

Clinical Protocol

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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

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CLINICAL PROTOCOL

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

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Amendment 2	3.0	<ul style="list-style-type: none">• To change reference MTB Oral-B Indicator 1-2-3 toothbrush (SOFT) to Oral-B Indicator 1-2-3 toothbrush (MEDIUM)
Amendment 3	4.0	<ul style="list-style-type: none">• To include all updates as outlined in Protocol Change Letter 1 from Clinical Protocol Amendment 2• To clarify reference PTB demonstration during training visit (Visit 1)

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.



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1 PROTOCOL SUMMARY

Background and Rationale

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. *In vitro* testing conducted by GlaxoSmithKline Consumer Healthcare (GSKCH) has demonstrated statistically significant superior cleaning of the prototype PTB in comparison to commercially available PTBs (CCI 2016). However, there are aspects of its performance that cannot be addressed by *in vitro* testing such as differences in subjects' dental anatomy and user's manual dexterity and therefore a clinical study is considered necessary.

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.

Objectives and Endpoints

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	Change from pre-brushing to post-brushing RMNPI whole mouth score (sites A to I)

versus the 'Gumline' mode as measured by the RMNPI.	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.

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.

Study Products

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

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.

Type and Planned Number of Subjects

Approximately 40 subjects will be screened to randomize approximately 35 to ensure 30 evaluable subjects complete the entire study.

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

Statistical Analysis

The primary comparison will be between the prototype PTB when used in the ‘Gumline’ mode versus the reference MTB after a single brushing event. The change from pre-brushing in whole mouth plaque score will be analyzed using analysis of covariance (ANCOVA) with treatment, sequence (fixed effects), subject (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.

All other pairwise comparisons will be investigated under secondary comparisons. All secondary RMNPI variables will be derived in a similar manner based on relevant tooth sites and analyzed as per the primary variable.

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.

Schedule of Activities

The schedule of activities table provides an overview of the subject visits and study procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1-1 Schedule of Activities

Procedure / Assessment	Screening	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						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 as described in [Supervised Power Toothbrush Training](#) section.
 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.

2 INTRODUCTION

Dental plaque is a diverse and organized community of micro-organisms on the tooth surface. They form a biofilm embedded in a matrix of polymers of host and bacterial origin (Marsh, 2006, Marsh 2004, Socransky and Haffajee 2002). Dental plaque forms via an ordered sequence of events that result in a structurally and functionally organized microbial biofilm (Marsh 2004, Marsh 2006). This process starts just minutes after toothbrushing with the formation of a saliva pellicle on the tooth surface. If dental plaque is left undisturbed, the biofilm can continue developing into a more pathogenic composition which could lead to periodontal disease. Bacteria that form biofilms in dental plaque are in general less susceptible to antimicrobial agents (van Steenberg et al 1984), and therefore mechanical removal methods are essential for dental plaque removal.

Tooth brushing is the most effective method of dental plaque control. In particular, 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 (Yaacob et al 2014). Clinical investigations and dental surveys in manual toothbrush (MTB) users have shown that a large percentage of dental plaque is not removed from the tooth surfaces (Morris et al 2001, van der Weijden and Hioe 2005) when subjects brush at home (De la Rosa et al 1979) or when supervised (Van der Weijden et al 1998). Therefore, PTB is a technology that has the potential to enhance motivation and compliance to achieve higher levels of dental plaque removal (for example by the use of their built in timers and quad pacers) and consequently improve gingival condition (van der Weijden and Hioe 2005) (Delaurenti et al 2017). A Cochrane review, and its subsequent updates, concluded that PTBs remove dental plaque and reduce gingivitis significantly more than manual toothbrushes in the short term (< 3 months) and long term (>3 months) (Heanue et al 2003, Robinson et al 2005, Yaacob et al 2014).

2.1 Study Rationale

In vitro testing has demonstrated statistically significant superior cleaning of the prototype PTB in comparison to the premium commercially available PTBs (CCI 2016). The prototype PTB design offers better cleaning along the gum line and interdentally than the commercially available PTBs tested *in vitro*. However, there are aspects of its performance that cannot be addressed by *in vitro* testing such as differences in subjects' dental anatomy and user's manual dexterity, and therefore, a clinical study is considered necessary. Moreover, oral tolerance aspects of the prototype PTB can only be assessed in a clinical study. It is proposed to perform an exploratory single-use dental plaque removal clinical study to investigate and compare whole mouth plaque removal efficacy of the prototype PTB versus a reference MTB after a single brushing event. Although the primary focus of this study is assessment of dental plaque removal in 'Gumline' mode, the 'Interdental' mode will also be assessed. This will allow assessment of dental plaque when the prototype is used in both 'Gumline' and 'Interdental' mode together, referred to as 'Combined'. Both modes are potential modes to be recommended to consumers for the final commercialized product.

The total brushing time for the prototype PTB in 'Gumline' mode will be 2 minutes, in line with the directions for use of all high-end commercially available PTBs and dental expert recommended advice. The current version of the prototype PTB to be tested in this study is an early prototype and the features of a timer are not currently present and therefore the total

brushing time will be controlled with the use of an external timer. The reference PTB will be used as per label usage instructions.

Complete information for this power toothbrush may be found in the single reference safety document (SRSD), which for this study is the Safety Statement.

2.2 Background

The prototype PTB device to be tested in this clinical study has an innovative technology which is proposed to offer superior cleaning at a constant, low speed of rotation. It comprises an innovative brush head to be used with a re-chargeable battery powered handle. Like other high end commercially available PTBs, the prototype PTB has different cleaning modalities. The prototype PTB operates in two different cleaning modes ('Gumline' and 'Interdental'), which can both be combined resulting in what will be referred to in this protocol as the 'Combined' mode. The 'Gumline' mode is intended to be the users 'standard' mode of use for 2 minutes, whilst use of the 'Interdental' mode after the 'Gumline' mode may provide additional cleaning efficacy.

The dental plaque removal efficacy of PTBs has been investigated clinically in studies of various durations, including up to 12 months usage. The first clinical studies with a new toothbrush to assess its efficacy commonly use a single use dental plaque removal study design (Van der Weijden 2002) (Conforti et al 2003) (Klukowska et al 2012b) (Biesbrock et al 2007) (Williams et al 2008) (Sharma et al 2011). These studies measure the level of dental plaque, using various clinical indices, pre- and post a single brushing event. The most commonly used dental plaque indices are the Turesky Modification of the Quigley Hein (TQHPI) or Rustogi Modified Navy Dental plaque Index (RMNPI) (Van der Weijden 2002) (Conforti et al 2003) (Klukowska et al 2012b) (Biesbrock et al 2007) (Williams et al 2008) (Sharma et al 2011). The RMNPI has been chosen as the measure of dental plaque in this study; this method scores dental plaque in proximal tooth areas (referred to as proximal score) and at the gum line (referred to as the marginal score) as well as the total tooth (referred to as whole mouth score). This index scores a greater number of tooth surfaces in comparison with other commonly used indices such as the TQHPI and therefore is more sensitive to smaller changes in dental plaque (Cugini et al 2006). The RMNPI can show a differentiation in dental plaque removal in the approximal tooth regions also, as it has been successfully used as the dental plaque endpoint for the evaluation of mechanical 'Interdental' cleaning devices (Mwatha et al 2017). RMNPI has been widely used in PTB studies (Biesbrock et al 2007, Goyal et al 2009, Goyal et al 2012, Klukowska et al 2012a, Sharma et al 2011) for the assessment of dental plaque.

Numerous clinical studies have evaluated the effect of PTBs on oral soft tissue, and there is a large body of evidence consistently showing that oscillating-rotating toothbrushes are considered as safe as using a MTB. PTBs do not seem to pose a clinically relevant concern to hard or soft tissues (Van der Weijden et al 2011), and there is no apparent relationship between the use of PTBs and soft tissue trauma (Robinson et al 2005). Overall, the published clinical research studies show that PTBs are comparable to MTBs in oral soft tissue features such as reported oral Adverse Events (AE) and abrasion. There are transient features that could occur with both types of brushes but should not persist (Van der Weijden et al 2011). An earlier prototype of the PTB planned for use in this study has been used in a GSK CH internal human use sensory study, where one treatment emergent, treatment related oral AE was reported which was mild in intensity, (CCI, 2016). In the present clinical investigation, oral tolerability will be assessed based upon the reported incidence, severity,

and frequency of treatment-emergent oral AEs, Oral Soft Tissue (OST), and Oral Hard Tissue (OHT) abnormalities. Full OST examinations will be carried out pre- and post each brushing event and a final OHT exam will be conducted before each subject exits the study. Incidents will be collected throughout from provision of signed informed consent.

The primary objective of this study is to investigate the efficacy of a prototype PTB in removing dental plaque following a single brushing event compared to a manual toothbrush.

The main purpose of the prototype PTB being tested here is to remove significant dental plaque when used as part of a daily oral hygiene routine. When dental plaque is left unremoved, it leads to gum disease; in the short term to gingivitis, which if untreated, can lead to periodontitis and result in tooth loss. Therefore, toothbrushing is the most important routine for maintenance of good oral health. As summarized above, numerous clinical investigations have shown that PTBs remove more dental plaque than MTB, and lead to a larger reduction in gingivitis (Yaacob et al 2014). Clinical investigations have also shown that PTB do not seem to pose a clinically relevant concern to oral hard or soft tissues (Van der Weijden et al 2011). In this clinical investigation, to minimize the subject's risk of misusing the investigational device in this study, toothbrushing will be performed under the direct supervision of suitably trained study site personnel.

