STATISTICAL REPORTING AND ANALYSIS PLAN

A randomized, controlled clinical study to evaluate the efficacy of a range of dental/denture products for improved oral health, compared to existing oral hygiene, in a population of partial denture wearers with generalized mild-moderate plaque-induced gingivitis

Protocol Number: 212401

Phase: 4

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

Property of GSK Consumer Healthcare
Confidential
May not be used, divulged, published or otherwise disclosed without the consent of GSK

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	29-Oct-2020	Not applicable

Table of contents

List of tables

Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
BDRM	Blind Data Review Meeting
BI	Bleeding Index
CI	Calculus Index
COVID-19	Coronavirus Disease of 2019
eCRF	electronic Case Report Form
GSK CH	GlaxoSmithKline Consumer Healthcare
κ	Kappa coefficient
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Master Formulation Code
MGI	Modified Gingival Index
mITT	Modified Intent-To-Treat
ml	millilitre
N/A	Not Applicable
ODI	Oral Debris Index
OHI	Oral Hygiene Index
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PDCI	Partial Denture Cleanliness Index
PDMP	Protocol Deviation Management Plan
PP	Per Protocol
ppm	parts per million
PT	Preferred Term
RAP	Reporting and Analysis Plan
RPD	Removable Partial Denture
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TPI	Turesky Plaque Index

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 212401, version 4.0, dated 30-Jul-2020.

1 Summary of Key Protocol Information

The study will examine the effects of an intervention with a range of dental/denture products (comprising use of 3 products, a dentifrice, a mouthrinse and a denture cleanser) used twice daily, compared to no intervention (use of existing oral hygiene) in a population with mild-moderate generalized gum problems and who wear a removable partial denture (RPD). The study will evaluate subjects' oral and gum health using established clinical indices for gingivitis, plaque and oral hygiene endpoints, denture cleanliness will be assessed by the partial denture cleanliness index (PDCI) and subjects' perceptions towards dental/denture cleaning will be explored via a questionnaire. This study is required to support the efficacy and safety of the sequential use of these 3 products.

1.1 Study Design

This will be a single-center, single-blind (to the examiner(s) performing the plaque, gingivitis, denture cleanliness and oral hygiene assessments), randomized, stratified (by denture material type and baseline mean overall Modified Gingival Index [MGI] score), two-treatment, parallel group, 12 week clinical study in generally healthy, adult volunteers with one conventional RPD (acrylic or cobalt chrome) and generalized, mild-moderate, plaque-induced gingivitis (as determined by clinical examiner) and ≥ 4 natural teeth in each arch that meet all study criteria at both the Screening and Baseline visits (including ≥ 30 evaluable surfaces for clinical evaluation of gingivitis and plaque).

There will be four visits to the study site: Screening, Baseline (when subjects are randomized), and after 6 weeks and 12 weeks use of the range of dental/denture products. Gingivitis will be assessed using the MGI and a Bleeding Index (BI). Plaque will be assessed by the Turesky modification of the Quigley & Hein Plaque Index (TPI). These indices are intended as markers of overall oral health. The cleanliness of the denture will be assessed by the examiner using the PDCI and overall oral hygiene will be assessed by the Oral Hygiene Index (OHI). The subject's perception of denture/dental cleanliness will be determined through a questionnaire. Safety will be assessed through examination of the subject's oral hard and soft tissues throughout the study, recorded Adverse Events (AEs) and incidents.

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	Visit 1		Visit 2	Visit 3	Visit 4
	Screening (Day -28 to -1)		Baseline (Day 0)[1]	Week 6 (Day 42±3)[1]	Week 12 (Day 84±3)[1]
Informed consent	X	1 – 28 days between Visit 1 and Visit 2[5]			
Demographics	X				
Medical history[2]	X				
Current / concomitant medication	X		X	X	X
Dental history	X				
Well-fit assessment of RPD	X				
Collect used study products & diary				X	X
Compliance checks including diary review				X	X
Subject completes questionnaire			X	X	X
Remove Removable Partial Denture (RPD)	X		X	X	X
Well-made assessment of RPD	X				
Partial denture cleanliness index (PDCI)			X	X	X
Photography of RPDs representing the range of PDCI scores [9]			X	X[8]	X[8]
Full oral soft tissue (OST) examination	X[3]		X	X	X
Full oral hard tissue (OHT) examination	X[3]				X
Gross gingival assessment	X				
Subject continuance				X	X
Modified Gingival Index (MGI) and Calculus Index (CI)			X	X	X
Disclosing followed by Plaque Index (TPI), Oral Debris Index (ODI) and Bleeding Index (BI)[11]			X	X	X
Inclusion / exclusion criteria	X		X		
Subject eligibility	X		X		
Stratification / randomization			X		
Repeat MGI and TPI assessments[7]			X	X	X
RPD cleansing and sub- & supra-gingival prophylaxis and flossing (with second clinician check after disclosing & residual plaque removal, if applicable i.e. confirmed plaque score of zero)			X		
Return RPD to subject	X		X	X	X

Dispense study products, toothbrush, product usage instructions, diary & timer[4]			X	X[12]	
Supervised subject brushing, mouth rinsing and denture cleansing at site including instruction in correct product usage[6]			X	X	
Optional dental prophylaxis and RPD cleansing					X[10]
Adverse events / incidents	X		X	X	X
Study conclusion					X

Abbreviations: OST = Oral Soft Tissue, OHT= Oral Hard Tissue, RPD = Removable Partial Denture, TPI= Turesky Plaque Index, BI= Bleeding Index, MGI= Modified Gingival Index, PDCI= partial denture cleanliness index, OHI= oral hygiene index, CI= calculus index, ODI= oral debris index.

Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) and medical device incidents will be collected immediately after a subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF).

1. Subjects will abstain from overnight toothbrushing for a minimum of 12 hours (maximum of 18 hours) immediately prior to the assessment visits (Visits 2, 3 & 4).
2. Including smoking / tobacco-use status.
3. In relation to the general dentition exclusion criteria.
4. Timer and diary only dispensed once, at Visit 2 only. Subjects randomized to the no intervention group will receive only the diary. All randomized subjects to receive standard oral care advice.
5. Subjects will be instructed to brush their teeth using their normal dentifrice, use their existing denture cleansing procedure following their normal routine between screening and baseline visits.
6. For subjects randomized to the interventional group only.
7. At least 2 repeatability assessments should be performed each day (≥1 in the morning; ≥1 in the afternoon).
8. Photographs should only be obtained at Visits 3 and 4 should insufficient photographs of sufficient quality not been obtained at Visit 2.
9. For a subset of subjects only.
10. After completion of all assessments if deemed necessary by the clinical examiner.
11. ODI to be assessed after TPI and BI to be assessed after ODI.
12. At Visit 3 the diary is returned to the subject following review by the study site.

