Clinical Protocol

212537

A Randomized, Examiner Blind, Clinical Study Investigating the Efficacy of a Stannous Fluoride Dentifrice in Improving Gingival Health after 3 Weeks Use

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CLINICAL PROTOCOL

A Randomized, Examiner Blind, Clinical Study Investigating the Efficacy of a Stannous Fluoride Dentifrice in Improving Gingival Health after 3 Weeks Use

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Document History

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Original protocol	1.0	Not applicable (N/A)
Amendment 1		
Amendment 2		

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.

Investigator Name:	
Investigator Qualifications:	
Investigator Signature:	PPD
Date of Signature/Agreement:	PPD DD-Mmm-YYYY

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1 PROTOCOL SUMMARY

Background and Rationale

This study is designed to evaluate the gingivitis efficacy of twice daily brushing with a 0.454% stannous fluoride (SnF_2) dentifrice over 3 weeks in a population with mild-moderate plaque-induced gingivitis. The study will compare a marketed dentifrice containing 0.454% SnF_2 with a negative control dentifrice. The design of this study follows very closely that of previous GSK CH gingivitis studies (Parkinson et al, 2014; Parkinson et al, 2015; Parkinson et al, 2018a; Parkinson et al, 2018b)

Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate the clinical efficacy of a 0.454% SnF_2 dentifrice in reducing gingivitis (following dental prophylaxis), as measured by the Bleeding Index (BI), compared to a negative control dentifrice, when used twice daily for 3 weeks.	Mean BI at Week 3
Secondary	
To evaluate the clinical efficacy of a 0.454% SnF_2 dentifrice in reducing gingivitis (following dental prophylaxis), as measured by the BI compared to a negative control dentifrice, when used twice daily for 2 weeks.	Mean BI at Week 2
To evaluate the clinical efficacy of a 0.454% SnF_2 dentifrice in reducing gingivitis (following dental prophylaxis), as measured by the number of bleeding sites (NBS), compared to a negative control dentifrice, when used twice daily for 2 and 3 weeks.	Mean NBS at Week 2 and Week 3
To evaluate the clinical efficacy of a 0.454% SnF_2 dentifrice in reducing gingival inflammation (following dental prophylaxis), as measured by the Modified Gingival Index (MGI), compared to a negative control dentifrice, when used twice daily for 2 and 3 weeks.	Mean MGI at Week 2 and Week 3
To evaluate the clinical efficacy of a 0.454% SnF_2 dentifrice in reducing supra – gingival plaque formation (following dental prophylaxis) as measured by the Turesky modification of the Quigley & Hein plaque index (TPI), compared to a negative control dentifrice, when used twice daily for 2 and 3 weeks.	Mean TPI (overall and interproximal) at Week 2 and Week 3
Safety	
To assess the safety and tolerability of a 0.454% SnF_2 dentifrice when used twice daily over 3 weeks.	Treatment emergent adverse events

Study Design

This will be a single center, controlled, single blind (examiner blind), randomized, stratified (gender and baseline mean whole mouth MGI score) two-treatment arm, parallel design, clinical study. Study subjects will be aged 18-65 years, non-smokers, in good general health with generalized mild-moderate plaque-induced gingivitis and ≥ 20 natural teeth that meet all study criteria at both the Screening and Baseline visits (including ≥ 40 evaluable surfaces for MGI, BI, and TPI).

Approximately 130 (n=65/group) subjects will be randomized to one of the study products.

This study will consist of four study visits. At Visit 1, Screening, after signing informed consent, subjects will undergo an Oral Soft Tissue (OST) examination, an Oral Hard Tissue (OHT) examination and a gross assessment of gingival health, in addition to the standard (inclusion, exclusion, medical history, demographics, prior/current medications) procedures to assess eligibility for the study. Subjects will return to site 1-28 days after the Screening Visit, for Visit 2, Baseline.

At the Baseline Visit, subjects will undergo, in the following order, a full OST examination followed by assessments of gingival inflammation (MGI), gingival bleeding (BI) and supra-gingival plaque using the Turesky Plaque Index (TPI). Eligible subjects will be stratified based on gender and baseline mean whole mouth MGI score (Low: ≤ 2.00/High >2.00), to ensure a balance of gingivitis across both treatment groups and then randomized to study product.

Subjects with mean MGI or TPI scores outside the study range will be discontinued from the study at this visit. To control inter-examiner variability, the same examiner will be used throughout the study for all clinical assessments (MGI, TPI, BI).

All randomized subjects will then receive a full mouth dental prophylaxis (followed by flossing) to remove sub and supra-gingival calculus, stain, plaque and debris from the teeth. All subjects will enter the treatment period with no visible plaque (TPI=0).

After all clinical assessments, subjects will be instructed to brush for 1 timed minute, in their usual manner, with their assigned study product and then instructed to continue using their assigned product twice daily (morning and evening), after which they will return to site for their Week 2 (Visit 3) assessments. Subjects will then continue using their assigned dentifrice for a further week, after which they will return for their Week 3 (Visit 4) assessments. Subjects will continue to record all brushing events in the diary provided, and this will be reviewed by the site at each study visit.

After the Week 3 visit, study closeout procedures (return of study product etc.) will take place and the subject may undergo an additional prophylaxis if it is deemed necessary by the examiner.

Safety and oral tolerability of the study products will be monitored over the 3-week treatment period by review of reported Adverse Events and Incidents.

Study Products

Test dentifrice: Sensodyne Repair and Protect containing 0.454% SnF_2 (1100 parts per million(ppm) fluoride)

Negative control dentifrice: Colgate Cavity Protection (1100ppm fluoride as sodium monofluorophosphate (SMFP).

Type and Planned Number of Subjects

Approximately 150 subjects will be screened to randomize 130 to ensure 60 evaluable subjects per treatment group complete the entire study.

Statistical Analysis

The primary variable is the mean BI at week 3.

The mean BI score will be analyzed using ANCOVA with treatment group, gender, and baseline MGI stratification (low/high) as factors and baseline score as a covariate. Adjusted means of the two treatments and treatment difference will be provided together with 95% CIs and P-values.

Secondary variables are: -

Mean BI at week 2

Mean NBS at week 2 and 3

Mean MGI at week 2 and 3

Mean TPI (Overall) at week 2 and 3

Mean TPI (Interproximal areas) at week 2 and 3

Each secondary variable will be analyzed separately as per the primary variable. For the analysis of MGI the stratification factor of MGI will not be included as the baseline value of MGI is included as a covariate.

1.1 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, to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1-1 Schedule of Activities

Procedure/Assessment	Visit 1 Screening	Lead-in Phase Minimum 1 day - Maximum 28 days	Visit 2 Day 0 Baseline	Visit 3 Week 2 (14± 2 days post V2)	Visit 4 Week 3 (21± 2 days post V3)
Informed consent	X				
Demographics	X				
Medical history	X				
Prior/current medications and treatments	X				
OST assessment	X		X	X	X
OHT assessment	X				X
Gross assessment of gingival health[1]	X				
Inclusion/Exclusion criteria	X		X		
Subject Eligibility	X		X		
Subject continuance				X	X
Concomitant medications and treatments			X	X	X
MGI assessment			X	X	X
Repeat MGI Assessment[2]			X	X	X
BI assessment			X	X	X
Disclose dental plaque			X	X	X
TPI Assessment			X	X	X
Repeat TPI Assessment[2]			X	X	X
Stratification/Randomization			X		
Dental Prophylaxis			X		
Post-prophylaxis examination to confirm whole mouth TPI=0			X		
Dispense study product, toothbrush and diary			X		
Supervised brushing with study product			X	X	
Subject brings study product, toothbrush and completed diary to site for compliance check[3]				X	X
Subject returns study product and diary to site					X
End of study dental prophylaxis (optional)					X
Adverse events/incidents[4]	X		X	X	X
Study conclusion					X

Abbreviations:

OST Oral soft tissue

OHT Oral hard tissue

MGI Modified gingival index

BI Bleeding index

TPI Turesky plaque index

Footnotes:

1. Subjects with generalized mild-moderate gingivitis, as determined by visual assessment of gingival health, will continue in the study.
2. At least 2 repeatability assessments should be performed each day (≥ 1 in the morning; ≥ 1in the afternoon)
3. Visits 2-4: Adherence to Lifestyle Guidelines/Medication Requirements;
   Visits 3-4: Compliance with use of study product (visual check if returned study supplies/review of diary)
4. Adverse events (AEs)/incidents will be recorded from the signing of informed consent until 5 days after the last dose of study product.