2.3 Mechanism of Action/Indication

The investigational device to be tested in this study is a prototype PTB, intended to be used in healthy subjects to assess its ability to remove dental plaque. The prototype PTB operates in two different cleaning modes, 'Gumline' and 'Interdental'. When these two modes are used subsequently to each other this is referred to as 'Combined' mode.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

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.

4 STUDY DESIGN

4.1 Overall 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. An overall schematic is shown in Figure 1.

Subjects will participate in this study following sequence of procedures and assessments described under STUDY PROCEDURES and STUDY ASSESSMENTS.

At the screening visit (Visit 1) subjects will give their written informed consent prior to any study procedures taking place. Female subjects of child bearing potential will be asked to carry out a urine pregnancy test before eligibility can be confirmed by a negative result. After a medical history and assessment of current medications, eligible subjects will undergo an oral soft tissue (OST) and oral hard tissue (OHT) examination. Eligible subjects will then undertake PTB training as described in [Supervised Power Toothbrush Training](#) to familiarize themselves with how the different modes and different PTBs to be used in this study operate. This will be

followed by an OST examination. Eligible subjects who successfully complete the PTB training will be provided with a fluoride washout toothpaste and toothbrush to use at home during the study. Diary cards will be dispensed to subjects and they will record each brushing occasion on the diary, and the time of their last brushing prior to their next scheduled appointment.

Subjects will return to their next scheduled appointment at Visit 2 after a minimum of 3 days having refrained from all oral hygiene for a minimum of 12 hours.

At Visit 2 and Visit 3, female subjects of child bearing potential will be asked to carry out further a urine pregnancy tests before continued eligibility can be confirmed by a negative result. All subjects will undergo an initial OST examination followed by plaque disclosing and a pre-brushing dental plaque assessment using the RMNPI index. Subjects meeting the entry criteria will be randomized (Visit 2 only) to the study treatment sequence with the prototype PTB and MTB used in a crossover manner in periods 1 and 2 (at Visit 2 or Visit 3). Subjects will receive the study treatment product corresponding to the randomization sequence. A trained study site member of staff will apply toothpaste to the brush head and demonstrate correct use of the assigned product (PTB or MTB) to the subject as per the provided Product Usage Instructions. Subjects will then brush (supervised) according to the brushing instructions provided by the trained member of staff followed by disclosing and post-brushing plaque assessments (RMNPI). For subjects assigned to the prototype PTB, it will be used for 2 minutes in ‘Gumline’ mode brushing, followed by an OST examination, plaque disclosing and post-brushing plaque assessments (RMNPI), and then a 1-minute brushing in ‘Interdental’ mode will be performed followed by further OST examination and plaque disclosing and post-brushing plaque assessments (RMNPI).

The reference PTB will always be used in the last period (i.e. period 3). Subjects will be randomized to receive both the prototype PTB and reference MTB in a pre-determined randomized order (AB/BA) design. 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 assessments (‘Gumline’ and ‘Interdental’ brushings) will occur in the same treatment period.

A minimum 3 days washout period will follow each treatment period during which subjects will brush with the standard washout toothpaste and toothbrush, and record in the diary card. Prior to each site Visit, subjects will abstain from all oral hygiene for at least 12 hours.

At Visit 4, female subjects of child bearing potential will be asked to carry out a final a urine pregnancy test before continued eligibility can be confirmed by a negative result. All subjects will undergo an OST examination followed by plaque disclosing and a pre-brushing dental plaque assessment using the RMNPI index as per Visits 2 and 3. Following these pre-brushing assessments all subjects will use the reference PTB as instructed by the member of site staff, followed by disclosing and post-brushing plaque assessments (RMNPI)

If the prototype PTB fails ([Interim Analysis](#)) prior to brushing, then the device will be replaced, and all subsequent assessments will be carried out as planned in the protocol. Device failure will be recorded in the corresponding page of the eCRF.

If the prototype PTB fails during brushing, then the subject will discontinue all brushing at that visit and no further efficacy data will be collected for that visit. The prototype PTB handle/head will not be replaced. Device failure will be recorded in the corresponding page of the eCRF

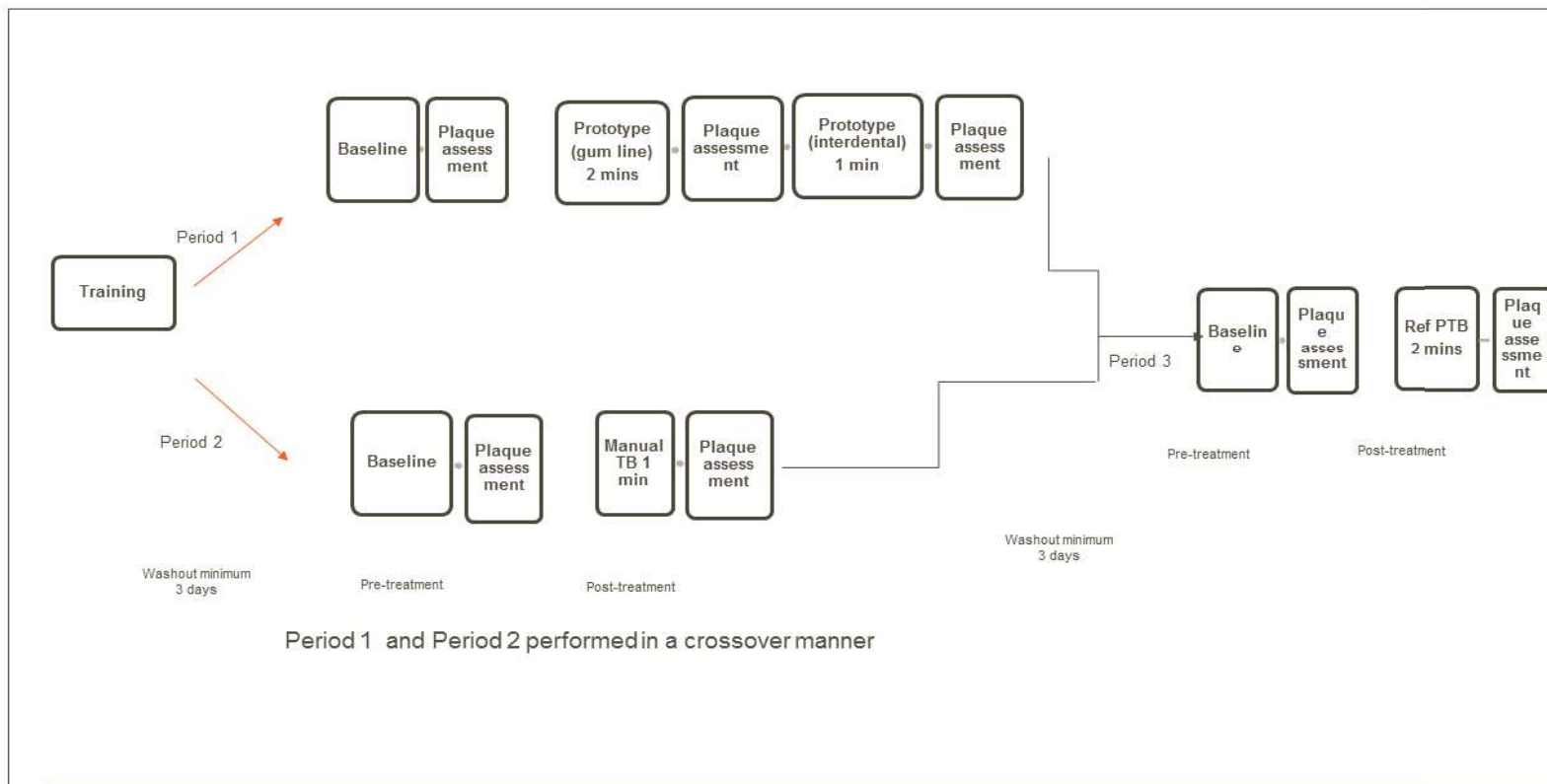
An OST examination will follow each brushing occasion at each visit. An OHT examination will be conducted at the first visit and at the last visit.

Subjects will complete a sensory questionnaire at the end of each brushing occasion at each visit after all clinical assessments.

At Visits 2, 3 and 4 repeatability data will be generated for plaque assessment from replicate examinations on the same subject as described in Repeatability dental plaque assessment. If deemed necessary by the examiner, plaque may be re-disclosed if the dye has faded.

Adverse events and incidents will be collected throughout the study.

Figure 1: Schematic of Overall Study Design



4.2 Rationale for Study Design

Clinical studies to initially assess a toothbrushes ability to clean adopt a commonly used single use dental plaque removal study design (Van der Weijden 2002) (Conforti et al 2003) (Klukowska et al 2012b) (Biesbrock et al 2007) (Williams et al 2008) (Sharma et al 2011). These studies measure the level of dental plaque, using various clinical indices, pre- and post a single brushing event against a MTB.

In this study, all toothbrushing at each treatment visit will be performed under the direct supervision of a suitably trained study site personnel. It will be performed in a different room to the clinical assessment. Sufficient training will be provided to the study site staff in advance for use of the prototype PTB.

The investigational PTB being tested in this study is an early prototype and therefore currently does not have all the features that would be expected of an optimised finished product. The reference PTB is a currently marketed high end PTB with built in timer, pressure sensor and many other features and therefore the user experience with the reference PTB could be inherently different. To minimise user bias, a partial cross-over design has been chosen to ensure that the prototype PTB is always used prior to the marketed reference PTB whilst still maintaining the primary objective of the study. The advantage of the crossover design will allow each subject to serve as his or her own control and therefore significantly reduces between-subject variability, allowing the detection of smaller effect sizes with reduced sample sizes.

