HALEON

STATISTICAL ANALYSIS PLAN

A Randomized, Examiner Blind, Crossover, *in situ* Erosion Study To Investigate The Efficacy Of An Experimental Dentifrice In Remineralization Of Softened Enamel Compared To Placebo and Reference Dentifrices

Protocol Number: 300057

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	23APR2024	Not applicable (N/A)

Amendments incorporate all revisions to date.

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Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
SMHR	Surface Microhardness Recovery
RER	Relative Erosion Resistance
ARR	Acid Resistance Ratio
EFU	Enamel Fluoride Uptake
TEAEs	Treatment-Emergent Adverse Events
KNO_3	Potassium Nitrate
BDR	Blind Data Review
PP	Per Protocol
ITT	Intent to Treat
SD	Standard Deviation
SE	Standard Error

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 300057.

1 Summary of Key Protocol Information

This study will investigate the ability of an experimental dentifrice containing 1150ppm fluoride to remineralize acid-softened dental enamel and help prevent further demineralization compared to a 0ppm fluoride placebo dentifrice and a marketed, fluoride-containing dentifrice (Reference Dentifrice). The study will utilize an established *in situ* model where partially demineralized enamel specimens will be placed in a dental palatal appliance, treated intra orally then allowed to remineralize *in situ* for 4 and 12 hours. Efficacy will be evaluated through laboratory measurement of the surface microhardness recovery (SMHR), relative erosion resistance (RER), acid resistance ratio (ARR) and the enamel fluoride uptake (EFU). Safety will be demonstrated through tabulation of treatment-emergent adverse events (TEAEs).

1.1 Study Design

This will be a randomized, controlled, single center, single- blind (to the dental examiner and specimen analysts), 3 period, 3 treatment, cross-over, *in situ* design. Previously demineralized bovine enamel specimens will be place intra orally using a palatal appliance and the remineralizing performance of the experimental, reference and placebo dentifrices evaluated at 4 and 12 hours post toothbrushing, based on surface micro hardness measurements of the bovine enamel specimens. This study will be carried out in healthy adults who meet the study eligibility as detailed in the study protocol. There will be 7 visits as shown in the schedule of activities.

The enamel specimens will be evaluated both prior to and after intra-oral exposure. Surface microhardness (SMH) will be used to evaluate changes in the mineral content of enamel and is used to calculate surface micro hardness recovery (%SMHR), relative erosion resistance (%RER) and acid resistance ratio (ARR). The incorporation of fluoride into the enamel specimens will be assessed by enamel fluoride uptake (EFU) measurements. For each treatment and subject, these measurements will be performed on the same enamel specimen as described in the Laboratory Procedure Document, in the four enamel specimens removed at each time point. The erosive acid challenges, with a commercially available grapefruit juice, will be carried out *ex vivo* and therefore does not pose a risk to the subject's teeth.

AEs and medical device incidents will be monitored throughout the study and recorded at every site visit following signing of informed consent.

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Schedule of Activities

Procedure/Assessment	Screening	Study Period 1			Study Period 2			Study Period 3		
	Visit 1		Visit 2 (Treatment)	Visit 3 (V2+1day)		Visit 4 (Treatment)	Visit 5 (V4+1day)		Visit 6 (Treatment)	Visit 7 (V6+1day)
Informed consent	X	Minimum 3 days including a 2 days washout using supplied non-fluoride dentifrice			Minimum 3 days including a 2 days washout using supplied non-fluoride dentifrice			Minimum 3 days including a 2 days washout using supplied non-fluoride dentifrice		
Demographics	X									
Medical history	X									
Current/prior/concomitant medication review	X		X	X		X	X		X	X
OST Examination[1]	X		X	X		X	X		X	X
OHT Examination	X									X
Assessment of stimulated and unstimulated saliva flow rate[2]	X									
Review of inclusion/exclusion criteria	X									
Try-in of palatal appliance	X									
Subject eligibility	X									
Dispense wash-out products and diary	X									

Procedure/Assessment	Screening	Study Period 1		Study Period 2			Study Period 3	
	Visit 1	Visit 2 (Treatment)	Visit 3 (V2+1day)	Visit 4 (Treatment)	Visit 5 (V4+1day)	Visit 6 (Treatment)	Visit 7 (V6+1day)	
Diary review		X	X	X	X	X	X	
Subject continuance		X	X	X	X	X		
Randomization to treatment sequence		X						
Place palatal appliance fitted with enamel specimens into subject's mouth[3]		X		X		X		
Supervised toothbrushing		X		X		X		
Intra oral phase 4 hours [3,4]		X		X		X		
Intra oral phase 12 hours [3,5]		X		X		X		
Adverse events review[6]	X	X	X	X	X	X	X	
Medical device incidents review[1]		X	X	X	X	X	X	
Return wash-out products						X		
Return palatal appliance			X		X		X	
Study conclusion							X	

Abbreviations: OST: Oral Soft Tissue, OHT: Oral Hard Tissue.

Footnotes:

1. At Visits 2, 4 & 6 OST examination will be performed prior to insertion of the appliance and at Visits 3, 5 & 7 when the subject returns their palatal appliance.
2. Re-evaluation of saliva flow may be required within the study should the subject begin a treatment of medications likely to induce xerostomia.
3. Laboratory analysis of enamel specimens performed prior to placing and after removing the specimens from the palatal appliance as described in the separate laboratory procedures document.
4. Four enamel specimens will be removed from the palatal appliance after wearing the appliance for 4 hours ± 10 min after toothbrushing. Subject will be offered lunch to be eaten over a 30 ±10 minute period and then be allowed to leave the site with instructions on how and when to eat dinner (30 ±10 minute period between hours 8.5 and 9), and remove (hour 13), store and return their appliance.
5. Subjects will remove their appliance after 12 hours ± 30 mins of wearing post toothbrushing (13 ±0.5 hours since brushing with product). Subjects will then rinse and store the appliance as instructed by the site staff. Subjects will return the appliance to the study site the following day. The study site staff will recover the 4 remaining enamel sections, then the appliance will be cleaned, disinfected and stored at site until the next treatment visit.
6. Adverse Events (AEs), Serious Adverse Events (SAEs) and medical device incidents collected from 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.