2 INTRODUCTION

Gingivitis is an inflammatory response to the presence of dental plaque (Kinane, 2001), which typically presents as redness, swelling (oedema) and/ or bleeding of the gums at the gingival margin surrounding the tooth. Gingivitis is a reversible condition but, if left untreated, can progress to the irreversible phase of periodontitis, where inflammation extends to the underlying tissues, periodontal ligament and alveolar bone. The resulting loss of these structures can eventually lead to tooth loss through destruction of the periodontal tissues supporting the tooth (Petersen and Ogawa, 2012). Periodontitis is reported to affect 5-20% of the world's population (Petersen and Ogawa, 2012). The maintenance of good gingival health is therefore important in preventing gingivitis and the development of periodontal disease (Chapple et al, 2015).

Dental plaque is a soft, sticky, colourless deposit of bacteria which collects on teeth and along the gingival margin; it is the causative agent of gingivitis and periodontitis (Chapple et al, 2015; Davies, 2008; Kinane, 2001; Silness and Löe, 1964; Theilade et al, 1966). Gingivitis develops when plaque elicits a local inflammatory response in the gingivae at the site of its accumulation (Davies, 2008; Marsh, 1992). Gingivitis is prevented and resolved through effective plaque control, primarily via mechanical plaque removal (i.e. toothbrushing) (Brook, 2003; Chapple et al, 2015; Davies, 2008; Marsh, 1992; Ower, 2003; Van der Weijden and Hioe, 2005).

Many people are unable to achieve adequate plaque control by toothbrushing alone. The effect of toothbrushing can be augmented by the use of dentifrice (Davies, 2008) and antimicrobial ingredients. Antimicrobial agents (such as metal salts, cetylpyridinium chloride and chlorhexidine) have been included in daily use dentifrice and mouth rinse formulations for many years, with a view to delivering improved plaque control and gum health benefits (Chapple et al, 2015). They complement mechanical plaque removal by inhibiting the growth of bacteria (via bacteriostatic and/or bactericidal activity) in areas of the mouth less accessible to the toothbrush and by interfering with the re-colonisation of plaque bacteria (Teles and Teles, 2009).

Stannous fluoride (SnF_2) is a well-known chemotherapeutic agent which has been incorporated into dentifrices since the 1940s for its oral health benefits (Makin, 2013; Miller et al, 1994; Van Loveren, 1990a; Van Loveren, 2001). The stannous ion (Sn[II]) is a broad-spectrum antimicrobial agent which has been shown to reduce bacterial biomass/ virulence and inhibit bacterial metabolism (Archila et al, 2004; Bellamy et al, 2012; He et al, 2012; Tinanoff, 1990; Tinanoff, 1995). Sn [II] ions rapidly oxidize to "inactive" stannic ions (Sn [IV]) and hydrolyse to form insoluble tin compounds (for example, stannous hydroxide) in the presence of water (and saliva) and saliva-derived ions (Makin, 2013). To maximise the delivery of bioavailable Sn[II] ions to the oral cavity, SnF_2 dentifrices are often "stabilized" by the addition of complexing agents or developed as low water content/anhydrous formulations.

Numerous clinical studies reported in the scientific literature demonstrate the anti-gingivitis/anti-plaque efficacy of 0.4-0.454% SnF_2 dentifrices for example, (Mallatt et al, 2007; Mankodi et al, 1997; Mankodi et al, 2005). GlaxoSmithKline Consumer Healthcare (GSKCH) has developed a 'stabilized' anhydrous 0.454% w/w SnF_2 dentifrice and confirmed its gingivitis efficacy in four clinical studies (Parkinson et al, 2014; Parkinson et al, 2015; Parkinson et al, 2018a; Parkinson et al, 2018b) in a population with mild-moderate plaque-induced gingivitis at timepoints ranging from 4 to 24 weeks.

The aim of the current clinical study is to evaluate the efficacy of a marketed 0.454% SnF_2 dentifrice (Sensodyne Repair and Protect, US market place product) in the treatment of

gingivitis (following dental prophylaxis) at earlier timepoints (over a 3-week treatment period) in a similar population. Efficacy will be compared to a negative control dentifrice.

2.1 Study Rationale

This study will compare a 0.454% SnF_2 dentifrice (Sensodyne Repair and Protect) versus a negative control dentifrice. The aim of this study is to evaluate the gum health efficacy of twice daily brushing with a 0.454% SnF_2 dentifrice over 3 weeks.

Several GSK CH studies (Parkinson et al, 2014; Parkinson et al, 2015; Parkinson et al, 2018a; Parkinson et al, 2018b) have previously investigated the gingival health benefits of SnF_2 at timepoints ranging from 4 to 24 weeks, but to date there have been no GSK CH studies that have looked at timepoints earlier than 4 weeks for this stabilized anhydrous 0.454% SnF_2 dentifrice. There is a desire to show an improvement in gum health at earlier timepoints than 4 weeks and it is believed that recordable gum health benefits may be feasible after 2 to 3 weeks of use (Löe et al, 1965). Therefore, this study is planned to investigate the efficacy of the dentifrice at reducing gingivitis and plaque at the earlier time points of 2 and 3 weeks.

As per the above-mentioned GSK CH studies, the main gingivitis indices that will be employed in this study will be the Bleeding Index (BI), number of bleeding sites (NBS), Modified Gingival Index (MGI) and the Turesky Plaque Index (TPI). This will be a parallel study design that will require subjects to use their assigned dentifrice twice daily for a maximum of 3 weeks, with measurements taken at 2 and 3 weeks.

This is a Phase IV study that is planned to be performed by a clinical site with experience in the above-mentioned gingivitis indices, and therefore a study site in the USA has been selected.

Complete information for the Sensodyne Repair and Protect dentifrice may be found in the single reference safety document (SRSD), which for this study is the Investigator Brochure.

2.2 Background

The effects of SnF_2 containing dentifrices on gingivitis has been described in several clinical studies (Paraskevas and Van der Weijden, 2006). Perlich (Perlich et al, 1995) demonstrated that using an aqueous stabilized 0.454% w/w SnF_2 dentifrice twice daily for 6 months resulted in 20.5% less gingivitis ($p<0.05$) and 33.4% less bleeding ($p<0.05$) when compared with a negative control dentifrice. Williams (Williams et al, 1997) reported that subjects who used a stabilized SnF_2 dentifrice twice daily for 6 months resulted in a statistically significant reduction in plaque when compared to a negative control dentifrice. These results have also been duplicated in other similar 6-month studies (Mallatt et al, 2007; Mankodi et al, 1997; Mankodi et al, 2005).

However, it is well established that SnF_2 reacts with water to form various stable stannous oxide and hydroxide species, and these stannous compounds may not be as therapeutic as the parent molecule. Literature evidence suggests that the largest reductions on gingivitis are observed following the use of "stabilized" SnF_2 (Tinanoff, 1990). Stabilization of the stannous fluoride for the formulations was achieved by chemical methods using phosphates salts. An alternative approach to stabilize SnF_2 is to use a non-aqueous based formulation. GSK CH has developed a non-aqueous SnF_2 dentifrice and has confirmed its gingivitis efficacy in several clinical studies. GSKCH has conducted one exploratory 12 week gingivitis study (Parkinson et al, 2014), two 24 week gingivitis studies (Parkinson et al, 2015; Parkinson et al, 2018a), and one 12 week gingivitis study in a population with "blood in expectorate" as an inclusion

criteria (Parkinson et al, 2018b), on a stabilized 0.454% w/w SnF_2 formulation. Most recently, a 12 week clinical trial in China showed the GSK formulation to provide reductions in BI and Plaque after 6 and 12 weeks (GSK Clinical Study 207014, 2017). All studies demonstrated statistically and clinically superior control of gingivitis (gingival bleeding and visual signs of gingival inflammation) and plaque compared to a fluoride only control toothpaste at 6 and 12 weeks (Parkinson et al, 2014; Parkinson et al, 2018b) and 12 and 24 weeks (Parkinson et al, 2015; Parkinson et al, 2018a). Study 205045 is the only study that has investigated a 4-week timepoint and this also showed a significant reduction in BI and MGI (TPI was not collected) versus a negative control.

