Statistical Analysis Plan for Protocol 208112

An Exploratory, Randomized, Single Center, Partial-Crossover, Clinical Study to Evaluate the Dental Plaque Removal Ability of a Prototype Power Toothbrush Versus a Manual Toothbrush After a Single Toothbrushing Event

NCT03809910

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1. Statistical Analysis Plan approval date: 12-Mar-2019
2. Amendment to Statistical Analysis Plan approval date: 12-Jul-2019

STATISTICAL REPORTING AND ANALYSIS PLAN

AN EXPLORATORY, RANDOMIZED, SINGLE CENTER, PARTIAL-CROSSOVER, CLINICAL STUDY TO EVALUATE THE DENTAL PLAQUE REMOVAL ABILITY OF A PROTOTYPE POWER TOOTHBRUSH VERSUS A MANUAL TOOTHBRUSH AFTER A SINGLE TOOTHBRUSHING EVENT

Protocol Number: 208112

Phase: 2a

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	12-Mar-2019	Not applicable (NA)
V2.0	12-Jul-2019	Updates to ensure document is in line with protocol: • Safety population definition. • Prior and concomitant medication definition. Additional outputs described to ensure safety data during the Training period is separately and adequately described.

Amendments incorporate all revisions to date.

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Abbreviation

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
CI	Confidence Interval
CRF	Case Report Form
DRM	Data Review Meeting
GSK CH	GlaxoSmithKline Consumer Healthcare
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-To-Treat
MTB	Manual Toothbrush
NA	Not Applicable
OST	Oral Soft Tissue
OHT	Oral Hard Tissue
PP	Per-Protocol
PT	Preferred Term
PTB	Power Toothbrush
RMNPI	Rustogi Modified Navy Plaque Index
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

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 208112 version 4.0 dated 28-March-2019.

1 Summary of Key Protocol Information

Tooth brushing is the most effective mean of dental plaque control. There is a large body of evidence amounting decades of research in power toothbrushes (PTB) indicating that they are safe to use, and in general, remove more dental plaque than a manual toothbrush (MTB). The investigational device to be tested in this study is a prototype of a novel PTB, to be investigated in healthy subjects for its ability to remove dental plaque after a single brushing event. The prototype PTB operates in two different cleaning modes ('Gumline' and 'Interdental'), which can then be combined resulting in a third brushing regimen ('Combined'). The main focus of this study will be to assess the 'Gumline' mode, in a group of healthy subjects, for its ability to remove dental plaque overall. In addition, the 'Interdental' mode will be investigated to gain an initial understanding of whether this regimen can provide any potential uplift in dental plaque removal efficacy compared to the 'Gumline' mode.

As a first step in the clinical development program for this project, it is proposed to conduct an exploratory single-use dental plaque removal study to demonstrate clinically the principle of the current prototype PTB to remove dental plaque.

1.1 Study Design

This study is an exploratory, randomized, single center, 4 treatment, 3 period, partial crossover study in healthy, right-handed MTB users with no signs of periodontal disease or excessive recession, to assess a prototype PTB in removing dental plaque after a single brushing event.

This study consists of a training period (Visit 1/ Screening) and 3 treatment periods (Visit 2, 3 and 4). During the Training period each eligible subject will undergo a supervised PTB training exercise. Subjects meeting the entry criteria, including inclusion criterion 4 (successful completion of investigational device training) will be randomized (Visit 2).

Subjects will be randomized to receive both, the prototype PTB and reference MTB in a pre-determined randomized order (AB/BA) design. The reference PTB will always be used in the last period (i.e. treatment period 3).

During the prototype PTB period, the subject will use the PTB twice; once in the 'Gumline' mode and once in the 'Interdental' mode. There will be clinical assessments after the 'Gumline' mode and after the 'Interdental' mode. So, the 'Gumline' mode and "Combined" mode ('Gumline' and 'Interdental' brushings) will occur in the same treatment period.

Each treatment arm is to be used once by each subject according to the sequence group assignment, under the supervision of suitably trained study site personnel.

The schedule of activities table (Table 1-1) provides an overview of the subject visits and study procedures.

