyses performed on the primary efficacy endpoint.

- The statistical methodology to be employed in the analysis of clinically-significant transitions in ICDAS caries severity scores between pairs of study visits has been re-expressed to provide more clarity.
- The change from fitting a multinomial model to the four categories of caries activity transitions (as specified in the protocol) to separate analyses of progressions in caries activity (changes from inactive to active caries) and regressions in caries activity (changes from active caries to inactive) was made in order to yield analyses providing treatment comparisons that will be more readily interpretable, and which will be more useful for supporting the study objective of recommending an Arginine concentration to be included in future investigations.

10.0 SUBJECT ENROLLMENT AND DISPOSITION

10.1 Subject Disposition

A summary table will be prepared indicating the number and percentage of enrolled subjects in each treatment group who were in each study population. Within each population, the number and percentage of subjects who did/did not complete the study will be presented.

Subjects who discontinue their participation in the study will be categorized by reason for discontinuation, and the percentage within each category will be provided.

Subject disposition will be presented in a listing.

10.2 Protocol Violations

Reported protocol violations will be presented in a listing.

11.0 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

11.1 Demographics

Subject demographics (age, gender, race, and ethnicity) will be summarized by treatment group and overall, for subjects in the Safety population. Age will be summarized as a continuous variable.

The data for subject demographics will be presented in a listing.

11.2 Inclusion and Exclusion Criteria

A listing will be prepared showing those subjects who failed to satisfy any of the inclusion or exclusion criteria.

12.0 MEDICAL HISTORY

The data for medical history will be presented in a listing.

13.0 CONCOMITANT MEDICATIONS

The data for concomitant medications will be presented in a listing.

14.0 SAFETY ANALYSIS

14.1 Adverse Events

14.1.1 Adverse Event Definitions

14.1.1.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigations subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Information to be collected for AEs will include:

- AE description
- Date of onset
- Date of resolution
- Outcome
- Severity
- Seriousness
- Relationship to study drug (causality)
- Actions taken.

Adverse events will be assessed by the investigator or designee for severity, relationship to the study product, possible etiologies, and whether the event meets the criteria as a serious adverse event and therefore requires immediate notification of the sponsor.

14.1.1.2 Severity of Adverse Events

Regardless of the classification of an AE as serious or not, its severity must be assessed according to the following categories:

- Mild: does not interfere with routine activities
- Moderate: interferes with routine activities
- Severe: impossible to perform routine activities.

14.1.1.3 Relationship of Adverse Events to Study Drug

The study examiner will assess the relationship between the study product and the AE, and categorize the AE according to the scale below:

- Definite
- Probable
- Possible
- Unlikely
- Not Related.

Further details regarding this categorization can be found in the study protocol.

14.1.1.4 Definition of a Serious Adverse Event (SAE)

An SAE is defined as an adverse event that results in any of the following outcomes:

- Death;
- Life-threatening (immediate risk of death);
- In-patient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability or incapacity;
- Congenital anomaly/birth defect.

Further details regarding these determinations are provided in the study protocol.

14.1.2 Adverse Event Summaries to be Provided

14.1.2.1 Overview of Adverse Events

The number and percentage of subjects who presented one or more adverse events (AEs) will be presented by treatment group and overall. Additionally, the number and percentage of subjects who presented one or more AE in each of the following categories will be presented: treatment-related AEs; severe or life-threatening AEs; serious AEs; serious, treatment-related AEs; and AEs leading to study treatment modification or discontinuation from study. The denominator for percentages will be the number of subjects in the treatment group being summarized.

14.1.2.2 Incidence of Adverse Events

The incidence of AEs will be presented by treatment group and overall. The total number of AEs will be presented. Additionally, the number and percentage of subjects who experience an AE will be presented, where this latter summary will be evaluated on the subject level – *i.e.*, within each level of summarization (body system; preferred term), subjects who experience more than one occurrence will only be counted once. The denominator for percentages will be the number of subjects in the treatment group being summarized.

14.1.2.3 Summary of Adverse Events by Severity

A summary of AEs by reported severity (Mild, Moderate, or Severe) will be prepared by treatment group and overall. In this summary, if a subject reports multiple occurrences of the same AE at the level being reported (body system; or preferred term within body), only the most severe occurrence will be presented.

14.1.2.4 Summary of Adverse Events by Relationship to Study Product

A summary of AEs by relationship to study product (Not Related, Unlikely, Possible, Probable, or Definite) will be prepared by treatment group and overall. In this summary, if a subject reports multiple occurrences of the same AE at the level being reported (body system; or preferred term within body), only the most closely-related occurrence will be presented.

14.1.2.5 Adverse Event Listings

The data for all AEs will be provided in a listing.

14.1.2.6 Serious Adverse Event Listings

The data for SAEs will be presented in a listing.

