Stannous fluoride (SnF_2)
216954

STATISTICAL REPORTING AND ANALYSIS PLAN

An 8 Week, Randomized, Examiner-blind, Controlled Clinical Study to Evaluate the Efficacy of a Stannous Fluoride Dentifrice in the Relief of Dentinal Hypersensitivity in a Chinese Population

Protocol Number: 216954

Phase: Not applicable

This document contains confidentiality statements that are not relevant for this publicly available version

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	04-Jun-2021	Not applicable (N/A)

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Abbreviation

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
BDRM	Blinded Data Review Meeting
CH	Consumer Healthcare
CI	Confidence Interval
COVID-19	Coronavirus Disease of 2019
CRF	Case Report Form
CSR	Clinical Study Report
DH	Dentinal Hypersensitivity
DHEQ	Dentine Hypersensitivity Experience Questionnaire
EAR	Erosion, Abrasion or Recession
eCRF	Electronic Case Report Form
GSK	GlaxoSmithKline
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Modified Gingival Index
mITT	Modified Intent-To-Treat
MoH	Ministry of Health
N/A	Not Applicable
OHT	Oral Hard Tissue
OHRQoL	Oral Health Related Quality of Life
OST	Oral Soft Tissue
PP	Per Protocol
PT	Preferred Term
QOL	Quality of Life
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation

Abbreviation	Term
SE	Standard Error
SnF_2	Stannous Fluoride
SOC	System Organ Class
TEAEs	Treatment Emergent Adverse Events

The purpose of this Statistical Reporting and Analysis Plan (RAP) is to describe the planned analyses and outputs to be included in the synopsis Clinical Study Report (CSR) for Protocol 216954 version 1.0, dated 19-Jan-2021.

1 Summary of Key Protocol Information

The Chinese Ministry of Health (MoH) guidelines stipulate that two clinical studies are required to support the efficacy of a functional toothpaste, with at least one of these studies (for each claimed benefit) to be conducted on a local Chinese population.

To support dentinal hypersensitivity (DH) efficacy claims GlaxoSmithKline Consumer Healthcare (GSK CH) holds an extensive global clinical data package for 0.454% SnF_2 dentifrices. To support long-term dentine hypersensitivity claims in China, two further DH clinical studies have been conducted.

The first DH study (GSK CH Clinical Study CCI 2017) met the primary objective (Schiff sensitivity score, at both 4 and 8 weeks), but did not meet the secondary objective (tactile threshold). A further clinical study was conducted (Tao, 2020), which demonstrated significantly reduced dentine hypersensitivity from baseline for the SnF_2 dentifrice, however, there was no between treatment differences when compared to a negative and positive control.

To support long-term DH relief claims of 0.454% stannous fluoride (SnF_2) containing toothpastes in China, a clinical study is required to be conducted in a local Chinese population.

1.1 Study Design

This will be a single center, randomized, controlled, examiner-blind, 3 treatment arm, parallel group design study, stratified by maximum baseline Schiff sensitivity score (of the 2 selected 'test teeth'), with a treatment period of 8 weeks, to investigate the clinical efficacy of a SnF_2 dentifrice in the reduction of DH in a Chinese population. The SnF_2 test dentifrice will be compared to commercialized negative and positive control dentifrices.

In line with published recommendations and the requirement of Chinese MoH guidelines for the testing of functional dentifrices (desensitizing), two independent stimulus-based efficacy measures will be employed (tactile and evaporative air sensitivity) to evaluate the DH efficacy of the test dentifrice. A tactile stimulus will be administered using a constant pressure probe (yeaple Probe). An evaporative (air) stimulus will be administered using a dental air syringe. Response to this stimulus will be evaluated using the Schiff sensitivity scale. DH assessments will be conducted at Baseline, 4, and 8 weeks.

Subjects will also be requested to complete a short-form version of the Dentine Hypersensitivity Experience Questionnaire (DHEQ-15) at the Baseline and Week 8 Visits.

A sufficient number of subjects will be screened to randomize approximately 195 subjects to ensure approximately 180 subjects (approximately 60 per treatment group) complete the study.