Table 1-1 Schedule of Activities

Procedure / Assessment	Screening	Wash out	Study Period				
			Period 1	Wash out	Period 2	Wash out	Period 3
	Visit 1		Visit 2		Visit 3		Visit 4
Informed consent	X	Minimum 3 days including a 12 -18 hrs abstinence from all oral hygiene		Minimum 3 days including a 12 -18 hrs abstinence from all oral hygiene		Minimum 3 days including a 12 -18 hrs abstinence from all oral hygiene	
Inclusion/Exclusion criteria	X						
Demographic and ethnicity	X						
Medical history	X						
Current medication	X						
Urine Pregnancy testing	X		X		X		X
OHT assessment	X						
OST assessment	X						
Instructions on Lifestyle restrictions	X						
Supervised subject PTB training [1]	X*						
Post PTB training OST	X						
Subject Eligibility	X						
Washout product and diary card dispensing	X						
Concomitant medication			X		X		X
Diary card review [2]			X		X		X
Lifestyle restrictions review			X		X		X
Pre- brushing OST			X		X		X
Pre- brushing dental plaque disclosure			X		X		X
Pre- brushing dental plaque assessment			X		X		X
Continued eligibility			X		X		X
Randomization			X				

Study product dispensing		X	X	X
Product usage instructions [3]		X	X	X
Supervised brushing [4,5]		X*	X*	X
Post brushing OST assessment [6]		X	X	X
Post brushing dental plaque disclosure		X[7a]	X[7a]	X
Post brushing dental plaque assessment		X[7b]	X[7b]	X
Sensory experience questionnaire [8]		X	X	X
Repeatability dental plaque assessment [9]		X	X	X
Post treatment phase OHT				X
Return of washout products and diary cards				X
Adverse Events [10]	X	X	X	X
Incidents [11]	X	X	X	X
Study conclusion				X

Abbreviations:

MTB: Manual toothbrush, OHT: Oral hard tissue, OST: Oral soft tissue, PTB: Power toothbrush Hrs: Hours

Footnotes:

* Assessment of prototype PTB with focus on functional quality

1. Training will be conducted for prototype PTB and Reference PTB

2. Diary cards will be reviewed at each visit to ensure subject compliance in using washout toothpaste and manual toothbrush twice daily for the period in between visits, and to collect any AE's, incidents or medications used.

3. Toothbrushing instructions will be verbally communicated to the subjects for the treatment they have been assigned to for that period to confirm understanding of product usage. Instructions will be provided to the site.

4. Each brushing event will be under the supervision of study site personnel, who will control the brushing timings.

5. Used with a regular Canadian market place fluoride toothpaste.

6. OST will follow each brushing occasion.

7a. For the prototype PTB arm, dental plaque will be disclosed after brushing in 'Gumline' mode and again after brushing in 'Interdental' mode prior to plaque assessments.

7b. For the prototype PTB arm, plaque assessments will be made after brushing in 'Gumline' mode and again after brushing in 'Interdental' mode.

8. A questionnaire will be provided by each subject at the end of each visit to assess their sensorial experience.

9. A repeatability dental plaque assessment will be performed on 2 subjects per assessment day.
10. Adverse Events (AEs) and, therefore, all Serious Adverse Events (SAEs), will be collected immediately after the subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF).
11. Incidents will be collected immediately after a subject provides consent to participate in the study by the completion of the ICF.

Note: Screening (Visit 1) is referred to throughout this document as "Training"

A washout period will be utilized between Screening and the first treatment to standardize oral hygiene procedures and products prior to treatment and to allow sufficient time to have passed since the subject last used any oral hygiene products that could interfere with the outcome of the study (e.g. triclosan containing toothpastes). The study will also employ a minimum 3-day washout period between treatments which is considered sufficient to avoid any carry over effects from the previous treatment.

The current study will be performed at a single clinical site by a single dental examiner, thus eliminating the possibility of inter-examiner variability. Intra-examiner variability will be investigated by conducting repeat assessments of dental plaque pre- and post-brushing in a small number of randomly selected subjects separated by a minimum of 10 minutes (2 subjects per visit, one pre- and one post brushing on a given visit).

As this is an exploratory study of a prototype PTB, a stopping rule has been introduced to ensure a focus on the functional quality of the prototype PTB.

1.2 Study Objectives

The study objectives are as follows:

