Clinical Protocol

207212

CONFIDENTIAL

SUMMARY INFORMATION

Title:	A Clinical Study Investigating the Efficacy of an Occluding Dentifrice in Providing Relief from Dentinal Hypersensitivity
Protocol Number:	207212
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH)St Georges Avenue, Weybridge, Surrey, KT13 0DE, United Kingdom (UK) Tel: PPD
Product Name:	Experimental Dentifrice containing CCI stannous fluoride (CCI fluoride)
Development Phase:	N/A

Expert Advice Outside of Normal Working Hours:	Tel: PPD

Key Protocol Authors:	
PRIMARY CONTACT **Clinical Study Manager:**	PPD, PhD GSK Consumer Healthcare Route de l'Etraz, 1260, Nyon, Switzerland Tel PPD
Clinical Research	PPD, MSc, CStat PPD, MSc, PhD
Biostatistician:	PPD, BSc, MSc
Clinical Supplies:	PPD, MSc

Principal Investigator:	Professor Nicola West, BDS, FDS, RCS, PhD, FDS
Study Site Name & Address:	Clinical Trials Unit (Periodontology) School of Oral and Dental Sciences Bristol Dental School and Hospital Lower Maudlin Street, Bristol BS1 2LY, UK
Study Site Telephone Number:	Tel: PPD Fax: PPD
Study Examiner:	PPD, BDS, MFDS RCPS (Tactile assessments and Evaporative air assessments)

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:	Prof Nicola West
Investigator Qualifications:	BDS, FDS, RCS, PhD, FDS
Investigator Signature:	PPD
Date of Signature/ Agreement:	PPD DD/MMM/YYYY

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PROCESS FOR AMENDING THE PROTOCOL

Protocol modifications to ongoing studies which could potentially adversely affect the safety of subjects or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria are considered major/substantial amendments and must be made only after appropriate consultation between an appropriate representative of GSKCH and the investigator.

Details of amendments to the protocols should be recorded on the following page. Protocol modifications must be prepared by a representative of GSKCH. All changes must be justified in the Reason for Amendment section of the following Protocol Amendment Page. Approval of amendments will be made by the original protocol signatories or their appropriate designees.

All major/substantial protocol modifications must be reviewed and approved by the appropriate IEC in accordance with local requirements, before the revised edition can be implemented.

All non-substantial/ minor/ administrative amendments should be submitted to the IEC as per country specific requirements. In some countries pre-approval of a minor amendment is not required and will just be held on file by the sponsor and investigator.

PROTOCOL AMENDMENT PAGE

Details of all amendments should be recorded in the table below. Affected sections should be listed in the table; the actual amendment/ change should be made in the relevant section of the main protocol.
To highlight the change, the following features will be used:
To **add** text: Use of **CAPITAL LETTERS, BOLD AND UNDERLINE**
To **delete** text: Use of Strikethrough e.g. ~~strikethrough~~

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.:	Non-Substantial/Minor ☐		Informed Consent ☐ Yes ☐ No Safety Statement ☐ Yes ☐ No CRF ☐ Yes ☐ No		Signature:
Protocol Version No.:	Substantial/ Major ☐				Date:
Amendment No.:	Non-Substantial/Minor ☐		Informed Consent ☐ Yes ☐ No Safety Statement ☐ Yes ☐ No CRF ☐ Yes ☐ No		Signature:
Protocol Version No.:	Substantial/ Major ☐				Date:

SCHEDULE OF EVENTS

Procedure/ Assessment	Visit 1	Acclimatisation Period (minimum 4 weeks – maximum 8 weeks)	Visit 2		Visit 3
	Screening		Day 0 Baseline (Pre-Treatment)	Day 0 Post-Treatment	Day 3
Informed consent	X				
Demographics and Medical History	X				
Current / Concomitant medication	X		X		X
Inclusion / Exclusion Criteria	X		X[1]		
Subject Eligibility	X		X		X
Continuation Criteria			X		X
Oral Soft Tissue (OST) Examination	X		X	X	X
Oral Hard Tissue Examination including Eligible Teeth Assessments (Dentition Exclusions, EAR, MGI, Tooth Mobility)	X				
Qualifying Evaporative Air Sensitivity Assessment (Y/N)	X				
Dispense Acclimatisation Toothpaste, Toothbrush, Timer	X				
Supervised Brushing with Acclimatisation Toothpaste	X				
Return Acclimatisation Toothpaste, Toothbrush			X		
Compliance Check			X[2]		X[7]
Tactile Sensitivity Assessment (Yeaple Probe)			X[3]		
Evaporative Air Sensitivity Assessments (Schiff sensitivity score)			X[4]		
Selection of two 'Test Teeth'			X[5]		
Stratification/Randomisation			X		
Dispense Study Supplies			X[6]		
Supervised direct application of allocated dentifrice (Test Teeth Only)			X[8]		
Tactile and Evaporative Air Assessments[9] (Test Teeth only)				X	X
Supervised Brushing				X[10]	
Return Study Supplies					X
Adverse Events / Incidents [11]	X		X	X	X
Study Conclusion					X

1. Inclusion criteria 5d
2. Subject asked to confirm that they have brushed with the acclimatisation product as directed during the acclimatisation period.
3. To be performed pre treatment on all teeth that meet the dentition exclusions, EAR, MGI and tooth mobility criteria at Screening until the examiner selects 2 teeth meet the study criteria, at which point no further teeth will be tested. Maximum force to be tested will be 20g.
4. To be performed pre-treatment on teeth that meet tactile threshold inclusion criterion (<=20g) at Baseline and should follow the tactile assessment with a minimum of 5 mins between the last tactile assessment and the first evaporative air assessment to allow the teeth recovery time.
5. Tactile assessment to be performed, on the two selected test teeth only. Maximum force to be tested will be 80g. Evaporative air assessment should follow the tactile assessment with a minimum of 5 mins between the last tactile assessment and the first evaporative air assessment to allow the teeth recovery time.
6. Experimental dentifrice, control dentifrice, toothbrush, product usage instructions, and diary. Timer dispensed in Visit 1 will be kept and re used.
7. Based on subject completed diary card
8. To be performed after stratification and randomisation
9. Tactile assessment to be performed, on the two selected test teeth only. Maximum force to be tested will be 80g. Evaporative air assessment should follow the tactile assessment with a minimum of 5 mins between the last tactile assessment and the first evaporative air assessment to allow the teeth recovery time.
10. Supervised whole mouth brushing before leaving the site (after all clinical assessments have been performed)
11. Incidents captured from Visit 2.

PROTOCOL SYNOPSIS FOR STUDY 207212

Brief Summary

This single centre study will be used to investigate the efficacy of an experimental stannous fluoride containing dentifrice in relieving dentinal hypersensitivity (DH) after short term use compared with a standard fluoride dentifrice.

The study will be conducted in subjects in good general health, with pre-existing self-reported and clinically diagnosed tooth sensitivity at screening.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To investigate the ability of an experimental CCI stannous fluoride dentifrice to provide relief from DH, as elicited by an evaporative (air) stimulus (Schiff sensitivity scale) after 3 days use.	Change from baseline in Schiff sensitivity score after 3 days use.
Secondary	
To investigate the ability of an experimental CCI stannous fluoride dentifrice to provide relief from DH, as elicited by a tactile stimulus (Yeaple probe) after 3 days use.	Change from baseline in a tactile threshold after 3 days use.
To investigate the ability of a CCI stannous fluoride dentifrice to provide relief from DH, as elicited by an evaporative (air) stimulus (Schiff sensitivity scale) and a tactile stimulus (Yeaple probe) after a single use (60 second direct application on selected teeth)	Change from baseline in Schiff sensitivity score after a single 60 second direct application. Change from baseline in tactile threshold after a single 60 seconds direct application.