1.2 Study Objectives

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to enhance remineralization of enamel compared to a placebo dentifrice (0ppm fluoride) after 4 hours of intra-oral exposure.	• %SMHR at 4 hrs.
Secondary Objectives	**Secondary Endpoints**
Efficacy	
• To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to inhibit demineralization of enamel compared to a placebo dentifrice (0ppm fluoride) after 4 hours of intra-oral exposure.	• %RER at 4 hrs.
• To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to enhance remineralization of enamel compared to a marketed, reference dentifrice containing 1100ppm fluoride after 4 hours of intra-oral exposure.	• %SMHR at 4 hrs.
• To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to enhance remineralization of enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed, reference dentifrice containing 1100ppm fluoride after 12 hours of intra-oral exposure.	• %SMHR at 12 hrs.
• To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to inhibit demineralization of enamel compared to a reference dentifrice containing 1100ppm fluoride after 4 hours of intra-oral exposure.	• %RER at 4 hrs.
• To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to inhibit demineralization of enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed, reference dentifrice containing 1100ppm fluoride after 12 hours of intra-oral exposure.	• %RER 12 hrs.
• To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to promote fluoride uptake in enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed, reference dentifrice containing 1100ppm fluoride after 4 and 12 hours of intra-oral exposure.	• EFU at 4 and 12 hrs.
• To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to reduce future acid-induced demineralization in enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed,	• ARR at 4 and 12 hrs.

Objectives	Endpoints
reference dentifrice containing 1100ppm fluoride after 4 and 12 hours of intra-oral exposure.	
• To investigate the efficacy of a marketed, reference dentifrice containing 1100ppm fluoride. to enhance remineralization, inhibit demineralization, to reduce future acid-induced demineralization and to promote fluoride uptake in enamel compared to a placebo dentifrice (0ppm fluoride) after 4 and 12 hours of intra-oral exposure.	• %SMHR, %RER, EFU, ARR at 4 and 12 hrs.
Safety	
• To assess the oral tolerability of an experimental dentifrice containing 1150ppm fluoride and 5% KNO_3.	• Treatment emergent adverse events
Exploratory Objectives	**Exploratory Endpoints**
• To calculate the proportion of subjects who evidence a RER ratio (%RER 0ppm fluoride placebo and 5% KNO_3 : %RER experimental dentifrice containing 1150 ppm fluoride) >=3 and >=2.5	• %RER at 4 and 12 hrs.

1.3 Treatments

Test Dentifrice	Placebo Control	Reference Dentifrice
Experimental Dentifrice containing 1150ppm fluoride and 5% KNO_3*	0ppm fluoride dentifrice containing 5% KNO_3	Crest Pro-Health Densify Daily Protection

* KNO_3 is commonly used in other marketed anti sensitive toothpaste.

All dentifrices will be applied in the same manner by brushing 1.5±0.1g of dentifrice on to the buccal surfaces of their natural teeth for 25 timed seconds and then swishing the resulting dentifrice slurry around the mouth, without further brushing, for a timed period of 95 seconds.

Subjects will use a 0ppm fluoride washout dentifrice twice daily for 2 days prior to each treatment visit in place of their usual oral hygiene practice.

All subjects will be centrally randomized to 1 of 6 sequences using an Interactive Response Technology (IRT) based on a schedule consisting of randomized blocks of 6-sequences from a 3-treatment Williams Square design.

All study site staff will be blinded except for those staff members directly dealing with dispensing study products. Site staff, study statistician(s), data management staff and other employees of the sponsor and vendors acting on behalf of the sponsor, who may influence study outcomes will be blinded to the product allocation.

1.4 Sample Size Calculation

A sufficient number of healthy subjects will be screened to ensure that up to 33 subjects will be randomized to participate in the study to ensure at least 30 evaluable subjects complete the study. With a sample size of 30 subjects completing the study, there will be 97% power to detect

a difference in means of 7.5% in %SMHR at 12 hours, assuming a standard deviation (SD) of differences of 9.94% using a paired t-test with a 0.05 two-sided significance level.

These differences and variability were observed when comparing a similar test product to a similar Placebo Control and Reference Dentifrice at 4 hours in GSKCH study 208166. In the absence of any historical studies with results at 12 hours, the result at 12 hours will be assumed to be similar to 4 hours for the purpose of sample size calculation.

A recent network meta-analysis (Haleon study 300033) across 14 studies using the same design involving 22 different grouped type of study products suggests a SD of differences as high as 12.16% at 4 hours. Even with such a higher SD, there would still be 90% (80%) power to detect a difference in means of 7.5% (6.5%) in %SMHR at 12 hours.

Previous Haleon study 208166 and network meta-analysis 300033 suggest respective SD of differences for %RER between 17.5% and 20.3%. Such estimates of variability would give 90% (80%) power to detect respective difference in means of 10.7% and 12.4% (9.3% and 10.7%).

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 and a Blind Data Review (BDR) Meeting have been completed.
3. Database has been locked.
4. 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

Other than the Baseline indentation lengths (see section 4.4) there will be no definition of Baseline used in this study.