Objective(s)	Endpoint(s)
Primary	
To investigate and compare plaque removal efficacy of a prototype PTB when used in the 'Gumline' mode versus a reference MTB after a single brushing event as measured by the Rustogi Modified Navy Plaque Index (RMNPI) - whole mouth score.	Change from pre-brushing to post-brushing RMNPI whole mouth score (sites A to I)
Secondary	
Efficacy	
To investigate and compare plaque removal efficacy of a prototype PTB when used in the 'Gumline' mode versus a reference MTB after a single brushing event as measured by the RMNPI – marginal and proximal score.	Change from pre-brushing to post-brushing RMNPI marginal score (sites A to C) Change from pre-brushing to post-brushing RMNPI proximal score (sites D and F)
To investigate and compare plaque removal efficacy of a prototype PTB when used in the 'Combined' mode versus a reference MTB after a single brushing event as measured by the RMNPI.	Change from pre-brushing to post-brushing RMNPI whole mouth score (sites A to I) Change from pre-brushing to post-brushing RMNPI marginal score (sites A to C) Change from pre-brushing to post-brushing RMNPI proximal score (sites D and F)
To investigate and compare plaque removal efficacy of a prototype PTB when used in the 'Combined' mode versus the 'Gumline' mode as measured by the RMNPI.	Change from pre-brushing to post-brushing RMNPI whole mouth score (sites A to I) Change from pre-brushing to post-brushing RMNPI marginal score (sites A to C) Change from pre-brushing to post-brushing RMNPI proximal score (sites D and F)
To investigate and compare plaque removal efficacy of a prototype PTB when used in the 'Gumline' and 'Combined' modes versus a reference PTB after a single brushing event as measured by the RMNPI.	Change from pre-brushing to post-brushing RMNPI whole mouth score (sites A to I) Change from pre-brushing to post-brushing RMNPI marginal score (sites A to C) Change from pre-brushing to post-brushing RMNPI proximal score (sites D and F)

Safety	
To evaluate the oral tolerance of the prototype PTB in 'Gumline' and 'Interdental' mode, the reference MTB, and the reference PTB following a single brushing event.	Proportion of treatment emergent oral adverse events post-brushing
Exploratory	
To assess subject sensory experience of the prototype PTB, the reference MTB, and the reference PTB following a single brushing event.	Subject response to each sensory experience question.

This study will be considered successful if the prototype PTB used in 'Gumline' mode achieves a greater reduction in whole mouth plaque score post a single brushing event compared to a MTB.

1.3 Treatments

There are four treatments used in this study but only 3 treatment periods. The 4 treatments are:

Prototype PTB device

i) prototype PTB in 'Gumline' mode

ii) prototype PTB in Combined mode ('Gumline' mode followed by 'Interdental' mode)

Reference devices

iii) reference MTB

iv) reference PTB

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

Table 1-2 Investigational/Study Product Supplies

	Investigational Product (Prototype PTB)	**Reference Products**	
	Treatment 1	**Treatment 2**	**Treatment 3**
Product Description	Prototype PTB handle and brush head *(GSK - ID* CCI	Oral-B Indicator 1-2-3 toothbrush (MEDIUM) (reference MTB)	Oral-B Genius 8000 rechargeable PTB Handle with Oral-B Cross Action toothbrush head (reference PTB)
Product ID Code	Head = MFC CCI Handle = CCI	Commercially available in the UK market.	Commercially available in the Canadian market.
Dose	Single use		
Route of Administration	Oral Topical use		

	Investigational Product (Prototype PTB)	Reference Products	
Dosing Instructions	Apply 1.3 (+/-0.1) grams (weighed) of fluoride toothpaste (supplied) to the toothbrush head. This will be performed by a suitably trained member of site staff.		
	Subjects will be instructed to brush their teeth in 'Gumline' mode for 2-timed minutes under the supervision of a suitably trained member of site staff. Following disclosing and plaque assessments, subjects will brush for a further 1-timed minute in 'Interdental' mode.	Subjects will be instructed to brush their teeth for 1-timed minute in their usual manner under the supervision of a suitably trained member of site staff.	Subjects will brush their teeth for 2-timed minutes in 'Daily Clean' mode under supervision of a suitably trained member of site staff as per commercial pack label instructions.
	Instructions for use will be provided to the study site. The reference PTB will use commercial pack instructions for use.		

All treatments will be used with the fluoride toothpaste (Colgate Cavity Protection Toothpaste containing 0.76% w/w sodium monofluorophosphate). This paste will also be used through the washout periods.

1.4 Sample Size Calculation

A sufficient number of healthy subjects will be screened to randomize approximately 35 subjects to ensure 30 evaluable subjects complete the entire study.

The primary objective for this study is to compare the efficacy of the prototype PTB in 'Gumline' mode against the MTB after a single brushing event. With 30 subjects in a crossover design, it will be possible to detect a mean treatment difference of 0.025 (standard deviation (SD)=0.048) between the prototype PTB in 'Gumline' mode against the MTB in the pre-post brushing RMNPI whole mouth score after a single use with 80% power and a 5% significance level.

There is no previous GSK CH PTB study, therefore the estimated SD was obtained from published literature (Sharma et al 2011). This study has a similar design comparing a MTB with a PTB and using the RMNPI as an end-point, following a single brushing event.