14.2 Other Safety Data

Examinations of the oral soft and hard tissues will be performed at all study visits.

The soft tissue structures examined will include the lips, soft palate, hard palate, gingival mucosa, buccal mucosa, mucogingival folds, tongue, sublingual and submandibular areas, salivary glands, tonsillar and pharyngeal areas. Observations will be listed as “Normal” and “Abnormal” and abnormalities will be described.

The hard tissue structures examined will include assessing for enamel irregularities, tooth fracture, pathologic tooth wear, cavitated lesion, active non-cavitated lesion, residual root, faulty restoration, and implant. Observations will be listed as “Absent” or “Present” and conditions noted as present will be described.

A summary of the hard- and soft-tissue findings will be provided, showing the incidence of findings in each treatment group.

The data for oral soft and hard tissue examinations will be provided in a listing.

15.0 EFFICACY ANALYSIS

Efficacy analyses will be performed on subject-wise endpoints that characterize the presence of dental caries in the subject's mouth (caries prevalence), and the change in the level of dental caries during the time span between examinations (caries increment).

Analyses as described below will be performed on both the PP population, and the ITT population.

15.1 Data Reported at Each Caries Examination

At the Baseline, 6 Month, and 12 Month study visits, caries examinations will be performed, and data as described below will be recorded.

15.1.1 Reported Surface-wise Scores

Each tooth in a subject's mouth is identified by a number between 1 and 32 that indicates the tooth's position in the mouth. On each tooth, assessments will be made for each of the tooth's surfaces. The surfaces examined in this study are as follows:

Tooth Numbers *	Surfaces
2 - 5	Mesial (M), Distal (D), Buccal (B), Lingual (L), Occlusal (O)
6 – 11 **	Mesial (M), Distal (D), Buccal (B), Lingual (L)
12 – 15	Mesial (M), Distal (D), Buccal (B), Lingual (L), Occlusal (O)
18 – 21	Mesial (M), Distal (D), Buccal (B), Lingual (L), Occlusal (O)
22 – 27 **	Mesial (M), Distal (D), Buccal (B), Lingual (L)
28 - 31	Mesial (M), Distal (D), Buccal (B), Lingual (L), Occlusal (O)
* Teeth designated by the number 1, 16, 17, or 32 are not included in this study.	
** A tooth designated by a number in this range does not have an occlusal surface.	

At each caries examination, the following three assessments will be reported for each scorable tooth surface.

15.1.1.1 Surface Condition

Surface condition is a parameter that reports the condition of the tooth surface using the 4-point categorical scale presented in the following table:

Reported Condition Score	Definition
0	No filling, No sealant
1	Sealant (partial or complete)
2	Filling: when a permanent or temporary filling is present, missing or defective (e.g. composite, amalgam, crown, etc.)
3	Restoration: restored due to other reasons (e.g. cervical lesions, residual composite due to ortho or aligners, diastema closure, etc.)

15.1.1.2 ICDAS Caries Severity Score

The ICDAS caries severity score is a parameter that reports the level of caries activity on a tooth surface using the 7-point ordinal scale presented in the following table:

Caries Severity	Reported ICDAS Score	Visual Assessment Criteria
Healthy	0	Sound tooth surface
Initial	1	First Visual change in enamel
	2	Distinct visual change in enamel
Moderate	3	Localized enamel breakdown due to caries with no visible dentin
	4	Underlying dark shadow from dentin, with or without localized enamel breakdown
Extensive	5	Distinct cavity with visible dentin
	6	Extensive distinct cavity with visible dentine

15.1.1.3 Caries Activity Score

The caries activity score is a parameter that reports the level of caries activity on a tooth surface utilizing a binary (yes/no) categorical scale:

- 1 = active dental caries is present on the surface
- 0 = no active dental caries is present on the surface.

15.1.2 Reported Tooth-wise Scores

At each caries examination, a tooth profile score is recorded for each scorable tooth in the subject's mouth using the following categorical scale:

Profile Score	Condition	Assessment Criteria
1	Filling	When a permanent or temporary filling is present, missing, or defective
7	Excluded	Not counted, unerupted teeth, congenitally missing or supernumerary teeth, teeth removed for reasons other than dental caries, and primary teeth retained in the permanent dentition
8	Trauma	Trauma; poor prognosis (Not Counted)
9	Missing	When a tooth has been extracted due to caries

15.2 Surface-wise Parameters to be Derived Based on the Data Reported from Caries Examinations

To facilitate the calculation of the subject-wise efficacy endpoints, several surface-wise parameters will be calculated.

15.2.1 Surface-wise Parameters Based Data from Each Individual Study Visit

Using the caries examination data described in section 15.1 above, the following two variables will be derived for each tooth surface at each study visit:

- sScored
- sDMF.