3.2 Timepoints and Visit Windows

Visits and assessments will be conducted in line with the Schedule of Activities (section 1.1) and any which are out-of-window will be recorded as protocol deviations and assessed for exclusion from the Per-Protocol (PP) Population (section 4.1.2). Otherwise, the results from each scheduled visit and assessment will directly represent the result at the respective time-point in all analyses.

4 Data Analysis

Data analysis will be performed by the CCI CCI. The statistical analysis software used will be SAS version 9.4 in Windows environment.

Prior to database closure a Blind Data Review Meeting (BDRM) will be conducted in which various aspects of the trial will be discussed and agreed.

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

Subject disposition will be summarized as the number and percentage of subjects who complete the study, with the number who discontinue broken down by reason for discontinuation, by treatment group across study treatment periods (Table 14.1.1) and by sequence group and period (Table 14.1.2). Subject disposition including the subject status (completer, Yes/No), critical demographic data (age, sex, race), the timing of the discontinuation, treatment sequence group, and the specific reason for discontinuation will be listed for all subjects in the Screened population in Listing 16.2.1.1.

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.

Each PD will be assessed as part of the BDR, but possible PDs (list not exhaustive) which may impact the reliability of erosion parameters are non-compliance with the use of study product at the visit, lifestyle considerations or instructions for removal and return of palatal appliance, and therefore will be excluded from the per-protocol population (See Section 4.1.3).

The number and percentage of subjects with any important protocol deviations and with each type of important protocol deviations will be presented by treatment (Table 14.1.3) and listed in Listing 16.2.2.2.

4.1.3 Analysis Populations

The following analysis populations will be defined:

- The Screened population will include all subjects who are screened.
- The Intent-to-Treat (ITT) population will include all subjects who are randomized. Study product group will be assigned to each visit for analyses based on the study product sequence the subject was randomized to.
- The Safety population will include all randomized subjects who receive at least 1 dose of study product. Study product group will be assigned for analyses based on the last known study product the subject actually received prior to the safety event.
- The Per-Protocol (PP) population will include all subjects from the ITT population who have at least one visit with non-missing erosion parameters unaffected by protocol deviations. Study product group will be assigned to each visit for analyses based on the study product the subject received.

Subjects excluded from any of the ITT, Safety and PP analysis populations will be listed for all subjects in the Screened population in Listing 16.2.3, with the reason for exclusion.

4.2 Subject Demographics and Other Baseline Characteristics

4.2.1 Demographic Characteristics

Demographic data (age, sex, race, ethnicity) will be summarized descriptively.

4.2.2 General Medical History

Medical history will be collected in the CRF.

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

4.3.1 Study Product Compliance and Exposure

Non-compliance with study product will be captured as a PD and summarized.

4.3.2 Prior and Concomitant Medication

All prior and concomitant medications will be collected in the CRF.

4.3.3 Medical Device Incidents and Malfunctions

The toothbrushes to be used in this study are medical devices.

All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation and appropriately managed by the sponsor.

4.4 Analysis of Efficacy

Statistical testing of all endpoints in this study will be conducted at a two-sided significance level of 0.05. A sequential testing strategy will be applied to preserve the overall type-1 error control for the respective sequential comparisons between the Experimental dentifrice and Placebo Control at 4 hours for the %SMHR (primary endpoint) and %RER (secondary endpoint). There will be no further adjustments for multiplicity.

All analyses of erosion parameters will be primarily based on the ITT population. If there are more than a 10% of ITT population subjects with at least 1 visit with non-missing erosion parameters deemed to be affected by a protocol deviation, the PP analyses will also be performed as supportive analyses.

Summary statistics including the counts (missing and non-missing), mean, SD, standard error (SE), median, minimum, and maximum will be presented by study product for each parameter for each time-point (4 and 12 hours).

4.4.1 Primary Efficacy Endpoint - %SMHR at 4 hours (Test v Placebo)

4.4.1.1 Primary Efficacy Endpoint Definition

The primary endpoint will be the %SMHR at 4 hours and the comparison between the Experimental dentifrice and Placebo Control.

For each replicate within each specimen (collected after 4 hours *in situ* remineralization) within a particular study visit, the %SMHR (at the replicate level) will be derived as

[(E1-R)/(E1-B)] * 100

where:

B = indentation length (μm) of sound enamel at baseline

E1 = indentation length (μm) after first erosive challenge

R = indentation length (μm) after 4 hours *in situ* remineralization

The %SMHR at the subject visit level (to be used in the analysis) will be derived as the mean of the specimen means (across evaluable replicate %SMHR within a specimen) within that visit. Missing data or data deemed as non-evaluable by the laboratory will not be used in these derivations.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The null and alternative hypotheses are:

- H0: there is no difference between the products.
- H1: there is a difference between the products.

A mixed model (including results across all 3 study products) will be used to analyze the %SMHR at 4 hours with fixed effects for treatment and study visit, as well as random effect for subject. Kenward Rogers degrees of freedom approach will be applied. The least square means for each study product will be presented along with the differences between least square means (Experimental dentifrice - Placebo Control; including two-sided p-value and 95% confidence interval) to test for a difference between products.

The assumption of residual normality and variance homogeneity will be investigated from the mixed model through residual plots. If violated, a non-parametric method (Wilcoxon Signed Rank Test) will be performed for each pairwise comparison of interest as supportive analyses.

4.4.2 Secondary Efficacy Variables

4.4.2.1 %SMHR at 4 hours (Test v Reference and Reference v Placebo)

The results from the mixed model applied from the primary analysis for %SMHR at 4 hours will also be used to test and present the pairwise differences in %SMHR at 4 hours between the Experimental dentifrice versus the Reference dentifrice and the Reference dentifrice versus the Placebo Control.