2 Planned Analyses

2.1 Interim Analysis

No formal statistical analysis of interim data is planned for this study. However interim data reviews are planned to focus on the functionality of the prototype toothbrush (head and handle).

The purpose of the interim data review is to monitor mechanical failure rates of the prototype PTB (head and brush) on an ongoing basis and throughout the study (Visit 1 (Training Visit), 2 and 3).

Details of the interim analysis and stopping rules can be found in Section 12.2.10 of the Protocol and the Interim Analysis Charter (v1.0 dated 20-Feb-2019).

If the prototype PTB device failure count is reached as per the pre-defined descriptions in the Protocol and Interim Analysis Charter and the study is terminated, the site will contact all subjects to attend their final visit where final safety checks (oral soft tissue (OST) and oral hard tissue (OHT) assessments) will be performed. No efficacy assessments will be undertaken.

If the study is terminated early due to the number of incidents, no formal analyses of the efficacy will be performed. However the efficacy data will be summarized and more focus will be on the adverse events (AEs) and incidents reported.

2.2 Final Analyses

The final planned analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and database has been locked.
3. The randomization codes have been distributed.

3 Considerations for Data Analyses and Data Handling Conventions

3.1 Baseline Definition

Baseline values are defined as the pre-brushing measurement at each period.

3.2 Subgroups/Stratifications

No subgroups or stratification factors are defined in this study.

3.3 Centers Pools

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

3.4 Timepoints and Visit Windows

The timepoints and visits for this study are defined in the section “Schedule of Activities” of the protocol and in Section 1.1 in this document. Any deviation from the study schedule may

be reviewed on case-by-case basis at the Data Review Meeting (DRM) to determine whether the data should be excluded from the Per-Protocol (PP) population.

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

4 Data Analysis

Data analysis will be performed by Syneos Health. The statistical analysis software used will be SAS version 9.4 or higher.

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

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

4.1 Populations for Analysis

4.1.1 Subject Disposition

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. An enrolled subject is a subject who has signed informed consent and is eligible to proceed beyond the Screening visit. The number of subjects screened, subjects who participated in the supervised power toothbrush training, subjects not randomized, and subjects enrolled will be presented for the Overall set of subjects (all screened subjects) in Table 14.1.1.

The number of subjects randomized and the number and percentage of subjects starting and completing each study period and the number of subjects discontinued in each study period broken down by reason for discontinuation will be presented by product sequence in Table 14.1.1.

Subject disposition including subject status (completer, Yes/No), demographic information (age, sex and race), screening date, date and start time of brushing, date of study completion/withdrawal, duration (in days) in the study defined as [(date of completion or withdrawal – date of brushing in period 1) + 1] and the primary reason for withdrawal will be listed (Listing 16.2.1.1) by product sequence.

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

4.1.2 Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to unblinding and closure of the database to ensure all important deviations are captured and categorized. Subjects with important protocol deviations liable to

influence the efficacy outcomes will be excluded from the 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:

- Consent procedures
- Inclusion/Exclusion criteria
- Study procedures

The specific details of the important protocol deviations and how these will be assessed will be specified in the Data Review Plan and subjects with important protocol deviations will be identified at the DRM. Although treatment assignments and sequences are not fully blinded, the data review will be conducted without knowledge of the treatment allocation.

The number and percentage of subjects with at least one important protocol deviation, subjects with 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 product sequence (Table 14.1.2) and listed in Listing 16.2.2.1.

All protocol deviations collected on the protocol deviation case report form (CRF) page 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:

Population	Definition / Criteria	Analyses Evaluated
Safety	• Comprise of all subjects who are eligible to participate in the study • Have participated in the Supervised Power Toothbrush Training. The Safety population will include randomized and non-randomized subjects who participated in the Supervised Power Toothbrush Training.	• Safety Analysis
Randomized	• Comprise of all subjects in the Safety population • Randomized to study product sequence. All randomized population summaries and analyses will be presented according to the study product received.	• Safety Analysis
Modified Intent-To-Treat (MITT)	• Comprise of all randomized subjects. • Have received at least one of the study products (supervised brushing in study period 1, 2 or 3).	• Demographic and Baseline Characteristics • Efficacy Analysis

Population	Definition / Criteria	Analyses Evaluated
	• Have provided at least one post-brushing assessment of efficacy. All MITT population summaries and analyses will be presented according to the study product randomized.	
PP	• All subjects in the MITT population. • Have at least one assessment of efficacy considered unaffected by protocol violations. All PP population summaries and analyses will be presented according to the study product received.	• Demographic and Baseline Characteristics • Primary Efficacy Analysis
Repeatability (R)	• All subjects who have a repeat clinical assessment of efficacy at any visit.	• Exploratory

NOTES :

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

Subjects excluded from any of the analysis populations will be listed in Listing 16.2.3.1 for all screened subjects.

