STATISTICAL REPORTING AND ANALYSIS PLAN

RANDOMIZED CONTROLLED EXAMINER-BLIND PHASE II EXPLORATORY CLINICAL STUDY TO CHARACTERIZE THE EFFICACY PROFILE OF AN EXPERIMENTAL DUAL ACTIVE COMBINATION DENTIFRICE FOR THE RELIEF OF DENTIN HYPERSENSITIVITY, IN SUBJECTS WITH CLINICALLY DIAGNOSED DENTIN HYPERSENSITIVITY

Protocol Number: 209723

Phase: 2

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	30-May-2019	Not applicable (N/A)
RAP Amendment 1	27-Sep-2019	An InForm database outage prevented the direct entry of source data from twelve (12) subjects into the InForm eCRF database. Due to this data integrity issue a sensitivity analysis will be performed on primary end points for baseline records.

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Abbreviations

Abbreviation	Term
AEs	Adverse Events
ANCOVA	Analysis Of Covariance
BDRM	Blinded Data Review Meeting
CIs	Confidence Intervals
DH	Dentinal Hypersensitivity
DHEQ	Dentinal Hypersensitivity Experience Questionnaire
eCRF	Electronic Case Report Form
GSKCH	GlaxoSmithKline Consumer Healthcare
ICF	Informed Consent Form
IP	Investigational Product
KNO_3	Potassium Nitrate
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
N/A	Not Applicable
OHRQoL	Oral Health Related Quality of Life
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PDMP	Protocol Deviation Management Plan
PP	Per Protocol
PT	Preferred Term
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Events
SE	Standard Error
SD	Standard Deviation
SMFP	Sodium Monofluorophosphate
SnF_2	Stannous Fluoride
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

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 209723 v2.0 dated 16 Oct 2018.

1 Summary of Key Protocol Information

GlaxoSmithKline Consumer Healthcare (GSK CH) has developed an anhydrous 5% potassium nitrate (KNO_3) and 0.454% stannous fluoride (SnF_2) combination dentifrice for the relief of dentin hypersensitivity (DH). It is hypothesized that the combination of two anti-sensitivity active ingredients with complementary modes of action (KNO_3: nerve desensitization; SnF_2: dentin tubule occlusion) will deliver superior anti-sensitivity efficacy, compared to either active alone. Published clinical studies report DH efficacy for KNO_3/SnF_2 combination dentifrices and indicate greater clinical benefit for dual active formulations, compared to KNO_3 only formulations, with 4-8 weeks treatment. They do not provide any information regarding performance versus SnF_2 only formulations (no SnF_2 only dentifrices were evaluated). This exploratory study will characterize the efficacy profile of an experimental 5% KNO_3 and 0.454% SnF_2 combination dentifrice, compared to a 0.454% SnF_2 single active desensitizing dentifrice, across an 8-week treatment period.

1.1 Study Design

This will be a single center, 8-week, randomized, controlled, examiner-blind, two treatment arm, parallel design, stratified (by maximum Baseline Schiff sensitivity score of the two selected test teeth), Phase II, exploratory study to evaluate the DH efficacy of an experimental 5% KNO_3 and 0.454% SnF_2 combination dentifrice (Test), compared to a marketed 0.454% SnF_2 desensitizing dentifrice (Control). Study dentifrices will be applied twice daily, by tooth brushing, over the 8-week treatment period.

DH to tactile and evaporative air stimuli will be assessed at Screening (Visit 1) and Baseline (Visit 2), and after 3, 7, 14, 28 and 56 days treatment (Visits 3-7). Eligible subjects will complete an acclimatization phase (2-4 weeks) between the Screening and Baseline visits and will be randomized to study dentifrice following Baseline assessments. The safety and oral tolerability of the study products will be monitored over the treatment period by review of reported adverse events (AEs).