The schedule of activities table (Table 1-1) provides an overview of the subject visits and study procedures. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1-1 Schedule of Activities

Procedure/ Assessment	Screening		Study Period		
	Visit 1		Baseline Visit 2 Day 1 (Up to 28 days after Visit 1)	Visit 3 Day 29±3	Visit 4 Day 57±3
Informed consent	X	ACCLIMATISATION PERIOD 14 TO 28 DAYS			
Review of Subjects Oral Care Products to Confirm They Don't Contain any Anti-sensitivity Ingredients	X				
Review of Subjects Brushing Habits	X				
Demographics, Ethnicity	X				
Medical History and Prior Medication/Treatment	X				
Concomitant Medications			X	X	X
Full OST Examination	X		X	X	X
Full OHT Examination	X				X
Eligible Teeth Assessments (Dentition Exclusions, EAR, MGI, Tooth Mobility)	X				
Qualifying Tactile Assessment (Yeaple Probe)[1]	X				
Qualifying Evaporative Air Sensitivity (Schiff Sensitivity Score)[1]	X				
Identify Test Teeth	X				
Inclusion/Exclusion Criteria	X				
Subject Eligibility	X				
Dispense Acclimatization Dentifrice, Toothbrush, Rinsing Cups, Diary, and Timer[2]	X				
Supervised Brushing with Acclimatization Dentifrice[3]	X				

Procedure/ Assessment	Screening		Study Period		
	Visit 1		Baseline Visit 2 Day 1 (Up to 28 days after Visit 1)	Visit 3 Day 29±3	Visit 4 Day 57±3
Subject Adherence and Continuance		ACCLIMATISATION PERIOD 14 TO 28 DAYS	X	X	X
Subject completion of DHEQ-15			X		X
Tactile Assessment (Yeaple Probe)[4]			X	X	X
Evaporative Air Assessment (Schiff Sensitivity Score)[5]			X	X	X
Confirm Test Teeth[6]			X		
Stratification and Randomisation			X		
Dispense Randomised Dentifrice, Toothbrush, Rinsing Cups and Diary			X		
Supervised Brushing with Allocated Dentifrice and Reminder of Product Usage Instructions[7]			X	X	
Subjects Bring Study Supplies and Diary to Site			X	X	X
Weight Check of Returned Study Dentifrice and Subject Brushing Video's, and Compliance Discussion[7]			X	X	X
Adverse Events[8]	X		X	X	X
Study Conclusion					X

Abbreviations: OST = Oral Soft Tissue; OHT = Oral Hard Tissue; EAR = Erosion, Abrasion, Recession; MGI = Modified Gingival Index; SnF_2 = stannous fluoride; DHEQ = Dentine Hypersensitivity Experience Questionnaire.

Footnotes:

[1] Qualifying Schiff sensitivity and tactile threshold scores will be recorded in the case report form (CRF). Evaporative air assessment to follow tactile assessment; minimum 5 minutes time lapse between the two assessment types for tooth recovery. At Screening, maximum force for tactile = 20g.

[2] Subject is instructed to bring all supplies back to next visit.

[3] Study supplies to be returned to subject (for use at home) after supervised brushing.

[4] At Baseline, maximum force = 20g, at all subsequent visits maximum force = 80g.

[5] Evaporative air assessment to follow tactile assessment; minimum 5 minutes time lapse between the two assessment types for tooth recovery.

[6] Subject's with 'test teeth' that don't respond to tactile and/or Schiff at Baseline, will be required to have all eligible teeth identified at Screening re-assessed to identify 'test teeth'. A minimum of 5 minutes time lapse will be required between assessments.

[7] Subject is instructed to bring all supplies back to subsequent visits for compliance checks. Study supplies to be returned to subject after supervised brushing. Subject is re-dispensed a new toothbrush at Visit 3.

[8] Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides consent to participate in the study by the completion of the informed consent form (ICF).