The primary population for assessment of efficacy will be the MITT population. A PP analysis will be performed only on the primary variable (whole mouth plaque score) if there is more than 10% difference in the number of subjects between the PP and MITT populations, or in the case the study is stopped early as per the pre-defined criteria. The numbers of subjects included in each of the analysis populations will be presented in Table 14.1.1. A decision on whether a PP analysis will be performed will be made prior to study unblinding (release of randomization codes).

4.2 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the MITT and PP (if criteria met) population.

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 variables. These variables include age, sex, race and ethnicity and will be presented for the Overall MITT population (Table 14.1.3.1) and, if applicable, on PP population (Table 14.1.3.2).

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

4.2.2 General Medical History

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

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

The study product kit allocations will be listed (Listing 16.1.6.1), including kit number and study product information.

Randomization details will be listed, including the randomization number, the planned randomized study product sequence, the actual study product sequence subject received and the randomization date (Listing 16.1.7.1).

4.3.1 Study Product Compliance and Exposure

As each treatment is a single product use (brushing occasion) under direct supervision at study site, no summary of study product compliance will be done.

However the number and percentage of subjects with supervised brushing performed will be provided for all four product groups for all randomized subjects (Table 14.1.4).

Subjects will take home a washout toothpaste (Colgate Cavity Protection) and manual toothbrush (Colgate Extra Clean) to use during the washout period (between Screening and period 1), and washout periods (between periods 1, 2, and 3). Subjects will be instructed to brush their teeth twice a day (morning and evening) in their usual manner.

The number of missed or additional uses of study washout product will be captured on case report form (CRF) at visit 2, 3 and 4.

The washout product compliance will be listed (Listing 16.2.5.1) for all randomized subjects. This listing will display information of date and time of last brushing, number of missed product uses since the last visit and the number of additional product uses since the last visit.

4.3.2 Prior and Concomitant Medication

Prior or concomitant medication taken by or administered to a subject will be recorded in the CRF. Medication/treatments taken within 30 days of signing the informed consent form will be documented as a prior medication/treatment. Medications/treatments taken after signing the informed consent form will be documented as concomitant medication/treatments.

The prior and concomitant medications will be coded using an internal validated medication dictionary, GSKDrug. Prior medications will be listed by subject, with drug name, GSK drug synonym, reason, route, dose, frequency, start date and end date, for all screened subjects (Listing 16.2.5.2). Prior medications are defined as those which stopped before the date of informed consent.

Concomitant medications and concomitant non-drug treatments will be listed similarly for all randomized subjects (Listing 16.2.5.3) and for non-randomized subjects (Listing 16.2.5.4) with either ongoing or end date displayed. Concomitant medications are defined as medications that are ongoing or started on or after the date of informed consent.

Unknown dates will not be imputed, however if the start or stop date is unknown, or incomplete, and the medication cannot be considered as stopped prior to signing informed consent, then it will be assumed to be concomitant medication (unless the partial start date or stop date indicates differently).

Ongoing medications at the time of signing the ICF will be assigned to the Training period (Screening). Medications starting on or after the date of informed consent until the date of first randomized study product use will also be assigned to the Training period (Screening).

Concomitant medication starting after the date of first randomized study product use will be assigned to the product used at the time of medication. Medications starting between periods will be assigned to the product used in the previous period. Medications with a date after last product or the end of the study will be assigned to the product used in the last period.

4.4 Analysis of Efficacy

The MITT population will be considered as primary population for primary and secondary analysis.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

