STATISTICAL REPORTING AND ANALYSIS PLAN

A Randomized Controlled Examiner-Blind Phase II Proof-Of-Principle Clinical Study Investigating The Efficacy of an Experimental Dentifrice Containing Sodium Bicarbonate, High Molecular Weight Sodium Hyaluronate and Sodium Fluoride on Gingivitis and Plaque Removal in a Population with Mild-Moderate Plaque-Induced Gingivitis

Protocol Number: 208175

Phase: IIa

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	07-Dec-2020	Not applicable (N/A)
RAP Amendment 1, Final V1.0	10-Jun-2021	• Correction of typographical error, NBS (Number of Bleeding Sites) instead of BI (Bleeding Index), in Section 4 of RAP text. • Change in Schedule of visit as per Protocol Amendment 3 Version 4 07Feb2021. • Change in description of Listing 16.2.6.1 on account of an additional column in mock shell for total number of NBS per subject, per visit. • Correction in Section 4.4.3.3: NBS strata added as factor in ANCOVA model for statistical analysis of Mean MGI in compliance with Protocol. • Section 5 - Change in planned analysis as described in protocol for Sub-Group analysis (Section 4.4.3.5). Interaction effect between Low and High NBS and study product group added in ANCOVA model. • Figure 14.2.1 Number of Bleeding Sites Over Time for All Study Product Groups (mITT Population), updated to topline in list of TLFs. • Table 14.2.3.1 Statistical analysis of Number of Bleeding Sites at Week 6 (mITT Population), updated to topline in list of TLFs.

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Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
BDRM	Blind Data Review Meeting
BDR	Blind Data Review
BI	Bleeding Index
CI	Confidence Interval
COVID-19	Coronavirus Disease of 2019
CRF	Case Report Form
GSK CH	GlaxoSmithKline Consumer Healthcare
HMW	High molecular weight
ICF	Informed Consent Form
K	Kappa coefficient
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Master Formulation Code
MGI	Modified Gingival Index
mITT	Modified Intent-To-Treat
n	number of subjects
NA	Not Applicable
NBS	Number of bleeding sites
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PDMP	Protocol Deviation Management Plan
PoP	Proof-of-Principle
PP	Per Protocol
Ppm	parts per million
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
RAP	Reporting and Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TPI	Turesky Plaque Index
vs	Versus
w/w	weight for weight

The purpose of this Statistical Reporting and Analysis Plan is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 208175 version 4.0 dated 07-Feb-2021.

1 Summary of Key Protocol Information

GlaxoSmithKline Consumer Healthcare (GSKCH) has developed an experimental dentifrice containing 67% weight for weight (w/w) sodium bicarbonate, 0.2% w/w high molecular weight (HMW) sodium hyaluronate and 0.221% w/w sodium fluoride for the treatment of gingivitis and plaque accumulation. At the time of writing the clinical protocol, no published clinical data investigating the efficacy of sodium hyaluronate (hyaluronic acid, HA) in a toothpaste for the treatment of gingivitis was available. Therefore, a Proof-of-Principle (PoP) clinical study is required to explore the inclusion of HMW sodium hyaluronate in a twice daily use sodium bicarbonate/ sodium fluoride toothpaste.

This PoP study will investigate the efficacy of an experimental dentifrice containing 0.2% w/w HMW sodium hyaluronate in a twice daily use 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride toothpaste compared to a regular fluoride dentifrice, and also whether this provides any additional benefit in reducing gingival inflammation/bleeding compared with a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride containing toothpaste.

1.1 Study Design

This will be a single center, controlled, single blind (examiner blind), randomized, stratified (gender and baseline number of bleeding sites), three-product arm, parallel design, clinical study. Study subjects will be aged 18-65 years, non-smokers, in good general health with generalized mild to moderate plaque-induced gingivitis and ≥ 20 natural teeth that meet all study criteria at both the Screening and Baseline visits, including ≥ 40 evaluable surfaces for Modified gingival index (MGI), Bleeding Index (BI), and Turesky Plaque Index (TPI).

This study will consist of 6 study visits. The schedule of activities in 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, in order 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 (-28 to -10 days)		Visit 2 Day 0[1] Baseline	Visit 3 Day 3+1 days[1]	Visit 4 Day 7±2 (Week 1)[1]	Visit 5 Day 14±2 (Week 2)[1]	Visit 6 Day 42±3 (Week 6)[1]
Informed consent	X						
Demographics	X						
Medical History	X						
Prior/ current medications and treatments	X		X				
Oral soft tissue (OST) examination	X		X	X	X	X	X
Oral hard tissue (OHT) examination	X		X				X
Gross gingival assessment[2]	X						
Urine pregnancy test[7]	X		X				
Inclusion/ Exclusion Criteria	X		X				
Subject Eligibility	X		X				
Subject Continuance				X	X	X	X
Dispense washout dentifrice, toothbrush, diary & timer	X						
Oral hygiene instruction & supervised brushing with washout dentifrice	X						
Return washout products/ compliance checks			X				
Concomitant medications & treatments			X	X	X	X	X
Modified Gingival Index (MGI) assessment[3]			X	X	X	X	X
MGI repeat assessment[3]			X	X	X	X	X
Bleeding Index (BI) assessment			X	X	X	X	X
Plaque disclosure & Plaque Index (TPI) assessments			X	X	X	X	X
TPI repeat assessment[3]			X	X	X	X	X