This study is designed to investigate the efficacy of a 0.454% SnF_2 dentifrice (Sensodyne Repair and Protect) at reducing gingivitis over a 3-week period when compared to a negative control dentifrice in a population with mild-moderate plaque-induced gingivitis. The design of this study will follow closely that of those summarized above and also recommendations from dental research communities and is consistent with the American Dental Association (ADA) guidelines for such studies (ADA, 2016).

2.3 Mechanism of Action/Indication

Stannous fluoride (SnF_2) is a well-known chemotherapeutic agent, incorporated into dentifrices since the 1940s for its anti-caries, anti-dentin hypersensitivity and anti-plaque/anti-gingivitis benefits (Makin, 2013; Miller et al, 1994; Van Loveren, 2001; Van Loveren, 1990b) .

The stannous ion (Sn [II]) is a broad-spectrum antimicrobial with bacteriostatic and bactericidal properties (Archila et al, 2004; Bellamy et al, 2012; He et al, 2012; Tinanoff, 1995). It has been shown to interfere with the development and maturation of the plaque biofilm, inhibiting bacterial adherence and colonization of the oral surfaces, and penetrating the cell wall to interfere with bacterial metabolism (Tinanoff, 1990; Wilson and Pratten, 1999) . These effects have been shown to carry through to *in vivo* effects on a range of microbial activities, resulting in anti-plaque benefits (Bacca et al, 1997; Kasturi et al, 1995; White et al, 1995).

The clinical anti-gingivitis efficacy of stannous fluoride in an anhydrous dentifrice format will be investigated in subjects with clinically diagnosed gingivitis.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	**Primary**
To evaluate the clinical efficacy of a 0.454% SnF_2 dentifrice in reducing gingivitis (following dental prophylaxis), as measured by the Bleeding Index (BI), compared to a negative control dentifrice, when used twice daily for 3 weeks.	Mean BI at Week 3
Secondary	
To evaluate the clinical efficacy of a 0.454% SnF_2 dentifrice in reducing gingivitis (following dental prophylaxis), as measured by the BI compared to a negative control dentifrice, when used twice daily for 2 weeks.	Mean BI at Week 2
To evaluate the clinical efficacy of a 0.454% SnF_2 dentifrice in reducing gingivitis (following dental prophylaxis), as measured by the number of bleeding sites (NBS), compared to a negative control dentifrice, when used twice daily for 2 and 3 weeks.	Mean NBS at Week 2 and Week 3
To evaluate the clinical efficacy of a 0.454% SnF_2 dentifrice in reducing gingival inflammation (following dental prophylaxis), as measured by the Modified Gingival Index (MGI), compared to a negative control dentifrice, when used twice daily for 2 and 3 weeks.	Mean MGI at Week 2 and Week 3
To evaluate the clinical efficacy of a 0.454% SnF_2 dentifrice in reducing supra-gingival plaque formation (following dental prophylaxis) as measured by the Turesky modification of the Quigley & Hein plaque index (TPI), compared to a negative control dentifrice, when used twice daily for 2 and 3 weeks.	Mean TPI (overall and interproximal) at Week 2 and Week 3
Safety	
To assess the safety and tolerability of a 0.454% SnF_2 dentifrice when used twice daily over 3 weeks.	Treatment emergent adverse events

This study will be considered successful if there is a statistically significant difference in Bleeding index after 3 weeks of twice daily brushing with the SnF_2 dentifrice compared to the control dentifrice and the difference is in favour of the SnF_2 dentifrice.

4 STUDY DESIGN

4.1 Overall Design

This will be a single center, controlled, single blind (examiner blind), randomized, stratified (gender and baseline mean whole mouth MGI score) two-treatment arm, parallel design, clinical study. Study subjects will be aged 18-65 years, non-smokers in good general health with generalized mild-moderate plaque-induced gingivitis and ≥ 20 natural teeth that meet all study criteria at both the Screening and Baseline visits (including ≥ 40 evaluable surfaces for MGI, BI, and TPI).

Approximately 130 (n=65/group) subjects will be randomized to one of the study products.

This study consists of 4 study visits. At Visit 1, Screening, after signing informed consent, subjects will be assessed for eligibility based on the inclusion/exclusion criteria and will undergo Oral Soft and Hard Tissue (OST, OHT) assessments.

Subjects will return between 1 and 28 days following the Screening Visit for the Visit 2, Baseline where they will undergo, in the following order, a full OST examination followed by assessments of gingival inflammation (MGI), gingival bleeding (BI) and supra-gingival plaque (TPI). Eligible subjects will be stratified based on gender and baseline mean whole mouth MGI score (Low: ≤2.00/High >2.00), to ensure a balance of gingivitis across both treatment groups and then randomized to study product.

All randomized subjects will receive full mouth dental prophylaxis (followed by flossing) to remove sub and supra-gingival calculus, stain, plaque and debris from the teeth. All subjects will enter the treatment period with no visible plaque (TPI=0). After all clinical assessments, subjects will be instructed to brush for 1 timed minute at site with their assigned study product, after which they will be instructed to continue using this twice daily (morning and evening) for 2 weeks. After 2 weeks they will return to site for their Week 2 (Visit 3) assessments. They will then continue using their test dentifrice for a further week and will continue to record all brushing events in the diary provided, after which they will return for their Week 3 (Visit 4) assessments. All assessments will be carried out on the facial and lingual/palatal surfaces of each incisor, canine, pre-molar and molar, excluding third molars. To control inter-examiner variability, the same examiner will be used throughout the study for each clinical index.

After the Week 3 visit, study closeout procedures (return of study product etc.) will take place and the subject may undergo an additional prophylaxis if it is deemed necessary by the examiner.

Adverse events and incidents will be recorded from informed consent and at the end of each study visit.

4.2 Rationale for Study Design

The main aim of this study is to investigate the efficacy of a 0.454% stannous fluoride toothpaste in reducing gingivitis compared to a negative control dentifrice, after 3 weeks of twice daily brushing as measured by the Bleeding Index. The efficacy of SnF_2 dentifrices has been demonstrated after 4, 6, 12 and 24 weeks twice daily use. Clinically relevant changes in gingival health are not expected earlier than 2 weeks use of a dentifrice.

This design is typical of many studies conducted to evaluate the clinical efficacy of dentifrices in the treatment of gingivitis. Study subjects with a pre-specified level of gingivitis are randomized to study product; efficacy is determined after professional dental cleaning and a

period of twice-daily brushing, compared to a control/comparator dentifrice. A standard fluoride dentifrice has been chosen as the negative control dentifrice in this study, as this is likely to reflect a subject's typical oral care product use.

Healthy subjects with mild-moderate gingivitis will be included in the study population. The defined level of gingivitis at baseline, will help to minimize the risk of an atypical or potential lack of treatment response for subjects with high levels of gingivitis that may otherwise be managed professionally rather than solely via home use of a twice daily dentifrice. Healthy subjects with mild-moderate gingivitis will be stratified according to their gender and Baseline MGI score to ensure a balance in gingival health across all treatment groups. Gender is a known modifier of the initiation and outcome of conditions related to gingival health (Alam et al, 2012). Stratifying by MGI will facilitate evaluation of BI and MGI in low and high MGI subgroups.

