STATISTICAL REPORTING AND ANALYSIS PLAN

A Proof of Principle Study to Investigate the Stain Control of Two Stannous Fluoride Dentifrices

Protocol Number: 207872

Phase: NA

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	15-Sept-2017	Not applicable (N/A)

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Glossary

AE	Adverse Event
ANCOVA	Analysis of covariance
BDRM	Blind Data Review Meeting
CI	Confidence Interval
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Manufacture Formulation Code
MLSI	MacPherson modification of the Lobene stain index
PP	Per Protocol
RAP	Statistical Reporting and Analysis Plan
RDA	Relative Dentine Abrasivity
RLR	Review Listing Requirement
SAE	Serious Adverse Event
SOC	System Organ Class

The purpose of this Statistical Reporting and Analysis Plan is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 207872.

1 Summary of Key Protocol Information

This proof of principal (PoP) single centre, randomised, examiner blind, four-treatment arm, parallel design study will be used to evaluate and compare the stain build up of two 0.454% stannous fluoride (SnF_2)/5% sodium tripolyphosphate (STP) dentifrices of differing abrasivity levels, with a marketed standard fluoride dentifrice and a marketed SnF_2 dentifrice.

Stain will be assessed following a full professional dental prophylaxis, at intervals over a 4 week treatment period, using an established clinical measure of extrinsic dental stain - the MacPherson modification [Macpherson, 2000] of the Lobene stain index [Lobene, 1968] (MLSI). Subjects will be stratified by pre-prophylaxis MLSI score (total MLSI Area x Intensity (A×I) for the facial surfaces of the 12 anterior teeth) and smoking status.

The study will be conducted in healthy subjects, aged 18-65 years with a minimum of 16 natural teeth (including the 12 anterior teeth) and in good general health, with a propensity for extrinsic dental stain (in the opinion of the examiner) on the facial surfaces of the anterior teeth.

1.1 Study Design

This is a single-centre, examiner-blind, randomised, four treatment, parallel group study, stratified by baseline total MLSI (A×I) score for the facial surfaces of at least 11 of the 12 anterior teeth (<45 (low); ≥45 (high)) and smoking status (smoker; non smoker). A single dental examiner will perform a full MLSI assessment of the area and intensity of extrinsic dental stain on the facial surfaces of the 6 maxillary and 6 mandibular anterior teeth (universal numbering: 6-11 and 22-27), and the lingual surfaces of the 6 mandibular anterior teeth (universal numbering: 22-27), at baseline (Visit 2), and following 2 and 4 weeks twice daily brushing (Visits 3 and 4).

Potential subjects will be pre-screened via telephone and later attend a screening visit during which they will give their written informed consent to participate in the study. Demography, medical history and concomitant medications will be recorded, followed by an oral examination. This will include an oral soft tissue (OST) examination, a full oral hard tissue (OHT) examination and a visual MLSI stain assessment. Subjects deemed (in the opinion of the examiner) to have a sufficient level of extrinsic dental staining (assessed to be formed due to ingestion of food or drinks, or use of tobacco products) on the facial surfaces of the scorable anterior (maxillary and mandibular) teeth, as well as meeting all other study criteria, will be considered as eligible to proceed with the study. Eligible subjects will continue to use

their own dentifrice at home until their baseline visit. Prior to the baseline visit, subjects will be asked to abstain from oral hygiene for at least 6 hours.

At baseline, each subject will undergo an OST and a full OHT, and then brush their anterior teeth for 30 seconds using a wetted toothbrush (with tap water), prior to undergoing a full MLSI stain assessment. Subjects with a sufficient level of extrinsic dental stain (in the opinion of the examiner) on the facial surfaces of the scorable anterior (maxillary and mandibular) teeth, who continue to meet all study criteria, will be stratified (based on pre-prophylaxis baseline total MLSI (A×I) score and smoking status) and randomised to treatment. The stratification factor will give rise to four strata:

- MLSI Score High (≥45), Smoker
- MLSI Score Low (<45), Smoker
- MLSI Score High (≥45), Non Smoker
- MLSI Score Low (<45), Non Smoker

A dental hygienist will professionally clean each subject's teeth using a conventional dental prophylaxis paste followed by flossing (carried out by the hygienist) to remove all visible stain, plaque, debris, and all sub-and supra-gingival calculus from the anterior teeth. A second dental examiner will confirm all sub- and supra-gingival calculus, visible stain (Total MLSI (A×I) = 0), plaque and debris has been removed from the facial, palatal/lingual surfaces of the anterior teeth (visually and by tactile assessment using a dental explorer). Subjects will then be requested to brush twice daily (morning and evening) with their allocated study dentifrice for the next 4 weeks. They will receive verbal and written product usage instructions. First product use will be supervised on site, with a further supervised brushing at Visit 3. Subjects will be asked to record each product use in a diary, and note any significant changes to diet or smoking status, medications and health during the course of the study, and confirmed by the site at each visit.

Subjects will return to the site at Visits 3 and 4, having abstained from oral hygiene for at least 6 hours prior to their visit. Subjects will brush their anterior teeth for 30 seconds using a wetted toothbrush, prior to undergoing a full MLSI stain assessment. Subjects will be asked to bring their study dentifrice, toothbrush and completed diary card to each visit to facilitate compliance checks.

Randomised subjects who request so will be offered a full mouth dental prophylaxis on completion of Visit 4 procedures, or on completion of the visit where they exit the study.

Repeat examinations will be performed by the dental examiner at each full MLSI assessment visit. Ten subjects will be randomly selected for repeat examinations across each assessment window (a total of 30 repeat examinations over the duration of the study) at Visits 2 (pre-prophylaxis), 3 and 4. There will be a minimum of 10 minutes, and a maximum of 30 minutes between repeatability examinations.