Washout Period: minimum 10 Days/ maximum 28 days

Procedure/Assessment	Screening		Study Period				
	Visit 1 (-28 to -10 days)		Visit 2 Day 0[1] Baseline	Visit 3 Day 3+1 days[1]	Visit 4 Day 7±2 (Week 1)[1]	Visit 5 Day 14±2 (Week 2)[1]	Visit 6 Day 42±3 (Week 6)[1]
Stratification/randomization			X				
Sub- & supra-gingival prophylaxis with 2nd examiner to confirm TPI=0 via plaque disclosure			X				
Dispense study products[4]			X				
Collect study products, assess compliance and return to subject				X	X	X	
Oral hygiene instruction & supervised brushing with study product at site			X	X	X	X	
Return all study products to site							X
End of study dental prophylaxis (optional)[5]							X
Adverse Events/ Incidents[8]	X		X	X	X	X	X
Study Conclusion							X

Abbreviations: OST = Oral Soft Tissue; OHT = Oral Hard Tissue; MGI = Modified Gingival Index; BI =Bleeding Index; TPI = Turesky Plaque Index

Footnotes:

1. Subjects will abstain from overnight toothbrushing for a minimum of 12hrs (+6hr, -2hr) immediatelyprior to the assessment visits (Visits 2, 3, 4, 5 and 6)
2. In relation to the general dentition inclusion/ exclusion criteria
3. At least 2 repeatability assessments should be performed each day (≥ 1 in the morning; ≥ 1 in the afternoon)
4. Study products include study dentifrice, toothbrush, study instructions, diary & timer. Subjects will beinstructed to bring all supplies to site at subsequent visits to determine treatment compliance, prior to being returned to the subject.

5. Prophylaxis will be offered to subjects who are deemed to require it in the opinion of the investigator/examiner after all efficacy measures have been completed. This will be documented in the CRF.

7. Female subjects of child bearing potential only

8. Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs), and Incidents will be collected immediately after a subject provides consent to participate in the study by the completion ofthe Informed Consent Form (ICF).

1.2 Study Objectives

The study objectives are as follows:

Objective(s)	Endpoint(s)
Primary	
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), after 6 weeks' twice daily toothbrushing.	Number (no.) of bleeding sites at 6 weeks.
Secondary	
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), after 6 weeks' twice daily toothbrushing.	Number (no.) of bleeding sites at 6 weeks.
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), after 6 weeks' twice daily toothbrushing.	Number (no.) of bleeding sites at 6 weeks.
Exploratory	
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), over 2 weeks' twice daily use.	No. of bleeding sites at 3 days, 1 and 2 weeks.
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of gingivitis, as	Mean BI at 3 days, 1, 2 and 6 weeks.

Objective(s)	Endpoint(s)
measured by a Bleeding Index (BI), over 6 weeks' twice daily use.	
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by Modified Gingival Index (MGI), over 6 weeks twice daily use.	Mean MGI at 3 days, 1, 2 and 6 weeks.
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of plaque accumulation, as measured by a Plaque Index (TPI; overall and interproximal), over 6 weeks twice daily use.	Mean TPI (overall and interproximal) at 3 days, 1, 2 and 6 weeks.
To evaluate and compare MGI and mean BI in low (<45 bleeding sites) and high (≥45 bleeding sites) BI subgroups following twice daily use of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride, a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice and a fluoride control dentifrice, over 6 weeks twice daily use.	Mean MGI and mean BI at 3 days, 1, 2 and 6 weeks within each subgroup (low and high number of bleeding sites)
Safety	
To assess the oral tolerability of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride, a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, and a fluoride control dentifrice over 6 weeks twice daily use.	Treatment-emergent adverse events over 6 weeks.