A washout period will be utilised between screening and the first treatment to standardise 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.

When assigned to the prototype PTB treatment arm, all subjects will use the prototype PTB in ‘Gumline’ mode for 2 minutes after which plaque assessments will be performed. Subjects will then brush for a further 1 minute in ‘Interdental’ mode after which further plaque assessments will be performed. This will allow within-subject control of brushing using the prototype PTB and allow assessment of the prototype PTB in ‘Gumline’ mode and also after the combined ‘Gumline’ and ‘Interdental’ mode usage. There will be no washout between these two treatments.

The prototype PTB is still at prototype stage and has not previously been tested in subjects who are left handed, therefore to mitigate against any potential unknown differences between subjects who are left and right handed, only subjects who brush with their right hand will be included.

The effects of smoking on periodontal health are well documented in the scientific literature. Smoking decreases blood flow within the gingival microvasculature and interferes with neutrophil function, suppressing the inflammatory response to dental plaque and masking the clinical signs of periodontal disease (Machuca, 2000; Obeid, 2000; Kinane 2001). Smokers and tobacco users will therefore be excluded from this clinical study.

A reference MTB has been selected to allow comparisons of dental plaque scores of the prototype PTB against those of a MTB. The majority of brushing clinical studies use the American Dental Association (ADA) reference brush, however this is now being discontinued. The reference MTB chosen for use in this study is close in design to the ADA reference brush.

The reference PTB has been chosen as it uses the same/similar power output for number of oscillations and pulses or strokes per min as the prototype PTB. In this study the reference PTB will be used in 'Daily Clean' mode.

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). 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 analysis.

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.

4.3 Justification for Dose

Dental professionals recommend a toothbrushing routine of 2 minutes twice a day, which is in line with the product usage instructions of all high-end commercially available PTB that include a 2-minute timer and 30 second quadpacers. Therefore, the prototype PTB when used in 'Gumline' mode and the reference PTB will be used for a total of 2 minutes. The use of the prototype PTB will be timed using an external timer as this feature is currently unavailable in the prototype. The reference PTB will be used as per label instructions with its in-built timer.

After the plaque assessments for the prototype PTB have been completed after 'Gumline' mode usage, the prototype PTB will be used by subjects for a further 1 minute in 'Interdental' mode. Additional plaque disclosure and further plaque assessments will be performed after use in 'Interdental' mode. The 1-minute use in 'Interdental' mode has been chosen based on the ratio of 'Gumline' to 'Interdental' brushing used in the *in-vitro* testing.

This study will compare the standard consumer usage of a PTB versus a standard consumer usage of a MTB. Based on numerous clinical investigations, the estimated at home brushing time with a MTB is of approximately 60 seconds or less (Van der Weijden et al 1993, Van der Weijden et al 1998) (Emling et al 1981, van der Weijden and Hioe 2005) (Emling et al 1981, van der Weijden and Hioe 2005) (Macgregor et al 1986) (Rugg-Gunn and Macgregor 1978) (Rugg-Gunn et al 1979). Therefore in clinical investigations, MTBs are used per the subject customary manner without a specific time (Conforti et al 2003, Klukowska et al 2012b, Sharma et al 2011) (Klukowska et al 2014) (Sharma et al 2012) or for 1-timed minute (Conforti et al 2003). In this study, a 1-minute brushing time for the MTB will be used as this closely represents the average duration of the consumer brushing time with a MTB.

In all treatment arms, subjects will brush their teeth under supervision with a fluoride toothpaste. The weight of toothpaste to be used in this study will be controlled across treatment arms. A weight of 1.3g (+/-0.1g) will be applied to the toothbrush head. This amount has been chosen

based on work conducted internally as the average amount that is dispensed by individuals on the prototype PTB and reference PTB heads.

4.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

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

The end of this study is defined as the date of the last subjects last visit day.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Approximately 40 subjects will be screened to randomize approximately 35 to ensure 30 evaluable subjects complete the entire study.

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this protocol.

Subject eligibility to participate in the clinical study should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

5.2 Inclusion Criteria

An individual must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is male or female who, at the time of screening, is between the ages of 18 and 65 years, inclusive.
3. A subject who is willing and able to comply with scheduled visits, treatment plan, and other study procedures.
4. A subject that successfully completes the investigational device training visit, understands and is willing to follow product usage instructions, in the opinion of the investigator or designee.
5. A subject in good general and mental health, in the opinion of the investigator or medically qualified designee; no clinically significant and relevant abnormalities in medical history or upon oral examination.

6. A subject with good dental health based on medical history and oral soft tissue examination at screening.
7. A subject with a minimum of 20 permanent gradable teeth (gradable teeth are those where restorative materials cover less than 25% of the tooth surface graded).
8. For continued eligibility after the Screening visit, a subject must have a mean RMNPI whole mouth plaque score of ≥ 0.6 at Visit 2, 3 and 4.
9. A subject that regularly uses a manual toothbrush in their daily oral hygiene routine.
10. A subject that regularly brushes their teeth with their right hand.

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will not be eligible for enrollment into the study:

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSK CH employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.
3. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
4. A subject who is a pregnant female (evidenced by positive urine pregnancy test).
5. A subject who is a breastfeeding female.
6. A male subject able to father children or female subject of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for 5 days after the last assigned treatment.
7. A female subject who is of childbearing potential must meet requirements in Section 5.5.3.
8. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
9. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.
10. A subject unwilling or unable to comply with the [Lifestyle Considerations](#) described in this protocol.
11. A subject who has received a dental prophylaxis within 4 weeks of Screening visit.
12. A subject who has received teeth bleaching/whitening (including professional or at home use) within 8 weeks prior to Screening visit.
13. A subject who is receiving or has received treatment for periodontal disease (including surgery) within 12 months of Screening.

14. A subject who has received orthodontic therapy or scaling or root planing within 3 months of Screening.
15. A subject with high levels of extrinsic stain or calculus deposits which might interfere with dental plaque assessments
16. A subject that has current active caries, excessive gingival recession, severe gingivitis or periodontitis that may, in the opinion of the investigator, compromise the study or the oral health of the subject if they participate in the study.
17. A subject with the presence of oral or peri-oral ulceration including herpetic lesions at the time of screening.
18. A subject who is at risk of spasms.
19. A subject with restorations in a poor state of repair that may, in the opinion of the investigator, compromise the study or the oral health of the subject if they participate in the study.
20. A subject with the presence of orthodontic bands or appliances, extensive crowns, partial or full dentures, or fixed retainers on the maxillary or mandibular teeth.
21. A subject with a tongue or lip piercing, or any other oral feature that could interfere with the usage of the toothbrush.
22. A subject who has used antibiotic treatment within 14 days prior to Screening visit.
23. A subject with diagnosed xerostomia or taking any medication that in view of the investigator causes xerostomia.
24. A subject with any electronic medical devices (such as pacemakers).
25. A subject that has used a chlorhexidine mouthwash within 14 days of Screening visit or used any oral care product that under the criteria of the principal investigator could interfere with dental plaque formation.
26. A subject unwilling to abstain from using other oral care products besides those assigned to them in the study.
27. A subject with a recent history (within past year) of alcohol or other substance abuse.
28. A subject that smokes or uses chew tobacco, or regularly smokes E-cigarettes.
29. A subject who has previously been enrolled in this study.

5.4 Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

5.5 Lifestyle Considerations

During the entire study:

- Subjects will be requested not to have any elective dental procedures including teeth professionally cleaned, excluding emergency dental treatment.
- Subjects will be requested not to have whitening treatment (including professional or at home use) during the duration of the study.

- Subjects will not be permitted to use any other oral care products (i.e. oral rinses, tongue cleaners, whitening, bleaching products) besides the products supplied for this study.
- Eligible subjects will be asked to stop using their regular dentifrice and toothbrush from the Screening visit for the duration of the study.
- Subjects should abstain from interproximal cleaning (i.e. dental floss, oral irrigators, interdental brushes) for the duration of the study. Subjects will be permitted to use toothpicks or floss to remove impacted food only.

Prior to Visit 2, 3 and 4:

- Subjects should abstain from all oral hygiene procedures for at least 12 hours prior to the scheduled time of their Visit 2, 3 and 4 appointments.

5.5.1 Meals and Dietary Restrictions

- On study visit days (Visits 2, 3 and 4) subjects must abstain from all food and drink (except water) at least 4 hours prior to their scheduled visits until all measurements have been taken. Water is permitted until 1 hour prior to investigational product administration.
- Subjects must abstain from chewing gum and consuming confectionary containing xylitol (e.g. mints) at least 4 hours prior to their scheduled visit.

5.5.2 Alcohol, Caffeine and Tobacco

- On study visit days (Visits 2, 3 and 4) subjects must abstain from all alcohol until all measurements have been taken.
- Subjects will abstain from caffeine-containing products for at least 4 hours prior to their scheduled Visit 2, 3 and 4 until all measurements have been taken.
- Subject will abstain from smoking, chewing tobacco, or smoking E-cigarettes throughout the study.

5.5.3 Contraception

All male subjects able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active study period and for 5 days after the last assigned treatment.

The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

The following is the all-inclusive list of the highly effective methods for avoiding pregnancy that meets the GSK definition (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label).

The list does not apply to females of reproductive potential with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from site personnel review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until (at least five half-lives of study medication OR for a cycle of spermatogenesis following five terminal half-lives) after the last dose of study medication.