Study Design

Overall Design
This will be a single centre, three day, randomised, examiner blind, two treatment arm, parallel design, stratified (by maximum baseline Schiff sensitivity score of the two selected test teeth), controlled study, in subjects with at least two sensitive teeth that meet all the criteria at the screening and baseline (pre-treatment) visits. DH will be assessed at baseline (pre-treatment), post-treatment and after 3 days twice daily brushing.

Visit 1 - Screening Visit
The following assessments will be conducted: • Written informed consent. • Inclusion/exclusion criteria • Review of the oral care products the subject is currently using to confirm they do not contain any ingredients intended for treating sensitive teeth. • Demographics, current/concomitant medications and medical history. • Oral examination including an oral soft tissue (OST) and oral hard tissue (OHT) examinations and assessments to determine eligible teeth Oral Hard Tissue Examination including Eligible Teeth Assessments (Dentition Exclusions, EAR, MGI, Tooth Mobility). • Qualifying evaporative air sensitivity. • Confirmation of subject eligibility. • Dispensation of acclimatisation toothpaste, toothbrush and timer. • Supervised brushing with acclimatisation toothpaste. • Adverse Events (AEs) and incidents will be documented from completion of the supervised brushing with acclimatisation toothpaste.
Visit 2 - Baseline Visit (Pre-treatment)
The following assessments will be conducted: • Review of current/concomitant medications, AEs. • Return of acclimatisation toothpaste and toothbrush. • Compliance check of acclimatisation product usage during acclimatisation period. • Confirmation of subject eligibility and continuance. • OST examination. • Tactile sensitivity assessment of eligible teeth. • Evaporative air sensitivity assessment of eligible teeth which meet the tactile sensitivity entry criterion. • Inclusion criteria 5d. • Selection of two test teeth. • Stratification and Randomisation. • Dispensation of study toothpaste and toothbrush with usage instructions and diary. • Supervised direct application using finger with allocated study treatment (test teeth only) • Adverse events and Incidents.
Visit 2 – Post-treatment
The following assessments will be conducted: • Review of AEs and incidents.

• OST examination. • Tactile sensitivity assessment of the two selected test teeth. • Evaporative air sensitivity assessment of the two selected test teeth. • Supervised brushing (whole mouth) with allocated study treatment before leaving site after all clinical assessments performed.
Visit 3 – Day 3
The following procedures will be conducted: • Review of current/concomitant medications, AEs and incidents. • Subject adherence • Return of study supplies (toothpaste, toothbrush) and diary. • Review of completed diary to determine usage compliance. • OST examination. • Tactile sensitivity assessment of the two selected test teeth. • Evaporative air sensitivity assessment of the two selected test teeth. • Subjects will be reminded to report AEs and incidents for 5 days after last treatment. • Study conclusion.

Type and Planned Number of Subjects

A sufficient number of subjects will be screened in order that approximately 210 subjects enter the acclimatisation phase so that approximately 190 subjects (approximately 95 per treatment arm) are randomised. This should ensure approximately 184 subjects (approximately 92 per treatment arm) complete the study.

Diagnosis and Main Criteria for Inclusion

Subjects aged 18-65 years of age, with a minimum of 20 natural teeth and in good general health who suffer from tooth sensitivity. At Screening, subjects must have a minimum of two accessible non adjacent teeth (incisors, canines, or pre-molars) with signs of erosion or abrasion or facial/cervical gingival recession (EAR), with a modified gingival index (MGI) =0 adjacent to the test area and a clinical mobility of ≤1, and with signs of sensitivity measured by qualifying evaporative air assessment. At Baseline subjects must have a minimum of two, non-adjacent accessible teeth (incisors, canines or pre-molars), with signs of sensitivity, measured by qualifying tactile stimulus (Yeaple ≤ 20g) and evaporative air assessment (Schiff Sensitivity Score ≥ 2).

Product Information

	Test dentifrice	Control dentifrice
Treatment Description	Experimental dentifrice containing [redacted] stannous fluoride ([redacted] fluoride)	Dentifrice containing [redacted] sodium monofluorophosphate ([redacted] fluoride)
MFC or Commercial product	[redacted]	Colgate Cavity Protection (USA Marketed Product)
Route of administration	Topical oral use	
Supervised direct application time (Test Teeth only)	60 seconds	60 seconds
Supervised direct application (Test Teeth only) dosing instructions	Subjects will directly apply (under supervision) a pea-sized dose to each of the two qualifying teeth using their washed, clean finger by direct application and gently rubbing into the tooth's cervical margin for the allocated time. No rinsing will be permitted.	
Supervised brushing (Visit 2)	Before leaving the site (after all the clinical assessments have been completed), subjects will dose a dry toothbrush with a full strip of toothpaste. Subjects will then brush each of the two selected sensitive test teeth first, followed by the whole mouth thoroughly for at least 1 minute. Subjects will be permitted to rinse with 5 ml tap water (kept at room temperature) for a maximum 5 timed seconds.	Before leaving the site (after all the clinical assessments have been completed), subjects will dose a dry toothbrush with a full strip of toothpaste Subjects will brush their whole mouth thoroughly for at least 1 minute under. Subjects will be permitted to rinse with 5 ml tap water (kept at room temperature) for a maximum 5 timed seconds.

Home use instructions **Twice daily (morning/ evening)**	Subjects will be instructed to dose a dry toothbrush with a full strip of toothpaste. Subjects will then brush each of the two selected sensitive test teeth first, followed by the whole mouth thoroughly for at least 1 minute. Subjects will be permitted to rinse with tap water.	Subjects will be instructed to dose a dry toothbrush with a full strip of toothpaste. Subjects will then brush the whole mouth thoroughly for at least 1 minute. Subjects will be permitted to rinse with tap water.

Statistical Methods

Change from baseline (pre-treatment) to post-treatment time point (single use and after 3 days use) in Schiff sensitivity score will be analysed using an analysis of covariance (ANCOVA) model. The model will include treatment and baseline Schiff Sensitivity Score as a covariate.

Change from baseline (pre-treatment) to post-treatment time point (single use and after 3 days use) in tactile score will be analysed using ANCOVA with treatment and baseline Schiff stratification as factors and the baseline tactile score as a covariate.

Adverse events (AEs), incidents, and OST abnormalities will be listed by treatment.

1. INTRODUCTION

Dentinal hypersensitivity (DH) is described by Addy et al 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 pathology' [Addy 1985]. The definition was later revised to replace the word 'pathology' with 'disease' to avoid confusion with pain origins from other dental conditions [Canadian Advisory Board, 2003]. DH originates from aetiologic factors such as gingival recession, erosion and/or abrasion that result in loss of enamel or cementum and exposure of underlying dentine with patent dentinal tubules [Orchardson, 1987]. Brännström's hydrodynamic theory of DH hypothesises movement of the fluid within the dentine tubules when an external stimulus is applied to the dentine, which in turn stimulates nerve processes in the pulpal area of the dentine and produces pain impulse transmission [Brannstrom, 1964].

Currently there are two approaches to the management of DH.

- Nerve depolarisation
- Dentinal tubule occlusion.

Nerve depolarising agents, such as potassium nitrate, 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, 1975]. Tubule occluding agents such as strontium salts, stannous salts, bioglasses or silicas serve to physically seal or block the dentine tubules and thereby reduce the effect of external stimuli.