1.3 Treatments

There are 4 products used in this study – 1 washout product and 3 investigational/study products. The three study product groups in this study are:

- Experimental Dentifrice
- Positive Control Dentifrice
- Negative Control Dentifrice

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

Table 1-2 Investigational/Study Product Supplies

	Washout Product	Experimental Product	Positive control	Negative control
Product Name	Dentifrice containing 1000ppm fluoride as SMFP (Colgate Cavity Protection)	Experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w sodium hyaluronate and 0.221% w/w sodium fluoride	Dentifrice containing 67% w/w sodium bicarbonate and 0.221% w/w sodium fluoride	Dentifrice containing 1100ppm fluoride as sodium fluoride (Crest Cavity Protection)
Product Master Formulation Code (MFC)	Canadian marketed product (NPN no. CCI)	CCI	CCI (NPN no. CCI)	Canadian marketed product (NPN CCI)
Dose/ Application	Full ribbon of toothpaste to cover the head of toothbrush provided			
Route of Administration	Oral topical			
Usage Instructions	Subjects will brush their teeth for one timed minute twice a day (morning and evening)			
Return Requirements	All used/unused samples to be returned			

1.4 Sample Size Calculation

No formal study powering was conducted. Forty (40) randomized subjects per product group are deemed to be sufficient for generating sufficient efficacy and safety data to evaluate the combination product (sodium bicarbonate and sodium hyaluronate), with sodium bicarbonate dentifrice and regular fluoride dentifrice in this PoP study.

Sufficient subjects will be screened (approximately 160) by the study site so that at least 120 subjects (approximately 40 per product group) who fulfil all the entry criteria will be randomized, which should ensure that approximately 36 evaluable subjects per group complete the week 6 assessment (thus allowing for a 10% drop-out rate).

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:

- All subjects have completed the study as defined in the protocol.
- All required database cleaning activities have been completed and database has been locked.
- 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 (Visit 2, Day 0).

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

3.2 Subgroups/Stratifications

Subjects will be stratified by gender (Male/Female) and baseline number of bleeding sites (NBS) (Low: < 45 bleeding sites; High: ≥ 45 bleeding sites).

Based on above stratification factors, there will four strata as follows:

- Stratum 1: Male, Baseline NBS < 45.
- Stratum 2: Male, Baseline NBS ≥ 45.
- Stratum 3: Female, Baseline NBS < 45.
- Stratum 4: Female, Baseline NBS ≥ 45.

All eligible subjects will be stratified based on above four strata, to ensure a balance of gender and gingivitis across all study product groups and then randomized to a study product.

A subgroup analysis to evaluate and compare mean MGI and NBS in low (< 45) and high (≥ 45) bleeding sites groups will be conducted at 3 days (Visit 3), Week 1 (Visit 4), Week 2 (Visit 5) and Week 6 (Visit 6).

3.3 Centre Pools

Since this is a single centre study, pooling of centres is not applicable.

3.4 Time points and Visit Windows

The time points and visits for this study are defined in Table 1-1, “Schedule of Activities”. Deviations from the scheduled assessment times should be avoided or kept to a minimum as far as possible. Any deviation from the study schedule may be reviewed on a case-by-case basis at the Blinded Data Review Meeting (BDRM) before database lock 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

Syneos Health will perform data analysis with oversight from GSK CH. The statistical analysis software 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. In addition, the assessment of any subjects who may have dropped or discontinued from the study due to Coronavirus Disease of 2019 (COVID-19) pandemic related events and the potential need of a sensitivity analysis will be discussed during BDRM. Any major changes to planned analyses will need an amendment to RAP.

Unless otherwise described, all listings will be produced on 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, enrolled and randomized will be presented in CCI. The number and percentage of screen failure subjects (subjects not randomized) with reasons why subjects are not randomized will also be displayed. Percentages for screen failure subjects will be based on the total number of subjects screened.

The number and percentage of subjects who complete and discontinue the study, broken down by reason for discontinuation, will be presented by study product group and overall in CCI. The percentages will be based on the number of subjects randomized.

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

Subject disposition including demographic data (age, sex and race), screening date, washout product start date and time, the subject status (completer, Yes/No), study completion/withdrawal date, duration (in days) in the study (defined as [(date of completion or withdrawal – washout product start date) + 1], the primary reason for withdrawal and further details for withdrawal will be listed CCI) for all randomized subjects.

Subject disposition information will be listed for non-randomized subjects (CCI), including 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.

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

- Violation of inclusion or exclusion criteria
- Non-compliance with study product use
- Use of prohibited treatment or medication before or during the study

- Violation of visit windows

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. The specific details of the important protocol deviations and how these will be assessed will be specified in the Blind Data Review (BDR) Plan with reference to the Protocol Deviation Management Plan (PDMP). Subjects with important protocol deviations will be identified at the BDRM. The BDRM will be conducted in a manner to ensure that the study statisticians and clinical research scientist remain blinded to every extent possible. Further details regarding maintaining the blindness during the BDRM will be described in the BDR Plan.

The number and percentage of subjects with at least one important protocol deviation, important protocol deviations not leading to exclusion from PP population with reasons for deviations and subjects with important protocol deviations leading to exclusion from the PP population with reasons for deviations will be presented by study product group and overall (CCI) and listed (CCI) for all randomized subjects.