Each of these is an indicator variable, and will be scored 0 or 1, where a score of 0 indicates 'no', and a score of 1 indicates 'yes'.

For each surface, the variable sScored will be set equal to 0 if any of the following conditions are met:

- The Tooth Profile score reported for the tooth on which the surface is located was either 7 or 8.

For surfaces meeting none of these conditions, the value of sScored will be set equal to 1.

For any surface for which sScored=0, no value of sDMF will be derived.

For surfaces for which sScored=1, the value of sDMF will be set equal to 1 if any of the following conditions is met:

- The reported ICDAS severity score for the surface was 3, 4, 5, or 6.
- The reported ICDAS condition score for the surface was 2.
- The reported Tooth Profile score for the tooth on which the surface is located was 9.

For any surface with sScored=1 for which none of the conditions above is met, the value of sDMF will be set equal to 0.

15.2.2 Derived Surface-wise Parameters Based on Transitions in ICDAS Severity Scores Between Pairs of Study Visits

Two at-risk parameters

1. sP-Risk (indicating a surface which could possibly undergo progression)
2. sR-Risk (indicating a surface which could possibly undergo regression)

and three transition parameters

1. sProg (progression)
2. sRegr (regression)
3. sNCSC (no clinically significant change)

(each with values 0, 1, or NA) will be derived based on reported surface-wise ICDAS severity scores at each of the following chronologically-ordered pairs of study visits:

- Baseline and Six Month
- Baseline and One Year
- Six Month and One-Year.

For each visit pair, the values of these derived variables will be reported only for those tooth surfaces for which an ICDAS severity score was reported at both visits (scorable surfaces).

For each scorable tooth surface, the values of sP-Risk and sR-Risk will be assigned based solely on the ICDAS severity score reported at the earlier of the two visits, as follows:

- sP-Risk will be set equal to 1 if the ICDAS severity score at the earlier visit was between 0 and 4; and will be set equal to 0 otherwise.
- sR-Risk will be set equal to 1 if the ICDAS severity score at the earlier visit was between 2 and 6; and will be set equal 0 otherwise.

The values of sProg, sRegr, and sNCSC will be assigned based on the ICDAS severity scores reported at both the earlier and the later of the two visits, as illustrated in the following table:

ICDAS Severity Score at the Earlier Visit	For each scorable surface, using the row corresponding to the ICDAS severity score at the earlier visit, assign each variable the value 1 if the ICDAS severity score at the later visit is listed in the cell below its name; and assign the value 0 otherwise. NA= not applicable; no value assigned.		
	sProg	**sRegr**	**sNCSC**
0	2, 3, 4, 5, 6	NA	0, 1
1	3, 4, 5, 6	NA	0, 1, 2
2	3, 4, 5, 6	0, 1	2
3	5, 6	0, 1	2, 3, 4
4	5, 6	0, 1	2, 3, 4
5	NA	0, 1	2, 3, 4, 5, 6
6	NA	0, 1	2, 3, 4, 5, 6

15.3 Tooth-wise Parameters to be Derived for Each Individual Study Visit

To facilitate the calculation of the subject-wise efficacy endpoints, for each study visit the following indicator variable parameters will be derived based on the derived surface-wise scores at that visit as described in section 15.2.1 above:

- tScored
- tDMF (decayed, missing, or filled)

The variable tScored will be assigned the value 1 if the surface-wise parameter sScored was equal to 1 for any surface on the tooth; and will be set equal to 0 if the surface-wise parameter sScored was equal to 0 for all surfaces on the tooth.

For a tooth assigned the value tScored=0, no value for the parameter tDMF will be assigned. Otherwise, for a tooth assigned the value tScored=1, tDMF will be set equal to 1 if sDMF is equal to 1 for any surface on the tooth; and will be set equal to 0 otherwise.

15.4 Derived Subject-wise Caries Parameters

To facilitate the calculation of the subject-wise efficacy endpoints, several subject-wise parameters will be derived based on the surface-wise and tooth-wise parameters introduced above.

15.4.1 Subject-wise Caries Parameters at Each Individual Study Visit

At the Baseline, 6 Month, and 12 Month study visits, the following subject-wise caries prevalence parameters will be calculated.

15.4.1.1 DMFS

The DMFS value is the number of scorable tooth surfaces in the subject's mouth that are decayed, missing, or filled. Using the surface-wise parameters introduced in section 15.2.1, DMFS is calculated by tallying the number of surfaces among those for which sScored=1 for which sDMF = 1. If no tooth surface for which sScored = 1 satisfies this additional condition, then DMFS is set equal to 0.

15.4.1.2 DMFT

The DMFT value is the number of scorable teeth in the subject's mouth that are decayed, missing, or filled. Using the tooth-wise parameters introduced in section 15.3, DMFT is calculated by tallying the number of teeth among those for which tScored=1 for which tDMF = 1. If no surface on any of the teeth for which tScored=1 satisfies this additional condition, then DMFT is set equal to 0.