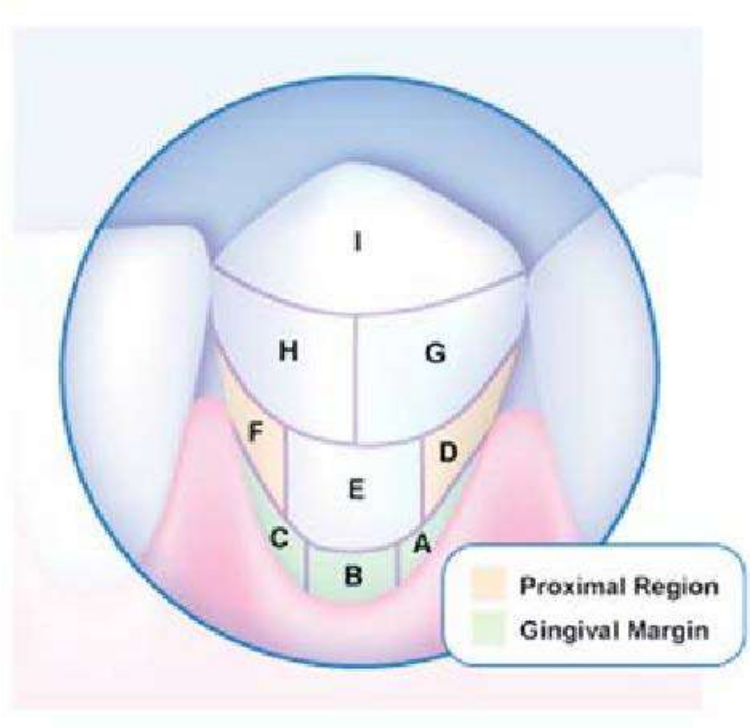
The primary efficacy variable is the change from pre-brushing to post-brushing in whole mouth RMNPI score (A-I sites) for all teeth, excluding third molars, crowns and surfaces with cervical restorations, for a maximum of 28 eligible teeth.

The change from pre-brushing is derived at each individual site for each tooth first (all tooth sites A-I, Figure 4-1). Then the whole mouth RMNPI score for each subject is derived as the average change across the available tooth site change from pre-brushing scores in the whole mouth.

The change from pre-brushing for ‘Gumline’ mode is defined as the post-brushing plaque score after the ‘Gumline’ mode usage minus the pre-brushing plaque score.

Each tooth section is scored with 0 (no dental plaque) or 1 (dental plaque) and an average of all measured sites calculated.

Figure 4-1 Rustogi modified Navy Dental Plaque Index.



4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

Descriptive statistics (n, number of missing observations, mean, SD, standard errors [SE], median, minimum, and maximum values) of the pre-brushing, post-brushing and change from pre-brushing whole mouth RMNPI scores will be provided for all four product groups (Table 14.2.2.1.1) for all subjects in MITT population.

The primary comparison is between the prototype PTB when used in the 'Gumline' mode versus the reference MTB after a single brushing event.

The null hypothesis for the primary endpoint is that the whole mouth RMNPI score for 'Gumline' mode is equal between the two product groups.

H_0: $\mu_1 = \mu_2$

The alternative hypothesis for the primary endpoint is that the whole mouth RMNPI score for 'Gumline' mode is not equal between the two product groups.

H_0: $\mu_1 \neq \mu_2$

The change from pre-brushing in whole mouth RMNPI score (Table 14.2.2.1.2) will be analyzed using analysis of covariance (ANCOVA) with product group, sequence as fixed effects, subject as a random effect, and two baseline terms as covariates; (i) the subject-level baseline score calculated as the mean pre-brushing score across all periods within a subject, and (ii) the period level baseline minus the subject-level baseline.

The adjusted mean change from pre-brushing, SE, 95% confidence interval (CI), and p-value for the prototype PTB 'Gumline' and reference MTB product groups will be presented. The adjusted mean difference between the two groups along with, SE, and 95% CI for difference from reference MTB, and p-value will be presented. All statistical tests of hypothesis will be two-sided and will employ a level of significance of $\alpha = 0.05$.

The assumptions underlying ANCOVA analysis will be checked and in case of any deviation from them, an appropriate transformation to the data will be performed to facilitate the above method of analysis. In the absence of an appropriate data transformation, non-parametric analyses will be performed (Wilcoxon matched pairs Signed Rank test).

The listing of RMNPI measurements (whole mouth score, marginal score, and proximal score) by subject will be presented for all randomized subjects (Listing 16.2.6.1). This listing will include subject number, study period, date and start time of RMNPI assessment, pre-brushing values, post-brushing values, and change from pre-brushing to post-brushing.

All RMNPI index data collected in the CRF will be listed in Listing 16.2.6.2.

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 (Table 14.2.2.2.1) and the same ANCOVA model defined for primary analysis will be applied on PP population (Table 14.2.2.2.2).

4.4.2 Secondary Efficacy Variables

See section 4.5.1.

4.4.3 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.

4.5 Analysis of Secondary Objectives

All secondary analyses will be conducted only on MITT population.