The MGI and the BI are established clinical measures of gingival inflammation and gingival bleeding, respectively (i.e. gingival health); the TPI is an established clinical measure of supra-gingival plaque accumulation. To avoid inter-examiner variability, a single examiner will be responsible for the conduct of each of the clinical indices (MGI, BI, TPI). To assess examiner reproducibility across the treatment period, repeat MGI and TPI assessments will be performed on selected subjects at Visits 2-4. Due to the invasive nature of the index, repeatability assessments are not feasible for the BI.

A parallel group design has been selected as more appropriate for this investigation. Anticipated differential changes in clinical variables among treatment groups could lead to carryover effects and an altered oral health state should a crossover design be employed. The dosage regimen of twice daily use (morning and evening) will be the same for each treatment group and is based on consumer habit and common practice within oral care clinical trials. The use of a Washout period prior to Baseline is not a requirement under the ADA guidelines (ADA, 2011), however it is recommended that subjects should not use antimicrobial mouth rinses or other dental products that might affect a subject's plaque or gingivitis status. A minimum of 1 to maximum 28 days lead-in Phase is appropriate to allow subjects to comply with study and lifestyle restrictions prior to Baseline Visit.

Within 1 to 28 days of Screening (Visit 1), eligible subjects will return to the site for the Baseline visit (Visit 2) with overnight plaque (subjects will abstain from oral hygiene for 12hours (+6 hours; -2 hours) i.e. overnight immediately before the visit). At the Baseline visit (prior to randomisation), subjects will undergo, in the following order, a full OST and assessments of gingival inflammation (MGI), gingival bleeding (BI) and plaque disclosure followed by supra-gingival plaque (TPI). The baseline levels of measures of gingivitis and plaque are consistent with previous GSKCH gingivitis studies including those investigating a sodium bicarbonate containing dentifrice with mean MGI 1.75-2.30 considered representative of generalised mild-moderate gingivitis. Furthermore, a minimum of 20 permanent gradable teeth is similarly consistent with GSKCH gingivitis clinical studies and representative of a minimum of a "shortened dental arch" (Kayser, 1989) equating to anywhere between 20-28 gradable teeth (excluding 3rd molars) per subject.

At Baseline Visit 2, following the clinical examinations (including initial MGI, BI & TPI assessments) dental prophylaxis will be performed for each subject using a standard polishing dental compound prophylaxis paste and periodontal instruments as required, followed by flossing by the clinician. Subjects teeth will then be re-disclosed using a disclosing solution to check for residual plaque. A second clinician will check to ensure all plaque has been removed. Any residual plaque remaining will be removed by the clinician as required and including dental

polishing with a standard polishing dental compound, sufficient to bring the subject to zero plaque (i.e. TPI=0). Dental prophylaxis removes all calculus and stain from the surface of the teeth (plaque retentive factors that could influence plaque accumulation) and ensures study subjects enter the treatment period with no visible plaque (TPI = 0). A dental prophylaxis is included as this is considered industry standard in agreement with Food and Drug Administration (FDA) guidelines (FDA., 2005), and is consistent with previous GSKCH gingivitis clinical studies, along with a lack of dental calculus/ staining that could otherwise act as plaque retentive factors for subjects participating in the clinical study.

Hormonal changes during pregnancy may affect the response of the gingival tissue to plaque bacteria and could impact the gingivitis efficacy measurements (Figuero et al, 2010). Therefore, women who are pregnant at screening will be excluded and woman who become pregnant during the course of the study will be discontinued. It should be noted however, that there are no safety concerns with pregnant women using any of the study products.

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 et al, 2000; Obeid and Bercy, 2000). A 14-day experimental gingivitis model reported much less gingival bleeding in smokers compared to non-smokers, even though plaque levels and the composition of the oral microflora were similar between the two groups (Lie et al, 1998). Smokers will therefore be excluded from this investigation of product efficacy for the treatment of plaque-induced gingivitis.

According to International Conference on Harmonisation (ICH) guidelines [ICH, 1996], for a study to be classed as truly double blind, not only does the examiner (and any member of staff who may be involved in the dispensing of products and/or analysis of data) need to be blind to the treatment a subject receives, but the products under test must be identical in every way (color, flavour, appearance, packaging). It can be difficult to achieve identical sensory profiles and visual appearance for products evaluated in oral care clinical studies. Where this is not possible, as in the current study, the level of blinding is described as ‘examiner-blind’.

4.3 Justification for Dose

Subjects will be instructed to dose a strip of dentifrice to cover the full brush head, and brush for 1 timed minute. The dosing regimen of twice daily use for 1 minute will be the same for each treatment and is based on consumer habit and common practice within other oral care clinical trials.

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, Section 1.1.

The end of this study is defined as the date of last visit of the last subject in the study.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Approximately 150 subjects will be screened to randomize 130 to ensure 60 evaluable subjects per treatment group complete the entire study.

An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process directly, and has successfully met eligibility criteria to proceed beyond the screening visit and enter the Lead-In phase, as applicable for the protocol design.

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 study.

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 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 18-65years, inclusive.
3. A subject who is willing and able to comply with scheduled visits, treatment plan and other study procedures.
4. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, no clinically significant or relevant abnormalities in medical history or upon oral examination, or condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.
5. **AT SCREENING (Visit 1):**
   a. Subject with at least 20 natural, permanent teeth excluding 3rd molars.
   b. Subjects with at least 40 evaluable surfaces.
      An evaluable surface is defined as having 2/3rds of the natural tooth surface gradable for the selected clinical indices. The following should not be included in the evaluable surface count- third molars; fully crowned/extensively restored, grossly carious, orthodontically banded/bonded or abutment teeth; surfaces with calculus deposits which, in the opinion of the clinical examiner, would interfere with the baseline assessments of the selected clinical indices.
   c. Subject with generalized mild-moderate plaque-induced gingivitis, in the opinion of the clinical examiner, as confirmed by visual examinations.
6. **AT BASELINE- Prior to Dental Prophylaxis (Visit 2):**

a. Subject with ongoing hard tissue eligibility and, in the opinion of the clinical examiner, at least 40 evaluable surfaces.

b. Mean whole mouth MGI ≥ 1.75 to ≤ 2.30

c. Mean whole mouth supra-gingival TPI score ≥ 1.5

d. ≥ 20 bleeding sites

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. Subjects with, in the opinion of the investigator or medically qualified designee, any clinically significant/relevant abnormalities in medical history or oral examination, or any other condition, that would affect the individual's ability to understand and follow study procedures and requirements.
5. Subjects with any medical condition which, in the opinion of the investigator or medically qualified designee, is causing xerostomia.
6. Subjects with any medical condition which in the opinion of the investigator or medically qualified designee, could directly influence gingival bleeding.
7. A subject who is pregnant or intending to become pregnant over the duration of the study (self-reported).
8. A subject who is breastfeeding.
9. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
10. Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
11. Subjects with recent history (within the last year) of alcohol or other substance abuse.
12. Subject who is a current smoker or an ex- smoker who stopped within 6 months of Screening.
13. Subject who currently uses smokeless forms of tobacco (e.g. chewing tobacco, gutkha, pan containing tobacco, nicotine-based e-cigarettes).
14. Subjects with a severe oral condition (e.g. acute necrotizing ulcerative gingivitis or oral or peri-oral ulceration including herpetic lesions) that would, in the opinion of the

investigator, compromise study outcomes or the oral health of the subject/ examiner if they were to participate in the study.