Table 1-1 Schedule of Activities

Procedure/ Assessment	Visit 1 Day -28 to -14 Screening		Visit 2 Day 0 Baseline	Visit 3 Day 3	Visit 4 Day 7 (+1day)	Visit 5 Day 14 (±1day)	Visit 6 Day 28 (±2days)	Visit 7 Day 56 (±2days)
Informed Consent	X	Acclimatization Period (2-4 Weeks)						
Demographics	X							
Medical History	X							
Prior/Current Medications and Treatments	X							
Review Subject's Current Oral Care Products	X							
Subject Returns with Acclimatization Dentifrice, Toothbrush and Completed Diary[1]			X					
Subject Returns with Study Treatment, Toothbrush and Completed Diary[1]				X	X	X	X	X
Compliance Checks[2]			X	X	X	X	X	X
Concomitant Medications and Treatments			X	X	X	X	X	X
Urine Pregnancy Test (UPT)[3]	X		X					
Subject Continuance				X	X	X	X	X
Dentine Hypersensitivity Experience Questionnaire (DHEQ)[4]			X				X	X
Oral Soft Tissue (OST) Examination	X		X	X	X	X	X	X
Oral Hard Tissue (OHT) Examination	X							X
Eligible Teeth Assessments (Dentition Exclusions, Erosion/Abrasion/Recession [EAR], Modified Gingival Index [MGI], Tooth Mobility)	X							

Procedure/ Assessment	Visit 1 Day -28 to -14 Screening		Visit 2 Day 0 Baseline	Visit 3 Day 3	Visit 4 Day 7 (+1day)	Visit 5 Day 14 (±1day)	Visit 6 Day 28 (±2days)	Visit 7 Day 56 (±2days)
Qualifying Tactile Sensitivity Assessment (Tactile Threshold)[5]	X		X					
Qualifying Evaporative Air Sensitivity Assessment (Schiff sensitivity score)[6]	X		X					
Inclusion / Exclusion Criteria	X		X					
Subject Eligibility	X		X					
Clinical Examiner Selects Two 'Test Teeth' *Eligible Subjects Only*			X					
Stratification/Randomization			X					
Dispense Acclimatization dentifrice, Toothbrush, Diary and Timer	X							
Supervised Brushing with Acclimatization Dentifrice	X							
Dispense Study Treatment, Toothbrush and Diary			X					
Tactile Sensitivity Assessment (Yeaple Probe)[5] *Test Teeth Only*				X	X	X	X	X
Evaporative Air Sensitivity (Schiff sensitivity score)[6] *Test Teeth Only*				X	X	X	X	X
Evaporative Air Sensitivity (Schiff sensitivity score)[6] *Remaining Eligible Teeth from Screening*			X	X	X	X	X	X
Supervised Brushing with Study Treatment			X	X	X	X	X	
Return Study Treatment/Toothbrush and Diary to Subject				X	X	X	X	
Adverse Events/Incidents[7]	X		X	X	X	X	X	X
Study Conclusion								X

Footnotes:

1. Subject will be required to bring their study supplies (minus timer) to every visit.
2. Perform visual check of returned study supplies and review diary (Visit 2: compliance with use of acclimatization dentifrice; Visits 3-7: compliance with use of study treatment). Check compliance with Lifestyle Guidelines/Medication Requirements.
3. Female subjects of child bearing potential only.
4. DHEQ must be completed prior to OST examination/clinical assessments.
5. Visits 1-2: maximum force 20 g (Screening and Baseline); Visits 3-7: maximum force 80 g.
6. Evaporative air assessment will follow tactile assessment, with minimum 5 minutes between last tactile assessment and first evaporative (air) assessment (to allow tooth recovery). Visits 3-7: Complete evaporative (air) assessments for 2 test teeth first, before assessing remaining eligible teeth from Screening.
7. AEs, and therefore all Serious Adverse Events (SAEs), and incidents will be recorded from immediately after a subject consents to participate in the study (by the completion of the Informed Consent Form [ICF]) until 5 days after last dose of study treatment.

