GlaxoSmithKline
Consumer Healthcare

STATISTICAL REPORTING AND ANALYSIS PLAN

A RANDOMIZED, EXAMINER-BLIND, PROOF OF PRINCIPAL STUDY TO INVESTIGATE THE STAIN AND PLAQUE REMOVAL CAPABILITY OF TWO EXPERIMENTAL 5% POTASSIUM NITRATE DENTIFRICES IN HEALTHY SUBJECTS WITH THE PROPENSITY FOR EXTRINSIC DENTAL STAIN

Protocol Number: 208078

Phase: II

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	05-Oct-2017	Not applicable (N/A)

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The purpose of this Statistical Reporting and Analysis Plan (RAP) is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 208078. The RAP will be finalized prior to data base freeze and treatment code un-blinding.

1 Summary of Key Protocol Information

The purpose of this trial is to demonstrate the efficacy and safety of 5% Potassium Nitrate (KNO3) / Sodium Fluoride (NaF) to treat the symptoms of extrinsic dental stain. Efficacy will be demonstrated through evaluating and comparing the extrinsic dental stain and plaque removal of an experimental low abrasivity 0.5% spherical silica dentifrice and a marketed low abrasivity 6% standard silica abrasive dentifrice, and an experimental moderate abrasivity 1% spherical silica / 5% sodium tripolyphosphate (STP) dentifrice and a marketed high abrasivity 16% standard abrasive silica / 5% STP dentifrice. Safety will be demonstrated through assessment of the incidence of adverse events (AEs).

1.1 Study Design

This is an 8 week, single-centre, examiner-blind, randomized, four treatment, parallel group study conducted in healthy subjects with a propensity for extrinsic dental stain (based on the judgement of the examiner).

This proof of principle (PoP) study will be used to evaluate and compare the extrinsic dental stain and plaque removal of an experimental low abrasivity 0.5% spherical silica dentifrice and a marketed low abrasivity 6% standard silica abrasive dentifrice, and an experimental moderate abrasivity 1% spherical silica / 5% STP dentifrice and a marketed high abrasivity 16% standard abrasive silica / 5% STP dentifrice. This study has not been designed to demonstrate the specific contribution that spherical silica or STP, are having on the overall reduction of stain and plaque.

A sufficient number of subjects will be screened to randomize at least 124 subjects to ensure 120 evaluable subjects complete the entire study. This will ensure approximately 30 evaluable subjects per treatment arm).

Subjects will be stratified by their baseline total Macpherson modification of the Lobene stain index (MLSI (Area × Intensity)) score of the facial surfaces of 4 of the 12 anterior teeth (<15 (low); ≥15 (high)). A single dental examiner will perform an assessment of the area and intensity of extrinsic dental stain on the facial surfaces of 4 qualifying teeth selected (based on the judgement of the examiner) from the 6 maxillary and 6 mandibular anterior teeth (universal numbering: 6-11 and 22-27), using the MLSI, at baseline
(Visit 2), and following 2, 4 and 8 weeks (Visits 4, 5 and 6) twice daily brushing. Subjects will return to the study site the day after baseline (MLSI) and Week 8 visits for pre- and post-

brushing full mouth Turesky modification of the Quigley Hein Index (TPI) plaque assessments (Visits 3 and 7) of the facial and lingual surfaces of all gradable teeth.

1.2 Study Objectives

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To evaluate the ranking order in extrinsic dental stain removal, as measured by overall MLSI (A×I), of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 8 weeks twice daily brushing.	• Change from baseline in overall MLSI at 8 weeks.
Secondary Objectives	**Secondary Endpoints**
Efficacy	
• To compare the removal of extrinsic dental stain, as measured by overall MLSI (A×I), of a 0.5% spherical silica dentifrice and a marketed 6% abrasive silica dentifrice, after 8 weeks twice daily brushing	• Change from baseline in overall MLSI at 8 weeks.
• To compare the removal of extrinsic dental stain, as measured by overall MLSI (A×I), of a moderate abrasivity 1% spherical silica / 5% STP dentifrice and a marketed higher abrasivity 5% STP whitening dentifrice, after 8 weeks twice daily brushing.	• Change from baseline in overall MLSI at 8 weeks.
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the ranking order of plaque removal, as measured by TPI, of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after a single use.	• Change from pre-brushing to post-brushing TPI after single use.

Objectives	Endpoints
• To evaluate the ranking order of plaque removal, as measured by TPI, of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 8 weeks twice daily brushing.	• Change from baseline (pre-brushing) in overall post-brushing TPI at 8 weeks.
• To evaluate the ranking order of Interproximal plaque removal, as measured by TPI, of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 8 weeks twice daily brushing.	• Change from baseline (pre-brushing) in overall post-brushing interproximal TPI at 8 weeks.
• To compare the removal of extrinsic dental stain, as measured by interproximal (mesial + distal) MLSI (A×I), of a 0.5% spherical silica dentifrice and a marketed 6% abrasive silica dentifrice, after 2, 4 and 8 weeks twice daily brushing.	• Change from baseline in overall interproximal MLSI at 2, 4 and 8 weeks.
• To compare the removal of extrinsic dental stain, as measured by interproximal (mesial + distal) MLSI (A×I), of a 1% spherical silica / 5% STP dentifrice and a marketed 16% abrasive silica / 5% STP whitening dentifrice, after 2, 4 and 8 weeks twice daily brushing.	• Change from baseline in overall interproximal MLSI at 2, 4 and 8 weeks.
• To evaluate the ranking order in extrinsic dental stain removal, as measured by interproximal (mesial + distal) MLSI (A×I), of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 2, 4 and 8	• Change from baseline in overall interproximal MLSI at 2, 4 and 8 weeks.

Objectives	Endpoints
weeks twice daily brushing.	
• To evaluate the ranking order in extrinsic dental stain removal, as measured by overall MLSI Area (A), of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 2, 4 and 8 weeks twice daily brushing.	• Change from baseline in overall MLSI Area at 2, 4 and 8 weeks.
• To evaluate the ranking order in extrinsic dental stain removal, as measured by overall MLSI Intensity (I), of a low abrasivity 0.5% spherical silica dentifrice, a marketed low abrasivity dentifrice, a moderate abrasivity 1% spherical silica / 5% STP dentifrice, and a marketed higher abrasivity 5% STP whitening dentifrice, after 2, 4 and 8 weeks twice daily brushing.	• Change from baseline in overall MLSI Intensity at 2, 4 and 8 weeks.
Safety Objective	**Safety Endpoint**
• To evaluate the safety and oral tolerability of the test dentifrices when used twice daily for 8 weeks.	• Adverse Events

1.3 Treatments

The following study products will be supplied by the Clinical Supplies Department, GSK CH:

- Test product 1: 5% KNO_3 / 0.2542% NaF dentifrice with 0.5% spherical silica (RDA~38); CCI [redacted]
- Test product 2: 5% KNO_3 / 0.2542% NaF dentifrice with 1% spherical silica and 5% STP (RDA~58); CCI [redacted].
- Reference Product 1: 5% KNO_3 / 0.2542% NaF dentifrice with 6% abrasive silica (RDA~36); Sensodyne Pronamel Daily Protection - Mint Essence (CCI [redacted] - USA marketed dentifrice).
- Reference Product 2: 5% KNO_3 / 0.2543% NaF dentifrice with 16% abrasive silica

and 5% STP (RDA~166); Sensodyne Extra Whitening (CCI - USA marketed dentifrice).

1.4 Sample Size Calculation

CCI

A sufficient number of subjects will be screened to randomize at least 124 subjects to ensure 120 evaluable subjects complete the entire study. This will ensure approximately 30 evaluable subjects per treatment arm.

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 randomization codes have been met and the randomization codes have been distributed.

3 Considerations for Data Analyses and Data Handling Conventions

3.1 Baseline Definition

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

3.2 Subgroups/Stratifications

Subjects will be stratified by their baseline total MLSI (A×I) score for the facial surfaces of 4 of the 12 anterior teeth (<15 (low); ≥15 (high)), and depending on which strata they fall under

will be assigned their allocated test product from either the "low" or "high" randomization schedule. The strata will be identified as:

Strata 1: Low (MLSI <15)

Strata 2: High (MLSI ≥15)

Efficacy variables will be analysed accounting for strata. Subgroups are not defined for this trial.

3.3 Timepoints and Visit Windows

Time windows required for this study are as the following:

- Visit 2 (MLSI Baseline) is minimum 24 hours and maximum two weeks from Visit 1 (Screening)
- Visit 3 (TPI Baseline) is 24 hours after Visit 2
- Visit 4 (Week 2) is 14 ± 1 days from Visit 2.
- Visit 5 (Week 4) is 28 ± 2 days from Visit 2.
- Visit 6 (Week 8) is 56 ± 3 days from Visit 2.
- Visit 7 (Week 8) is 57 ± 3 days from Visit 2.

Visits outside of the above time windows will be reviewed during the Blinded Data Review Meeting (BDRM).

4 Data Analysis

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

Prior to database closure a BDRM will be conducted in which various aspects of the trial will be discussed and agreed.

Unless otherwise described below, all listings will be produced for all randomized subjects.

4.1 Populations for Analysis

Tables described in this section other than disposition will be produced for all randomized subjects.

4.1.1 Subject Disposition

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A summary will be provided of the number of subjects screened and the number of screen failures with reasons why subjects were not randomized.

Subject disposition will be summarized as the number and percentage of subjects (out of the number of randomized subjects) who complete the study, with the number who discontinue broken down by reason for discontinuation (Table 14.1.1). The table will also summarize the number and percent of subjects assigned to each analysis population (refer to section 4.1.3).

Subject disposition including the subject status (completer, Yes/No), critical demographic data (age, sex, race, ethnicity), the duration of treatment before discontinuation and the specific reason for discontinuation, will be listed in for randomized subjects (Listing 16.2.1.1.1) by treatment group and in for non-randomized subjects (Listing 16.2.1.1.2).

4.1.2 Protocol Deviations

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

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

Violations that influence the efficacy outcome will be given in the "Review Listing Requirement (RLR)" document and important violations will be identified in blinded data review stage.

All protocol deviations will be listed (Listing 16.2.2).

4.1.3 Analysis Populations

Five analysis populations are defined.

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 randomized.	• Disposition, AE listing
Randomized	• All subjects who are randomized and may or may not receive the application of the study products. • Any subject who receives a treatment randomization number will be considered to have been randomized.	• Protocol violations
Safety	• Comprise of all subjects who are randomized and receive at least one dose of study treatment. • This population will be based on the treatment the subject actually received.	• Safety Population

Population	Definition / Criteria	Analyses Evaluated
Intent-To-Treat	• Comprises of all randomized subjects who receive the study treatment at least once and provide at least one post-baseline (post treatment) assessment of efficacy. • This population will be based on the treatment to which the subject was randomize	• Efficacy
Repeatability	• Any subject who has a repeat stain or plaque assessment. The repeat stain and plaque populations will be separate populations.	• Repeatability Population

The numbers of subjects included in each of the analysis populations, and the number excluded from each population (except repeatability 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), with the reason for exclusion.

4.2 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the ITT and Safety populations by treatment group.

4.2.1 Demographic Characteristics

Categorical demographic variables include sex, race, strata and ethnicity. These variables will be summarized by the number and percentage of subjects with each relevant characteristic in each treatment group. Age will be summarized by the mean, standard deviation (SD), median (med), minimum (min) and maximum (max) values in each treatment group. All demographic information will be tabulated in Table 14.1.4.1 for the Safety population, Table 14.1.4.2 for the ITT population and listed in Listing 16.2.4.1.

4.2.2 General Medical History

Medical diagnoses/surgeries will be listed in Listing 16.2.4.2, with start date and end date or ongoing at the start of study drug.