4.4.2.2 %SMHR at 12 hours

4.4.2.2.1 Secondary Efficacy Endpoint Definition

%SMHR at 12 hours: %SMHR at the subject visit level (to be used in the analysis) will be derived from within specimen replicate results in similar fashion to the %SMHR at 4 hours.

For each replicate within each specimen (collected after 12 hours *in situ* remineralization) within a particular study visit, the %SMHR (at the replicate level) will be derived as

[(E1-R)/(E1-B)] * 100

where:

B = indentation length (µm) of sound enamel at baseline

E1 = indentation length (µm) after first erosive challenge

R = indentation length (µm) after 12 hours *in situ* remineralization

The %SMHR at the subject visit level (to be used in the analysis) will be derived as the mean of the specimen means (across evaluable replicate %SMHR within a specimen) within that visit. Missing data or data deemed as non-evaluable by the laboratory will not be used in these derivations.

4.4.2.2.2 Statistical Hypothesis, Model, and Method of Analysis

The null and alternative hypotheses are:

- H0: there is no difference between the products.
- H1: there is a difference between the products.

The same mixed model as applied for the primary analysis for %SMHR at 4 hours will be applied for the %SMHR at 12 hours. The same 3 pairwise comparisons of interest will be presented.

4.4.2.3 %RER at 4 and 12 hours

4.4.2.3.1 Secondary Efficacy Endpoint Definition

%RER at 4 hours and at 12 hours: The R in the derivation of each secondary endpoint represents the indentation length (μm) after the 4 or 12 hours *in situ* remineralization as appropriate.

The %RER at the subject visit level (to be used in the analysis) will be derived from within specimen replicate results in similar fashion to the %SMHR. The %RER (at the replicate level) will be derived as

$$[(E1-E2)/(E1-B)] * 100$$

where:

B = indentation length (μm) of sound enamel at baseline

E1 = indentation length (μm) after first erosive challenge

E2 = Indentation length (μm) after second erosive challenge.

The %RER at the subject visit level (to be used in the analysis) will be derived as the mean of the specimen means (across evaluable replicate %RER within a specimen) within that visit. Missing data or data deemed as non-evaluable by the laboratory will not be used in these derivations.

4.4.2.3.2 Statistical Hypothesis, Model, and Method of Analysis

The null and alternative hypotheses are:

- H0: there is no difference between the products.
- H1: there is a difference between the products.

The same mixed model as applied for the primary analysis for %SMHR at 4 hours will be applied for %RER at 4 and 12 hours. The same 3 pairwise comparisons of interest will be presented. The residuals from each model will be examined and similar to the primary analysis, supporting non-parametric results be presented if required.

4.4.2.3.3 Exploratory Analysis

The proportion of subjects who evidence a RER ratio (Placebo Control : Experimental dentifrice) >=3 and >=2.5 will be presented along with asymptotic 95% confidence intervals for both 4 and 12 hour time points. Assignments will be made in certain scenarios of RER values at the time point as follows:

- Experimental dentifrice RER ≥ 0 and Placebo Control < 0 = Subject evidenced RER ratio
- Placebo Control ≥ 0 = Subject did not evidence RER ratio

4.4.2.4 % ARR at 4 and 12 Hours

4.4.2.4.1 Secondary Efficacy Endpoint Definition

ARR at 4 hours and at 12 hours: The R in the derivation of each secondary endpoint represents the indentation length (µm) after the 4 or 12 hours *in situ* remineralization as appropriate. The ARR at the subject visit level (to be used in the analysis) will be derived from within specimen replicate results in similar fashion to the %SMHR. The ARR will be derived as

$$1 - [(E2-R)/(E1-B)].$$

where:

B = indentation length (µm) of sound enamel at baseline

R = indentation length (µm) after 4 hours or 12 hours *in situ* remineralization

E1 = indentation length (µm) after first erosive challenge

E2 = Indentation length (µm) after second erosive challenge.

The ARR at the subject visit level (to be used in the analysis) will be derived as the mean of the specimen means (across evaluable replicate ARR within a specimen) within that visit. Missing data or data deemed as non-evaluable by the laboratory will not be used in these derivations.

4.4.2.4.2 Statistical Hypothesis, Model, and Method of Analysis

The null and alternative hypotheses are:

- H0: there is no difference between the products.
- H1: there is a difference between the products.

The same mixed model as applied for the primary analysis for %SMHR at 4 hours will be applied for the ARR at 4 and 12 hours. The same 3 pairwise comparisons of interest will be presented. The residuals from each model will be examined and similar to the primary analysis, supporting non-parametric results be presented if required.

4.4.2.5 EFU at 4 and 12 Hours

4.4.2.5.1 Secondary Efficacy Endpoint Definition

EFU at 4 hours and at 12 hours: The EFU result will be received from the laboratory per specimen, pooled across multiple microdrill enamel biopsies within each specimen. The mean across specimens relating to a specific timepoint (4 or 12 hours) will be derived. The natural log of this mean will be used to represent the subject visit level EFU at the timepoint to be used in the analysis.

Missing data or data deemed as non-evaluable by the laboratory will not be used in these derivations.

4.4.2.5.2 Statistical Hypothesis, Model, and Method of Analysis

The null and alternative hypotheses are:

- H0: there is no difference between the products.
- H1: there is a difference between the products.

The same mixed model as applied for the primary analysis for %SMHR at 4 hours will be applied for the EFU at 4 and 12 hours. The same 3 pairwise comparisons of interest will be presented. The residuals from each model will be examined and similar to the primary analysis, supporting non-parametric results be presented if required. The back-transformed values will be presented to represent the least square geometric means and geometric mean ratio (and 95% CIs).