1. Vasectomy with documentation of azoospermia. The documentation on male sterility can come from site personnel: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.
2. Male condom plus partner use of one of the contraceptive options below that meets the effectiveness criteria including a <1% rate of failure per year, as stated in the product label:
 - Contraceptive subdermal implant
 - Intrauterine device or intrauterine system
 - Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
 - Injectable progestogen [Hatcher, 2011]
 - Contraceptive vaginal ring [Hatcher, 2011]
 - Percutaneous contraceptive patches [Hatcher, 2011]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography, screen failure details (e.g. withdrawal of consent), eligibility criteria, and any AEs or incidents as applicable.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

5.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical/dental personnel for the study is documented in the Study Contact List located in the investigator study master file held at the study site.

The contact number is only to be used by investigational staff seeking advice on medical/ dental questions or problems in the event that the established communication pathways between the investigational site and the study team are not available.

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects will be provided with a contact card. The contact card will provide, as a minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Rater/Clinical Assessor Qualifications

The same clinical assessor will be used for all safety and efficacy assessments throughout the duration of the study. The clinical assessor will be a qualified dentist that has been trained and calibrated in the RMNPI.

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and GSK policy, investigational product is defined as a pharmaceutical form of an active ingredient, a non-medicinal product (marketed or investigational), or a placebo, being tested or used as a reference (positive or negative control), in a clinical trial. This includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

6.1 Investigational/Study Product Supplies

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

Table 6-1 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 = CCI Handle = CCI	Commercially available in the UK market.	Commercially available in the Canadian market.
Dose	Single use		
Route of Administration	Oral Topical use		
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.

Table 6-2 Sundry Items

Item	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
Colgate Extra Clean manual toothbrush (Soft bristles) Washout brush	GSK CH	Commercial pack – Canadian marketplace	One toothbrush to be dispensed to each subject at the Screening visit, and re-dispensed if required throughout the study.	Return to GSK CH vendor for disposal	Return
Colgate Cavity Protection Toothpaste containing 0.76% w/w sodium monofluorophosphate (1000ppm fluoride) – washout phases and on-site use (NPN number 00327360)	GSK CH	Commercial pack – Canadian Marketplace	One tube to be dispensed to each subject at the Screening visit, and re-dispensed if required throughout the study.	Return to GSK CH vendor for disposal	Return
Urine pregnancy testing kits	GSK CH	Commercial pack – Canadian Marketplace	1 test to be used by each female subject of child bearing potential at every visit.	Destroy at site using site disposal procedures	Return
Countdown timer	GSK CH	Commercial pack	N/A	Subjects to retain or to be destroyed at site using site disposal procedures	Return
Dosing Cups	GSK CH	Commercial pack	N/A	Destroy at site using site disposal procedures	N/A
Trace Dental plaque (Young Dental) disclosing solution	Site	Commercial pack	As per product label instructions.	Destroy at site using site disposal procedures	Return
Power toothbrush chargers (for the prototype PTB and the Reference PTB)	GSK CH	Commercial pack	N/A	Return to GSK CH, or GSK CH vendor for disposal	Return

Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction which will be provided by GSK CH during the course of the study in time for the study close out visit.

6.1.1 Dosage Form and Packaging

Prototype PTB handles, prototype PTB heads, reference MTBs and reference PTBs will be supplied by GSK CH to the site in individual containers. Each subject will receive an individual PTB handle (prototype and reference) to be used at the screening and treatment visits, which will be clearly labelled with the subject screening number and appropriately stored by the study site personnel as described in Investigational/Study Product Storage. Each subject will receive a sufficient number of prototype PTB heads to cover usage during the training and treatment phase of the study.

The study prototype PTB, reference MTB and reference PTB will be supplied in labelled packaging.

The standard toothpaste to be used during the washout phase, and with all treatment arms (Colgate Cavity Protection) will be sourced from the Canadian marketplace and supplied in its commercial tube (with no overwrapping) with a study label affixed. Each subject will receive a sufficient number of tubes to cover usage during the washout phases.

The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the GSK CH Global Clinical Supplies group. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. Subjects should be instructed to not remove or deface any part of the study label.

All products supplied are for use only in this clinical study and should not be used for any other purpose.

6.1.2 Preparation and Dispensing

All PTBs will be fully charged by study site personnel according to the PTB Charging Instructions prior to use. The prototype PTB, reference MTB and reference PTB, will be prepared, applied with the standard toothpaste and dispensed for subject use at the clinical site by qualified unblinded dispensing study site personnel according to the Product Usage Instructions. Subjects will be instructed on the correct usage instructions for each treatment arm as per the product Instructions for use.

Each of the study products will be dispensed for use by subjects at the clinical site only by qualified unblinded site personnel per the dosage/administration instructions. These staff members will not be involved in any safety, efficacy assessments, or other aspects of the study that could be influenced by the knowledge of product a subject has been assigned to use. An additional site member of site staff should ensure the dispensing and administration procedures are completed accurately.

Subjects will be assigned to treatment arms in accordance with the randomization schedule generated by an approved GSK CH vendor, prior to the start of the study, using validated software.

Subjects will be dispensed the washout toothbrush (Colgate Extra Clean manual toothbrush) and study toothpaste (Colgate Cavity Protection) to be used at home during the washout period between visits to maintain their regular oral hygiene for the duration of the study.

6.2 Administration

To ensure consistency in product usage instructions, a single suitably trained member of study site staff will provide instructions to each subject. The instructions will be specific according to the Instructions for Use for the treatment arm that the subject is to use at that treatment visit.

During the screening visit, each eligible subject will be dispensed with an individual prototype PTB and a reference PTB with corresponding toothbrush heads to be used during the training exercise. Each handle should be clearly labelled with the subject screening number.

Following the screening assessments, each eligible subject will undergo a PTB training exercise, where he or she will be instructed in a single use of each of the PTBs to familiarize themselves with the operation of the different types of brush. Study site staff will apply toothpaste to the brush head prior to each use and instruct the subject in the correct usage according to the provided directions for each specific type of brush.

Following the PTB training exercise, each brush handle will be clearly labelled with the subject screening number and appropriately stored by the study site personnel as described in Investigational/Study Product Storage.

At Visits 2, 3 and 4 and following the pre-brushing assessments, subjects will receive their allocated product as per the randomization schedule. A trained member of site staff will apply toothpaste to the brush head (weighed) and instruct subjects to brush according to the respective usage instructions. The trained member of staff will supervise the subjects and time the use of the prototype PTB and MTB treatment arms using the external timer and the reference PTB using the internal brush timer.

Following the training and treatment period visit, suitably trained study site personnel will store each of the PTB handles in a resealable storage bag clearly labelled with the subject screening number. The PTB heads used during the training period do not need to be retained as each subject will be supplied with a new brush head according to the randomization schedule to use for the treatment period.

Subjects will take home a washout toothpaste (Colgate Cavity Protection) and manual toothbrush (Colgate Extra Clean) to use during the washout period (between Visits 1 and 2), and washout periods (between Visits 2, 3 and 4). Subjects will be instructed to brush their teeth twice a day (morning and evening) in their usual manner.

6.2.1 Dosing Errors

Dosing errors may result, in this study, from the administration or consumption of:

- the wrong product,
- the wrong brushing mode,
- by the wrong subject,

- at the wrong time,
- or at the wrong dosage.

Such dosing errors occurring to a study subject are to be captured in the CRF. In the event of a dosing error, the sponsor should be notified within 24 hours of the site becoming aware of the dosing error.

Dosing errors are reportable irrespective of the presence of an associated AE, including:

- Dosing errors involving subject exposure to any of the study products;
- Potential dosing errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

If a dosing error is accompanied by an AE or an Incident, as determined by the investigator, the dosing error and, any associated AEs are to be captured in the CRF AE form.

6.3 Investigational/Study Product Storage

The investigator, or designee, will ensure that all study products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and the product label and the Clinical supplies study checklist.

The prototype PTB must be stored and used in controlled conditions (15 °C -25°C).

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of first product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product-label storage conditions and the storage range stated in the Clinical supplies study checklist should be reported to appropriate site staff upon discovery and communicated to sponsor as soon as possible. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Excursions from the storage requirements, including any actions taken, must be documented as a protocol deviation and reported to the Sponsor.

Once an excursion is identified, the affected product (or products) must be quarantined and not used until the sponsor provides documentation of permission to use. Use of any of the affected product(s) prior to sponsor approval will be considered a protocol deviation.

Site staff will instruct subjects on the proper storage requirements for all take-home products.

6.4 Investigational/Study Product Accountability

All products supplied are for use only in this clinical study and should not be used for any other purpose.

All study products must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only the staff have access. Upon receipt, all study products should be stored according to the instructions specified on the product labels. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

The accountability records must be available for inspection by the study monitor during the study. Monitoring of product accountability will be performed by the monitor during site visits and at the completion of the study.

Subjects must return their wash out toothbrush and toothpaste which will then be sent to the designated GSK CH vendor for destruction.

6.4.1 Destruction of Investigational/Study Product Supplies

At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH (study monitor), will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study will be returned to the designated GSK CH vendor using the return instructions provided. All used product will be returned/destroyed as per the instructions provided, and all unused products will be returned to the designated GSK CH using the return instructions provided.

6.5 Blinding and Allocation/Randomization

All subjects will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided to each site. Study products will be dispensed according to the instruction received through the IRT at the appropriate study visits.

Returned study products should not be re-dispensed to any subject.

Due to the design of this study it is difficult to fully blind this study. Therefore, this study will be open-label.

Staff involved in the preparation and dispensing of study products and providing instructions for use will work in a separate area.

Dispensing staff will not be involved in any efficacy/safety assessment procedures during the study.

6.6 Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind (confirming the product used). The method will be an electronic process.

The electronic system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's product assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a subject's product assignment unless this could delay emergency treatment of the subject.

