GlaxoSmithKline
Consumer Healthcare

CLINICAL PROTOCOL

A Randomized, 8 Week Clinical Study to Evaluate the Efficacy of an Experimental Stannous Fluoride Dentifrice in the Relief of Dentinal Hypersensitivity

Active Name:	Stannous Fluoride (SnF_2)
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	N/A
Other Regulatory Agency Identified Number:	N/A
Protocol Number:	208153
Phase:	N/A

Sponsor information

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Document History

Document	Version Date	Summary of Changes
Original protocol	18-August-2017	Not applicable (N/A)

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, independent ethics committee (EC), etc.

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current 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:	Professor Feng Xiping
Investigator Qualifications:	DDS, MDS
Investigator Signature:	PPD
Date of Signature/ Agreement:	PPD DD/MMM/YYYY

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SCHEDULE OF ACTIVITIES

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

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

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening		Study Period		End of Treatment
	Visit 1		Visit 2 Day 1 Baseline	Visit 3 Day 29±3	Visit 4 Day 57±3
Informed consent	X				
Demographics, Ethnicity	X				
Medical History, Current Medications	X				
Concomitant Medications			X	X	X
Review of Subjects Current Oral Care Products to Confirm They Don't Contain any Anti-sensitivity Ingredients	X				
Urine Pregnancy Test in Female Subjects of Childbearing Potential			X		
OST Examination	X		X	X	X
OHT Examination	X				
Eligible Teeth Assessments (Dentition Exclusions, EAR, MGI, Tooth Mobility)	X				
Qualifying Tactile Assessment (Yeaple Probe)[1]	X				
Qualifying Evaporative Air Sensitivity (Schiff Sensitivity Score)[1]	X				
Inclusion/Exclusion Criteria	X		X[2]		
Subject Eligibility	X		X		
Dispense Acclimatization Dentifrice, Toothbrush, Diary and Timer[3]	X				
Supervised Brushing with Acclimatization Dentifrice[4]	X				
Return Acclimatization Dentifrice, Toothbrush, Diary			X		
Subject Adherence and Continuance			X	X	X
Tactile Assessment (Yeaple Probe)[5]			X	X	X
Evaporative Air Assessment (Schiff Sensitivity Score)[6]			X	X	X
Identify Two Test Teeth			X		
Stratification and Randomization			X		
Dispense Randomized Dentifrice, Toothbrush, Diary and Timer[7]			X	X	
Supervised Brushing with Allocated Dentifrice[4]			X	X	
Subjects Return Study Supplies to Site				X	X

Acclimatization period 2-6 weeks

Procedure/Assessment	Screening	Acclimatization period 2-6 weeks	Study Period		End of Treatment
	Visit 1		Visit 2 Day 1 Baseline	Visit 3 Day 29±3	Visit 4 Day 57±3
Visual Compliance Check of Returned Study Dentifrice and Review of Subject Diary			X	X	X
Adverse Events[8]	X		X	X	X
Study Conclusion					X

Abbreviations: OST = Oral Soft Tissue; OHT = Oral Hard Tissue; EAR = Erosion, Abrasion, Recession; MGI = Modified Gingival Index.

1. Qualifying Schiff sensitivity and tactile threshold scores will be recorded in the case report form (CRF). Evaporative air assessment to follow tactile assessment; minimum 5 minutes time lapse between the two assessment types for tooth recovery. At Screening, maximum force for tactile = 20g.
2. Inclusion criteria 6d and exclusion criteria 13b.
3. Subject is instructed to bring all supplies back to next visit.
4. Study supplies to be returned to subject (for use at home) after supervised brushing.
5. At Baseline, maximum force = 20g., at all subsequent visits maximum force = 80g.
6. Evaporative air assessment to follow tactile assessment; minimum 5 minutes time lapse between the two assessment types for tooth recovery.
7. Subject is instructed to bring all supplies back to subsequent visits for compliance checks. Study supplies to be returned to subject after supervised brushing. At the Week 4 visit subjects will be re-dispensed with a new diary and new tubes of their allocated dentifrice prior to conducting their supervised brushing.
8. Any serious adverse event assessed as related to study participation that occurs subsequent to the signing of informed consent and any adverse event that occurs subsequent to the first dose of the acclimatization dentifrice will be recorded.

1 INTRODUCTION

Dentine hypersensitivity (DH) has been defined as 'pain derived from exposed dentine in response to chemical, thermal, tactile, or osmotic stimuli which can't be explained as arising from any other dental defect or disease' [Addy, 1985; Canadian Advisory Board on Dentin Hypersensitivity, 2003]. The primary aetiological factors associated with the onset of DH include gingival recession and/or enamel loss (e.g. through erosion or abrasion) that result in exposure of dentine with patent dentinal tubules [Orchardson, 1987]. The hydrodynamic theory of DH hypothesises that a stimulus external to the tooth (e.g. a temperature/osmotic differential) causes transport of the fluid resident within dentinal tubules [Brännström, 1962]. This fluid movement may stimulate nerve processes in the pulpal area of the dentine including irritation of odontoblasts, pulpal neurons, and even subodontonblastic blood vessels [Hall, 2000], resulting in the characteristic short, sharp pain of DH.

Currently there are two approaches to the management of DH: either nerve depolarization or dentinal tubule occlusion. Nerve depolarising agents, typically potassium salts, generally require a period of use (for example, 14 to 28 days) before their benefit is established. The delivery of potassium ions to the dentine-pulp junction (odontoblastic layer) *via* dentinal tubules is believed to result in depolarisation of the afferent nerve membrane thereby blocking the pain response [Orchardson, 2000]. The second approach uses tubule occluding agents which physically block the exposed end of the dentinal tubules, thus reducing dentinal fluid movement and pulpal irritation. Tubule occluding agents, like stannous salts, serve to seal or block the dentine tubules and thereby reduce the effect of external stimuli. Such agents are believed to function by precipitating insoluble materials onto the dentine surface and/or within the dentinal tubules to reduce dentinal fluid transport [Pashley, 1986].

Stannous fluoride (SnF_2) has been incorporated into oral hygiene products indicated for the reduction of DH since the 1960's [Schiff, 2006]. SnF_2 provides relief from DH by the occlusion of the dentinal tubules through chemical precipitation of stannous oxides and hydroxides onto the surface of the dentine. More recently Proctor and Gamble (P&G) and GSK CH have marketed SnF_2-containing dentifrices indicated for DH relief, with published evidence demonstrating longitudinal clinical efficacy [Ni, 2011; Parkinson, 2011; Makin, 2013]. In this study the efficacy of an experimental formulation containing 0.454% w/w SnF_2 will be compared to a negative control dentifrice and a Chinese marketed positive control dentifrice (Crest 7-Effects Strengthen Dental Enamel) for the relief of DH pain.

1.1 Mechanism of Action/Indication

Stannous fluoride is a dentine tubule occluding agent that is being investigated in subjects with DH. Such agents are believed to function by precipitating insoluble materials onto the dentine surface and/or within the dentinal tubules to reduce dentinal fluid transport [Pashley, 1986].

1.2 Background and Rationale

1.2.1 Justification on the Requirement to Conduct the Study

A similarly designed randomized, examiner-blind, two treatment arm parallel group DH study was previously conducted in a Chinese population [GSK CH Study 205794]. The results of this study demonstrated a statistically significant reduction in DH for Schiff sensitivity score for the experimental product containing SnF_2 compared to a regular fluoride dentifrice, but failed to demonstrate a statistically significant greater reduction in tactile threshold. Given that a number of successful 8 week DH studies have been conducted on SnF_2 containing dentifrices by GSK CH and competitors, there is a need to repeat this study in a Chinese population to demonstrate statistically significant improvements in both sensitivity measures that meet the Chinese Ministry of Health guidelines [Ministry of Health (China), 2010].

1.2.2 Study Design and Dose Rational

A randomized, examiner-blind, parallel group design is a recognized approach for providing evidence of the clinical effectiveness of a product in the reduction of DH [Holland, 1997]. In order to establish longitudinal performance, with the opportunity for benefit to be observed, an eight week treatment period will be used [Murray, 1994; Irwin, 1997; Ministry of Health (China), 2010].