Study Schedule

Procedure	Pre-screening	Visit 1 Screening	Visit 2 Baseline (Day0)	Visit 3 Week 2 (Day14 ± 2)	Visit 4 Week 4 (Day28 ± 2)
Telephone Screening of Subjects	✓				
Inform Consent		✓			
Demographics, Medical History, Smoking Status		✓			
Current / Concomitant Medication		✓	✓	✓	✓
Oral Soft Tissue (OST) Examination		✓	✓		
Full Oral Hard Tissue (OHT) Examination		✓	✓		
Visual MLSI Stain Assessment		✓			
Inclusion / Exclusion Criteria		✓	✓		
Eligibility		✓	✓		
Brush Anterior Teeth for 30 Seconds with Tap Water Prior to Stain Assessment			✓	✓	✓
Pre-prophylaxis Full MLSI Stain Assessment of the Anterior Teeth[1]			✓		
Stratification / Randomisation			✓		
Dental Prophylaxis[2]			✓		
Post-prophylaxis Visual MLSI Stain Assessment			✓		
Full MLSI Stain Assessment[1]				✓	✓
Dispense Study Dentifrice, Timer, Toothbrush and Diary/Instructions Card			✓		
Supervised Brushing on Site			✓[3]	✓	
Adverse Events			✓	✓	✓
Incidents			✓[4]	✓	✓
Subject Adherence and Continuance				✓	✓
Diary Compliance Check[5]				✓	✓
Return Dentifrice, Toothbrush and Diary Card				✓	✓
Post Treatment Dental Prophylaxis					✓[6]
Study End					✓

1. Ten subjects will be randomly selected for repeat examinations across each assessment window (a total of 30 repeat examinations over the duration of the study).
2. AEs will be recorded from and including dental prophylaxis onwards.
3. Time of first brushing will be captured to distinguish dentifrice AEs from prophylaxis AEs.
4. Incidents will be collected from first use of the tooth brush, prior to stain assessment.
5. Time of each brushing occasion in addition to missed/additional brushings, and changes to smoking status will be captured in the subject diary.
6. Once all efficacy assessments have been completed randomised subjects who request so will be given a full dental prophylaxis, and will be recorded in the eCRF

1.2 Study Objectives

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of two experimental 0.454% SnF_2 / 5% STP dentifrices with that of a marketed standard fluoride dentifrice, after 4 weeks twice daily use.	Overall MLSI at week 4
Secondary Objectives	**Secondary Endpoints**
To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of two experimental 0.454% SnF_2 / 5% STP dentifrices with that of a marketed SnF_2 dentifrice, after 4 weeks twice daily use.	Overall MLSI at week 4.
To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of a marketed SnF_2 dentifrice with that of a marketed standard fluoride dentifrice, after 4 weeks twice daily use.	Overall MLSI at week 4.
Exploratory Objectives	**Exploratory Endpoints**
To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of an experimental 0.454% SnF_2 / 5% STP, 2.0% abrasive silica dentifrice with that of an experimental 0.454% SnF_2 / 5% STP, 3.5% abrasive silica	Overall MLSI at week 4.

Objectives	Endpoints
dentifrice, after 4 weeks twice daily use.	
To evaluate and compare the build up of extrinsic tooth stain , as measured by overall MLSI (A×I), of two experimental 0.454% SnF_2 / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF_2 dentifrice, after 2 weeks twice daily use.	Overall MLSI at week 2.
To evaluate and compare the build up of extrinsic tooth stain, as measured by overall Interproximal (Distal + Mesial) MLSI, of two experimental 0.454% SnF_2 / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF_2 dentifrice, after 2 and 4 weeks twice daily use.	Overall Interproximal (Distal + Mesial) MLSI at weeks 2 and 4.
To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI Area (A), of two experimental moderate abrasivity 0.454% SnF_2 / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF_2 dentifrice, after 2 and 4 weeks twice daily use.	Overall MLSI Area at weeks 2 and 4.
To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI Intensity (I), of two experimental moderate abrasivity 0.454% SnF2 / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF2 dentifrice, after 2 and 4 weeks twice daily use.	Overall MLSI Intensity at weeks 2 and 4.

1.3 Treatments

	Test Product 1	Test Product 2	Reference Product 1	Reference Product 2
Product Name	Experimental dentifrice containing 0.454% SnF_2 / 5% STP; 2.0% abrasive silica (RDA~58)	Experimental dentifrice containing 0.454% SnF_2 / 5% STP; 3.5% abrasive silica (RDA~77)	Dentifrice containing 1000ppm fluoride as Sodium Monofluorophoshate (SMFP; Colgate Cavity Protection®, Canada Marketed dentifrice) moderate abrasivity (RDA~80)	Dentifrice containing 0.454% SnF_2 (Sensodyne Complete Protection, Canada Marketed dentifrice) higher abrasivity (RDA~120)
Short Product Name	Test dentifrice (RDA~58)	Test dentifrice (RDA~77)	Reference dentifrice (RDA~80)	Reference dentifrice (RDA~120)
Product Formulation Code (MFC)	CCI	CCI	Commercially Available	Commercially Available

1.4 Sample Size Calculation

A sufficient number of subjects will be screened to randomise at least 220 subjects to ensure 200 evaluable subjects complete the study. This will ensure approximately 50 evaluable subjects per treatment arm. This study has not been formally powered to make any claims, and is appropriately sized as a PoP study for the purpose of observing meaningful trends.

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 have been completed and database has been locked.
3. All criteria for unblinding the randomisation codes have been met and the randomisation codes have been distributed.

3 Considerations for Data Analyses and Data Handling Conventions

3.1 Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value.