4.3 Study Product Compliance and Use of Other Therapy

4.3.1 Study Product Compliance

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

4.3.2 Prior and Concomitant Medication

Prior medications will be listed by subject, with, indication, dose, dose form, frequency, route, start date and end date (Listing 16.2.5.5). Prior medications are defined as those stopped before the first administration of the study products. Concomitant medications will be listed similarly (Listing 16.2.5.6). Concomitant medications are defined as those ongoing or started on or after the first administration of the study products.

4.4 Analysis of Efficacy

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary efficacy variable is the change from baseline in overall MLSI score. The primary time-point is 8 weeks. The overall MLSI (AxI) for each subject is derived at a tooth site level first before averaging over all the non-missing teeth sites assessed. The change from baseline is derived from the individual sites first before calculating the average change across the sites assessed.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The primary objective is to evaluate the ranking order in extrinsic dental stain removal, as measured by overall MLSI (A×I), of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 8 weeks twice daily brushing.

Summary statistics including mean, SD, median, min, max will be provided for baseline and Week 8 by randomized treatment group (Table 14.2.2.1).The change from baseline in overall MLSI will be analyzed using analysis of covariance (ANCOVA) with treatment as a fixed effect and baseline overall MLSI as a covariate.

There are no comparisons for the primary objective as the main objective is to look at the rank order of the treatments in level of stain reduction after 8 weeks of treatment. This will be achieved via the adjusted means and confidence intervals (CIs) for the means along with plots of MLSI over time. Adjusted means of all treatments will be provided together with their 95% CIs and p-values (Table 14.2.2.2).

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated. Violation of this assumption will be overcome using a suitable data transformation or a non-parametric technique (e.g. Wilcoxon Rank Sum test).

4.4.1.3 Supportive Analyses

Not Applicable

4.4.2 Secondary Efficacy Variables

The secondary efficacy variable is same as the primary efficacy variable.

4.5 Analysis of Secondary Objectives

4.5.1 Efficacy

The hypothesis is that the test products will reduce stain to a similar, or greater extent than the reference products.

Two comparisons of interest will be done under the secondary objectives. These comparisons are:-

Test Product 1 vs Reference Product 1

Test Product 2 vs Reference Product 2.

The change from baseline in overall MLSI at Week 8 will be analyzed using ANCOVA with treatment as a fixed effect and baseline overall MLSI as a covariate.

From the above ANCOVA model, treatment differences between groups (Test Product 1 vs Reference Product 1 and Test Product 2 vs Reference Product 2), 95% CIs and p-values, will be provided (Table 14.2.2.2).

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated. Violation of this assumption will be overcome using a suitable data transformation or a non-parametric technique (e.g. Wilcoxon Rank Sum test).

4.6 Analysis of Exploratory Objectives

4.6.1.1 Exploratory Efficacy Endpoint Definition

The exploratory variables are;

- Change from baseline in overall interproximal MLSI (AxI) stain score at Weeks 2, 4 and 8
- Change from baseline in overall area (A) stain score at Weeks 2, 4 and 8
- Change from baseline in overall intensity (I) stain score at Weeks 2, 4 and 8
- Change from baseline (pre-treatment) in overall TPI for Day 2 post-treatment, Week 8 pre-treatment and Week 8-post treatment

- Change from baseline (pre-treatment) in interproximal TPI for Day 2 post-treatment, Week 8 pre-treatment and Week 8 post-treatment

All stain variables will be derived in a similar way based on relevant tooth sites. The interproximal stain sites are the mesial and distal tooth sites.

The overall TPI for each subject is derived at a tooth site level first before averaging over all the teeth sites assessed. The change from baseline is derived at the individual sites first before calculating the average change across the sites assessed.

The interproximal TPI is based on the mesial and distal tooth sites. The interproximal TPI score and change from baseline are calculated in the same way as for the overall TPI.

4.6.1.2 Analysis of Exploratory Variables

Summary statistics including mean, SD, median, min, and max will be provided for week 2 and week 4 by randomized treatment group (Table 14.2.2.1).

All stain variables will be analyzed as per the primary efficacy variable using the appropriate baseline values as a covariate.

The change from baseline in TPI variables will be analyzed using analysis of covariance (ANCOVA) with treatment and MLSI stratification as fixed effects and appropriate baseline (pre-treatment) TPI as a covariate.

From ANCOVA model, the adjusted mean for each treatment group will be provided with 95% CIs and corresponding p-values.

Results for overall interproximal MLSI (A×I) score, overall MLSI area score, overall MLSI intensity score, overall TPI score and overall Interproximal TPI Score will be presented in Table 14.2.3.1, 14.2.3.2, Table 14.2.4.1, 14.2.4.2, Table 14.2.5.1, 14.2.5.2, Table 14.2.6.1, 14.2.6.2 and Table 14.2.7.1, 14.2.7.2 respectively.

4.6.2 Handling of Missing Values/Censoring/Discontinuations

Missing data will not be replaced or imputed. Dropouts will be included in analyses up to the point of discontinuation.

4.7 Analysis of Safety

4.7.1 Adverse Events and Serious Adverse Events

All summaries of safety will be performed using the safety population and will be analyzed based on treatment actually received. No formal statistical testing will be performed on summary comparisons related to safety related measurements.

All AEs will be coded using the medical dictionary for regulatory activities (MedDRA). AEs will be classified by system organ class (SOC) and by preferred term (PT). In addition, prior to database lock all AEs will be reviewed by the Clinical Research Director (or designee) and categorized as either oral or non-oral. Safety will be assessed based on any oral AEs (this includes those that are identified as treatment emergent oral soft tissue (OST) abnormalities and spontaneously reported oral AEs). Any new or worsening OST condition that occurs after the OST examinations at Screening will be recorded as an AE.

AEs will be summarized using descriptive statistics (frequency tables) by treatment group. Summary tables will indicate both the number of events and the number (percent) of subjects involved. Summaries of AEs will include only treatment emergent adverse events (TEAEs) unless otherwise noted. TEAEs are defined as new AEs that occur on or after the date/time of the first supervised use of the randomized treatment (or events aggravated in severity following treatment). Events with an onset date/time prior to first use of a treatment will be considered as non-treatment emergent. Listing of AEs (including non-treatment emergent from All Subjects) will be provided.

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

- Table of treatment emergent AEs by SOC and Preferred Term (Table 14.3.1.1.1)
- Table of treatment emergent AEs by Oral/Non-Oral and Preferred Term (Table 14.3.1.1.2)
- Table of treatment emergent treatment related AEs by SOC and Preferred Term (Table 14.3.1.3.1)
- Table of Treatment emergent treatment related AEs by Oral/Non-Oral and Preferred Term (Table 14.3.1.3.2)
- Table of Non-serious treatment emergent AEs by SOC and PT (only produced if there are more than 5 SAEs) (Table 14.3.1.4)
- Listing of all AEs (including all subjects: Listing 16.2.7.1.1 for all randomized subjects; Listing 16.2.7.1.2 for non-randomized 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 (Listing 16.2.7.2). Oral soft issue data will be listed (Listing 16.2.7.3)

4.8 Analysis of Other Variables

To assess the repeatability of the stain and TPI assessments, replicate examinations will be performed by the same qualified dental examiner at each assessment visit. Five subjects will be randomly selected for repeat MLSI and TPI assessments across each assessment window.

The repeat stain and plaque assessments will be compared to the original assessments and will not be used in any efficacy analysis. The first and second assessments on each tooth site will be cross tabulated. 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. Results for repeat MLSI area and intensity assessments will be in Table 14.2.8.1 and Table 14.2.8.2 respectively. Also result for repeat TPI assessment will be Table 14.2.8.3.

5 Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
• Section 10.2.1: Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for demographic baseline characteristics concomitant medication, medical history and compliance.	• We are not providing descriptive statistics for concomitant medications, medical histories and compliance.	• Summary tables are not required for reporting

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
• 10.2.4- Safety Analysis(es) Listing of SAEs (if there are none a null listing will be produced; if there are more than 5 treatment emergent SAEs a table will be produced instead by SOC and PT)	• Analysis of Safety Listing of death (Listing 14.3.2.1); Listing of non-fatal SAEs (Listing 14.3.2.2)	• As per RAP template and list of required TLF list for Oral studies, two listings have been added in RAP.
• 10.2.6 Definition of Analysis Populations	• We have added two populations in RAP which are all screened subjects and randomized population.	• We will require these population for some TLFs.
• Safety Analysis(es)	• The below table is not included in the RAP: Treatment emergent AEs by Intensity presented by System Organ Class (SOC) and PT	• It is not required since it is study dependent and not required for this study.

6 Abbreviation

Abbreviation	Term
AE	adverse event
TEAE	treatment-emergent adverse event
ANCOVA	analysis of covariance
CI	confidence interval
ITT	intent-to-treat
KNO_3	potassium nitrate
NaF	sodium fluoride
STP	sodium tripolyphosphate
MedDRA	medical Dictionary for Regulatory Activities
MLSI	Macpherson modification of the Lobene Stain Index
OST	oral soft tissue
SAE	serious adverse event

Abbreviation	Term
SOC	system organ class
PT	preferred term
TPI	Turesky modification of the Quigley Hein Index
A	Area
I	Intensity
SD	standard deviation
Med	median
Min	minimum
Max	maximum
RLR	review listing requirement
BDRM	blinded data review meeting
SAS	statistical analysis system
GSK CH	GlaxoSmithKline Consumer Healthcare
POP	proof of principle

7 Attachment 1: List of Data Displays

Study 208078_List of Outputs.xlsx

8 Appendix 1: Template 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 Product 1
- Test Product 2
- Reference Product 1
- Reference Product 2

The treatment comparison will be in below order;
Test Product 1 Vs Test Product 2
Reference Product 1 Vs Reference Product 2

The below footnotes will be used for each outputs;
Test Product 1: 5% KNO_3 / 0.2542% NaF dentifrice with 0.5% spherical silica (RDA~38)
Test Product 2: 5% KNO_3 / 0.2542% NaF dentifrice with 1% spherical silica and 5% STP (RDA~58)

Reference Product 1: Sensodyne Pronamel Daily Protection (RDA~36).
Reference Product 2: Sensodyne Extra Whitening (RDA~166).

Protocol 208078 Program Run Date: DDMMMYYYY

Table 14.1.1
Subject Disposition
All Screened Subjects

Study Population: All Screened Subjects (N=xxx)

	Test Product 1 N (%)	Test Product 2 N (%)	Reference Product 1 N (%)	Reference Product 2 N (%)	Overall N (%)
TOTAL SUBJECTS SCREENED					xxx
SUBJECTS NOT RANDOMIZED					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 RANDOMIZED	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 Product 1 N (%)	Test Product 2 N (%)	Reference Product 1 N (%)	Reference Product 2 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)

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

Protocol 208078 Program Run Date: DDMMYYYY

Table 14.1.3
Analysis Populations
All Randomized Population

Study Population: All Randomized 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 (%)
NUMBER OF 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)
...					
NUMBER OF 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)
...					