Stannous fluoride has been incorporated into oral hygiene products indicated for the reduction of DH since the 1960s [Schiff, 2006]. Its long-term efficacy has been reported in a number of published studies with treatment periods of 2-8 weeks [Schiff, 2000a, 2000b, 2005, 2006; Sharma, 2010; Chaknis, 2011; Du, 2011; Ni, 2011; Parkinson, 2013], with some studies also reporting short term efficacy [He, 2011b; Sharma, 2011]. More recently, studies have also demonstrated relief of DH following a single treatment with an occlusion technology dentifrice at the start of a period of twice daily brushing. The single treatment involves direct application of a dentifrice to the sensitive dentine, either by massaging the sensitive tooth with dentifrice or by focused toothbrushing of the sensitive teeth prior to brushing the whole mouth. The direct application approach has been shown to be effective for two occlusion technologies to date (strontium acetate and arginine) [Ayad, 2009; Nathoo,

2009; Schiff, 2009; Fu, 2010; Mason, 2010] and focussed toothbrushing for stannous fluoride dentifrices[GSKCH Study RH01324; He, 2011a; Sharma, 2011].

GSK consumer healthcare (GSKCH) has conducted several short term studies with stannous fluoride dentifrices looking at DH relief with up to 14 days treatment [GSKCH Study RH01324; GSKCH Study RH01327; GSKCH Study Z7871335]. Stannous fluoride dentifrices were applied using the 'focused brushing' application which involved brushing the sensitive teeth prior to brushing the whole mouth.

The current study will investigate the ability of an experimental CCI stannous fluoride dentifrice in providing relief from DH after 3 days twice daily use, and after an initial direct application to the cervical margin.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To investigate the ability of an experimental CCI stannous fluoride dentifrice to provide relief from DH, as elicited by an evaporative (air) stimulus (Schiff sensitivity scale) after 3 days use.	Change from baseline in Schiff sensitivity score after 3 days use.
Secondary	
To investigate the ability of an experimental CCI stannous fluoride dentifrice to provide relief from DH, as elicited by a tactile stimulus (Yeaple probe) after 3 days use.	Change from baseline in a tactile threshold after 3 days use.
To investigate the ability of a CCI stannous fluoride dentifrice to provide relief from DH, as elicited by an evaporative (air) stimulus (Schiff sensitivity scale) and a tactile stimulus (Yeaple probe) after a single use (60 second direct application on selected teeth).	Change from baseline in Schiff sensitivity score after a single 60 second direct application. Change from baseline in tactile threshold after a single 60 second direct application.

3. STUDY PLAN

3.1. Study Design

Overall Design

This will be a single centre, three day, randomised, examiner blind, two treatment arm, parallel design, stratified (by maximum baseline Schiff sensitivity score of the two selected test teeth), controlled study, in subjects with at least two sensitive teeth that meet all the criteria at the screening and baseline (pre-treatment) visits. DH will be assessed at baseline (pre-treatment), post-treatment and after 3 days twice daily brushing.

At the Screening visit, subjects will give their written informed consent to participate in the study. Demography, medical history and concomitant medications will be recorded, followed by an oral examination. This will include an oral soft tissue (OST) and oral hard tissue (OHT) examination, dentition exclusions, assessment of erosion, abrasion, recession (EAR), gingival status, tooth mobility and subject response to a qualifying air sensitivity assessment (Y/N). Eligible subjects will be supplied with a standard fluoride dentifrice to use twice daily (morning and evening) during the acclimatisation period between the Screening and Baseline (pre-treatment). First use of the acclimatisation dentifrice will be carried out under supervision at the study site.

At the Baseline visit (pre-treatment), eligibility to continue will be assessed. Subjects will undergo an OST examination, followed by tooth sensitivity assessments (to a tactile stimulus [Yeaple probe, maximum 20g pressure], and an evaporative air stimulus [with Schiff Sensitivity Scale]), and a review of the inclusion/exclusion criteria. Eligible subjects will be stratified according to their maximum baseline Schiff sensitivity score of the two selected teeth (2 / 3) and then randomised to treatment.

At Visit 2, randomised subjects will directly apply assigned treatment to the two selected teeth (under supervision) as per the instructions provided. Following direct application of the assigned treatment (and within 5 minutes of it), tooth sensitivity of the two test teeth will be assessed to a tactile and evaporative air stimuli. Before leaving the site (after all the clinical assessments have been completed), subjects will brush their whole mouth for at least one minute under supervision. Subjects will brush at least once on the day of baseline (first brushing will be supervised at site). Subjects will return to the study site on day 3 (Visit 3) after six brushings. Every effort will be made to ensure similar appointment times are kept for subjects at Visit 3 as per Visit 2. Subjects will undergo an OST examination, followed by tooth

sensitivity assessments (to a tactile stimulus [Yeaple probe, maximum 80g pressure], and an evaporative air stimulus [with Schiff Sensitivity Scale]). Following review of AEs and incidents subjects will be exited from the study.

Visit 1 - Screening Visit

The following assessments will be conducted:

- Written informed consent.
- Inclusion/exclusion criteria
- Review of the oral care products the subject is currently using to confirm they do not contain any ingredients intended for treating sensitive teeth.
- Demographics, current/concomitant medications and medical history.
- Oral examination including an oral soft tissue (OST) and oral hard tissue (OHT) examinations, including eligible teeth assessments (Dentition Exclusions, EAR, MGI, Tooth Mobility).
- Qualifying evaporative air sensitivity.
- Confirmation of subject eligibility.
- Dispensation of acclimatisation toothpaste, toothbrush, and timer.
- Supervised brushing with acclimatisation toothpaste.
- Adverse Events (AEs) and incidents will be documented from completion of the supervised brushing with acclimatisation toothpaste.

Visit 2 - Baseline (Pre-treatment)

The following assessments will be conducted:

- Review of current/concomitant medications, AEs.
- Return of acclimatisation toothpaste and toothbrush.
- Compliance check of acclimatisation product usage during acclimatisation period.
- OST examination.
- Tactile sensitivity assessment of eligible teeth.
- Evaporative air sensitivity assessment of eligible teeth which meet the tactile sensitivity entry criterion.
- Inclusion criteria 5d.
- Selection of two test teeth.
- Stratification and Randomisation.
- Dispensation of study toothpaste with usage instructions and diary.
- Supervised direct application using finger with allocated study treatment (test teeth only).
- Adverse events and Incidents.

Visit 2 – Post-treatment
The following assessments will be conducted: • Review of AEs and incidents. • OST examination. • Tactile sensitivity assessment of the two selected test teeth. • Evaporative air sensitivity assessment of the two selected test teeth. • Supervised brushing with allocated study treatment.
Visit 3 – Day 3
The following procedures will be conducted: • Review of current/concomitant medications, AEs and incidents. • Subject adherence • Return of study supplies (toothpaste, toothbrush) and diary. • Review of completed diary to determine usage compliance. • OST examination. • Tactile sensitivity assessment of the two selected test teeth. • Evaporative air sensitivity assessment of the two selected test teeth. • Subjects will be reminded to report AEs and incidents for 5 days after last treatment. • Study conclusion.

3.2. Subject Restrictions

Lifestyle/ Dietary
For the duration of the study (Screening – last visit): • Eligible subjects will be asked to stop using their regular oral care products from Screening for the duration of the study. • Subjects will not be permitted to use any oral care products (e.g. mouthwashes, tongue cleaners, whitening/bleaching products) other than those provided to them. • Subjects will not be permitted to use any dental products, including home remedies, intended for treating sensitive teeth. • Subjects will not be permitted to chew gum. • Subjects will not be permitted to floss, except to remove impacted food ***Prior to study visits (Baseline - Day 3):*** • Subjects will be asked to refrain from all oral hygiene procedures for **at least 8 hours**, and from eating and drinking for at **least 4 hours** in order to standardise oral hygiene practices. Within 4 hours of a visit (but not within one hour of the

visit), small sips of room-temperature water will be permitted to take medications and relieve thirst if necessary

- Subjects will be requested to refrain from excessive alcohol consumption for 24 hours prior to the Baseline and all subsequent visits. If, in the opinion of the Investigator, the subject has consumed an excessive amount of alcohol prior to a visit, the visit may be rescheduled. If this is not possible, the subject should be treated as per section 4.4.