15. Presence of a tongue or lip piercing, or any other oral feature that could interfere with the usage of a toothbrush
16. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.
17. A subject unwilling or unable to comply with the Lifestyle Considerations described in this protocol.
18. A subject that has used an anti-bacterial mouthwash (e.g. chlorhexidine) or use of any oral care product that in the view of the investigator could interfere with plaque formation or measures of gingivitis, within 14 days of the Baseline Visit.
19. **Periodontal Exclusions:**
    a) Subject with signs of active periodontitis.
    b) Subject with gingivitis which, in the opinion of the investigator, is not expected to respond to treatment with an over-the-counter dentifrice.
    c) A subject who is receiving or has received treatment for periodontal disease (including surgery) within 12 months of Screening
20. **Dental Exclusions:**
    a) Subject with active caries that could, in the opinion of the investigator, compromise study outcomes or the oral health of the subject if they were to participate in the study.
    b) Subject with dentures (partial or full).
    c) Subject with an orthodontic appliance (bands, appliances or fixed/ removable retainers).
    d) A subject who has received orthodontic therapy within 12 months of Screening
    e) Subject with numerous restorations in a poor state of repair.
    f) Subject with any dental condition (e.g. overcrowding) that could, in the opinion of the investigator, compromise study outcomes or the oral health of the subject if they were to participate in the study.
    g) Subject who has had dental prophylaxis within 12 weeks of Screening
    h) Subject who has had teeth bleaching within 12 weeks of Screening
    i) A subject with high levels of extrinsic stain or calculus deposits that might interfere with plaque assessments.
21. **Medication Exclusions**

    AT SCREENING (Visit 1):
    a) Subject who requires antibiotics prior to dental prophylaxis or other dental procedures.
    b) Subject who is currently taking antibiotics
    c) Subject who is currently taking an anti-inflammatory medication which, in the opinion of the Investigator, could affect gingival condition (e.g. ibuprofen).

c) Subject who is currently taking anti-coagulant medication which, in the opinion of the Investigator, could affect gingival condition (e.g. warfarin).

d) Subject who is currently taking a systemic medication or traditional/herbal remedy which, in the opinion of the Investigator, could affect gingival condition (e.g. immunosuppressants such as cyclosporine, phenytoin, calcium channel blockers, aspirin therapy).

22. **Medication Exclusions**

AT BASELINE (Visit 2):

a) Subject who has taken antibiotics in the 14 days prior to Baseline

b) Subject who has taken an anti-inflammatory medication in the 14 days prior to Baseline which, in the opinion of the Investigator, could affect gingival condition (e.g. ibuprofen).

c) Subject who has taken anti-coagulant medication in the 14 days prior to Baseline which, in the opinion of the Investigator, could affect gingival condition (e.g. warfarin).

d) Subject who has taken a systemic medication or traditional/herbal remedy in the 14 days prior to Baseline which, in the opinion of the Investigator, could affect gingival condition (e.g. immunosuppressants such as cyclosporine, phenytoin, calcium channel blockers, aspirin therapy).

e) Subject who has used an antibacterial dentifrice or mouth rinse in the period between Screening and Baseline.

23. Subject who is unwilling or unable to comply with the Lifestyle/Study Restrictions described in the study protocol.
24. Any subject who has previously been enrolled in this study.
25. Subjects who, in the judgement of the investigator, or medically qualified designee should not participate on the study.

5.4 Randomization Criteria

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

5.5 Lifestyle Considerations

5.5.1 Dental Product/Treatment and Oral Hygiene Restrictions

From Screening (Visit 1) to the Subject's Last Study Visit

- Subjects should not carry out any interproximal dental cleaning. Use of dental floss, toothpicks, waterpicks or inter-dental brushes is prohibited (except for the removal of impacted food with non-antimicrobial products only).
- Subjects should not chew gum or consume any confectionery containing xylitol (e.g. sugar-free mints).
- Subjects should delay any non-emergency dental treatment until after study completion (including dental prophylaxis).

From Baseline (Visit 2) to the Subject's Last Study Visit

- Subjects should not use any other oral care products (e.g. dentifrices, toothbrushes, mouthrinses) than those provided during the study.

Before Clinical Efficacy Assessment Visits: Baseline (Visit 2), Week 2 (Visit 3) and Week 3 (Visit 4)

- Subjects should refrain from oral hygiene procedures for 12 hours (+6 hours, -2 hours) before their visit and attend the study site with overnight plaque growth.

5.5.2 Dietary Restrictions

Before Clinical Efficacy Assessment Visits: Baseline (Visit 2), Week 2 (Visit 3) and Week 3 (Visit 4)

- Subjects must abstain from all food and drink (except water) for at least 4 hours prior to their scheduled assessment visits and until all assessments are complete during visit days. Water is permitted until 1 hour prior to their scheduled study visits.

5.5.3 Medication and Treatment Restrictions

The following medication and treatment restrictions apply for the duration of the study:

- If current/ concomitant medications/ treatments or traditional herbal ingredients/ treatments are used during the study, their identity, as well as their dosage and frequency, start and stop dates must be reported to the Investigator and recorded in the Case Report Form (CRF).

For more information on concomitant medications, please refer to Section 6.8.

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 adverse events 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

Clinical examiners involved in screening and efficacy assessments will be qualified dental professionals, registered to practice in the USA. Oral examinations to determine subject eligibility and all safety and efficacy assessments will be performed by appropriately trained clinical examiners. The clinical examiner(s) performing the MGI, BI and TPI assessments should have a demonstratable history of use of these indices in clinical trials.

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 Products	
	Test Product	**Negative Control Dentifrice**
Product Name	Sensodyne Repair and Protect	Colgate Cavity Protection
Pack Design	Carton of 2 over-wrapped tubes	Carton of 2 over-wrapped tubes
Dispensing Details	1 carton of 2 tubes- Baseline visit	1 carton of 2 tubes- Baseline visit
Product Master Formulation Code (MFC)	Commercial Product (USA Market place product) (CCI [redacted]	Commercial Product (USA Market place product)
Dose/Application	Full ribbon of toothpaste on head of toothbrush provided	Full ribbon of toothpaste on head of toothbrush provided
Route of Administration	Oral topical	Oral topical

Usage Instructions	Subjects will brush their teeth for one timed minute twice a day (morning and evening) in their usual manner	Subjects will brush their teeth for one timed minute twice a day (morning and evening) in their usual manner
Return Requirements	All used/unused samples to be returned	All used/unused samples to be returned

Table 6-2 Sundry Items

Sundry Items to be supplied GSK CH

Item	**Supplied By**	**Pack Design**	**Dispensing Details**	**Return/Disposal Details**	
				Used Samples	**Unused Samples**
Toothbrush (Aquafresh Clean Control)	GSK CH	Individual commercial pack – 2 per subject	2 at baseline for use with study product	Subject to keep or destroyed at site using site disposal procedures	Destroy at site using site disposal procedure
Countdown Timer	GSK CH	Individual commercial pack – 1 per subject	Baseline visit	Subject to keep or destroyed at site using site disposal procedures	Destroy at site using site disposal procedure
Prophylaxis paste	GSK CH	Not dispensed to subjects; only used at study site	Baseline visit	Destroy at site using site disposal procedures	Destroy at site using site disposal procedure
Non-antimicrobial dental floss	GSK-CH	Not dispensed to subjects; only used at study site	Baseline visit	Destroy at site using site disposal procedures	Destroy at site using site disposal procedure
Trace Red Plaque disclosing solution	GSK-CH	Not dispensed to subjects; only used at study site	Baseline visit; Visit 3 (wk 2); Visit 4 (Wk 3)	Destroy at site using site disposal procedures	Destroy at site using site disposal procedure
Opaque recyclable bags	GSK-CH	1 per subject	Baseline visit; Visit 3 (wk 2); Visit 4 (Wk 3)	Destroy at site using site disposal procedures	Destroy at site using site disposal procedure

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

6.1.1 Dosage Form and Packaging

The investigational dentifrice and negative control dentifrice will be supplied to the clinical site by GSK CH. Both products will be supplied in commercial tubes and will be overwrapped in white opaque vinyl (to mask the identity and obscure any branding) with a study label affixed. Two tubes will be placed into a plain white carton and a study label will be applied to the carton. 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.

Each eligible subject will receive sufficient tubes of their assigned study product to cover usage during the treatment period. Sundry items will be supplied in their commercial packaging for dispensing by study staff as required.

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 study products will be prepared and/or dispensed by qualified unblinded site personnel according to the dosage and administration instructions.

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

The product dispensing area will be separate from the clinical examination area. Study products will be dispensed in a blinded fashion and staff members involved in dispensing 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. An additional member of site staff should verify the dispensing procedures are completed accurately.