Protocol: 208078 Program Run Date: DDMMMYYYY

Table 14.1.4.1.1
Demographic and Baseline Characteristics
Safety Population

Study Population: Safety Population (N=xxx)

	Test Product 1 N (%)	Test Product 2 N (%)	....	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 (%)				
AFRICAN AMERICAN/AFRICAN HERITAGE	XX (XX.X)	XX (XX.X)	...	XX (XX.X)
AMERICAN INDIAN OR ALASKAN NATIVE	XX (XX.X)	XX (XX.X)		XX (XX.X)
ASIAN - CENTRAL/SOUTH ASIAN HERITAGE	XX (XX.X)	XX (XX.X)		XX (XX.X)
ASIAN - EAST ASIAN HERITAGE	XX (XX.X)	XX (XX.X)	...	XX (XX.X)
ASIAN - SOUTH EAST ASIAN HERITAGE	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 - ARABIC/NORTH AFRICAN HERITAGE	XX (XX.X)	XX (XX.X)	...	XX (XX.X)
WHITE - WHITE/CAUCASIAN/EUROPEAN HERITAGE	XX (XX.X)	XX (XX.X)	...	XX (XX.X)
			...	
ETHNICITY N (%)				
HISPANIC OR LATINO	XX (XX.X)	XX (XX.X)		XX (XX.X)
NOT HISPANIC OR LATINO	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
MINIMUM	XX	XX	.....	XX
MAXIMUM	XX	XX	...	XX
STRATIFICATION				
STRATA 1: LOW (MLSI <15)	XX (XX.X)	XX (XX.X)		XX (XX.X)
STRATA 2: HIGH (MLSI ≥15)	XX (XX.X)	XX (XX.X)		XX (XX.X)

Protocol 208078 Program Run Date: DDMMMYYYY

Table 14.2.2.1
Summary of Overall MLSI Score
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)

		Test Product 1 (N=XX)		Test Product 2 (N=XX)		……..	Overall (N=XXX)	
Visit		Observed Value	Change from Baseline	Observed Value	Change from Baseline	……..	Observed Value	Change from Baseline
BASELINE	N	XX		XX		……..	XX	
	MEAN	X.XX		X.XX		……..	X.XX	
	SD	X.XXX		X.XXX		……..	X.XXX	
	MEDIAN	X.XX		X.XX		……..	X.XX	
	MINIMUM	X.XX		X.XX		……..	X.XX	
	MAXIMUM	X.XX		X.XX		……..	X.XX	
WEEK 2	N	XX	XX	XX	XX	……..	XX	XX
	MEAN	X.XX	X.XX	X.XX	X.XX	……..	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX	X.XXX	……..	X.XXX	X.XXX
	MEDIAN	X.X	X.X	X.X	X.X	……..	X.X	X.X
	MINIMUM	X.X	X.X	X.X	X.X	……..	X.X	X.X
	MAXIMUM	X.X	X.X	X.X	X.X	……..	X.X	X.X
WEEK 4	SAME AS ABOVE							

Protocol 208078 Program Run Date: DDMMMYYYY

Table 14.2.2.2
Statistical Analysis of Overall Change Baseline in MLSI Score
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)

Visit		Test Product 1 (N=XX)	Test Product 2 (N=XX)	Reference Product 1 (N=XX)	Reference Product 1 (N=XX)
WEEK 2	ADJUSTED MEANS (SE)[1]	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)
	95 % CI [1]	(X.XX, X.XX)	(X.XX, X.XX)	(X.XX, X.XX)	(X.XX, X.XX)
	P-VALUE [1]	0.XXXX	0.XXXX	0.XXXX	0.XXXX
	COMPARISON	DIFFERENCE (SE) [1,2]	95% CI [1]	P-VALUE [1]	
	TEST PRODUCT 1 VS REFERENCE PRODUCT 1	X.XX (X.XXX)	(X.XX, X.XX)	0.XXXX	
	TEST PRODUCT 2 VS REFERENCE PRODUCT 2	X.XX (X.XXX)	(X.XX, X.XX)	0.XXXX	
WEEK 4	SAME AS ABOVE				

[1] From ANCOVA with treatment as factors and baseline overall MLSI score as a covariate

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

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PPD

Programming note: The same summary would be provided for the Week 8 also.

Protocol 208078 PROGRAM RUN DATE: DDMMMYYYY

Table 14.2.6.1
Summary of TPI Score
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)

Visit	TimePoint		Test Product 1 (N=XX)		Test Product 2 (N=XX)		.....	Overall (N=XX)	
			Observed Values	Change from Pre-brushing	Observed Values	Change from Pre-brushing	.....	Observed Values	Change from Pre-brushing
BASELINE	PRE-BRUSHING	N	XX		XX		.....	XX	
		MEAN	X.XX		X.XX		.....	X.XX	
		SD	X.XXX		X.XXX		.....	X.XXX	
		MEDIAN	X.XX		X.XX		.....	X.XX	
		MINIMUM	X.XX		X.XX		.....	X.XX	
		MAXIMUM	X.XX		X.XX		.....	X.XX	
							.....		
	POST-BRUSHING	N	XX	XX	XX	XX	.....	XX	XX
		MEAN	X.XX	X.XX	X.XX	X.XX	.....	X.XX	X.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX	.....	X.XXX	X.XXX
		MEDIAN	X.XX	X.XX	X.XX	X.XX	.....	X.XX	X.XX
		MINIMUM	X.XX	X.XX	X.XX	X.XX	.....	X.XX	X.XX
		MAXIMUM	X.XX	X.XX	X.XX	X.XX	.....	X.XX	X.XX
WEEK 8	SAME AS ABOVE								

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Protocol 208078 Program Run Date: DDMMMYYYY

Table 14.2.6.2
Statistical Analysis of Overall Change from Baseline (Pre-brushing) in TPI Score
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)

Visit		Test Product 1 (N=XX)	Test Product 2 (N=XX)	Reference Product 1 (N=XX)	Reference Product 1 (N=XX)
BASELINE POST-BRUSHING	ADJUSTED MEANS (SE)[1]	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)
	95 % CI [1]	(X.XX, X.XX)	(X.XX, X.XX)	(X.XX, X.XX)	(X.XX, X.XX)
	P-VALUE [1]	0.XXXX	0.XXXX	0.XXXX	0.XXXX
	COMPARISON	DIFFERENCE (SE) [1,2]	95% CI [1]	P-VALUE [1]	
	TEST PRODUCT 1 VS REFERENCE PRODUCT 1	X.XX (X.XXX)	(X.XX, X.XX)	0.XXXX	
	TEST PRODUCT 2 VS REFERENCE PRODUCT 2	X.XX (X.XXX)	(X.XX, X.XX)	0.XXXX	
WEEK 8 PRE-BRUSHING	SAME AS ABOVE				
WEEK 8 POST-BRUSHING	SAME AS ABOVE				

[1] From ANCOVA with treatment and MLSI stratification as factors and appropriate baseline (Pre-treatment) TPI score as a covariate

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

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PPD

Programming note: The same summary would be provided for the Week 8 pre-brushing and Week 8 post-brushing also.

Protocol 208078

Program Run Date: DDMMMYYYY

Table 14.2.8.1
Repeatability for MLSI Intensity Score
Repeatability Population

Study 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.

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Note to Programmer: For Table 14.2.8.2 and 14.2.8.3, use area and TPI scoring descriptions in footnote.

Protocol 208078 Program Run Date: DDMMYYYY

Table 14.3.1.1.1
Treatment Emergent Adverse Event by SOC and Preferred Term
Safety Population

Study Population: Safety Population (N=xx)

SOC Preferred Term	Test Product 1 (N=XX)		Test Product 2 (N=XX)		Reference Product 1 (N=XX)		Reference Product 1 (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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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.1.7
Randomization Information
All Randomized Population

Stratum 1: Low (MLSI <15)

Subject Number	Age/Sex/ Race [1]	Randomization Number	Treatment Randomized [2]	Date of Randomization
PPD				

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] A= Reference Product 1; B= Reference Product 2; C= Test Product 1; D= Test Product 2.
The block size for this randomization was used 8.

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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.1.1.1
Subject Disposition
All Randomized Population

Subject	Age/Sex/ Race/ Ethnicity [1]	Screening Date	Treatment Start Date and Time	Date of Completion or Withdrawal	Duration of Treatment (Days) [2]	Completed	Primary Reason for Withdrawal	Further Details [3]
PPD								

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] Treatment duration is calculated as date of completion or withdrawal minus treatment start date.
[2] Further details of reasons for withdrawal.

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PPD

Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.2
All Protocol Deviations
All Randomized Population

Treatment Group: Test Product 1

Subject Number	Age/Sex/Race[1]	Deviation Sequence	Start Date/Time	End Date/Time	Protocol Deviation
PPD					

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.

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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.3.1
Exclusion from Analysis Population
All Randomized population

Subject Number	Age/Sex/Race[1]	Treatment Start Date and Time	Safety Population	ITT Population	Reasons for Exclusion
PPD					

[1] Age in years; Sex: F = Female, M = Male ; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.

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Programming Note for Listing 16.2.3.1: This listing is based on population definition document.

Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.4.1
Demographic Characteristics
All Randomized Population

Treatment Group: Test Product 1

Subject Number	Age (years)	Sex	Race	Ethnicity	Stratification
PPD					

Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.4.2
Medical History and Current Medical Conditions
All Randomized Population

Treatment Group: Test Product 1

Subject	Age/Sex/Race [1]	Any Medical History?	Medical Condition	Start Date	Ongoing?	End Date
PPD						

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.

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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.5.6
Concomitant Medications and Non-drug Therapies Taken During Treatment
All Randomized Population

Subject Number	Age/Sex/Race[1]	Sequence Number	Treatment [GSK Drug Synonym]	Reason for Treatment	Route of Administration	Dose per Administration	Frequency	Start Date (Study Day [2])	End Date/ Ongoing
PPD									

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] Study day relative to the date of randomization.

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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.6.1
Individual MLSI Stain Index
All Randomized Population

Treatment Group: Test Product 1

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

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] Intensity Score: 0=No Stain; 1=light Stain;2=Moderate Stain; 3=Heavy Stain. Missing means non-scorable; X=Missing.
[3] Area Score: 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 208078 Program Run Date: DDMMYYYY

Listing 16.2.6.2
Individual Turesky Plaque Index (TPI)
All Randomized Population

Treatment Group: Test Product 1

Subject Number	Age/Sex/Race[1]	Visit	PRE/POST	Tooth Number (universal/FDI)	Surface	Site	TPI Score [2]	Average Whole Mouth TPI	Change from Bassline Score
PPD									

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] 0 = No plaque; 1 = Slight flecks of plaque at the cervical margin of the tooth; 2 = A thin continuous band of plaque (1 mm or smaller) at the cervical margin of the tooth; 3 = A band of plaque wider than 1 mm but covering less than 1/3 of the crown of the tooth; 4 = Plaque covering at least 1/3 but less than 2/3 of the crown of the tooth; 5 = Plaque covering 2/3 or more of the crown of the tooth; X = Missing Tooth; N = Not Scorable

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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.7.1.1
All Adverse Events
All Randomized Population

Treatment Group: Test Product 1

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 classified as Oral AEs.
[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[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 16.2.7.1.2:

- *Repeat the same layout for listing 16.2.7.1.2*
- *Population should be used 'Non randomized Subjects'*
- *The fourth column should be only 'Start Date'*
- *Add footnote 'Only SAEs are collected for non randomized subjects'*
- *Delete the footnote related to study day and adjust the numbers accordingly.*

Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.7.3
Oral Soft Tissue Examination
All Randomized Population

Treatment Group: Test Product 1

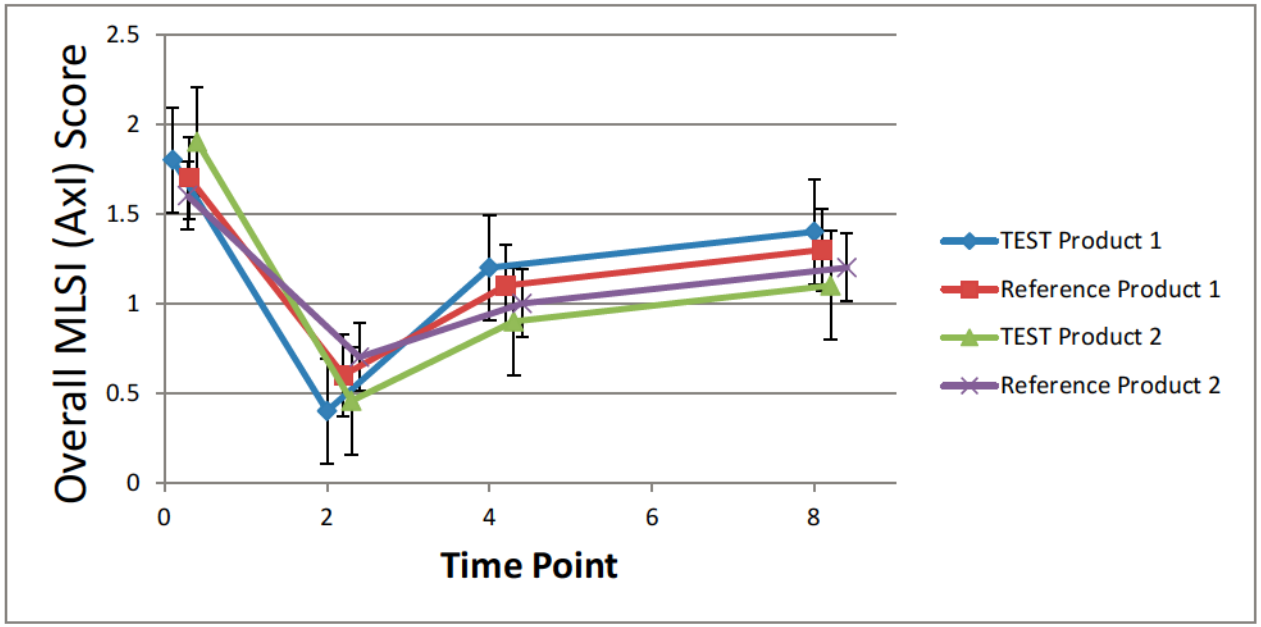
Subject Number	Age/Sex/Race[1]	Visit	Area	Condition	Details
PPD					

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.