In line with published recommendations [Holland, 1997] and the requirement of Chinese Ministry of Health guidelines [Ministry of Health (China), 2010] for the testing of functional dentifrices (desensitizing), two independent stimulus-based efficacy measures will be employed (tactile and evaporative air sensitivity) to evaluate the DH efficacy of the experimental dentifrice. A tactile stimulus will be administered using a constant pressure probe (Yeaple Probe [Polson, 1980]). An evaporative (air) stimulus will be administered using a dental air syringe. Response to this stimulus will be evaluated using the Schiff sensitivity scale [Schiff, 1994].

One of the eligibility criteria at Screening in earlier DH studies was subject response to evaporative air sensitivity. In this study a qualifying response to a tactile stimulus will be included followed by a qualifying air blast on all teeth qualifying for tactile. At Screening and Baseline subjects will have a minimum of two teeth with a tactile score of $\leq$20g and Schiff sensitivity score of $\geq$2. To ensure consistent responders are entered into the study, the two test teeth selected at Baseline must be selected from those teeth eligible for both Schiff and tactile at Screening.

Orchardson & Collins tested 516 sensitive teeth and found that while around half were sensitive to both evaporative air and tactile stimuli, 33% were sensitive only to an evaporative air stimulus and 16% were sensitive only to a tactile probe [Orchardson, 1987]. Given that individual teeth may react differently to different stimuli it would be pragmatic to say the same for people. Therefore, some people may respond well to evaporative air sensitivity at Screening, but perhaps not to the same degree for tactile at Baseline, hence why both tactile

and evaporative air stimuli have been included at the Screening visit. This will help ensure that consistent responders to both stimuli are entered into the study, but will also enable more data to be gathered to understand the disparate response between the different stimuli that has been seen in previous studies.

Post-randomization, the two selected test teeth will be assessed using each of the clinical efficacy assessments. The selection of two 'test teeth' to evaluate changes in DH is common practice in sensitivity studies [Docimo, 2009]. The subjects will be stratified at the Baseline visit according to their maximum Schiff sensitivity score to enable the treatment groups to be balanced in terms of the subject's sensitivity severity.

The dosage regimen of twice daily treatment (morning and evening) brushing will be the same for all subjects, and has been selected based on widely recommended oral hygiene practice, and typical consumer habit.

According to ICH guidelines, for a study to be classed as truly double blind, not only does the examiner (and any appropriate member of staff who may be involved in the dispensing of products, analysis of data etc.) need to be blinded as to the treatment the subject receives, but the products under test must be identical in every way (color, flavor, appearance, packaging). Given it is almost impossible to ensure identical appearance, taste and packaging for the dentifrices evaluated in oral care studies, the level of blindness for this study is described as 'examiner blind' only.

Clinical trials evaluating clinical end points relating to pain can be prone to 'placebo effects' [Addy, 1985; West, 1997]. Such effects are frequently observed in dentine hypersensitivity studies. A study conducted to evaluate the natural history of the dentine hypersensitivity condition highlighted the existence of a 'no treatment' effect characterised by an improvement in sensitivity simply as a function of clinical study participation [Leight, 2008]. To help minimise the potential impact of such 'placebo' and 'no treatment' effects, an acclimatization period of 2-6 weeks will be included in this study from Screening, ahead of the Baseline assessments and randomization. During this period subjects will be provided with a toothbrush and a marketed, standard fluoride dentifrice to use in place of their regular oral hygiene products. Use of the acclimatization dentifrice will also help provide a standardised oral hygiene regimen prior to the Baseline visit. Subjects will brush twice daily, in line with recommended oral hygiene practice, and typical consumer habit, during this period.

The proposed examiners will be clinically qualified and will have been trained and have experience in the clinical assessments of DH, using both the Schiff sensitivity scale and a Yeaple probe. To minimize assessment variability, the same examiner will be responsible for a given clinical assessment from the Screening visit to the end of the study.

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

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2-1 Study objectives and endpoints

Objectives	Endpoints
Efficacy	
Primary	
• To compare the clinical efficacy of an experimental 0.454% w/w SnF_2 dentifrice for the relief of DH, as elicited by an evaporative air stimulus (with Schiff sensitivity score), against a negative control dentifrice, when used twice daily for 8 weeks.	• Change from Baseline in Schiff sensitivity score at 8 weeks.
Secondary	
• To compare the clinical efficacy of an experimental 0.454% w/w SnF_2 dentifrice for the relief of DH, as elicited by a tactile stimulus (yeaple probe), against a negative control dentifrice, when used twice daily for 8 weeks.	• Change from Baseline in tactile threshold at 8 weeks.
Exploratory	
• To compare the clinical efficacy of an experimental 0.454% w/w SnF2 dentifrice for the relief of DH, as elicited by an evaporative air stimulus (with Schiff sensitivity score), against a positive control dentifrice, when used twice daily for 4 and 8 weeks.	• Change from Baseline in Schiff sensitivity score at 4 and 8 weeks.
• To compare the clinical efficacy of an experimental 0.454% w/w SnF_2 dentifrice for the relief of DH, as elicited by an evaporative air stimulus (with Schiff sensitivity score), against a negative control dentifrice, when used twice daily for 4 weeks.	• Change from Baseline in Schiff sensitivity score at 4 weeks.
• To compare the clinical efficacy of an experimental 0.454% w/w SnF_2 dentifrice for the relief of DH, as elicited by a tactile stimulus (yeaple probe), against a negative control dentifrice,	• Change from Baseline in tactile threshold at 4 weeks.

when used twice daily for 4 weeks.	
• To compare the clinical efficacy of an experimental 0.454% w/w SnF_2 dentifrice for the relief of DH, as elicited by a tactile stimulus (yeaple probe), against a positive control dentifrice, when used twice daily for 4 and 8 weeks.	• Change from Baseline in tactile threshold at 4 and 8 weeks.
• To compare the clinical efficacy of a positive control dentifrice for the relief of DH, as elicited by a tactile stimulus (yeaple probe), against a negative control dentifrice, when used twice daily for 4 and 8 weeks.	• Change from Baseline in tactile threshold at 4 and 8 weeks.
• To compare the clinical efficacy of a positive control dentifrice for the relief of DH, as elicited by an evaporative air stimulus (with Schiff sensitivity score) against a negative control dentifrice, when used twice daily for 4 and 8 weeks.	• Change from Baseline in Schiff sensitivity score at 4 and 8 weeks
Safety	
• To evaluate the safety and oral tolerability of the test dentifrices when used twice daily for 8 weeks.	• Adverse Events

This study will be considered successful if there is a statistically significant difference in the primary efficacy variable, change from baseline in Schiff sensitivity score, after 8 weeks of treatment. The difference should be viewed as clinically relevant in addition to being statistically significant

3 STUDY DESIGN AND SUBJECT POPULATION

This will be a single centre, randomized, controlled, examiner-blind, 3 treatment arm, parallel group design study, stratified by maximum baseline Schiff sensitivity score (of the two selected test teeth), with a treatment period of 8 weeks, to investigate the clinical effectiveness of an experimental SnF_2 dentifrice in the reduction of DH. DH will be assessed at Baseline, and after 4 and 8 weeks treatment.

The study will be conducted in healthy subjects with pre-existing self-reported and clinically diagnosed tooth sensitivity at Screening, in a Chinese population. A sufficient number of subjects will be screened to randomize approximately 180 subjects to ensure 165 subjects complete the study.

The age range over which an individual can experience DH is wide (from early teens to 70s) [Fischer, 1992], with peak incidence known to occur between the ages of 20-40 years [Graf, 1977; Flynn, 1985]. The fall in prevalence observed in later decades reflects age related changes in the dentine and pulp of the tooth which act to reduce dentine permeability and the tooth's response to the external triggers of DH [Seltzer, 1975; Pashley, 2008]. Given that the dental pain experienced by older members of the population is less likely to be diagnosed as DH [Rees, 2000], the age range of 18-70 selected for this study targets individuals suffering from tooth sensitivity which is most likely due to DH. This will facilitate recruitment and minimise inconvenience to older participants who may be more likely to be rejected at Screening.

An acclimatization period of 2-6 weeks will be included in this study, given that 2 weeks is understood to be an expected amount of time to minimize the potential for carry over effects from prior use of anti-sensitivity products.