1.2 Study Objectives

Study objectives and endpoints are defined in Table 1-2:

Table 1-2 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To compare the clinical efficacy of a 0.454% w/w SnF_2 dentifrice for the relief of DH, as elicited by an evaporative air stimulus (with Schiff sensitivity score), against a negative control dentifrice, when used twice daily for 8 weeks.	Change from Baseline in Schiff sensitivity score at 8 weeks.
Secondary	
To compare the clinical efficacy of a 0.454% w/w SnF_2 dentifrice for the relief of DH, as elicited by a tactile stimulus (yeaple probe), against a negative control dentifrice, when used twice daily for 8 weeks.	Change from Baseline in tactile threshold at 4 and 8 weeks.
To compare the clinical efficacy of a 0.454% w/w SnF_2 dentifrice for the relief of DH, as elicited by an evaporative air stimulus (with Schiff sensitivity score), against a negative control dentifrice, when used twice daily for 4 weeks.	Change from Baseline in Schiff sensitivity score at 4 weeks.
To compare the clinical efficacy of a positive control dentifrice for the relief of DH, as elicited by an evaporative air stimulus (with Schiff sensitivity score) and a tactile stimulus (yeaple probe), against a	Change from Baseline in Schiff sensitivity score and tactile threshold at 4 and 8 weeks.

negative control dentifrice, when used twice daily for 8 weeks.	
Safety	
To evaluate the safety and oral tolerability of the test dentifrices when used twice daily for 8 weeks.	Adverse Events
Exploratory	
To characterize Oral Health Related Quality of Life (OHRQoL) as measured by the short-form of the Dentine Hypersensitivity Experience Questionnaire (DHEQ-15) after 8 weeks treatment with a 0.454% w/w SnF_2 dentifrice compared to a negative control dentifrice.	At 8 weeks, 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 and Identity Domains
To characterize OHRQoL as measured by the short-form of the DHEQ-15 after 8 weeks treatment with a positive control dentifrice compared to a negative control dentifrice.	At 8 weeks, 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 and Identity Domains

This study will be considered successful if there is a statistically significant difference in the primary efficacy variable, change from baseline in Schiff sensitivity score and a between treatment difference in favor of the SnF_2 dentifrice compared to the negative control, after 8 weeks of treatment. The size of the effect is important to meet Chinese MoH guidelines, a 15% difference between the SnF_2 dentifrice and the negative control must be observed.

1.3 Treatments

The following study products (Table 1-3) will be supplied by the Clinical Supplies Department, GSK CH or designated vendor:

Table 1-3 Investigational Product Supplies

Investigational Product	Test Product	Reference Product (Negative Control)	Reference Product (Positive Control)
Product Name	Sensodyne Sensitivity & Gum (Chrysanthemum); Chinese commercialized toothpaste containing 0.454% SnF_2	Crest Cavity Protection Fresh Lime (1150ppm fluoride as NaF); Chinese commercialized daily fluoride dentifrice	Sensodyne Repair and Protect; Chinese commercialized dentifrice containing 5.0% w/w calcium sodium phosphosilicate
Pack Design	Carton of 4 over-wrapped tubes	Carton of 4 over-wrapped tubes	Carton of 4 over-wrapped tubes
Dispensing Details	One carton – baseline visit	One carton – baseline visit	One carton – baseline visit
Product Master Formulation Code (MFC)	Commercial Product CCI [redacted]	Commercial Product	Commercial Product CCI [redacted]
Usage Instructions	Apply a full ribbon of toothpaste on the head of the toothbrush provided. Brush teeth for 1*-timed minute, followed by brushing of the qualifying sensitive teeth. Following brushing rinse once with 10 ml of water from the rinsing cup provided.	Apply a full ribbon of toothpaste on the head of the toothbrush provided; brush teeth for 1*-timed minute. Following brushing rinse once with 10 ml of water from the rinsing cup provided.	Apply a full ribbon of toothpaste on the head of the toothbrush provided; brush teeth for 1*-timed minute. Following brushing rinse once with 10 ml of water from the rinsing cup provided.
Route of Administration	Oral topical	Oral topical	Oral topical
Return Requirements	All used/unused samples to be returned	All used/unused samples to be returned	All used/unused samples to be returned

*Following toothbrushing and/or rinsing subjects may also conduct a discretionary tongue clean using the provided toothbrush, but this is not a study requirement.