4.5.1 Efficacy (Secondary)

The secondary efficacy variables are:

- Change from pre-brushing in RMNPI whole mouth score (Sites A to I)
- Change from pre-brushing in RMNPI gingival margin (Sites A to C)
- Change from pre-brushing in RMNPI proximal (Sites D and F)

The comparisons of interest are:

- Prototype PTB 'Gumline' vs reference MTB (excluding the primary comparison)
- Prototype PTB 'Combined' vs reference MTB
- Prototype PTB 'Combined' vs Prototype PTB 'Gumline'
- Prototype PTB 'Gumline' vs reference PTB
- Prototype PTB 'Combined' vs reference PTB

Where 'Combined' is the RMNPI (plaque assessment result) of the 'Gumline' mode brushing and the 'Interdental' mode brushing. The change from pre-brushing for 'Combined' mode is defined as the post-brushing plaque score after the 'Interdental' mode minus the pre-brushing plaque score.

Descriptive statistics (n, number of missing observations, mean, SD, standard errors [SE], median, minimum and maximum values) of the pre-brushing, post-brushing and change from pre-brushing marginal (Table 14.2.3.1) and proximal (Table 14.2.4.1) RMNPI scores will be provided for all four product groups for all subjects in MITT population.

No alpha – type I error adjustments will be made for multiple secondary endpoints due to the exploratory nature of the inferences. All statistical tests of hypothesis will use the same model detailed for primary efficacy analysis and will be two-sided with 0.05 level of significance. Table 4-1 provides details of the statistical analysis tables to be presented for the different product comparisons.

Table 4-1 Details of the statistical analysis

Table	Statistical Analysis	Comparisons
Table 14.2.2.1.2	Statistical Analysis of Change from Pre-brushing in Whole Mouth RMNPI Scores	Prototype PTB 'Combined' vs Reference MTB Prototype PTB 'Combined' vs a Prototype PTB Gumline' Prototype PTB 'Gumline' vs a Reference PTB Prototype PTB 'Combined' vs a Reference PTB
Table 14.2.3.2	Statistical Analysis of Change from Pre-brushing in Marginal RMNPI Score	Prototype PTB 'Gumline' vs Reference MTB Prototype PTB 'Combined' vs Reference MTB Prototype PTB 'Combined' vs a Prototype PTB Gumline' Prototype PTB 'Gumline' vs a Reference PTB Prototype PTB 'Combined' vs a Reference PTB

Table	Statistical Analysis	Comparisons
Table 14.2.4.2.	Statistical Analysis of Change from Pre-brushing in Proximal RMNPI Score	Prototype PTB 'Gumline' vs Reference MTB Prototype PTB 'Combined' vs Reference MTB Prototype PTB 'Combined' vs a Prototype PTB Gumline' Prototype PTB 'Gumline' vs a Reference PTB Prototype PTB 'Combined' vs a Reference PTB

4.5.2 Pharmacokinetic (Secondary)

Not applicable for this study.

4.6 Analysis of Safety

All safety data will be reported for the Safety population or for all randomized subjects as per actual product used, based on the study period (training or treatment period) presented. The safety profile of the study products will be assessed with respect to AEs, OST, OHT 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). The AE classified as Oral and Non-Oral will be captured on AE page of CRF.

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

In this crossover trial, events will be assigned to product group based on the product being received at the onset of the event. TEAEs with an onset date time between products periods will be assigned the product received in the previous period. TEAEs with an onset after last product or at the end of study will be assigned to the product used in the last period. If an emergent AE continues to another product period, the AE will be considered emergent in the period in which it was started.

Training adverse events are defined as non-treatment emergent AEs with an onset date/time during the Training period. This will be carried out on the Safety population so that it includes non-randomized as well as randomized subjects.

The following summary tables and listings will be presented by study product, for all randomized subjects, unless otherwise specified.

- Table of treatment-emergent AEs by SOC and PT (Table 14.3.1.1.1). Summary of the number and percentage of subjects with at least one AE, total number of AEs, number and percentage of AEs within each SOC and PT will be displayed.
- Table of treatment-emergent AEs by Oral/Non-Oral and PT (Table 14.3.1.1.2)
- Table of Training AEs by SOC and PT for all subjects combined (Overall) (Table 14.3.1.1.3) (Safety Population). Only presented if the number of AEs classified as Training AEs is greater than 10.
- Table of treatment-emergent treatment-related AEs by SOC and PT (Table 14.3.1.2.1)
- Table of treatment-emergent treatment-related AEs by Oral/Non-Oral and PT (Table 14.3.1.2.2)
- Listing of all treatment-emergent AEs (Listing 16.2.7.1)
- Listing of Training AEs (Listing 16.2.7.2) (Safety Population)
- Listing of deaths (Listing 14.3.2.1)
- Listing of non-fatal SAEs (Listing 14.3.2.2)
- Listing of treatment-emergent AEs leading to study or product discontinuation (Listing 14.3.2.3)
- Listing of treatment-emergent AEs classified as oral (Listing 14.3.2.4)

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

4.6.2 Other Safety Variables

OST and OHT Examination

OST examinations will be performed at Screening and before and after toothbrushing in each of the three study periods.