1.2 Study Objectives

Table 1-2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival bleeding (following dental prophylaxis), as measured by the Bleeding Index (BI), compared to no intervention (existing oral hygiene), when used twice daily for 12 weeks.	BI at 12 weeks.
Secondary	
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival bleeding (following dental prophylaxis), as measured by the number of bleeding sites, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	Number of bleeding sites at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival inflammation (following dental prophylaxis), as measured by the Modified Gingival Index (MGI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	MGI at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival plaque formation (following dental prophylaxis), as measured by the Turesky Plaque Index (TPI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	TPI (overall and interproximal) at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival bleeding (following dental prophylaxis), as measured by the Bleeding Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 weeks.	BI at 6 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining the cleanliness of partial dentures, as measured by the Partial Denture Cleanliness Index (PDCI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	PDCI scores at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival calculus formation (following dental prophylaxis), as measured by the calculus index (CI) component of the oral hygiene index (OHI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	CI scores at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing oral debris (following dental prophylaxis), as measured by the oral debris index component of the OHI, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	ODI scores at 6 and 12 weeks.

Objectives	Endpoints
To evaluate the clinical efficacy of a range of dental/denture products in improving oral hygiene (following dental prophylaxis), as measured by the OHI score (composite score of calculus and oral debris indices), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	OHI scores at 6 and 12 weeks.
Exploratory	
To evaluate subject's perceptions of dental/denture cleaning at 6 and 12 weeks.	Scores from Cleaning Perceptions Questionnaire at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gum problems associated with denture abutment teeth (following dental prophylaxis), as measured by the Bleeding Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	BI associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gum problems associated with denture abutment teeth (following dental prophylaxis), as measured by the number of bleeding sites, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	Number of bleeding sites associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gum problems associated with denture abutment teeth (following dental prophylaxis), as measured by the Modified Gingival Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	MGI associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival plaque formation associated with denture abutment teeth (following dental prophylaxis), as measured by the modified Turesky Plaque Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	TPI associated with abutment teeth (overall and interproximal) at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival calculus formation associated with denture abutment teeth (following dental prophylaxis), as measured by the calculus index (CI) component of the oral hygiene index (OHI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	CI associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing oral debris associated with denture abutment teeth (following dental prophylaxis), as measured by the oral debris index component of the OHI, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	ODI associated with abutment teeth at 6 and 12 weeks.

Objectives	Endpoints
To evaluate the clinical efficacy of a range of dental/denture products in improving oral hygiene associated with denture abutment teeth (following dental prophylaxis), as measured by the OHI score (composite score of calculus and oral debris indices), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	OHI associated with abutment teeth at 6 and 12 weeks.
To capture photographic images of RPDs for each of the scores in the PDCI scale to assist study site staff with consistent evaluation of the PDCI over the duration of the study, to assist with future studies that might use this scale, and to aid to interpretation of results (including publication of the study outcomes).	Photographs of RPDs.
Safety	
To assess the safety and tolerability of a range of dental/denture products when used twice daily for 12 weeks.	Treatment emergent adverse events and incidents.

1.3 Treatments

Subjects will be randomized to one of two treatment groups:

- Intervention Group subjects will use the following range of dental/denture products twice daily (morning and evening) for 12 weeks:
  - Experimental dentifrice containing 0.454% stannous fluoride (currently non-marketed)
    - A strip of the dentifrice (full brush head) will be applied to the full length of the toothbrush head and used to brush the teeth for 2 timed minutes.
  - Denture cleansing foam (COREGA Purfrisch Reinigungsschaum - German Marketplace product).
    - The subject will clean their denture using 2 pumps of the denture cleansing foam and a denture cleaning brush for 90 timed seconds outside of the mouth.
  - Experimental mouthrinse containing 90 ppm fluoride as sodium fluoride (currently non-marketed)
    - 10 ml of the mouthrinse will then be swished around the mouth for 1 timed minute.
- No Intervention Group subjects will continue with their existing oral hygiene habits.

The following study products will be supplied by the Clinical Supplies Department, GlaxoSmithKline Consumer Healthcare (GSK CH):

Table 1-3 Investigational/Study Product Supplies

	Intervention Group	No Intervention Group
Product Description	Range of Dental/Denture Products	N/A Subjects will continue with their existing oral hygiene
Product Names (Formulation Codes)	Experimental Dentifrice containing 0.454% stannous fluoride CCI COREGA Purfrisch Reinigungsschaum Denture Foaming Cleanser – German Marketplace CCI Experimental Mouthrinse containing 90ppm sodium fluoride CCI	N/A
Dose	A strip of dentifrice (full brush head) brushed for 2 timed minutes, 2 pumps of denture cleanser foam brushed onto RPD for 90 timed seconds and 10 ml of mouthrinse for swished around the mouth for 1 timed minute.	N/A
Route of Administration	Dentifrice and mouthrinse applied topically orally. Denture cleanser applied to denture external to the mouth prior to rinse off.	N/A
Dosing Instructions	As per the Product Usage Instructions	N/A

1.4 Sample Size Calculation

A sufficient number of subjects will be screened to randomize at least 150 (maximum 175) subjects to ensure approximately 128 evaluable subjects complete the entire study CCI

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:

- 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 pre-treatment assessment on Visit 2, Day 0.

3.2 Subgroups/Stratifications

Eligible subjects will be stratified based on denture material type (acrylic or cobalt chrome) and baseline mean overall MGI score (Low: ≤2.0/High: >2.0) to ensure a balance in treatments across the strata, and then randomized into one of two treatment groups (Intervention Group/No Intervention Group).