Medications and Treatments

For the duration of the study (Screening –last visit):

- If concomitant medications and traditional herbal ingredients/treatments are used during the study, their identity, as well as their dosage and frequency, start and stop dates must be recorded in the CRF.
- 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, the subject should be treated as per section 4.4.
- Subjects who enter the study will be requested to delay having any non - emergency, elective dental treatment until after study completion (including dental prophylaxis).

3.3. Type and Planned Number of Subjects

A sufficient number of subjects will be screened in order that approximately 210 subjects enter the acclimatisation phase so that approximately 190 subjects (approximately 95 per treatment arm) are randomised. This should ensure approximately 184 subjects (approximately 92 per treatment arm) complete the study.

Subjects will be recruited by the clinical site, primarily from their volunteer database. Subjects may also be recruited via posters or by word of mouth.

3.4. Study Design and Dose Justification

A randomized, single-blind (examiner blind), parallel group design is a recognized approach for providing evidence of the clinical effectiveness of a treatment for the reduction of DH [Holland, 1997].

In line with published recommendations [Holland, 1997], two independent stimulus-based efficacy measures will be employed (tactile and evaporative air sensitivity). To avoid inter-examiner variation, a single examiner will be responsible for the conduct

of a given clinical measure of DH for the duration of the entire study for all study subjects.

A tactile stimulus will be administered using a constant pressure probe (Yeaple Probe [Polson, 1980]). Response to this stimulus will be evaluated as:

- **Tactile Threshold:** The constant pressure probe allows the examiner to vary the force applied to the dentine surface from 10 g to an upper threshold of 80 g in increments of 10 g. The tactile threshold is the maximum pressure applied without the subject reporting pain or discomfort. The greater the tactile threshold, the less sensitive the tooth.

An evaporative air stimulus will be administered using a dental air syringe. Response to this stimulus will be evaluated using:

- **Schiff Sensitivity Scale** [Schiff, 1994]: This is an examiner assessment of the subject's response to an evaporative air stimulus. It is scored immediately following the stimulus and 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.

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 characterized by an improvement in sensitivity simply as a function of clinical study participation [Leight, 2008]. To help minimize the potential impact of such 'placebo' and 'no treatment' effects, an acclimatisation period will be included in this study from Screening, ahead of the Visit 2 assessments and randomisation. During this period subjects will be provided with a toothbrush and a marketed, standard fluoride toothpaste to use in place of their regular oral hygiene products. Use of the acclimatisation toothpaste will also help provide a standardized oral hygiene regimen prior to Visit 2. Subjects will brush twice daily, in line with recommended oral hygiene practice, and typical consumer habit, during this period.

The selection of two 'test teeth' to evaluate changes in DH is common practice in sensitivity studies [Docimo, 2009].

Other causes of dental pain can present with the same symptoms as DH, for example cracked tooth syndrome, fractured restorations, chipped tooth, dental caries, post-restorative sensitivity and teeth in acute hyperfunction [Dababneh, 1999]. While the age range over which an individual can experience DH is wide (from early teens to

70s) [Fischer, 1992], peak incidence is 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 18-65 selected for this study targets individuals suffering from tooth sensitivity which is most likely due to DH. This will facilitate recruitment and minimize inconvenience to older participants who are more likely to be rejected at screening.

A dose of twice daily brushing has been selected to be in line with dental professional recommendation, and is standard practice in clinical studies to evaluate DH efficacy. Dose for the direct application has been selected to be in line with similar published methodologies [Ayad, 2009].

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Safety Statement

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. CONSENT
Demonstrates understanding of the study procedures, restrictions and willingness to participate as evidenced by voluntary written informed consent and has received a signed and dated copy of the informed consent form.

2. AGE
Aged 18-65 years inclusive

3. COMPLIANCE
Understands and is willing, able and likely to comply with all study procedures and restrictions.

4. GENERAL HEALTH
Good general and mental health with, in the opinion of the investigator or medically qualified designee: a) No clinically significant and relevant abnormalities of medical history or oral examination. b) Absence of any condition that would impact on the subject's safety or wellbeing or affect the individual's ability to understand and follow study procedures and requirements.

5. DENTAL HEALTH
At Visit 1 (Screening): a) Self-reported history of dentinal hypersensitivity (DH) lasting more than six months but not more than 10 years. b) Minimum of 20 natural teeth. c) Minimum of 2 accessible non-adjacent natural teeth (incisors, canines, pre-molars), preferably in different quadrants, that meet all of the following criteria: – Signs of facial/cervical gingival recession and/or signs of erosion or abrasion (EAR). – Tooth with MGI score =0 adjacent to the test area (exposed dentine) only [Lobene, 1986] and a clinical mobility of ≤1 – Tooth with signs of sensitivity measured by qualifying evaporative air assessment (Y/N response) ***At Visit 2, Baseline (Pre-treatment)***: d) Minimum of two, non-adjacent accessible teeth (incisors, canines, pre-molars), that meet all of the following criteria: – Tooth with signs of sensitivity, measured by qualifying tactile stimulus (Yeaple ≤ 20g) and evaporative air assessment (Schiff sensitivity score ≥ 2) ***Note: Teeth which meet the EAR, MGI and mobility inclusion criteria and none of the dentition exclusion criteria at Screening should be assessed by tactile stimulus at Visit 2. Those teeth which meet the required tactile threshold (Yeaple ≤ 20g) should then be assessed by evaporative air stimulus. When two teeth that meet the study criteria are identified, no further testing is necessary.*** The examiner will select two *Test Teeth* from those which meet ***both*** the tactile threshold and Schiff sensitivity score criteria. *Test Teeth* should not be adjacent to each other and preferably in different quadrants.

4.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. PREGNANCY
A woman who is known to be pregnant or who is intending to become pregnant over the duration of the study.

2. BREAST-FEEDING
A woman who is breast-feeding

3. ALLERGY/ INTOLERANCE
Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.

4. CLINICAL STUDY/ EXPERMENTAL PRODUCT
a) Participation in another clinical study (including cosmetic studies) or receipt of an investigational drug within 30 days of the screening visit. b) Previous participation in this study. c) Participation in study 205084

5. SUBSTANCE ABUSE
Recent history (within the last year) of alcohol or other substance abuse.

6. PERSONNEL
An employee of the sponsor or the study site or members of their immediate family The site for this protocol is the Clinical trials Unit in the Bristol Dental School and Hospital. Employees of the Bristol Dental School and Hospital not associated with the Clinical Trials unit are eligible to participate.

7. DISEASE
a) Presence of chronic debilitating disease which, in the opinion of the investigator, could affect study outcomes. b) Any condition which, in the opinion of the investigator, causes xerostomia.

8. GENERAL DENTITION EXCLUSIONS
a) Dental prophylaxis within 4 weeks of Screening. b) Tongue or lip piercing. 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) Vital teeth bleaching within 8 weeks of Screening.

e) Desensitizing treatment within 8 weeks of Screening (professional sensitivity treatments and non-dentifrice sensitivity treatments).

9. SPECIFIC DENTITION EXCLUSIONS FOR *TEST TEETH*

a) Tooth with evidence of current or recent caries, or reported treatment of decay within 12 months of Screening.

b) Tooth with exposed dentine but with deep, defective or facial restorations, teeth used as abutments for fixed or removable partial dentures, dental implants, 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) Sensitive tooth not expected to respond to treatment with an over-the-counter dentifrice in the opinion of the investigator

10. PRODUCT USE

Use of an oral care product indicated for the relief of dentine hypersensitivity 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).