15.4.1.3 ICDAS Caries-Active Surfaces

This parameter is equal to the number of surfaces in the mouth which present active dental caries, and is calculated by taking the sum of the caries activity scores (introduced in section 15.1.1.3 above) over all surfaces in the subject's mouth for which a score was assigned.

15.4.2 Subject-wise Caries Parameters Based on Changes Between Pairs of Study Visits

Subject-wise caries parameters will be calculated based on the changes between each of the following chronologically-ordered pairs of study visits:

- Baseline and Six-Month
- Baseline and One Year
- Six-Month and One Year.

15.4.2.1 DMFS Increment

DMFS increment is defined as the change in DMFS score between two specified time points. For each of the ordered pairs of visits specified above, the DMFS increment will be calculated for each subject by subtracting their subject-wise DMFS at the earlier visit from their subject-wise DMFS at the later visit. For any subject who did not present a DMFS score at both visits, no value for the DMFS increment will be assigned.

15.4.2.2 DMFT Increment

DMFT increment is defined as the change in DMFT score between two specified time points. For each of the ordered pairs of visits specified above, the DMFT increment will be calculated for each subject by subtracting their subject-wise DMFT at the earlier visit from their subject-wise DMFT at the later visit. For any subject who did not present a DMFT score at both visits, the no value for the DMFT increment will be assigned.

15.4.2.3 Change in ICDAS Caries-Active Surfaces

For each subject, the subject-wise change in ICDAS caries-active surfaces between a specified pair of study visits will be based on the binary surface-wise ICDAS caries activity scores (defined in section 15.1.1.3 above), and will be expressed as the number of tooth surfaces for which the scores at the two visits fall into each of the following four categories:

- 00 (score of 0 at both visits)
- 01 (score of 0 at the earlier visit, and 1 at the later visit)
- 10 (score of 1 at the earlier visit, and 0 at the later visit)
- 11 (score of 1 at both visits).

The number of surfaces at risk for caries activity progression (change from caries inactive to caries active) is the number scored 0 at the earlier visit (sum of surfaces in categories 00 and 01); and the number of caries activity progressions will equal the number of surfaces in category 01. Analogously, the number of surfaces at risk for caries activity regression (change from caries active to caries inactive) is the number scored 1 at the earlier visit (sum of surfaces in categories 10 and 11); and the number of caries activity regressions will equal the number of surfaces in category 10.

15.4.2.4 Subject-wise Number of Tooth Surfaces Presenting Clinically Significant Changes in ICDAS Severity Scores

For each pair of study visits, for each subject, the following five parameters based on the surface-wise ICDAS severity score transition parameters described in section 15.2.2 above will be calculated:

- nPRisk

nPRisk represents the number of surfaces at risk for progression, and is calculated by tallying the number of surfaces for which sP-Risk = 1.

- nRRisk

  nRRisk represents the number of surfaces at risk for regression, and is calculated by tallying the number of surfaces for which sR-Risk = 1.

- nProg

  nProg represents the number of surfaces that presented progression, and is calculated by tallying the number of surfaces for which sProg = 1.

- nReg

  nReg represents the number of surfaces that presented regression, and is calculated by tallying the number of surfaces for which sRegr = 1.

- nNCSC

  nNCSC represents the number of surfaces that presented no clinically significant change, and is calculated by tallying the number of surfaces for which sNCSC = 1.

15.5 Primary Efficacy Endpoint

The primary efficacy endpoint will be the incremental subject-wise DMFS score after one year of product use (*i.e.*, between the Baseline and 12 Month examinations).

A score summary for the primary efficacy endpoint will be provided, and will include a 95% confidence interval for each treatment group.

15.6 Secondary Efficacy Endpoints

Secondary efficacy endpoints based on subject-wise DMFS and DMFT scores will include:

- Incremental subject-wise DMFS score after 6-months of product use;
- Incremental subject-wise DMFS score between 6-months and one year of product use;
- Incremental subject-wise DMFT scores after 6-months and after one year of product use.

Secondary efficacy endpoints based on change in ICDAS severity scores will include:

- Clinically significant change in ICDAS severity scores between the baseline and the six-month examinations;
- Clinically significant change in ICDAS severity scores between the baseline and the one-year examinations;
- Clinically significant change in ICDAS severity scores between the six-month and the one-year examinations.

For the secondary efficacy endpoints based on DMFS and DMFT, a continuous-data summary including a 95% confidence interval will be provided for each treatment group at each assessment time point.

For the secondary efficacy endpoints based on changes in ICDAS severity scores, for each treatment group at each assessment time point, a categorical summary will be provided for each of the subject-wise parameters specified in section 15.4.2.4 above.