OST will be summarized (number of subjects and percentages) for each of the four study products by shift table (Table 14.3.4.1) comparing normal/abnormal results of pre-brushing to post-brushing for all randomized subjects. A listing focused on subjects with OST abnormalities during the prototype PTB mode will be presented (Listing 14.3.4.2) for all randomized subjects. Also, a listing focused on subjects with OST abnormalities during the Training period will be presented (Listing 14.3.4.3) for the Safety population.

Listing 16.2.9.1.1 of all OST examinations during the treatment period will be provided for all randomized subjects. In addition, a listing of all OST examinations during the Training period will be provided for the Safety population (Listing 16.2.9.1.2).

The results of OHT examinations captured in the study will be listed (Listing 16.2.9.2).

Incidents

Medical devices are being provided by GSK CH for use in this study; the medical devices in this study are the prototype PTB and the reference PTB, and reference manual toothbrush, washout toothbrush and disclosing solution.

A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.

All incidents during the treatment period will be listed in Listing 16.2.9.3.1 for all randomized subjects. In addition, all incidents during the Training period will be listed in Listing 16.2.9.3.2 for the Safety population.

4.7 Analysis of Other Variables

Exploratory variables are:

- Change from pre-brushing in RMNPI whole mouth score (Sites A to I)
- Change from pre-brushing in RMNPI gingival margin (Sites A to C)
- Change from pre-brushing in RMNPI proximal (Sites D and F)
- Repeatability dental plaque score
- Sensorial experience questionnaire

The comparison of interest for the RMNPI assessment is:

- Reference PTB vs MTB (whole mouth, gingival and proximal)

Change from pre-brushing in RMNPI score

The change from pre-brushing in whole mouth, marginal and proximal RMNPI score between the reference PTB and the reference MTB will be analyzed using the same model detailed for primary efficacy analysis (Table 14.2.2.1.2, Table 14.2.3.2 and Table 14.2.4.2, respectively).

Repeatability dental plaque score

Repeatability data will be generated for RMNPI from replicate examinations. Depending on subject visit scheduling, every effort will be made to complete two repeatability examinations during each clinical day, one pre-brushing and one post-brushing. Repeatability examinations will be separated by a minimum of 10 minutes and, where possible, separated by another subject.

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

The first and repeat plaque assessments on each tooth site will be cross tabulated (Table 14.2.5) and a weighted Kappa coefficient (κ) using Fleiss-Cohen method of weighting will be presented, along with the 95% CI to assess the intra-examiner reliability. The weighted kappa coefficient on 2 levels is actually the same as a simple kappa coefficient in this specific case.

The data will be deemed to represent excellent replication if the Kappa coefficient per index is greater than 0.75, as fair to good replication if the value is between 0.4 and 0.75, and as poor replication if the value is below 0.4.

The analyses will be conducted on the Repeatability population.

Sensorial experience questionnaire

For the sensorial experience questionnaire, frequency count (n) and percentages (%) will be provided for each question by product group (Table 14.2.6).

The results of sensorial experience questionnaire will also be listed (Listing 16.2.9.4).

5 Changes to the Protocol Defined Statistical Analysis Plan

The 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	Report and Analysis Plan	
Statistical Analysis Section	**Statistical Analysis Plan**	**Rationale for the changes**
• **Section12.2.5 Primary Analysis** Any potential carryover effects will also be investigated.	• **Section 4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis**	The protocol suggested testing for carryover effects, however it was decided this was not required as the study design and washout period should adequately eliminate any carryover effects.

Attachment 1: List of Data Displays

208112 (CCI)
List of TFLs Final v2.0

Syneos Health	Sponsor Approval Form: Final Statistical Analysis Plan Text and/or Shells

Project Identifiers	
Sponsor: GSK CH	Protocol No.: 208112
Project ID Code: CCI [redacted]	Protocol Version (date): 4.0 (28-March-2019)
Statistical Analysis Plan (SAP) Text Version\Date: Final 2.0 (12-Jul-2019)	
SAP Shells Version\Date: Final 2.0 (12-Jul-2019)	
SAP Author: CCI [redacted]	

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

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

APPROVALS		
Syneos Health Approval		
PPD Principal Biotatistician Name, Title Lead Biostatistician	PPD Signature	PPD Date (DD-Mmm-YYYY)
GSK CH Approval		
PPD Manager Biostatistics Name, Title Sponsor Contact	PPD Signature	PPD Date (DD-Mmm-YYYY)