11. CONCOMITANT MEDICATION

a) Daily doses of medication/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.

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

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

12. OTHER

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

4.3. Screening/ Baseline Failures

Screen failures are defined as subjects who consent to participate in the study but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events. Re-screening of subjects will not be allowed in this study.

4.4. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. Where applicable, if a subject withdraws or is withdrawn from the study, all human biological samples collected before they left will be analyzed and reported unless the subject requests otherwise. A subject may request for their human biological samples to be destroyed. In these cases, the investigator must document this in the site study records and the samples should not be used for any further research.

If the reason for removal of a subject from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the electronic case report form (CRF). If a subject is withdrawn from the study because of a product limiting AE, thorough efforts should be clearly made to document the outcome. Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilizes, is otherwise explained, or the subject is lost to follow-up.

Should a subject take an analgesic medication within 8 hours of a treatment visit, or should any other factor, in the opinion of the investigator, be thought to affect study outcomes (e.g. excessive alcohol consumption), every attempt will be made to reschedule the subject. If they cannot be reappointed they will be withdrawn from the study.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, at least 2 telephone calls). The contact attempt should be documented in the subject's record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

4.5. Subject Replacement

Subjects who withdraw from the study post allocation of study product will not be replaced.

4.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study. The end of the study is defined as the date of the last subject's last visit.

5. PRODUCT INFORMATION

5.1. Study Product

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

	Test dentifrice	Control dentifrice
Treatment Description	Experimental dentifrice containing [redacted] stannous fluoride ([redacted] fluoride)	Dentifrice containing [redacted] sodium monofluorophosphate ([redacted] fluoride)
MFC or Commercial product	[redacted]	Colgate Cavity Protection (USA Marketed Product)
Route of administration	Topical oral use	
Supervised direct application time (Test Teeth only)	60 seconds	60 seconds
Supervised direct application (Test Teeth only) dosing instructions	Subjects will directly apply (under supervision) a pea-sized dose to each of the two qualifying teeth using their washed, clean finger by direct application and gently rubbing into the tooth's cervical margin for the allocated time. No rinsing will be permitted.	
Supervised brushing (Visit 2)	Before leaving the site (after all the clinical assessments have been completed), subjects will dose a dry toothbrush with a full strip of toothpaste. Subjects will then brush each of the two selected sensitive test teeth first, followed by the whole mouth thoroughly for at least 1 minute. Subjects will be permitted to rinse with 5 ml tap water (kept at room temperature) for a maximum 5 timed seconds.	Before leaving the site (after all the clinical assessments have been completed), subjects will dose a dry toothbrush with a full strip of toothpaste Subjects will brush their whole mouth thoroughly for at least 1 minute under. Subjects will be permitted to rinse with 5 ml tap water (kept at room temperature) for a maximum 5 timed seconds.

Home use instructions **Twice daily (morning/ evening)**	Subjects will be instructed to dose a dry toothbrush with a full strip of toothpaste. Subjects will then brush each of the two selected sensitive test teeth first, followed by the whole mouth thoroughly for at least 1 minute. Subjects will be permitted to rinse with tap water.	Subjects will be instructed to dose a dry toothbrush with a full strip of toothpaste. Subjects will then brush the whole mouth thoroughly for at least 1 minute. Subjects will be permitted to rinse with tap water.

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

Name of Item	Purpose
Signal® Family Protection dentifrice containing CCI fluoride as sodium monofluorophosphate (SMFP), (UK marketed product)	Acclimatisation product - to standardize oral hygiene practice prior to treatment phase. Subjects will dose the dry toothbrush provided with a full strip of toothpaste and brush teeth for one timed minute twice daily (morning and evening).
Aquafresh Clean Control (Everyday Clean) toothbrushes (UK marketed product)	Toothpaste application by tooth brushing
Countdown timers	To ensure accurate brushing/direct application duration
Graduated dosing cups	For rinsing with water after brushing
Product usage instructions	To ensure correct product use
Subject Diaries	To document product usage.

® Signal is a registered trademark of Unilever plc.

5.2. Dose Schedule

During the acclimatisation period, subjects will apply a full brush head of the study toothpaste and brush for one timed minute twice daily (morning and evening) in their usual manner.

At Visit 2 (Post-treatment) subjects will perform a supervised direct application (Test teeth only) as described in Section 5.1.

Subjects will brush with the study product twice on the day of Baseline (first brushing will be supervised at site). Subjects will return to the study site on day 3 (Visit 3) after six brushings.

5.3. Dose Modification

No dose modification is permitted in this study.

5.4. Product Compliance

A compliance check will be carried out at baseline to confirm that the acclimatisation product has been used according to study instructions throughout the acclimatisation period. If in the opinion of the investigator there are significant deviations in the subjects compliance during the acclimatisation period, this will be captured in the eCRF.

Diaries will be completed throughout the treatment period of the study to facilitate compliance during the study.

5.5. Precautions

No special precautions are necessary provided the study is carried out in accordance with this protocol.

5.6. Overdose

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

Overdose is not likely to occur in this study. Limited quantities of the product will be supplied, and closely monitored by the site for each subject.

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

5.7. Rescue Therapy

No rescue therapy is required in this study.

5.8. Product Assignment

Subjects will be assigned to study product in accordance with the randomisation schedule generated by the Biostatistics Department, GSKCH, prior to the start of the study, using validated internal software.

5.8.1 Randomisation

A unique screening number will identify each subject screened for study participation. Screening numbers will be assigned in ascending numerical order as each subject signs their consent form. Subjects who meet all inclusion and exclusion criteria will be randomized according to the randomisation schedule. Randomisation numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible.

Subjects will be stratified according to their maximum baseline Schiff of the two selected teeth (2 / 3). Randomisation numbers within each stratum will be assigned in ascending numerical order according to appearance at the study site on the day subjects are randomised. The stratification factor will give rise to two strata.

- **Stratum 1:** Subjects with maximum baseline Schiff sensitivity score of 2 for the two selected test teeth
- **Stratum 2:** Subjects with the maximum baseline Schiff sensitivity score of 3 for the two selected test teeth.

The study site will receive two versions of the randomisation 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 randomisation numbers only and will not include any coded description, just a letter A or B.

The ‘Emergency Use Only’ randomisation schedule will only be removed from the sealed envelope in an emergency situation (see Section 5.8.3). This schedule will

have a randomisation number followed by the letter A or B. The schedule will have a footnote with a key for A or B identifying the two treatments regimen arms. However, to maintain the blinding of the study as far as possible, all treatment allocations for all randomisation numbers on this randomisation schedule will be masked with scratch-off panels. Only the panels required for the unblinding the particular subject should be removed.

5.8.2 Blinding

The study statistician and other employees 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. In addition, subjects should be treated in a separate area. The dispensing staff will not be involved in any clinical assessments during the study.

As the instructions for the two products are slightly different the subjects will be given usage instructions on a separate sheet to the diary. Only the dispensing staff should have sight of the dosing instructions.

5.8.3 Code Breaks

The blind must only be broken in an emergency where it is essential to know which product a subject received in order to give the appropriate medical care. Wherever possible the Investigator (or designee) must contact the Sponsor prior to breaking the blind. The investigator must document the reason for breaking the code and sign and date the appropriate document.

The study blind must be returned to GSKCH at the end of the study.

5.9. Packaging and Labelling

The acclimatisation product (Signal Family Protection Toothpaste) will be sourced from the UK market and supplied in its commercial tube (no overwrapping) with a study label affixed. Each subject will receive a sufficient number of tubes to cover usage during the acclimatisation phase.

