GSK Consumer Healthcare
Clinical Protocol
Protocol Number: 216954

CLINICAL PROTOCOL

An 8 Week, Randomised, Examiner-blind, Controlled Clinical Study to Evaluate the Efficacy of a Stannous Fluoride Dentifrice in the Relief of Dentinal Hypersensitivity in a Chinese Population

Protocol Number:	216954
Compound/Product Name:	Stannous fluoride (SnF_2)
United States (US) Investigational New Drug (IND) Number:	Not applicable
European Clinical Trials Database (EudraCT) Number:	Not applicable
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Phase:	Not applicable

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** PPD
Sponsor Contact Details	**GlaxoSmithKline Consumer Healthcare (China) Co, Ltd** PPD

Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable
Amended protocol	2.0	The following administrative changes have been made: 1) clarifications in the administrative change letter dated 24 February 2021 have been added 2) clarification in "Section 12.3.1 Primary Analysis(es)" for the calculation of the % difference between treatment was added

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

Principal Investigator Protocol Agreement Page

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

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

Short Title:

A Randomised Controlled Clinical Study to Evaluate the Efficacy of a Dentifrice in the Relief of Dentinal Hypersensitivity in a Chinese Population.

Background and Rationale:

The Chinese Ministry of Health (MoH) guidelines (Ministry of Health China, 2010) stipulate that two clinical studies are required to support the efficacy of a functional toothpaste, with at least one of these studies (for each claimed benefit) to be conducted on a local Chinese population.

To support long-term dentinal hypersensitivity (DH) relief claims of 0.454% stannous fluoride (SnF_2) containing toothpastes in China, a clinical study is required to be conducted in a local Chinese population.

Objectives and Endpoints:

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

against a negative control dentifrice, when used twice daily for 4 weeks.	
To compare the clinical efficacy of a positive control dentifrice for the relief of DH, as elicited by an evaporative air stimulus (with Schiff sensitivity score) and a tactile stimulus (yeaple probe), against a negative control dentifrice, when used twice daily for 8 weeks.	Change from Baseline in Schiff sensitivity score and tactile threshold at 4 and 8 weeks.
Safety	
To evaluate the safety and oral tolerability of the test dentifrices when used twice daily for 8 weeks.	Adverse Events
Exploratory	
To characterise Oral Health Related Quality of Life (OHRQoL) as measured by the short-form of the Dentine Hypersensitivity Experience Questionnaire (DHEQ-15) after 8 weeks treatment with a 0.454% w/w SnF_2 dentifrice compared to a negative control dentifrice.	At 8 weeks, change from Baseline in: • responses to Questions 7-9, DHEQ Section 1 • Total Score, Questions 1-15, DHEQ Section 2 • Restrictions, Adaptation, Social Impact, Emotional Impact & Identity Domains
To characterise OHRQoL as measured by the short-form of the DHEQ-15 after 8 weeks treatment with a positive control dentifrice compared to a negative control dentifrice.	At 8 weeks, change from Baseline in: • responses to Questions 7-9, DHEQ Section 1 • Total Score, Questions 1-15, DHEQ Section 2 • Restrictions, Adaptation, Social Impact, Emotional Impact & Identity Domains

Study Design:

This will be a single centre, randomised, controlled, examiner-blind, 3 treatment arm, parallel group design study, stratified by maximum baseline Schiff sensitivity score (of the 2 selected 'test teeth'), with a treatment period of 8 weeks, to investigate the clinical efficacy of a SnF_2

dentifrice in the reduction of DH in a Chinese population. The SnF_2 test dentifrice will be compared to commercialised negative and positive control dentifrices.

Study Products:

Investigational Product	Test Product	Reference Product (Negative Control)	Reference Product (Positive Control)
Product Name	Sensodyne Sensitivity & Gum (Chrysanthemum); Chinese commercialised dentifrice containing 0.454% SnF_2.	Crest Cavity Protection Fresh Lime (1150ppm fluoride as NaF); Chinese commercialised daily fluoride dentifrice.	Sensodyne Repair and Protect; Chinese commercialised dentifrice containing 5.0% w/w calcium sodium phosphosilicate.
Product Master Formulation Code (MFC)	Commercial Product CCI [redacted]	Commercial Product	Commercial Product CCI [redacted]
Usage Instructions	Apply a full ribbon of toothpaste on the head of the toothbrush provided. Brush teeth for 1*-timed minute, followed by brushing of the qualifying sensitive teeth. Following brushing rinse once with 10 ml of water from the rinsing cup provided.	Apply a full ribbon of toothpaste on the head of the toothbrush provided; brush teeth for 1*-timed minute. Following brushing rinse once with 10 ml of water from the rinsing cup provided.	Apply a full ribbon of toothpaste on the head of the toothbrush provided; brush teeth for 1*-timed minute. Following brushing rinse once with 10 ml of water from the rinsing cup provided.

*Following toothbrushing and/or rinsing subjects may also conduct a discretionary tongue clean using the provided toothbrush, but this is not a study requirement.

Type and Planned Number of Subjects:

A sufficient number of subjects will be screened to randomise approximately 195 subjects to ensure approximately 180 subjects (approximately 60 per treatment group) complete the study, allowing for dropouts.

Statistical Analysis Summary:

The primary efficacy variable is the change from baseline in Schiff score at 8 weeks. The primary comparison is between the test product and the negative control.

The secondary efficacy variables with corresponding comparisons are as follows:

- Change from baseline in tactile threshold at 4 and 8 weeks; “test product versus negative control” and “positive control versus negative control”.
- Change from baseline in Schiff sensitivity score at 4 weeks; “test product versus negative control” and “positive control versus negative control”.
- Change from baseline in Schiff sensitivity score 8 weeks; “positive control versus negative control”.

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

Tactile is analysed in the same way with the addition of a factor for baseline Schiff stratification.

Table 1-1 Schedule of Activities

The schedule of activities table provides an overview of the subject visits and study procedures. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, to conduct evaluations or assessments required to protect the well-being of the subject.

Procedure/ Assessment	Screening		Study Period		
	Visit 1		Baseline Visit 2 Day 1 (Up to 28 days after Visit 1)	Visit 3 Day 29±3	Visit 4 Day 57±3
Informed consent	X	ACCLIMATISATION PERIOD 14 TO 28 DAYS			
Review of Subjects Oral Care Products to Confirm They Don't Contain any Anti-sensitivity Ingredients	X				
Review of Subjects Brushing Habits	X				
Demographics, Ethnicity	X				
Medical History and Prior Medication/Treatment	X				
Concomitant Medications			X	X	X
Full OST Examination	X		X	X	X
Full OHT Examination	X				X
Eligible Teeth Assessments (Dentition Exclusions, EAR, MGI, Tooth Mobility)	X				
Qualifying Tactile Assessment (Yeaple Probe)[1]	X				
Qualifying Evaporative Air Sensitivity (Schiff Sensitivity Score)[1]	X				
Identify Test Teeth	X				
Inclusion/Exclusion Criteria	X				
Subject Eligibility	X				
Dispense Acclimatisation Dentifrice, Toothbrush, Rinsing Cups, Diary and Timer[2]	X				
Supervised Brushing with Acclimatisation Dentifrice[3]	X				
Subject Adherence and Continuance			X	X	X
Subject completion of DHEQ-15			X		X
Tactile Assessment (Yeaple Probe)[4]			X	X	X
Evaporative Air Assessment (Schiff Sensitivity Score)[5]			X	X	X
Confirm Test Teeth[6]			X		
Stratification and Randomisation			X		
Dispense Randomised Dentifrice, Toothbrush, Rinsing Cups and Diary			X		

Supervised Brushing with Allocated Dentifrice and Reminder of Product Usage Instructions[7]			X	X	
Subjects Bring Study Supplies and Diary to Site			X	X	X
Weight Check of Returned Study Dentifrice and Subject Brushing Video's, and Compliance Discussion[7]			X	X	X
Adverse Events[8]	X		X	X	X
Study Conclusion					X

Abbreviations: OST = Oral Soft Tissue; OHT = Oral Hard Tissue; EAR = Erosion, Abrasion, Recession; MGI = Modified Gingival Index; ; SnF_2 = stannous fluoride; DHEQ = Dentine Hypersensitivity Experience Questionnaire.

Footnotes:
[1] Qualifying Schiff sensitivity and tactile threshold scores will be recorded in the case report form (CRF). Evaporative air assessment to follow tactile assessment; minimum 5 minutes time lapse between the two assessment types for tooth recovery. At Screening, maximum force for tactile = 20g.
[2] Subject is instructed to bring all supplies back to next visit.
[3] Study supplies to be returned to subject (for use at home) after supervised brushing.
[4] At Baseline, maximum force = 20g, at all subsequent visits maximum force = 80g.
[5] Evaporative air assessment to follow tactile assessment; minimum 5 minutes time lapse between the two assessment types for tooth recovery.
[6] Subject's with 'test teeth' that don't respond to tactile and/or Schiff at Baseline, may be required to have all eligible teeth identified at Screening re-assessed to identify 'test teeth'. A minimum of 5 minutes time lapse will be required between assessments.
[7] Subject is instructed to bring all supplies back to subsequent visits for compliance checks. Study supplies to be returned to subject after supervised brushing. Subject is re-dispensed a new toothbrush at Visit 3.
[8] Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides consent to participate in the study by the completion of the informed consent form (ICF).