3.2 Subgroups/Stratifications

Eligible subjects will be stratified by baseline total MLSI (A×I) score (Low: <45; High: ≥45) and smoking status into four strata in study treatment randomization.

- MLSI Score High (≥45), Smoker
- MLSI Score Low (<45), Smoker
- MLSI Score High (≥45), Non Smoker
- MLSI Score Low (<45), Non Smoker

Subjects identified as being in the wrong strata will be placed in correct strata prior to analysis and will also be considered for protocol deviations and potential exclusion from a PP analysis.

3.3 Timepoints and Visit Windows

Time windows required for this study are as the following:

- Visit 2 (Baseline) is minimum 24 hours and maximum two weeks from Visit 1 (Screening)
- Visit 3 (Week 2) is 14 ± 2 Days from Visit 2
- Visit 4 (Week 4) is 28 ± 2 Days from Visit 2

4 Data Analysis

Data analysis will be performed by inVentiv Health Clinical. 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. The statistical analysis software used will be SAS version 9.4.

All listings will be produced for all randomized subjects, unless otherwise stated.

4.1 Populations for Analysis

Except otherwise specified, tables described in this section will be produced for all randomised subjects.

4.1.1 Subject Disposition

Screen failures will be defined as subjects who consent to participate in the study but are never subsequently randomised. A summary will be provided of the number of subjects screened and the number of screen failures.

Subject disposition will be summarised as the number and percentage of subjects (out of the number of randomised subjects) who complete the study, with the number who discontinue broken down by reason for discontinuation (Table 14.1.1). The table will also summarise the number and percent of subjects assigned to each analysis population (defined in Section 2.1.3). The summary will be presented by treatment and overall.

Subject disposition will be listed for randomised subjects (Listing 16.2.1.1) and non-randomised subjects (Listing 16.2.1.2) separately.

4.1.2 Protocol Deviations

Important major protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study. All deviations will be reviewed prior to unblinding and closure of the database to ensure all important deviations are captured and categorised.

Major deviations of the protocol procedures identified as liable to influence the efficacy outcome may include the following

- Deviation from the inclusion/exclusion criteria
- Use of prohibited medication
- Not receiving randomised treatment

Further deviations liable to influence the efficacy outcome will be given in the "Review Listing Requirement (RLR)" document and major deviations will be identified in blinded data review stage. The number and percentage of subjects with any major protocol deviations and with each type of major protocol deviations will be presented by treatment (Table 14.1.2) for randomised subjects and listed in Listing 16.2.2.1. Any minor protocol deviations will be listed similarly (Listing 16.2.2.2).

4.1.3 Analysis Populations

Six populations are defined below.

Population	Definition / Criteria	Analyses Evaluated
All Screened Subjects	All subjects who enter the study and sign the informed consent form. This population includes screen failures as well as those that are randomised	Disposition, AE listing
Randomised	All subjects who are randomised and may or may not receive the application of the study products.	Protocol violations
Safety	All subjects who are randomised and receive at least one dose of investigational product. The Safety population will be reported by treatment received.	Safety analysis
Intent-to-Treat (ITT)	The 'Intent to treat' (ITT) population will include all subjects who are randomised, receive at least one dose of investigational product and have at least one post-baseline efficacy assessment. The ITT population will be reported by randomised treatment.	MLSI analysis
Per-Protocol (PP)	The 'Per-Protocol' (PP) population will include all subjects in the ITT population who have at least one efficacy assessment considered unaffected by protocol deviations. Efficacy assessments considered affected by protocol deviations will be excluded from PP analysis.	MLSI analysis
Repeatability population	All subjects who have an initial and a repeat stain examination at each full MLSI assessment visit.	MLSI repeatability analysis

The primary population for assessment of efficacy will be the ITT population. A PP analysis will be performed on the primary variable (MLSI at week 4) only if more than 20% of the subjects in the ITT population are excluded from the PP population.

The numbers of subjects excluded from each population broken down by the reason for exclusion will be presented (Table 14.1.3). Subjects excluded from any of the analysis populations will be listed (Listing 16.2.3.1).

4.2 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the ITT.

4.2.1 Demographic Characteristics

Categorical demographic variables include sex and race. These variables will be summarised by the number and percentage of subjects with each relevant characteristic (Table 14.1.4.1 for the Safety population, Table 14.1.4.2 for the ITT population). Age will be summarised by the mean, standard deviation (SD), median, minimum and maximum values. Baseline stratification will also be summarised by the number and percentage of subjects in each stratum. All summaries will be presented by treatment, and overall. All demographic information will be listed for randomised subjects (Listing 16.2.4.1).

4.2.2 General Medical History

Medical history data will be listed for all randomised subjects in Listing 16.2.4.2 with start date and end date or ongoing at the start of study drug. A data listing will also be produced for evaluation of protocol deviations at the blinded data review stage.

4.3 Treatments (Study Product Compliance and, Concomitant Therapies)

4.3.1 Study Product Compliance

Brushing compliance (using study products twice daily) will be listed and checked at the blinded data review stage for evaluation of protocol deviations.

4.3.2 Prior and Concomitant Medication

Prior and concomitant medication/non-drug treatments data will be listed in Listing 16.2.5.1, 16.2.5.2. Prior medications are defined as those stopped before the first administration of the study products. Concomitant medications are defined as those ongoing or started on or after the the first administration of the study products.

A data listing will also be produced for evaluation of protocol deviations at the blinded data review stage.

4.4 Analysis of Efficacy

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary endpoint is the Week 4 overall MLSI (A×I).