The study toothpaste tubes [Test dentifrice (Experimental dentifrice containing CCI [redacted] stannous fluoride, CCI [redacted] and Control Dentifrice (Colgate cavity Protection, fluoride toothpaste, US marketed product)] will be overwrapped in white vinyl to obscure any branding on the commercial tube pack. Each tube will have

study label affixed. Each subject will receive a sufficient number of tubes to cover usage during the treatment phase.

The contents of the label will be in accordance with all applicable regulatory requirements and will be the responsibility of the Clinical Supplies Department, GSKCH.

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.

5.9.1. Accountability of Product

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

The investigator or designee will maintain a full record of study product accountability. A Product Dispensing Log must be kept current and will contain the following information:

- The identification of the subject to whom the study product was dispensed.
- The date(s) and quantity of the study product dispensed to the subject.
- The date(s) and quantity of the study product returned by the subject (if applicable).

The inventory must be available for inspection by the study monitor during the study. At the end of the study, study product supplies 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 the GSKCH Clinical Supplies Department or designated vendor.

5.9.2. Storage of Product

Study product supplies must be stored in compliance with the label requirements in a secure place with limited or controlled access.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Schedule of Events section.

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

6.1. Visit 1 - Screening Visit

6.1.1. Informed Consent

The investigator, or designee, must obtain written (signed and dated by the subject) informed consent from each subject prior to their participation 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 GSKCH. 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 or should be provided with a copy of the signed and dated amended consent form. The date of consent will be recorded on the CRF.

6.1.2. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, age, gender, and race.

6.1.3. Medical History and Concomitant Medication

Medical history will be assessed as related to the inclusion/exclusion criteria by the Investigator or medically qualified designee. Details of any relevant medical or surgical history (within the last year), including allergies or drug sensitivity, will be

recorded on the CRF. Any concomitant therapy taken in the 30 days prior to the Screening Visit and throughout the study will also be recorded.

6.1.4. 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 toothpastes will be recorded as an AE.

An OST examination will be conducted at every study visit prior to any clinical assessments. While it is preferable to use the same OST examiner throughout the study, to facilitate subject flow, OST examinations may be carried out by different examiners.

6.1.5. Oral Hard Tissue (OHT) Visual Examination

A suitable qualified individual will perform an examination of the oral hard tissue to confirm that the subject has a minimum of 20 natural teeth and to evaluate dentition exclusions. The examination will be performed by direct observation.

6.1.6. Eligible Tooth Assessment

Eligible tooth assessment will include an oral hard tissue examination (visual assessment only to evaluate dentition exclusions - see Exclusion Criteria 8 and 9); erosion, abrasion and/or gingival recession; gingival index; tooth mobility and qualifying evaporative air assessment. Assessments will be carried out by the Investigator or medically qualified designee against the inclusion/exclusion criteria and recorded in the CRF.

6.1.6.1. Erosion, Abrasion and Recession (EAR) assessment

The presence of cervical erosion, abrasion and/or gingival recession [Addy, 2000] will be determined on the facial surfaces of individual teeth. Teeth exhibiting EAR will be assessed to ensure they do not meet any of the general dentition exclusion criteria and the specific dentition exclusion criteria for test teeth (see Exclusion Criteria 8 and 9).

6.1.6.2. Modified Gingival Index (MGI) Assessment

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

6.1.6.3. Tooth Mobility Assessment

The clinical mobility assessment will only be performed on teeth exhibiting facial cervical erosion, abrasion and/or recession and that have a MGI = 0. Clinical mobility will be classified in the following way (based on a modification to the Miller Index) [Laster, 1975] and the degree of mobility will be recorded. A clinical mobility of ≤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.

6.1.6.4. Qualifying Evaporative air Sensitivity

The screening dentist will assess sensitivity by a simple air blast on the facial surface of all teeth that meet the EAR, MGI and mobility criteria. This assessment is made by directing a one second application of air from a standard dental syringe perpendicular to the tooth surface approximately 1- 2 mm coronal to the free gingival margin and

from a distance of approximately 1cm. Following the air blast, the dentist will ask the subject if they experienced sensitivity. In order to qualify, the subject should confirm they experienced sensitivity and a simple "yes/no" response will be recorded.

6.1.7. Acclimatisation Product Supervised Brushing

Subjects will apply a strip of dentifrice to cover the head of the toothbrush provided and brush teeth for one timed minute.

6.2. Visit 2 – Baseline (Pre-treatment)

6.2.1. Oral Soft Tissue (OST) Examination

Complete as described in Section 6.1.5.

6.2.2. Tactile Assessment (Yeaple probe)

Tactile assessments will be performed by a single trained examiner.

Testing shall begin at 10 g and increase by 10 g 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 10 g and continue until a force is found which elicits two consecutive "yes" responses. If no sensitivity is found below the session maximum, the tooth is disqualified from further testing. The gram setting, which elicits the two consecutive "yes" responses, will be recorded as the threshold.

At this visit (pre-treatment) 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 tactile testing.

The recording/calibration assistant or 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).

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.

6.2.2.1 Subject Response

The probe tip should be placed perpendicular to the buccal surface and moved in a slow motion while 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.

The evaporative air stimulus should follow the tactile assessment, with a minimum of five minutes in between each assessment type to allow recovery time.

6.2.2.2 Calibration of the Yeaple Probe

A digital video disc (DVD) demonstration of this procedure will be provided.

Either of the two procedures described below are preferred; however other comparable procedures may be acceptable.

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.

1. 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.

2. The yeaple probe is fixed to a clamp attached to a ring stand so that the top is perpendicular to the pan of an ohaus dial-o-gram® balance or equivalent. The probe tip is positioned to just touch the pan when the balance is set at zero grams. The probe dial is set to the microamp setting and the gram setting is increased on the balance until the probe trips. The gram setting is recorded and the yeaple probe reset to the next microamp value.

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.

6.2.3. 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 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), that qualified for the tactile assessment using the Schiff Sensitivity Scale. Two test teeth will be selected according to specific eligibility criteria in an individual subject.

6.2.3.1. 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. Those teeth which meet the tactile threshold inclusion criterion (tactile threshold ≤ 20g) will be assessed. 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

Those teeth which meet the required tactile threshold (Yeaple ≤ 20g) should then be assessed by evaporative air stimulus. When two teeth that meet the study criteria are identified, no further testing is necessary.

6.2.4. Selection of Two Test Teeth

Two test teeth will be selected by the examiner that meets the inclusion criteria.

6.2.5. Study treatment direct application

Subjects will apply (under supervision, the supervising person should be someone other than the examiner undertaking the assessments) a pea-sized dose to each of the two qualifying teeth using their washed, clean finger by direct application and gently rubbing into the tooth's cervical margin for the allocated time.
No rinsing will be permitted.

See Section 5.1 for dosing instructions.

6.3. Visit 2 (Post-treatment)

6.3.1. Oral Soft Tissue (OST) Examination

Complete as described in Section 6.1.5.

6.3.2. Tactile Assessment (Yeaple probe)

Tactile assessment will be conducted as described in Section 6.2.2 of the two selected test teeth only. At Visit 2 (post-treatment), the upper force setting will be 80g. If no sensitivity is found, the threshold will be recorded as >80g.

6.3.3. Evaporative Air Sensitivity Assessment

The evaporative air assessment should follow the tactile assessment with a minimum of 5 mins between the last tactile assessment and the first evaporative air assessment to allow the teeth recovery time.

6.3.3.1. Schiff Sensitivity Scale

The examiner will record the subjects' response to each of the two selected test teeth immediately following administration of the evaporative air stimulus as described in Section 6.2.3.