2 INTRODUCTION

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

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

Stannous fluoride (SnF_2) has been incorporated into oral hygiene products indicated for the reduction of DH since the 1960's (Schiff, 2006). SnF_2 provides relief from DH by the occlusion of the dentinal tubules through chemical precipitation of stannous oxides and hydroxides onto the surface of the dentine. Proctor and Gamble (P&G) and GlaxoSmithKline Consumer Healthcare (GSK CH) have marketed SnF_2-containing dentifrices indicated for DH relief, with published evidence demonstrating longitudinal clinical efficacy (Ni, 2010; Parkinson, 2011; Makin, 2013).

2.1 Study Rationale and Background

The Chinese Ministry of Health (MoH) guidelines (Ministry of Health China, 2010) stipulate that two clinical studies are required to support the efficacy of a functional toothpaste, with at least one of these studies (for each claimed benefit) to be conducted on a local Chinese population.

To support DH efficacy claims GSK CH holds an extensive global clinical data package for 0.454% SnF_2 dentifrices (Creeth et al, 2019; Goyal et al, 2017; Parkinson et al, 2013; Parkinson

et al, 2015; Parkinson et al, 2016;). To support long-term dentine hypersensitivity claims in China, two further DH clinical studies have been conducted.

The first DH study (GSK CH Clinical Study 205794, 2017) met the primary objective (Schiff sensitivity score, at both 4 and 8 weeks), but did not meet the secondary objective (tactile threshold). A further clinical study was conducted (Tao, 2020), which demonstrated significantly reduced dentine hypersensitivity from baseline for the SnF_2 dentifrice, however, there was no between treatment differences when compared to a negative and positive control.

To support long-term DH relief claims of 0.454% SnF_2 containing toothpastes in China, a clinical study is required to be conducted in the local Chinese population.

2.2 Benefit/Risk Assessment

Complete information for the acclimatization and study products may be found on the product labels.

2.3 Mechanism of Action/Indication

SnF_2 is a dentine tubule occluding agent that is being investigated in subjects with DH. Such agents have been shown to function by precipitating insoluble materials onto the dentine surface and/or within the dentinal tubules to reduce dentinal fluid transport (Parkinson 2011; Parkinson 2013).

3 STUDY OBJECTIVES AND ENDPOINTS

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

To compare the clinical efficacy of a 0.454% w/w SnF_2 dentifrice for the relief of DH, as elicited by an evaporative air stimulus (with Schiff sensitivity score), against a negative control dentifrice, when used twice daily for 4 weeks.	Change from Baseline in Schiff sensitivity score at 4 weeks.
To compare the clinical efficacy of a positive control dentifrice for the relief of DH, as elicited by an evaporative air stimulus (with Schiff sensitivity score) and a tactile stimulus (yeaple probe), against a negative control dentifrice, when used twice daily for 8 weeks.	Change from Baseline in Schiff sensitivity score and tactile threshold at 4 and 8 weeks.
Safety	
To evaluate the safety and oral tolerability of the test dentifrices when used twice daily for 8 weeks.	Adverse Events
Exploratory	
To characterise Oral Health Related Quality of Life (OHRQoL) as measured by the short-form of the Dentine Hypersensitivity Experience Questionnaire (DHEQ-15) after 8 weeks treatment with a 0.454% w/w SnF_2 dentifrice compared to a negative control dentifrice.	At 8 weeks, change from Baseline in: • responses to Questions 7-9, DHEQ Section 1 • Total Score, Questions 1-15, DHEQ Section 2 • Restrictions, Adaptation, Social Impact, Emotional Impact & Identity Domains
To characterise OHRQoL as measured by the short-form of the DHEQ-15 after 8 weeks treatment with a positive control dentifrice compared to a negative control dentifrice.	At 8 weeks, change from Baseline in: • responses to Questions 7-9, DHEQ Section 1 • Total Score, Questions 1-15, DHEQ Section 2 • Restrictions, Adaptation, Social Impact, Emotional Impact & Identity Domains

This study will be considered successful if there is a statistically significant difference in the primary efficacy variable, change from baseline in Schiff sensitivity score and a between treatment difference in favour of the SnF_2 dentifrice compared to the negative control, after 8 weeks of treatment. The size of the effect is important to meet Chinese MoH guidelines, a 15% difference between the SnF_2 dentifrice and the negative control must be observed.

4 STUDY DESIGN

4.1 Overall Design

This will be a single centre, randomised, controlled, examiner-blind, 3 treatment arm, parallel group design study, stratified by maximum baseline Schiff sensitivity score (of the 2 selected 'test teeth'), with a treatment period of 8 weeks, to investigate the clinical efficacy of a SnF_2 dentifrice in the reduction of DH in a Chinese population. The SnF_2 test dentifrice will be compared to commercialised negative and positive control dentifrices.

In line with published recommendations (Holland, 1997) and the requirement of Chinese Ministry of Health guidelines (Ministry of Health (China), 2010) for the testing of functional dentifrices (desensitising), two independent stimulus-based efficacy measures will be employed (tactile and evaporative air sensitivity) to evaluate the DH efficacy of the test dentifrice. A tactile stimulus will be administered using a constant pressure probe (yeaple Probe (Polson, 1980)). An evaporative (air) stimulus will be administered using a dental air syringe. Response to this stimulus will be evaluated using the Schiff sensitivity scale (Schiff, 1994). DH assessments will be conducted at Baseline, 4 and 8 weeks.

Subjects will also be requested to complete a short-form version of the Dentine Hypersensitivity Experience Questionnaire (DHEQ-15) at the Baseline and Week 8 Visits.

A sufficient number of subjects will be screened to randomise approximately 195 subjects to ensure approximately 180 subjects (approximately 60 per treatment group) complete the study.

4.2 Scientific Rationale for Study Design

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

The proposed examiners will be dentally qualified and trained in the clinical assessments of DH, using both the air syringe (Schiff sensitivity scale) and yeaple probe (Tactile threshold). To minimise assessment variability, where feasible the same examiner will be responsible for a given clinical assessment from Screening until the end of the study. To manage logistics at the

clinical study site, additional dentally qualified examiners who may have not trained in the clinical assessments of DH will be permitted to conduct oral hard tissue (OHT)/oral soft tissue (OST) assessments and those screening procedures that do not use the air syringe (Schiff sensitivity scale) and yeaple probe (Tactile threshold).

Subjects will be asked to bring their regular oral care products to the Screening visit, and following signature of the informed consent form (ICF), their products will be checked to ensure that they do not contain any ingredients that are known to impart a DH benefit. This will provide confidence that subjects currently using any oral care products for the treatment of anti-sensitivity are not enrolled into the study. Following this product check, subjects will then be asked to demonstrate their daily oral care regimen using their own products in the manner that they normally would at home. A member of the study site staff will observe subjects, and anyone who rinses with water during the first minute of toothbrushing will be excluded from undergoing any further screening procedures. Subjects who rinse after brushing will not be excluded.

Subjects will be asked to attend the study site for the Baseline visit and then every 4 weeks for the duration of the study. At each visit subjects will be requested to conduct a supervised brushing and reminded of the product usage instructions. Subjects will also be sent daily reminders on WeChat to brush with their allocated study product as directed and adhere to study lifestyle restrictions.

To monitor subject adherence to the product usage instructions, subjects will be asked to record 2 brushing occasions per week using their smartphone video. Every 2 weeks a designated member of the clinical study team will review these videos and confirm compliance with product usage instructions in the case report form (CRF). These video's will not be considered to be source data. Subjects confirmed as non-compliant (Eg. subjects who don't correctly follow the product use instructions) will be reminded about the product usage instructions and documented as a protocol deviation. A check-list will be provided to the clinical study site so that they correctly understand what is considered to be compliant with the product usage instructions.

In line with published recommendations (Holland, 1997) and the requirement of Chinese Ministry of Health guidelines (Ministry of Health (China), 2010) for the testing of functional dentifrices (desensitising), two independent stimulus-based efficacy measures will be employed (tactile and evaporative air sensitivity) to evaluate the DH efficacy of the experimental dentifrice. A tactile stimulus will be administered using a constant pressure probe (yeaple probe (Polson, 1980)). An evaporative (air) stimulus will be administered using a dental air syringe. Response to this stimulus will be evaluated using the Schiff sensitivity scale (Schiff, 1994). In accordance with the MoH guidelines, the mean values of each index should decrease during the clinical trial, and have statistical significance compared with the control group. When one of the mean values of the indices decreases by 15% or more than 15%, then the trial group can be considered to have DH efficacy (Ministry of Health China, 2010).