15.7 Comparisons Between Treatment Groups

Although the objective of this study is descriptive in nature, and the sample sizes were not selected for the purpose of providing power for any comparisons between study treatments, nevertheless comparisons between the treatment groups with respect to the primary and secondary efficacy endpoints will be performed to serve as another characterization of the findings from the study, and to aid the study Sponsor in the determination of treatment groups to employ in any future, pivotal studies.

Although the study is not powered to detect differences among the treatment groups, statistical models will still be implemented for the primary and secondary efficacy endpoints. An analysis of covariance model that includes the baseline score as a covariate will be employed for the analyses of the DMFS and DMFT endpoints.

For the endpoints based on clinically significant transitions in ICDAS severity scores (separately for both for progressions, and for regressions), a generalized linear model with a fixed factor treatment group will be fit to the data, in which the dependent variable will be the number of transitions, and in which the number of surfaces at risk for transition will be employed as an offset. This model will specify a Poisson distribution, and a log link function.

The analyses of the transitions in caries activity will be performed analogously. Separately for both for progressions, and for regressions, a generalized linear model with a fixed factor treatment group will be fit to the data, in which the dependent variable will be the number of transitions in caries activity, and in which the number of surfaces at risk for transition will be employed as an offset. This model will specify a Poisson distribution, and a log link function. It is noted that in the analyses performed on the Per-Protocol population, the number of subjects presenting non-missing data for progressions and/or regressions may be less than the total number of Per-Protocol subjects, since it is possible that not all subjects will necessarily have a non-zero number of surfaces at risk for both progressions and regressions.

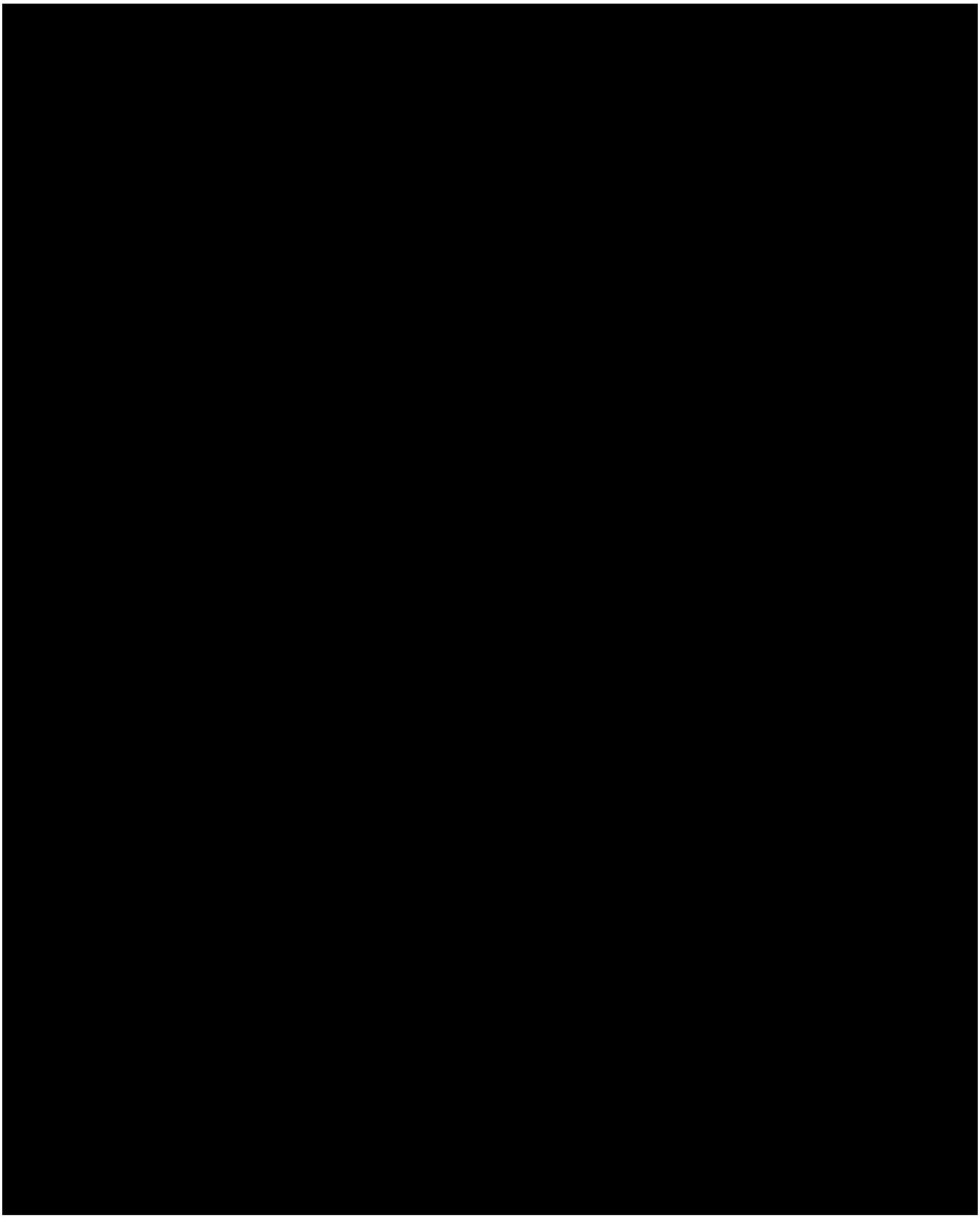
All statistical tests will be performed using a two-tailed 5% significance level. 95% confidence intervals for the differences between treatments will also be calculated based on the models. In addition, the models will yield estimates of the pooled within group variance which can be used for planning further studies.