1.2 Study Objectives

Objectives	Endpoints
Primary	
To characterize the efficacy profiles of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice and a 0.454% w/w SnF_2 only dentifrice in reducing DH, with twice daily use for 8 weeks.	*At Baseline, Days 3, 7, 14, 28, 56;* Schiff sensitivity score Tactile threshold (grams [g]) Number of sensitive teeth (Schiff sensitivity score ≥ 1)
Secondary	
To investigate the clinical efficacy of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice in reducing DH to an evaporative air stimulus (Schiff sensitivity score), compared to a 0.454% w/w SnF_2 only dentifrice, after 8 weeks twice daily use.	Change from Baseline in Schiff sensitivity score at Day 56
To investigate the clinical efficacy of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice in reducing DH to a tactile stimulus (tactile threshold), compared to a 0.454% w/w SnF_2 only dentifrice, after 8 weeks twice daily use.	Change from Baseline in tactile threshold (g) at Day 56
Safety	
To assess the safety and tolerability of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice with twice daily use for 8 weeks.	Treatment emergent adverse events
Other	
To investigate the clinical efficacy of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice in reducing DH to evaporative air (Schiff sensitivity score) and tactile (tactile threshold) stimuli, compared to a 0.454% w/w SnF_2 only dentifrice, after 3, 7, 14 & 28 days twice daily use.	*At Days 3, 7, 14 & 28;* Change from Baseline in Schiff sensitivity score Change from Baseline in tactile threshold (g)
To monitor Oral Health Related Quality of Life (OHRQoL) as measured by the Dentine Hypersensitivity Experience Questionnaire (DHEQ) after 4 and 8 weeks treatment with an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice and a 0.454% w/w SnF_2 only dentifrice.	*At Days 28 & Day 56;* Change from Baseline in - responses to Questions 7-9, DHEQ Section 1 - Total Score, Questions 1-15, DHEQ Section 2 - Restrictions, Adaptation, Social Impact, Emotional Impact & Identity Domains

1.3 Treatments

	Acclimatization Dentifrice	Test Dentifrice	Control Dentifrice
Treatment Description	Dentifrice containing 1000 parts per million (ppm) fluoride as sodium monofluoro-phosphate (SMFP)	Dentifrice containing 5% w/w KNO_3 and 0.454% w/w SnF_2 (1100 ppm fluoride)	Dentifrice containing 0.454% SnF_2 (1100 ppm fluoride)
Product Name	Colgate Cavity Protection (Canadian market)	Experimental dentifrice	Sensodyne Rapid Relief Regular (registered as a Non-prescription Natural Health Product [NNHP] in Canada)

Only the Test and Control denrifrices are considered to be study products.

1.4 Sample Size Calculation

No formal sample size has been produced for this exploratory clinical study to characterize the DH efficacy profile of the Investigational Product (IP), as measured by Schiff sensitivity score and tactile threshold, over time. Based on previous GSK CH studies evaluating DH efficacy of 0.454% w/w SnF_2 dentifrices, approximately 50 evaluable subjects per treatment group is considered sufficient to provide reliable estimates of treatment effect for the purposes of this study and to aid in the design of future clinical studies. Approximately 104 subjects will be randomized to study treatment (approximately 52 per treatment group) to achieve approximately 50 evaluable subjects per treatment group, allowing for a dropout rate of approximately 4%.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned.

2.2 Final Analyses

The final planned 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 Day 0 (Visit 2) pre-treatment assessment with a non-missing value.

Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

3.2 Subgroups/Stratifications

Subgroups are not defined for this trial.

Subjects will be stratified according to the maximum Baseline Schiff sensitivity score of their two selected 'test teeth'. The stratification factor will give rise to two strata.