4.4.3 Handling of Missing Values/Censoring/Discontinuations

Exclusions of any data from the analyses will be determined during a Blinded Data Review (BDR) meeting prior to database lock and unblinding.

If it is not possible to derive the erosion parameter at the visit level due to missing data from specimens not collected and/or data deemed to be non-evaluable by the laboratory, the data will be treated as missing in the Intent-To-Treat (ITT) analyses.

4.5 Analysis of Safety

AEs will be regarded as treatment emergent if they occur on or after the date of first use of study product in the study. In this crossover trial, events will be assigned to the study product being received at the onset of the event. Treatment-emergent adverse events (TEAEs) with an onset date/time between visits will be assigned to the study product received in the previous period. TEAEs with an onset after last use of any study product will be assigned to the last study product used.

The number of distinct events and the number and percentage of subjects having at least one event will be presented by study product and overall for the following:

- AEs (overall only)
- SAEs (overall only)
- TEAEs
- Serious TEAEs
- Oral TEAEs
- Product Related TEAEs
- Device related AEs
- Device Incidents

All AEs and device incidents will be listed providing all relevant details collected in the CRF.

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/protocol amendment (Dated: DD/MMM/YYYY).

Appendix 4: List of Data Displays

	Type	Number	Title	Population	Topline Output
Tables and Figures					
14.1 Demographic Data Summary figures and tables.					
	Table	14.1.1	Subject Disposition by Treatment Group Across Study Treatment Periods	ITT Population	
	Table	14.1.2	Subject Disposition by Sequence Group and Period	ITT Population	
	Table	14.1.3	Incidence of Important Protocol Deviations	ITT Population	
	Table	14.1.4.1	Demographic Characteristics	Safety Population	
	Table	14.1.4.2	Demographic Characteristics	ITT Population	
	Table	14.1.4.3	Demographic Characteristics	PP Population	
14.2 Objectives Data Summary figures and tables.					
	Table	14.2.1.1.1	Statistical Analysis of Surface Microhardness Recovery (%SMHR) at 4 Hours by Treatment Group	ITT Population	Yes
	Table	14.2.1.1.2	Statistical Analysis of Surface Microhardness Recovery (%SMHR) at 4 Hours by Treatment Group	PP Population	Yes
	Table	14.2.1.2.1	Statistical Analysis of Surface Microhardness Recovery (%SMHR) at 12 Hours by Treatment Group	ITT Population	Yes
	Table	14.2.1.2.2	Statistical Analysis of Surface Microhardness Recovery (%SMHR) at 12 Hours by Treatment Group	PP Population	Yes

	Figure	14.2.1.3	Bar Chart with Error Bars (±SE) for Adjusted Mean Surface Microhardness Recovery (%SMHR) at 4 and 12 hours	ITT Population	
	Table	14.2.2.1.1	Statistical Analysis of Relative Erosion Resistance (%RER) at 4 Hours by Treatment Group	ITT Population	Yes
	Table	14.2.2.1.2	Statistical Analysis of % Relative Erosion Resistance (%RER) at 4 Hours by Treatment Group	PP Population	Yes
	Table	14.2.2.2.1	Statistical Analysis of % Relative Erosion Resistance (%RER) at 12 Hours by Treatment Group	ITT Population	Yes
	Table	14.2.2.2.2	Statistical Analysis of % Relative Erosion Resistance (%RER) at 12 Hours by Treatment Group	PP Population	Yes
	Figure	14.2.2.3	Bar Chart with Error Bars (±SE) for Adjusted Mean Relative Erosion Resistance (%RER) by Treatment Group	ITT Population	
	Table	14.2.3.1.1	Statistical Analysis of Acid Resistance Ratio (ARR) at 4 Hours by Treatment Group	ITT Population	
	Table	14.2.3.1.2	Statistical Analysis of Acid Resistance Ratio (ARR) at 4 Hours by Treatment Group	PP Population	
	Table	14.2.3.2.1	Statistical Analysis of Acid Resistance Ratio (ARR) at 12 Hours by Treatment Group	ITT Population	
	Table	14.2.3.2.2	Statistical Analysis of Acid Resistance Ratio (ARR) at 12 Hours by Treatment Group	PP Population	
	Figure	14.2.3.3	Bar Chart with Error Bars (±SE) for Adjusted Mean Acid Resistance Ratio (ARR) at 4 and 12 hours	ITT Population	
	Table	14.2.4	Summary Table of Indents Measures (B/E1/R/E2) by Timepoint and Treatment Group	ITT Population	
	Table	14.2.5.1	Statistical Analysis of Enamel Fluoride Uptake (EFU) at 4 Hours by Treatment Group	ITT Population	
	Table	14.2.5.2	Statistical Analysis of Enamel Fluoride Uptake (EFU) at 12 Hours by Treatment Group	ITT Population	
	Figure	14.2.5.3	Bar Chart with 95% CI for Adjusted Geometric Mean Enamel Fluoride Uptake (EFU)	ITT Population	
14.3 Safety Data					
14.3.1 Displays of Adverse Events					