A record of product dispensing to each subject will be maintained in the dispensing log; completion of the dispensing procedure will be recorded in the eCRF.

6.2 Administration

Subjects will be instructed to self-administer their assigned product per the usage instructions provided to them along with their diaries. To help subjects understand the correct dose and usage instructions:

- Site staff will demonstrate dispensing a full ribbon of dentifrice (along the length of the toothbrush head) to each eligible subject and supervise their first brushing with assigned test dentifrice/first diary entry at the end of Baseline, Visit 2 after all clinical assessments have been completed.

- Supervised brushings with study product/diary entry will be carried out at the end of the Baseline (Visit 2) and Week 2 (Visit 3) visits - after all clinical assessments have been completed.

To facilitate compliance with dentifrice usage, subjects will use the diary provided to record the date/time of each brushing occasion throughout the treatment periods. They will also use the diary to note any additional brushings, the reasons for any missed or additional brushings, any issues with the dentifrice used, oral problems, adverse events and any additional medications taken.

6.2.1 Medication/Dosing Errors

Study product/dosing errors may result, in this study, from the administration or consumption of:

- the wrong product,
- by the wrong subject,
- at the wrong time,
- or at the wrong dosage.

Such study product/dosing errors occurring to a study subject are to be captured in the eCRF. In the event of study product dosing error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours.**

Study product /dosing errors are reportable irrespective of the presence of an associated AE, including:

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

If a study product /dosing error is accompanied by an AE, as determined by the investigator, the study product /dosing error and, any associated adverse event(s) are to be captured in the eCRF AE form.

6.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a product at an amount higher than specified in the protocol.

Overdose is not likely to occur in this study.

Limited quantities of the study product(s) will be supplied, and closely monitored by the site for each subject.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (and serious adverse event (SAE), if appropriate). For reporting, follow the AE and SAE reporting instructions.

6.3 Investigational/Study Product Storage

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

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 at site should be reported to the appropriate site staff upon discovery and communicated to the 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 at site 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 site, 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.

Study product (used and unused) will be returned to the clinical study site at Visit 4. Monitoring of product accountability will be performed by the study monitor during site visits and at completion of the study.

6.4.1 Destruction of Investigational/Study Product Supplies

At the end of the study, the Principal Investigator (PI) 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 (including empty dentifrice tubes) will be returned for destruction to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided. Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction will be provided by GSK CH during the study in time for study close out visit.

6.5 Blinding and Allocation/Randomization

All subjects will be centrally randomized to one of the study arms using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided to the study 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.

The investigator's knowledge of the product allocation should not influence the decision to enroll a subject or affect the order in which subjects are enrolled.

This study is described as examiner-blind (the clinical examiner will be blinded to the product received). The study statistician, other employees of the Sponsor (including CRS) and vendors acting on behalf of the sponsor, who may influence study outcomes will also be blinded to the product allocation.

To ensure the examiner remains blinded throughout the study, staff involved in the preparation and dispensing of study products will work in a separate area. The examiner is not permitted in any area where study product is stored, dispensed, or in use.

Subjects will be instructed not to remove study products from the opaque bags provided outside of the dispensing room, while at the study site. Dispensing staff will not be involved in any efficacy/safety assessment procedures during the study. Subjects will be stratified by gender (male and female) and their baseline mean whole mouth MGI score (Low: ≤2.00/High >2.00). This will lead to 4 strata in total.

6.6 Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. 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 Compliance

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

A diary will be supplied to promote compliance and to capture details of product use throughout the study period. 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 eCRF as appropriate.

The number of any missed or additional applications or doses will be captured as protocol deviations and transcribed from the diary into the eCRF. Subjects will be re-instructed in the correct usage requirements and diary completion as needed.

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 eCRF with indication, reason for use, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about 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 first dosing at Visit 2 will be documented as concomitant medication/treatments.

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, 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

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 eCRF.

7.2 Lost to Follow up

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 the subject wishes to and/or should continue in the study.

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. 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 an OST and OHT examination.

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 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 1.1.

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.

The following procedures will be completed, and data recorded in the eCRF:

- Informed consent.
- Demographics, medical history, prior/current medication (including non-drug therapy), & smoking status.
- The oral care products the subject is currently using will be reviewed to confirm that they do not contain an anti-bacterial mouthwash (e.g. chlorhexidine) or use of any oral care product that in the view of the investigator could interfere with plaque formation or measures of gingivitis. Subjects will be required to bring the products to the study

site to enable study staff to check ingredient listings to ensure compliance with exclusion criteria 18.
- Oral soft tissue (OST) examination.
- Oral hard tissue (OHT) examination.
- Gross gingival assessment.
- Inclusion/exclusion criteria.
- Subject eligibility / continuance.
- Adverse events & Incidents.

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 Informed Consent Form as this is the point at which all Adverse Events will be captured from. The date and time of consent will be transcribed to the eCRF.

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 eCRF.

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 eCRF: year of birth, gender, ethnicity and race.

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. This is required for this study as the product is marketed in the US and allows for summary of data across different clinical studies, and different launch markets. This aids in a better understanding of potential differences across ethnicities.

8.1.3 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history (in the last 1 year), including allergies or drug sensitivity, will be documented in the eCRF.

Prior/current 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 eCRF.

8.1.4 Oral Examination/Assessment

Inclusion and exclusion criteria information will be documented in the eCRF. The following screening procedures should be carried out by a qualified dental professional:

- Oral soft tissue (OHT) examination (as per Section 9.1.1).
- Oral hard tissue (OST) examination (as per Section 9.1.2).
- Gross assessment of gingival health (as per Section 9.1.3) The oral examinations/assessments should be carried out as described in Section 9. All findings will be recorded in the eCRF.

8.1.5 Inclusion/Exclusion Criteria

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

8.1.6 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 eCRF.

To prepare for study participation, subjects will be instructed in the Lifestyle Guidelines (Section 5.5) and any Concomitant Medication/Treatment(s) (Section 6.8) requirements of the protocol.

8.2 Study Period

8.2.1 Visit 2/Day 1 (Baseline)

Subjects will be admitted to the clinical study site 1 to 28 days after the Screening visit. The following procedures/ assessments will take place in the order listed below as much as possible and recorded in the eCRF:

- Review of concomitant medications and non-drug treatments/ procedures and lifestyle restrictions.
- Full oral soft tissue (OST) examination (Section 9.1.2).
- MGI assessment (& repeatability assessment, where applicable) (Section (9.2.1).
- BI assessment (Section 9.2.2).
- Plaque disclosure (Section 9.2.3).
- TPI assessment (& repeatability assessment, where applicable) (Section 9.2.4).
- Inclusion/exclusion criteria.
- Subject eligibility / continuance.
- Stratification/randomization.

- Sub- & supra-gingival prophylaxis & flossing.
- Plaque disclosure followed by first examiner and second clinician check with residual plaque removal, if applicable following prophylaxis
- Confirmed TPI= 0 following dental prophylaxis.
- Dispense study dentifrice, toothbrush, study instructions, diary & timer.
- Supervised subject brushing at site.
- Adverse events & Incidents (Section 10).

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

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 eCRF.

8.2.2 Visit 3/Day 14 (Week 2)

The following procedures/ assessments will take place in the order listed below as much as possible and recorded in the eCRF:

- Collect study dentifrice, toothbrush & diary from subject.
- Review of concomitant medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions.
- Compliance checks including diary review.
- Subject eligibility / continuance.
- Full OST examination (Section 9.1.2).
- MGI assessment (& repeatability assessment, where applicable) (Section (9.2.1).
- BI assessment (Section 9.2.2).
- Plaque disclosure (Section 9.2.3).
- TPI assessment (& repeatability assessment, where applicable) (Section 9.2.4)
- Return study dentifrice, toothbrush, study instructions and diary to subject.
- Supervised subject brushing at site.
- Adverse events & Incidents (Section 10).

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

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 eCRF.