- **Stratum 1:** maximum Schiff sensitivity score = 2
- **Stratum 2:** maximum Schiff sensitivity score = 3

3.3 Timepoints and Visit Windows

The time points and visits for this study are defined in Table 1-1 "Schedule of Activities". Any deviation from the study schedule will be reviewed on case-by-case basis at the Blinded Data Review Meeting (BDRM) to determine whether the data should be excluded from the Per-Protocol (PP) population.

4 Data Analysis

Data analysis will be performed by Syneos Health. Statistical analysis software SAS (Studio) version 9.4 or higher will be used.

Prior to database closure a BDRM will be conducted at which various aspects of the trial will be discussed and necessary actions, including exclusions from the Safety, modified Intent to Treat (mITT) and PP populations.

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

4.1 Populations for Analysis

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

4.1.1 Subject Disposition

Subject disposition will be presented in Table 14.1.1.

Subject disposition will be summarized as the number and percentage of subjects in each analysis population (defined in Section 4.1.3), who complete the study and who were discontinued from the study (by reason for discontinuation). The summary will be presented by study product and overall. The percentages will be based on the total number of subjects randomized.

Subject disposition including demographic data (age, sex, race and ethnicity), screening date, study product start date and time, study product end date and time, subject status (completer, Yes/No), study completion/withdrawal date, duration (in days) in the study (defined as [(date of completion or withdrawal minus date of signing ICF) + 1], duration (in days) of study product usage (defined as: [(date of last study product use minus date of first study product use)+1]) and the primary reason for withdrawal will be listed (Listing 16.2.1.1) by study product group.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. An enrolled subject is a subject who has signed informed consent and is eligible to proceed beyond the screening visit. The number of subjects screened, enrolled and randomized will be presented.

The number and percentage of screen failures with reasons why subjects were not randomized will be presented. Percentage of screen failures will be based on the total number of subjects screened.

Subject disposition information will be listed for non-randomized subjects (Listing 16.2.1.2), displaying subject number, demographic information (age, sex, race and ethnicity), screening date, reason for screen failure and any further details of reason for screen failure.

4.1.2 Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to unblinding and closure of the database to ensure all important deviations are captured and categorized. Subjects with important protocol deviations liable to influence the efficacy outcomes will be excluded from the PP population. Subjects may also be identified as having important protocol deviations not leading to exclusion from the PP population.

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

- Consent procedures
- Inclusion/exclusion criteria
- Study procedures

The specific details of important protocol deviations will be listed in Protocol Deviation Management Plan (PDMP) and assessment process will be specified in the Blind Data Review Plan. Subjects with important protocol deviations will be identified at the BDRM.

The number and percentage of subjects with at least one important protocol deviation, with at least one important protocol deviation not leading to exclusion from PP population (with reasons for deviations) and with important protocol deviations leading to exclusion from the PP population (with reasons for deviations) will be presented in Table 14.1.2 by study product and listed in Listing 16.2.2.1.

Protocol deviations collected on the protocol deviation page of the electronic Case Report Form(eCRF) will be listed in Listing 16.2.2.2. The listing will present date of deviation, type of deviation and deviation description.

4.1.3 Analysis Populations

Three analysis populations are defined.

Population	Definition / Criteria	Analyses Evaluated
Safety	All randomized subjects who receive at least one dose of study product. Any subject who receives a randomization number will be considered to have been randomized. This population will be based on the product the subject received.	Safety
mITT	The mITT population will include all randomized subjects who receive at least one dose of study product and have at least one post baseline efficacy measurement. Any subject who receives a randomization number will be considered to have been randomized. This population will be based on the study product to which the subject was randomized.	Efficacy

Population	Definition / Criteria	Analyses Evaluated
PP	All randomized subjects who do not have any protocol deviations that could confound the interpretation of analyses conducted on the mITT.	Efficacy
NOTES: Please refer to Attachment 1: List of Data Displays which details the population to be used for each display being generated.		

Subjects excluded from any of the analysis populations will be listed in Listing 16.2.3.1.