All protocol deviations collected on the protocol deviation case report form (CRF) will be listed in CCI . 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 as follows:

Table 4-1 Analysis Populations

Population	Definition/Criteria	Analyses Evaluated
Safety	All randomized subjects who receive at least one dose of the study product. This population will be based on the study product the subject actually received.	Safety
Modified Intent-To-Treat (mITT)	All randomized subjects who received at least one dose of the study product and provided at least one post-baseline assessment of efficacy. All mITT population summaries and analyses will be presented according to the study product randomized.	Efficacy
Per Protocol (PP)	All randomized subjects who are part of mITT population and fully comply with all study procedures and restrictions. Subjects with a protocol violation that is deemed to affect efficacy for only some (but not all) of the efficacy assessments will be part of the PP population, but their data will be	Efficacy analyses for BI score

Population	Definition/Criteria	Analyses Evaluated
	excluded from the assessment at which the protocol violation occurred.	
MGI Repeatability	Subjects with at least one initial and repeat assessment of MGI at any visit.	Repeatability analyses
TPI Repeatability	Subjects with at least one initial and repeat assessment of TPI at any visit.	Repeatability analyses

The primary population for assessment of efficacy will be the mITT Population. A PP analysis will be performed only on the primary efficacy variable (NBS), if more than 10% of subjects in the mITT population are excluded from the PP Population.

Any repeat clinical data collected for the repeatability assessment will only be used to assess repeatability. The main assessment of efficacy will be based on the initial efficacy assessments.

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

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 [%] for categorical variables) will be presented for demographic characteristics by study product group and overall. These variables include gender, race, and age (years) which will be presented for the Safety population (CCI), the mITT population (CCI) and if applicable, for the PP population (CCI).

Demographic characteristic information will be listed for all randomized subjects in CCI.

4.2.2 Baseline Characteristics

Descriptive statistics will be presented for baseline characteristics by study product group and overall. These variables include Mean BI, Mean MGI, Mean TPI, Stratification factors (gender and high/low number of bleeding sites), and will be presented for the Safety population (CCI), the mITT population (CCI) and if applicable, for the PP population CCI).

Baseline characteristic information will be listed for all randomized subjects in CCI .

4.2.3 General Medical History

Medical history data will be listed (CCI) for all randomized subjects with start date and end date or ongoing at the start of the study.

4.3 Treatments (Study Product, Other Concomitant Therapies, Compliance)

Randomization details will be listed, including the randomization number, stratification group, the planned randomized product, the actual study product the subject received and the randomization date (CCI).

The study product kit allocations also will be listed, including kit list number and study product information (CCI).

4.3.1 Study Product Compliance and Exposure

Product compliance will be measured as number of missed brushings since last visit and number of additional brushings since last visit.

Compliance will be calculated for each visit interval and overall as:

- Compliance (%) = (Actual number of brushings / Expected number of brushings) x 100.

Where:

- Expected number of brushings = (Date of $Visit_n$ – Date of $Visit_{n-1}$) x 2.
- Actual number of brushings = Expected number – missed brushings + additional brushings.

A threshold of compliance with allocated study product has been set as 80% of the recommended doses. Subjects with overall compliance <80% will be considered protocol deviations and assessed at the time of BDRM for exclusion from the PP population.

The number of missed brushings, additional brushings and percentage compliance (as continuous variable and by groups [< 80%; between 80% and 120%; > 120%]) will be summarized by study product group for each visit interval and for overall study product duration, in CCI for the mITT population.

Exposure to study product will be calculated for each visit interval and overall study product duration as follows:

- Exposure (Days) = Date of $Visit_n$ – Date of $Visit_{n-1}$.

Product exposure (days) will be summarized by study product group for each visit interval and for overall study product duration, in CCI for the mITT population.

Compliance and exposure data will be listed for all randomized subjects (CCI).

Overall exposure and compliance will be calculated for Baseline (Visit 2), Day 3 (Visit 3), Week 1 (Visit 4), Week 2 (Visit 5) and Week 6 (Visit 6).

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/stop dates of administration. All subjects will be questioned about concomitant medication/treatments at each site visit.

The prior and concomitant medications will be coded using an internal validated medication dictionary, CCI .

Prior medications are defined as those taken within 30 days of signing the informed consent form. If the stop date is unknown or incomplete and the medication cannot be considered as stopped prior to the first use of study product, then the medication will be considered as a concomitant medication.

Prior medication will be listed by subject, with drug name, GSK drug synonym, reason for medication, dose, frequency, route, start date, study day relative to first use of study product and end date (CCI) for all randomized subjects.

Concomitant medications and significant non-drug therapy will be listed similarly (CCI) with either ongoing or end date displayed. Concomitant medications are defined as medications that started or stopped on or after the date of first use of the study product, or are ongoing. In this study, any medications recorded after signing the ICF will be considered a concomitant medication.

Unknown dates will not be imputed, however if the start or stop date is unknown, then it will be assumed to be concomitant medication unless the partial start date or stop date indicates differently.

4.4 Analysis of Efficacy

The analysis of primary and secondary efficacy variables will be based on the initial assessment. The mITT population will be considered as primary population for efficacy analyses.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary time point is week 6 and primary comparison is between the 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride (Experimental Dentifrice) and the fluoride control dentifrice (Negative Control Dentifrice).