A qualifying response to a tactile stimulus followed by a qualifying air blast on all teeth qualifying for tactile will be included in this study. At Screening and Baseline subjects will have a minimum of two teeth with a tactile score of ≤20g and Schiff sensitivity score of ≥2. To ensure consistent responders are entered into the study, the 2 'test teeth' must be selected from those teeth eligible for both Schiff and tactile at Screening, and confirmed at Baseline.

Orchardson & Collins tested 516 sensitive teeth and found that while around half were sensitive to both evaporative air and tactile stimuli, 33% were sensitive only to an evaporative air stimulus and 16% were sensitive only to a tactile probe (Orchardson, 1987). Given that individual teeth may react differently to different stimuli it would be pragmatic to say the same for people. Therefore, some people may respond well to evaporative air sensitivity at Screening, but perhaps not to the same degree for tactile at Baseline, hence both tactile and evaporative air stimuli have been included at the Screening visit. This will help ensure that consistent responders to both stimuli are entered into the study.

At all visits following Screening, the 2 selected 'test teeth' will be assessed using each of the clinical efficacy assessments. The selection of 2 'test teeth' to evaluate changes in DH is common practice in sensitivity studies (Docimo, 2009). The subjects will be stratified at the Baseline visit according to their maximum Schiff sensitivity score of the 2 selected 'test teeth' to enable the treatment groups to be balanced in terms of the subject's sensitivity severity.

Subjects will also be requested to complete the short-form version of the DHEQ-15 at the Baseline and Week 8 Visits. Measuring a change from Baseline in DHEQ end-points will provide a richer understanding of the impact of using a 0.454% SnF_2 dentifrice on subject perceived Oral Health Related Quality of Life (OHRQoL) parameters related to DH. The DHEQ has been previously validated in a Chinese population and demonstrated that individuals with greater severity of DH suffered from poorer OHRQoL (He, 2015; He 2015*).

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

Clinical trials evaluating clinical end points relating to pain can be prone to 'placebo effects' (Addy, 1985; West, 1997). Such effects are frequently observed in dentine hypersensitivity studies. A study conducted to evaluate the natural history of the dentine hypersensitivity condition highlighted the existence of a 'no treatment' effect characterised by an improvement in sensitivity simply as a function of clinical study participation (Leight, 2008). To help minimise the potential impact of such 'placebo' and 'no treatment' effects, an acclimatisation period of 2-4 weeks will be included in this study from Screening, ahead of the Baseline assessments and randomisation. During this period subjects will be provided with a toothbrush

and a marketed, standard fluoride dentifrice to use in place of their regular oral hygiene products. Crest Cavity Protection has been selected as it is a daily use regular fluoride dentifrice that is currently sold in China. Use of the acclimatisation dentifrice will also help provide a standardised oral hygiene regimen prior to the Baseline visit. Subjects will brush twice daily, in line with recommended oral hygiene practice, and typical Chinese consumer habit, during this period.

In line with Chinese Ministry of Health guidelines (Ministry of Health (China), 2010) for the testing of functional dentifrices (desensitising), a standard fluoride dentifrice with no specific anti-sensitivity, anti-gingivitis and anti-plaque activity will be included as the negative control. Crest Cavity Protection has been selected as it has been evaluated not to have any DH clinical efficacy (GSK CH clinical study RH02294).

A 5.0% w/w calcium sodium phosphosilicate containing positive control dentifrice (Chinese marketed Sensodyne Repair and Protect) with proven long-term DH efficacy in China (GSK CH clinical studies: RH01422 and RH01748), in clinical studies that satisfied the MoH requirements, will be included in this study as a benchmark of performance in the Chinese population.

In this study the MGI inclusion criteria has been set at ≤1 for the area adjacent to the 2 'test teeth'. In previous DH studies, MGI for the area adjacent to the 2 'test teeth' has been set at 0. This has been modified due to a request from the Investigator, as it is understood from general dental practise in China that a MGI score of 0 is atypical, and MGI ≥1 is more prevalent in a Chinese population. A score of 1 represents relatively subtle localised mild inflammation, and this would not be expected to impact on DH efficacy measures.

4.3 Justification for Dose and Regimen

The dosage regimen of twice daily (morning and evening) brushing with a full ribbon of dentifrice on the supplied toothbrush for 1-timed minute will be the same for all subjects, and has been selected based on the minimum amount of time required to achieve DH efficacy in previously conducted clinical studies containing a SnF_2 dentifrice (Parkinson, 2011; Makin, 2013). Additional focused brushing of the identified 'test teeth' has been included for the Test dentifrice to ensure that the 'test teeth' are being treated, and to standardise treatment and facilitate monitoring of compliance. These instructions for use are aligned with the current product usage instructions in the USA, as determined by the US FDA Monograph for OTC Oral Health Care Drug Products; *"Apply at least a 1-inch strip of the product onto a soft bristle toothbrush. Brush teeth thoroughly for at least 1 minute twice a day (morning and evening) or as recommended by a dentist or doctor. Make sure to brush all sensitive areas of the teeth"* (FDA, 1991). Focused brushing of the sensitive teeth is not required for the Negative control as it is not marketed as an anti-sensitivity dentifrice, and therefore the usage instructions reflect those of a standard daily fluoride dentifrice, and do not require the sensitive areas of the teeth to be brushed. The usage instructions of the positive control dentifrice containing 5% w/w

calcium sodium phosphosilicate are aligned with the usage instructions that were used in GSK CH clinical studies where long-term DH efficacy was demonstrated in China (GSK CH clinical studies: RH01422 and RH01748).

Discretionary tongue cleaning with the supplied toothbrush has also been included in this study, as this is typical oral hygiene practise in China. Subjects will be asked not to rinse with water during toothbrushing. It is understood that the dentifrice needs to be present in the oral cavity for a minimum of 1-minute to provide DH efficacy. Therefore, it can be hypothesised that if subjects rinse excessively with water during toothbrushing that the active ingredient responsible for providing DH relief may be expectorated and not adhere to the surface of the tooth and block the patent tubules. During a recent consumer study (GSK CH data on file) that observed Chinese consumers following their daily oral care regimen at home it was noted to be common practice for subjects to rinse with excessive water following toothbrushing, therefore subjects will be allowed to rinse with water following toothbrushing. In this same consumer study, the volume of water that subjects rinsed with was quite variable, therefore, to standardise subject rinsing, subjects will be provided with a rinsing cup with a 10 ml dosing line and will be allowed to rinse once with 10 ml of water following each brushing occasion.

4.4 End of Study Definition

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

The end of this study is defined as the date of the last scheduled procedure, for the last subject, shown in the Schedule of Activities

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

To meet MoH guidelines (Ministry of Health China, 2010), subjects will be located in China. Subjects will be male or female, with good general health and oral health, with a minimum of 20 natural teeth and with self-reported history of DH.

The age range over which an individual can experience DH is wide (from early teens to 70s) (Fischer et al, 1992), with peak incidence known to occur between the ages of 20-40 years (Flynn et al, 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 (Pashley, 2008; Seltzer and Bender, 1975). Given that the dental pain experienced by older members of the population is less likely to be diagnosed as DH (Rees, 2000), the age range of 18-70 selected for this study targets individuals suffering from tooth sensitivity which is most likely due to DH. This will facilitate recruitment and

minimise inconvenience to older participants who may be more likely to be excluded at Screening.

Diversity in clinical trials is increasingly important and should be representative of the population being studied. To promote clinical diversity a balanced female:male ratio (heavy bias towards female participants to date) should be considered. Whilst there is no known evidence demonstrating that gender may influence DH, a 2009 National DH Survey conducted in rural China showed that a greater proportion of those diagnosed with DH were female (35.8%), in comparison to a lower proportion that were male (23.4%) (Liang, 2017). Therefore, an approximate female:male ratio of 3:2 should be attempted to be recruited.

A sufficient number of subjects will be screened to randomise approximately 195 subjects to ensure approximately 180 subjects (approximately 60 per treatment group) complete the study, allowing for dropouts.

An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process directly or via their legally authorised representative and successfully met eligibility criteria to proceed beyond the screening visit as applicable for the protocol design.

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

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

5.2 Inclusion Criteria

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

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is male or female who, at the time of screening, is between the ages of 18 to 70 years, inclusive.
3. A subject who is willing and able to comply with scheduled visits, treatment plan, and other study procedures.
4. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, no clinically significant or relevant abnormalities in medical history or upon oral examination, or condition, that would impact the subject's safety,

wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.