Each tooth site will be evaluated for stain level and will be assigned an intensity score (I) and an area score (A) by the examiner. Overall MLSI (A×I) score for each subject at each visit (Baseline, Week 2 and Week 4) is calculated as the mean MLSI (A×I) score over all gingival, body, mesial and distal sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth. It is

possible that some sites could have missing values, in that case the mean is calculated over all non-missing sites

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

Summary statistics including mean, SD, median, min, max will be provided for baseline and Week 4 by randomised treatment group (Table 14.2.1.1.1). The overall MLSI score at Week 4 will be analysed using analysis of covariance (ANCOVA) with treatment and smoking status (smoker/non-smoker) as factor and pre-prophylaxis baseline overall MLSI score as covariate.

The primary comparisons are

- Test dentifrice (RDA-58) vs. Reference dentifrice (RDA-80)
- Test dentifrice (RDA-77) vs. Reference dentifrice (RDA-80).

All other comparisons associated with secondary and exploratory objectives will also be presented under the same analysis, namely

- Test dentifrice (RDA-58) vs. Reference dentifrice (RDA-120) (secondary)
- Test dentifrice (RDA-77) vs. Reference dentifrice (RDA-120) (secondary)
- Reference dentifrice (RDA-120) vs. Reference dentifrice (RDA-80) (secondary)
- Test dentifrice (RDA-58) vs. Test dentifrice (RDA-77) (exploratory)

Adjusted means of all treatments will be provided. Treatment differences of above mentioned comparisons will be provided together with their 95% CIs and p-values (Table 14.2.1.1.2). The assumption of residual normality in ANCOVA analysis will be investigated. If violated, data transformation or a non-parametric method (e.g., the Wilcoxon rank sum test) will be applied.

There will be no multiplicity adjustment for treatment comparisons as this study is an exploratory POP study.

Efficacy will be evaluated based on the ranking performance of the study treatments on the stain variables. The minimum requirement will be similar, or lower levels of stain for at least one of the experimental products compared to the standard fluoride dentifrice (Colgate Cavity Protection®). The marketed SnF_2 dentifrice (Sensodyne Complete Protection) will be expected to demonstrate a comparable, or statistically significantly better performance on the stain variables versus the experimental products and Colgate Cavity Protection®.

4.4.1.3 Supportive Analyses

The assumption of residual normality in ANCOVA analysis will be investigated. If violated, data transformation or a non-parametric method (e.g., the Wilcoxon rank sum test) will be applied.

4.4.2 Secondary Efficacy Variables

Secondary efficacy variable is Week 4 overall MLSI (A×I) for comparisons of

- Test dentifrice (RDA-58) vs. Reference dentifrice (RDA-120)
- Test dentifrice (RDA-77) vs. Reference dentifrice (RDA-120)
- Reference dentifrice (RDA-120) vs. Reference dentifrice (RDA-80).

These are covered under the primary efficacy section.

4.4.3 Exploratory Efficacy Variables

In addition to Week 4 overall MLSI (A×I) for the comparion between two test products (as covered in primary efficacy section), the following exploratory variables will be assessed in this study.

- Overall MLSI (A×I) score at Week 2, which will be calculated in the same way as described in Section 4.4.1.1.
- Overall interproximal MLSI (A×I) scores at Week 2 and Week 4, which will be calculated as the mean MLSI (A×I) score over all interproximal (mesial+distal) sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.
- Overall MLSI (A) scores at Week 2 and Week 4, which will be calculated as the mean MLSI (A) score over all gingival, body, mesial and distal sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.
- Overall MLSI (I) scores at Week 2 and Week 4, which will be calculated as the mean MLSI (I) score over all gingival, body, mesial and distal sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.

4.4.4 Handling of Missing Values/Censoring/Discontinuations

Missing data will not be replaced or imputed. Subjects who withdraw from the study prematurely will be included in the statistical analyses up to the point of discontinuation.

4.5 Analysis of Secondary Objectives

Seconary objectives on Week 4 overall MLSI (A×I) have been covered in primary efficacy section.

4.6 Analysis of Exploratory Objectives

Week 4 overall MLSI (A×I) for the comparion between two test products has been covered in primary efficacy section.

For Overall MLSI (AxI) at Week 2, Overall interproximal MLSI (AxI), MLSI (A) and MLSI (I) at Week 2 & 4, summary statistics (N, Mean, SD, Median, Min, Max) will be presented. These variables will also be analysed using ANCOVA with treatment and smoking status as factor and corresponding baseline overall MLSI score (interproximal, area or intensity) as covariate. Adjusted means of all treatments will be provided and treatment differences for comparisons

- Test dentifrice (RDA-58) vs. Reference dentifrice (RDA-80)
- Test dentifrice (RDA-77) vs. Reference dentifrice (RDA-80)
- Test dentifrice (RDA-58) vs. Reference dentifrice (RDA-120)
- Test dentifrice (RDA-77) vs. Reference dentifrice (RDA-120)
- Reference dentifrice (RDA-120) vs. Reference dentifrice (RDA-80)
- Test dentifrice (RDA-58) vs. Test dentifrice (RDA-77)

will be provided together with their 95% CIs and p-values. Results for overall interproximal MLSI (A×I) score, overall MLSI area score and overall MLSI intensity score will be presented in Table 14.2.2.1, 14.2.2.2, Table 14.2.3.1, 14.2.3.2 and Table 14.2.4.1, 14.2.4.2 respectively.

4.7 Analysis of Safety

4.7.1 Adverse Events and Serious Adverse Events

All safety data will be reported for the Safety population as per actual treatment received. All subjects screened will be included in the list of AEs.

AE will be regarded as treatment emergent if they occur on or after the start date and time of the first treatment usage (as determined by start date and time from the EXPOSURE/dispensing panel; if this date is missing a suitable alternative will be used eg date and time of randomisation). All other AEs prior to this will be considered non-treatment emergent.

All AEs will be reviewed by Clinical Research prior to database freeze and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). During this review stage, AEs will be further categorized as oral or non-oral.