The primary efficacy variable is the NBS and will be derived from the BI, whereby a site will be considered bleeding if the bleeding index score is 1 or 2 and will be considered not bleeding if the bleeding index score is 0.

The BI scoring system will be as follows:

Table 4-2 The Bleeding Index (BI)

Score	Description
0	Absence of bleeding on probing
1	Bleeding observed within 30 seconds of probing
2	Bleeding observed immediately on probing

As there is, only a single primary objective no adjustment for multiple comparisons is required.

The BI is assessed on the facial and lingual gingival surfaces of each scorable tooth. Three scores (according to the scale below) are recorded buccally/labially (distal, body, mesial sites) and three scores lingually/palatally. All scorable teeth in one quadrant are probed for approximately 30 seconds before recording the number of gingival units, which bleed.

Descriptive statistics (n, mean, SD, standard error [SE], median, minimum, maximum) of the primary variable will be provided at Baseline, Day 3 (Visit 3), Week 1 (Visit 4), Week 2 (Visit 5) and Week 6 (Visit 6) by study product group for the mITT population (CCI [redacted]).

The mean and SE of the NBS for each study product group will be presented graphically over time for the mITT population in CCI [redacted].

The BI obtained for each site along with the details of whether or not the site was bleeding (i.e. 'Yes' if BI score for a site is 1 or 2) and total number of bleeding sites will be listed by subject and visit in CCI [redacted] for all randomized subjects.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The primary analysis is the comparison of number of bleeding sites at 6 weeks between the following study products:

- Experimental Dentifrice versus (*vs)* Negative Control Dentifrice

The NBS at 6 weeks will be analyzed using an Analysis of Covariance (ANCOVA) model with study product group and gender as factors and baseline NBS as covariate. Note that since the baseline NBS will be included as a covariate, the NBS stratification value will not be included in the model.

The null hypothesis for the primary endpoint is that there is no difference in the NBS between the experimental product and the negative control study product groups.

$\mathbf{H_0}$: $\mu_1 = \mu_2$

The alternative hypothesis is that there is a difference in the NBS between the two study product groups.

$\mathbf{H_1}$: $\mu_1 \neq \mu_2$

Using the above model, within-product adjusted means and corresponding SEs will be displayed with the study product group adjusted mean difference, SE, 95% confidence interval (CI) of the difference, between-product p-value and percent difference between study product groups in CCI for mITT population.

Percent difference will be calculated as:

- Percent Difference = (Adjusted Mean Difference/Adjusted Mean of Negative Control Dentifrice) x 100.

All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

This study will be considered successful if a statistically significant difference between the adjusted mean NBS of the two study product groups at Week 6 is observed to be in favor of the Experimental Dentifrice.

The assumption of residual normality and variance homogeneity in ANCOVA analysis will be investigated through residual plots. If violated, data transformation or a nonparametric method (such as Van Elteren test adjusting for gender and baseline NBS stratification) will be used.

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 of the primary efficacy variable will be presented for all subjects in the PP population (CCI), mean and SE will be presented graphically over time (CCI) and the same ANCOVA model applied to the primary analysis will be performed on the PP population (CCI).

4.4.2 Secondary Efficacy Variables

4.4.2.1 Number of Bleeding Sites at Week 6

The NBS at Week 6 (Visit 6) will be calculated in the same way as stated in Section 4.4.1.1 for following product comparisons:

- Experimental Dentifrice *vs* Positive Control Dentifrice
- Positive Control Dentifrice *vs* Negative Control Dentifrice

4.4.3 Exploratory Efficacy Variables

For all statistical analyses described in subsections below, the assumption of residual normality and variance homogeneity in ANCOVA models will be investigated. Violation of this assumption will be overcome using a suitable data transformation or a non-parametric technique (e.g. Van Elteren test).

4.4.3.1 Number of Bleeding Sites at 3 Days, 1 and 2 Weeks

The NBS at 3 Days (Visit 3), Week 1 (Visit 4) and Week 2 (Visit 5) will be analyzed in the same way as stated in Section 4.4.1.1 for the following product comparisons:

- Experimental Dentifrice *vs* Positive Control Dentifrice
- Experimental Dentifrice *vs* Negative Control Dentifrice
- Positive Control Dentifrice *vs* Negative Control Dentifrice

4.4.3.2 Mean BI at 3 Days, 1, 2 and 6 Weeks

Mean BI will be assessed at 3 Days (Visit 3), Week 1 (Visit 4), 2 (Visit 5) and Week 6 (Visit 6) for the following product comparisons:

- Experimental Dentifrice *vs* Positive Control Dentifrice
- Experimental Dentifrice *vs* Negative Control Dentifrice
- Positive Control Dentifrice *vs* Negative Control Dentifrice

In addition to the primary analysis based on the NBS, an analysis of gingival bleeding will be performed on the full BI. The mean BI score will be calculated taking the average over all tooth sites for a subject. The mean whole mouth BI score for each subject will be derived from the total BI score divided by the number of tooth sites scored. Refer to Section 4.4.1.1 and Table 4.2 for more details on BI.