	Table	14.3.1	Summary of Adverse Events and Device Incidents Overall and by Treatment Group	Safety Population	
SAS Output					
16.1.9 Documentation of statistical methods.					
	SAS Output File	16.1.9.1	Statistical Analysis of Surface Microhardness Recovery (%SMHR) at 4 Hours by Treatment Group	ITT Population	Yes
	SAS Output File	16.1.9.2	Statistical Analysis of Surface Microhardness Recovery (%SMHR) at 4 Hours by Treatment Group	PP Population	Yes
	SAS Output File	16.1.9.3	Statistical Analysis of Surface Microhardness Recovery (%SMHR) at 12 Hours by Treatment Group	ITT Population	Yes
	SAS Output File	16.1.9.4	Statistical Analysis of Surface Microhardness Recovery (%SMHR) at 12 Hours by Treatment Group	PP Population	Yes
	SAS Output File	16.1.9.5	Statistical Analysis of Relative Erosion Resistance (%RER) at 4 Hours by Treatment Group	ITT Population	Yes
	SAS Output File	16.1.9.6	Statistical Analysis of % Relative Erosion Resistance (%RER) at 4 Hours by Treatment Group	PP Population	Yes
	SAS Output File	16.1.9.7	Statistical Analysis of % Relative Erosion Resistance (%RER) at 12 Hours by Treatment Group	ITT Population	Yes
	SAS Output File	16.1.9.8	Statistical Analysis of % Relative Erosion Resistance (%RER) at 12 Hours by Treatment Group	PP Population	Yes
	SAS Output File	16.1.9.9	Statistical Analysis of Acid Resistance Ratio (ARR) at 4 Hours by Treatment Group	ITT Population	
	SAS Output File	16.1.9.10	Statistical Analysis of Acid Resistance Ratio (ARR) at 4 Hours by Treatment Group	PP Population	
	SAS Output File	16.1.9.11	Statistical Analysis of Acid Resistance Ratio (ARR) at 12 Hours by Treatment Group	ITT Population	
	SAS Output File	16.1.9.12	Statistical Analysis of Acid Resistance Ratio (ARR) at 12 Hours by Treatment Group	PP Population	

	SAS Output File	16.1.9.13	Statistical Analysis of Enamel Fluoride Uptake (EFU) at 4 Hours by Treatment Group	ITT Population	
	SAS Output File	16.1.9.14	Statistical Analysis of Enamel Fluoride Uptake (EFU) at 12 Hours by Treatment Group	ITT Population	
16.2 Patient Data Listings					
16.2.1 Discontinued patients.					
	Listing	16.2.1	Subject Disposition	Screened Population	
16.2.2 Protocol deviations.					
	Listing	16.2.2	Protocol Deviations	ITT Population	
16.2.3 Patients excluded from the efficacy analysis.					
	Listing	16.2.3	Exclusions from Efficacy Analysis	ITT Population	
16.2.7 Adverse event listings					
	Listing	16.2.7.1	Adverse Events	ITT Population	
	Listing	16.2.7.2	Device Incidents	ITT Population	

Appendix 5: Table Shells

Each table when output from the SAS analysis program will include the program run date in the top right header and the program name in the bottom left footnote.

Table 14.1.1, Subject Disposition by Treatment Group Across Study Treatment Periods, ITT Population

Study Period		Test	Reference	Placebo	Overall
1	Randomized	N			
	Discontinued Study Prior To Visit	n (x.x%)			
	<reason n>				
	Attended Visit				
	Evaluable Erosion Data				
	<reason if not n>				
. .					
3					
. .					
Overall	Randomized				
	Discontinued Study Prior To Visit				
	<reason n>				
	Attended Visit				
	Evaluable Erosion Data				

Percentages are based on all subjects randomized to each specific period based on randomized sequence.

Table 14.1.2, Subject Disposition by Sequence Group and Period, ITT Population

Study Period		ABC (N=X)	ACB (N=X)	BAC (N=X)	BCA (N=X)	CAB (N=X)	CBA (N=X)	Overall (N=XX)
1	Discontinued Study Prior To Visit	n (x.x%)						
	<reason n>							
	Attended Visit							
	Evaluable Erosion Data							
	<reason if not n>							
: :								
3								
: :								
Overall	Completed Study							
	Discontinued Study							
	<reason n>							

A = Test, B = Reference, C= Placebo
Percentages are based on all subjects randomized within each specific sequence.

Table 14.1.3, Incidence of Important Protocol Deviations, ITT Population

	Test	Reference	Placebo	Overall (N=XXX)
Any Important Protocol Deviation	n (x.x%)			
<PD type 1>				
: :				
<PD type n>				
Any Important Protocol Deviation Leading to Data Exclusion from PP analysis				
<PD type 1>				
: :				
<PD type n>				

Percentages are based on all subjects randomized in the ITT population.

Table 14.1.4, Demographic Characteristics, ITT Population

		Overall (N=XXX)
Age	n, Mean (SD), Median, min-max	x, x.x (x.x), x.x, x-x
Sex	Female	n (x.x%)
	Male	n (x.x%)
Race	American Indian or Alaska Native	n (x.x%)
	Asian	n (x.x%)
	Black or African American	n (x.x%)
	Native Hawaiian or Other Pacific Islander	n (x.x%)
	White	n (x.x%)
	Multiracial	n (x.x%)
	Other	n (x.x%)
Ethnicity	Hispanic or Latino	n (x.x%)
	Not Hispanic or Latino	n (x.x%)

Percentages are based on all subjects randomized in the ITT population.

Table 14.2.1.1.1, Statistical Analysis of Surface Microhardness Recovery (%SMHR) at 4 Hours by Treatment Group, ITT Population (similar table for PP Population if necessary)

Parameter	Test	Reference	Placebo
%SMHR at 4 hours (N=XXX)			
n	x	x	x
Mean (SD, SE)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)
Median	x.xx	x.xx	x.xx
Minimum to Maximum	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
Adjusted Mean (SE, 95% CI)*	x.xx (x.xxx, x.xxx to x.xxx)	x.xx (x.xxx, x.xxx to x.xxx)	x.xx (x.xxx, x.xxx to x.xxx)
vs Placebo (SE)	x.xx (x.xxx)	x.xx (x.xxx)	
95% CI	x.xxx to x.xxx	x.xxx to x.xxx	
p-value	x.xxxx	x.xxxx	
vs Reference (SE)	x.xx (x.xxx)		
95% CI	x.xxx to x.xxx		
p-value	x.xxxx		

*A mixed model with fixed effects for treatment and study visit, and random effect for subject.