There will be four strata according to denture material type (acrylic or cobalt chrome) and baseline mean overall MGI score (Low: ≤2.0/High: >2.0):

- Stratum 1: Denture material is acrylic, Baseline MGI ≤2.0
- Stratum 2: Denture material is acrylic, Baseline MGI >2.0
- Stratum 3: Denture material is cobalt chrome, Baseline MGI ≤2.0
- Stratum 4: Denture material is cobalt chrome, Baseline MGI >2.0

The primary and secondary analysis will include gender (Male/Female), denture material type (acrylic or cobalt chrome) and mean baseline MGI (Low: ≤2.0/High: >2.0) as factors, with the exception of the analysis of MGI, for which the stratification factor of MGI will not be included as the baseline value of MGI will be included as a covariate.

No subgroup analyses are planned for this study.

3.3 Centers Pools

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

3.4 Timepoints and Visit Windows

The timepoints, visits and visit windows 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 Blind Data Review Meeting (BDRM) before database lock to determine whether the data should be excluded from the Per Protocol (PP) population.

4 Data Analysis

Data analysis will be performed by Syneos Health. The statistical analysis software used will be SAS 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. This will include the assessment of the number of subjects who have dropped or discontinued from the study due to COVID-19 (Coronavirus Disease of 2019) pandemic related events and the potential need of additional analysis (e.g. a sensitivity analysis). Any major changes to planned analyses as a result of COVID-19 findings will be provided in an amendment to this RAP (Reporting and Analysis Plan) prior to database lock.

4.1 Populations for Analysis

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

4.1.1 Subject Disposition

Screen failures will be 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 Table 14.1.1. 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 treatment group and overall in Table 14.1.1. The percentages will be based on the 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 treatment group and overall. Percentages will be based on the number of subjects randomized in the relevant treatment group or overall.

Subject disposition including demographic data (age, gender and race), screening date, study treatment start date (Visit 2, Day 0), the subject status (completer, Yes/No), date of study completion or withdrawal, duration (in days) in the study (defined as [(date of completion or

withdrawal – study treatment start date) + 1], the primary reason for withdrawal and further details for withdrawal will be listed (Listing 16.2.1.1).

Subject disposition information will be listed for non-randomized subjects (Listing 16.2.1.2), including demographic information (age, gender 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 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 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

The specific details of the important protocol deviations and how these will be assessed will be specified in the Blind Data Review 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 blind during the BDRM will be described in the Blind Data Review 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 analysis populations with reasons for deviations will be presented by treatment group and overall, for all randomized subjects (Table 14.1.2) and listed in Listing 16.2.2.1.

All protocol deviations collected on the protocol deviation case report form will be listed in Listing 16.2.2.2. The listing will present date of deviation, type of deviation and deviation description.

4.1.3 Analysis Populations

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 have at least one post-baseline efficacy measurement performed (BI, MGI, TPI, PDCI, CI, ODI). All mITT population summaries and analyses will be presented according to the study product randomized.	Efficacy
Per Protocol (PP)	• Subset of the mITT population which excludes subjects with a protocol violation that is deemed to affect efficacy for all efficacy assessments. 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 excluded from the assessment at which the protocol violation occurred.	Efficacy analyses for BI score

Repeatability	• Comprise of all subjects who have a repeat clinical assessment of efficacy at any visit. There will be a separate population for repeat MGI assessment and repeat TPI assessment:
	  • MGI Repeatability population: Subjects with at least one initial and repeat assessment of MGI at any visit.
	  • TPI Repeatability population: 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 Modified Intent-To-Treat (mITT) population. A PP analysis will be performed on the primary efficacy variable (BI score) only if 10% or more 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 assessment.

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

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, frequency count (n) and percentage (%) of subjects for categorical variables] will be presented for demographic characteristics by treatment group and overall. These variables include gender, race, ethnicity and age (years), and will be presented for the Safety population (Table 14.1.3.1), the mITT population (Table 14.1.3.2) and if applicable, for the PP population (Table 14.1.3.3).

Demographic information will be listed for all randomized subjects in Listing 16.2.4.1.1.

4.2.2 Baseline Characteristics

Descriptive statistics (n, mean, SD, median, minimum and maximum for continuous variables, n and % of subjects for categorical variables) will be presented for baseline characteristics by treatment group and overall. Baseline characteristics presented for the Safety population (Table 14.1.4.1) include denture material type (acrylic or cobalt chrome), baseline mean MGI score and category (low: ≤2.0/high: >2.0) and the number and percentage of subjects included in each stratum as described in Section 3.2 (Subgroups/Stratifications). Baseline characteristics will also be presented for the mITT population (Table 14.1.4.2) and, if applicable, for the PP Population (Table 14.1.4.3).

Baseline characteristics will be listed for all randomized subjects in Listing 16.2.4.1.2.

4.2.3 General Medical History

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

4.2.4 Dental History

Descriptive statistics (n, mean, SD, median, minimum and maximum for continuous variables; n and % of subjects for categorical variables) will be presented for dental history by treatment group and overall.

Data collected on dental history and the RPD will be summarized for the Safety population (Table 14.1.5.1.1) and mITT population (Table 14.1.5.1.2), and includes the the number of teeth replaced by RPD, number of abutment teeth, duration of RPD use (years), the duration of the current RPD use (years), whether the subject normally sleeps with RPD in place (Yes/No), type of RPD based on the Kennedy Classification, the subject's overall satisfaction with the RPD and the cause of tooth loss leading to the RPD. These data will also be listed in Listing 16.2.4.3.2 for all randomized subjects.

Baseline data collected regarding the subject's current oral hygiene product usage will be summarized for the Safety population (Table 14.1.5.2.1) and mITT population

(Table 14.1.5.2.2), including the frequency of current toothpaste, mouthrinse and denture cleanser usage. These data will also be listed in Listing 16.2.4.3.4 for all randomized subjects.

The tooth numbers replaced by the RPD, the abutment teeth and the missing natural teeth will be presented in Listing 16.2.4.3.1 for all randomized subjects.

Data from the evaluation of well-fit partial denture and well-made partial denture will be listed in Listing 16.2.4.3.3 for all randomized subjects.

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

Randomization details will be listed, including the planned study treatment, the actual study treatment the subject was randomized to and the randomization date (Listing 16.1.7.1).

Batch numbers also will be listed, including Randomization Number, Bulk Kit Description, Date Dispensed, Visit, Lot ID and Quantity (Listing 16.1.6.1).