Protocol 208078 Program Run Date: DDMMYYYY

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

Study Population: Intent-to-Treat Population (N=XX)



Mean and SE plotted are from summary statistics in T 14.2.2.1.1

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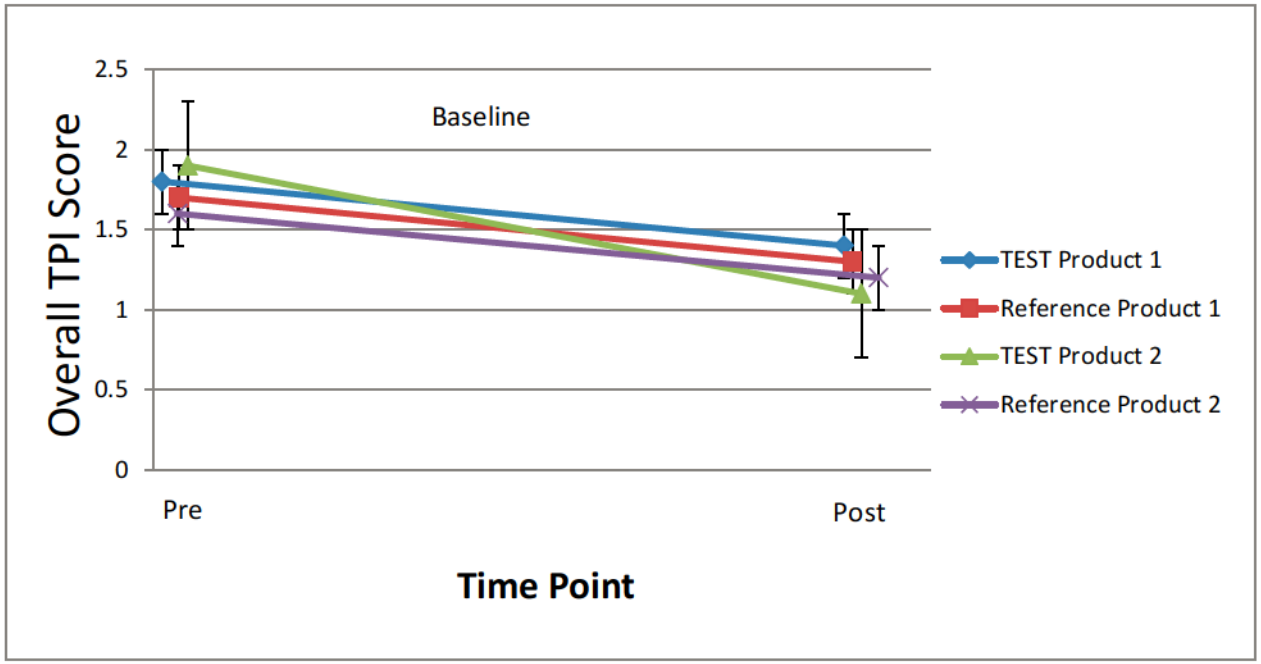
Protocol 208078 Program Run Date: DDMMYYYY

Figure 14.2.2
Overall TPI Score Mean (±SE) Plot over Time by Treatment
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)



Mean and SE plotted are from summary statistics in T 14.2.5.1.1

Programming Note: Please repeat figure for the Week 8 also.

GlaxoSmithKline
Consumer Healthcare

STATISTICAL REPORTING AND ANALYSIS PLAN

A RANDOMIZED, EXAMINER-BLIND, PROOF OF PRINCIPAL STUDY TO INVESTIGATE THE STAIN AND PLAQUE REMOVAL CAPABILITY OF TWO EXPERIMENTAL 5% POTASSIUM NITRATE DENTIFRICES IN HEALTHY SUBJECTS WITH THE PROPENSITY FOR EXTRINSIC DENTAL STAIN

Protocol Number: 208078

Phase: II

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	05-Oct-2017	Not applicable (N/A)
RAP Amendment Version 1.0	21-Nov-2017	Add brushing compliance listing in RAP rather than cover it in BDRM. Add eCRF comments listing Added major Protocol deviation table Amend the text of section 3.3 (Timepoints and Visit Window) Added the text in repeatability population of section 4.1.3

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The purpose of this Statistical Reporting and Analysis Plan (RAP) is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 208078. The RAP will be finalized prior to data base freeze and treatment code un-blinding.

1 Summary of Key Protocol Information

The purpose of this trial is to demonstrate the efficacy and safety of 5% Potassium Nitrate (KNO3) / Sodium Fluoride (NaF) to treat the symptoms of extrinsic dental stain. Efficacy will be demonstrated through evaluating and comparing the extrinsic dental stain and plaque removal of an experimental low abrasivity 0.5% spherical silica dentifrice and a marketed low abrasivity 6% standard silica abrasive dentifrice, and an experimental moderate abrasivity 1% spherical silica / 5% sodium tripolyphosphate (STP) dentifrice and a marketed high abrasivity 16% standard abrasive silica / 5% STP dentifrice. Safety will be demonstrated through assessment of the incidence of adverse events (AEs).

1.1 Study Design

This is an 8 week, single-centre, examiner-blind, randomized, four treatment, parallel group study conducted in healthy subjects with a propensity for extrinsic dental stain (based on the judgement of the examiner).

This proof of principle (PoP) study will be used to evaluate and compare the extrinsic dental stain and plaque removal of an experimental low abrasivity 0.5% spherical silica dentifrice and a marketed low abrasivity 6% standard silica abrasive dentifrice, and an experimental moderate abrasivity 1% spherical silica / 5% STP dentifrice and a marketed high abrasivity 16% standard abrasive silica / 5% STP dentifrice. This study has not been designed to demonstrate the specific contribution that spherical silica or STP, are having on the overall reduction of stain and plaque.

A sufficient number of subjects will be screened to randomize at least 124 subjects to ensure 120 evaluable subjects complete the entire study. This will ensure approximately 30 evaluable subjects per treatment arm).

Subjects will be stratified by their baseline total Macpherson modification of the Lobene stain index (MLSI (Area × Intensity)) score of the facial surfaces of 4 of the 12 anterior teeth (<15 (low); ≥15 (high)). A single dental examiner will perform an assessment of the area and intensity of extrinsic dental stain on the facial surfaces of 4 qualifying teeth selected (based on the judgement of the examiner) from the 6 maxillary and 6 mandibular anterior teeth (universal numbering: 6-11 and 22-27), using the MLSI, at baseline
(Visit 2), and following 2, 4 and 8 weeks (Visits 4, 5 and 6) twice daily brushing. Subjects will return to the study site the day after baseline (MLSI) and Week 8 visits for pre- and post-

brushing full mouth Turesky modification of the Quigley Hein Index (TPI) plaque assessments (Visits 3 and 7) of the facial and lingual surfaces of all gradable teeth.

1.2 Study Objectives

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To evaluate the ranking order in extrinsic dental stain removal, as measured by overall MLSI (A×I), of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 8 weeks twice daily brushing.	• Change from baseline in overall MLSI at 8 weeks.
Secondary Objectives	**Secondary Endpoints**
Efficacy	
• To compare the removal of extrinsic dental stain, as measured by overall MLSI (A×I), of a 0.5% spherical silica dentifrice and a marketed 6% abrasive silica dentifrice, after 8 weeks twice daily brushing	• Change from baseline in overall MLSI at 8 weeks.
• To compare the removal of extrinsic dental stain, as measured by overall MLSI (A×I), of a moderate abrasivity 1% spherical silica / 5% STP dentifrice and a marketed higher abrasivity 5% STP whitening dentifrice, after 8 weeks twice daily brushing.	• Change from baseline in overall MLSI at 8 weeks.
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the ranking order of plaque removal, as measured by TPI, of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after a single use.	• Change from pre-brushing to post-brushing TPI after single use.

Objectives	Endpoints
• To evaluate the ranking order of plaque removal, as measured by TPI, of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 8 weeks twice daily brushing.	• Change from baseline (pre-brushing) in overall post-brushing TPI at 8 weeks.
• To evaluate the ranking order of Interproximal plaque removal, as measured by TPI, of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 8 weeks twice daily brushing.	• Change from baseline (pre-brushing) in overall post-brushing interproximal TPI at 8 weeks.
• To compare the removal of extrinsic dental stain, as measured by interproximal (mesial + distal) MLSI (A×I), of a 0.5% spherical silica dentifrice and a marketed 6% abrasive silica dentifrice, after 2, 4 and 8 weeks twice daily brushing.	• Change from baseline in overall interproximal MLSI at 2, 4 and 8 weeks.
• To compare the removal of extrinsic dental stain, as measured by interproximal (mesial + distal) MLSI (A×I), of a 1% spherical silica / 5% STP dentifrice and a marketed 16% abrasive silica / 5% STP whitening dentifrice, after 2, 4 and 8 weeks twice daily brushing.	• Change from baseline in overall interproximal MLSI at 2, 4 and 8 weeks.
• To evaluate the ranking order in extrinsic dental stain removal, as measured by interproximal (mesial + distal) MLSI (A×I), of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 2, 4 and 8	• Change from baseline in overall interproximal MLSI at 2, 4 and 8 weeks.

Objectives	Endpoints
weeks twice daily brushing.	
• To evaluate the ranking order in extrinsic dental stain removal, as measured by overall MLSI Area (A), of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 2, 4 and 8 weeks twice daily brushing.	• Change from baseline in overall MLSI Area at 2, 4 and 8 weeks.
• To evaluate the ranking order in extrinsic dental stain removal, as measured by overall MLSI Intensity (I), of a low abrasivity 0.5% spherical silica dentifrice, a marketed low abrasivity dentifrice, a moderate abrasivity 1% spherical silica / 5% STP dentifrice, and a marketed higher abrasivity 5% STP whitening dentifrice, after 2, 4 and 8 weeks twice daily brushing.	• Change from baseline in overall MLSI Intensity at 2, 4 and 8 weeks.
Safety Objective	**Safety Endpoint**
• To evaluate the safety and oral tolerability of the test dentifrices when used twice daily for 8 weeks.	• Adverse Events

1.3 Treatments

The following study products will be supplied by the Clinical Supplies Department, GSK CH:

- Test product 1: 5% KNO_3 / 0.2542% NaF dentifrice with 0.5% spherical silica (RDA~38); CCI [redacted].
- Test product 2: 5% KNO_3 / 0.2542% NaF dentifrice with 1% spherical silica and 5% STP (RDA~58); CCI [redacted].
- Reference Product 1: 5% KNO_3 / 0.2542% NaF dentifrice with 6% abrasive silica (RDA~36); Sensodyne Pronamel Daily Protection - Mint Essence (CCI [redacted] - USA marketed dentifrice).
- Reference Product 2: 5% KNO_3 / 0.2543% NaF dentifrice with 16% abrasive silica

and 5% STP (RDA~166); Sensodyne Extra Whitening (CCI - USA marketed dentifrice).