Mean BI will be analyzed using ANCOVA model with product group, gender and number of bleeding sites strata as factors, and baseline BI score as covariate. Adjusted means for all products and all pairwise product differences will be provided along with 95% CI.

4.4.3.3 Mean MGI at 3 Days, 1, 2 and 6 Weeks

The mean MGI at 3 Days (Visit 3), Week 1 (Visit 4), Week 2 (Visit 5) and Week 6 (Visit 6) will be analyzed for the following product comparisons:

- Experimental Dentifrice *vs* Positive Control Dentifrice
- Experimental Dentifrice *vs* Negative Control Dentifrice
- Positive Control Dentifrice *vs* Negative Control Dentifrice

The MGI will be assessed for the facial and lingual/palatal gingiva of all evaluable teeth, four sites per tooth (facial surface - papilla and margin; lingual/palatal surface - papilla and margin).

Mean MGI will be calculated taking the average over all tooth sites for a subject.

The MGI scoring system will be as described in Table 4-3 and will be assessed by the same examiner on all evaluable teeth at 3 Days (Visit 3), Week 1 (Visit 4), Week 2 (Visit 5) and Week 6 (Visit 6).

Table 4-3 The Modified Gingival Index

Score	Description
0	Absence of inflammation
1	Mild inflammation: slight change in colour, little change in texture of any portion of the marginal or papillary gingival unit
2	Mild inflammation: criteria as [1] but involving the entire marginal or papillary gingival unit
3	Moderate inflammation: glazing, redness, edema, and/or hypertrophy of the marginal or papillary gingival unit
4	Severe inflammation: marked redness, edema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration

The mean whole mouth MGI score for each subject will be derived from the total MGI score divided by the number of tooth sites scored.

The mean MGI score will be analyzed using ANCOVA with study product group, gender and number of bleeding sites strata as factors and baseline mean MGI score as a covariate. Adjusted means and their SEs for each study product group will be displayed with the study product group difference, SE, 95% CI of the difference, between-product p-value and percent difference between study product groups for mITT population.

4.4.3.4 Turesky Plaque Index (Overall and Interproximal) at 3 Days, 1, 2 and 6 Weeks.

The mean TPI (Overall and Interproximal) at 3 Days (Visit 3), Week 1 (Visit 4), Week 2 (Visit 5) and 6 Weeks (Visit 6) will be analyzed for the following product comparisons:

- Experimental Dentifrice *vs* Positive Control Dentifrice
- Experimental Dentifrice *vs* Negative Control Dentifrice
- Positive Control Dentifrice *vs* Negative Control Dentifrice

Supra-gingival plaque will be assessed on the facial and lingual surfaces of the teeth using the Turesky Plaque Index (TPI). Each tooth surface will be divided into three areas; three scores will be recorded facially (mesiofacial, facial, distofacial) and three scores lingually (mesiolingual, lingual and distolingual) generating six scores per tooth. The plaque will be disclosed and scored for each site as follows:

Table 4-4 Turesky Plaque Index

Score	Description
0	No plaque
1	Separate flecks of plaque at the cervical margin
2	Thin continuous band of plaque (up to 1 mm) at the cervical margin
3	Band of plaque wider than 1 mm but covering < 1/3 of the tooth surface
4	Plaque covering ≥ 1/3 but < 2/3 of the tooth surface
5	Plaque covering ≥ 2/3 of the tooth surface

The mean Overall TPI score for each subject will be derived from the Total TPI score over all tooth sites divided by the number of tooth sites scored.

The mean Interproximal TPI score for each subject will be derived in the same way as for the overall scores but based on the mesiofacial, distofacial, mesiolingual and distolingual surfaces only.

The mean Overall TPI and mean Interproximal TPI scores will be analyzed using ANCOVA model with study product group, gender and number of bleeding sites strata as factors and baseline plaque score as covariate. Separately for Overall TPI score and Interproximal TPI score, adjusted means and their SEs for each study product group will be displayed with the study product group difference, SE, 95% CI of the difference, between-product p-value and percent difference between study product groups for mITT population.

4.4.3.5 Mean MGI and Mean BI at 3 days, 1, 2 and 6 Weeks within each subgroup (low and high number of bleeding sites)

Mean MGI and Mean BI at each visits will be analysed for the low and high NBS subgroup (Low NBS < 45, High NBS ≥ 45) for the following product comparisons:

- Experimental Dentifrice *vs* Positive Control Dentifrice
- Experimental Dentifrice *vs* Negative Control Dentifrice
- Positive Control Dentifrice *vs* Negative Control Dentifrice

Mean MGI score will be analyzed using ANCOVA model with treatment group, gender and number of bleeding sites strata as factors, baseline MGI score as covariate and NBS strata (Low and High NBS) into study product groups as interaction effect. Adjusted means for all treatments and all pairwise treatment differences will be provided along with 95% confidence intervals.