4.3.1 Study Treatment Compliance and Exposure

Product compliance will be recorded as the total number of brushing, mouth rinsing and denture cleaning occasions since the last visit. In addition, any missed or additional brushing, mouth rinsing or denture cleaning occasions since the last visit are collected for the Intervention Group and any deviation from the normal hygiene range or change in oral hygiene products are collected for the No Intervention Group.

Treatment exposure will be calculated for each visit interval and overall treatment duration as follows:

- Treatment Exposure (Days) = Visit Interval End Date – Visit Interval Start Date.

Compliance will be calculated for the Intervention Group for brushing, mouth rinsing and denture cleaning for each visit interval and overall as:

- Brushing/Mouth Rinsing/Denture Cleaning Compliance (%) = [(Number of Brushing/Mouth Rinsing/Denture Cleaning occasions) / (Treatment Exposure x 2)] x 100.

Overall exposure and compliance will be calculated from Visit 2 (Day 0) to Visit 4 (Week 12) [or the last available visit for subjects who discontinue prior to Visit 4 (Week 12)].

The number of brushing occasions, mouth rinsing occasions, denture cleaning occasions will be summarized by treatment group using descriptive statistics (n, mean, SD, median, minimum and maximum) for each visit interval and overall study treatment duration, in Table 14.2.1.1.1 for the Safety population and Table 14.2.1.1.2 for the mITT population. In addition, the percentage compliance (n, mean, SD, median, minimum and maximum) and the number and percentage of subjects <80%, between 80% - 120% and >120% compliant will also be presented for brushing, mouth rinsing and denture cleaning for the Intervention Group.

Treatment exposure (days) will be summarized by treatment group using descriptive statistics (n, mean, SD, median, minimum and maximum), for each visit interval and overall study treatment duration, in Table 14.2.1.2.1 for the Safety population.

Compliance and exposure data will be listed for all randomized subjects, including the start and end date and exposure (days) for each visit interval and overall. For subjects randomized to the Intervention Group (Listing 16.2.5.1), data listed for brushing, mouth rinsing and denture cleaning will include the number of occasions, the number of missed and additional brushing, mouth rinsing and denture cleaning occasions and the percentage compliance for each visit interval and overall. For subjects randomized to the No Intervention Group (Listing 16.2.5.2), data listed will include any deviation from the normal oral hygiene routine and change in oral hygiene products for each visit interval and the number of brushing, mouth rinsing and denture cleaning occasions for each visit interval and overall.

4.3.2 Prior and Concomitant Medication

Prior or concomitant medication taken by or administered to a subject will be recorded in the case report form. The prior and concomitant medications will be coded using an internal validated medication dictionary, CCI [redacted].

Prior medication and prior non-drug therapies will be listed by subject, with drug name, GSK drug synonym, reason for medication, dose, frequency, route, start date, study day relative to the study treatment start date (Visit 2) and end date (Listing 16.2.4.4). Prior medications are defined as those which stopped before the study treatment start date (Visit 2). If the stop date is unknown or incomplete and the medication cannot be considered as stopped prior to study treatment start date (Visit 2) then the medication will be considered as a concomitant medication.

Concomitant medications and concomitant non-drug therapies will be listed similarly (Listing 16.2.4.5) with either ongoing or end date displayed. Concomitant medications are defined as medications that started or stopped on or after the study treatment start date (Visit 2), or are ongoing.

For the assignment of prior and concomitant medications, the randomization date will be used as the study treatment start date for subjects randomized to the No Intervention Group.

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

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary efficacy endpoint is the BI score at Week 12. The BI score for each subject will be calculated as the average index value over all tooth sites scored as follows:

- BI Score = Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites.

The BI score has a range of 0 to 2.

The BI will be assessed on the facial and lingual gingival surfaces of each scorable tooth. Three scores should be recorded bucally/labially (distal, body, mesial sites) and three scores lingually/palatally (distal, body, mesial sites). The BI will be assessed by the same examiner on all evaluable teeth at Baseline (Visit 2), Week 6 (Visit 3) and Week 12 (Visit 4).

The BI scoring system is described in Table 4-2.

Table 4-2 The Bleeding Index

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

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The primary analysis is a comparison of the BI score between the Intervention Group and No Intervention Group at Week 12 for subjects eligible for the mITT population.

The null and alternative hypotheses to be tested in the primary analyses are:

H_0: There is no treatment difference in mean BI score after 12 weeks

H_1: There is a treatment difference in mean BI score after 12 weeks

An Analysis of Covariance (ANCOVA) model will be used for the primary analysis with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline BI score as a covariate. The adjusted means and standard errors (SEs) of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference, between-group p-value and the proportionate reduction will be provided in Table 14.2.2.1.2 for the mITT population.

The proportionate reduction will be calculated as:

- Proportionate reduction = [(Adjusted Mean of No Intervention Group – Adjusted Mean of Intervention Group)/Adjusted Mean of No Intervention Group]*100.

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated and if violated, data transformations will be investigated. If suitable transformations cannot be found, non-parametric tests will be performed, and results will be compared with the ANCOVA results. If the inferences from the two analyses are similar, then both sets of results will be reported and emphasis will be made on the ANCOVA results. In case of discrepancies between inferences of the ANCOVA and non-parametric analysis, results will be drawn from the non-parametric analysis.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the primary variable will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.2.1.1).

The raw mean and SE of the BI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.1.1 (mITT population).

The BI value obtained for each tooth, surface and site will be listed by subject and visit in Listing 16.2.6.1 for all randomized subjects. The BI score will also be listed by subject and visit in Listing 16.2.6.6.1 for all randomized subjects.

4.4.1.3 Supportive Analyses

If there is a difference of 10% or more 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 (Table 14.2.2.2.1), mean and SE will be presented graphically over time (Figure 14.2.1.2) and the same ANCOVA model applied to the primary analysis will be performed on the PP population (Table 14.2.2.2.2).

4.4.2 Secondary Efficacy Variables

4.4.2.1 Number of Bleeding Sites at Week 6 and Week 12

The number of bleeding sites for each subject is the number of sites with a BI value of 1 or 2. The BI scoring system is described in Section 4.4.1.1.

4.4.2.2 MGI Score at Week 6 and Week 12

The MGI score for each subject will be calculated as the average index value over all tooth sites scored as follows:

- MGI Score = Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites.

The MGI score has a range of 0 to 4.