1.4 Sample Size Calculation

CCI

A sufficient number of subjects will be screened to randomize at least 124 subjects to ensure 120 evaluable subjects complete the entire study. This will ensure approximately 30 evaluable subjects per treatment arm.

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 randomization codes have been met and the randomization codes have been distributed.

3 Considerations for Data Analyses and Data Handling Conventions

3.1 Baseline Definition

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

3.2 Subgroups/Stratifications

Subjects will be stratified by their baseline total MLSI (A×I) score for the facial surfaces of 4 of the 12 anterior teeth (<15 (low); ≥15 (high)), and depending on which strata they fall under

will be assigned their allocated test product from either the "low" or "high" randomization schedule. The strata will be identified as:

Strata 1: Low (MLSI <15)

Strata 2: High (MLSI ≥15)

Efficacy variables will be analysed accounting for strata. Subgroups are not defined for this trial.

3.3 Timepoints and Visit Windows

Time windows for this study are as the following:

- Visit 2 (MLSI Baseline) is minimum 24 hours and maximum two weeks from Visit 1 (Screening)
- Visit 3 (TPI Baseline) is 24 hours after Visit 2
- Visit 4 (Week 2) is 14 ± 1 days from Visit 2.
- Visit 5 (Week 4) is 28 ± 2 days from Visit 2.
- Visit 6 (Week 8) is 56 ± 3 days from Visit 2.
- Visit 7 (Week 8) is 57 ± 3 days from Visit 2.

All data will be accepted for the analysis. Deviations from the scheduled visit window are considered to be minor.

4 Data Analysis

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

Prior to database closure a BDRM will be conducted in which various aspects of the trial will be discussed and agreed.

Unless otherwise described below, all listings will be produced for all randomized subjects.

4.1 Populations for Analysis

Tables described in this section other than disposition will be produced for all randomized subjects.

4.1.1 Subject Disposition

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A summary will be provided of the number of subjects screened and the number of screen failures with reasons why subjects were not randomized.

Subject disposition will be summarized as the number and percentage of subjects (out of the number of randomized subjects) who complete the study, with the number who discontinue broken down by reason for discontinuation (Table 14.1.1). The table will also summarize the number and percent of subjects assigned to each analysis population (refer to section 4.1.3).

Subject disposition including the subject status (completer, Yes/No), critical demographic data (age, sex, race, ethnicity), the duration of treatment before discontinuation and the specific reason for discontinuation, will be listed in for randomized subjects (Listing 16.2.1.1.1) by treatment group and in for non-randomized subjects (Listing 16.2.1.1.2).

4.1.2 Protocol Deviations

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

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

Violations that influence the efficacy outcome will be given in the "Review Listing Requirement (RLR)" document and important violations will be identified in blinded data review stage.

The number and percentage of subjects with any important protocol deviations and with each type of major protocol deviations will be presented by treatment (Table 14.1.2). All protocol deviations will be listed (Listing 16.2.2).

4.1.3 Analysis Populations

Five analysis populations are defined.

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 randomized.	• Disposition, AE listing
Randomized	• All subjects who are randomized and may or may not receive the application of the study products. • Any subject who receives a treatment randomization number will be considered to have been randomized.	• Protocol violations
Safety	• Comprise of all subjects who are randomized and receive at least one dose of study treatment.	• Safety Analysis

Population	Definition / Criteria	Analyses Evaluated
	• This population will be based on the treatment the subject actually received.	
Intent-To-Treat	• Comprises of all randomized subjects who receive the study treatment at least once and provide at least one post-baseline (post treatment) assessment of efficacy. • This population will be based on the treatment to which the subject was randomize	• Efficacy
Repeatability	• Any subject who has a repeat stain or plaque assessment. The repeat stain and plaque populations will be separate populations. MLSI repeatability population and TPI repeatability population will be subset of the repeatability population.	• Repeatability Analysis

The numbers of subjects included in each of the analysis populations, and the number excluded from each population (except repeatability 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), with the reason for exclusion.

4.2 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the ITT and Safety populations by treatment group.

4.2.1 Demographic Characteristics

Categorical demographic variables include sex, race, strata and ethnicity. These variables will be summarized by the number and percentage of subjects with each relevant characteristic in each treatment group. Age will be summarized by the mean, standard deviation (SD), median (med), minimum (min) and maximum (max) values in each treatment group. All demographic information will be tabulated in Table 14.1.4.1 for the Safety population, Table 14.1.4.2 for the ITT population and listed in Listing 16.2.4.1.

4.2.2 General Medical History

Medical diagnoses/surgeries will be listed in Listing 16.2.4.2, with start date and end date or ongoing at the start of study drug.

4.3 Study Product Compliance and Use of Other Therapy

4.3.1 Study Product Compliance

Brushing compliance (using study products twice daily) will be listed (Listing 16.2.5.1). This listing will include expected number of brushing, actual number of brushing and percentage of compliance.

4.3.2 Prior and Concomitant Medication

Prior medications will be listed by subject, with, indication, dose, dose form, frequency, route, start date and end date (Listing 16.2.5.5). Prior medications are defined as those stopped before the first administration of the study products. Concomitant medications will be listed similarly (Listing 16.2.5.6). Concomitant medications are defined as those ongoing or started on or after the first administration of the study products.

4.4 Analysis of Efficacy

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary efficacy variable is the change from baseline in overall MLSI score. The primary time-point is 8 weeks. The overall MLSI (AxI) for each subject is derived at a tooth site level first before averaging over all the non-missing teeth sites assessed. The change from baseline is derived from the individual sites first before calculating the average change across the sites assessed.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The primary objective is to evaluate the ranking order in extrinsic dental stain removal, as measured by overall MLSI (A×I), of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 8 weeks twice daily brushing.

Summary statistics including mean, SD, median, min, max will be provided for baseline and Week 8 by randomized treatment group (Table 14.2.2.1).The change from baseline in overall MLSI will be analyzed using analysis of covariance (ANCOVA) with treatment as a fixed effect and baseline overall MLSI as a covariate.

There are no comparisons for the primary objective as the main objective is to look at the rank order of the treatments in level of stain reduction after 8 weeks of treatment. This will be achieved via the adjusted means and confidence intervals (Cis) for the means along with plots of MLSI over time. Adjusted means of all treatments will be provided together with their 95% Cis and p-values (Table 14.2.2.2).

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated. Violation of this assumption will be overcome using a suitable data transformation or a non-parametric technique (e.g. Wilcoxon Rank Sum test).

4.4.1.3 Supportive Analyses

Not Applicable

4.4.2 Secondary Efficacy Variables

The secondary efficacy variable is same as the primary efficacy variable.

4.5 Analysis of Secondary Objectives

4.5.1 Efficacy

The hypothesis is that the test products will reduce stain to a similar or greater extent than the reference products.

Two comparisons of interest will be done under the secondary objectives. These comparisons are:-

Test Product 1 vs Reference Product 1

Test Product 2 vs Reference Product 2.

The change from baseline in overall MLSI at Week 8 will be analyzed using ANCOVA with treatment as a fixed effect and baseline overall MLSI as a covariate.

From the above ANCOVA model, treatment differences between groups (Test Product 1 vs Reference Product 1 and Test Product 2 vs Reference Product 2), 95% Cis and p-values, will be provided (Table 14.2.2.2).

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated. Violation of this assumption will be overcome using a suitable data transformation or a non-parametric technique (e.g. Wilcoxon Rank Sum test).

4.6 Analysis of Exploratory Objectives

4.6.1.1 Exploratory Efficacy Endpoint Definition

The exploratory variables are;

- Change from baseline in overall interproximal MLSI (AxI) stain score at Weeks 2, 4 and 8
- Change from baseline in overall area (A) stain score at Weeks 2, 4 and 8
- Change from baseline in overall intensity (I) stain score at Weeks 2, 4 and 8
- Change from baseline (pre-treatment) in overall TPI for Day 2 post-treatment, Week 8 pre-treatment and Week 8-post treatment
- Change from baseline (pre-treatment) in interproximal TPI for Day 2 post-treatment, Week 8 pre-treatment and Week 8 post-treatment

All stain variables will be derived in a similar way based on relevant tooth sites. The interproximal stain sites are the mesial and distal tooth sites.

The overall TPI for each subject is derived at a tooth site level first before averaging over all the teeth sites assessed. The change from baseline is derived at the individual sites first before calculating the average change across the sites assessed.

The interproximal TPI is based on the mesial and distal tooth sites. The interproximal TPI score and change from baseline are calculated in the same way as for the overall TPI.

4.6.1.2 Analysis of Exploratory Variables

Summary statistics including mean, SD, median, min, and max will be provided for week 2 and week 4 by randomized treatment group (Table 14.2.2.1).

All stain variables will be analyzed as per the primary efficacy variable using the appropriate baseline values as a covariate.

The change from baseline in TPI variables will be analyzed using analysis of covariance (ANCOVA) with treatment and MLSI stratification as fixed effects and appropriate baseline (pre-treatment) TPI as a covariate.

From ANCOVA model, the adjusted mean for each treatment group will be provided with 95% Cis and corresponding p-values.

Results for overall interproximal MLSI (A×I) score, overall MLSI area score, overall MLSI intensity score, overall TPI score and overall Interproximal TPI Score will be presented in Table 14.2.3.1, 14.2.3.2, Table 14.2.4.1, 14.2.4.2, Table 14.2.5.1, 14.2.5.2, Table 14.2.6.1, 14.2.6.2 and Table 14.2.7.1, 14.2.7.2 respectively.

4.6.2 Handling of Missing Values/Censoring/Discontinuations

Missing data will not be replaced or imputed. Dropouts will be included in analyses up to the point of discontinuation.

4.7 Analysis of Safety

4.7.1 Adverse Events and Serious Adverse Events

All summaries of safety will be performed using the safety population and will be analyzed based on treatment actually received. No formal statistical testing will be performed on summary comparisons related to safety related measurements.

All Aes will be coded using the medical dictionary for regulatory activities (MedDRA). Aes will be classified by system organ class (SOC) and by preferred term (PT). In addition, prior to database lock all Aes will be reviewed by the Clinical Research Director (or designee) and categorized as either oral or non-oral. Safety will be assessed based on any oral Aes (this includes those that are identified as treatment emergent oral soft tissue (OST) abnormalities and spontaneously reported oral Aes). Any new or worsening OST condition that occurs after the OST examinations at Screening will be recorded as an AE.

Aes will be summarized using descriptive statistics (frequency tables) by treatment group. Summary tables will indicate both the number of events and the number (percent) of subjects involved. Summaries of Aes will include only treatment emergent adverse events (TEAEs) unless otherwise noted. TEAEs are defined as new Aes that occur on or after the date/time of the first supervised use of the randomized treatment (or events aggravated in severity following treatment). Events with an onset date/time prior to first use of a treatment will be considered as non-treatment emergent. Listing of Aes (including non-treatment emergent from All Subjects) will be provided.