The following summary tables and listings will be presented by treatment group.

- Table of treatment emergent AEs by Oral/Non-Oral and Preferred Term (Table 14.3.1.2)

- Table of treatment emergent AEs by SOC and Preferred Term (Table 14.3.1.1)
- Table of treatment emergent AEs by SOC, Preferred Term and Severity (Table 14.3.1.3)
- Table of Treatment emergent treatment related AEs by Oral/Non-Oral and Preferred Term (Table 14.3.1.4)
- Listing of all AEs (including all subjects: Listing 16.2.7.1 for all randomised subjects; Listing 16.2.7.2 for non-randomised subjects)
- Listing of death (Listing 14.3.2.1)
- Listing of non-fatal SAEs (Listing 14.3.2.2)
- Listing of treatment emergent AEs leading to withdrawal (Listing 14.3.2.3)
- Listing of treatment emergent AEs classified as oral (Listing 14.3.2.4)

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

4.7.2 Other Safety Variables

All incidents captured in the study will be listed in Listing 16.2.7.3.

4.8 Analysis of Other Variables

There will be ten subjects selected for repeated MLSI assessments to test the consistency of the examiner. .

The repeat MLSI area and intensity assessments will be cross tabulated (Table 14.2.5.1 and Table 14.2.5.2) and compared to the original assessments and will not be used in any efficacy analysis. A weighted Kappa coefficient (κ), along with the 95% CI will be calculated to assess the intra-examiner reliability. Fleiss-Cohen weighted kappa will be calculated for the repeatability analysis. Reliability will be deemed

- Excellent if $\kappa > 0.75$
- Fair to good if $0.4 \leq \kappa \leq 0.75$
- Poor if $\kappa < 0.4$

All subjects who have repeatability data will be included in this analysis.

5 Changes to the Protocol Defined Statistical Analysis Plan

There is an additional analysis to the originally planned statistical analysis specified in the protocol version 5.0 [(Dated: 30/May/2017)]. This additional analysis is the repeatability analysis described in Section 4.7.

6 References

Lobene RR. Effect of Dentifrices on Tooth Stains with Controlled Brushing. Journal of American Dentistry 1968: 77; 849-855.

Macpherson LM, Stephen KW, Joiner A, Schäfer F, Huntington E. Comparison of a conventional and modified tooth stain index. J Clin Periodontol. 2000: Nov; 27(11): 854-9.

Attachment 1: List of Data Displays

PPD

Attachment 2: Templates for Tables, Figures and Listings

This is a guideline which will give the guidance of treatment labels that will be used for the table header and in the figures, listings and in the footnotes.

The treatment labels for the column heading will be as follow:

- Test dentifrice (RDA-58)
- Test dentifrice (RDA-77)
- Reference dentifrice (RDA-80)
- Refrence dentifrice (RDA-120)

Protocol 207872 Program Run Date:xxxx

Table 14.1.1
Subject Disposition
All Screened Subjects

All Screened Subjects (N=xxx)

	Test Dentifrice (RDA-58) N (%)	Test Dentifrice (RDA-77) N (%)	Reference Dentifrice (RDA-80) N (%)	Reference Dentifrice (RDA-120) N (%)	Overall N (%)
TOTAL SUBJECTS SCREENED					xxx
SUBJECTS NOT RANDOMISED					xxx (xx.x)
DID NOT MEET STUDY CRITERIA					xxx (xx.x)
ADVERSE EVENT					Xxx (xx.x)
LOST TO FOLLOW UP					xxx (xx.x)
PROTOCOL VIOLATION					Xxx (xx.x)
WITHDRAWAL OF CONSENT					Xxx (xx.x)
OTHER					Xxx (xx.x)
SUBJECTS RANDOMISED	xxx	xxx	xxx	xxx	xxx
COMPLETED STUDY	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DID NOT COMPLETE STUDY	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DID NOT MEET STUDY CRITERIA	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
ADVERSE EVENT	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
LOST TO FOLLOW-UP	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PROTOCOL VIOLATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

	Test Dentifrice (RDA-58) N (%)	Test Dentifrice (RDA-77) N (%)	Reference Dentifrice (RDA-80) N (%)	Reference Dentifrice (RDA-120) N (%)	Overall N (%)
WITHDRAWAL OF CONSENT	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
OTHER	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
SAFETY POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
ITT POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PP POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Percentages for non-randomised category are based on number of screened subjects; percentages for randomised category are based on number of randomised subjects

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PPD

Protocol 207872 Program Run Date:xxxx

Table 14.1.2
Analysis of Population
Randomised Population

Randomised Population (N=xxx)

	Test Dentifrice (RDA-58) N (%)	Test Dentifrice (RDA-77) N (%)	Reference Dentifrice (RDA-80) N (%)	Reference Dentifrice (RDA-120) N (%)	Overall N (%)
SUBJECTS EXCLUDED FROM SAFETY POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
REASON 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
REASON 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...					
SUBJECTS EXCLUDED FROM ITT POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
REASON 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
REASON 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...					
SUBJECTS WITH AT LEAST ONE DATA POINT EXCLUDED FROM PP ANALYSIS	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
SUBJECTS COMPLETELY EXCLUDED FROM PP POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PROTOCOL DEVIAIONS LEADING TO EXCLUSION FROM PP					
EXCLUDING ALL					

	Test Dentifrice (RDA-58) N (%)	Test Dentifrice (RDA-77) N (%)	Reference Dentifrice (RDA-80) N (%)	Reference Dentifrice (RDA-120) N (%)	Overall N (%)
DEVIATION 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATION 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...					
EXCLUDING WEEK2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATION 3	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATION 4	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...					
EXCLUDING WEEK4	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATION 5	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATION 6	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...					