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

The MGI will be assessed by the same examiner on all evaluable teeth at Baseline (Visit 2), Week 6 (Visit 3) and Week 12 (Visit 4).

The MGI scoring system is described in Table 4-3.

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

4.4.2.3 Overall TPI Score at Week 6 and Week 12

The Overall TPI score for each subject will be calculated as the average index value over all tooth sites scored as follows:

- Overall TPI Score = Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites.

The TPI score has a range of 0 to 5.

Supra-gingival plaque will be assessed on the facial and lingual surfaces of all scorable teeth, six sites per tooth (three scores recorded bucally/labially [distal, body, mesial sites] and three scores lingually/palatally [distal, body, mesial sites]). The TPI will be assessed by the same examiner on all evaluable teeth at Baseline (Visit 2), Week 6 (Visit 3) and Week 12 (Visit 4).

The TPI scoring system is described in Table 4-4.

Table 4-4 The 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

4.4.2.4 Interproximal TPI Score at Week 6 and Week 12

The Interproximal TPI score for each subject will be calculated as the average index value over all interproximal tooth sites (distal and mesial) scored as follows:

- Interproximal TPI Score = Sum of index values over all evaluable interproximal tooth sites/Number of evaluable interproximal tooth sites.

The TPI scoring system is described in Section 4.4.2.3.

4.4.2.5 BI score at Week 6

The BI score at Week 6 will be calculated in the same way as stated in Section 4.4.1.1.

4.4.2.6 CI score at Week 6 and Week 12

The Calculus Index (CI) score for each subject will be calculated as the average index value over all tooth surfaces scored as follows:

- CI Score = Sum of index values over all evaluable tooth surfaces/Number of evaluable tooth surfaces.

The CI score has a range of 0 to 3.

The CI will be assessed on the facial and lingual surfaces all scorable teeth. The CI will be assessed by the same examiner for all subjects throughout the study on all evaluable teeth at Baseline (Visit 2), Week 6 (Visit 3) and Week 12 (Visit 4).

The CI scoring system is described in Table 4-5.

Table 4-5 The Calculus Index

Score	Description
0	No calculus present
1	Supragingival calculus covering not more than one third of the exposed tooth surface
2	Supragingival calculus covering more than one third but not more than two thirds of the exposed tooth surface or the presence of individual flecks of subgingival calculus around the cervical portion of the tooth or both
3	Supragingival calculus covering more than two thirds of the exposed tooth surface or a continuous band of subgingival calculus around the cervical portion of the tooth or both

4.4.2.7 ODI score at Week 6 and Week 12

The Oral Debris Index (ODI) score for each subject will be calculated as the average index value over all tooth surfaces scored as follows:

- ODI Score = Sum of index values over all evaluable tooth surfaces/Number of evaluable tooth surfaces.

The ODI score has a range of 0 to 3.

The ODI will be assessed on the facial and lingual surfaces of all scorable teeth. The ODI will be assessed by the same examiner for all subjects at Baseline (Visit 2), Week 6 (Visit 3) and Week 12 (Visit 4).

The ODI scoring system is described in Table 4-6.

Table 4-6 The Oral Debris Index

Score	Description
0	No debris or stain present
1	Soft debris covering not more than one third of the tooth surface, or the presence of extrinsic stains without other debris regardless of surface area covered
2	Soft debris covering more than one third, but not more than two thirds, of the exposed tooth surface
3	Soft debris covering more than two thirds of the exposed tooth surface

4.4.2.8 OHI score at Week 6 and Week 12

The OHI score is a composite of the CI and the ODI, calculated for each subject as the sum of the mean CI score and the mean ODI score.

The OHI score has a range of 0 to 6.

The CI score will be calculated as the average index value over all tooth surfaces scored, as described in Section 4.4.2.6.

The ODI score will be calculated as the average index value over all tooth surfaces scored, as described in Section 4.4.2.7.

4.4.2.9 PDCI score at Week 6 and Week 12

The PDCI score is reported as a single score for each subject based on the highest score of all surfaces of the RPD.

The PDCI score is an integer value with a range of 0 to 4.

All surfaces of the RPD should be assessed and the highest score applicable recorded. The PCDI will be assessed by the same examiner for all subjects at Baseline (Visit 2), Week 6 (Visit 3) and Week 12 (Visit 4).

The PCDI scoring system is described in Table 4-7.

Table 4-7 The Partial Denture Cleanliness Index

Score	Description
0	No visible plaque; no matter adherent to the dental probe on light scraping
1	No visible plaque; matter adherent to the dental probe on light scraping
2	Deposits of plaque just visible on careful examination without need to confirm by scraping

3	Deposits of plaque clearly visible
4	Gross plaque deposits (“velvet appearance”)

4.4.3 Exploratory Efficacy Variables

4.4.3.1 Cleaning Perceptions Questionnaire scores at Week 6 and Week 12

The cleaning perceptions questionnaire will be completed at Baseline (Visit 2), Week 6 (Visit 3) and Week 12 (Visit 4) to evaluate subject’s perceptions of dental/denture cleaning.

The questionnaire consists 5 questions relating to general oral care and 2 questions relating to oral care routine.

At Baseline the questions will be scored from 1 to 4 (with a response of 1 indicating not at all confident/motivated/likely and a response of 4 indicating very confident/motivated/likely).

At Week 6 and Week 12 the questions will be in comparison to the period before the subject begins this study and will be scored from 1 to 5 (with a response of 1 indicating a lot less confident/motivated/likely, a response of 3 indicating no difference and a response of 5 indicating a lot more confident/motivated/likely).

The mean general oral care confidence at Week 6 and at Week 12 will be derived for each subject as the average score of question 12 to question 16.

At Baseline, 4 additional questions relating to the subject’s attitude to oral care will be completed.

4.4.3.2 BI score associated with abutment teeth at Week 6 and Week 12

The BI scoring system is described in Section 4.4.1.1. The BI score associated with abutment teeth will be calculated as the average index value associated with abutment teeth only.

4.4.3.3 Number of bleeding sites associated with abutment teeth at Week 6 and Week 12

The number of bleeding sites associated with abutment teeth is the number of sites with a BI value of 1 or 2, associated with abutment teeth only.

4.4.3.4 MGI score associated with abutment teeth at Week 6 and Week 12

The MGI scoring system is described in Section 4.4.2.2. The MGI score associated with abutment teeth will be calculated as the average index value associated with abutment teeth only.