In line with Chinese Ministry of Health guidelines [Ministry of Health (China), 2010] for the testing of functional dentifrices (desensitizing), a standard fluoride dentifrice with no specific anti-sensitivity, anti-gingivitis and anti-plaque activity (Chinese marketed Colgate Triple Protection) will be included as the negative control. A Chinese marketed positive control dentifrice with sensitivity benefits (Crest 7-Effects Strengthen Dental Enamel toothpaste, containing stannous chloride ($SnCl_2$)) will also be included in this study design as a benchmark of performance in the Chinese population.

4 SUBJECT SELECTION

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 nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1 Inclusion Criteria

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

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

1. Evidence of a personally signed and dated informed consent indicating the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Male and female subjects who, at the time of screening, are between the ages of 18 and 70 years, inclusive.
3. Subjects who are willing and able to comply with scheduled visits, treatment plan, and other study procedures.

4. Good general and mental health, in the opinion of the investigator or medically qualified designee.
5. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 5 days after the last dose of assigned treatment, refer to Section 4.4.2 for guidance. Female subjects who are not of childbearing potential must meet requirements in Section 4.4.2.
6. The following oral and dental inclusions will apply at **Screening (Visit 1)**:
    a) Self-reported history of dentinal hypersensitivity lasting more than six months but not more than 10 years.
    b) Good general oral health, with a minimum of 20 natural teeth.
    c) Minimum of 2 accessible non-adjacent teeth (incisors, canines, pre-molars), preferably in different quadrants, that meet all of the following criteria:
        i. Signs of facial/cervical gingival recession and/or signs of erosion or abrasion (EAR).
        ii. Tooth with Modified Gingival Index (MGI) score =0 adjacent to the test area (exposed dentine) only [Lobene, 1986] and a clinical mobility of ≤1.
        iii. Tooth with signs of sensitivity measured by a qualifying tactile stimulus (Yeaple ≤20g) qualifying evaporative air assessment (Schiff sensitivity score ≥2).

The following dental inclusions will apply at **Baseline (Visit 2)**:

    d) Minimum of two, non-adjacent accessible teeth (incisors, canines, pre-molars), with signs of sensitivity, measured by response to a qualifying tactile stimulus (Yeaple ≤20g) and evaporative air assessment (Schiff sensitivity score ≥2). The two selected test teeth must have also qualified at Screening for this criteria.

Note: The Investigator will select two *Test Teeth* from those which meet *both* the tactile threshold and Schiff sensitivity score criteria, in addition to meeting all other criteria. *Test Teeth* should not be adjacent to each other and preferably in different quadrants.

4.2 Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are GSK employees directly involved in the conduct of the study.
2. Participation in another clinical study (including cosmetic studies), or receipt of an investigational drug within 30 days prior to the Screening visit and/or during study participation.

3. Participation in another tooth desensitizing treatment study within 8 weeks of the Screening visit.
4. Acute or chronic medical or psychiatric condition 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, would make the subject inappropriate for entry into this study.
5. Pregnant female subjects. This will be confirmed verbally at Screening and confirmed by Urine pregnancy testing (carried out on all female subjects of child bearing potential) at the Baseline visit.
6. Breastfeeding female subjects.
7. Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
8. Recent history (within the last year) of alcohol or other substance abuse.
9. Unwilling or unable to comply with the lifestyle guidelines described in this protocol.
10. Subjects who have previously been enrolled in this study.
11. General oral and dental exclusions:
    a) Dental prophylaxis within 4 weeks of Screening.
    b) Tongue or lip piercing or presence of dental implants.
    c) Gross periodontal disease, treatment of periodontal disease (including surgery) within 12 months of Screening, scaling or root planning within 3 months of Screening.
    d) Teeth bleaching within 8 weeks of Screening.
    e) Use of an over-the-counter (OTC) desensitizing product (eg. dentifrice) and/or professional desensitizing treatment within 8 weeks of Screening. Subjects will be required to bring their current oral care products to the site in order to verify the absence of known anti-sensitivity ingredients.
12. Specific dental exclusions for test teeth:
    a) Sensitive tooth not expected to respond to treatment with an over-the-counter dentifrice in the opinion of the investigator.
    b) Tooth with exposed dentine but with deep, defective or facial restorations, teeth used as abutments for fixed or removable partial dentures, teeth with full crowns or veneers, orthodontic bands or cracked enamel. Sensitive teeth with contributing aetiologies other than erosion, abrasion or recession of exposed dentine.
    c) Tooth with evidence of current or recent caries, or reported treatment of decay within 12 months of Screening.
13. Concomitant Medication:
    a) Daily doses of medication/treatments or traditional herbal ingredients/treatments which, in the opinion of the investigator, could interfere

with the perception of pain. Examples of such medications include analgesics, anticonvulsants, antihistamines that cause marked or moderate sedation, sedatives, tranquilisers, anti-depressants, mood-altering and anti-inflammatory drugs. Examples of herbal ingredients/treatments include clove oil, olive oil, or other treatments that are directly applied to the oral cavity for the treatment of oral health conditions.

b) Currently taking antibiotics or has taken antibiotics within 2 weeks of Screening and/or Baseline.

c) Daily dose of a medication which, in the opinion of the investigator, is causing xerostomia.

d) Individuals who require antibiotic prophylaxis for dental procedures.

14. Any subject who, in the judgment of the investigator, should not participate in the study.

4.3 Randomization Criteria

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

4.4 Lifestyle Guidelines

For the duration of the study (Screening to LSLV):

- Eligible subjects will be asked to stop using their regular oral care products from Screening for the duration of the study.
- Use of dental floss will be for the removal of impacted food only.
- Subjects will not be permitted to use any other oral care products (i.e., oral rinses, tongue cleaners, whitening/bleaching products, inter-dental brushes) other than those provided to them in this study.
- Subjects will not be permitted to use any other dental products (other than those provided to them in this study), including home remedies, intended for treating sensitive teeth.
- Subjects will not be permitted to chew gum.

Prior to study days (Baseline to Week 8):

- Subjects will be asked to refrain from all oral hygiene procedures for **at least 8 hours** in order to standardize oral hygiene practices.

4.4.1 Dietary and Alcohol Restrictions

Prior to study days (Baseline to Week 8):

- Subjects will be asked to refrain from eating and drinking for **at least 4 hours**. Before each visit small sips of water will be allowed for the purpose of taking medication, but subjects will be asked to refrain from doing this 1 hour before attending the study site.
- Subjects will be requested to refrain from excessive alcohol consumption for 24 hours prior to the Baseline, Week 4 and Week 8 visits. If in the opinion of the Investigator the subject has consumed an excessive amount of alcohol prior to the visit, every effort will be made to reappoint them to the next day. If this is not possible then the subject should be treated as per Section 6.4.

4.4.2 Contraception

All male subjects and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active study period and for at least 5 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject will select an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for the correct use of at least 1 of the selected methods of contraception. The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e., perfect use) and include the following:

1. Established use of oral, inserted, injected, transdermal, or implanted hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness as deemed appropriate by the investigator.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (i.e., foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).
6. Female who meets the criteria for non-childbearing potential as described below.

Female subjects of non-childbearing potential must meet at least one of the following criteria:

a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;

b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

c. Have medically confirmed ovarian failure.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

4.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. In order 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 serious adverse events (SAEs).

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

4.6 Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical/dental personnel for the study is documented in the study contact list located in the study file.

The contact number can be used by investigational staff if they are seeking advice on medical/dental questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical/dental questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol identifiers, subject study numbers, contact information for the investigational site, and contact details in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem identified from the subject's healthcare professional other than the investigator.

5 STUDY TREATMENTS

5.1 Blinding and Allocation to Treatment/Randomization

This study is described as examiner blind, however, to minimize the potential of unblinding the study statistician, other employees of the sponsor, and vendors acting on behalf of the sponsor, who may influence study outcomes are blinded to the product allocation of subjects. The examiner will be blinded to the treatment received. To ensure the examiner remains blinded throughout the study, the examiner is not permitted in the room whilst product is dispensed, and subjects will be asked not to remove study products from their bags outside of the dispensing room and until they are home. In addition, subjects should be treated in a separate area. The dispensing staff will not be involved in any efficacy assessments during the study.