5. Subject must own a smartphone with the WeChat application installed.
6. A subject who presents the following oral and dental inclusions will apply at **Screening (Visit 1)**:
    a) Self-reported history of dentinal hypersensitivity lasting more than six months but not more than 10 years.
    b) Good general oral health, with a minimum of 20 natural teeth.
    c) Minimum of 2 accessible non-adjacent teeth (incisors, canines, pre-molars), preferably in different quadrants, that meet all of the following criteria:
        i. Signs of facial/cervical gingival recession and/or signs of erosion or abrasion (EAR).
        ii. Tooth with MGI score ≤1 adjacent to the test area (exposed dentine) only (Lobene, 1986) and a clinical mobility of ≤1.
        iii. Tooth with signs of sensitivity measured by a qualifying tactile stimulus (yeaple ≤20g) and qualifying evaporative air assessment (Schiff sensitivity score ≥2).

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

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

Note: The Investigator will select 2 'test teeth' from those which meet both the tactile threshold and Schiff sensitivity score criteria, in addition to meeting all other criteria. Test teeth should not be adjacent to each other and preferably in different quadrants.

5.3 Exclusion Criteria

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

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSK CH employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.

3. A subject who has participated in another tooth desensitising treatment study within 8 weeks of the Screening visit.
4. A subject with, in the opinion of the investigator or medically qualified designee, has an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
5. A subject who is pregnant or intending to become pregnant over the duration of the study. This will be confirmed verbally at Screening.
6. A subject who is breastfeeding.
7. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
8. A subject who rinses with water during the first minute of toothbrushing at the Screening visit.
9. A subject unwilling or unable to comply with product usage instructions or Lifestyle Considerations that will be described in the protocol.
10. A subject with history of regular alcohol and/or substance abuse.
11. A subject who has received treatment with another investigational product within 30 days of the first dose of investigational product
12. A subject who has had dental prophylaxis within 4 weeks of Screening, or who requires antibiotic prophylaxis for dental procedures.
13. A subject with a tongue or lip piercing.
14. A subject with advanced periodontal disease, treatment of periodontal disease (including surgery) within 12 months of Screening, scaling or root planning within 3 months of Screening.
15. A subject who has had teeth bleaching within 8 weeks of Screening.
16. A subject who has used an over-the-counter (OTC) desensitising product (Eg. dentifrice) and/or professional desensitising treatment within 8 weeks of Screening. Subjects will be required to bring their current oral care products to the site in order to verify the absence of known anti-sensitivity ingredients.
17. A subject with exposed tooth dentine but with deep, defective or facial restorations, teeth used as abutments for fixed or removable partial dentures, teeth with full crowns or veneers, orthodontic bands or cracked enamel.
18. A subject with sensitive teeth with contributing aetiologies other than erosion, abrasion or recession of exposed dentine Eg. current or recent dental caries, or reported treatment of decay within 12 months of Screening.

19. A subject who has taken daily doses of medication/treatments or traditional herbal ingredients/treatments which, in the opinion of the investigator, could interfere with the perception of pain. Examples of such medications include analgesics, anticonvulsants, antihistamines that cause marked or moderate sedation, sedatives, tranquilisers, anti-depressants, mood-altering and anti-inflammatory drugs. Examples of herbal ingredients/treatments include clove oil, olive oil, or other treatments that are directly applied to the oral cavity for the treatment of oral health conditions.
20. A subject who is taking antibiotics and/or has taken antibiotics within 2 weeks of Screening and/or Baseline.
21. A subject who has taken daily dose of a medication which, in the opinion of the investigator, is causing xerostomia.
22. Any subject who, in the judgment of the investigator, should not participate in the study.

5.4 Randomisation Criteria and Stratification

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

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

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

5.5 Lifestyle Considerations

5.5.1 Oral Care Restrictions

Eligible subjects will be asked to stop using their regular oral care products, and will only be allowed to use the oral care products provided from Screening for the duration of the study. Use of dental floss will be for the removal of impacted food only.

Subjects will not be permitted to chew gum.

Prior to study visit days (Visits 2 to 4) subjects will be asked to refrain from all oral hygiene procedures for at least 8 hours prior to their appointment in order to standardise oral hygiene

practices. Subjects will be sent a WeChat reminder the day before their appointment reminding them of this.

5.5.2 Meals and Dietary Restrictions

A subject must not eat or drink (except water) for at least 2 hours before Visits 2 to 4. Small sips of room-temperature water will be permitted to take medications and relieve a dry mouth within 1 hour before their visit.

5.5.3 Alcohol

Subjects will be requested to refrain from excessive alcohol consumption for 24 hours before each visit. If, in the opinion of the Investigator, the subject has consumed an excessive amount of alcohol they will be withdrawn from the study.

5.5.4 Contraception

No drug is being utilised in this clinical study, the study products are commercialised toothpastes in China, and are regulated as General Goods. Therefore, pregnancy testing and contraceptive requirements are not deemed necessary for this study.

5.6 Screen Failures

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

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

5.7 Sponsor's Qualified Medical Personnel

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

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

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects will be provided with a contact card. The contact card will provide, as a

minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Rater/Clinical Assessor Qualifications

The clinical examiner(s) responsible for Schiff and tactile assessments will be dentally qualified and trained in the clinical assessments of DH, using both the air syringe (Schiff sensitivity scale) and yeaple probe (Tactile threshold). To minimise assessment variability, where possible the same examiner will be responsible for a given clinical assessment from Screening until the end of the study.

To manage logistics at the clinical study site, additional dentally qualified examiners who have not trained in the clinical assessments of DH will be permitted to conduct OHT/OST assessments and those screening procedures that do not use the air syringe (Schiff sensitivity scale) and yeaple probe (Tactile threshold).

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and GSK policy, study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Investigational/Study Product Supplies

The following investigational/study products will be supplied by the Clinical Supplies Department, GSK CH or designated vendor:

Table 6-1 Investigational Product Supplies

Investigational Product	Test Product	Reference Product (Negative Control)	Reference Product (Positive Control)
Product Name	Sensodyne Sensitivity & Gum (Chrysanthemum); Chinese commercialised toothpaste containing 0.454% SnF_2	Crest Cavity Protection Fresh Lime (1150ppm fluoride as NaF); Chinese commercialised daily fluoride dentifrice	Sensodyne Repair and Protect; Chinese commercialised dentifrice containing 5.0% w/w calcium sodium phosphosilicate

Pack Design	Carton of 4 over-wrapped tubes	Carton of 4 over-wrapped tubes	Carton of 4 over-wrapped tubes
Dispensing Details	One carton – baseline visit	One carton – baseline visit	One carton – baseline visit
Product Master Formulation Code (MFC)	Commercial Product CCI [redacted]	Commercial Product	Commercial Product CCI [redacted]
Usage Instructions	Apply a full ribbon of toothpaste on the head of the toothbrush provided. Brush teeth for 1*-timed minute, followed by brushing of the qualifying sensitive teeth. Following brushing rinse once with 10 ml of water from the rinsing cup provided.	Apply a full ribbon of toothpaste on the head of the toothbrush provided; brush teeth for 1*-timed minute. Following brushing rinse once with 10 ml of water from the rinsing cup provided.	Apply a full ribbon of toothpaste on the head of the toothbrush provided; brush teeth for 1*-timed minute. Following brushing rinse once with 10 ml of water from the rinsing cup provided.
Route of Administration	Oral topical	Oral topical	Oral topical
Return Requirements	All used/unused samples to be returned	All used/unused samples to be returned	All used/unused samples to be returned

*Following toothbrushing and/or rinsing subjects may also conduct a discretionary tongue clean using the provided toothbrush, but this is not a study requirement.

Table 6-2 Acclimatisation Product Supplies

	Acclimatisation Product
Product Name	Crest Cavity Protection Fresh Lime; Chinese commercialised daily fluoride dentifrice (1150ppm fluoride as NaF)
Pack Design	Carton of 2 over-wrapped tubes

Dispensing Details	One carton – Screening visit
Product MFC	Commercial Product
Usage Instructions	Apply a full ribbon of toothpaste on the head of the toothbrush provided; brush teeth for 1*-timed minute. Following brushing rinse once with 10 ml of water from the rinsing cup provided.
Route of Administration	Oral topical
Return Requirements	All used/unused samples to be returned

*Following toothbrushing and/or rinsing subjects may also conduct a discretionary tongue clean using the provided toothbrush, but this is not a study requirement.

Table 6-3 Sundry Items

Item	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
Lion Thin Bristle Chinese commercialised Toothbrush	GSK CH or designated vendor	Individual commercial pack – 3 per subject	1 at screening for use with acclimatisation product 1 at baseline for use with investigational product 1 at Visit 3.	Destroy at site using site disposal procedures	Return
Countdown Timer	GSK CH or designated vendor	Individual commercial pack – 1 per subject	Screening visit	Subject to keep or destroyed at site using site disposal procedures	Return

Rinsing cups	GSK CH or designated vendor	N/A	Screening visit and baseline	Subject to keep or destroyed at site using site disposal procedures	Return
Plastic bags	GSK CH or designated vendor	N/A	Screening visit and baseline	Subject to keep or destroyed at site using site disposal procedures	Return

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

6.1.1 Dosage Form and Packaging

The test product, negative and positive controls, acclimatisation product and toothbrush will be sourced from China.