If a subject's product assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Any AE associated with breaking the blind must be recorded and reported as specified in this protocol. The study site may also be required to inform the IRB/EC if the blind is broken.

6.7 Subject Compliance

Study products will be administered under the supervision of investigator site personnel.

A diary will be supplied to subjects at the Screening Visit and completed throughout the study to promote compliance and adherence to protocol lifestyle restrictions and to capture details of product use throughout the study washout periods. Subjects may also record additional information such as AEs or medications used. Any additional details relevant to efficacy or safety should be reviewed by the investigator (or suitably qualified designee) with the subjects and transcribed to the CRF as appropriate.

The time of last brushing prior to subject's scheduled treatment visit should be recorded and transcribed into the CRF.

6.8 Concomitant Medication/Treatment(s)

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

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.

Subjects will abstain from all concomitant treatments, except for contraceptives and those used for the treatment of AEs.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, by the Sponsor based on the pre-defined stopping rules, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

The following circumstances require discontinuation of study product and/or premature subject withdrawal:

- Protocol violation that may impact the subject's safety
- Withdrawal of informed consent
- Subject lost to follow-up
- Unblinding of the subject
- Pregnancy
- Device failure

If a subject is discontinued or prematurely withdraws from the study, the reason(s) for discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the CRF.

7.2 Lost to Follow up

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

If a subject fails to return to the site for a required study visit the site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all products that they had been dispensed and if appropriate request that the subject return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs).

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion, which could include the following:

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow up.

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study visit. The timing of each procedure is listed in the Schedule of Activities section.

Adherence to the study design requirements, including all procedures are essential and required for study conduct.

8.1 Visit 1/Screening

Screening procedures will be conducted by the Investigator, or suitably qualified designee.

8.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Two copies of the informed consent form (ICF) will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a signed and dated consent will be provided by either the investigator or by GSK CH.

The investigator, or designee, should sign and date each copy of the ICF to confirm that the consent process was completed correctly after the subject has signed.

The time the subject signed the informed consent form will also be captured on the ICF as this is the point at which all AEs will be captured from. The date and time of consent will be transcribed to the CRF.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Each subject should be provided with a copy of the signed and dated amended consent form. The date of re-consent will be recorded on the CRF.

After signing the ICF, subjects will undergo the screening assessments to confirm that they meet all the inclusion criteria and none of the exclusion criteria. If the subject is confirmed eligible by the investigator (or designee) to participate in the study the subject is considered enrolled in the study.

8.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, gender and race. Ethnicity will be self-reported, and the choices offered will be Hispanic or Latino and Not Hispanic or Latino. Ethnicity will be captured by the Investigator or designee and recorded on the CRF.

Ethnicity and race of subjects will be recorded in accordance with FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials, 2005 to support any future submissions required for the USA.

8.1.3 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be documented in the CRF.

8.1.4 Lifestyle Restrictions

Lifestyle guidelines as described in [Lifestyle Considerations](#) will be communicated.

8.1.5 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history (in the last year), including allergies or drug sensitivity, will be documented in the CRF.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days and prior to signing the informed consent form, will be documented in the CRF.

8.1.6 Urine Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, will be performed at the Screening visit. Results will be obtained prior to any product use.

8.1.7 Subject Eligibility

The investigator and/or medically qualified designee will review inclusion/exclusion criteria, medical history, prior medications to confirm subject eligibility to participate in the clinical trial. This will be documented in the CRF.

To prepare for study participation, subjects will be instructed in the [Lifestyle Considerations](#) and any [Concomitant Medication/Treatment\(s\)](#) requirements of the protocol.

8.1.8 Screening Procedures

8.1.8.1 Screening Oral Hard Tissue (OHT) assessment

An OHT examination will be carried out at the Screening visit as described in Safety and Other Assessments. Any changes to the OHT after Screening will be recorded as AEs.

8.1.8.2 Screening Oral Soft Tissue (OST) assessment

An OST examination will be carried out at the Screening visit as described in Safety and Other Assessments and will be recorded in the CRF. Any changes to the OST after the PTB training exercise will be recorded as AEs.

8.1.9 Supervised Power Toothbrush Training

Eligible subjects will be dispensed with an individual prototype PTB and reference PTB handle and a corresponding brush head by the dispenser as described in [Administration](#).

A trained member of site staff will demonstrate the prototype PTB product usage instructions as per the Product Instructions for Use using a dentition model. Both ‘Gumline’ and ‘Interdental’ modes will be demonstrated. Subjects will then brush their teeth with the prototype PTB using a fluoride toothpaste (provided) as instructed in each of the two cleaning modes under close supervision of the trained site personnel until they are familiar with their use, per the criteria of the study site personnel.

A trained member of site staff will also demonstrate usage of the reference PTB as per the pack insert instructions verbally and using a dentition model. Subjects will not brush their teeth with the reference PTB.

Successful completion of the PTB training visit will be recorded in the CRF.

8.1.9.1 Post Training Oral Soft Tissue (OST) assessment

An OST examination will be carried out after the PTB training as described in Safety and Other Assessments and will be recorded in the CRF. Any changes or new findings will be recorded as AEs.

8.1.10 Washout product and diary cards dispensing

Eligible subjects will be dispensed with the washout toothpaste (Colgate Cavity Protection) and manual toothbrush (Colgate Extra Clean) to use during the washout period (between Visits 1 and 2), and between Visits 2, 3 and 4. Subjects will be instructed to brush their teeth twice a day (morning and evening) in their usual manner. Subjects will receive a diary card to record twice daily toothbrushing. The time of subjects last brushing prior to the scheduled visit should be recorded. Subjects will also be asked to record any changes to their medications or any report of feeling unwell on the diary.

To prepare for study participation, subjects will be instructed on the use of the [Lifestyle Guidelines](#) and [Concomitant Treatment\(s\)](#) sections of the protocol.

If subjects require additional or new washout products during the study, they will be re-dispensed by the study site. Information will be recorded in the CRF.

8.1.11 Adverse Events and Incidents

Adverse Events and Incidents will be recorded in the CRF as described in [Adverse Event and Serious Adverse Events](#).

8.2 Study Period

There will be an interval of at least 3 days between visits (i.e., subsequent use of investigational product will not occur until at least 3 days after the previous use of investigational product). Subjects will continue to use the washout paste with the toothbrush provided throughout this period.

Subjects will be reminded to inform the site if they experience any untoward medical occurrence or use any medications during the washout periods.

8.2.1 Visit 2 (Period 1)

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF.

Visit 2 will take place at least 3 days after the screening visit. Subjects will attend Visit 2 after abstaining from oral hygiene procedures for 12 to 18 hours.

The following assessments will be conducted in the order written as much as is practical:

8.2.1.1 Concomitant Medication

Changes in concomitant medication or non-drug treatment/procedures will be documented in the CRF.

8.2.1.2 Lifestyle restrictions review

Lifestyle guidelines as described in [Lifestyle Considerations](#) will be reviewed.

8.2.1.3 Diary cards review

Investigator or designee will review diary cards of washout product usage during wash out period.

8.2.1.4 Urine Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, will be performed at the visit. Results will be obtained prior to any product use.

8.2.1.5 Pre-brushing Oral Soft Tissue assessment

OST examination as described in [Safety and Other Assessments](#). Any changes or new findings will be recorded as an AE. An OST will be conducted after each brushing occasion.

8.2.1.6 Pre-brushing dental plaque disclosure

Twenty (20) drops (approximately 2.5 ml) of undiluted dental plaque disclosing solution is dispensed directly from the manufacturer’s original bottle into plastic dosage cups. Subjects will be given the dosage cup to swish the disclosing solution orally for 15 seconds and then expectorate. Subjects will then rinse with 10 ml of tap water for 10 seconds and expectorate.

8.2.1.7 Pre-brushing dental plaque assessment

RMNPI score will be assessed on all teeth excluding third molars, crown and surfaces with restorations as described in [Efficacy Assessments](#) for a minimum of 18 and a maximum of 28 eligible teeth.

8.2.1.8 Continued eligibility

Subject continued eligibility will be reviewed.

8.2.1.9 Randomization

Subjects will be randomized to the study treatment sequence.

8.2.1.10 Study product dispensing

Subjects will receive the study treatment product corresponding to the randomization sequence. Treatments are described in [Investigational/Study products](#) section.

8.2.1.11 Product Usage Instructions

Unblinded trained study site member of staff will demonstrate correct use of the assigned product to the subjects as per the Product Usage Instructions of the allocated treatment.

8.2.1.12 Supervised brushing

Subjects will then brush according to the brushing instructions provided by the trained member of the site staff. The subject will be supervised throughout this time as described in [Investigational/Study products](#) section.

8.2.1.13 Post-brushing Oral Soft Tissue assessment

OST examination as described in [Safety and Other Assessments](#) section. Any changes or new findings will be recorded as an AE.

8.2.1.14 Post-brushing dental plaque disclosure

As per [Pre-brushing dental plaque disclosure](#).

8.2.1.15 Post-brushing dental plaque assessment

Plaque will be assessed using the RMNPI index on all teeth excluding third molars, crown and surfaces with restorations as described in [Efficacy Assessments](#) for a minimum of 18 and a maximum of 28 eligible teeth.

8.2.1.16 Further assessments for Prototype PTB arm only

For subjects randomized to the prototype PTB arm a further 1-minute toothbrushing in 'Interdental' mode will be performed. Plaque will be assessed using the RMNPI index on all teeth excluding third molars, crown and surfaces with restorations as described in [Efficacy Assessments](#) for a minimum of 18 eligible teeth. This will be followed by a [Post-brushing Oral](#)

[Soft Tissue assessment](#) and [Post-brushing dental plaque disclosure](#). Plaque will be re-assessed using the RMNPI index as described in [Post-brushing dental plaque assessment](#).