The primary population for assessment of efficacy will be the mITT Population. A PP analysis will be performed on the primary and secondary efficacy variables if more than 10% of the subjects in the mITT Population are excluded from the PP Population. A decision on whether a PP analysis will be performed will be made prior to study unblinding (release of randomization codes).

4.2 Subject Demographics and Other Baseline Characteristics

4.2.1 Demographic Characteristics

Descriptive statistics (number of subjects (n), mean, standard deviation (SD), median, minimum and maximum for continuous variables, frequency count (n) and percentage (%) of subjects for categorical variables) will be presented for demographic variables and baseline characteristics by study product group and overall. These variables include age, gender, race, ethnicity and baseline Schiff stratification score and will be presented for the Safety population (Table 14.1.3.1) and mITT population (Table 14.1.3.2).

Demographic information will be listed (Listing 16.2.4.1) for all randomized subjects.

4.2.2 General Medical History

Medical history data will be listed (Listing 16.2.4.2) with start date and end date or ongoing at the start of study.

4.3 Treatments (Study Drug, Rescue Medication, Other Concomitant Therapies, Compliance)

Compliance data will be summarized for the mITT population. Exposure will be summarized for the Safety population. The study product kit allocations will be listed (Listing 16.1.6.1), including kit number and study product information. Randomization details will be listed (Listing 16.1.7.1), including the planned randomized study product, the actual study product received, and the randomization date.

Other concomitant therapies will be listed from all subjects from the signing of the Informed Consent Form (ICF).

4.3.1 Study Product Compliance and Exposure

Study product compliance (number of brushings/missed brushings/additional brushings) will be listed in Listing 16.2.5.4 for all randomized subjects. Compliance data will be summarized for the mITT population in Table 14.2.1. Total number of brushings, number of missed brushings and number of additional brushings will be summarized as separate categories in Table 14.2.1.

Supervised brushings (subject number, date and time of supervised brushing, reason why supervised brushing was not performed according to the protocol) will be listed (Listing 16.2.5.5) for all randomized subjects.

4.3.2 Prior and Concomitant Medication

Medication/treatments taken within 30 days of signing the ICF will be documented as a prior medication/treatment. Medications/treatments taken after signing the ICF will be documented as concomitant medication/treatments.

Prior medications, concomitant medications and significant non-drug therapies taken during the study, from signing the informed consent, will be recorded in the eCRF. Prior and concomitant medications will be coded using an internal validated medication dictionary, GSKDrug.

Prior medications will be listed by subject, with drug name, GSK drug synonym, dose, dose form, frequency, route, start date, study day relative to study product start date and end date (Listing 16.2.5.1). Concomitant medications will be listed similarly (Listing 16.2.5.2 for randomized subjects and Listing 16.2.5.3 for non-randomized subjects).

Unknown dates will not be imputed. If the stop date is unknown, or incomplete, and the medication cannot be considered as stopped prior to the date of signing the ICF then the medication will be considered as a concomitant medication (unless partial start or stop dates indicate differently).

4.4 Analysis of Efficacy

The primary population for assessment of efficacy will be the mITT Population

4.4.1 Primary Efficacy Endpoints

4.4.1.1 Primary Efficacy Endpoint Definition

The primary efficacy variables are Schiff sensitivity score and tactile threshold (g), both calculated as the average score of the two test teeth, and the number of sensitive teeth

(Schiff sensitivity score ≥ 1) at Day 0 (Baseline), Day 3, Day 7, Day 14, Day 28 and Day 56.

4.4.1.2 Statistical Hypothesis, Model and Method of Analysis

No formal efficacy analysis is planned for primary endpoint.

Summary statistics (mean, median, standard error (SE), SD, minimum, maximum) will be presented for each outcome variable at each assessment time point in Table 14.2.2.1.1, Table 14.2.2.2.1 and Table 14.2.2.3.1 for Schiff sensitivity score, tactile threshold (g) and the number of sensitive teeth respectively. Raw means (± SE) of the Schiff sensitivity score, tactile threshold (g) and number of sensitive teeth at each time point will be plotted by study product group in Figure 14.2.1, Figure 14.2.2 and Figure 14.2.3 respectively.