Mean BI will be analyzed using ANCOVA model with treatment group and gender and number of bleeding sites strata as factors, baseline BI score as covariate and NBS strata (Low and High NBS) into study product groups as interaction effect. Adjusted means for all treatments and all pairwise treatment differences will be provided along with 95% confidence intervals.

4.4.4 Handling of Missing Values/Censoring/Discontinuations

Missing data will not be replaced or imputed. Subjects who withdraw from the study early will be included in the statistical analysis up to the point of withdrawal. Subjects who withdraw will not be replaced.

4.5 Analysis of Secondary and Exploratory Objectives

Each secondary and exploratory variable will be analyzed separately. All analyses will be conducted on the mITT population only.

4.5.1 Analysis of Secondary Objectives

4.5.1.1 Number of Bleeding Sites at Week 6

Using the same methodology as described above for primary analyses, pairwise product differences will be provided along with 95% CI (CCI [redacted]) for the following product comparisons:

- Experimental Dentifrice *vs* Positive Control Dentifrice
- Positive Control Dentifrice *vs* Negative Control Dentifrice

The mean and SE of the NBS for each study product group will be presented graphically over time for the mITT population in CCI [redacted].

The BI obtained for each site along with the details of whether or not the site was bleeding (i.e. 'Yes' if BI score for a site is 1 or 2) and total number of bleeding sites will be listed by subject and visit in CCI [redacted] for all randomized subjects.Analysis of Exploratory Objectives

4.5.1.2 Number of Bleeding Sites at 3 Days, 1 and 2 Weeks

Using the same methodology as described above for primary analyses, pairwise product differences will be provided along with 95% CI (CCI [redacted]) for the following product comparisons:

- Experimental Dentifrice *vs* Positive Control Dentifrice
- Positive Control Dentifrice *vs* Negative Control Dentifrice
- Experimental Dentifrice *vs* Negative Control Dentifrice

The mean and SE of the NBS for each study product group will be presented graphically over time for the mITT population in CCI.

The BI obtained for each site along with the details of whether or not the site was bleeding (i.e. 'Yes' if BI score for a site is 1 or 2) and total number of bleeding sites will be listed by subject and visit in CCI for all randomized subjects.

4.5.1.3 Mean BI at 3 Days, 1, 2 and 6 Weeks

Summary statistics including n, mean, SD, SE, median, minimum, maximum will be provided by visit and randomized product group for the mITT population (CCI). Mean BI will be analyzed using ANCOVA model in CCI for mITT population.

Raw means and SE will also be plotted over time by product group (CCI).

The mean whole mouth BI score will be listed by subject and visit in CCI for all randomized subjects.

4.5.1.4 Mean MGI at 3 Days, 1, 2 and 6 Week

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the mean MGI score will be provided by visit and randomized study product group for the mITT population (CCI). The mean MGI score will be analyzed using ANCOVA model in CCI for mITT population.

The raw mean and SE of the MGI score will be presented graphically over time by study product group for the mITT population in CCI.

The MGI obtained for each tooth, surface and site will be listed by subject and visit in CCI for all randomized subjects. The mean whole mouth MGI score will be listed by subject and visit in CCI for all randomized subjects.

4.5.1.5 Mean TPI (Overall and Interproximal) at Day 3, 1, 2 and 6 Weeks

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the mean Overall TPI score (CCI) and mean Interproximal TPI score (CCI) will be provided by visit and study product group for the mITT population.

Results from ANCOVA analyses will be presented in CCI (mean Overall TPI score) and in CCI (mean Interproximal TPI score) for the mITT population.

The raw mean and SE of the Overall TPI score for each study product group will be presented graphically over time for the mITT population in CCI .

The TPI obtained for each tooth, surface and site will be listed by subject and visit in CCI for all randomized subjects. The mean Overall TPI score and mean Interproximal TPI score will be listed by subject and visit in CCI for all randomized subjects.

4.5.1.6 Mean MGI and Mean BI at 3 days, 1, 2 and 6 weeks within each subgroup (low and high number of bleeding sites)

Mean MGI and Mean BI will be analysed in the same way as described in Section 4.4.3.5 or the subgroup of low and high number of bleeding sites (Low NBS < 45, High NBS ≥ 45) and summary will be presented in CCI and CCI , respectively for the subgroup of low and high NBS for mITT population.

Mean MGI for low and high NBS will be analysed the same way as described in Section 4.4.3.5 or all visits (CCI). The raw mean and SE of the Mean MGI score for each NBS group will be presented graphically over time by study product group in CCI .