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

- Table of treatment emergent Aes by SOC and Preferred Term (Table 14.3.1.1.1)
- Table of treatment emergent Aes by Oral/Non-Oral and Preferred Term (Table 14.3.1.1.2)
- Table of treatment emergent treatment related Aes by SOC and Preferred Term (Table 14.3.1.3.1)
- Table of Treatment emergent treatment related Aes by Oral/Non-Oral and Preferred Term (Table 14.3.1.3.2)
- Table of Non-serious treatment emergent Aes by SOC and PT (only produced if there are more than 5 SAEs) (Table 14.3.1.4)

- Listing of all Aes (including all subjects: Listing 16.2.7.1.1 for all randomized subjects; Listing 16.2.7.1.2 for non-randomized 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 (Listing 16.2.7.2). Oral soft issue data will be listed (Listing 16.2.7.3). All eCRF comments will be listed (Listing 16.2.3).

4.8 Analysis of Other Variables

To assess the repeatability of the stain and TPI assessments, replicate examinations will be performed by the same qualified dental examiner at each assessment visit. Five subjects will be randomly selected for repeat MLSI and TPI assessments across each assessment window.

The repeat stain and plaque assessments will be compared to the original assessments and will not be used in any efficacy analysis. The first and second assessments on each tooth site will be cross tabulated. 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. Results for repeat MLSI area and intensity assessments will be in Table 14.2.8.1 and Table 14.2.8.2 respectively. Also result for repeat TPI assessment will be Table 14.2.8.3.

5 Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	Statistical Analysis Plan	Rationale for Changes

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
• Section 10.2.1: Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for demographic baseline characteristics concomitant medication, medical history and compliance.	• We are not providing descriptive statistics for concomitant medications, medical histories and compliance.	• Summary tables are not required for reporting
• 10.2.4- Safety Analysis(es) Listing of SAEs (if there are none a null listing will be produced; if there are more than 5 treatment emergent SAEs a table will be produced instead by SOC and PT)	• Analysis of Safety Listing of death (Listing 14.3.2.1); Listing of non-fatal SAEs (Listing 14.3.2.2)	• As per RAP template and list of required TLF list for Oral studies, two listings have been added in RAP.
• 10.2.6 Definition of Analysis Populations	• We have added two populations in RAP which are all screened subjects and randomized population.	• We will require these population for some TLFs.
• Safety Analysis(es)	• The below table is not included in the RAP: Treatment emergent Aes by Intensity presented by System Organ Class (SOC) and PT	• It is not required since it is study dependent and not required for this study.
• 10.2.6 Definition of Analysis Populations	• We have added two subsets population for repeatability population in RAP.	• It is not possible to keep the repeated subjects for stain and plaque assessment under the same population. Therefore we have developed subset population for MLSI and TPI repeatability.

6 Abbreviation

Abbreviation	Term
AE	adverse event
TEAE	treatment-emergent adverse event
ANCOVA	analysis of covariance
CI	confidence interval
ITT	intent-to-treat
KNO_3	potassium nitrate
NaF	sodium fluoride
STP	sodium tripolyphosphate
MedDRA	medical Dictionary for Regulatory Activities
MLSI	Macpherson modification of the Lobene Stain Index
OST	oral soft tissue
SAE	serious adverse event
SOC	system organ class
PT	preferred term
TPI	Turesky modification of the Quigley Hein Index
A	Area
I	Intensity
SD	standard deviation
Med	median
Min	minimum
Max	maximum
RLR	review listing requirement
BDRM	blinded data review meeting
SAS	statistical analysis system
GSK CH	GlaxoSmithKline Consumer Healthcare
POP	proof of principle

7 Attachment 1: List of Data Displays

Study 208078_List of Outputs.xlsx

8 Appendix 1: Template 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 Product 1
- Test Product 2
- Reference Product 1
- Reference Product 2

The treatment comparison will be in below order;
Test Product 1 Vs Test Product 2
Reference Product 1 Vs Reference Product 2

The below footnotes will be used for each outputs;
Test Product 1: 5% KNO_3 / 0.2542% NaF dentifrice with 0.5% spherical silica (RDA~38)
Test Product 2: 5% KNO_3 / 0.2542% NaF dentifrice with 1% spherical silica and 5% STP (RDA~58)

Reference Product 1: Sensodyne Pronamel Daily Protection (RDA~36).
Reference Product 2: Sensodyne Extra Whitening (RDA~166).

Protocol 208078 Program Run Date: DDMMMYYYY

Table 14.1.1
Subject Disposition
All Screened Subjects

Study Population: All Screened Subjects (N=xxx)

	Test Product 1 N (%)	Test Product 2 N (%)	Reference Product 1 N (%)	Reference Product 2 N (%)	Overall N (%)
TOTAL SUBJECTS SCREENED					xxx
SUBJECTS NOT RANDOMIZED					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 RANDOMIZED	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 Product 1 N (%)	Test Product 2 N (%)	Reference Product 1 N (%)	Reference Product 2 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)
REPEATABILITY POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
MLSI REPEATABILITY POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
TPI REPEATABILITY POPULATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

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

Protocol 208078 Program Run Date: DDMMYYYY

Table 14.1.2
Incidence of Major Protocol Deviations
All Randomized Population

Study Population: All Randomized Population (N=xxx)

	Test Product 1 N (%)	Test Product 2 N (%)	Reference Product 1 N (%)	Reference Product 2 N (%)	Overall N (%)
NUMBER OF SUBJECTS WITH AT LEAST ONE IMPORTANT PROTOCOL DEVIATIONS	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATIONS 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATIONS 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATIONS 3	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATIONS 4	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
...					

Protocol 208078 Program Run Date: DDMMYYYY

Table 14.1.3
Analysis Populations
All Randomized Population

Study Population: All Randomized 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 (%)
NUMBER OF 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)
...					
NUMBER OF 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)
...					

Protocol: 208078 Program Run Date: DDMMMYYYY

Table 14.1.4.1
Demographic and Baseline Characteristics
Safety Population

Study Population: Safety Population (N=xxx)

	Test Product 1 N (%)	Test Product 2 N (%)	....	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 (%)				
AFRICAN AMERICAN/AFRICAN HERITAGE	XX (XX.X)	XX (XX.X)	...	XX (XX.X)
AMERICAN INDIAN OR ALASKAN NATIVE	XX (XX.X)	XX (XX.X)		XX (XX.X)
ASIAN - CENTRAL/SOUTH ASIAN HERITAGE	XX (XX.X)	XX (XX.X)		XX (XX.X)
ASIAN - EAST ASIAN HERITAGE	XX (XX.X)	XX (XX.X)	...	XX (XX.X)
ASIAN - SOUTH EAST ASIAN HERITAGE	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 - ARABIC/NORTH AFRICAN HERITAGE	XX (XX.X)	XX (XX.X)	...	XX (XX.X)
WHITE - WHITE/CAUCASIAN/EUROPEAN HERITAGE	XX (XX.X)	XX (XX.X)	...	XX (XX.X)
			...	
ETHNICITY N (%)				
HISPANIC OR LATINO	XX (XX.X)	XX (XX.X)		XX (XX.X)
NOT HISPANIC OR LATINO	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
MINIMUM	XX	XX	.....	XX
MAXIMUM	XX	XX	...	XX
STRATIFICATION				
STRATA 1: LOW (MLSI <15)	XX (XX.X)	XX (XX.X)		XX (XX.X)
STRATA 2: HIGH (MLSI ≥15)	XX (XX.X)	XX (XX.X)		XX (XX.X)

Protocol 208078 Program Run Date: DDMMMYYYY

Table 14.2.2.1
Summary of Overall MLSI Score
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)

		Test Product 1 (N=XX)		Test Product 2 (N=XX)		……..	Overall (N=XXX)	
Visit		Observed Value	Change from Baseline	Observed Value	Change from Baseline	……..	Observed Value	Change from Baseline
BASELINE	N	XX		XX		……..	XX	
	MEAN	X.XX		X.XX		……..	X.XX	
	SD	X.XXX		X.XXX		……..	X.XXX	
	MEDIAN	X.XX		X.XX		……..	X.XX	
	MINIMUM	X.XX		X.XX		……..	X.XX	
	MAXIMUM	X.XX		X.XX		……..	X.XX	
WEEK 2	N	XX	XX	XX	XX	……..	XX	XX
	MEAN	X.XX	X.XX	X.XX	X.XX	……..	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX	X.XXX	……..	X.XXX	X.XXX
	MEDIAN	X.X	X.X	X.X	X.X	……..	X.X	X.X
	MINIMUM	X.X	X.X	X.X	X.X	……..	X.X	X.X
	MAXIMUM	X.X	X.X	X.X	X.X	……..	X.X	X.X
WEEK 4	SAME AS ABOVE							

Protocol 208078 Program Run Date: DDMMMYYYY

Table 14.2.2.2
Statistical Analysis of Overall Change Baseline in MLSI Score
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)

Visit		Test Product 1 (N=XX)	Test Product 2 (N=XX)	Reference Product 1 (N=XX)	Reference Product 1 (N=XX)
WEEK 2	ADJUSTED MEANS (SE)[1]	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)
	95 % CI [1]	(X.XX, X.XX)	(X.XX, X.XX)	(X.XX, X.XX)	(X.XX, X.XX)
	P-VALUE [1]	0.XXXX	0.XXXX	0.XXXX	0.XXXX
	COMPARISON	DIFFERENCE (SE) [1,2]	95% CI [1]	P-VALUE [1]	
	TEST PRODUCT 1 VS REFERENCE PRODUCT 1	X.XX (X.XXX)	(X.XX, X.XX)	0.XXXX	
	TEST PRODUCT 2 VS REFERENCE PRODUCT 2	X.XX (X.XXX)	(X.XX, X.XX)	0.XXXX	
WEEK 4	SAME AS ABOVE				

[1] From ANCOVA with treatment as factors and baseline overall MLSI score as a covariate

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

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PPD

Programming note: The same summary would be provided for the Week 8 also.

Protocol 208078 PROGRAM RUN DATE: DDMMMYYYY

Table 14.2.6.1
Summary of TPI Score
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)

Visit	TimePoint		Test Product 1 (N=XX)		Test Product 2 (N=XX)		.....	Overall (N=XX)	
			Observed Values	Change from Pre-brushing	Observed Values	Change from Pre-brushing	.....	Observed Values	Change from Pre-brushing
BASELINE	PRE-BRUSHING	N	XX		XX		.....	XX	
		MEAN	X.XX		X.XX		.....	X.XX	
		SD	X.XXX		X.XXX		.....	X.XXX	
		MEDIAN	X.XX		X.XX		.....	X.XX	
		MINIMUM	X.XX		X.XX		.....	X.XX	
		MAXIMUM	X.XX		X.XX		.....	X.XX	
							.....		
	POST-BRUSHING	N	XX	XX	XX	XX	.....	XX	XX
		MEAN	X.XX	X.XX	X.XX	X.XX	.....	X.XX	X.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX	.....	X.XXX	X.XXX
		MEDIAN	X.XX	X.XX	X.XX	X.XX	.....	X.XX	X.XX
		MINIMUM	X.XX	X.XX	X.XX	X.XX	.....	X.XX	X.XX
		MAXIMUM	X.XX	X.XX	X.XX	X.XX	.....	X.XX	X.XX
WEEK 8	SAME AS ABOVE								

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Protocol 208078 Program Run Date: DDMMMYYYY

Table 14.2.6.2
Statistical Analysis of Overall Change from Baseline (Pre-brushing) in TPI Score
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)

Visit		Test Product 1 (N=XX)	Test Product 2 (N=XX)	Reference Product 1 (N=XX)	Reference Product 1 (N=XX)
BASELINE POST-BRUSHING	ADJUSTED MEANS (SE)[1]	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)	X.XX (X.XXX)
	95 % CI [1]	(X.XX, X.XX)	(X.XX, X.XX)	(X.XX, X.XX)	(X.XX, X.XX)
	P-VALUE [1]	0.XXXX	0.XXXX	0.XXXX	0.XXXX
	COMPARISON	DIFFERENCE (SE) [1,2]	95% CI [1]	P-VALUE [1]	
	TEST PRODUCT 1 VS REFERENCE PRODUCT 1	X.XX (X.XXX)	(X.XX, X.XX)	0.XXXX	
	TEST PRODUCT 2 VS REFERENCE PRODUCT 2	X.XX (X.XXX)	(X.XX, X.XX)	0.XXXX	
WEEK 8 PRE-BRUSHING	SAME AS ABOVE				
WEEK 8 POST-BRUSHING	SAME AS ABOVE				

[1] From ANCOVA with treatment and MLSI stratification as factors and appropriate baseline (Pre-treatment) TPI score as a covariate

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

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Programming note: The same summary would be provided for the Week 8 pre-brushing and Week 8 post-brushing also.