All dentifrices in this study will be presented to the clinical study site in tubes that have been overwrapped in white vinyl to obscure any branding on the commercial packs with a study label affixed. The contents of the label will be in accordance with all applicable regulatory requirements and will be the responsibility of the Global Clinical Supplies Department, GSK CH. Each subject will receive a sufficient number of tubes to cover usage during the treatment phase.

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.

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

6.1.2 Preparation and Dispensing

Study products will be prepared and/or dispensed by qualified unblinded site personnel according to the dosage and administration instruction. To help mitigate against unblinding the same personnel responsible for preparing and/or dispensing will also be responsible for reviewing subject's brushing video's.

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

Study product will be dispensed by qualified unblinded site personnel. These staff members will not be involved in any safety, efficacy assessments or other aspects of the study that could be influenced by the knowledge of product a subject has been assigned to use. An additional member of site staff should ensure the dispensing procedures are completed accurately. The investigational products will be dispensed in blinded fashion to the subject.

A record of product dispensing to each subject will be maintained in the dispensing log; completion of the dispensing procedure will be recorded in the case report form (CRF).

6.2 Administration

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

Subjects will be instructed to brush with their assigned dentifrice according to the product use instructions provided to the subject. Subjects will receive a brushing instruction/diary sheet. This will outline the brushing instructions and will be used to record each brushing occasion during the treatment period. Subjects will also be asked to note any missed brushings, and to use the diary to record any changes in medications, or new medications, or to diet. To ensure that subjects understand the dose of dentifrice to be used, staff will demonstrate what is meant by a 'full ribbon' (i.e. covering the length of the toothbrush head) and provide detailed oral hygiene instruction during the supervised toothbrushing in agreement with the study schedule and product usage instructions.

6.2.1 Medication/Dosing Errors

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

- the wrong product,
- by the wrong subject,

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

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

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

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

6.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a product at an amount higher than specified in the protocol. Overdose is not likely to occur in this study.

6.3 Investigational/Study Product Storage

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study products received and any discrepancies are reported and resolved before use according to the supplied shipping documentation.

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

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

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

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

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

6.4 Investigational/Study Product Accountability

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

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

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

Subjects will return used and unused tubes of the acclimatisation dentifrice to the investigator site at their Baseline visit (Visit 2). Subjects will return used and unused tubes of their assigned study dentifrice to the investigator site at their visits to the clinical study site as per the Schedule of Activities, with all study products returned at the end of the study (for most subjects this will be Visit 4). Study product return will be documented using the investigational/study product accountability form/record.

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

6.4.1 Destruction of Investigational/Study Product Supplies

At the end of the study, the Principal Investigator (PI) or an appropriate designee, and a representative of GSK CH (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study, will be returned for destruction to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided. Detailed instructions for the return of study product/study supplies (including empty tubes) for the accountability checks and subsequent destruction will be provided by GSK CH during the study in time for study close out visit.

6.5 Blinding and Allocation/Randomisation

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

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

This study is described as examiner-blind (the subjects, investigator and clinical examiner(s) will be blinded to product received). The study statistician, other employees of the Sponsor

(including the Clinical Research Scientist (CRS)) and vendors acting on behalf of the sponsor, who may influence study outcomes will also be blinded to product allocation.

To ensure the examiner remains blinded throughout the study, staff involved in the preparation and dispensing of study products will work in a separate area. The examiner is not permitted in any area where study product is stored, dispensed, or in use. Examiners must also not have any visibility, or access to subject brushing video's. The same personnel responsible for preparing and/or dispensing will also be responsible for reviewing subject's brushing video's, and the study examiners will not be permitted in the area where these video's are viewed.

Subjects will be instructed not to remove study products from the opaque bags provided outside of the dispensing room, while at the study site. They will also be instructed not to discuss the use of their study products with any of the study examiners. Dispensing staff will not be involved in any efficacy/safety assessment procedures during the study.

6.6 Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind in case of emergency. The method will be an electronic process.

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

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

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

6.7 Compliance

Throughout the duration of the study subjects will be sent daily reminders on WeChat to brush with their allocated dentifrice as per the usage instructions, and to adhere to study lifestyle restrictions.

To monitor subject adherence to the usage instructions subjects will also be asked to record 2 brushing occasions per week using their smartphone video. At each visit to the clinical study site a designated member of the clinical study team will check these videos from the previous 2 weeks and confirm compliance with the product usage instructions. After 2 and 6 weeks of

using their allocated study product, subjects will be requested to send their brushing video's from the previous 2 weeks (2 per week) to the study site using WeChat. A member of the clinical study site staff will confirm compliance with the product usage instructions, as per protocol To assist the clinical study staff to determine which subjects are non-compliant with the brushing instructions a check-list has been provided (Appendix 15.3). Subjects confirmed as non-compliant (Eg. Subjects that have a "no" response to any of the check-list items)) will be reminded about the study product use instructions. Non-compliance will be recorded as a protocol deviation, and subjects who are repeatedly non-compliant, defined as ≥5 brushing occasions that were not conducted according to the product usage instructions may be withdrawn from the study. Missed video recordings will be considered as non-compliance and recorded as a protocol deviation.

Subjects will also be requested to bring their study products to each clinical study site visit, where a member of the clinical study team will weigh the returned dentifrice. If treatment use is deemed to be outside of the pre-defined acceptable range, subjects will be re-educated on the correct dosage amount. Where the amount of dentifrice used is outside of the pre-defined allowable range, a protocol deviation will be recorded in the CRF and subjects will be re-educated on the correct dose. In this study the pre-defined range will be calculated as the expected weight of dentifrice used for the treatment window (Section 12.3.7.1). The amount of dentifrice used during each treatment period will be recorded in a source document and later transcribed to the CRF.

At the same visit subjects will be asked to conduct a supervised and timed brushing according to the product usage instructions. Confirmation of supervised brushing per protocol will be captured in the CRF. Any deviations from the product usage instructions will be captured as a protocol deviation in the CRF, and subjects will be reminded of the correct directions for use.

A paper diary will also be supplied to promote compliance and to capture details of daily product use throughout the study period. Subjects may also record additional information such as AEs or medications used. Any additional details relevant to efficacy or safety should be reviewed by the investigator (or suitably qualified designee) with the subjects and transcribed to the CRF as appropriate.

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

6.8 Concomitant Medication/Treatment(s)

Any medications, treatments or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken during the study, from signing the informed consent, must be recorded in the CRF with indication, reason for use, unit dose, daily dose, and start and

stop dates of administration. All subjects will be questioned about medications/treatments at each site visit.

Medication/treatments taken within 30 days of signing the informed consent form will be documented as a prior medication/treatment. Medications/treatments taken after signing the informed consent form will be documented as concomitant medication/treatments.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

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

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

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

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

7.2 Lost to Follow up

If a subject fails to return to the site for a required study visit the site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented. If contact

is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all products that they had been dispensed and if appropriate request that the subject return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs).

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion, which could include an examination of the oral soft tissue and/or oral hard tissue.

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

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

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

8 STUDY PROCEDURES

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

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

8.1 Visit 1/ Screening

Subjects will be screened within 28 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study.

The following procedures and assessments will be completed, and where practically feasible they should be completed in the order listed below:

8.1.1 Informed Consent

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

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

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

The time the subject signed the ICF will be captured as this is the point at which all AEs will be captured from. The date and time of consent will be captured in the CRF.

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

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

8.1.2 Review of Subjects Oral Care Products

Subjects will be requested to bring their current oral care products from home and a member of the clinical study site staff will verify that they don't contain any ingredients known to impart an anti-sensitivity benefit, or make any anti-sensitivity treatment claims on the product packaging. This product check will be documented in the CRF.

8.1.3 Review of Subjects Brushing Habits

Subjects who have not been using an anti-sensitivity oral care product will then be asked to demonstrate their daily oral care regimen using their own products in the manner that they normally would at home. A member of the study site staff will observe subjects, and anyone who rinses with water during toothbrushing will be excluded from undergoing any further screening procedures.

8.1.4 Demographics and Ethnicity

The following demographic information will be recorded in the CRF: year of birth, gender and race. Ethnicity will also be recorded in the CRF.

8.1.5 Medical History and Prior Medication/Treatment

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

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

8.1.6 Full Oral Soft Tissue (OST) and Oral Hard Tissue (OHT) Examinations

Full OST and OHT assessments as described in Study Assessments will then be conducted by an appropriately trained clinical examiner(s) and recorded in the CRF.

8.1.7 Eligible Teeth and Qualifying Sensitivity Assessments

Eligible teeth and qualifying sensitivity assessments to be conducted:

- Eligible teeth assessments (dentition exclusions, Erosion, Abrasion, Recession (EAR), modified gingival index (MGI), tooth mobility).
- Qualifying evaporative air sensitivity.
- Qualifying tactile threshold.