InVentiv Health will create the randomization schedules and provide to Global Clinical Supplies (GCS). GCS will print the randomization schedules and supply the clinical study site with two versions of the randomization schedule, each in a sealed envelope and clearly marked as either "For Dispensing" or "Emergency Use Only".

The "For Dispensing" schedule will contain the list of randomization numbers only and will not include any coded description, just a letter A, B or C.

The 'Emergency Use Only' randomization schedule will only be removed from the sealed envelope in an emergency situation. This schedule will have a randomization number followed by the letter A, B or C. The schedule will have a footnote with a key for A, B and C identifying the three treatments arms. However, to maintain the blinding of the study as far as possible, all treatment allocations for all randomization numbers on this randomization schedule will be masked with scratch-off panels.

Subjects will be stratified according to their maximum baseline Schiff sensitivity score of the two selected teeth (sensitivity score of 2 or 3) with randomization numbers within each stratum assigned in ascending numerical order as each subject is determined to be fully eligible. The stratification factor will give rise to two strata.

- **Stratum 1:** Maximum Schiff=2. These are subjects with maximum baseline Schiff sensitivity score of 2 for the two selected test teeth.
- **Stratum 2:** Maximum Schiff=3. These are subjects with the maximum baseline Schiff sensitivity score of 3 for the two selected test teeth.

In accordance with the randomization numbers, the subject will receive the study treatment assigned to the corresponding randomization number.

5.2 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 a manual process, whereby only scratch-off panels will be removed

for subjects that require unblinding. Blinding codes should be broken only in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator should consult with a member of the study team prior to breaking the blind unless the delay would endanger the subject's health. When the blinding code is broken, the reason must be fully documented and entered in the CRF.

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

5.3 Subject Compliance

Subjects will be asked to bring all tubes of study dentifrice to each study visit for a visual compliance check of each product. Any suspected product over use, or under use will be documented in the CRF and subjects will be re-educated on the correct dosing amount and instructions.

Subjects will be provided with a diary at Screening and again at the Baseline and Week 4 visits, which they will return at their following visit to the study site. The number of missed or extra brushings will be recorded in the CRF.

5.4 Investigational Product Supplies

The following study products will be supplied by GCS, GSK CH:

- **Test product:** Experimental dentifrice containing 0.454% SnF_2 and 0.072% NaF (1450ppm fluoride in total); CCI .
- **Control product 1:** Colgate Triple Protection dentifrice containing 1400ppm fluoride as sodium monofluorophosphate (SMFP); Chinese Marketplace.
- **Control product 2:** Crest 7-Effects Strengthen Dental Enamel dentifrice containing $SnCl_2$ and 0.15% NaF (1450ppm fluoride in total); Chinese marketplace.

Other items to be supplied by the Clinical Supplies Department, GSK CH:

- **Acclimatization dentifrice:** Colgate Strengthen Fresh Dentifrice containing 1400ppm fluoride as SMFP (Chinese Marketplace).
- Aquafresh Clean Control Toothbrush (UK market place).
- Countdown timers.

Subject diaries (including product usage instructions) will be supplied by GSK CH China.
Urine pregnancy test kits (to test for pregnancy on female subjects of child bearing potential) will be provided by the site.

5.4.1 Dosage Form and Packaging

All investigational dentifrices are intended for oral use, and will be administered as detailed in Section 5.5.

The control and acclimatization dentifrices (Colgate Triple Protection, Crest 7-Effects and Colgate Strengthen Fresh) will be sourced from the Chinese market. The test dentifrice will be manufactured and filled into white aluminum barrier laminate (ABL) tubes and supplied by GSK CH.

The test and control dentifrices will be presented to the clinical study site in tubes that have been overwrapped in white vinyl to obscure any branding on the commercial packs with a study label affixed. The acclimatization dentifrice will be supplied in its commercial packaging with a study label affixed. The contents of the dentifrice labels will be in accordance with all applicable regulatory requirements and will be the responsibility of GCS, GSK CH. Each subject will receive a sufficient number of acclimatization and investigational dentifrice tubes to cover usage during the treatment phase. The investigational dentifrice will be dispensed at the Baseline and Week 4 visits.

All 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.

5.4.2 Preparation and Dispensing

The examiner will be blinded to the treatment received. To ensure the examiner remains blinded throughout the study, the examiner will not be permitted in the room where the test products are stored or dispensed. The product dispensing area will be separate from the subjects' examination area. All study dentifrices will be dispensed by qualified site personnel who are not involved in any study efficacy assessments. The investigational products will be dispensed in blinded fashion to the subject. A second member of site personnel will verify that the correct dentifrice has been dispensed to each subject. A record of the product dispensed to each subject will be recorded in a treatment dispensing log, and assigned against each subject number.

5.5 Administration

A record of the administration of the study products will be kept using a dispensing log and the CRF.

Subjects will be instructed to self-administer their investigational product according to the product use instructions provided to the subject. Subjects will receive a brushing instruction/diary sheet. This will outline the brushing instructions and will be used to record the date and time of each brushing occasion during the treatment period (Appendix I).

Subjects will also be asked to note any missed brushings, and to use the diary to record any illness, medication or significant changes to diet. To ensure that subjects understand the dose of dentifrice to be used, staff will demonstrate what is meant by a 'full ribbon' (i.e. covering the length of the toothbrush head) at the Screening, Baseline and Week 4 visits, and subjects will conduct a supervised brushing. Subjects will brush in their usual manner with a full brush head of their assigned dentifrice for 1 timed minute and expectorate.

5.5.1 Medication Errors

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

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

Such medication errors occurring to a study participant are to be captured in the subject diary and later transcribed by the site into the CRF.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not a medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated AE(s) is captured on an AE CRF page.

5.6 Investigational Product Storage

The investigator, or an approved representative, will ensure that all investigational products including any comparator, marketed and acclimatization products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and 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 investigational 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 should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

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

5.7 Investigational Product Accountability

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

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

The clinical study site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational product will be accounted for using an investigational product accountability form/record.

At the end of the study subjects will return all study products back to the clinical study site, which will be verified by the monitor. Study product supplies will then be either collected by the study monitor or returned by the investigator or designee to GCS, GSK CH, or designated vendor.

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

5.7.1 Destruction of Investigational Product Supplies

At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH will inventory all used and unused investigational study treatment. The study treatment inventory record for returned study treatment will then be completed. All investigational and acclimatization dentifrices for this clinical study (empty containers), as well as all unused study product will be returned to the GSK CH designated vendor using the return instructions provided.

5.8 Concomitant Treatment(s)

Details of any **relevant** dental, medical or surgical history (within the last year prior to Screening), including allergies or drug sensitivity, will be recorded in the CRF.

All concomitant treatments taken during the study must be recorded with indication, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 30 days before the first dose of acclimatization product will be documented as a prior treatment. Treatments taken after the first dose of acclimatization product will be documented as concomitant treatments.

During the entire study (Screening - LSLV):

- Subjects who enter the study will be requested to delay having any non-emergency, elective dental treatment until after study completion (including prophylaxis).
- If 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).
- Should a randomised subject start a course of treatment during the study which includes the daily or intermittent use of an analgesic, the identity of that medication/treatment, dosage and frequency and start date will be recorded. The subject will not be withdrawn.
- Should a subject take an analgesic within **8 hours** of a scheduled visit, every effort will be made to reappoint them to the next day. If this is not possible then the subject should be treated as per Section 6.4.
- Subjects should not participate in another clinical study (including cosmetic studies), or be in receipt of an investigational drug.

6 STUDY PROCEDURES

6.1 Screening - Visit 1 (FSFV)

The following procedures/assessments will take place in the order listed below (where possible) and recorded in the CRF:

- Obtain written informed consent.
- Collect demography and ethnicity. The following demographic parameters will be captured by the Investigator or designee: year of birth, gender and race.
- Obtain medical history, including history of illegal drug, alcohol and tobacco use.
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 30 days prior to the Screening visit.
- Review of the oral care products the subject is currently using to confirm that they do not contain any ingredients intended for treating sensitive teeth. Subjects will be

asked to bring these to the clinical study site to enable a member of the clinical study staff to check the ingredients list.