Protocol 208078 Program Run Date: DDMMMYYYY

Table 14.2.8.1
Repeatability for MLSI Intensity Score
MLSI Repeatability Population

Study Population: MLSI 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.

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Note to Programmer: For Table 14.2.8.2 and 14.2.8.3, use area and TPI scoring descriptions in footnote.

Protocol 208078 Program Run Date: DDMMYYYY

Table 14.3.1.1.1
Treatment Emergent Adverse Event by SOC and Preferred Term
Safety Population

Study Population: Safety Population (N=xx)

SOC Preferred Term	Test Product 1 (N=XX)		Test Product 2 (N=XX)		Reference Product 1 (N=XX)		Reference Product 1 (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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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.1.7
Randomization Information
All Randomized Population

Stratum 1: Low (MLSI <15)

Subject Number	Age/Sex/ Race [1]	Randomization Number	Treatment Randomized [2]	Date of Randomization
PPD				

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] A= Reference Product 1; B= Reference Product 2; C= Test Product 1; D= Test Product 2.
The block size for this randomization was used 8.

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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.1.1.1
Subject Disposition
All Randomized Population

Subject	Age/Sex/ Race [1]	Ethnicity	Screening Date	Treatment Start Date and Time	Date of Completion or Withdrawal	Duration of Treatment (Days) [2]	Completed	Primary Reason for Withdrawal	Further Details [3]
PPD									

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] Treatment duration is calculated as date of completion or withdrawal minus treatment start date.
[2] Further details of reasons for withdrawal.

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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.2
All Protocol Deviations
All Randomized Population

Treatment Group: Test Product 1

Subject Number	Age/Sex/Race[1]	Deviation Sequence	Start Date/Time	End Date/Time	Protocol Deviation
PPD					

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.

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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.3
eCRF Comments
All Randomized Population

Treatment Group: Test Product 1

Subject Number	Age/Sex/Race[1]	Visit Name	Section	Item	Comments
PPD					

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.

Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.3.1
Exclusion from Analysis Population
All Randomized population

Subject Number	Age/Sex/Race[1]	Treatment Start Date and Time	Safety Population	ITT Population	Reasons for Exclusion
PPD					

[1] Age in years; Sex: F = Female, M = Male ; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.

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Programming Note for Listing 16.2.3.1: This listing is based on population definition document.

Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.4.1
Demographic Characteristics
All Randomized Population

Treatment Group: Test Product 1

Subject Number	Age (years)	Sex	Race	Ethnicity	Stratification
PPD					

Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.4.2
Medical History and Current Medical Conditions
All Randomized Population

Treatment Group: Test Product 1

Subject	Age/Sex/Race [1]	Any Medical History?	Medical Condition	Start Date	Ongoing?	End Date
PPD						

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.

Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.5.1
Brushing Compliance
All Randomized Population

Treatment Group: Test Product 1

Subject Number	Age/Sex/Race [1]	Period	Expected Number of Brushing [2]	Actual Number Brushing [3]	Compliance [4]
PPD					

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] Expected Number of Brushing = 2*Number of Days between the Two Visits;
[3] Actual Number of Brushing = Expected Number – Missed brushing + Additional Brushing;
[4] Compliance = Actual Number / Expected Number *100 (%)

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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.5.6
Concomitant Medications and Non-drug Therapies Taken During Treatment
All Randomized Population

Subject Number	Age/Sex/Race[1]	Sequence Number	Treatment [GSK Drug Synonym]	Reason for Treatment	Route of Administration	Dose per Administration	Frequency	Start Date (Study Day [2])	End Date/ Ongoing
PPD									

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] Study day relative to the date of randomization.

Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.6.1
Individual MLSI Stain Index
All Randomized Population

Treatment Group: Test Product 1

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

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] Intensity Score: 0=No Stain; 1=light Stain;2=Moderate Stain; 3=Heavy Stain. Missing means non-scorable; X=Missing.
[3] Area Score: 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 208078 Program Run Date: DDMMYYYY

Listing 16.2.6.2
Individual Turesky Plaque Index (TPI)
All Randomized Population

Treatment Group: Test Product 1

Subject Number	Age/Sex/Race[1]	Visit	PRE/POST	Tooth Number (universal/FDI)	Surface	Site	TPI Score [2]	Average Whole Mouth TPI	Change from Bassline Score
PPD									

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] 0 = No plaque; 1 = Slight flecks of plaque at the cervical margin of the tooth; 2 = A thin continuous band of plaque (1 mm or smaller) at the cervical margin of the tooth; 3 = A band of plaque wider than 1 mm but covering less than 1/3 of the crown of the tooth; 4 = Plaque covering at least 1/3 but less than 2/3 of the crown of the tooth; 5 = Plaque covering 2/3 or more of the crown of the tooth; X = Missing Tooth; N = Not Scorable

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Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.7.1.1
All Adverse Events
All Randomized Population

Treatment Group: Test Product 1

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 classified as Oral AEs.
[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[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 16.2.7.1.2:

- *Repeat the same layout for listing 16.2.7.1.2*
- *Population should be used 'Non randomized Subjects'*
- *The fourth column should be only 'Start Date'*
- *Add footnote 'Only SAEs are collected for non randomized subjects'*
- *Delete the footnote related to study day and adjust the numbers accordingly.*

Protocol 208078 Program Run Date: DDMMYYYY

Listing 16.2.7.3
Oral Soft Tissue Examination
All Randomized Population

Treatment Group: Test Product 1

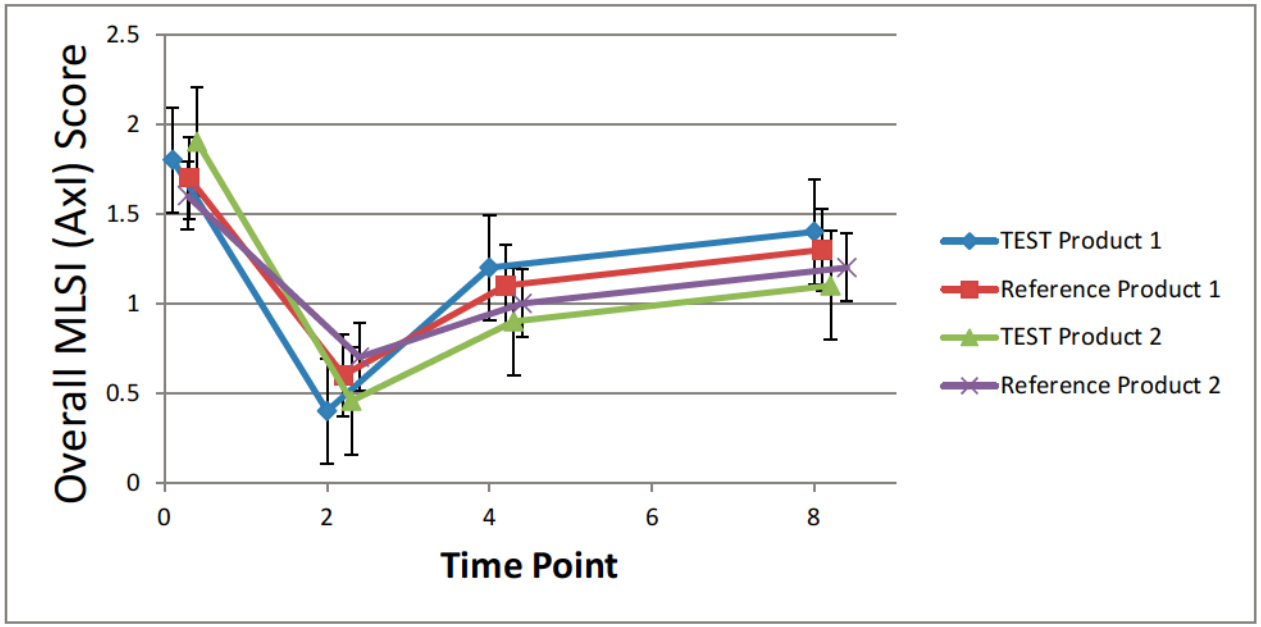
Subject Number	Age/Sex/Race[1]	Visit	Area	Condition	Details
PPD					

[1] Age in years; Sex: F = Female, M = Male; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.

Protocol 208078 Program Run Date: DDMMYYYY

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

Study Population: Intent-to-Treat Population (N=XX)



Mean and SE plotted are from summary statistics in T 14.2.2.1.1

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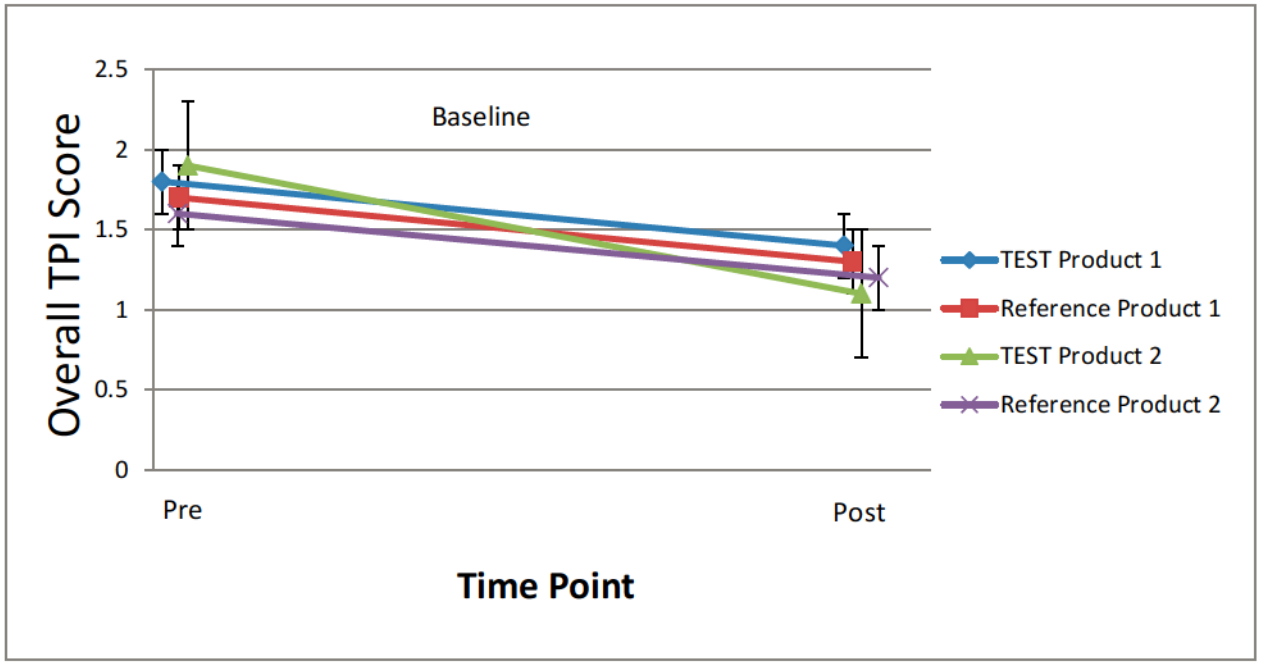
Protocol 208078 Program Run Date: DDMMYYYY

Figure 14.2.2
Overall TPI Score Mean (±SE) Plot over Time by Treatment
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)



Mean and SE plotted are from summary statistics in T 14.2.5.1.1

Programming Note: Please repeat figure for the Week 8 also.