8.2.1.17 Repeatability dental plaque assessment

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. These data will not be used for assessment of efficacy.

8.2.1.18 Sensory experience questionnaire

Subjects will receive a questionnaire ([Appendix 1](#)) in paper form, which they will complete unsupervised following the completion of all assessments. An unblinded study site designee will collect the subject's completed questionnaire and record the questionnaire's responses in the CRF.

8.2.1.19 Adverse Events and Incidents

Adverse Events and Incidents will be recorded in the CRF as described in [Adverse Event and Serious Adverse Events](#).

8.2.1.20 Lifestyle restrictions

Subjects will be reminded of the [Lifestyle Considerations](#) and any [Concomitant Medication/Treatment\(s\)](#) requirements of the protocol.

8.2.2 Visit 3 (Period 2)

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

Visit 3 will take place at least 3 days after Visit 2, Subjects will attend Visit 3 after abstaining from oral hygiene procedures for 12 to 18 hours.

Procedures will follow as per [Study Period](#), with the exception of Randomization.

8.2.3 Visit 4 (Period 3)

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

Visit 4 will take place at least 3 days after Visit 3. Subjects will attend Visit 4 after abstaining from oral hygiene procedures for 12 to 18 hours.

Procedures will follow as per [Study Procedures](#), with the exception of Randomization.

8.2.3.1 Oral Hard Tissue (OHT) assessment

A post treatment phase OHT examination will be carried out at Visit 4 as described in Safety and Other Assessments. Any changes will be recorded as AEs.

8.2.3.2 Return of washout products

Subjects will return washout products (toothpaste, toothbrush) and diary cards.

8.3 Diary Review

The diary should be reviewed at every visit by the investigator, or suitably qualified designee, and the subject. Any subject comment captured in the diary which is considered an adverse event will be assessed and reported as per the defined procedure in this protocol. Adverse event reporting procedures are summarized in [Adverse Event and Serious Adverse Events](#).

Any additional comments relating to medications/treatments provided in the diary will be reviewed by the investigator or medically qualified designee with the subject and entered into the CRF as appropriate.

Additional and missed product applications will be considered deviations from the protocol and will be recorded on the Deviations Log. The time of last brushing prior to their scheduled treatment visit will also be recorded and transcribed into the CRF.

8.4 Study Conclusion

The Study Conclusion page of the CRF will be completed for all subjects whether they completed all study procedures or if they were discontinued from the study early. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page.

If a subject has any clinically significant, study-related abnormalities or AEs at the conclusion of the study, the GSK CH medical monitor (or designated representative) should be notified and, the subject may be asked to remain at the clinical site or be asked to return for a follow-up visit to ensure any issue is resolved or deemed not clinically significant.

In the event the study is stopped early, the study site will contact all ongoing subjects and advise them to stop using all study products immediately and schedule them for their study conclusion visit. At this visit only, safety assessments (OST and OHT) will be conducted and completion of the study conclusion page. No assessment of efficacy will be performed.

8.5 Follow-up Visit/Phone Call

The study site may contact a subject to follow up an AE post-study completion/withdrawal and, in some circumstances, request they return to the site for additional follow-up visits (final safety assessments). If needed, additional examinations may be carried out at such visits.

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to complete an assessment. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments in a timely manner.

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the [Study Procedures](#) section of this protocol.

9.2 Efficacy Assessments

The following efficacy assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the [Study Procedures](#) section of this protocol.

9.3 Rustogi Modification of the Navy Dental plaque Index (Rustogi et al 1992)

This procedure should be conducted by a single dental examiner.

Subjects will undergo plaque disclosing as described in [Pre-brushing dental plaque disclosure](#).

The RMNPI dental plaque is evaluated as either present or absent (1 or 0) on each of the nine areas of the buccal and each of the nine areas of the lingual tooth surfaces (Figure 9-1). Dental plaque is assessed on all teeth excluding third molars (Universal Numbering System teeth 2 to 15, and 18 to 31), crowns and surfaces with cervical restorations for a maximum of 28 eligible teeth. This will result on a maximum of 504 gradable sites, with a minimum number of 18 teeth or 324 gradable sites. Information will be recorded in the CRF per each tooth site. If a tooth site is not scored, it will be recorded as not assessed in the CRF.

Subjects' RMNPI scores will be calculated on a whole mouth basis (sites A-I), along the gingival margin (sites A, B, C) and proximal (sites D and F) (Figure 9-1). Results of the whole mouth, gingival margin and interproximal scores (variables) will be analyzed as described below ([Statistical Considerations and Data Analyses](#)).

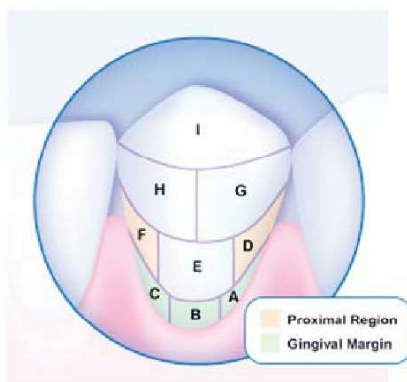


Figure 9-1 Rustogi modified Navy Dental plaque index. Each tooth section is scored with 0 (no dental plaque) or 1 (dental plaque) and an average of all measured sites calculated. Image from (Cugini et al 2006)

9.4 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the [Study Procedures](#) section of this protocol.

9.4.1 Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, will be performed at the Screening visit, and each study visit. Results will be obtained prior to product use during each period.

The investigator and site personnel will remind subjects at each visit to inform site personnel if their menstrual cycle has changed or if they have any other reason to suspect they may be pregnant (e.g. had unprotected intercourse since the last visit).

A negative pregnancy result is required before the subject is considered eligible to participate in the study at the Screening visit and at each subsequent study visit after for continued eligibility. Pregnancy tests may also be repeated as per request of IRBs/ECs or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

9.4.2 Oral Hard Tissue Examination (OHT)

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee for all subjects. Subjects with evidence of gross intra-oral neglect or the need for extensive dental therapy will be excluded.

The OHT examination will assess grossly carious lesions or erosive wear, enamel irregularities, tooth fracture, gross decay, decalcification and faulty restorations.

Observations will be listed as “Absent” or “Present” and conditions noted as present will be described. Examination findings will be described and documented in the CRF. Any

observation that changes from “Absent” to “Present” from the screening assessment must be recorded as an AE.

9.4.3 Oral Soft Tissue Examination (OST)

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee for all subjects for the duration of the study. The examination will be accomplished by direct observation and palpation with retraction aids as appropriate. The examiner will include examination of the labial mucosa (including lips), buccal mucosa, mucogingival folds, gingival mucosa, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands.

The results of the examination will be recorded in the CRF as either normal or abnormal, with details of any abnormalities. Any post-treatment soft tissue abnormality, or worsening of a pre-existing condition, observed by the examiner or reported by the subject will be recorded on the CRF. Any abnormalities, or worsening of pre-existing conditions, that occur after the PTB training at Visit 1 will be recorded as AEs.

An OST examination will be conducted following each brushing occasion.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

10.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product (or medical device), whether or not considered related to the study product, including any washout or lead-in product (or medical device).

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study product including any washout or lead-in product (or medical device).

Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE if they fulfill the definition of an AE.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g. appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is a particular category of an adverse event where the adverse outcome is serious. If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life-threatening**
 - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
 - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.
 - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- **Results in persistent or significant disability/incapacity**
 - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
 - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Results in congenital anomaly/birth defect**
- **Other situations:**
 - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
 - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Note: Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements.

10.3 Reporting of Adverse Events

10.3.1 Reporting Period

All AEs, and therefore all SAEs will be collected immediately after a subject provides consent to participate in the study by the completion (signature) of the ICF and until 5 days following last administration of the study product (or last procedure).

Medical occurrences that began before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF not the AE section.

Details recorded by the subject on a diary or similar document that meet the definition of an AE must also be discussed with the subjects and transcribed in the AE section of the CRF.

10.4 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up on AEs that are serious, considered related to the study product(s), participation in the study, or a study procedure, or that caused the subject to discontinue the study product or study.

The investigator (or medically qualified designee) is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for a SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE occurs, it is the responsibility of the investigator (or medically qualified designee) to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE in the CRF and all details relating to an SAE in the paper SAE Form provided.

It is **not** acceptable for the investigator (or medically qualified designee) to send photocopies of the subject's medical records to GSK CH in lieu of completion of the AE CRF page/SAE form.

There may be instances when copies of medical records for certain cases are requested by GSK CH. In this instance, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records prior to submission to GSK CH.

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be the documented as the AE/SAE where known and not the individual signs/symptoms. (e.g. upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

AEs elicited by the investigator (or medically qualified designee) in a standard manner at the study visits should also be recorded in the AE section of the CRF and/or using the SAE form (subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

10.4.1 Reporting of an Adverse Event

All AEs will be reported on the AE page of the CRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the AE CRF page and the SAE form must be completed in a consistent manner. For example, the same AE term should be used on both. AEs should be reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE CRF page, an SAE form should be completed, as fully as possible. Hard copies of the 'paper' SAE form will be provided in the investigator study master file. Original SAE forms will be retained in the investigator study master file.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available

- Investigator opinion of relationship to study product (or study procedure, if appropriate)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and GSK CH assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken in relation to the study product
- Outcome if known

The SAE form, completed as fully as possible, must be scanned and e-mailed to the GSK CH Clinical Operations Safety Reporting email box with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. The investigator will submit any updated SAE data to the sponsor, **immediately and under no circumstance should this exceed 24 hours** of it being available. The GSK CH Study Manager should also be notified of the situation by telephone or email.