An acclimatization product will also be supplied by the Clinical Supplies Department, GSK CH or designated vendor between Screening and Baseline visits.

1.4 Sample Size Calculation

A sufficient number of subjects will be screened to randomize approximately 195 subjects to ensure approximately 180 subjects (approximately 60 per group) complete the study, allowing for dropouts.

Change from baseline in Schiff sensitivity score will be used evaluate treatment effects and is the primary outcome variable. With 60 evaluable subjects per group, the study has 90% power to detect a mean difference of 0.3 (standard deviation [SD] =0.501) in change from baseline in Schiff sensitivity score after 8 weeks of treatment. The difference of 0.3 represents roughly a 15% difference between treatment groups. The estimate of SD was obtained from GSK CH studies [redacted]. The sample size is based on carrying out a 2-tailed 2 sample t-test at a 5% significance level.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned for this study.

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 latest (non-missing) value obtained prior to any study product administration.

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 their maximum baseline Schiff sensitivity score of the two selected teeth (sensitivity score of 2 or 3). The stratification factor will give rise to two strata.

- **Stratum 1:** Maximum Schiff = 2. These are subjects with the maximum baseline Schiff sensitivity score of 2 for the 2 selected 'test teeth'.
- **Stratum 2:** Maximum Schiff = 3. These are subjects with the maximum baseline Schiff sensitivity score of 3 for the 2 selected 'test teeth'.

3.3 Centers Pools

Since this is a single center study, pooling of centers is not applicable.

3.4 Timepoints and Visit Windows

The timepoints and visits for this study are defined in the Section 1-1 "Schedule of Activities" of the protocol and in Table 1-1 of this document. Any deviation from the study schedule may be reviewed on case-by-case basis at the Blinded Data Review Meeting (BDRM) to determine whether the data should be excluded from the analysis populations. A time window non-compliance listing will be produced for the BDRM.

All data included will be by nominal visits and visit windows will not be considered.

4 Data Analysis

Data analysis will be performed by Syneos Health with oversight from GSK CH. The statistical analysis software that will be used will be SAS (Studio) version 9.4 or higher.

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

One aspect that will be considered during BDRM is the assessment of the number of subjects who have dropped or discontinued from the study due to pandemic related events (e.g. Coronavirus Disease of 2019 [COVID-19]) and the potential need of a sensitivity analysis. Any major changes to planned analyses will need an amendment to RAP.

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

4.1 Populations for Analysis

4.1.1 Subject Disposition

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, subjects not randomized, and subjects enrolled will be presented for all screened subjects in Table 14.1.1.

Table 14.1.1 will also display the number and percentage of screen failure subjects (subjects not randomized) with reasons why subjects are not randomized. Percentages for screen failure subjects will be based on the total number of subjects screened.

The number and percentage of subjects randomized, who complete the study and who discontinue the study broken down by reason for discontinuation, by study product and overall will also be displayed. The percentages will be based on the total number of subjects randomized.

Table 14.1.1 will also present the number and percentage of subjects in each of the defined analysis populations by study product and overall. Percentages will be based on the number of subjects randomized.

Subject disposition including demographic data (age, sex and race), screening date, study product start date and time, study product end date and time, duration of study product in days (defined as [(last date of study product administration - start date of study product) + 1] for all subjects completing the study as per protocol, and [(date of withdrawal - start date of study product) + 1] for all subjects dropping out of the study), subject status (completer, Yes/No), study completion/withdrawal date, duration in the study in days (defined as [(date of completion or withdrawal - start date of study product) + 1], and the primary reason for withdrawal will be listed (Listing 16.2.1.1) by study product for all randomized subjects.

Subject disposition information will be listed for non-randomized subjects (Listing 16.2.1.2), displaying subject number, demographic information (age, sex and race), 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 per protocol (PP) population. Subjects may also be identified as having important protocol deviations not leading to exclusion from the PP population.

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

- Consent procedures
- Inclusion/Exclusion criteria
- Non-compliance with product administration
- Study procedures
- Inadmissible concomitant medication

The specific details of important protocol deviations will be listed in Protocol Deviation Management Plan 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 overall for all randomized subjects and listed in Listing 16.2.2.1 for all randomized subjects.