Data for eligible teeth assessments, tactile stimuli (yeaple probe) and evaporative air stimuli (Schiff sensitivity score) may be recorded on a source document and later transcribed into the CRF, or directly entered into the CRF. This will be done by the designated scribe.

Eligible teeth and qualifying sensitivity assessments as described in Study Assessments will be conducted by an appropriately trained clinical examiner(s).. Assessments may be recorded on a source document and later transcribed into the CRF, or directly entered into the CRF. This will be done by the designated scribe.

8.1.7.1 Selection of Test Teeth

The 2 ‘test teeth’ with be identified in the CRF.

8.1.8 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be documented in the CRF. Pregnancy status will be confirmed verbally by the subject.

8.1.9 Subject Eligibility

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

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

- Adverse Events (AEs) will be documented from the time that informed consent is taken. Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as “How do you feel?”
- To prepare for study participation, subjects will be reminded of the requirements of the use of the Lifestyle Guidelines and Concomitant Treatment(s) sections of the protocol.

Subjects will be asked to show a member of the clinical study site staff their mobile phone to confirm that they have the WeChat application installed.

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

8.1.10 Dispense Acclimatisation Products

The acclimatisation dentifrice, toothbrush, rinsing cups, diary and timer will be dispensed to each subject.

8.1.11 Supervised Brushing with Acclimatisation Dentifrice

Subjects will be instructed to perform a supervised and timed brushing according to the product usage instructions as detailed in Table 6-2. Confirmation of supervised brushing per protocol will be captured in the CRF and an entry recorded on the subject diary card.

Subjects will be reminded to bring their study products to their next clinical study site visit

8.1.12 Adverse Events

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

8.2 Study Period

8.2.1 Visit 2 (Baseline/Day 1)

The following procedures and assessments will take place on Visit 2 (Baseline/Day1) following subject Screening at Visit 1, and where practically feasible they should be completed in the order listed below:

8.2.1.1 Concomitant Medications.

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

8.2.1.2 Full OST Examination

Full OST examination as described in Study Assessments will be conducted by the appropriately trained clinical examiner(s) and recorded in the CRF.

8.2.1.3 Subject Adherence and Continuance

Subject adherence to the Lifestyle Guidelines and Study Schedule will be documented in the CRF.

8.2.1.4 Subject Completion of DHEQ

Subjects will complete a paper copy of the short-form version of the validated DHEQ at the clinical study site. Subject responses will be later transcribed into the CRF.

8.2.1.5 Tactile Sensitivity Assessment.

The tactile sensitivity assessments as described in Study Assessments will be conducted by an appropriately trained clinical examiner. Where possible, the same clinical examiner will be responsible for all tactile assessments conducted at all assessment visits. Assessments may be recorded on a source document and later transcribed into the CRF, or directly entered into the CRF. This will be done by the designated scribe.

8.2.1.6 Evaporative Air Sensitivity Assessment (Schiff Sensitivity Score)

The evaporative air sensitivity assessments as described in Study Assessments will be conducted by an appropriately trained clinical examiner. Where possible, the same clinical examiner will be responsible for all Schiff sensitivity assessments conducted at all assessment visits. Assessments may be recorded on a source document and later transcribed into the CRF, or directly entered into the CRF. This will be done by the designated scribe.

8.2.1.7 Confirm Test Teeth

If any of the 'test teeth' identified at Screening do not respond to either tactile and/or Schiff, all eligible teeth that qualified at Screening may be re-assessed for tactile and Schiff, and the new 2 'test teeth' will be identified in the CRF. Subjects will be informed of the sensitive teeth that have been identified

8.2.1.8 Stratification and Randomisation

Subjects will be stratified to one of two strata as described in Section 5.4.

Subject stratum will be entered directly into the CRF. Each subject will be assigned a randomisation number from their designated stratum in ascending numerical order, and as each subject is determined to be fully eligible.

8.2.1.9 Dispense Randomised Dentifrice and Study Products

Each subject will be assigned their randomised dentifrice, study toothbrush, diary card and rinsing cups. The randomised dentifrice code will be entered directly into the CRF.

8.2.1.10 Supervised Brushing with Study Dentifrice

Subjects will be asked to conduct a supervised and timed brushing according to the study product usage instructions, as detailed in Table 6-1. Confirmation of supervised brushing per protocol will be captured in the CRF and an entry recorded on the subject diary card. Any

deviations from the product usage instructions will be captured as a protocol deviation, and subjects will be reminded of the correct directions for use.

Subjects will be reminded to bring their study products to their next clinical study site visit.

8.2.1.11 Compliance Check on Returned Dentifrice and Brushing

A member of the clinical study site staff will weigh the returned dentifrice, and if treatment use is deemed to be outside of the expected range, as detailed under Compliance, subjects will be re-educated on the correct dosage amount.

Subjects will then show their brushing video's from the acclimatisation period (2 per week) to a member of the clinical study site staff and confirmation of compliance with the product usage instructions, as per protocol, will be captured in the CRF. Any deviations from the product usage instructions or missed video brushings will be captured as a protocol deviation and subjects will be re-educated on the correct directions for use. To assist the clinical study staff to determine which subjects are non-compliant with the product usage instructions a check-list has been provided (Appendix 15.3).

8.2.1.12 Adverse Events

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

At the end of the visit subjects should be reminded to note any untoward medical occurrence, use of any new medications or new treatments in their diary or report to study site between visits, and to inform the site at their next visit as required

8.2.2 Visit 3 (Day 29±3) and Visit 4 (Day 57±3)

The following procedures and assessments will take place on Visit 3 (Day 29±3) and Visit 4 (Day 57±3), and where practically feasible they should be completed in the order listed below:

8.2.2.1 Concomitant Medications.

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

8.2.2.2 Full OST Examination

Full OST examination as described in Study Assessments will then be conducted by the appropriately trained clinical examiner(s) and recorded in the CRF.

8.2.2.3 Full OHT Examination

Full OHT examination as described in Study Assessments will then be conducted by the appropriately trained clinical examiner(s) and recorded in the CRF. **Note: this is only applicable at Visit 4, and should not be completed at Visit 3.**

8.2.2.4 Subject Adherence and Continuance

Subject adherence to the Lifestyle Guidelines and Study Schedule will be documented in the CRF.

8.2.2.5 Subject Completion of DHEQ

Subjects will complete a paper copy of the short-form version of the validated DHEQ at the clinical study site at Visit 4. Subject responses will be later transcribed into the CRF.

Note: this is only applicable at Visit 4, and should not be completed at Visit 3.

8.2.2.6 Tactile Sensitivity Assessment.

The tactile sensitivity assessments as described in Study Assessments will be conducted by the appropriately trained clinical examiner. Where, possible the same clinical examiner will be responsible for all tactile assessments conducted at all assessment visits. Assessments may be recorded on a source document and later transcribed into the CRF, or directly entered into the CRF. This will be completed by the designated scribe.

8.2.2.7 Evaporative Air Sensitivity Assessment (Schiff Sensitivity Score).

The evaporative air sensitivity assessments as described in Study Assessments will be conducted by the appropriately trained clinical examiner. Where possible, the same clinical examiner will be responsible for all Schiff sensitivity assessments conducted at all assessment visits. Assessments may be recorded on a source document and later transcribed into the CRF, or directly entered into the CRF. This will be completed by the designated scribe.

8.2.2.8 Supervised Brushing with Randomised Dentifrice

At Visit 3 subjects will be instructed to perform a supervised and timed brushing according to the product usage instructions, as detailed in Table 6-1. Confirmation of supervised brushing per protocol will be captured in the CRF and an entry recorded on the subject diary card. Any deviations from the product usage instructions will be captured as a protocol deviation, and subjects will be reminded of the correct directions for use.

Subjects will be re-dispensed a new toothbrush at Visit 3 and reminded to bring their study products to their next clinical study site visit.

Note: this is only applicable at Visit 3, and is not required at Visit 4.

8.2.2.9 Compliance Check on Dentifrice and Brushing

A member of the clinical study site staff will weigh the returned dentifrice, and if treatment use is deemed to be outside of the expected range, as detailed under Compliance, subjects will be re-educated on the correct dosage amount.

Subjects will then show their brushing video's from the previous 2 weeks (2 per week) to a member of the clinical study site staff and confirmation of compliance with the product usage instructions, as per protocol, will be captured in the CRF. Any deviations from the product usage instructions or missed video brushings will be captured as a protocol deviation and subjects will be re-educated on the correct directions for use. To assist the clinical study staff to determine which subjects are non-compliant with the product usage instructions a check-list has been provided (Appendix 15.3).

8.2.2.10 Adverse Events

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

At the end of Visit 3 subjects should be reminded to note any untoward medical occurrence, use of any new medications or new treatments in their diary (if used) or report to study site between visits, and to inform the site at their next visit as required.