4.4.3.5 Overall TPI score associated with abutment teeth at Week 6 and Week 12

The TPI scoring system is described in Section 4.4.2.3. The Overall TPI score associated with abutment teeth will be calculated as the average index value over sites associated with abutment teeth only.

4.4.3.6 Interproximal TPI score associated with abutment teeth at Week 6 and Week 12

The TPI scoring system is described in Section 4.4.2.3. The Interproximal TPI score associated with abutment teeth will be calculated as the average index value over interproximal sites (distal and mesial) associated with abutment teeth only.

4.4.3.7 CI score associated with abutment teeth at Week 6 and Week 12

The CI scoring system is described in Section 4.4.2.6. The CI score associated with abutment teeth will be calculated as the average index value associated with abutment teeth only.

4.4.3.8 ODI score associated with abutment teeth at Week 6 and Week 12

The ODI scoring system is described in Section 4.4.2.7. The ODI score associated with abutment teeth will be calculated as the average index value associated with abutment teeth only.

4.4.3.9 OHI score associated with abutment teeth at Week 6 and Week 12

The OHI score associated with abutment teeth is a composite score of the CI and the ODI calculated as the sum of the mean CI score and the mean ODI score associated with abutment teeth only.

4.4.4 Handling of Missing Values/Censoring/Discontinuations

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

Also, missing due to COVID-19 will be assessed separately at BDRM and necessary actions will be taken on analysis for primary and key secondary endpoints (see section 4 for more details).

4.5 Analysis of Secondary and Exploratory Objectives

4.5.1 Efficacy (Secondary)

Each secondary variable will be analyzed separately as per the primary variable (Section 4.4.1.2). All analyses will be conducted on the mITT population only. For all of the secondary analyses, normality assumptions in ANCOVA models will be checked and accounted for in the same way as for the primary variable.

4.5.1.1 Number of Bleeding Sites at Week 6 and Week 12

At each post-baseline visit, the average number of bleeding sites will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline number of bleeding sites as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference, between-group p-value and the proportionate reduction will be provided in Table 14.2.3.1.2 for the mITT population.

The proportionate reduction will be calculated as:

- Proportionate reduction = [(Adjusted Mean of No Intervention Group – Adjusted Mean of Intervention Group)/Adjusted Mean of No Intervention Group]*100.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the number of bleeding sites will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.3.1.1).

The raw mean and SE of the number of bleeding sites (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.2 (mITT population).

The number of bleeding sites will be listed by subject and visit in Listing 16.2.6.6.1 for all randomized subjects.

4.5.1.2 MGI Score at Week 6 and Week 12

At each post-baseline visit, the MGI score will be analyzed using an ANCOVA model with treatment group, gender and denture material type (acrylic or cobalt chrome) factors and the baseline MGI score as a covariate. For the analysis of MGI the stratification factor of MGI will not be included as the baseline value of MGI is included as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference, between-group p-value and the proportionate reduction will be provided in Table 14.2.4.1.2 for the mITT population.

The proportionate reduction will be calculated as:

- Proportionate reduction = [(Adjusted Mean of No Intervention Group – Adjusted Mean of Intervention Group)/Adjusted Mean of No Intervention Group]*100.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the MGI score will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.4.1.1).

The raw mean and SE of the MGI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.3 (mITT population).

The MGI value obtained for each tooth, surface and site will be listed by subject and visit in Listing 16.2.6.2 for all randomized subjects. The MGI score will be listed by subject and visit in Listing 16.2.6.6.1 for all randomized subjects.

4.5.1.3 Overall TPI Score at Week 6 and Week 12

At each post-baseline visit, the Overall TPI score will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline Overall TPI score as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference and between-group p-value will be provided in Table 14.2.5.1.2 for the mITT population.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the Overall TPI score will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.5.1.1).

The raw mean and SE of the Overall TPI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.4 (mITT population).

The TPI value obtained for each tooth, surface and site will be listed by subject and visit in Listing 16.2.6.3 for all randomized subjects. The Overall TPI score will be listed by subject and visit in Listing 16.2.6.6.1 for all randomized subjects.

4.5.1.4 Interproximal TPI Score at Week 6 and Week 12

At each post-baseline visit, the Interproximal TPI score will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline Interproximal TPI score as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference and between-group p-value will be provided in Table 14.2.6.1.2 for the mITT population.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the Interproximal TPI score will be provided at Baseline, Week 6 and Week 12 visits by treatment group for (and overall for Baseline only) the mITT population (Table 14.2.6.1.1).

The Interproximal TPI score will be listed by subject and visit in Listing 16.2.6.6.1 for all randomized subjects.

4.5.1.5 Bleeding Index at Week 6

The mean BI score at Week 6 will be analyzed and presented in the same way as stated in Section 4.4.1.2 for the primary analysis.

4.5.1.6 PDCI score at Week 6 and Week 12

At each post-baseline visit, the PDCI score will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline PDCI score as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference and between-group p-value will be provided in Table 14.2.7.1.2 for the mITT population.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the PDCI score will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.7.1.1).

The raw mean and SE of the PDCI score will be presented graphically over time for each treatment group in Figure 14.2.5 (mITT population).

The PDCI score will be listed by subject and visit in Listing 16.2.6.4 for all randomized subjects.

4.5.1.7 CI score at Week 6 and Week 12

At each post-baseline visit, the CI score will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline CI score as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference and between-group p-value will be provided in Table 14.2.8.1.2 for the mITT population.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the CI score will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.8.1.1).

The raw mean and SE of the CI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.6 (mITT population).

The CI value obtained for each tooth and surface will be listed by subject and visit in Listing 16.2.6.5 for all randomized subjects. The CI score will be listed by subject and visit in Listing 16.2.6.6.2 for all randomized subjects.

4.5.1.8 ODI score at Week 6 and Week 12

At each post-baseline visit, the ODI score will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline ODI score as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference and between-group p-value will be provided in Table 14.2.9.1.2 for the mITT population.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the ODI score will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.9.1.1).

The raw mean and SE of the ODI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.7 (mITT population).

The ODI value obtained for each tooth and surface will be listed by subject and visit in Listing 16.2.6.5 for all randomized subjects. The ODI score will be listed by subject and visit in Listing 16.2.6.6.2 for all randomized subjects.