All protocol deviations collected on the protocol deviation electronic Case Report Form (eCRF) will be listed in Listing 16.2.2.2 by study product for all randomized subjects. The listing will present date of deviation, type of deviation, and deviation description.

4.1.3 Analysis Populations

The analysis populations defined for this study are presented in Table 4-1.

Table 4-1 Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Safety	Comprise all randomized subjects who receive at least one dose of the study product. Any subject who receives a randomization number will be considered to have been randomized. This population will be based on the study product the subject actually received.	Safety Analysis
Modified Intent-To-Treat (mITT)	Comprise all randomized subjects who receive at least one dose of the study product and provide at least one post-baseline assessment of efficacy (Schiff sensitivity assessment or Tactile sensitivity assessment). 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.	Demographic and Baseline Characteristics, Efficacy Analysis
PP	Comprise all subjects included in the mITT population who have at least one assessment of efficacy (Schiff sensitivity assessment or Tactile sensitivity assessment) considered unaffected by protocol violations.	Efficacy Analysis

NOTE:
Please refer to Attachment 1: List of Data Displays which details the population to be used for each displays being generated.

The primary population for assessment of efficacy will be the mITT population. A PP analysis will be performed on the primary and secondary variables (Schiff score and Tactile threshold)

if there is more than 10% difference in the number of subjects between the PP and mITT population. A decision will be made to perform PP analysis after the BDRM but prior to study unblinding (release of the randomization codes).

The numbers of subjects included in each of the analysis populations will be presented in Table 14.1.1 by study product and overall. Subjects excluded from any of the analysis populations will be listed in Listing 16.2.3.1 by study product.

4.2 Subject Demographics and Other Baseline Characteristics

4.2.1 Demographic Characteristics

Descriptive statistics (number of subjects [n], mean, SD, median, minimum and maximum for continuous variables and frequency count [n] and percentage [%] of subjects for categorical variables) will be presented for demographic variables and baseline characteristics by study product and overall. These variables include age, gender, race, ethnicity and baseline Schiff stratification score, and will be presented for Safety and mITT populations (Table 14.1.3.1 and Table 14.1.3.2, respectively) and PP population (Table 14.1.3.3) if criteria for PP analysis is met.

Demographic and baseline characteristics information will be listed (Listing 16.2.4.1) for all randomized subjects by study product.

4.2.2 General Medical History

Since results will be reported in a synopsis CSR, collected data for Medical history will not be tabulated or listed.

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

Randomization details will be listed, including the randomization number, stratification group, planned study product, actual study product and the randomization date (Listing 16.1.7.1).

The study product kit allocations will be listed (Listing 16.1.7.2), including kit number and study product information.

4.3.1 Study Product Compliance and Exposure

Study product compliance data will be summarized for the mITT population and will be assessed by:

- Number of brushings
- Study dentifrice weight

Number of brushings, brushing compliance (%), number of missed brushings, number of additional brushings and amount of product used (g) will be summarized using descriptive statistics as separate categories by study product in Table 14.2.1.1 by visit and overall.

Number of brushings is defined as: [(date of $Visit_n$ – date of $Visit_{n-1}$ + 1) multiplied by 2 – number of missing brushings + number of additional brushings] by visits, and [(date of Visit 4 – date of Visit 2 + 1) multiplied by 2 – number of missing brushings + number of additional brushings] by overall.

Brushing compliance (%) is defined as: [100 x (Number of brushings / Expected number of brushings)], where expected number of brushings is defined as: [(date of $Visit_n$ - date of $Visit_{n-1}$ + 1) multiplied by 2] by visits, and [(date of Visit 4 – date of Visit 2 + 1) multiplied by 2] by overall.

Study product compliance (number of brushings / brushing compliance [%] / number of missed brushings / number of additional brushings / amount of product used [g]) will be listed in Listing 16.2.5.1 for all randomized subjects by study product.

Supervised study product brushings will also be summarized for the mITT population in Table 14.2.1.2 by visit. In addition, details (including subject number, date and start time of supervised brushing) for supervised study product brushings will be listed (Listing 16.2.5.2) for all randomized subjects by study product.