Schiff sensitivity score and tactile threshold (g) for the two test teeth will be listed for each subject by Visit in Listing 16.2.6.1 and Listing 16.2.6.2 respectively. All Schiff sensitivity scores and tactile threshold (g) values recorded throughout the study will be listed by subject in Listing 16.2.6.4 and Listing 16.2.6.5 respectively. The number of sensitive teeth will be listed by subject in Listing 16.2.6.3.

An InForm database outage occurred on 28 May 2019 that prevented the direct entry of source data from twelve (12) subjects into the InForm eCRF database. Subjects PPD qualifying oral data (Oral Soft Tissue (OST) Examination, Qualifying Tactile Sensitivity Assessment (Tactile Threshold) and Qualifying Evaporative Air Sensitivity Assessment (Schiff sensitivity score) were recorded manually on the back of the paper "Subject Source / Medical Record" document. The entries were not signed and dated. Due to this data integrity issue a sensitivity analysis will be performed to compare the results by excluding these subjects to make an inference about the study.

Baseline summary statistics will be repeated for all three primary endpoints (Table 14.2.2.1.1.1 for Schiff sensitivity score, Table 14.2.2.2.1.1 for tactile threshold (g) and Table 14.2.2.3.1.1 for the number of sensitive teeth) based on mITT population but excluding these 12 subjects and with only with these 12 subjects Supportive Analyses

If there is more than 10% difference in the overall number of subjects between the PP and mITT populations, a summary of the primary efficacy variables will be presented for the PP population in Table 14.2.2.1.2, Table 14.2.2.2.2 and Table 14.2.2.3.2 for Schiff sensitivity score, tactile threshold (g) and the number of sensitive teeth respectively.

4.4.2 Secondary Efficacy Variables

Secondary efficacy variables are defined in Section 4.5

4.4.3 Handling of Missing Values/Dropouts/Discontinuations

Subjects who withdraw from the study early will be included in the study analysis up to the point of withdrawal. Subjects who withdraw will not be replaced. No data will be imputed in the case of dropouts or missing data.

4.5 Analysis of Secondary Objectives

4.5.1 Efficacy (Secondary)

4.5.1.1 Secondary Efficacy Variable 1

4.5.1.1.1 Secondary Efficacy Endpoint 1 Definition

The first Secondary Efficacy Variable is change from Baseline in Schiff sensitivity score at Day 56. Change from Baseline will be derived for the individual teeth first before calculating the average change for the two test teeth.

4.5.1.1.2 Statistical Hypothesis, Model and Method of Analysis

Study product differences will be tested under the null hypothesis:

- H_0: there is no treatment difference versus the alternate hypothesis;
- H_1: there is a treatment difference

Change in Schiff sensitivity score will be analysed at Day 56 using an Analysis of Covariance (ANCOVA)model which will include study product as a factor and Baseline Schiff sensitivity score as a covariate. Note that since the Baseline Schiff sensitivity score will be included as a covariate, the Baseline Schiff stratification value will not be included in the model.

Using the above model, adjusted mean change from Baseline, along with 95% confidence intervals (CIs) will be reported by study product group. P-values testing for non-zero change from Baseline will be presented for both study product groups. Mean difference between study product groups, 95% CIs and p-values will be provided for Schiff sensitivity score in Table 14.2.2.4.1. Significance testing will be conducted at the two-sided 5% significance level; no adjustment for multiple comparisons will be made.

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated, and if violated, an appropriate data transformation or non-parametric method, for example, the van Elteren test, adjusting for the maximum baseline Schiff Sensitivity scores, will be performed.

4.5.1.1.3 Supportive Analyses

If there is more than 10% difference in the overall number of subjects between the PP and the mITT populations, a PP analysis will be performed for Secondary Efficacy Variable 1 and summarized in Table 14.2.2.4.2.