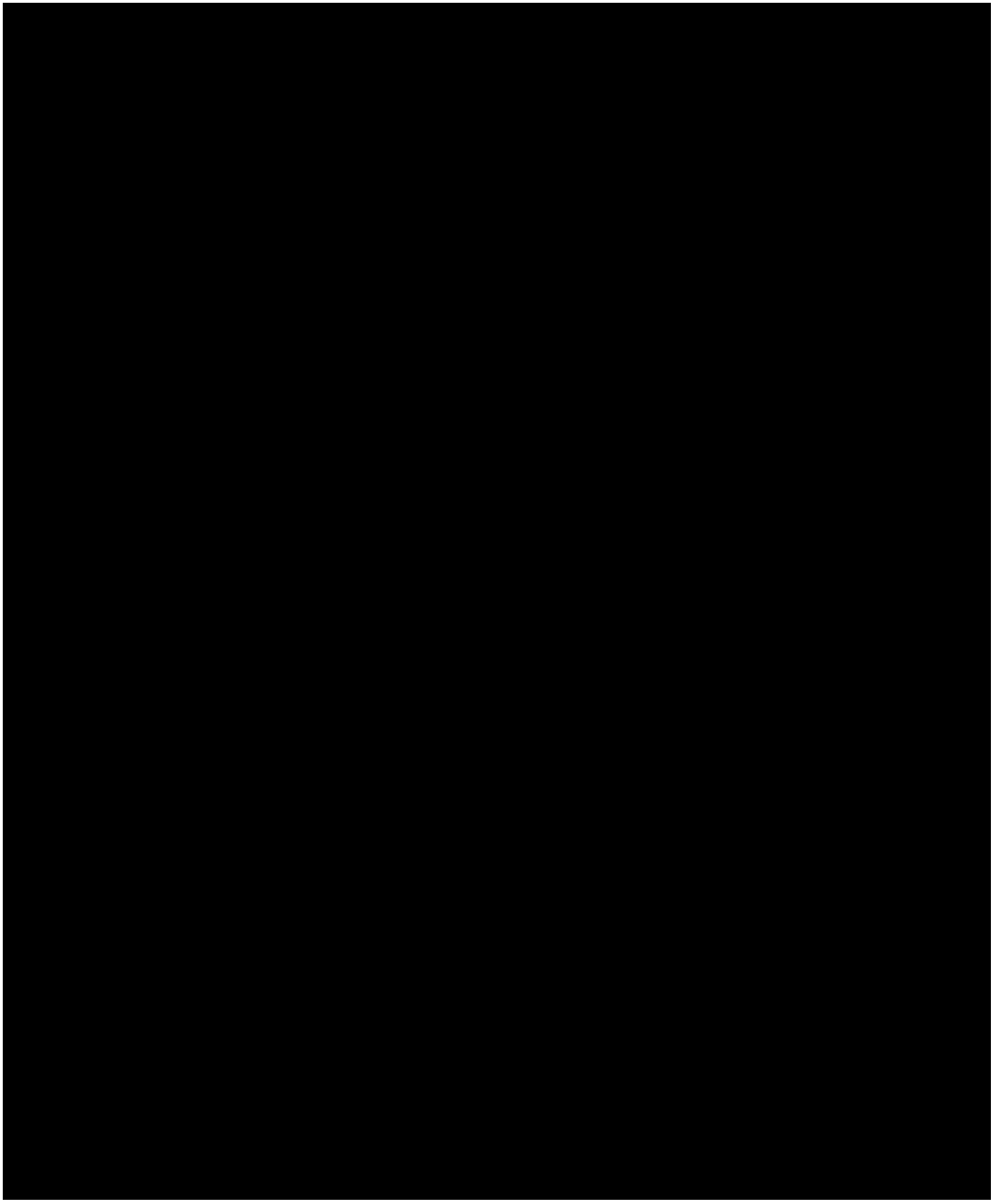
15.8 Additional Summaries to be Reported on Subject-wise Dental Caries Parameters

In addition to the summaries and analyses described above, a score summary for each of the subject-wise caries prevalence parameters mentioned above will be provided for each treatment group at each assessment time point.