4.5.1.9 OHI score at Week 6 and Week 12

At each post-baseline visit, the OHI score will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline OHI score as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference and between-group p-value will be provided in Table 14.2.10.1.2 for the mITT population.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the OHI score will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.10.1.1).

The raw mean and SE of the OHI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.8 (mITT population).

The OHI score will be listed by subject and visit in Listing 16.2.6.6.2 for all randomized subjects.

4.5.2 Efficacy (Exploratory)

With the exception of the cleaning perceptions questionnaire, each exploratory variable will be analyzed in a similar manner as described for the primary and secondary endpoints (Section 4.4.1.2 and Section 4.5.1). All analyses will be conducted on the mITT population only. For all of the exploratory analyses, normality assumptions in ANCOVA models will be checked and accounted for in the same way as for the primary variable.

4.5.2.1 Cleaning Perceptions Questionnaire scores at Week 6 and Week 12

For the cleaning perceptions questionnaire, frequency count (n) and percentages (%) will be provided for each question and response category by treatment group for baseline (overall for Baseline only) for the mITT population (Table 14.2.11.1). Simillary Q12 to Q18 will be presented in Table 14.2.11.2 by visit and treatent group, in addition, the mean general oral care confidence (n, mean, SD, median, minimum and maximum) with t-test (mean difference, 95 % CI and p-value) will be presented for Week 6 and Week 12.

A treatment comparison also will be performed by using Cochran Mantel-Haenszel test on Q12 to Q18 and p-value will be presented for Week 6 and Week 12 in Table 14.2.11.2.

The results of the cleaning perceptions questionnaire will also be listed (Listing 16.2.6.8).

4.5.2.2 BI score associated with abutment teeth at Week 6 and Week 12

At each post-baseline visit, the BI score associated with abutment teeth will be analyzed using an ANCOVA model with treatment group, gender and denture material type (acrylic or cobalt chrome) factors and the baseline BI score (associated with abutment teeth) as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference, between-group p-value and the proportionate reduction will be provided in Table 14.2.2.3.2 for the mITT population.

The proportionate reduction will be calculated as:

- Proportionate reduction = [(Adjusted Mean of No Intervention Group – Adjusted Mean of Intervention Group)/Adjusted Mean of No Intervention Group]*100.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the BI score associated with abutment teeth will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.2.3.1).

The raw mean and SE of the BI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.1.1 (mITT population).

Abutment teeth are indicated in the listing of BI (Listing 16.2.6.1). The BI score associated with abutment teeth will be listed by subject and visit in Listing 16.2.6.7.1 for all randomized subjects.

4.5.2.3 Number of bleeding sites associated with abutment teeth at Week 6 and Week 12

At each post-baseline visit, number of bleeding sites associated with abutment teeth will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline number of bleeding sites (associated with abutment teeth) as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference, between-group p-value and the proportionate reduction will be provided in Table 14.2.3.2.2 for the mITT population.

The proportionate reduction will be calculated as:

- Proportionate reduction = [(Adjusted Mean of No Intervention Group – Adjusted Mean of Intervention Group)/Adjusted Mean of No Intervention Group]*100.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the number of bleeding sites associated with abutment teeth will be provided at Baseline, Week 6 and Week 12

visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.3.2.1).

The raw mean and SE of the number of bleeding sites (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.2 (mITT population).

The number of bleeding sites associated with abutment teeth will be listed by subject and visit in Listing 16.2.6.7.1 for all randomized subjects.

4.5.2.4 MGI score associated with abutment teeth at Week 6 and Week 12

At each post-baseline visit, the MGI score associated with abutment teeth will be analyzed using an ANCOVA model with treatment group, gender and denture material type (acrylic or cobalt chrome) factors and the baseline MGI score (associated with abutment teeth) as a covariate. For the analysis of MGI the stratification factor of MGI will not be included as the baseline value of MGI is included as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference, between-group p-value and the proportionate reduction will be provided in Table 14.2.4.2.2 for the mITT population.

The proportionate reduction will be calculated as:

- Proportionate reduction = [(Adjusted Mean of No Intervention Group – Adjusted Mean of Intervention Group)/Adjusted Mean of No Intervention Group]*100.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the MGI score will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.4.2.1). The raw mean and SE of the MGI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.3 (mITT population).

Abutment teeth are indicated in the listing of MGI (Listing 16.2.6.2). The MGI score associated with abutment teeth will be listed by subject and visit in Listing 16.2.6.7.1 for all randomized subjects.

4.5.2.5 Overall TPI score associated with abutment teeth at Week 6 and Week 12

At each post-baseline visit, the Overall TPI score associated with abutment teeth will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline Overall TPI score (associated with abutment teeth) as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference and between-group p-value will be provided in Table 14.2.5.2.2 for the mITT population.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the Overall TPI score associated with abutment teeth will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.5.2.1).

The raw mean and SE of the Overall TPI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.4 (mITT population).

Abutment teeth are indicated in the listing of TPI (Listing 16.2.6.3). The Overall TPI score associated with abutment teeth will be listed by subject and visit in Listing 16.2.6.7.1 for all randomized subjects.

4.5.2.6 Interproximal TPI score associated with abutment teeth at Week 6 and Week 12

At each post-baseline visit, the Interproximal TPI score associated with abutment teeth will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline Interproximal TPI score (associated with abutment teeth) as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference and between-group p-value will be provided in Table 14.2.6.2.2 for the mITT population.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the Interproximal TPI score associated with abutment teeth will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.6.2.1).

Abutment teeth are indicated in the listing of TPI (Listing 16.2.6.3). The Interproximal TPI score associated with abutment teeth will be listed by subject and visit in Listing 16.2.6.7.1 for all randomized subjects.

4.5.2.7 CI score associated with abutment teeth at Week 6 and Week 12

At each post-baseline visit, the CI score associated with abutment teeth will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline CI score (associated with abutment teeth) as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference and between-group p-value will be provided in Table 14.2.8.2.2 for the mITT population.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the CI score associated with abutment teeth will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.8.2.1).

The raw mean and SE of the CI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.6 (mITT population).

Abutment teeth are indicated in the listing of OHI components – CI and ODI (Listing 16.2.6.5). The CI score associated with abutment teeth will be listed by subject and visit in Listing 16.2.6.7.2 for all randomized subjects.