All of the tables listed below will be similar to 14.2.1.1.1 (other than decimal places used: SMHR/RER/EFU 2 decimal places for mean, 3 for sd/se/ci; ARR 3 decimals for mean and 4 for sd/se/ci):
Table 14.2.1.2.1, Statistical Analysis of Surface Microhardness Recovery (%SMHR) at 12 Hours by Treatment Group, ITT Population (similar table for PP Population if necessary)
Table 14.2.3.1.1, Statistical Analysis of Acid Resistance Ratio (ARR) at 4 Hours by Treatment Group, ITT Population (similar table for PP Population if necessary)
Table 14.2.3.2.1, Statistical Analysis of Acid Resistance Ratio (ARR) at 12 Hours by Treatment Group, ITT Population (similar table for PP Population if necessary)

Table 14.2.2.1.1, Statistical Analysis of Relative Erosion Resistance (%RER) at 4 Hours by Treatment Group, ITT Population (similar table for PP Population if necessary); Similar table for 14.2.2.2.1, Statistical Analysis of % Relative Erosion Resistance (%RER) at 12 Hours by Treatment Group, ITT Population (similar table for PP Population if necessary)

Parameter	Test	Reference	Placebo
%RER at 4 hours (N=XXX)			
n	x	x	x
Mean (SD, SE)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)
Median	x.xx	x.xx	x.xx
Minimum to Maximum	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
Adjusted Mean (SE, 95% CI)*	x.xx (x.xxx, x.xxx to x.xxx)	x.xx (x.xxx, x.xxx to x.xxx)	x.xx (x.xxx, x.xxx to x.xxx)
vs Placebo (SE)	x.xx (x.xxx)	x.xx (x.xxx)	
95% CI	x.xxx to x.xxx	x.xxx to x.xxx	
p-value	x.xxxx	x.xxxx	
RER Ratio >= 3	x.x% (x.x% to x.x%)		
RER Ratio >=2.5 (95% CI)	x.x% (x.x% to x.x%)		
vs Reference (SE)	x.xx (x.xxx)		
95% CI	x.xxx to x.xxx		
p-value	x.xxxx		

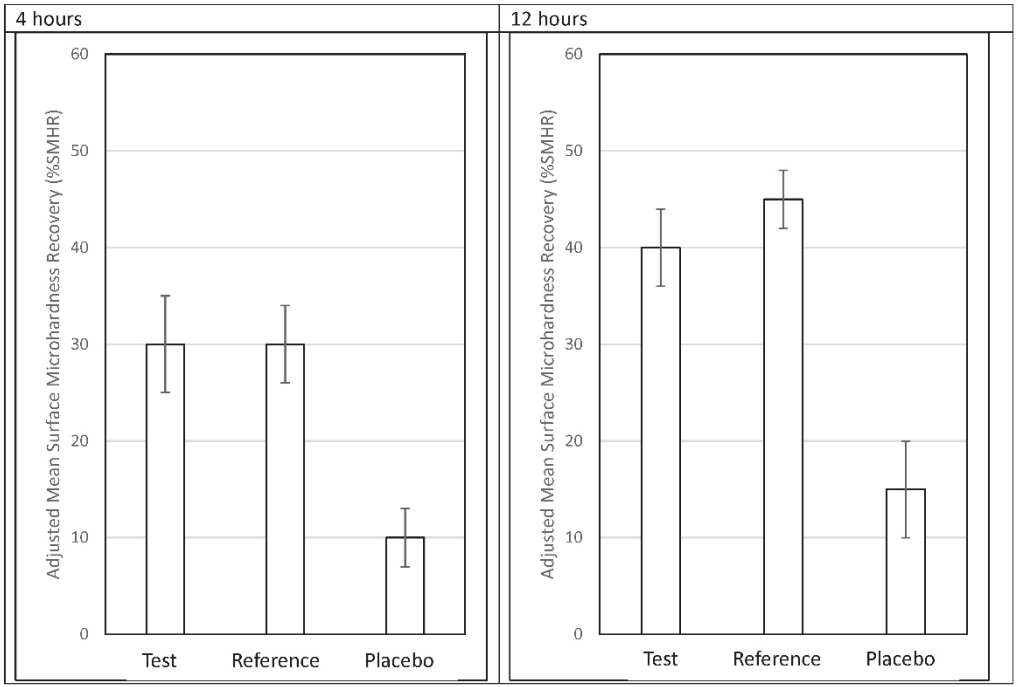
*A mixed model with fixed effects for treatment and study visit, and random effect for subject.

Table 14.2.5.1, Statistical Analysis of Enamel Fluoride Uptake (EFU) at 4 Hours by Treatment Group, ITT Population; Similar table for 14.2.5.2, Statistical Analysis of Enamel Fluoride Uptake (EFU) at 12 Hours by Treatment Group, ITT Population

Parameter	Test	Reference	Placebo
EFU at 4 hours (ug F/cm2) (N=XXX)			
n	x	x	x
Mean (SD, SE)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)
Median	x.xx	x.xx	x.xx
Minimum to Maximum	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
Adjusted Geometric Mean (95% CI)*	x.xx (x.xxx to x.xxx)	x.xx (x.xxx, x.xxx to x.xxx)	x.xx (x.xxx, x.xxx to x.xxx)
vs Placebo, Geometric Mean Ratio (95% CI)	x.xx (x.xxx to x.xxx)	x.xx (x.xxx to x.xxx)	
p-value	x.xxxx	x.xxxx	
vs Reference, Geometric Mean Ratio (95% CI)	x.xx (x.xxx)		
p-value	x.xxxx		

*A mixed model on log transformed EFU with fixed effects for treatment and study visit, and random effect for subject. Estimates are back-transformed.