Email Serious Adverse Events to:

PPD

The GSK CH Study Manager or designee will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox (PPD).

The initial report will be followed up with more information as relevant, or as requested by the GSK CH study manager.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

The investigator or medically qualified designee will make an assessment of intensity for each AE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both non-serious AEs and SAEs can

be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.5.2 Assessment of Causality

The causality assessment is one of the criteria used when determining regulatory reporting requirements. For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE CRF page and the SAE form (subject to the classification of the AE). The investigator will also document in the medical notes that he/she has reviewed the AE and assessed causality, where applicable.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The investigator will use clinical judgment to determine the relationship and will also consult the Investigator Brochure (IB), Safety Statement and/or Product Information, for marketed products, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK CH.** The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.6 Follow-up of Adverse Events

After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.

All AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK CH to elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded on the AE CRF page and on the SAE form (subject to the classification of the AE).

The investigator will submit any updated SAE data to GSK CH within 24 hours of receipt of the information.

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the investigator will promptly notify GSK CH by emailing the information to the GSK CH Clinical Operations Safety Reporting email box (PPD [REDACTED]). The GSK CH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD [REDACTED]).

The investigator will submit any updated SAE data to GSK CH within the designated reporting time frames.

10.7 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined.

10.7.1 Sponsor's Reporting Requirements to Regulatory Authorities and Ethics Committees

GSK CH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK CH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK CH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure in the investigator study master file, and will notify the IRB/IEC, if appropriate according to local requirements.

10.8 Pregnancy

10.8.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the signing of informed consent until 5 days after last administration of study product.

10.8.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the GSK CH Clinical Operations Safety Reporting email box (PPD [REDACTED]) within 24 hours of learning of the subject becoming pregnant. The GSK CH Study Manager or designee will be responsible for forwarding the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox (PPD [REDACTED]). Original pregnancy information forms will be retained in the investigator study master file.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the investigator to the GSK CH Clinical Operations Safety Reporting email box and the GSK CH Study Manager or designee will forward this information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD [REDACTED]). Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

10.9 Definition of and Procedure for Reporting Medical Device 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 (Class II Medical Device), and reference manual toothbrush, washout toothbrush and disclosing solution (Class I medical device).

10.10 Definition of an Incident

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.

Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

An **incident** associated with a device happened and

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include any of the following:
- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents:

- A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A subject's study treatment is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A subject's health deteriorates due to medical device failure.

10.11 Reporting of Incidents and Malfunctions

All incidents must be reported to GSK CH within 24 hours (or sooner if possible) of the investigator or designee becoming aware of the situation.

Any medical device incident occurring during the study will be documented in the subject's medical records, if in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE (serious and non-serious), the appropriate AE CRF page and SAE form will be completed and reported as per the AE and SAE reporting sections.

The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK CH. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.

The completed Incident Report Form should be scanned and emailed to the GSK CH Clinical Operations Safety Reporting email box with the study number and subject number in the subject line of the email as soon as possible, **but not more than 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE form should be sent together with this report form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will be retained in the investigator study master file.

The GSK CH Study Manager should be notified of the situation by telephone or email.

Email the Incident Report Forms to:

PPD

The GSK CH Study Manager or designee will be responsible for forwarding the Incident Report Form to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox (PPD), responsible for the study and other GSK CH personnel as appropriate.

The initial report will be followed up with more information as relevant, or as requested by the GSK CH study manager.

The investigator will follow the following directions regarding the reporting of a device failure (malfunction):

- Notify GSK CH immediately (by following the process described above).
- Schedule the subject to return to the site promptly to return the failed device.
- Record any incidents on the CRF and Incident Report Form following instructions given in the section above.
- Return the failed device to the sponsor as soon as possible, including documentation of the details of the failure.

10.11.1 Follow-up of Medical Device Incidents

Medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all subjects, including those who discontinue study product or are withdrawn from the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed Incident Report form with all changes signed and dated by the investigator.

10.11.2 Regulatory and Ethics Reporting Requirements for Incidents

To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during all periods of the study in which the medical device is used.

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

11 DATA MANAGEMENT

As used in this protocol, the term CRF is understood to refer to either a paper form or an electronic data record or both, depending on the data collection method.

For this study, subject data will be entered into an electronic CRF (eCRF), using a validated system. Data relating to SAEs, pregnancy and incidents will also be collected on paper forms.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries, questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in Section 8 and 9. The CRF/Diary can be used as a source document at the discretion of data management.

Each subject will be assigned and identified by a unique Screening Subject Number. Any reference made to an individual subject within the study must be done using their unique Screening Subject Number.

11.1 Case Report Form

A CRF is a printed, optical, or electronic document designed to record the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent/assent the CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Management of clinical data will be performed in accordance with Third Party BDM Vendor applicable standards and data cleaning procedures with oversight by GSK CH to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

To protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or full birth date) is to be recorded in the CRF or as part of the query text.

All CRF pages should be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor.

GSK CH will obtain and retain all CRFs and associated study data as applicable at the completion of the study.

11.2 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.

Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using an internal validated medication dictionary, GSKDrug.

11.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

The study monitor will perform ongoing review the of the CRFs in accordance with the monitoring plan, to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

11.3 Processing Patient Reported Outcomes

Paper based patient reported outcome (PRO) data may be collected from a diary, questionnaire, or other specified document, etc. and entered into the data management system (DMS).

Electronic Patient reported outcome (ePRO) data may be collected using electronic devices and transferred electronically to GSKCH or Third-party DM vendor.

All PRO source data should be reviewed by the study staff and the study monitor in order to ensure accurate transcription of data and that any potential AEs or concomitant medications reported on these documents are discussed with the subject and transcribed accurately to the CRF and/or DMS. PROs that are classed as source data will be retained by the investigator and true/certified copies may be sent to a designated vendor or GSK CH as required.

To protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded on any PRO/ePRO that will be forwarded to GSK CH or Third-Party Vendor.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

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 (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.

12.2 Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior to study unblinding (release of randomization codes).

Treatment comparisons will be tested under the null hypothesis:

H_0 : there is no treatment difference, versus the following alternate hypothesis.

H_1 : there is a treatment difference.

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

- i) prototype PTB in ‘Gumline’ mode
- ii) prototype PTB in Combined mode (‘Gumline’ mode followed by ‘Interdental’ mode)
- iii) reference MTB
- iv) reference PTB.

The reference PTB will always be used in the last period (i.e. period 3). Subjects will be randomized to receive both the prototype PTB and reference MTB in a pre-determined randomized order (AB/BA) design. 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 assessments (‘Gumline’ and ‘Interdental’ brushings) will occur in the same treatment period.

12.2.1 Definition of Analysis Populations

All assessments of safety will be based on the Safety population, defined as all subjects who are eligible to participate in the study and participate in the [Supervised Power Toothbrush Training](#).

The primary population for efficacy assessment will be the modified intent-to-treat (m-ITT) population, defined as all subjects who are randomized, received at least one of the study treatments and provide at least one post-brushing assessment of efficacy. All m-ITT population summaries and analyses will be presented according to the treatment randomized.

The per protocol (PP) population is defined as all subjects in the m-ITT population who have at least one assessment of efficacy considered unaffected by protocol violations.

The Repeatability population is defined as all subjects who have a repeat clinical assessment of efficacy (R) at any visit.

12.2.2 Exclusion of Data from Analysis

Exclusion of any data from the analyses will be determined during a Blind Data Review Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

PP analysis will be performed only on those data considered unaffected by protocol violations.

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 m-ITT populations, or in the case the study is stopped early as per the pre-defined criteria. A decision on whether a PP analysis will be performed will be made prior to study unblinding (release of the randomization codes).

12.2.3 Demographic and Baseline Characteristics

Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for demographic and baseline characteristics. Demographic and baseline characteristics will be summarized by treatment sequence group.

12.2.4 Study Drug/Product Compliance and Use of Other Therapies

12.2.4.1 Study Drug/Product Compliance

As each treatment is a single product use (brushing occasion) under direct supervision at study site, no summary of product use is planned. Data may be listed.

12.2.4.2 Prior and Concomitant Medications

Prior medications, concomitant medications and significant non-drug therapies taken during the study will be listed for the safety population.

12.2.5 Primary Analysis

The primary efficacy variable is the change from pre-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 primary comparison is between the prototype PTB when used in the 'Gumline' mode versus the reference MTB after a single brushing event.

As this is an exploratory study and the primary objective has been clearly defined no adjustments for multiplicity are required. All other pairwise comparisons will be investigated under secondary and exploratory comparisons.

The whole mouth RMNPI score for each subject is derived from the total number of tooth sites with dental plaque present (all tooth sites A-I, [Figure 9-1](#)) divided by the total number of tooth sites scored for all areas per tooth (A-I sites, [Figure 9-1](#)). The change from pre-brushing is

derived from the individual sites for each tooth first before calculating the average change in the whole mouth score.

During the prototype PTB treatment period there will be two assessments for efficacy (RMNPI scores), the first after the ‘Gumline’ mode and the second after the ‘Interdental’ mode.

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.

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

Any potential carryover effects will also be investigated.

The change from pre-brushing in whole mouth plaque score will be analyzed using analysis of covariance (ANCOVA) with treatment, 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 assumption of normality and homogeneity of variance in the ANCOVA model will be investigated. Violation of this assumption will be overcome using a suitable data transformation or a non-parametric technique (e.g. Wilcoxon matched pairs Signed Rank test).