4.5.2.8 ODI score associated with abutment teeth at Week 6 and Week 12

At each post-baseline visit, the ODI score associated with abutment teeth will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline ODI score (associated with abutment teeth) as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference and between-group p-value will be provided in Table 14.2.9.2.2 for the mITT population.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the ODI score associated with abutment teeth will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.9.2.1).

The raw mean and SE of the ODI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.7 (mITT population).

Abutment teeth are indicated in the listing of OHI components – CI and ODI (Listing 16.2.6.5). The ODI score associated with abutment teeth will be listed by subject and visit in Listing 16.2.6.7.2 for all randomized subjects.

4.5.2.9 OHI score associated with abutment teeth at Week 6 and Week 12

At each post-baseline visit, the OHI score associated with abutment teeth will be analyzed using an ANCOVA model with treatment group, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline OHI score (associated with abutment teeth) as a covariate. The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference and between-group p-value will be provided in Table 14.2.10.2.2 for the mITT population.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of the OHI score associated with abutment teeth will be provided at Baseline, Week 6 and Week 12 visits by treatment group (and overall for Baseline only) for the mITT population (Table 14.2.10.2.1).

The raw mean and SE of the OHI score (whole mouth and associated with abutment teeth) will be presented graphically over time for each treatment group in Figure 14.2.8 (mITT population).

The OHI score associated with abutment teeth will be listed by subject and visit in Listing 16.2.6.7.2 for all randomized subjects.

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 treatments will be assessed with respect to AEs, incidents, oral soft tissue (OST) abnormalities and oral hard tissue (OHT) abnormalities.

Safety will be assessed through examination of the subject's oral hard and soft tissues throughout the study, recorded AEs and incidents.

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 case report form (eCRF).

Treatment emergent adverse events (TEAEs) are defined as AEs with an onset date/time on or after the study treatment start date/time (Visit 2). AEs with an onset date prior to the study treatment start date/time (Visit 2) will be considered as non-treatment emergent.

For the assignment of TEAEs, the randomization date will be used as the study treatment start date for subjects randomized to the No Intervention Group.

The following summary tables (by treatment group and overall for subjects in the Safety population) and listings (for all randomized subjects unless otherwise specified) will be presented:

- Table of TEAEs by SOC and PT (Table 14.3.1.1). Summary of the number and percentage of subjects with at least one TEAE, total number of TEAEs, number and percentage of TEAEs within each SOC and PT will be displayed.
- Table of TEAEs by Oral/Non-Oral and PT (Table 14.3.1.2)
- Table of related TEAEs by Oral/Non-Oral and PT (Table 14.3.1.3)
- Table of AEs related to COVID-19 by SOC and PT (Table 14.3.1.4)
- 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 incidents (Listing 16.2.7.4)
- Listing of deaths (Listing 14.3.2.1)
- Listing of non-fatal serious adverse events (SAEs) (Listing 14.3.2.2)
- Listing of TEAEs leading to study or drug discontinuation (Listing 14.3.2.3)
- Listing of TEAEs classified as oral (Listing 14.3.2.4)

Additionally, COVID-19 diagnosis and assessment and the symptoms for symptomatic subjects data will be listed (Listing 16.2.7.5 and Listing 16.2.7.6, respectively) for all screened subjects.

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

4.6.2 Other Safety Variables

A shift table of OST by examination will be provided by treatment group (Table 14.3.4.1), comparing baseline results to post-baseline results at Week 6 and Week 12, for the Safety population.

The results of OST and OHT examinations will be listed (Listing 16.2.8.1 and Listing 16.2.8.2 respectively) for all randomized subjects.

All Incidents will be listed in Listing 16.2.7.4 for all randomized subjects.

4.7 Analysis of Other Variables

Repeat MGI and TPI assessments will be performed by the clinical examiner at Baseline (Visit 2), Week 6 (Visit 3) and Week 12 (Visit 4). 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.

The first and repeat assessments for each tooth site will be cross tabulated for MGI (Table 14.2.12.1) and for TPI (Table 14.2.12.2).

A weighted Kappa coefficient (κ), along with the 95% confidence interval will be calculated to assess the intra-examiner repeatability. Fleiss-Cohen weighted kappa will be calculated for the repeatability analysis. Repeatability will be deemed:

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

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

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**
Sections 12.2.5, 12.2.6.1, 12.2.6.2, 12.2.6.5 The adjusted means of the two treatments, the treatment difference and the proportionate reduction for each treatment group will be provided together with 95% CI and P-values.	Sections 4.4.1.2, 4.5.1, 4.5.2 The adjusted means and SEs of the two treatment groups together with the treatment difference, SE, 95% confidence interval of the difference, between-group p-value and the proportionate reduction will be provided.	Text updated to clarify. Proportionate reduction refers to a comparison of the intervention to the control and is calculated per visit and endpoint.
Sections 12.2.1 The repeatability population is defined as all subjects who have a repeat clinical assessment (MGI or TPI) at any visit.	Section 4.1.3 Comprise of all subjects who have a repeat clinical assessment of efficacy at any visit. There will be a separate population for repeat MGI assessment and repeat TPI assessment: MGI Repeatability population: Subjects with at least one initial and repeat assessment of MGI at any visit. TPI Repeatability population: Subjects with at least one initial and repeat assessment of TPI at any visit.	Text added to clarify that there will be separate populations for MGI repeatability and TPI repeatability.
Section 12.1.4.2 Prior medications, concomitant medications, and other concomitant non-drug therapies will be listed for the safety population.	Section 4.3.2 Prior and concomitant medication will be listed for all randomized subjects.	As per standard listings for prior and concomitant medication based on all randomizaed subjects.

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
• N/A	• Section 4.6 Safety analysis for COVID subjects added	This is not part of the protocol and covered under RAP
Section 12.2.10 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.	Section 4.4.4 Missing data will not be replaced or imputed. Subjects who withdraw from the study prematurely will be included in the statistical analyses up to the point of discontinuation. Also, missing due to COVID-19 will be assessed separately at BDRM and necessary actions will be taken on analysis for primary and key secondary endpoints (see section 4 for more details).	Wording slightly updated to match with the RAP text template, also added the COVID missing data assessment.

Attachment 1: List of Data Displays

CCI [redacted]