- Full oral soft tissue (OST) examination conducted by a qualified dental examiner.
- Full oral hard tissue (OHT) examination conducted by a qualified dental examiner.
- Eligible teeth assessments (dentition exclusions, Erosion, Abrasion, Recession (EAR), modified gingival index (MGI), tooth mobility) conducted by a qualified dental examiner. All teeth that satisfy these criteria will then be assessed for the following:
  i. Qualifying tactile threshold conducted by a qualified dental examiner. To ease subject flow, scores may be recorded on a score sheet and then transcribed into the CRF.
  ii. Qualifying evaporative air sensitivity of all teeth qualifying on tactile threshold (≤20g), conducted by a qualified dental examiner. The examiner should allow at least 5 minutes between completion of all tactile assessments and then start the evaporative air assessment. To ease subject flow, scores may be recorded on a score sheet and then transcribed into the CRF.
- Review Inclusion and Exclusion criteria. Pregnancy status will be confirmed verbally by the subject.
- Confirmation of subject eligibility.
- Dispensation of acclimatization dentifrice, toothbrush, diary with usage instructions and timer.
- Supervised brushing with acclimatization dentifrice. Site staff must observe subjects for the entire dosing and brushing period.
- Adverse Events (AEs) will be documented from completion of the supervised brushing with acclimatisation dentifrice. Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- To prepare for study participation, subjects will be instructed on the use of the Lifestyle Guidelines (Section 4.4) and Concomitant Treatment(s) (Section 5.8) sections of the protocol.

6.2 Study Period

6.2.1 Day 1; Baseline - Visit 2

Subjects will be admitted to the clinical study site 2-6 weeks after the Screening visit, having refrained from eating or drinking for at least 4 hours, and from all oral hygiene procedures for at least 8 hours. Prior to randomization the following procedures will be completed in the following order (where possible), and recorded in the CRF:

- Review of concomitant medications, AEs.

- Urine pregnancy testing will be carried out on all female subjects of child bearing potential.
- Return of acclimatization dentifrice, toothbrush and diary.
- Review of completed diary and visual check of acclimatization dentifrice by study site staff to determine usage compliance. Any potential dentifrice underuse or overuse will be noted in the CRF and subjects will be re-educated on the correct dose amount.
- Confirmation of subject adherence and continuance.
- Full OST examination conducted by a medically qualified dental examiner.
- Tactile sensitivity assessment of eligible teeth identified at screening (all teeth (incisors, canines, pre-molars), with signs of sensitivity, measured by response to a qualifying tactile stimulus (Yeaple ≤20g) and evaporative air assessment (Schiff sensitivity score ≥2)). Assessments will be carried out by a qualified dental examiner. To ease subject flow, scores may be recorded on a paper score sheet and then transcribed into the CRF.
- Evaporative air sensitivity assessment of eligible teeth that meet the tactile sensitivity at Baseline. Assessments will be carried out by a qualified dental examiner. The examiner should allow at least 5 minutes between completion of all tactile assessments and then start the evaporative air assessment. To ease subject flow, scores may be recorded on a score sheet and then transcribed into the CRF.
- Inclusion criteria 6d and exclusion criteria 13b.
- Selection of two test teeth for all subsequent assessments by a qualified dental examiner.
- Confirmation of subject eligibility.
- Stratification and randomization.

Following randomization, the following procedures/assessments will be completed in the following order (where possible) and recorded in the CRF, unless stated otherwise:

- Dispensation of allocated study dentifrice, toothbrush and diary, usage instructions.
- Supervised brushing with allocated study dentifrice. Site staff must observe subjects for the entire dosing and brushing period.
- AEs captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

6.2.2 Day 29 (±3 days) - Visit 3

Subjects will be admitted to the clinical site 4 weeks (±3 days) after the Baseline visit, having refrained from eating or drinking for at least 4 hours, and from all oral hygiene procedures for at least 8 hours. The following procedures will be completed after admission to the clinical study site, in the following order (where possible), and recorded in the CRF:

- Review of concomitant medications and AEs.
- Return of study dentifrice, toothbrush and diary.

- Review of completed diary and visual check of dentifrice by study site staff to determine usage compliance. Any potential dentifrice underuse or overuse will be noted in the CRF and subjects will be re-educated on the correct dose amount.
- Confirmation of subject adherence and continuance.
- Full OST examination conducted by a qualified dental examiner.
- Tactile sensitivity assessment of the two selected test teeth by a qualified dental examiner. To ease subject flow, scores may be recorded on a score sheet and then transcribed into the CRF.
- Evaporative air sensitivity assessment of the two selected test teeth by a qualified dental examiner. The examiner should allow at least 5 minutes between completion of all tactile assessments and then start the evaporative air assessment. To ease subject flow, scores may be recorded on a score sheet and then transcribed into the CRF.
- Return study products to subject. Subjects will also be re-dispensed new tubes of their allocated dentifrice.
- Supervised brushing by subject with allocated study dentifrice after all assessments completed. Site staff must observe subjects for the entire dosing and brushing period.
- AEs captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.2.3 Day 57 (±3 days) - Visit 4

Subjects will be admitted to the clinical site 8 weeks (±3 days) after the Baseline visit, having refrained from eating or drinking for at least 4 hours, and from all oral hygiene procedures for at least 8 hours. The following procedures will be completed after admission to the clinical study site, in the following order (where possible), and recorded in the CRF:

- Review of concomitant medications and AEs.
- Return of study dentifrice, toothbrush and diary.
- Review of completed diary and visual check of dentifrice by study site staff to determine usage compliance. Any potential dentifrice underuse or overuse will be noted in the CRF and subjects will be re-educated on the correct dose amount.
- Confirmation of subject adherence and continuance.
- Full OST examination conducted by a qualified dental examiner.
- Tactile sensitivity assessment of the two selected test teeth by a qualified dental examiner. To ease subject flow, scores may be recorded on a score sheet and then transcribed into the CRF.
- Evaporative air sensitivity assessment of the two selected test teeth by a qualified dental examiner. The examiner should allow at least 5 minutes between completion of all tactile assessments and then start the evaporative air assessment. To ease subject flow, scores may be recorded on a score sheet and then transcribed into the CRF.

- AEs captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?". AEs will be recorded for 5 days after last treatment. Subjects will be asked to contact the site if they feel unwell in the 5 days following their last visit.
- Study conclusion.

6.3 Follow-up Phone Call

Where applicable, the clinical study site will contact any subject(s) with AEs and in some circumstances request that they return for a final follow-up visit. If deemed to be required, an OST may be conducted by a qualified dental examiner at this visit.

6.4 Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

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

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

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

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The Investigator or clinical study site staff should attempt to contact the subject twice. After two attempts, clinical study site staff must send a registered letter. If no response is received from the subject, the subject will be considered lost to follow up. All attempts to contact the subject and information received during contact attempts must be documented in the CRF. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, and request that the subject return all used and unused investigational products request and where applicable,

return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs).

It may be appropriate for the subject to return to the clinical site for final safety assessments. Subjects should be questioned regarding their reason for withdrawal. An OST may be conducted at the investigator's discretion.

7 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 perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test 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 study team must be informed of these incidents in a timely manner.

7.1 Screening

7.1.1 Informed Consent

The investigator, or designee, must obtain written (signed and dated by the subject) informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

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 written consent will be provided by the investigator or by GSK CH. The investigator, or designee, should sign and date the consent form to confirm that the consent process was completed correctly. The subject, will be provided with a copy of their signed and dated consent form and any other written information which they should be instructed to retain.

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. Subjects will be provided with a copy of the signed and dated amended consent form.

7.1.2 Eligible Tooth Assessments

Eligible tooth assessment will include an OHT examination to evaluate dentition exclusions; erosion, abrasion and/or gingival recession; modified gingival index; tooth mobility and qualifying tactile and evaporative air assessments. Assessments will be carried out by the

Investigator or qualified designee against the inclusion/exclusion criteria and recorded in the CRF.

7.1.2.1 Erosion, Abrasion and Recession (EAR) assessment

The presence of cervical erosion, abrasion and/or gingival recession (EAR) [Addy, 2000] will be determined on the facial surfaces of individual teeth. Teeth which do not meet any of the general dentition exclusion criteria and the specific dentition exclusion criteria for eligible teeth will be assessed for EAR.