15.9 Listings of Dental Caries Parameters

Data listings will be prepared for all the surface-wise, tooth-wise, and subject-wise dental caries parameters mentioned above.





17.0 VALIDATION OF STATISTICAL PROGRAMS

All statistical programs used to produce tables will be validated by using programming components which have been previously validated by independent programming. Programs used to produce listings will be validated by checking against the SAS datasets being displayed.

18.0 DATA REPORTING CONVENTIONS

18.1 Reporting Conventions for Tables

Means, medians, and standard deviations will be presented using one more decimal place than the number of decimal places recorded on the electronic case report form (eCRF). Minimum and maximum values will be presented using the same number of decimal places as recorded on the eCRF. Distributions will be presented by displaying the number of subjects in a category (as a whole number), followed by the parentheses that include the percentage of subjects in that category expressed to one decimal place [*i.e.*, XX (XX.X%)]. Percentages that result from frequency counts of all subjects, or one hundred percent, will be displayed without the decimal place (*e.g.* 100% and not 100.0%). Percentages that result from a frequency count of zero will be suppressed to draw attention to the zero.

All summary statistics with a magnitude of less than 1 will include a zero to the left of the decimal (*e.g.*, 0.XXX).

All p-values will be presented to four decimal places. P-values that are less than 0.0001 will be presented as <0.0001; p-values that are greater than 0.9999 will be presented as >0.9999.

18.2 Reporting Conventions for Listings

Due to the great amount of data to be included in the listings enumerated in Appendix 2 below, some of the resulting files would be too large to manage. Consequently, the following two-step process was employed:

1) When necessary due to file size, a listing was broken down into separate components for each of the nine study sites included in this study. The numbering of such listings would then include an additional decimal point which identifies which study site is included. The study sites were ordered in terms of their identification in the CDISC database provided. The numbering schema for the added decimal is as follows:

Added Decimal	Site ID
1	PRI-0001
2	USA-0001
3	USA-0002
4	USA-0003
5	USA-0004
6	USA-0005
7	USA-0006
8	USA-0007
9	USA-0008

2) If the file sizes for any of the nine listings described in Step 1 were still too large, the files were then further broken down into four separate listings for each study site: one for the subjects in each of the four study treatment groups. The numbering schema for the resulting listings entailed adding a mnemonic additional text after the added decimal value. These were as follows:

Added Text After Decimal	Study Treatment Group
A1	1.5% arginine/0 ppm F dentifrice

A4	4.0% arginine/0 ppm F dentifrice
A8	8.0% arginine/0 ppm F dentifrice
FL	0% arginine/sodium fluoride 0.24% (1100 ppm F) dentifrice

It is noted that these additional components of the listing numbers are not reflected in the listing numbers provided in Appendix 2 below.

19.0 REFERENCES

1) SAS for the Windows Operating System (SAS® Version 9.4, Cary, NC: SAS Institute, Inc., 2016).

APPENDIX 1: SCHEDULE OF STUDY EVENTS

Assessment	Baseline	3 Month (±1 Month)	6 Month (±1 Month)	9 Month (±1 Month)	12 Month (±1 Month)
Informed Consent/Assent	X				
Baseline Medical History/ Concomitant Medications	X				
Hard and Soft Tissue Examinations	X	X	X	X	X
Conformance with Entry Criteria	X				
Caries Examination	ICDAS	Visual Monitoring for Safety	ICDAS	Visual Monitoring for Safety	ICDAS
Medical History Update/ Concomitant Medications		X	X	X	X
Visit Form (Continuance)		X	X	X	X
Dentist Notice/Referral (when Necessary)	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X
Randomization, Study Group Assignment and Initial Toothpaste and Toothbrush Supply	X				
Study toothpaste and toothbrush re-supply		X	X	X	
Collection of previously dispensed study toothpaste and toothbrush		X	X	X	X
Assessment of Product Use Compliance		X	X	X	X
[redacted]					
Periodic/End of Study Report Form			X		X