Potassium Nitrate / Sodium Fluoride
208078
Final Statistical Reporting and Analysis plan Addendum 1, 01FEB2018

GlaxoSmithKline
Consumer Healthcare

STATISTICAL REPORTING AND ANALYSIS PLAN
Addendum 1

A RANDOMIZED, EXAMINER-BLIND, PROOF OF PRINCIPAL STUDY TO INVESTIGATE THE STAIN AND PLAQUE REMOVAL CAPABILITY OF TWO EXPERIMENTAL 5% POTASSIUM NITRATE DENTIFRICES IN HEALTHY SUBJECTS WITH THE PROPENSITY FOR EXTRINSIC DENTAL STAIN

Protocol Number: 208078

Phase: II

Potassium Nitrate / Sodium Fluoride
208078
Final Statistical Reporting and Analysis plan Addendum 1, 01FEB2018

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	05-Oct-2017	Not applicable (N/A)
RAP Amendment Version 1.0	21-Nov-2017	Add brushing compliance listing in RAP rather than cover it in BDRM. Add eCRF comments listing Added major Protocol deviation table Amend the text of section 3.3 (Timepoints and Visit Window) Added the text in repeatability population of section 4.1.3
RAP Addendum Version 1.0	01-Feb-2018	Add the figure based on the Adjusted mean change from baseline for MLSI and TPI and add the 16.1.9 SAS outputs in the section 7. Correct the presentation of Figure 14.2.2 based on raw means to be consistent with the Figure 14.2.4 template.

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1 Introduction

This RAP addendum describes the clarification of the text related to figures and addition of figures to the planned analysis described in the Statistical Reporting and Analysis Plan Amendment 1.These changes were identified during draft topline TFLs review stage, and hence was after unblinding but prior to development of the non-topline TFLs. These changes will be reflected in the final CSR.

The sections below provide the updated text that are required from the planned analysis, with section 5.0 providing further details on what was planned, the change and the reason for the change. A summary of the changes/clarifications are:

- To add the figures based on the adjusted means change from baseline values for MLSI and TPI parameters.
- To add a note about the presentation of Figure 14.2.2 based on raw means to be consistent with the Figure 14.2.4 template. To add the 16.1.9 SAS outputs in the section "Attachment 1: List of displays".

5 Changes to the Statistical Analysis Plan

Any changes from the originally planned statistical analysis specified in the RAP amendment (dated 21-NOV-2017) are outlined in Table 1.

Table 1 Changes to SAP amendment Defined Analysis Plan

SAP Analysis Plan Amendment 1	Statistical Analysis Plan Addendum	Rationale for Changes
• Section 7.0 Attachment 1: List of displays	• Section 7.0 Attachment 1: List of displays	• While delivering the non-topline TLFs, it was observed that the outputs related to Section 16.1.9 was developed but was missed to number correctly in the RAP amendment. Therefore it is decided to include the listing numbers.
• Section 8.0 Appendix1: Template for Table, Figure and Listings	• Section 8.0 Appendix 1: Template for Table, Figure and Listings	• All figures were planned based on the raw mean (+/-) SE and provided as part of the topline and non-topline delivery. However the text in section of 4.4.1.2 of the RAP amendment was "*This will be achieved via the adjusted means and confidence intervals (CIs) for the means along with plots of MLSI over time*". • It was realized while reviewing the draft topline TLFs that, the figures based on the adjusted

SAP Analysis Plan Amendment 1	Statistical Analysis Plan Addendum	Rationale for Changes
		means and CI will be more appropriate. This adjusted means will be used for ranking the study treatments for interpretation. Therefore it was decided to include the figures based on adjusted means change from baseline (+/- 95% CIs) in the RAP addendum. • While creation of the Figure 14.2.2 as part of non-topline delivery, it was observed that the presentation of Figure 14.2.2 in RAP amendment template was not appropriate. Therefore it was decided to change the presentation of Figure 14.2.2 to be consistent with Figure 14.2.4.

7 Attachment 1: List of Data Displays

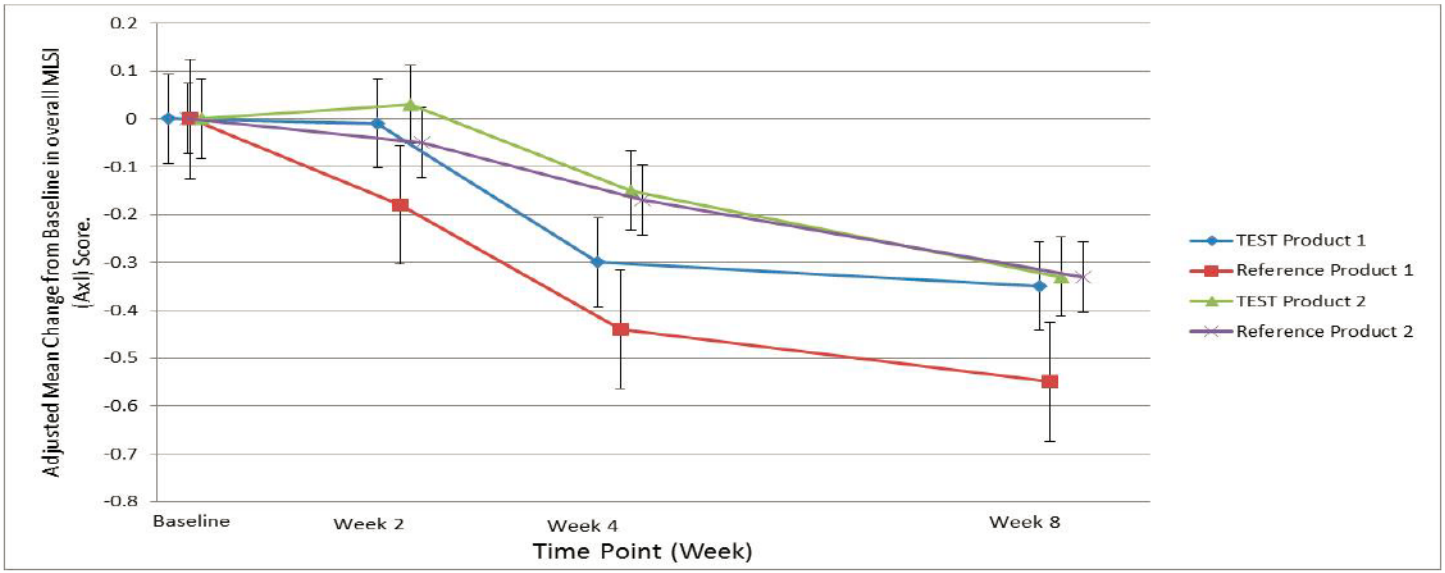
Study 208078_List of Outputs.xlsx

8 Appendix 1: Template for Tables, Figures and Listings

Protocol 208078 Program Run Date: DDMMYYYY

Figure 14.2.3
Change from Baseline in Overall MLSI (AxI) Score Adjusted Means (±95%CIs) Plot Over Time by Treatment
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)



Values are adjusted means +/- 95%CIs
PPD

Test Product 1: 5% KNO3 / 0.2542% NaF dentifrice with 0.5% spherical silica (RDA~38)
Test Product 2: 5% KNO3 / 0.2542% NaF dentifrice with 1% spherical silica and 5% STP (RDA~58)
Reference Product 1: Sensodyne Pronamel Daily Protection (RDA~36).

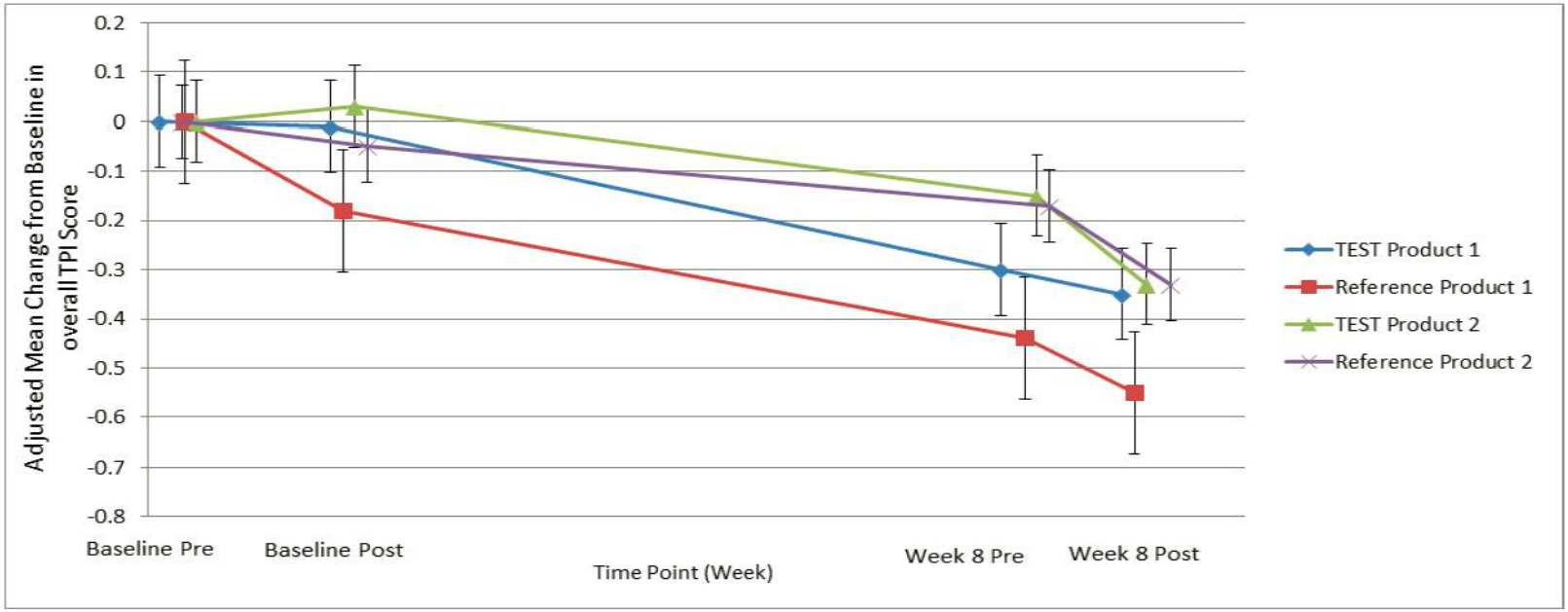
Reference Product 2: Sensodyne Extra Whitening (RDA~166).
PPD

Programming Note: 1) Adjusted Means and CIs plotted are from summary statistics PPD .
2) Baseline should start from zero and CIs should not applicable.

Protocol 208078 Program Run Date: DDMMYYYY

Figure 14.2.4
Change from Baseline (Pre-brushing) in Overall TPI Score Adjusted Means (±95%CI) Plot Over Time by Treatment
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N=XX)



Values are adjusted means +/- 95%CIs

PPD

Test Product 1: 5% KNO3 / 0.2542% NaF dentifrice with 0.5% spherical silica (RDA~38)
Test Product 2: 5% KNO3 / 0.2542% NaF dentifrice with 1% spherical silica and 5% STP (RDA~58)
Reference Product 1: Sensodyne Pronamel Daily Protection (RDA~36).

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Reference Product 2: Sensodyne Extra Whitening (RDA~166).

Programming Note: 1) Adjusted Means and CIs plotted are from summary statistics PPD
2) Baseline should start from zero and CIs should not applicable.

PPD

Note: Use the same template as Figure 14.2.4 for the figure 14.2.2.