7.1.2.2 Modified Gingival Index (MGI) Assessment

The MGI is a non-invasive visual evaluation of gingival health scored on a scale of 0-4 [Lobene, 1986]. MGI will only be assessed for the facial gingiva adjacent to the test area (exposed dentine) of teeth exhibiting facial cervical erosion, abrasion and/or recession. MGI = 0 is required for eligible teeth.

Score	Description
0	Absence of inflammation
1	Mild inflammation; slight change in colour, little change in colour; little change in texture of any portion of the marginal or papillary gingival unit.
2	Mild inflammation; criteria as above but involving the entire marginal or papillar 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.

7.1.2.3 Tooth Mobility Assessment

The clinical mobility assessment will only be performed on teeth exhibiting facial cervical EAR and with a MGI = 0. Clinical mobility will be classified in the following way (based on a modification to the Miller Index) [Laster, 1975]; clinical mobility ≤1 is required for eligible teeth.

Degree 0	No movement or mobility of the crown of the tooth < 0.2mm in a horizontal direction.
Degree 1	Mobility of the crown of the tooth 0.2 - 1mm in a horizontal direction

Degree 2	Mobility of the crown of the tooth exceeding 1mm in a horizontal direction
Degree 3	Mobility of the crown of the tooth in a vertical direction as well.

7.1.2.4 Qualifying Tactile Threshold

Only teeth that do not meet any of the dentition exclusion criteria and meet the EAR, MGI and mobility criteria will be tested. The same qualified dental examiner will be used for all tactile assessments throughout the duration of the study.

Prior to the conduct of any tactile assessments the yeaple probe must be calibrated (Section 7.2.1.1). This assessment will be made by placing the probe tip perpendicular to the buccal surface and moving in a slow motion while being drawn across the tooth surface in order to ensure application of the stimulus across the sensitive area of the exposed dentine. After each challenge, subjects will be asked to indicate whether the sensation caused pain or discomfort. Only "yes" and "no" are acceptable answers. The examiner will tell the subject that they should indicate "yes" only if they feel PAIN or DISCOMFORT each time the probe is applied to their tooth. The subject may respond "yes" if they feel pressure, so it is important to remind them, as much as necessary, that they will feel pressure but to only respond "yes" if they feel pain or discomfort. If the subject fails to give a definite answer, the examiner should re-prompt them to provide a “yes” or “no” response. If they continue to be reluctant, their uncertainty should be indicated on the score sheet and the next stimulus should be at the next step in the upward direction. The gram setting, which elicits the two consecutive “yes” responses, will be recorded as the threshold on the score sheet. Where scores are recorded on a score sheet they must be transcribed into the CRF at a later point in time. At this visit the upper test limit is 20g. If no pain response is found, the threshold will be recorded as >20 g and the tooth will be disqualified from further testing.

7.1.2.5 Qualifying Evaporative Air Sensitivity

Evaporative air sensitivity will be assessed a minimum of 5 minutes after the tactile threshold stimulus. The qualified dental examiner will assess evaporative air sensitivity by a simple air blast on the facial surface of all teeth that do not meet any of the dentition exclusion criteria and meet the EAR, MGI, mobility and tactile threshold criteria. The same dental examiner will be used for all evaporative air assessments throughout the duration of the study. This assessment is made by directing a one second application of air from a standard dental syringe held perpendicular to the tooth surface approximately 1-2mm coronal to the free gingival margin and from a distance of approximately 1cm. The examiner should take appropriate measures to isolate the tooth surface to prevent stimulation of adjacent teeth or surrounding soft tissue.

Response to this stimulus will be evaluated using the Schiff sensitivity scale (Section 7.2.2.1). In order for a tooth to qualify it must have a Schiff score ≥2. The qualifying score will be recorded on the score sheet. Where scores are recorded on a score sheet they must be

transcribed into the CRF at a later point in time. If no pain response is found, the score will be recorded as <2 and the tooth will be disqualified from further testing.

7.2 Efficacy

The following efficacy assessments will be performed at times defined in the Study Procedures (Section 6) section of this protocol.

7.2.1 Tactile Sensitivity Assessment (Yeaple probe)

Tactile assessments will be performed by a single trained examiner. The same qualified dental examiner will be used for all tactile assessments throughout the duration of the study. Prior to the conduct of any tactile assessments the yeaple probe must be calibrated (Section 7.2.1.1).

This assessment will be made by placing the probe tip perpendicular to the buccal surface and moving in a slow motion while being drawn across the tooth surface in order to ensure application of the stimulus across the sensitive area of the exposed dentine. After each challenge, subjects will be asked to indicate whether the sensation caused pain or discomfort. Only "yes" and "no" are acceptable answers. The examiner will tell the subject that they should indicate "yes" only if they feel PAIN or DISCOMFORT each time the probe is applied to their tooth. The subject may respond "yes" if they feel pressure, so it is important to remind them, as much as necessary, that they will feel pressure but to only respond "yes" if they feel pain or discomfort. Testing shall begin at 10g and increase by 10g with each successive challenge until a "yes" response is recorded. The force setting which elicited the “yes” response will be repeated. If a second "yes" is not obtained, the force setting will be increased by 10g and continue until a force is found which elicits two consecutive "yes" responses. The gram setting, which elicits the two consecutive “yes” responses, will be recorded as the threshold. If the subject fails to give a definite answer, the examiner should re-prompt them to provide a “yes” or “no” response. If they continue to be reluctant, their uncertainty should be indicated on the score sheet and the next stimulus should be at the next step in the upward direction. If no sensitivity is found below the session maximum, the tooth is disqualified from further testing.

At Baseline (Visit 2) all teeth that qualified for evaporative air sensitivity at Screening will be tested; the upper test limit is 20g. If no pain response is found, the threshold will be recorded as >20g and the tooth will be disqualified from further tactile testing.

At Visits 3 and 4 the tactile assessments will be conducted as described on the two selected test teeth only, the upper force setting will be 80g. If no sensitivity is found, the threshold will be recorded as >80g.

The recording/calibration assistant/examiner will make adjustments and record the micro-amperage force setting and subject's responses onto the source document. The assistant will not give verbal cues to the examiner (the individual applying the probe tip to the tooth) other than when it is okay to proceed as this may bias the subject's response. For example, if the assistant feels that the subject did not give a true response, they may then elect to repeat

the same force setting without telling the examiner. In this respect the examiner is also blinded, to avoid investigator bias. Since this places more responsibility on the assistant, it is imperative that the assistant be well trained in this procedure. It is also possible that the investigator may be unsure of the reliability of the subject's response. In this case, the investigator may then opt to re-probe at the same force setting. This can be indicated to the assistant by a non-verbal signal (i.e. a hand gesture).

7.2.1.1 Calibration of the Yeaple Probe

The Yeaple probe will be calibrated before use on each day subjects are assessed. The microamp settings will vary from day to day (partly due to battery power consumption), but the difference should not be significant. Thus, previous probe settings will serve as a guide. Calibration should start at the lowest microamp setting and then increase.

The procedure described below is preferred; however other comparable procedures may be acceptable.

The Yeaple probe is fixed to a clamp attached to a ring stand so that the probe tip is vertical. A small paper cup attached with cotton thread is balanced over the end of the Yeaple probe, without the probe tripping. The probe dial is set to the microamp setting and water is fed into the paper cup using a dropper until the probe trips. The gram setting is recorded and the Yeaple probe reset to the next microamp value. The procedure is repeated until data has been collected to more than 80 grams.

The data are plotted and the points connected with line segments in order to interpolate the micro-amp values equivalent to 10, 20, 30, 40, 50, 60, 70 and 80 grams. This calibration should be repeated three times, and the average of the three used for the day's settings.

The settings will be recorded on the Yeaple probe calibration record. This form must also be dated and initialled by whoever performs the calibration. For convenience a separate form should be used for each probe (record the unit's serial number on the form). This record will serve as the guide for the force setting for that day's examinations.

7.2.2 Evaporative Air Sensitivity Assessment

This assessment will be conducted by a single examiner for all subjects at each visit by directing a maximum one second application of air from a dental air syringe to the exposed dentine surface from a distance of approximately 1 cm. The examiner should take appropriate measures to isolate the test tooth surface in order to prevent stimulus exposure to adjacent tooth or surrounding soft tissue. Response to this stimulus will be evaluated using the Schiff sensitivity scale. The evaporative air stimulus (with Schiff sensitivity score) should follow the tactile assessment, with a minimum of five minutes in between each assessment type to allow recovery time.