8.3 Study Conclusion

The Study Conclusion page of the CRF will be completed for all subjects whether they completed all study procedures, or if they were discontinued from the study early. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page. Unless subjects were discontinued early the Study Conclusion page of CRF will be completed at Visit 4.

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

At the end of Visit 4 subjects should be reminded to inform the site if they experience any untoward medical occurrence in the next 5 days (i.e. for 5 days after their last dose of study treatment).

8.4 Diary Review

The diary should be reviewed at every visit by the investigator, or suitably qualified designee, and the subject. Any subject comment captured in the diary which is considered an adverse

event will be assessed and reported as per the defined procedure in this protocol. Adverse event reporting procedures are summarised in Adverse Event and Serious Adverse Events.

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

Additional and missed product applications will be considered deviations from the protocol and will be recorded as a protocol deviation in the CRF.

8.5 Brushing Compliance Check at 2 and 6 Weeks

After 2 and 6 weeks of using their allocated study product, subjects will be requested to send their brushing video's from the previous 2 weeks (2 per week) to the study site using WeChat. A member of the clinical study site staff will confirm compliance with the product usage instructions, as per protocol. This will be captured in the CRF, and any deviations from the product usage instructions or missed video brushings will be captured as a protocol deviation and subjects will be re-educated on the product usage instructions. To assist the clinical study staff to determine which subjects are non-compliant with the product usage instructions a check-list has been provided (Appendix 15.3).

8.6 Follow-up Visit"/ Phone Call"

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

9 STUDY ASSESSMENTS

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

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained clinical examiner(s) at the times, and in the order, defined in the Study Procedures section of this protocol.

9.1.1 Eligible Tooth Assessments

Eligible tooth assessments will include an OHT examination to evaluate dentition exclusions; erosion, abrasion and/or gingival recession; modified gingival index; tooth mobility and qualifying evaporative air and tactile threshold assessments. Assessments will be carried against the inclusion/exclusion criteria and recorded in the CRF.

9.1.1.1 Erosion, Abrasion and Recession (EAR) assessment

The presence of cervical erosion, abrasion and/or gingival recession (EAR) (Addy, 2000) will be determined on the facial surfaces of individual teeth. Teeth 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 eligible teeth.

9.1.1.2 Modified Gingival Index (MGI) Assessment

The MGI is a non-invasive visual evaluation of gingival health, scored on a scale of 0-4 (Lobene, 1986). MGI will only be assessed for the facial gingiva adjacent to the test area (exposed dentine); MGI ≤1 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.

9.1.1.3 Tooth Mobility Assessment

Clinical mobility will be classified in the following way (based on a modification to the Miller Index) (Laster, 1975); clinical mobility ≤1 is required for eligible teeth.

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

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

9.1.2 Qualifying Tactile Sensitivity

Qualifying tactile sensitivity assessments will be conducted at Screening (Visit 1) by an appropriately trained examiner who is dentally qualified and trained in the clinical assessments of DH. The tactile sensitivity of incisor, canine and pre-molar teeth as detailed in Figure 9-1 exhibiting none of the dentition exclusions, and meeting the EAR, MGI and clinical mobility criteria, will be assessed using a constant pressure probe (yeaple probe (Polson, 1980).

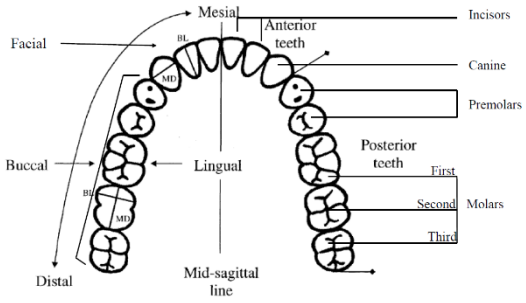

Figure 9-1 Dental Nomenclature. (Dempsey, 2001)

The probe tip will be placed perpendicular to the facial surface of the tooth and drawn slowly across the exposed dentine to ensure application of the stimulus across the potentially 'sensitive' area.

After each application, 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 examiner will generally make the force setting adjustments (may be carried out by an assistant/scribe) and the scribe will record the micro-amperage force setting and subject's responses. If unsure of the reliability of the subject's response, the examiner may 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 gram setting, which elicits the two consecutive "yes" responses, will be recorded as the tactile threshold. At Screening (Visit 1), the upper force

setting is 20g. In order for a tooth to qualify at Screening, it must have a tactile threshold ≤20g. If no pain response is found, the tactile threshold will be recorded as >20 g and the tooth will be disqualified from further testing.

9.1.3 Qualifying Evaporative Air Sensitivity

Qualifying evaporative air sensitivity assessments will be conducted at Screening (Visit 1) by an appropriately trained examiner who is dentally qualified and trained in the clinical assessments of DH. Qualifying evaporative air sensitivity will be assessed on the facial surfaces of incisor, canine and pre-molar teeth as detailed in Figure 9-1, exhibiting none of the dentition exclusions, and meeting the EAR, MGI, clinical mobility and tactile threshold (≤20g) criteria, a minimum of 5 minutes after the tactile assessments have been completed.

The assessment will be made by directing a one second application of air from a standard dental syringe held perpendicular to the tooth surface, approximately 1-2 mm coronal to the gingival margin, and from a distance of approximately 1 cm. The dental examiner will take appropriate measures to isolate the tooth surface to prevent stimulation of adjacent teeth or surrounding soft tissue.

9.1.4 Selection of Test Teeth

From the teeth that meet the tactile threshold (yeaple ≤20g) and Schiff sensitivity score criteria (Schiff ≥2) the 2 ‘test teeth’ will be selected. Teeth must be non-adjacent and preferably in different quadrants.

9.2 Dentine Hypersensitivity Assessments

The following assessments will be performed by examiners who are dentally qualified and have been trained in the clinical assessments of DH, using both the air syringe (Schiff sensitivity scale) and yeaple probe (tactile threshold). Assessments will be conducted at the times and in the order defined in the Study Procedures section of this protocol. Where possible, the same examiner will be responsible for a given dentin hypersensitivity assessment (Schiff and/or Tactile) from Screening and for the remaining duration of the study.

If in the opinion of the dental examiner a subject is between defined grades/scores, a conservative approach should be used to provide the final score. The same approach should be applied throughout the study to ensure consistency in the grading of the scores at all timepoints.

9.2.1 Tactile Sensitivity Assessment (Yeaple Probe)

The dental examiner may assess the tactile sensitivity of all clinically eligible teeth that qualify on EAR, MGI and tooth mobility criteria, without any of the dentition exclusions, and meet the qualifying tactile threshold and Schiff sensitivity score criteria at screening. The stimulus will

be administered as described in Section 9.1.2. Where possible the same examiner will assess the tactile sensitivity of the same teeth determined to be clinically eligible teeth at Screening

At Baseline (Visit 2) the 2 'test teeth' identified at Screening will be tested first; the upper test limit is 20g. If no pain response is found, the threshold will be recorded as >20g and the tooth will be disqualified from further tactile testing. If any of the test teeth identified at Screening do not respond to tactile, all eligible teeth that qualified at Screening may be re-assessed for tactile threshold and Schiff sensitivity until 2 new 'test teeth' are qualified. Before the teeth are re-assessed subjects must wait a minimum of 5 minutes recovery time.

At Visits 3 and 4 the tactile assessments will be conducted as described on the 2 selected 'test teeth' only, the upper force setting will be 80g. If no sensitivity is found, the threshold will be recorded as >80g.

The response will be evaluated as described in Section 9.1.2. The gram setting, which elicits the two consecutive "yes" responses, will be recorded as the tactile threshold.

9.2.2 Evaporative Air Sensitivity Assessment

After 5 minutes recovery time following completion of the tactile assessments the evaporative air sensitivity assessments will be completed. Where possible the same examiner will assess the evaporative air sensitivity of the same teeth determined to be clinically eligible teeth at Screening. This assessment will be conducted by directing a maximum one second application of air from a dental air syringe to the exposed dentine surface, as described in Section 9.1.3.

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

Score	Description
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

If any of the test teeth identified at Screening do not respond to the stimulus, all eligible teeth that qualified at Screening may be re-assessed for tactile threshold and Schiff sensitivity until 2 new 'test teeth' are qualified. Before the teeth are re-assessed subjects must wait a minimum of 5 minutes recovery time.

9.3 Safety and Other Assessments

The following safety assessments will be performed by an appropriately trained clinical examiner, at the times and in the order defined in the Study Procedures section of this protocol.

9.3.1 Oral Hard Tissue (OHT) Examination

Subjects with evidence of gross intra-oral neglect or the need for extensive dental therapy will be excluded. The OHT examination will assess for enamel irregularities, tooth fracture, grossly carious lesions/gross decay, defective/faulty restorations (all direct & indirect restorations including fixed/removal prostheses), non-carious tooth surface loss (abrasion, attrition, abfraction and erosion), any other hard tissue irregularity (e.g. hypo/hypermineralisation, decalcification) and tooth staining. Observations will be listed as "Absent" or "Present" and conditions noted as present will be described. Examination findings will be described and documented in the CRF. Any observation that changes from "Absent" to "Present" from the screening assessment must be recorded as an AE.