6.3.3.2. Supervised brushing

At Visit 2, before leaving the site (after all the clinical assessments have been completed), all subjects will brush their whole mouth for at least one minute under supervision with the assigned treatment according to instructions in section 5.1 for test dentifrice or control dentifrice. Subjects will be permitted to rinse with 5ml tap water (kept at room temperature) for a maximum 5 timed seconds.

6.4. Visit 3 (Day 3)

6.4.1. Oral Soft Tissue (OST) Examination

Complete as described in section 6.1.5.

6.4.2. Tactile Assessment (Yeaple Probe)

Tactile assessment will be conducted as described in section 6.2.2 of the two selected test teeth only. At visit 3, the upper force setting will be 80g. If no sensitivity is found, the threshold will be recorded as >80g.

6.4.3. Evaporative Air Sensitivity Assessment

The evaporative air assessment should follow the tactile assessment with a minimum of 5 mins between the last tactile assessment and the first evaporative air assessment to allow the teeth recovery time.

6.4.3.1. Schiff Sensitivity Scale

The examiner will record the subjects' response to each of the two selected test teeth immediately following administration of the evaporative air stimulus as described in section 6.2.3.

6.4.4. Study Conclusion

Subjects will be evaluated to determine if they completed all study procedures or if they were discontinued from the study early. If the subject discontinued at any point during the study, the primary reason for withdrawal should be recorded on the study conclusion page of the crf by selecting one of the options below.

- Subject did not meet study criteria
- Adverse event
- Lost to follow up
- Protocol violation
- Withdrawal of consent
- Other

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of an investigational or washout product, whether or not considered related to the investigational or washout 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 an investigational or washout product.

Events meeting AE definition include:
• Any abnormal laboratory test results (if applicable) or other safety assessments, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition(s) detected or diagnosed after study product administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder/ condition 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): the condition that leads to the procedure is an AE. • 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.

7.1.2. Serious Adverse Events

Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:
A. Results in death
B. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
C. Requires hospitalization or prolongation of existing hospitalization NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency

ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

D. Results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

E. Is a congenital anomaly/birth defect

F. Other Situations

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are 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 or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:

- The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.
- The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF.
- 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 of 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).

- AEs will be collected from the start of the investigational product and until 5 days following last administration of the study product.
- SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

The investigator or designee will make an assessment of intensity 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. - 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.

Note: An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality:

- The investigator is obligated to assess the relationship between study product and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or

Product Information, for marketed products, in the determination of his/her assessment.

- For each AE/SAE the investigator **must** document in the medical notes (source document) or CRF that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- 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, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

- AEs will be recorded in the AE section of the CRF.
- Medical conditions recorded by the subject on a diary card or similar document that meet the definition of an AE must also be recorded in the AE section of the CRF, if not previously well-characterized by the investigator in 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. The investigator or designee must ask the subject the following question during each visit including any follow-up visits: ***"Have you felt unwell, experienced any symptoms or taken any medication (since your last visit) (today) (since your last dose) (since the last session)?"***
- The medically qualified investigator should review adverse events in a timely manner; this review should be documented in writing in the source document or in the CRF.
- After the study is completed at a given site, and the site has received their study data on Compact Discs (CDs), the electronic data collection tool will be removed from the internet to prevent the entry of new data or changes to existing data.

SAE Reporting to GSKCH:

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 (see section 8.3)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and GSKCH 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, and SAE fax cover sheet must be faxed or e-mailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax Serious Adverse Events to:
UK: PPD

The GSKCH Study Manager will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Phamacovigilance, the Medical Director responsible for the study and other GSKCH personnel as appropriate via email.

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

7.5. Follow-up of Adverse Events and Serious Adverse Events

Follow-up of AEs and SAEs:

- 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.
- 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 GSKCH.

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

Regulatory and ethics reporting requirements for SAEs:

- The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH 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 GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.
- GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC and investigators.
- Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.
- An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the Investigator Brochure (or safety statement) and will notify the IEC , if appropriate according to local requirements.

7.6. Definition of and Procedure for Reporting Medical Device Incidents

Medical devices are being provided by GSKCH for use in this study; the medical device in this study is the study toothpaste (Test Dentifrice). GSKCH medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator on the CRF throughout the study.

7.6.1. Definition of an Incident

Definition of an Incident:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have lead to the death of a patient or user or of other persons or to a serious deterioration in their state of health.

7.6.2. Reporting of Incidents and Malfunctions

Incident Reporting to GSKCH:

- **All incidents must be reported to GSKCH within 24 hours (or sooner if possible) of the investigator or designee becoming aware of the situation.**
- Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE or an SAE, the appropriate AE CRF page or SAE form will be completed and reported as per the AE and SAE reporting sections.
- The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSKCH. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
- The completed Incident Report Form should be faxed or emailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE pages should be sent together with this report form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will remain with the subject's records.
- The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax the Incident Report Forms to:
UK: PPD

- The GSKCH Study Manager will be responsible for forwarding the Incident Report Form to the Case Management Group, Global Clinical Safety and Pharmacovigilance, the Medical Director responsible for the study and other GSKCH personnel as appropriate.

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

Reporting of Malfunctions to GSKCH:

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

- Notify GSKCH immediately.
- Schedule the subject to return to the site promptly to return the failed device.
- Record any incidents on the CRF and Incident Report Form following instructions given in the section above.
- Return the failed device to the sponsor as soon as possible, including

documentation of the details of the failure.

7.6.3. Follow-up of Incidents

Follow-up of Incidents:

During the study:

- All incidents will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

After the study:

- Investigators are not obligated to actively seek reports of incidents in former subjects. However, if the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a GSKCH medical device provided for the study, the investigator will promptly notify GSKCH.

Regulatory and Ethics Reporting Requirements for Incidents:

- The investigator will promptly report all incidents occurring with any GSKCH medical device provided for use in the study within 24 hours. GSKCH has a legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies. Prompt notification of incidents by the investigator to GSKCH is essential in order to meet legal obligations and ethical responsibility towards the safety of subjects.
- The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IEC.

7.7. Collection of Pregnancy Information

7.7.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:

- Pregnancy information will be collected on all pregnancies reported following administration of any investigational product (or washout product). Information on pregnancy identified during the screening phase and prior to investigational product (or washout product) administration does not need to be collected.

7.7.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:
• 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 submit it to GSKCH within 2 weeks of learning of the subject becoming pregnant. 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 to GSKCH. 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, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE. • A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject completed the study and considered by the investigator as possibly related to the investigational product, must be promptly forwarded to GSK. • While the investigator is not obliged to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting. • If the subject becomes pregnant during the study they will be withdrawn from the study and this should be recorded in the appropriate section of the CRF.

8. DATA MANAGEMENT

For this study subject data will be entered into an electronic case report form, using a GSKCH validated data system.

8.1. Source Documents/ Data

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in the Source Document Designation Form. In some cases the CRF can be used as a source document.

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

8.2. Electronic 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 GSKCH 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 birth date) is to be recorded in the CRF or as part of the query text.

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

Subject data will be entered into GSKCH defined CRFs and transmitted electronically to GSKCH in a validated (21 CFR Part 11 compliant) web-based electronic data capture system (InForm™).

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.

The CRFs (including queries, query responses and audit trails) will be retained by GSKCH. Site data archived compact discs (CD(s)) prepared by a third party will be sent to the investigator to maintain as the investigator copy following the decommissioning of the study.

8.3. 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.

8.3.1. Data 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) are reported 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. Monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction

8.4. Processing Patient Reported Outcomes

Patient reported outcome (PRO) data are collected directly from the subject PRO measures e.g. diary cards, questionnaires etc, and entered into the sponsor's clinical data management system (DMS) by the study site representative. In instances where the PRO data is entered into the DMS by GSKCH, the PROs will be anonymised, and forwarded to GSKCH for entry, as agreed and documented ahead of the study starting. PROs that are source will be retained by the investigator and certified copies will be sent to GSKCH.