The examiner will assess the evaporative air sensitivity of all clinically eligible teeth identified at Screening (teeth that qualified on EAR, MGI and tooth mobility criteria, and had

none of the dentition exclusions). At Baseline only those teeth which meet the tactile threshold inclusion criterion (tactile threshold ≤20g) will be assessed. Two test teeth will be selected according to specific eligibility criteria in an individual subject. At Visits 3 and 4 only the eligible test teeth will be assessed.

7.2.2.1 Subject Response - Schiff Sensitivity Scale

This is an examiner based index [Schiff, 1994], scored immediately following administration of the evaporative air stimulus. This scale focuses on a combination of specific, observable, physical, behavioural and verbal responses from the subject as a result of the stimulation of exposed dentine, rather than solely an oral request from the subject to discontinue stimulation and may facilitate discrimination. The examiner will indicate the subject's response to the evaporative air stimulus, after the stimulation of each individual tooth, using the Schiff sensitivity scale as follows.

0	Subject does not respond to air stimulation
1	Subject responds to air stimulus but does not request discontinuation of stimulus
2	Subject responds to air stimulus and requests discontinuation or moves from stimulus
3	Subject responds to stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus

7.3 Safety

The following safety assessments will be performed at times defined in the Study Procedures (Section 6) section of this protocol.

7.3.1 Oral Soft Tissue (OST) Examination

Where possible, this procedure should be conducted by a single trained dental examiner. The examination will be accomplished by direct observation and palpation with retraction aids as appropriate. The examiner will include examination of the Labial Mucosa (including lips), Buccal Mucosa, and Mucogingival folds, Gingival Mucosa, Hard Palate, Soft Palate, Tonsilar Area, Pharyngeal Area, Tongue, Sublingual Area, Submandibular Area and Salivary Glands. The results of the examination will be recorded in the CRF as either normal or abnormal with details of any abnormalities. A brief description of any abnormality observed by the examiner or reported by the subject at the application site following the administration of the acclimatisation or treatment dentifrices will be recorded as an AE.

An OST examination will be conducted at every study visit prior to any clinical assessments. To ensure consistency in evaluations, every effort should be made to use the same OST

examiner throughout the study, however if this is not achievable e.g. because of examiner illness, OST examinations may be carried out by different examiners.

7.3.2 Full Oral Hard Tissue (OHT) Examination

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

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

Observations will be listed as "Absent" or "Present" and conditions noted as present will be described. Examination findings will be described and documented in the eCRF. Any observation that changes from "Absent" to "Present" from the screening assessment must be recorded as an AE.

7.3.3 Urine Pregnancy Test

Urine pregnancy testing will be performed on females of child bearing potential at Baseline (Visit 2) according to the test kit manufacturer's instructions. Urine collected for urine pregnancy testing will be disposed of as appropriate immediately following the test result.

Female subjects of non-childbearing potential must meet at least one of the following criteria:

- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;
- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

8 ADVERSE EVENT AND OTHER EVENTS OF SPECIAL INTEREST REPORTING

8.1 Definitions of Adverse Events and Serious Adverse Events

8.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of an investigational or acclimatization product, whether or not considered related to the investigational or acclimatization product.

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 treatment.

Events Meeting the AE Definition:

- Any abnormal safety assessments (eg, OST findings, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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 treatment 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 treatment 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" per se will not be reported as an AE or SAE. 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 or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition:

- Any 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.

8.1.2 Serious Adverse Event

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 participant 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 participant 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 AE. 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 (eg, 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 participant 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.

8.2 Reporting Period

8.2.1 Adverse Event

AEs will be collected from the time of the first supervised brushing with the acclimatization dentifrice and until 5 days following last administration of the investigational product.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

8.2.2 Serious Adverse Event

SAEs assessed as **not related** or **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy), or related/not related to a GSK concomitant medication will be recorded from the time a subject signs the ICF, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product and until 5 days following last administration of the investigational product.

8.3 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study treatment and/or the study, or that caused the participant to discontinue the study treatment.

The investigator 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 SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, 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/SAE in the CRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK AE/SAE CRF page.

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

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the

AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

AEs elicited by the investigator in a standard manner at the study visits should also be recorded in the AE section of the CRF. Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.1 Adverse Event

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

8.3.2 Serious Adverse Event

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product
- 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 on study product
- Outcome if known

The SAE form, completed as fully as possible, must be 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.

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

GSK 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 is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC 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 eg, summary or listing of SAE) from the sponsor will review and then file it along with the Safety Statement and will notify the IEC, if appropriate according to local requirements.

8.4 Evaluating Adverse Events and Serious Adverse Events

8.4.1 Severity Assessment

The investigator or designee will make an assessment of severity for each AE and SAE 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 will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both 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.

8.4.2 Causality Assessment

The causality assessment is one of the criteria used when determining regulatory reporting requirements. 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.

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 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.

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.** 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.

8.5 Withdrawal Due to an Adverse Event and Serious Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of 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 below.

8.6 Pregnancy

8.6.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported following administration of any investigational product or acclimatization product and until 5 days after the last dose.

8.6.2 Action to be Taken if Pregnancy Occurs

The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product or washout product. The investigator will record pregnancy information on the appropriate form 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 information form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox PPD

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 (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be and should be recorded as an SAE.

Any female participant who becomes pregnant while participating will discontinue study treatment.

8.7 Follow-up of Adverse Events and Serious 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/SAEs 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 to elucidate as fully as possible the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed CRF.

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

Investigators are not obliged to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including the death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify GSK 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 within the designated reporting time frames.

9 DATA MANAGEMENT

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

For this study subject data will be entered into an electronic CRF using a validated data system.

9.1 Source Documents/ Data

The source documents (eg. Score cards) which contain the source of data recorded in the CRF should be specified in Section 6. The CRF and diary can be used as a source document at the discretion of data management.

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

9.2 Case Report Form

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

For each subject who has given informed consent/assent and has been screened, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with applicable GSK CH standards and data cleaning procedures to ensure the integrity of the data e.g. removing errors and inconsistencies in the data.

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

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

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

9.3 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.

Any corrections to the entries made to the paper source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

9.3.1 Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the CRF data, 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 (Adverse Events and Drugs) appropriately.

The study monitor at the study site will review the CRFs in accordance with the monitoring plan, and 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.

9.4 Processing Patient Reported Outcomes

Patient reported outcome (PRO) data may be collected from diary cards, questionnaires, etc, and entered into the sponsor's clinical data management system (DMS). In instances where the PRO data is entered into the DMS by GSK CH, the PROs will be anonymized as agreed

and documented prior to study initiation. PROs that are source will be retained by the investigator and certified copies will be sent to GSK CH.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded on all PRO's that will be forwarded to GSK CH.

10 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1 Sample Size Determination

Change from baseline in Schiff sensitivity score will be used to evaluate treatment effects with regard to the primary objective. With 55 evaluable subjects per group, the study will have 80% power to detect a mean difference of 0.33 (SD=0.619) in change from baseline in Schiff sensitivity score after 8 weeks of treatment.

The estimate of SD was obtained from GSKCH study 205794. The sample size is based on carrying out two-tailed two sample t-test at a 5% significance level.

Therefore, to allow for dropouts a sufficient amount of subjects will be screened to randomize approximately 180 subjects to ensure 165 subjects (approximately 55 per arm) complete the study.

10.2 Statistical Methods and Analytical Plan

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

10.2.1 Demographic and Baseline Characteristics

Descriptive statistics (percentages, means and standard deviations) of demographic baseline characteristics, medical history, current/concomitant medication and compliance will be tabulated.

10.2.2 Primary Analysis

The primary efficacy variable is the change from baseline in Schiff sensitivity score at 8 weeks. The primary comparison is between the Experimental formulation and the negative control. As there is only a single primary objective no adjustment for multiple comparisons is required.

The Schiff sensitivity score is derived as the average score of the two test teeth. The change from baseline is derived from the individual teeth first before calculating the average change of the two test teeth.