Protocol 207872 Program Run Date:xxxx

Table 14.1.3.1
Subject Demographics and Baseline Characteristics
Safety Population

Safety Population (N=XX)

	Test Dentifrice (RDA-58) (N=XX)	Test Dentifrice (RDA-77) (N=XX)	....	Overall (N=XX)
SEX n (%)				
MALE	xx (xx.x)	xx (xx.x)	...	xx (xx.x)
FEMALE	xx (xx.x)	xx (xx.x)	...	xx (xx.x)
RACE n (%)				
ASIAN	xx (xx.x)	xx (xx.x)	...	xx (xx.x)
BLACK or AFRICAN	xx (xx.x)	xx (xx.x)	...	xx (xx.x)
AMERICAN INDIAN OR ALASKA NATIVE	xx (xx.x)	xx (xx.x)	...	xx (xx.x)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	xx (xx.x)	xx (xx.x)	...	xx (xx.x)
WHITE	xx (xx.x)	xx (xx.x)	...	xx (xx.x)
MULTIPLE	xx (xx.x)	xx (xx.x)	...	xx (xx.x)
AGE (YEARS)				
n	XX	XX	...	XX
MEAN	XX.X	XX.X	...	XX.X
SD	XX.XX	XX.XX	...	XX.XX
MEDIAN	XX.X	XX.X	...	XX.X

	Test Dentifrice (RDA-58) (N=XX)	Test Dentifrice (RDA-77) (N=XX)	....	Overall (N=XX)
MINIMUM	XX	XX	...	XX
MAXIMUM	XX	XX	...	XX
STRATIFICATION				
MLSI HIGH, SMOKER	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MLSI LOW, SMOKER	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MLSI HIGH, NON-SMOKER	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MLSI LOW, NON-SMOKER	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Protocol 207872 Program Run Date:xxxx

Table 14.2.1.1.1
Summary of Overall MLSI (AXI) Score
Intent-to-Treat Population

Intent-to-Treat Population (N=XX)

Visit		Test Dentifrice (RDA-58) (N=XX)	TestDentifrice (RDA-77) (N=XX)	Reference Dentifrice (RDA-80) (N=XX)	Reference Dentifrice (RDA-120) (N=XX)	Overall (N=XXX)
Baseline	N	Xx	Xx	xx	Xx	xx
	MEAN	x.xx	x.xx	x.xx	x.xx	x.xx
	SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
	SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
	MEDIAN	x.xx	x.xx	x.xx	x.xx	x.xx
	MINIMUM	X.xx	X.xx	x.xx	X.xx	x.xx
	MaxIMUM	X.xx	X.xx	x.xx	X.xx	x.xx
Week 2	N	Xx	Xx	xx	Xx	
	MEAN	x.xx	x.xx	x.xx	x.xx	
	SD	x.xxx	x.xxx	x.xxx	x.xxx	
	SE	x.xxx	x.xxx	x.xxx	x.xxx	
	MEDIAN	x.x	x.x	x.x	x.x	
	MINIMUM	X.x	X.x	x.x	X.x	
	MAXIMUM	X.x	X.x	x.x	X.x	
Week 4	Same as above					

Protocol 207872 Program Run Date:xxxx

Table 14.2.1.1.2
Statistical Analysis of Overall MLSI (AXI) Score
Intent-to-Treat Population

Intent-to-Treat Population (N=XX)

Visit		Test Dentifrice (RDA-58) (N=XX)	Test Dentifrice (RDA-77) (N=XX)	Reference Dentifrice (RDA-80) (N=XX)	Reference Dentifrice (RDA-120) (N=XX)
Week 2	LSmean (SE)[1]	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)

Comparison[1],[2]	Difference	95% CI	P-value
Test Dentifrice (RDA-58) vs Reference Dentifrice (RDA-80)	x.xx	(x.xx, x.xx)	0.xxxx
Test Dentifrice (RDA-77) vs Reference Dentifrice (RDA-80	x.xx	(x.xx, x.xx)	0.xxxx
Test Dentifrice (RDA-58) vs Reference Dentifrice (RDA-120)	x.xx	(x.xx, x.xx)	0.xxxx
Test Dentifrice (RDA-77) vs Reference Dentifrice (RDA-120)	x.xx	(x.xx, x.xx)	0.xxxx
Test Dentifrice (RDA-58) vs Test Dentifrice (RDA-77)	x.xx	(x.xx, x.xx)	0.xxxx
Reference Dentifrice (RDA-120) vs Reference Dentifrice (RDA-80)	x.xx	(x.xx, x.xx)	0.xxxx

Week 4	Same as above

[1] From ANCOVA with treatment and smoking status as factors and baseline [variable] score as covariate

[2] Difference is first named treatment minus second named treatment such that a negative difference favours the first named treatment

PPD

Protocol 207872 Program Run Date:xxxx

Table 14.2.5.1
Repeatability for MLSI Intensity Score
Repeatability Population

Repeatability Population (N=XX)

	Initial \ Repeated	Missing	0	1	2	3
	Missing	xx	xx	xx	xx	xx
	0	xx	xx	xx	xx	xx
	1	xx	xx	xx	xx	xx
	2	xx	xx	xx	xx	xx
	3	xx	xx	xx	xx	xx
Kappa	0.xx					
95% CI	(0.xx, 0.xx)					

Intensity Score: 0=No Stain; 1=light Stain; 2=Moderate Stain; 3=Heavy Stain. Missing means non-scorable.

PPD

Note to Programmer: For Table 14.2.5.2, use area scoring descriptions in footnote.