8.2.3 Visit 4 /Day 21 (Week 3)

The following procedures/ assessments will take place in the order listed below as much as possible and recorded in the eCRF:

- Collect study dentifrice, toothbrush, diary & timer (all study supplies) from subject.
- Review of concomitant medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions.
- Compliance checks including diary review.

- Subject eligibility / continuance.
- Full OHT examination (Section 9.1.1).
- Full OST examination (Section 9.1.2).
- MGI assessment (& repeatability assessment, where applicable) (Section (9.2.1).
- BI assessment (Section 9.2.2).
- Plaque disclosure (Section 9.2.3).
- TPI assessment (& repeatability assessment, where applicable) (Section 9.2.4).
- End of study dental prophylaxis (optional - if deemed necessary by examiner).
- Adverse events & Incidents (Section 10).
- Study conclusion

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

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 eCRF.

8.2.4 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 Section 10.

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 eCRF as appropriate.

Additional and missed product applications will be considered deviations from the protocol and will be recorded on the Deviations Log and entered into the eCRF as appropriate.

8.2.5 Dental Prophylaxis

Randomized subjects will receive a full mouth dental prophylaxis (using conventional prophylaxis paste and periodontal instruments as required), followed by flossing, to remove sub- and supra-gingival calculus, stain, plaque and debris from the teeth. A second clinician will confirm all sub- and supra-gingival calculus, visible stain, plaque and debris has been removed (visually, and by tactile examination using a dental explorer). If necessary, additional dental cleaning will be carried out to achieve this. Prophylaxis may be carried out by different clinicians to facilitate subject flow.

Following prophylaxis, it should be confirmed that the subject whole mouth post-prophylaxis TPI = 0. Completion of this procedure should be recorded in the eCRF.

8.3 Study Conclusion

The Study Conclusion page of the eCRF 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 end 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.

8.4 End of Study Optional Prophylaxis

Subjects who, in the opinion of the clinical examiner, would benefit from dental prophylaxis following their participation in the study will be offered full mouth dental prophylaxis (using conventional prophylaxis paste and periodontal instruments as required) on completion of all clinical assessments. Prophylaxis may be carried out by different, appropriately qualified clinicians to facilitate subject flow.

8.5 Follow-up Visit

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. Any follow-up details and updates/changes on AEs will be recorded in the eCRF.

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. A single examiner will be responsible for the conduct of the clinical measures of gingivitis/ plaque accumulation for the duration of the study.

Eligible tooth assessments will be accomplished by oral examination and will evaluate dentition exclusions along with a gross gingival assessment in relation to the general dentition inclusion/ exclusion criteria. Assessments will be carried out by the investigator, or qualified designee, against the inclusion/ exclusion criteria. Ineligible subjects will not be re-screened.

9.1.1 Oral Hard Tissue (OHT) Assessment

Examination of the oral hard tissues (all facial, lingual/ palatal, mesial/distal and occlusal surfaces) will be accomplished by direct observation, using retraction aids as appropriate. The presence of restorations (for example, amalgams, composites, veneers, crowns, bridges, implants), carious lesions, non-carious hard tissue loss (abrasion, attrition, abfraction and erosion) and any other hard tissue irregularity (for example, fractures, staining) will be recorded.

Observations will be listed as either absent or present, and conditions noted as present will be described in the eCRF. Any abnormality or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject from the OST examination carried out at Screening will be recorded as an AE. Findings from this Screening examination will be used to determine subject eligibility.

In addition to the to the OHT, the presence of partial/full dentures, fixed or removable orthodontic braces/bands and fixed orthodontic retainers will also be recorded as part of the inclusion and exclusion criteria.

9.1.2 Oral Soft (OST) Assessment

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee. The examination will be accomplished throughout the study 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 eCRF as either normal or abnormal, with details of any abnormalities. Any abnormality or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject from the OST examination carried out at Screening will be recorded as an AE.

Findings from this examination performed at the Screening Visit will be used to determine subject eligibility.

9.1.3 Gross Assessment of Gingival Health

Visual assessment of gingival health will be performed to record the presence/absence of generalized mild-moderate plaque-induced gingivitis as per the inclusion criteria. (MGI/BI will not be recorded for this assessment).

Findings from this examination performed at the Screening Visit will be used to determine subject eligibility.

9.2 Efficacy Assessments

The following clinical efficacy assessments will be performed by a single, appropriately trained clinical examiner (at the times and in the order defined in the Study Procedures, Section 8), in the same room (with consistent light levels) for the duration of the study, to standardize assessment conditions.

An evaluable tooth surface is defined as having 2/3rd of the natural tooth surface gradable for the selected clinical indices. Gingivitis or plaque accumulation associated with third molars, fully crowned/extensively restored, grossly carious or abutment teeth will not be assessed. In addition, surfaces with calculus deposits which, in the opinion of the clinical examiner, would interfere with the baseline assessments of the selected clinical indices, will not be assessed.

9.2.1 Modified Gingival Index (MGI)

The MGI is a non-invasive modification of the original GI (Löe and Silness, 1963) which focuses on the visual symptoms of gingivitis (redness, texture, edema) (Lobene, 1986) . The

MGI will be assessed for the facial and lingual/palatal gingiva of all evaluable teeth, four sites per tooth (facial surface - papilla and margin; lingual/palatal surface - papilla and margin). The MGI scoring system will be as described in Table 9-1 and will be assessed by the same examiner on all evaluable teeth at Visit 2 (Baseline), Visit 3 (Wk 2) and Visit 4 (Wk 3).

Table 9-1 The Modified Gingival Index

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

9.2.2 Bleeding Index (BI)

Gingival bleeding will be assessed as a measure of gingival health for facial and lingual/palatal gingiva of all evaluable teeth, six sites per tooth (mesiobuccal, buccal, distobuccal, mesiolingual/palatal, lingual/palatal and distolingual/palatal), using the Bleeding Index (BI) (Saxton and Van der Ouderaa, 1989).

To perform the assessment, a round-end probe (for example, a CPITN probe [CPITN = Community Periodontal Index of Treatment Needs]) is inserted approximately 1mm into the gingival sulcus (at approximately 60 degrees) and moved around the tooth, from the distal interproximal area to the mesial interproximal area, gently stretching the gingival epithelium. Contact with the tooth surface will be avoided. Gingival bleeding is assessed 30 secs after probing. Assessments will be performed one quadrant at a time; BI scores will be recorded before moving to the next quadrant. The scoring system is described in Table 9-2. Sites with a score of 1 or 2 will be classified as 'bleeding' sites. The BI will be assessed by the same examiner on all evaluable teeth at Visit 2 (Baseline), Visit 3 (Wk 2) and Visit 4 (Wk 3).

Table 9-2 The Bleeding Index (BI)

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

9.2.3 Plaque Disclosure

Dental plaque is colorless and so is usually disclosed ('stained') prior to assessment. The disclosing solution will be used according to the manufacturer's instructions.

- At the request of the subject, the clinician may apply a thin layer of petroleum jelly to the subject's lips, as a barrier to help minimize staining by the disclosing solution. Care should be taken to ensure no petroleum jelly comes into contact with the labial surfaces of the anterior teeth as this could impact clinical assessments in this region.
- The subject will rinse their mouth with 10 mL tap water for 10 seconds to remove any food debris and expectorate.
- The clinician will then apply the Plaque disclosing solution as per the label instructions. Care will be taken not to dislodge the plaque during this process. The subject will then rinse with 10 mL tap water for 10 seconds and expectorate to remove excess solution.

Plaque may be redisclosed between the TPI and repeat assessments at the discretion of the clinical examiner.

9.2.4 Turesky Plaque Index (TPI)

Supra-gingival plaque will be assessed on the facial and lingual surfaces of the teeth using the TPI (Lobene et al, 1982; Turesky et al, 1970). Third molars can be included in the assessment if, as a result tooth loss, they are functioning as second molars and gradable for TPI.