12.2.6 Secondary Analysis(es)

Secondary 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’ regimen vs reference MTB (excluding the primary comparison)
- Prototype PTB ‘Combined’ regimen vs reference MTB
- Prototype PTB ‘Combined’ regimen vs Prototype PTB ‘Gumline’ regimen
- Prototype PTB ‘Gumline’ regimen vs reference PTB
- Prototype PTB ‘Combined’ regimen vs reference PTB

Where ‘Combined’ is the plaque assessment result of the ‘Gumline’ mode use and the ‘Interdental’ mode brushing.

All RMNPI variables will be derived in a similar way based on relevant tooth sites and analyzed as per the primary variable. No adjustment will be applied to these secondary comparisons.

12.2.7 Safety Analysis(es)

All AEs will be coded using MedDRA. AEs will be categorised as oral and non-oral by the Clinical Research Director/ Scientist or designee prior to database lock. Treatment-emergent adverse events (Oral AEs as well as all AEs) will be associated with the most recent treatment

received. The number of AEs and number of subjects with AEs will be listed and tabulated by treatment. The results of OST exams will be tabulated. Incidents will be listed.

12.2.8 Other Analysis(es)

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 is:

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

All RMNPI variables will be derived in a similar way based on relevant tooth sites and analyzed as per the primary variable with no adjustment for multiple comparisons.

Repeatability assessment

The repeat dental plaque assessments will be compared to the original assessments and 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. A weighted Kappa coefficient (κ), along with the 95% CI will be calculated to assess the intra-examiner reliability. Fleiss-Cohen weighted kappa will be calculated for the repeatability analysis. Reliability will be deemed

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

All subjects who have repeatability data will be included in this analysis.

The sensorial experience questionnaires will be summarized by treatment and reported with frequency counts and summary statistics.

12.2.9 Handling of Dropouts and Missing Data

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.

12.2.10 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).

The study will be terminated following a decision by the Decision Group Committee based on the criteria defined below.

Decision Group Committee

No formal DMC (Data monitoring Committee) is required although a Decision Group Committee (DGC) will be set up internally within the Sponsor GSKCH. The DGC will consist of the Head of Clinical Development and Medical Affairs and the Head of Biostatistics and Data Management.

The number of subjects, the number of prototype PTB devices tested/used, and the number of prototype PTB device failures (handles and/or heads), will initially be shared with the Director of Clinical Research (Oral Health and Skin Health) who will liaise directly with the DGC.

Definition of a device failure

Any failure/malfunction of the prototype PTB that does not allow the subject to initiate/complete a study visit as per the protocol whether resulting in an AE or not. Each prototype PTB consists of a brush head and a handle (charging unit is excluded as it is a commercial charger).

Device unit failures/malfunctions include but are not limited to: -

- Device shows any signs of abnormal behavior (for example getting excessively hot or emitting smoke or liquids)
- If after 24 hours charging, LED 4 (as per user manual) is still illuminated
- Brush head mechanism failure (e.g. failure to rotate, does not rotate in mode indicated by LED)
- Device fails to operate after a full charge/excessive loss of charge
- Any other unexpected event that may occur with the prototype PTB during training or study use.

Device unit failures will be assessed and monitored by the study site staff who are responsible for the oversight of the supervised brushing.

Stopping Rule

The study will be terminated when an observed failure rate of approximately 20% has been reached during the study as per the stopping criteria defined below.

- For Visit 1 (training period), the study will be terminated if 8 device failures are observed within this period.
- For Visit 2 and 3 (treatment period), the study will be terminated if 7 device failures are observed within this period.

As new brush heads will be provided to subjects after randomization, the number of device failures will be specified separately for the training and treatment periods.

Impact on main statistical analysis and p-value adjustment

There will be no impact on the efficacy statistical analysis as the plaque levels are the focus of this study and not mechanical device failure. The interim data review is focused on the

mechanical failure of the prototype device units. Based on this information, no adjustment to type I error rate is required in the efficacy statistical analysis.

Blinding

The study is open label.

Timing and Process

The number of subjects, number of prototype PTB devices tested/used, number of prototype PTB device failures (handles and/or heads), will be communicated by Stats/DM daily to the Director of Clinical Research (Oral Health and Skin Health) and the DGC.

In addition to these daily reports, ad hoc reports may also be extracted from the electronic clinical database to monitor devices failures.

Dissemination of DGC Decision

The DGC will be responsible to make the decision on whether to stop the study early, based on the pre-defined criteria and will document this decision. The DGC will inform the Director of Clinical Research (Oral Health and Skin Health) and Regional Clinical Operations of this decision. If the study is to be stopped early, as a minimum the study team (including MQP) and study site and any other relevant personnel will be informed as soon as the decision is made.

Reporting

In the event the study is terminated after the above stopping criteria are met, collected data up to the point of study discontinuation will be reported. Further details of handling of data will be provided in the reporting analysis plan.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

In accordance with applicable regulations including GCP, and GSK CH procedures, GSK CH or designee (i.e. third-party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK CH requirements.

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK CH or designee will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The extent and nature of monitoring will be described in a written monitoring plan on file at GSK CH. The investigator (or designee) agrees to allow the monitor direct access to all relevant

documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK CH may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

The investigator(s) will notify GSK CH or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with GSK CH or its agents to prepare the study site for the inspection and will allow GSK CH or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply copies of the inspection finding to GSK CH or its agent. Before response submission to the regulatory authority, the investigator will provide GSK CH or its agents with an opportunity to review and comment on responses to any such findings.

The sponsor will be available to help investigators prepare for an inspection.

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, investigator brochure/safety statement (including any updates) and other relevant documents, e.g. recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to GSK CH prior to the initiation of the study, and also when subsequent amendments to the protocol are made.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and GSK CH in writing immediately after the implementation.

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

13.3.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to GSK CH and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by GSK CH in order to de-identify study subjects.

The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, GSK CH will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed informed consent document.

13.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

GSK CH will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

13.3.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

Within GSK CH a serious breach is defined as a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in GSK CH-sponsored human subject research studies.

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new

information that might influence the evaluation of the benefits and risks of the investigational product, GSK CH should be informed immediately.

In addition, the investigator will inform GSK CH immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13.4 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable GSK CH processes.

GSK intends to make anonymized subject-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

13.5 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK CH site or other mutually-agreeable location.

GSK CH will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK CH Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

13.6 Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g. for a GSK CH audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSK CH, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSK CH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR) or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK CH standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSK CH and the investigator. The investigator must notify GSK CH of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of the prototype PTB at any time. For multicenter studies (if applicable), this can occur at one or more or at all sites.

Any incident (malfunction/failure) of the prototype PTB as defined in [Interim Analysis](#) after the signing of the informed consent does not allow the subject to initiate/complete a study visit as per the protocol will be considered a device failure.

If at any time in the trial, the stopping rules defined in [Interim Analysis](#) are reached the study will be terminated. No further products will be dispensed or used by any subject.

If a study is prematurely terminated, GSK CH will promptly notify the investigator. After notification, the investigator must promptly contact all participating subjects and should assure appropriate therapy/ follow-up for the subjects. As directed by GSK CH, all study materials must be collected and all CRFs completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authority(ies) and the investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

If the IRB/EC terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the GSK CH and provide GSK CH with a detailed written explanation of the termination or suspension.

Upon completion or premature discontinuation of the study, the GSK CH monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK CH Standard Operating Procedures.

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15 APPENDICES

15.1 APPENDIX 1: Sensorial Experience Questionnaire (Version 1, 16 June 2017)

Q1: How EASY WAS IT TO FOLLOW THE USAGE INSTRUCTIONS?		
Extremely easy	5	<input type="checkbox"/>
Very easy	4	<input type="checkbox"/>
Somewhat easy	3	<input type="checkbox"/>
Not very easy	2	<input type="checkbox"/>
Not at all easy	1	<input type="checkbox"/>

Q2: How COMFORTABLE WAS THE TOOTHBRUSH TO USE?		
Extremely comfortable	5	<input type="checkbox"/>
Very comfortable	4	<input type="checkbox"/>
Somewhat comfortable	3	<input type="checkbox"/>
Not very comfortable	2	<input type="checkbox"/>
Not at all comfortable	1	<input type="checkbox"/>

Q3: How would you rate how EASY IT WAS TO REACH THE BACK TEETH?		
Extremely easy	5	<input type="checkbox"/>
Very easy	4	<input type="checkbox"/>
Somewhat easy	3	<input type="checkbox"/>
Not very easy	2	<input type="checkbox"/>
Not at all easy	1	<input type="checkbox"/>

15.2 APPENDIX 2: ABBREVIATIONS

The following is a list of abbreviations that may be used in the protocol.

Table 15-1 Abbreviations

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DMS	clinical data management system
EC	ethics committee
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GSK CH	GlaxoSmithKline Consumer Healthcare
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
IRB	institutional review board
IRT	Interactive Response Technology
ITT	intention to treat
MedDRA	medical Dictionary for Regulatory Activities
ml	milliliters
MTB	manual toothbrush
N/A	not applicable
OHT	oral hard tissue
OST	oral soft tissue
PI	principal investigator
PII	personally identifiable information
PP	per protocol
PRO	patient reported outcome
PT	preferred term
PTB	power toothbrush
RMNPI	Rustogi Modification of the Navy Dental Plaque Index
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	study end

Abbreviation	Term
SOC	System organ class
SRSD	single reference study document
SS	safety statement
SUSAR	Suspected unexpected serious adverse reactions
TQHPI	Turesky Modification of the Quigley Hein
US	United States