The change from baseline in Schiff sensitivity score will be analysed using analysis of covariance (ANCOVA) with treatment as factor and baseline Schiff sensitivity score as a covariate. Note that since the baseline Schiff sensitivity score will be included as a covariate, the baseline Schiff stratification value will not be included in the model.

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated. In case of violation of these assumptions a suitable transformation or a non-parametric method eg the van Elteren test, adjusting for the maximum baseline Schiff Sensitivity scores will be performed and results will be compared with the ANCOVA results. If the inferences from the two analyses are similar, then both sets of results will be reported and emphasis will be made on the ANCOVA results. If there are differences between the inferences, then the emphasis will be on the non-parametric analysis.

10.2.3 Secondary Analyses

The secondary efficacy variable is change from baseline in Tactile threshold at 8 weeks (Test Product vs Control Product 1).

Tactile score including the change is derived in the same manner as for the Schiff score.

The change from baseline in tactile threshold will be analysed using ANCOVA with treatment and baseline Schiff stratification included as factors and baseline tactile threshold included as a covariate.

The assumption of normality and homogeneity of variance in ANCOVA model will be assessed as described for the primary efficacy analysis.

10.2.4 Exploratory Analyses

The exploratory efficacy variables are:

- Change from baseline in Schiff sensitivity at 8 weeks (Test Product vs Control Product 2 and Control Product 2 vs Control Product 1).
- Change from baseline in Tactile threshold at 8 weeks (Test Product vs Control Product 2 and Control Product 2 vs Control Product 1).
- Change from baseline in Schiff sensitivity at 4 weeks (Test Product vs Control Product 1, Test Product vs Control Product 2 and Control Product 2 vs Control Product 1).
- Change from baseline in Tactile threshold at 4 weeks (Test Product vs Control Product 1, Test Product vs Control Product 2 and Control Product 2 vs Control Product 1).

Schiff and tactile score is derived as per the primary analysis including the change.

Both change from baseline in Schiff and tactile sensitivity will be analysed in the same way as per the primary and secondary analyses.

10.2.5 Safety Analyses

Safety population will be used for safety assessments. Safety analyses will be performed according to the treatment that the subject received (using variable ATRT). All AEs will be reviewed by the Clinical Research Scientist or Designee prior to database lock and unblinding and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). During this review stage, AEs will be further categorized as oral or non-oral. AEs will be listed and summarized by treatment received. Serious AEs will also be listed. AEs will be regarded as treatment emergent if they occur on or after the first treatment application at the baseline visit. The following AEs tables split by treatment will be produced:

- Listing of all AEs (including Non-treatment emergent AEs from all subjects)
- Listing of all AEs for screened subjects
- Treatment emergent AEs by Oral/Non-Oral Preferred Term (PT)
- Treatment emergent AEs by System Organ Class (SOC) and PT
- Treatment emergent AEs by SOC, PT and intensity
- Treatment emergent treatment related AEs by Oral/Non-Oral
- Treatment emergent treatment related AEs by SOC and PT
- Listing of SAEs (if there are none a null listing will be produced; if there are more than 5 treatment emergent serious SAEs a table will be produced instead by SOC and PT)
- Non-serious treatment emergent AEs by SOC and PT (only produced if there are more than 5 SAEs)

OST abnormalities will be listed and tabulated. The tabulation will show changes in abnormality from baseline to each follow-up assessment.

Exposure to study product will also be tabulated and listed by treatment group.

10.2.6 Definition of Analysis Populations

- The safety population includes all subjects who are randomized and receive investigational product and analysed as per treatment received
- The ITT population includes all randomized subjects who receive at least one dose of investigational product and analysed as randomized.
- The PP population includes all subjects who fully comply with all study procedures and restrictions and is a sub-set of the ITT population. Any protocol deviations that would lead to subjects/data being excluded will be removed from the PP population.

10.2.7 Exclusion of Data from Analysis

Any of the following will be considered a protocol violation which may warrant exclusion of data or the subject from efficacy analysis:

- Violation of inclusion or exclusion criteria that are deemed to affect efficacy.
- Medical history which is deemed to affect efficacy.
- Use of prohibited treatment or medication before or during the study, which is felt to affect the assessment of efficacy.
- Not receiving randomised treatment.
- Treatment non-compliance.
- Assessments outside the scheduled time windows.
- Protocol deviations.
- Any other reason identified likely to affect efficacy.

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

10.2.8 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.

10.2.9 Interim Analysis

No interim analysis is planned for this study.

10.2.10 Other Analyses

To cover the Chinese requirement to demonstrate a 15% difference between the Test Product and Control product 1, the difference between treatments in the raw means of the actual score (note not change from baseline) will be calculated and presented. This will be done for Schiff and tactile at weeks 4 and 8. The calculation is: -

100*(Test-Ref 1)/Ref 1

11 STUDY GOVERNANCE CONSIDERATIONS

11.1 Quality Control

In accordance with applicable regulations including GCP, and GSK procedures, GSK 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 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 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.

11.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK 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 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.

11.3 Regulatory and Ethical Considerations

11.3.1 Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, safety statement (including any updates) and other relevant documents, e.g., recruitment advertisements, if applicable, from the IEC. All correspondence with the IEC should be retained in the investigator file. Copies of IEC 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 IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IEC and GSK CH in writing immediately after the implementation.

11.3.2 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), 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.

11.3.3 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 IEC before use, and available for inspection.

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

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

11.3.4 Subject Recruitment

Advertisements approved by IECs and investigator databases may be used as recruitment procedures. Use of IEC 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.

11.3.5 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.

11.4 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 processes.

11.5 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 site or other mutually-agreeable location.

GSK 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 Policy.

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

11.6 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 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)/ 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 local laws or regulations, GSK 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 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.

11.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IEC, or investigational product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of SnF_2 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 CRFs completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authority(ies) and the investigator should promptly inform the IEC and provide the IEC a detailed written explanation of the termination or suspension.

If the IEC 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.

11.8 Definition of Study End/ End of Study

The end of the study will be the date of the Last Subject Last Visit (LSLV). For this study the LSLV will be the primary completion date (PCD).

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13 APPENDIX

13.1 Appendix I – Instructions

INSTRUCTIONS

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

Each time you brush:

- Dispense a ribbon of toothpaste covering the length of the toothbrush head (see below picture).
- Set your timer for 1 minute, and then brush all the teeth in your mouth in your usual manner for 1 timed minute.
- Record each brushing in the diary. Note any changes to these brushing procedures and reasons for changes (e.g. missed brushings, extra brushings) too.

- Record any changes in your smoking habits, health, medications (prescription and over the counter medications) or treatments in the diary.
- Bring your diary card (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 (taste, color and smell).

13.2 Appendix II - Abbreviations

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

Table 13-1 Abbreviations

Abbreviation	Term
ABL	aluminum barrier laminate
AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
CRF	case report form
DMS	data management system
DH	dentine hypersensitivity
EAR	erosion, abrasion, recession
EDC	electronic data capture
EDP	exposure during pregnancy
FSFV	first subject first visit
FSH	follicle stimulating hormone

Abbreviation	Term
GCP	Good Clinical Practice
GCS	Global Clinical Supplies
GSK CH	GlaxoSmithKline Consumer Healthcare
IB	investigator's brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ITT	intent to treat
IUD	intrauterine device
LSLV	last subject last visit
MedDRA	medical Dictionary for Regulatory Activities
MoH	Ministry of Health
MGI	Modified Gingival Index
NaF	sodium fluoride
N/A	not applicable
OHT	oral hard tissue
OST	oral soft tissue
OTC	over-the-counter
P&G	Proctor and Gamble
PI	principal investigator
PII	personally identifiable information
PP	per protocol
PT	preferred term
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SnF_2	stannous fluoride
$SnCl_2$	stannous chloride
SMFP	sodium monofluorophosphate
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
SS	safety statement

Abbreviation	Term
SSRD	single reference safety document
TMF	trial master file

SIGNATURE PAGE

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Date	Signed By
21-Aug-2017 03:58:31	PPD
Justification	Approved

Date	Signed By
21-Aug-2017 10:22:45	PPD
Justification	Approved

Date	Signed By
23-Aug-2017 05:58:16	PPD
Justification	Biostatistics Approval

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