4.3.2 Prior and Concomitant Medication

Any medications, treatments or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken during the study, from signing the informed consent, must be recorded in the CRF with indication, reason for use, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about medications/treatments at each site visit.

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.

Since results will be reported in a synopsis CSR, collected data for Prior and Concomitant Medications will not be tabulated or listed.

4.4 Analysis of Efficacy

The mITT population will be considered as primary population for primary analyses.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary efficacy variable is the change from baseline in Schiff sensitivity score at 8 weeks, derived as the average score of the 2 test teeth. The change from baseline is derived from the individual teeth first before calculating the average change of the 2 test teeth.

Descriptive statistics (n, missing, mean, SD, standard error [SE], median, minimum, and maximum) will be presented for Schiff sensitivity score calculated as the average score of the 2 test teeth at each assessment time point together with the change from baseline in Table 14.2.2.1.1 for all subjects in mITT population by study product. Raw means (± SE) of the Schiff sensitivity score at each time point will be plotted by study product in Figure 14.2.1 for all subjects in mITT population.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The primary comparison is between the test product and the negative control. As there is only a single primary objective no adjustment for multiple comparisons is required.

Study product differences will be tested under the null hypothesis:

- H_0: there is no difference between test product and negative control;
- H_1: there is a difference

Change from baseline in Schiff sensitivity score at 8 weeks will be analyzed using analysis of covariance (ANCOVA) with 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. P-values testing for non-zero change from baseline will be presented for both study products. Mean difference between study products, 95% CIs and p-values will be provided for Schiff sensitivity score in Table 14.2.2.1.2. 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. In case of violation of these assumptions a suitable transformation or a non-parametric method (e.g. the van Elteren test), adjusting for the maximum baseline Schiff Sensitivity scores will be performed and results will be compared with the ANCOVA results.

4.4.1.3 Supportive Analyses

If there is more than 10% difference in the overall number of subjects between PP and mITT populations, a summary and analysis of the primary efficacy variable will be presented for the PP population in Table 14.2.2.2.1 and Table 14.2.2.2.2, respectively.

4.4.2 Secondary Efficacy Variables

See Section 4.5.

4.4.3 Handling of Missing Values/Censoring/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

The mITT population will be considered as primary population for secondary analyses.

4.5.1 Efficacy (Secondary)

The secondary efficacy variables with corresponding comparisons are as follows:

- Change from baseline in Tactile threshold at 4 and 8 weeks; "test product versus negative control" and "positive control versus negative control".
- Change from baseline in Schiff sensitivity score at 4 weeks; "test product versus negative control" and "positive control versus negative control".
- Change from baseline in Schiff sensitivity score 8 weeks; "positive control versus negative control".

Tactile score including the change is derived in the same manner as for the Schiff score, i.e., derived as the average score of the 2 test teeth. The change from baseline is derived from the individual teeth first before calculating the average change of the 2 test teeth. The tooth recorded as >20 g (for screening and baseline) or >80 g (for post baseline) will be rounded up to the next increment of 10g for the calculation of average tactile threshold (g).

Schiff sensitivity score calculated as the average score of the 2 test teeth for secondary efficacy variables will be summarized in Table 14.2.2.1.1. Descriptive statistics (n, missing, mean, SD, SE, median, minimum, and maximum) will be presented for Tactile threshold (g) calculated as the average score of the 2 test teeth at each assessment time point together with the change from baseline in Table 14.2.3.1.1 for all subjects in mITT population by study product. Raw means (± SE) of the Tactile threshold (g) at each time point will be plotted by study product in Figure 14.2.2 for all subjects in mITT population.

Change from baseline in Schiff sensitivity score for secondary efficacy variables will be analyzed as per the primary variable (Table 14.2.2.1.2). Change from baseline in Tactile threshold (g) for secondary efficacy variables will be analyzed using ANCOVA with study product and baseline Schiff stratification as factors and baseline Tactile threshold as a covariate (Table 14.2.3.1.2).

The assumption of normality and homogeneity of variance in ANCOVA model will be assessed as described for the primary efficacy analysis.