Protocol 207872 Program Run Date:xxxx

Table 14.3.1.1
Treatment Emergent Adverse Event by System Organ Class and Preferred Term
Safety Population

Safety Population (N=xx)

System Organ Class Preferred Term	Test Dentifrice (RDA-58) (N=XX)		Test Dentifrice (RDA-77) (N=XX)		Reference Dentifrice (RDA-80) (N=xx)		Reference Dentifrice (RDA-120) (N=xx)		Overall (N=XX)	
	n (%)	nAE	n (%)	nAE	n (%)	nAE	n (%)	nAE	n (%)	nAE
NUMBER OF SUBJECTS WITH AT LEAST ONE AE	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
NUMBER OF SUBJECTS WITH NO AE	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ERYTHEMA	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
DERMATITIS	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
GASTROINTESTINAL SYSTEM	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ABDOMINAL PAIN	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
DRY MOUTH	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
VOMITTING	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Etc.										

n (%) = Number (percent) of subjects nAE = Number of adverse events.

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PPD

Note to Programmer: For Table 14.3.1.2, change 'System Organ Class' to 'Oral/Non-Oral'

Protocol 207872 Program Run Date:xxxx

Table 14.3.1.3
Treatment Emergent Adverse Event by System Organ Class, Preferred Term and Severity
Safety Population

Safety Population (N=xx)

System Organ Class Preferred Term	Test Dentifrice (RDA-58) (N=XX)						...	Overall (N=XX)					
	Mild		Moderate		Severe			Mild		Moderate		Severe	
	n (%)	nAE	n (%)	nAE	n (%)	nAE		n (%)	nAE	n (%)	nAE	n (%)	nAE
NUMBER OF SUBJECTS WITH AT LEAST ONE AE	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ERYTHEMA	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
DERMATITIS	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
GASTROINTESTINAL SYSTEM	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ABDOMINAL PAIN	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
DRY MOUTH	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
VOMITTING	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

n (%) = Number (percent) of subjects nAE = Number of adverse events.

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Protocol 207872 Program Run Date:xxxx

Listing 16.1.7
Randomisation Information
Randomised Population

Stratum 1: MLSI High, Smoker (Seed: xxxxxx)

Subject Number	Age/Sex/ Race [1]	Randomisation Number	Treatment Randomised	Date of Randomisation
PPD				

* Block size of the study is X.
[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple

Protocol 207872 Program Run Date:xxxx

Listing 16.2.1.1
Subject Disposition
Randomised Population

Treatment Group: Test Dentifrice (RDA-58)

Subject	Age/Sex/ Race [1]	Screening Date	Treatment Start Date and Time	Date of Completion or Withdrawal	Duration of Treatment (Days)	Completed (Yes/No)	Primary Reason for Withdrawal
PPD							
….							

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.

Protocol 207872 Program Run Date:xxxx

Listing 16.2.1.2
Subject Disposition
Non-Randomised Subjects

Subject Number	Age/Sex/ Race [1]	Screening Date	Reason for Screen Failure
PPD			

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.

Protocol 207656 Program Run Date:xxxx

Listing 16.2.2.1
Major Protocol Deviations
All Randomized Subjects

Treatment Group: XXXXXX

Subject	Sex/Age/ Race [1]	Week(s) Excluded from PP Population	Deviation Reason
PPD			

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.

Protocol 207872 Program Run Date:xxxx

Listing 16.2.2.2
Minor Protocol Deviations
Randomised Population

Treatment Group: Test Dentifrice (RDA-58)

Subject Number	Age/Sex/Race[1]	Visit	Deviation Sequence	Protocol Deviation
PPD				xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, O = Multiple.

Protocol 207872 Program Run Date:xxxx

Listing 16.2.3.1
Exclusion from Analysis Population
Randomised population

Treatment Group: Test Dentifrice (RDA-58)

Subject Number	Age/Sex/Race[1]	Treatment Start Date and Time	Safety Population (Yes/No)	ITT Population (Yes/No)	PP population (Yes/No)
PPD					

[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, O = Multiple.

PPD

Programming Note for Listing 16.2.3: This listing is based on population definition document.

Protocol 207872 Program Run Date:xxxx

Listing 16.2.4.1
Demographic Characteristics
Randomised Population

Treatment Group: Test Dentifrice (RDA-58)

Subject Number	Age (years)	Sex	Race	Stratification
PPD				

Protocol 207872 Program Run Date:xxxx

Listing 16.2.4.2
Medical History and Current Medical Conditions
Randomised Population

Treatment Group: Test Dentifrice (RDA-58)

Subject	Age/Sex/Race [1]	Any Medical History? (Yes/No)	Medical Condition	Start Date	Ongoing? (Yes/No)	End Date
PPD			xxxxxxxxxxx	DDMMMYYYY	PPD	DDMMMYYYY
….						

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.

Protocol 207872 Program Run Date:xxxx

Listing 16.2.5.2
Concomitant Medications and Significant Non-drug Therapies Taken During Treatment
Randomised Population

Treatment Group: Test Dentifrice (RDA-58)

Subject Number	Age/Sex/Race[1]	Sequence Number	Treatment	Reason for Treatment	Frequency	Start Date	Ongoing? (Yes/No)
PPD			xxxxx	xxxxxx	xx	PPD	

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.