Mean BI for low and high NBS will be analysed the same way as mentioned in Section 4.4.3.5 for all visits CCI). The raw mean and SE of the Mean BI score for each NBS group will be presented graphically over time by study product group in CCI .

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, incidents, Oral Soft Tissue (OST) examination and Oral Hard Tissue (OHT) examination.

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 the electronic CRF.

Treatment emergent adverse events (TEAEs) are defined as AEs with an onset date/time on or after the date/time of first study product use. AEs with an onset date/time prior to the first study product use will be considered as non-treatment emergent.

The following summary tables and listings will be presented by study product group:

- Table of TEAEs by system organ class (SOC) and Preferred Term (PT) (CCI).
- Table of TEAEs by Oral/Non-Oral and PT (CCI).

- Table of treatment-related TEAEs by Oral/Non-Oral and PT (CCI).
- Table of AEs related to COVID-19 by SOC and PT (CCI).
- Listing of all AEs (CCI for all randomized subjects; CCI for non-randomized subjects).
- Listing of all AEs related to COVID-19 Subjects (CCI for all screened subjects).
- Listing of incidents (CCI).
- Listing of deaths (CCI).
- Listing of non-fatal SAEs (CCI).
- Listing of treatment-emergent AEs leading to study or drug discontinuation (CCI).
- Listing of treatment-emergent AEs classified as oral (CCI).

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

4.6.2 Other Safety Variables

The OST examination will be accomplished throughout the study (Screening [Visit 1] to Week 6 [Visit 6]). The examination will include assessment of the labial mucosa (including lips), buccal mucosa, 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 post-product usage soft tissue abnormality, or worsening of a preexisting condition, observed by the examiner or reported by the subject will be recorded on the CRF. Any abnormalities or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject from the OST examination carried out at Screening will be recorded as an AE.

The OHT examination will be accomplished on Screening (Visit 1), Baseline (Visit 2) and week 6 (Visit 6). The OHT examination will assess grossly carious lesions or signs of erosive wear, enamel irregularities, tooth fracture, gross decay, decalcification, faulty restorations and implants. Observations will be listed as absent or present and conditions noted as present will be described. Any abnormalities or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject from the OHT examination carried out at Screening will be recorded as an AE.

Oral soft tissue (OST) and oral hard tissue examination (OHT) data will be listed (CCI and CCI respectively) for all randomized subjects.

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

4.7 Analysis of Other Variables

Repeat MGI and TPI assessments will be performed by the clinical examiner at Baseline (Visit 2), Day 3 (Visit 3), Week 1 (Visit 4), Week 2 (Visit 5) and Week 6 (Visit 6). At least 2 repeat assessments should be performed for each index on each clinical assessment day (≥1 in the morning; ≥1 in the afternoon). 'Repeat' subjects will be selected at random from those in attendance. Different subjects can be used for repeat MGI and TPI assessments.

The repeat dental assessments (MGI and TPI) will be compared to the original assessments and will be used to investigate intra-examiner variability. The repeat assessments will not be used in any efficacy analyses.

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 $\kappa < 0.4$

The first and repeat assessments for each tooth site will be cross tabulated for MGI (CCI [redacted]) and for TPI (CCI [redacted]). This analysis will be conducted for MGI using the MGI Repeatability population and for TPI using the TPI Repeatability population.

5 Changes to the Protocol Defined Statistical Analysis Plan

All 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**
12.2.8 Exploratory Analyses Mean BI will be analyzed using ANCOVA model with treatment group and gender and number of bleeding sites strata as factors, and baseline BI score as covariate. Adjusted means for all treatments and all pairwise treatment differences will be	4.4.3.5 Mean MGI and Mean BI at 3 days, 1, 2 and 6 Weeks within each subgroup (low and high number of bleeding sites) Mean MGI score will be analyzed using ANCOVA model with treatment group, gender and number of bleeding sites strata as	ANCOVA model has been updated to incorporate interaction effect between high and low NBS and study product groups.

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
provided along with 95% confidence intervals. Mean MGI score will be analyzed using ANCOVA model with treatment group, gender and number of bleeding sites strata as factors and baseline MGI score as covariate. Adjusted means for all treatments and all pairwise treatment differences will be provided along with 95% confidence intervals. A subgroup analysis to evaluate and compare mean MGI and number of bleeding sites in low (<45) and high (≥45) bleeding sites groups will be conducted using the same methodology as described above for each respective endpoint.	factors, baseline MGI score as covariate and NBS strata (Low and High NBS) into study product groups as interaction effect. Adjusted means for all treatments and all pairwise treatment differences will be provided along with 95% confidence intervals. Mean BI will be analyzed using ANCOVA model with treatment group and gender and number of bleeding sites strata as factors, baseline BI score as covariate and NBS strata (Low and High NBS) into study product groups as interaction effect. Adjusted means for all treatments and all pairwise treatment differences will be provided along with 95% confidence intervals.	

Attachment 1: List of Data Displays

CCI