4.5.1.2 Secondary Efficacy Variable 2

4.5.1.2.1 Secondary Efficacy Endpoint 2 Definition

The second Secondary Efficacy Variable is change from Baseline in tactile threshold (g) at Day 56. Change from Baseline will be derived for the individual teeth first before calculating the average change for the two test teeth.

4.5.1.2.2 Statistical Hypothesis, Model and Method of Analysis

Study product differences will be tested under the null hypothesis:

- H_0: there is no treatment difference versus the alternate hypothesis;
- H_1: there is a treatment difference

Change in tactile threshold (g) will be analysed at Day 56 using an ANCOVA model with study product and Baseline Schiff stratification included as factors and Baseline tactile threshold included as a covariate.

Using the above model, adjusted mean change from Baseline, along with 95% CIs will be reported by study product group. P-values testing for non-zero change from Baseline will be presented for both study product groups. Mean difference between study product groups, 95% CIs and p-values will be provided for tactile threshold (g) in Table Table 14.2.2.5.1. Significance testing will be conducted at the two-sided 5% significance level; no adjustment for multiple comparisons will be made.

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated, and if violated, an appropriate data transformation or non-parametric method, for example, the van Elteren test, adjusting for the maximum baseline Schiff Sensitivity scores, will be performed.

4.5.1.2.3 Supportive Analyses

If there is more than 10% difference in the overall number of subjects between the PP and the mITT populations, a PP analysis will be performed for Secondary Efficacy Variable 2 and summarized in Table 14.2.2.5.2.

4.5.2 Pharmacokinetic

N/A.

4.6 Analysis of Safety

4.6.1 Adverse Events and Serious Adverse Events

Safety data will be reported for the Safety Population as per study product received. The safety and oral tolerability of the study products will be monitored over the 8-week treatment period by review of reported AEs and incidents. All AEs will be reviewed by the Clinical Research Scientist or Designee prior to database lock and unblinding and will be coded to a system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be classified as oral or non-oral on the AE page of the eCRF.

Treatment emergent adverse events (TEAEs) are defined as AEs that occur on or after the first study product application at the Baseline visit (if this date is missing a suitable alternative will be used e.g., date of randomization). AEs with an onset date/time prior to the first study product application will be considered as non-treatment emergent.

The following AE tables and listings will be produced, presented by study product group and overall:

- Table of TEAEs by SOC and PT (Table 14.3.1.1)
- Table of TEAEs by Oral/Non-Oral and PT (Table 14.3.1.2)
- Table of treatment-related TEAEs by Oral/Non-Oral and PT (Table 14.3.1.3)
- Table of treatment-emergent treatment-related SAEs by SOC and PT (Table 14.3.1.4) [only produced if there are more than 5 SAEs]
- Table of treatment-related non-serious TEAEs by SOC and PT (Table 14.3.1.5) [only produced if there are more than 5 SAEs]
- Listing of all AEs (Listing 16.2.7.1 randomized subjects; Listing 16.2.7.2 non-randomized subjects)
- Listing of deaths (Listing 14.3.2.1)
- Listing of non-fatal SAEs (Listing 14.3.2.2)
- Listing of TEAEs leading to study or treatment withdrawal (Listing 14.3.2.3)

In the event there is nothing to report, a null table or listing will be produced.

4.6.2 Other Safety Variables

OST and OHT Examination:

The results of the OST examinations will be summarized (number of subjects and percentages) by visit and study product group in Table 14.3.4.1 for Safety Population. The results of the OST and OHT examinations will be listed for all randomized subjects in Listing 16.2.9.1 and Listing 16.2.9.2 respectively.

Incidents:

Medical devices are being provided by GSK CH for use in this study; the medical device is the Oral B Sensi-soft toothbrush (Canadian market). A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of subject/user/other person or to a serious deterioration in his/her state of health. Incidents will be listed in Listing 16.2.7.3 (if there are no incidents, a null listing will be produced).