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 GSKCH.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Sample Size Determination

Change from baseline in Schiff Sensitive Score will be used to evaluate treatment effects with regard to the primary objective. A sufficient number of subjects will be screened in order to ensure that 92 evaluable subjects per group complete the study.

With 92 evaluable subjects per group, it will be possible to detect a mean difference of 0.25 (SD=0.5198) in change from baseline in Schiff sensitive score after 3 days use

between treatments with 90% power. The estimate of SD was obtained from a review of GSKCH studies [GSKCH Study 205710; GSKCH Study205697, GSKCH Study 205084]. The sample size is based on carrying out two-tailed two sample t-test at a 5% significance level and assumes that the group variances are equal.

Therefore, allowing for dropouts approximately 190 subjects will be randomised to ensure approximately 184 subjects (approximately 92 per arm) complete the study.

9.2. General Considerations

9.2.1. Definition of Analysis Populations

All assessments of safety will be based on the safety population, defined as all subjects who are randomised and receive at least one dose of study treatment during the study. Safety population summaries will be presented by treatment received.

The primary population for efficacy assessment will be the intent-to-treat (ITT) population, defined as all subjects who are randomized, receive the study treatment at least once and provide at least one post-baseline (post treatment) assessment of efficacy. All ITT population summaries and analyses will be presented by treatment randomized.

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

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

Efficacy analysis on the PP population will be performed on the clinical sensitivity measures (tactile threshold and Schiff sensitivity score) only if there is more than 10% difference in the number of subjects between PP and ITT populations. A decision on whether a PP analysis will be performed will be made prior to study unblinding.

9.2.2. 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 captured in CRF.
- Any other reason identified likely to affect efficacy

Protocol violations which warrant exclusion from efficacy analysis will be identified between the statistician and medical director or designee ahead of database lock and breaking the study blind.

9.2.3. Criteria for Evaluation

DH measures captured in the study will be used for efficacy evaluations of the study treatments. OST abnormalities, incidents and AEs reported in the study will be used for safety evaluations of the study treatments.

9.2.4. Criteria for Assessing Efficacy

The success criterion for this study is to observe a statistically significant greater reduction in evaporative air sensitivity (Schiff Sensitivity Scale) for subjects using the experimental CCI stannous fluoride dentifrice, compared to use of a dentifrice containing CCI sodium monofluorophosphate, after 3 days use.

9.2.5. Criteria for Assessing Tolerability

The assessment for safety will be based on OST abnormalities, incidents and AEs reported following dosing with study treatment.

9.2.6. 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.

9.2.7. Other Issues

An interim analysis is not planned for this study.

9.3. 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 / analysis (as appropriate).

All statistical analyses will be conducted under the null hypothesis (H_0) of no difference between treatments versus the alternate hypothesis (H_1) of a difference between treatments. All tests will be two sided with a significance level of 5%.

9.3.1. Demographic and Baseline Characteristics

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

9.3.2. Primary Analysis

9.3.2.1 Schiff Sensitivity Score following three days of treatment

The change from baseline in Schiff sensitivity score after 3 days use will be the primary efficacy variable. This will be calculated as the subject level mean change (on two teeth) from Baseline (pre-treatment) of the two selected test teeth..

The change from baseline in Schiff sensitivity score will be analysed using analysis of covariance (ANCOVA) with treatment included as a factor and baseline Schiff sensitivity score included as a covariate. Note that since the Baseline Schiff sensitivity score was included as a covariate, the Baseline Schiff stratification value was not included in the model. The adjusted mean for each treatment, and difference between treatments together with their 95% confidence interval and p-value for the between treatments comparison, will be provided. In addition, to assess efficacy within treatments, the adjusted mean change from baseline (with 2-sided 95% CIs) and p-values from the above model will be presented.

The assumption of normality and homogeneity of variance in ANCOVA model will be investigated. Violation of these assumptions may be overcome using suitable transformation or performing a non-parametric test (e.g., the Wilcoxon Rank Sum test).

9.3.3. Secondary Analyses

9.3.3.1 Schiff Sensitivity Score following a single use

The secondary analysis for the change from baseline in Schiff Sensitivity Score will be conducted after a single use using the same model as the primary analysis, with similar statistics reported.

9.3.3.2 Tactile sensitivity followinga single use and 3 days treatment

The secondary efficacy variable, tactile threshold will be calculated as the subject level mean change (on two test teeth) from Baseline (pre-treatment) after a single use and after 3 days use. This will be analysed using analysis of covariance (ANCOVA) with treatment and Schiff sensitivity strata included as a factors and baseline tactile score included as a covariate. The adjusted mean for each treatment, and difference between treatments together with their 95% confidence interval and p-value for the between treatments comparison, will be provided. In addition, to assess efficacy within treatments, the adjusted mean change from baseline (with 2-sided 95% CIs) and p-values from the above model will be presented.

For all secondary analyses, the assumption of normality and homogeneity of variance in ANCOVA model will be investigated. Violation of these assumptions may be overcome using suitable transformation or performing a non-parametric test (e.g., the Wilcoxon Rank Sum test).

9.3.4. Safety Analyses

For the assessment of safety/tolerability, incidents and AEs will be listed. AEs will be summarised by treatment group. AEs will be regarded as treatment emergent if they occur on or after the first treatment application at the baseline visit.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IEC for the trial protocol (including amendments), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), investigator brochure/ safety statement (including any updates) and any other written information to be provided to subjects. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also when subsequent amendments to the protocol are made.
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IEC.
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

10.3. Quality Control (Study Monitoring)

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 GSKCH. 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.

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

10.5. Conditions for Terminating the Study

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

Both GSKCH and the Investigator reserve the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies (if applicable), this can occur at one or more or at all sites.

If the trial is prematurely terminated or suspended for any reason, the investigator site should promptly inform the trial subjects and should assure appropriate therapy/ follow-up for the subjects. Where required by the applicable regulatory requirements, GSKCH should inform the regulatory authority(ies).
In addition:

- If the investigator terminates or suspends a trial without prior agreement of GSKCH, the investigator site should promptly inform the sponsor and the IEC, and should provide the sponsor and the IEC a detailed written explanation of the termination or suspension.

- If the GSKCH terminates or suspends a trial, 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 GSKCH and provide GSKCH with a detailed written explanation of the termination or suspension.

10.6. 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 GSKCH, 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 GSKCH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements (GSKCH recommends that documents be kept for 10 years). The investigator is also required to keep subject identification codes on file for at least 15 years after completion or discontinuation of the study. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSKCH 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.

10.7. Provision of Study Results to Investigators, posting of Information on Publicly Available Clinical Trials Registers and Publication

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.

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12. APPENDICES

12.1. Appendix 1 - Abbreviations and Trademarks

Abbreviations

ANCOVA	Analysis of Covariance
AE	Adverse Event
CD	Compact Disc
CRF	Case Report Form
DH	Dentinal Hypersensitivity
DMS	Data Management System
EAR	Erosion, Abrasion or facial/gingival Recession
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GSKCH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Modified Gingival Index
OHT	Oral Hard Tissue Examination
OST	Oral Soft Tissue Examination
PII	Personally Identifiable Information
PP	Per Protocol
SAE	Serious Adverse Event
PRO	Patient Reported Outcome

SIGNATURE PAGE

207212 Clinical Protocol

Date	Signed By
26-Aug-2016 06:03:15	PPD
Justification	Clinical Operations Approval

Date	Signed By
26-Aug-2016 11:05:18	PPD
Justification	Biostatistics Approval

Date	Signed By
28-Aug-2016 15:37:22	PPD
Justification	Approved

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	