If there is more than 10% difference in the overall number of subjects between PP and mITT populations, a summary and analysis of the secondary efficacy variable (Tactile threshold) will be presented for the PP population in Table 14.2.3.2.1 and Table 14.2.3.2.2, respectively.

4.5.2 Pharmacokinetic (Secondary)

N/A

4.6 Analysis of Safety

All safety data will be reported for the Safety Population as per actual study product received. The safety profile of the study products will be assessed with respect to AEs, OST findings, OHT findings and exposure.

4.6.1 Adverse Events and Serious Adverse Events

All AEs will be reviewed by the Clinical Research Scientist or Designee prior to database lock 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 and non-oral on the AE page of eCRF.

Treatment emergent adverse events (TEAEs) are defined as new AEs that occur on or after the start date of first study product usage (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 usage will be considered as non-treatment emergent.

The following summary tables and listings will be presented by study product 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 SOC and PT (Table 14.3.1.3).
- Table of treatment-related TEAEs by Oral/Non-Oral and PT (Table 14.3.1.4).
- Table of AEs related to COVID-19 by SOC and PT (Table 14.3.1.5).
- Listing of all AEs (Listing 16.2.7.1 for all randomized subjects; Listing 16.2.7.2 for non-randomized subjects).
- Listing of all AEs related to COVID-19 Subjects (Listing 16.2.7.3 for all screened 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 product discontinuation (Listing 14.3.2.3).
- Listing of TEAEs classified as Oral (Listing 14.3.2.4) [only produced if there are Oral TEAEs].

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

In case of more than 5 SAEs reported during the conduct of the study, additional outputs will be prepared to support safety analysis.

4.6.2 Other Safety Variables

Other safety variables are listed below:

- COVID-19 infection diagnosis and assessment
- COVID-19 infection diagnosis and assessment – symptoms for symptomatic subjects
- OST examination
- OHT examination
- Exposure

COVID-19 diagnosis and assessment and the symptoms for symptomatic subjects data will be listed (Listing 16.2.8.1 and Listing 16.2.8.2, respectively) for all screened subjects.

An OST examination will be conducted for each subject at every visit prior to any clinical assessments. The examination will be accomplished by direct observation and palpation with retraction aids as appropriate. The examiner will include examination of the labial mucosa (including lips), buccal mucosa, and mucogingival folds, gingival mucosa, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands. The results of the examination will be recorded in the CRF as either normal or abnormal with details of any abnormalities. Any observation that changes from "Normal" to "Abnormal" from the screening assessment must be recorded as an AE.

OST will be summarized (number of subjects and percentages with abnormalities, without abnormalities or OST not examined) by visit and study product in Table 14.3.4.1 for all subjects in Safety Population. OST examination will be listed (Listing 16.2.8.3) for all randomized subjects.

The OHT examination will assess for enamel irregularities, tooth fracture, grossly carious lesions/gross decay, defective/faulty restorations (all direct & indirect restorations including fixed/removal prostheses), non-carious tooth surface loss (abrasion, attrition, abfraction and erosion), any other hard tissue irregularity (e.g. hypo/hypermineralisation, decalcification) and tooth staining. Observations will be listed as "Absent" or "Present" and conditions noted as present will be described. Examination findings will be described and documented in the CRF. Any observation that changes from "Absent" to "Present" from the screening assessment must be recorded as an AE.

Present abnormalities of OHT examination will be listed (Listing 16.2.8.4) for all randomized subjects.

Exposure to study product is covered under study product compliance and the number of brushings in Section 4.3.1.

4.7 Analysis of Other Variables

The exploratory efficacy variables are change from baseline in quality of life (QOL) (Total and each domain scores) at 8 weeks "test product versus negative control" and "positive control versus negative control".