Each tooth surface is divided into 3 areas; three scores are recorded facially (mesiofacial, facial, distofacial) and three scores lingually (mesiolingual, lingual and distolingual) generating a total of six scores per tooth. The plaque will be disclosed (as described in Section 9.2.3) and scored for each site as follows.

Table 9-3 Turesky Plaque Index

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

9.2.5 Repeatability Assessments

The clinical examiner selected for this study will have demonstrated their ability to replicate their own scores (intra-examiner repeatability) on a tooth site-by-tooth site basis in previous studies and/or calibration exercises. Repeat MGI and TPI assessments will be performed by the clinical examiner at Visits 2 - 4. At least 2 repeat assessments should be performed for each index on each clinical assessment day (≥1 in the morning; ≥1 in the afternoon). 'Repeat' subjects will be selected at random from those in attendance. Different subjects can be used for repeat MGI and TPI assessments.

There should be a delay of at least 10 minutes between original and repeat assessments for a given subject and ideally separated by another subject. No other procedure on the subject

should be carried out between the first and the repeat assessment. Where possible, the clinical examiner should assess a different subject in the intervening period.

Scores from the first assessment must not be visible to the examiner/scribe when the repeat assessment is carried out.

9.3 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.

9.3.1 Oral Hard Tissue Examination (OHT)

Carried out as described in Section 9.1.1.

Any change observed by the clinical examiner or reported by the subject from Screening will be recorded as an AE.

9.3.2 Oral Soft Tissue Examination (OST)

Carried out as described in Section 9.1.2.

Any change observed by the clinical examiner or reported by the subject from Screening will be recorded as an AE.

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.

- 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. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes 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 consents 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 eCRF 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 eCRF.

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 eCRF 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 eCRF 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, except for 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 eCRF 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 eCRF 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 eCRF. Where the same data are collected, the AE eCRF 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 eCRF 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 eCRF 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). 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).

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) 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 . 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). 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 discontinue study treatment and 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 device in this study is the toothbrush (Class 1 Medical Device) supplied to all subjects for use at site and throughout the treatment period.

10.9.1 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.

10.9.2 Reporting of Incidents and Malfunctions

All incidents must be reported to GSK CH **immediately and under no circumstance should this exceed 24 hours** 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 **immediately and under no circumstance should this exceed 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

10.9.3 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.

10.9.4 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. The 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 Personal Information (PI) (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 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 Personal Information (PI) (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.

11.4 External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSK CH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed quality control process will be performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSK CH.

Reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

A sufficient number of healthy subjects will be screened to randomize approximately 130 subjects (65 per treatment group) to ensure 60 evaluable subjects per treatment complete the entire study.

The primary objective for this study is to evaluate the clinical efficacy of a 0.454% SnF_2 dentifrice in reducing gingivitis (following dental prophylaxis), as measured by the Bleeding Index (BI), compared to a negative control dentifrice, when used twice daily for 3 weeks.

With 60 evaluable subjects per treatment group, it should be possible to detect a 0.1 difference in BI sd=0.17 (Parkinson et al, 2018b) with 90% power and a two sided 5% significance level. This difference would approximately represent a 23% difference between treatment groups.

This estimate will allow detection of a 5% difference in a key secondary variable MGI with 90% power.

12.2 Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the Statistical Report and Analysis Plan (RAP), 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.

12.2.1 Definition of Analysis Populations

All assessments of safety will be based on the Safety population. The Safety population will comprise all randomized subjects who receive at least one dose of the study product. This population will be based on the product the subject actually received.

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 dose of the study treatments and provided at least one post-baseline 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. There will be a separate population for repeat Plaque assessment and repeat MGI assessment.

12.2.2 Exclusion of Data from Analysis

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

A PP analysis will be performed only on the primary variable (BI score) if there is more than 10% difference in the number of subjects between the PP and m-ITT populations. A decision on whether a PP analysis will be performed will be made prior to study unblinding (release of the randomization codes).

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

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 group for the Safety and mITT populations and the PP population if a PP analysis is performed.

12.2.4 Study Drug/Product Compliance and Use of Other Therapies

12.2.4.1 Study Drug/Product Compliance

The number of brushings and compliance rate will be summarized by treatment group between treatment visits and across the whole duration.

Compliance will be defined as :-

100 x (number of brushings)/(2x($visit_n$ - $visit_{n-1}$);

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(es)

The Primary efficacy variable is the mean BI at week 3.

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

The BI score will be analyzed using analysis of covariance (ANCOVA) with treatment group, gender, and baseline MGI stratification as factors and baseline score as a covariate. Adjusted means of the two treatments and the treatment difference will be provided together with 95%CI and P-values and percent difference between treatment groups.

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. Van Elteren test).

12.2.6 Secondary Analysis(es)

Secondary variables are: -

Mean BI at week 2

Mean NBS at week 2 and 3

Mean MGI at week 2 and 3

Mean TPI (Overall) at week 2 and 3

Mean TPI (Interproximal areas) at week 2 and 3

Each variable will be calculated separately in a similar manner to the primary variable in that the whole mouth average will be calculated based on the total mouth score divided by the number of tooth sites assessed. The number of bleeding sites is derived from the BI Index where a bleeding site is a site scored as a 1 or 2. For interproximal plaque only the relevant sites will be used.

Each secondary variable will be analyzed separately as per the primary variable. For the analysis of MGI the stratification factor of MGI will not be included as the baseline value of MGI is included as a covariate.

The 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. Van Elteren test).

12.2.7 Safety Analysis(es)

Safety variables will focus on: -

Exposure

AEs

OST

Incidents

All AEs will be coded using MedDRA. AEs will be categorised as oral and non-oral by the primary investigator. 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.

Exposure to treatment is covered under treatment compliance and the number of brushings.

12.2.8 Other Analysis(es)

12.2.8.1 Repeatability assessment

The repeat dental assessments (MGI and TPI) will be compared to the original assessments and the repeat assessments will not be used in any efficacy analyses. The first and repeat 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 $\kappa < 0.4$

This analysis will be conducted using the Repeatability population.

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 interim analysis is planned for this study

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 (IRB/EC)

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.
Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (e.g. minor, decisional impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (e.g. parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

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 stannous fluoride dentifrices at any time. 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 eCRFs 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 APPENDICIES

15.1 Product Usage Instructions

INSTRUCTIONS

Brush twice a day (morning and evening) for 1 timed minute.

Each time you brush:

- Dispense a ribbon of toothpaste covering the entire length of the toothbrush head (see picture below).
- Set your timer for 1 minute, and then brush all the teeth in your mouth in your usual manner for 1 timed minute.
- Please record each brushing in the diary. Note any changes to these brushing procedures and reasons for changes (e.g. missed brushings, extra brushings).
- On the day before your next visit, **please record the actual time of your last brushing before attending site.** Please remember to not brush your teeth within 12 hours (+6 hours, -2 hours) before your scheduled study assessment visits.
- Please record any changes to your health, medications (prescription and over the counter medications) or treatments in the diary.
- Please bring your diary (completed and not completed), toothpaste and toothbrush to the next study visit.
- Please do not remove or deface any part of the study label

Please do not share your study toothpaste with anybody and do not discuss with the examiner your experience with your assigned toothpaste (e.g. taste, color or smell).

15.2 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
BI	Bleeding Index
ADA	American Dental Association
BDR	blinded data review
CI	confidence interval
CPITN	Community Periodontal Index of Treatment Needs
eCRF	Electronic case report form
DMS	Data Management System
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	institutional review board
IRT	Interactive Response Technology
ITT	Intention to Treat
MedRA	Medical Dictionary for Regulatory Activities
MGI	Modified Gingival Index
MFC	Master Formulation Code
NBS	Number of Bleeding Sites
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PI	principal investigator
PI	Personal information
PP	Per Protocol
ePRO	Electronic Patient Reported Outcome
PRO	Patient Reported Outcome
RAP	Statistical Report and Analysis Plan
SAE	serious adverse event
SMFP	Sodium monofluorophosphate
SnF_2	Stannous fluoride
SRSD	Single Reference Safety Document
TPI	Turesky Plaque Index
USA	United States of America
US	United States