Figure 14.2.1.3, Bar Chart with Error Bars (±SE) for Adjusted Mean Surface Microhardness Recovery (%SMHR) at 4 and 12 hours, ITT Population



All of the figures listed below will be similar to 14.2.1.3:
Figure 14.2.2.3, Bar Chart with Error Bars (±SE) for Adjusted Mean Relative Erosion Resistance (%RER) by Treatment Group, ITT Population
Figure 14.2.3.3, Bar Chart with Error Bars (±SE) for Adjusted Mean Acid Resistance Ratio (ARR) at 4 and 12 hours, ITT Population
Figure 14.2.5.3, Bar Chart with 95% CI for Adjusted Geometric Mean Enamel Fluoride Uptake (EFU), ITT Population

Table 14.2.4, Summary Table of Indents Measures (B/E1/R/E2) by Timepoint and Treatment Group, ITT Population

Parameter	Test	Reference	Placebo
(N=XXX)			
B at 4 hours			
n	x	x	x
Mean (SD, SE)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)
Median	x.xx	x.xx	x.xx
Minimum to Maximum	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
B at 12 hours			
n	x	x	x
Mean (SD, SE)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)
Median	x.xx	x.xx	x.xx
Minimum to Maximum	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
E1 at 4 hours			
n	x	x	x
Mean (SD, SE)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)
Median	x.xx	x.xx	x.xx
Minimum to Maximum	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
E1 at 12 hours			
n	x	x	x
Mean (SD, SE)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)

Median	x.xx	x.xx	x.xx
Minimum to Maximum	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
R at 4 hours			
n	x	x	x
Mean (SD, SE)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)
Median	x.xx	x.xx	x.xx
Minimum to Maximum	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
R at 12 hours			
n	x	x	x
Mean (SD, SE)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)
Median	x.xx	x.xx	x.xx
Minimum to Maximum	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
E2 at 4 hours			
n	x	x	x
Mean (SD, SE)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)
Median	x.xx	x.xx	x.xx
Minimum to Maximum	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
E2 at 12 hours			
n	x	x	x
Mean (SD, SE)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)	x.xx (x.xxx, x.xxx)
Median	x.xx	x.xx	x.xx

Minimum to Maximum	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx

Table 14.3.1, Summary of Adverse Events and Device Incidents Overall and by Treatment Group, Safety Population

	Test (N=XXX)	Reference (N=XXX)	Placebo (N=XXX)	Overall (N=XXX)
Any Adverse Event				n (x.x%)
Any Serious Adverse Event				n (x.x%)
Any Treatment Emergent Adverse Event (TEAE)	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Any Serious TEAE	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Any Oral TEAE	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Any Product Related TEAE	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Any Device Related AE				n (x.x%)
Any Device Incidents				n (x.x%)

Percentages are based on all subjects in the Safety population according to the study product received.

Listing 16.2.1, Subject Disposition, Screened Population

ID	Age / Sex / Race / Ethnicity	Visit Dates	Treatment Sequence Group	Analysis population	Completer	Reason for Discontinue	Date of Discontinue
	Age / Female or Male / Race / Ethnicity	V1: Date 1 V2: Date 2 V3: Date 3 V4: Date 4 V5: Date 5 V6: Date 6 V7: Date 7	ABC	ITT / SAF / PP	Yes or No	xxxxxxxxxxxxxxx	DDMMMYYYY

A = Test, B = Reference, C= Placebo

Listing, 16.2.2 Protocol Deviations, ITT Population

ID	Visit Dates	Treatment Sequence Group	Date of PD	Protocol Deviation (PD)	Important PD	Important PD affect efficacy and Visit data exclusion from PP analysis
	V1: Date 1 V2: Date 2 V3: Date 3 V4: Date 4 V5: Date 5 V6: Date 6 V7: Date 7	ABC	DDMMMYYYY	xxxxxxxxxxxxxxx	Yes or No	Yes or No, Vx

A = Test, B = Reference, C= Placebo
PP = Per-Protocol

Listing 16.2.3, Exclusions from Efficacy Analysis, ITT Population

ID	Treatment Sequence Group	Study Periods Excluded from PP analysis	Reason for Exclusion
	ABC	P1/P2/P3	xxxxxxxxxxxxxxxxxx

A = Test, B = Reference, C= Placebo

Listing 16.2.7.1, Adverse Events, ITT Population

ID	Visit Dates	Treatment Sequence Group	AE Description	AE Dates Start-Stop	TEAE / Last Study Product Used	Serious/ Severity / Related to Study Product / Oral	Frequency/ Outcome/ Action/ Withdraw from study
	V1: Date 1 V2: Date 2 V3: Date 3 V4: Date 4 V5: Date 5 V6: Date 6 V7: Date 7	ABC	xxxxxxxxxxxxxxxxxxx	DDMMMYYYY-DDMMMYYYY	Yes or No, A	Serious or Not Serious / Mild or Moderate or Severe / Related or Not Related / Oral or Not Oral	Xxxxx/ Xxxxx/ Xxxxx/ Yes or No

A = Test, B = Reference, C= Placebo

Listing 16.2.7.2, Device Incidents, Non-Randomized Subjects

ID	Visit Dates	Treatment Sequence Group	Incident Date	Incident Description	Incident related to AE
	V1: Date 1 V2: Date 2 V3: Date 3 V4: Date 4 V5: Date 5 V6: Date 6 V7: Date 7	ABC	DDMMMYYYY	xxxxxxxxxxxxxxxxxx	Yes or No

A = Test, B = Reference, C= Placebo