The following QOL scores derived from the DHEQ questionnaire will be investigated:

- Responses to Questions 7, 8 and 9 as separate questions (Section 1)
- Total (Section 2, Q1-15)
- Restrictions (Section 2, Q1-3)
- Adaptation (Section 2, Q4-6)
- Social Impact (Section 2, Q7-9)
- Emotional Impact (Section 2, Q10-12)
- Identity (Section 2, Q13-15)

4.7.1 Quality of Life

Descriptive statistics (n, missing, mean, SD, SE, median, minimum, and maximum for continuous variables and frequency count [n] and percentage [%] of subjects for categorical variables) will be presented for each DHEQ endpoint, including the individual questions from Section 1 Q1-9, at each assessment time point and, in the event of continuous variables, together with the change from baseline, for all subjects in mITT population by study product (Table 14.2.4.1.1 and Table 14.2.4.1.2 for DHEQ section 1 and Table 14.2.5.1 for DHEQ section 2) and listed in Listing 16.2.6.1 and Listing 16.2.6.2, respectively, for all randomized subjects.

Change from baseline in QOL variables (Section 1 (Q7-Q9) and Section 2 domain scores) at 8 weeks will be analyzed using ANCOVA with study product and baseline Schiff stratification as factors and baseline score of relevant variable as a covariate (Table 14.2.4.2 and Table 14.2.5.2 for DHEQ section 1 and DHEQ section 2 respectively).

The assumption of normality and homogeneity of variance in ANCOVA model will be assessed as described for the primary efficacy analysis.

5 Changes to the Protocol Defined Statistical Analysis Plan

Any changes from the originally planned statistical analysis specified in the protocol are outlined in Table 5-1.

Table 5-1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
9.3.2 Oral Soft Tissue (OST) Examination The results of the examination will be recorded in the CRF as either normal or abnormal with details of any abnormalities. Any observation that changes from "Absent" to "Present" from the screening assessment must be recorded as an AE.	4.6.2 Other Safety Variables The results of the examination will be recorded in the CRF as either normal or abnormal with details of any abnormalities. Any observation that changes from "Normal" to "Abnormal" from the screening assessment must be recorded as an AE.	"Absent" and "Present" have been changed to "Normal" and "Abnormal", respectively, to be consistent with eCRF.
12.2.2 Exclusion of Data from Analysis A PP analysis will be performed only on the primary variable (Schiff score) if there is more than 10% difference in the number of subjects between the PP and m-ITT populations.	4.1.3 Analysis Populations A PP analysis will be performed on the primary and secondary variables (Schiff score and Tactile threshold) if there is more than 10% difference in the number of subjects between the PP and mITT population.	Since both endpoints are require by the regulators in China, a PP analysis will be performed on secondary variable as well.
12.3.2 Secondary Analyses Change from baseline in Tactile variables will be analyzed using ANCOVA with treatment as a factor and baseline Schiff sensitivity score as a covariate.	4.5.1 Efficacy (Secondary) Change from baseline in Tactile threshold (g) for secondary efficacy variables will be analyzed using ANCOVA with study product and baseline Schiff stratification as factors and baseline Tactile threshold as a covariate.	ANCOVA model was updated in order to keep consistent across other GSK CH studies.
12.3.6 Demographic and Baseline Characteristics Demographic and baseline characteristics will be summarized by treatment group and study site for the Safety and mITT populations and the PP population if a PP analysis is performed.	4.2.1 Demographic Characteristics Descriptive statistics (number of subjects [n], mean, SD, median, minimum and maximum for continuous variables and frequency count [n] and percentage [%] of subjects for categorical variables) will be presented for demographic variables	Demographic variables and baseline characteristics will not be presented by study site because this is a single center study.

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
	and baseline characteristics by study product and overall.	
12.3.7.2 Prior and Concomitant Medications Prior medications, concomitant medications and significant non-drug therapies taken during the study will be listed for the Safety population.	4.3.2 Prior and Concomitant Medication Since results will be reported in a synopsis CSR, collected data for Prior and Concomitant Medications will not be tabulated or listed.	Since the results will be reported in a synopsis CSR, it was decided that no tables or data listings will be produced for prior and concomitant medications.
N/A	4.6 Analysis of Safety Safety analysis for COVID subjects added	This is not part of the protocol and covered under RAP.
N/A	4.6 Analysis of Safety Safety analysis for OHT examination added	Listing for OHT examination was added as required for synopsis CSR.

Attachment 1: List of Data Displays