Source: Study Protocol, Version 3.0

APPENDIX 2: LIST OF TABLES AND LISTINGS

Table Number	Title / Description / Analysis Population
14.1 Subject Information	
14.1.1	Subject Disposition
14.1.2.1	Demographics and Subject Characteristics / PP
14.1.2.2	Demographics and Subject Characteristics / ITT
14.2 Efficacy Data	
14.2.1.1	Summary of DMFS Increment Between Baseline and 12 Months (Primary Efficacy Endpoint) / PP
14.2.1.2	Summary of DMFS Increment Between Baseline and 12 Months (Primary Efficacy Endpoint) / ITT
14.2.1.3.1	Summary of DMFS Increment Between Baseline and 12 Months (Primary Efficacy Endpoint) / ITT with Imputed Missing Data (5 tables)
14.2.1.3.2	Summary of Estimation of Between-Treatment Differences in DMFS Increment Between Baseline and 12 Months Over All Five Imputations
14.2.2.1	Summary of DMFS Scores / PP
14.2.2.2	Summary of DMFS Scores / ITT
14.2.3.1	Summary of DMFT Scores / PP
14.2.3.2	Summary of DMFT Scores / ITT
14.2.4.1.1	Analysis of Tallies of Clinically Significant ICDAS Caries Severity Progressions Between Each Pair of Study Visits / PP

Table Number	Title / Description / Analysis Population
14.2.4.1.2	Analysis of Tallies of Clinically Significant ICDAS Caries Severity Progressions Between Each Pair of Study Visits / ITT
14.2.4.2.1	Analysis of Tallies of Clinically Significant ICDAS Caries Severity Regressions Between Each Pair of Study Visits / PP
14.2.4.2.2	Analysis of Tallies of Clinically Significant ICDAS Caries Severity Regressions Between Each Pair of Study Visits / ITT
14.2.5.1.1	Analysis of Tallies of ICDAS Caries Activity Progressions Between Each Pair of Study Visits / PP
14.2.5.1.2	Analysis of Tallies of ICDAS Caries Activity Progressions Between Each Pair of Study Visits / ITT
14.2.5.2.1	Analysis of Tallies of ICDAS Caries Activity Recessions Between Each Pair of Study Visits / PP
14.2.5.2.2	Analysis of Tallies of ICDAS Caries Activity Recessions Between Each Pair of Study Visits / ITT
14.3 Safety Endpoints	
14.3.1.1	Overview of Adverse Events
14.3.1.2	Adverse Events by MedDRA System Organ Class and Preferred Term
14.3.1.3	Adverse Events by Severity
14.3.1.4	Adverse Events by Relationship to Study Product
14.3.2	Oral Soft/Hard Tissue Exam (OSHT)(one table per area examined)
14.3.3	Oral Hard Tissue Exam (one table per area examined)

Table Number	Title / Description / Analysis Population

LISTINGS

Listing #	Title / Description
16.1 Treatment Assignment	
16.1.7	Randomization
16.2 Subject Data Listings	
16.2.1	Subject Disposition
16.2.2	Reported Protocol Deviations
16.2.3	Subjects Who Failed to Satisfy any of the Inclusion or Exclusion Conditions
16.2.4	Subject Demographic Data
16.2.5	Reported Medical History
16.2.6	Concomitant Medication Usage
16.2.7	Adverse Events Reported During the Study
16.2.8	Adverse Events Leading to Discontinuation of Study Treatment
16.2.9	Serious Adverse Events Reported During the Study
16.2.10	Oral Soft Tissue Examinations
16.2.11	Oral Hard Tissue Assessments
16.2.12	Surface-wise ICDAS Caries Examination Findings at Each Study Visit
16.2.13	Tooth-wise ICDAS Tooth Profile Findings Recorded at Each Study Visit

Listing #	Title / Description
16.2.14	Surface-wise and Tooth-wise DMF (Decayed, Missing or Filled) Status at Each Study Visit
16.2.15	Derived Surface-wise ICDAS Severity Transition Parameters for Each Pair of Study Visits
16.2.16	Subject-wise Caries Parameters (DMFS, DMFT, ICDAS Caries-active tallies) at Each Study Visit
16.2.17	Subject-wise Incremental DMFS and DMFT for Each Pair of Study Visits
16.2.18	Subject-wise Tallies of ICDAS Caries Activity Transitions for Each Pair of Study Visits
16.2.19	Subject-wise Tallies of ICDAS Severity Transition Parameters for Each Pair of Study Visits

APPENDIX 3: SAS CODE TO PERFORM MULTIPLE IMPUTATIONS

The SAS code employed to perform the multiple imputations is as follows:

```
proc mi data= <data source> seed=&randseed
out= <name of imputed dataset produced by SAS>

     minmaxiter=500
     maximum= 14
     minimum= -4
     nimpute = 5
     round=1.
     simple;
     class age sexn racen ethnicn siteid ;
     var dmfs15 dmfs1 age sexn racen ethnicn siteid ;
     fcs;
     run;
```

Please note: "&randseed" refers to a randomly-generated 9-digit seed value that is provided to SAS to be used in the random number generator that SAS employs to determine the imputed values of missing scores. The value of this seed will be stored in case it is needed in the future.

SAP Phase 2_2024.26.11_Colgate Protocol. CRO-2020-CAR-ARG-ED_v2.0

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