Protocol 207872 Program Run Date:xxxx

Listing 16.2.6.1
MLSI Stain Index
Randomised Population

Treatment Group: Test Dentifrice (RDA-58)

Subject Number	Age/Sex/Race[1]	Visit	Tooth Number (universal/FDI)	Surface	Site	Intensity (I) Score[2]	Area (A) Score[3]	AXI Score
PPD						x	x	x

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.
[2] Intensity Index: 0=No Stain; 1=light Stain;2=Moderate Stain; 3=Heavy Stain. Missing means non-scorable; X=Missing.
[3] Area Index: 0=No Stain; 1=Stain covering upto 1/3 of region; 2=Stain covering upto 1/3 of region, and no more than 2/3 of region ; 3=Stain covering more than 2/3 of region; X=Missing

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Protocol 207872 Program Run Date:xxxx

Listing 16.2.6.2
Overall MLSI Stain Score
Randomised Population

Treatment Group: Test Dentifrice (RDA-58)

Subject Number	Age/Sex/Race[1]	Visit	Overall MLSI (AXI) Score [2]	Overall Interproximal MLSI (AXI) Score [3]	Overall MLSI Area (A) Score [2]	Overall MLSI Intensity (I) Score [2]
PPD			x.xx	x.xx	x.xx	x.xx

[1] Age in years; Sex: F = Female, M = Male; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H = Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.
[2] Overall score is the mean over all assessed tooth sites.
[3] Overall interproximal score is the mean over all interproximal tooth sites.

Protocol 207872 Program Run Date:xxxx

Listing 16.2.7.1
All Adverse Events
Randomised Population

Treatment Group: Test Dentifrice (RDA-58)

Subject Number	Age/Sex/ Race[1]	Adverse Event (Preferred Term) [System Organ Class]	Start Date /Study Day[2]	Start Time	End Date	End Time	Frequency /Intensity [3]	Related to Study Product?	Action Taken re Study Product	Outcome	Serious?	Withdrew? [4]
PPD												

@@ Adverse Events with verbatim text ending in this are designated as Oral AEs.
[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H =Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.
[2] Study day is the day relative to start of treatment, day 1 being the day of first treatment.
[3] INT = Intermittent and SGLE = Single.
[4] Did subject withdraw from study as a result of this adverse event?

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Programming Note for Listing 16.2.7.2:

- *Repeat the same layout for listing 16.2.7.2*
- *Population should be used 'Non randomised Subjects'*
- *The fourth column should be only 'Start Date'*
- *Add footnote 'Only SAEs are collected for non randomised subjects'*

- *Delete the footnote related to study day and adjust the numbers accordingly.*

Protocol 207872 Program Run Date:xxxx

Listing 16.2.7.1
All Incidents
Randomised Population

Treatment Group: Test Dentifrice (RDA-58)

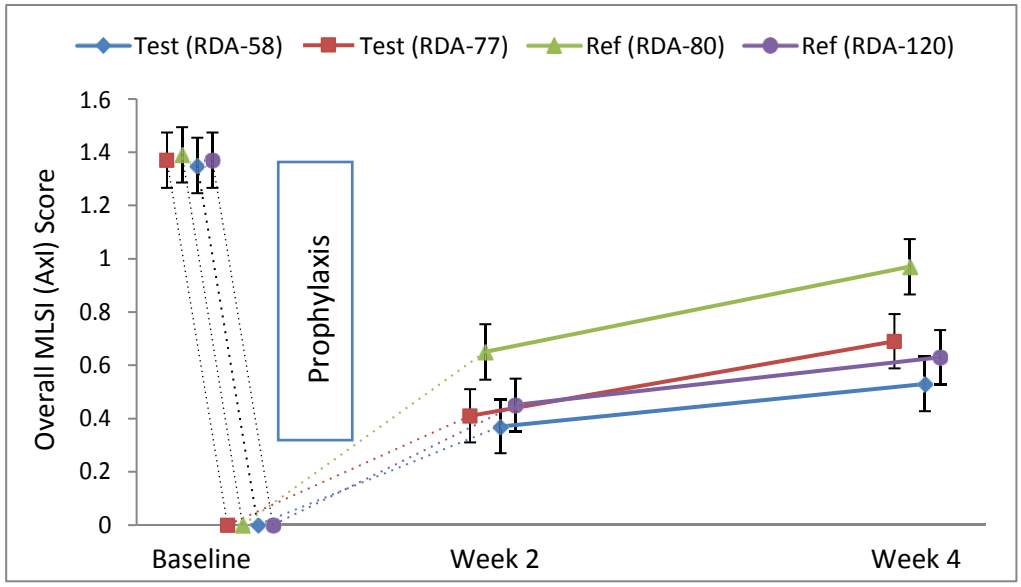
Subject Number	Age/Sex/Race[1]	Incident
PPD		xxxxxxxxx

[1] Age in years; Sex: F = Female, M = Male ; Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, H =Native Hawaiian or Other Pacific Islander, W = White, M = Multiple.

Protocol 207872 Program Run Date:xxxx

Figure 14.2.1
Overall MLSI (AxI) Score Mean (±SE) Plot Over Time by Treatment
Intent-to-Treat Population

Intent-to-Treat Population (N=XX)



Mean and SE plotted are from summary statistics in T 14.2.1.1.1

PPD

Programming Note: use dash line between baseline and week 2, use solid line between week 2 and week 4.

inVentiv Health	Client Approval Form: Final Statistical Analysis Plan Shells

Project Identifiers	
Client: GSKCH	Protocol No.: 207872
Project ID Code: CCI	Protocol Version (date): V5 (30-May-2017)
SAP Version: Final 1.0	SAP Author: PPD
SAP Date (DD-MMM-YYYY): 15-Sept-2017	

The signatures below acknowledge that the Statistical Analysis Plan Shells prepared by inVentiv Health for GSKCH are final.

Approved by: GSKCH	PPD PRINTED NAME	MANAGER BIOSTATISTICS TITLE
	PPD SIGNATURE	PPD DATE OF SIGNATURE (DDMMMYYYY)
Approved by: Lead Statistician, inVentiv Health	PPD PRINTED NAME	PRINCIPAL STATISTICIAN TITLE
	PPD SIGNATURE	PPD DATE OF SIGNATURE (DDMMMYYYY)