4.7 Analysis of Other Variables

4.7.1 Other Efficacy Variables 1

4.7.1.1 Other Efficacy Endpoints 1 Definitions

The first Other Efficacy Variables are change from Baseline in Schiff sensitivity score and tactile threshold (g) at Days 3, 7, 14 and 28.

4.7.1.2 Statistical Hypothesis, Model and Method of Analysis

Study product differences will be tested under the null hypothesis:

- H_0: there is no treatment difference versus the alternate hypothesis;
- H_1: there is a treatment difference

Change from Baseline in Schiff sensitivity score and tactile threshold (g) at Days 3, 7, 14 and 28 will be analyzed as per the secondary analyses: adjusted mean change from Baseline, along with 95% CIs will be reported by study product group (Table 14.2.2.4.1 and Table 14.2.2.5.1 respectively). Study product differences and 95% CIs will also be presented. No p-values will be reported.

4.7.1.3 Supportive Analyses

N/A

4.7.2 Other Efficacy Variables 2

4.7.2.1 Other Efficacy Endpoints 2 Definitions

The second Other Efficacy Variables are Change from Baseline in DHEQ (Short Form) endpoints at Days 28 and 56.

- Responses to Questions 7, 8 and 9, DHEQ Section 1 (as separate questions);
- Total Score for Questions 1 to 15, DHEQ Section 2;
- **Restrictions** Domain (total score for Questions 1 to 3, DHEQ Section 2);

- **Adaptation** Domain (total score for Questions 4 to 6, DHEQ Section 2);
- **Social Impact** Domain (total score for Questions 7 to 9, DHEQ Section 2);
- **Emotional Impact** Domain (total score for Questions 10 to 12, DHEQ Section 2);
- **Identity** Domain (total score for Questions 13 to 15, DHEQ Section 2);
- Change from Baseline at Day 28 and Day 56 for each DHEQ endpoint.

4.7.2.2 Statistical Hypothesis, Model and Method of Analysis

No formal efficacy analysis is planned for these endpoints.

Summary statistics (mean, median, SE, SD, minimum, maximum) will be presented for each DHEQ endpoint by study product group (Table 14.2.3.1 and Table 14.2.3.2 for DHEQ section I and DHEQ section 2 respectively) and listed in Listing 16.2.6.6 and Listing 16.2.6.7, respectively, for all randomized subjects.

4.7.2.3 Supportive Analyses

N/A

5 Changes to the Protocol Defined Statistical Analysis Plan

There are no changes from the originally planned statistical analysis specified in the protocol.

Attachment 1: List of Data Displays

GSKCH_209723_TFL List_Amendment Final

Syneos Health	**Sponsor Approval Form: Final Statistical Analysis Plan Amendment 1 Text and Shells**

Project Identifiers	
Sponsor:	Protocol No.: 209723
Project ID Code: PPD	Protocol Version (date) (DD-Mmm-YYYY): 2.0 (16-Oct-2018)
Statistical Analysis Plan Amendment 1 (SAP) Text Version\Date (DD-Mmm-YYYY): 1.0 (27-Sep-2019)	
SAP Amendment 1 Shells Version\Date (DD-Mmm-YYYY): 1.0 (27-Sep-2019)	
SAP Author: PPD	

Item(s) finalized: ☒ SAP Text ☒ Table, Listing and Figure Shells

The signatures below acknowledge that the Statistical Analysis Plan Amendment 1 Text and Shells prepared by Syneos Health for GSK CH are final.

APPROVALS

Syneos Health Approval

PPD, Senior Statistician I	PPD	PPD
Name, Title	Signature	Date (DD-Mmm-YYYY)
Lead Biostatistician		

GSK CH Approval

PPD Statistician	PPD	PPD
Name, Title		Date (DD-Mmm-YYYY)
Sponsor Contact		