9.3.2 Oral Soft Tissue (OST) Examination

An OST examination will be conducted for each subject at every visit prior to any clinical assessments. 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. Any observation that changes from "Absent" to "Present" from the screening assessment must be recorded as an AE.

9.3.3 Pregnancy Testing

This clinical study is investigating products classified as general goods in China. For GSK CH studies in which no drug is utilised a pregnancy test is not required.

Subjects will need to provide verbal confirmation of negative pregnancy status and this must be documented as part of the exclusion criteria.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

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

10.1 Definition of an Adverse Event (AE)

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

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

Events Meeting the AE Definition:

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

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

Events NOT meeting the AE definition:

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

10.2 Definition of a Serious Adverse Event (SAE)

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

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

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**
  - In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any

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

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

10.3 Time Period and Frequency for Collecting AE and SAE Information

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

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

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

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study product or study participation, the investigator must promptly notify the sponsor.

10.4 Reporting Procedures

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

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to non-leading such as “How do you feel” will be assessed and any AE’s recorded in the CRF and reported appropriately.

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

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

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

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

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

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

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be the

documented as the AE/SAE where known and not the individual signs/symptoms. (e.g. upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

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

10.4.1 Reporting of an Adverse Event

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

10.4.2 Reporting of a Serious Adverse Event

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

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (or study procedure, if appropriate)
- Criterion for seriousness.

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

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant

- Action taken in relation to the study product
- Outcome if known

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

Email Serious Adverse Events to:

PPD

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

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

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

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

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.5.2 Assessment of Causality

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

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

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

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

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

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

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

10.6 Follow-up of AEs and SAEs

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

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

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

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

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

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

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

10.7 Withdrawal Due to an Adverse Event

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

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

10.8 Regulatory Reporting Requirements for SAEs

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

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

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

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

10.9 Pregnancy

10.9.1 Time Period for Collecting Pregnancy Information

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

10.9.2 Action to be Taken if Pregnancy Occurs

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

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

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

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

11 DATA MANAGEMENT

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

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

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

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

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

11.1 Case Report Form

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

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

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

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

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

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

11.2 Data Handling

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

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

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

11.2.1 Data Queries

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

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

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

11.3 Processing Patient Reported Outcomes

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

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

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

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

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

A sufficient number of subjects will be screened to randomise approximately 195 subjects to ensure approximately 180 subjects (approximately 60 per group) complete the study, allowing for dropouts.

Change from baseline in Schiff sensitivity score will be used evaluate treatment effects and is the primary outcome variable. With 60 evaluable subjects per group, the study has 90% power to detect a mean difference of 0.3 (standard deviation (sd) =0.501) in change from baseline in Schiff sensitivity score after 8 weeks of treatment. The difference of 0.3 represents roughly a 15% difference between treatment groups. The estimate of sd was obtained from GSK CH studies CCI [redacted]. The sample size is based on carrying out a 2-tailed 2 sample t-test at a 5% significance level.

12.2 Populations for Analysis

12.2.1 Definition of Analysis Populations

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

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

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

12.2.2 Exclusion of Data from Analysis

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

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

12.3 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical reporting and analysis plan (RAP), which will be written following finalisation of the protocol and prior to database lock. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

12.3.1 Primary Analysis(es)

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

The Schiff sensitivity score is derived as the average score of the 2 test teeth. The change from baseline is derived from the individual teeth first before calculating the average change of the 2 test teeth.

A summary of the Schiff sensitivity score and change from baseline will be provided by treatment group and time.

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

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated. In case of violation of these assumptions a suitable transformation or a non-parametric method eg the van Elteren test, adjusting for the maximum baseline Schiff Sensitivity scores will be performed and results will be compared with the ANCOVA results.

If the inferences from the two analyses are similar then both sets of results will be reported and emphasis will be made on the ANCOVA results. In case of discrepancies between p-values of ANCOVA and non-parametric method, inferences will be drawn on the nonparametric anlayses. Ultimately inferences will be drawn on the size of difference rather than just the p-value and it is hoped to see a difference of >15% between treatment groups. This difference is based on the adjusted Test and Control means for the change from baseline: 100 x [Adjusted Mean Difference / Adjusted Mean of Negative Control] . This percentage difference will be reported and tabulated along with the change from baseline results.

12.3.2 Secondary Analyses

The secondary efficacy variables with corresponding comparisons are as follows:

- Change from baseline in tactile threshold at 4 and 8 weeks; “test product versus negative control” and “positive control versus negative control”.

- Change from baseline in Schiff sensitivity score at 4 weeks; "test product versus negative control" and "positive control versus negative control".
- Change from baseline in Schiff sensitivity score 8 weeks; "positive control versus negative control".

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

A summary of the secondary variables and change from baseline will be provided by treatment group and time.

Change from baseline in Schiff will be analysed as per the primary variable. Change from baseline in Tactile variables will be analysed using ANCOVA with treatment as a factor and baseline Schiff sensitivity score as a covariate.

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

12.3.3 Exploratory Analyses

The exploratory efficacy variables are change from baseline in QOL (Total and each domain scores) at 8 weeks "test product versus negative control" and "positive control versus negative control"

The following QOL domain scores derived from the DHEQ questionnaire will be investigated:

- Total (Section 2, Q1-15)
- Restrictions (Section 2, Q1-3)
- Adaptation (Section 2, Q4-6)
- Social Impact (Section 2, Q7-9)
- Emotional Impact (Section 2, Q10-12)
- Identity (Section 2, Q13-15).

A summary of the exploratory variables and change from baseline will be provided by treatment group and time. This includes the individual questions from Section 1 (Q1-9).

Change from baseline in QOL variables (Section 1 (Q7-Q9) and Section 2 domain scores) will be analysed using ANCOVA with treatment baseline Schiff stratification as factors and baseline score of relevant variable included as a covariate.

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

12.3.4 Safety Analysis(es)

Safety variables will focus on:

- Exposure
- AEs
- OST findings

All AEs will be coded using the latest version of MedDRA. AEs will be categorised as oral and non-oral by the primary investigator. Treatment-emergent adverse events (Oral AEs as well as all AEs) will be associated with the most recent treatment received. The number of AEs and number of subjects with AEs will be listed and tabulated by treatment. The results of OST findings will be tabulated.

Exposure to study product is covered under study product compliance and the number of brushings in Section 12.3.7.1.

12.3.5 Exclusion of Data from Analysis

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

12.3.6 Demographic and Baseline Characteristics

Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for demographic and baseline characteristics. Demographic and baseline characteristics will be summarised by treatment group and study site for the Safety and mITT populations and the PP population if a PP analysis is performed.

12.3.7 Study Product Compliance and Use of Other Therapies

12.3.7.1 Study Product Compliance

This will be assessed by:

- Number of brushings
- Study dentifrice weight

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

Number of brushings compliance will be calculated as :-

100 × (number of actual brushings)/(number of expected brushings)

Number of expected brushings = 2 × number of days between $Visit_n$ and $Visit_{n-1}$

For the study dentifrice weight, the study dentifrice will be weighed at each visit. the pre-defined range will be calculated as the expected weight of toothpaste used for the treatment window. E.g. (2g x 28 days) ± 40%, therefore, in a 4 week treatment period the expected amount of toothpaste used would be ≥33.6g and ≤78.4g. The amount of dentifrice used during each treatment period will be recorded in a source document and later transcribed to the CRF.

12.3.7.2 Prior and Concomitant Medications

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

12.3.8 Handling of Dropouts and Missing Data

Subjects who withdraw from the study early will be included in the study analysis up to the point of withdrawal. Subjects who withdraw will not be replaced. No data will be imputed in the case of dropouts or missing data.

12.3.9 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

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

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

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

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

The extent and nature of monitoring will be described in a written monitoring plan on file at GSK CH. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.2 Quality Assurance

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

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

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

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

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

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

13.3.2 Ethical Conduct of the Study

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

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

13.3.3 Subject Information and Consent

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

When study data are compiled for transfer to GSK CH and other authorised parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by GSK CH in order to de-identify study subjects. Note that the use of initials should be avoided.

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

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

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

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

13.3.4 Subject Recruitment

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

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

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

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

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, GSK CH should be informed immediately.

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

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

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

13.5 Provision of Study Results to Investigators

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

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

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

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

13.6 Records Retention

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

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

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

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

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

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

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

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of GSK CH.

If a study is prematurely terminated, GSK CH will promptly notify the investigator. After notification, the investigator must promptly contact all participating subjects and should assure

appropriate therapy/ follow-up for the subjects. As directed by GSK CH, all study materials must be collected and all CRF's completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authority(ies) and the investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

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

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

14 REFERENCES

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15 APPENDICIES

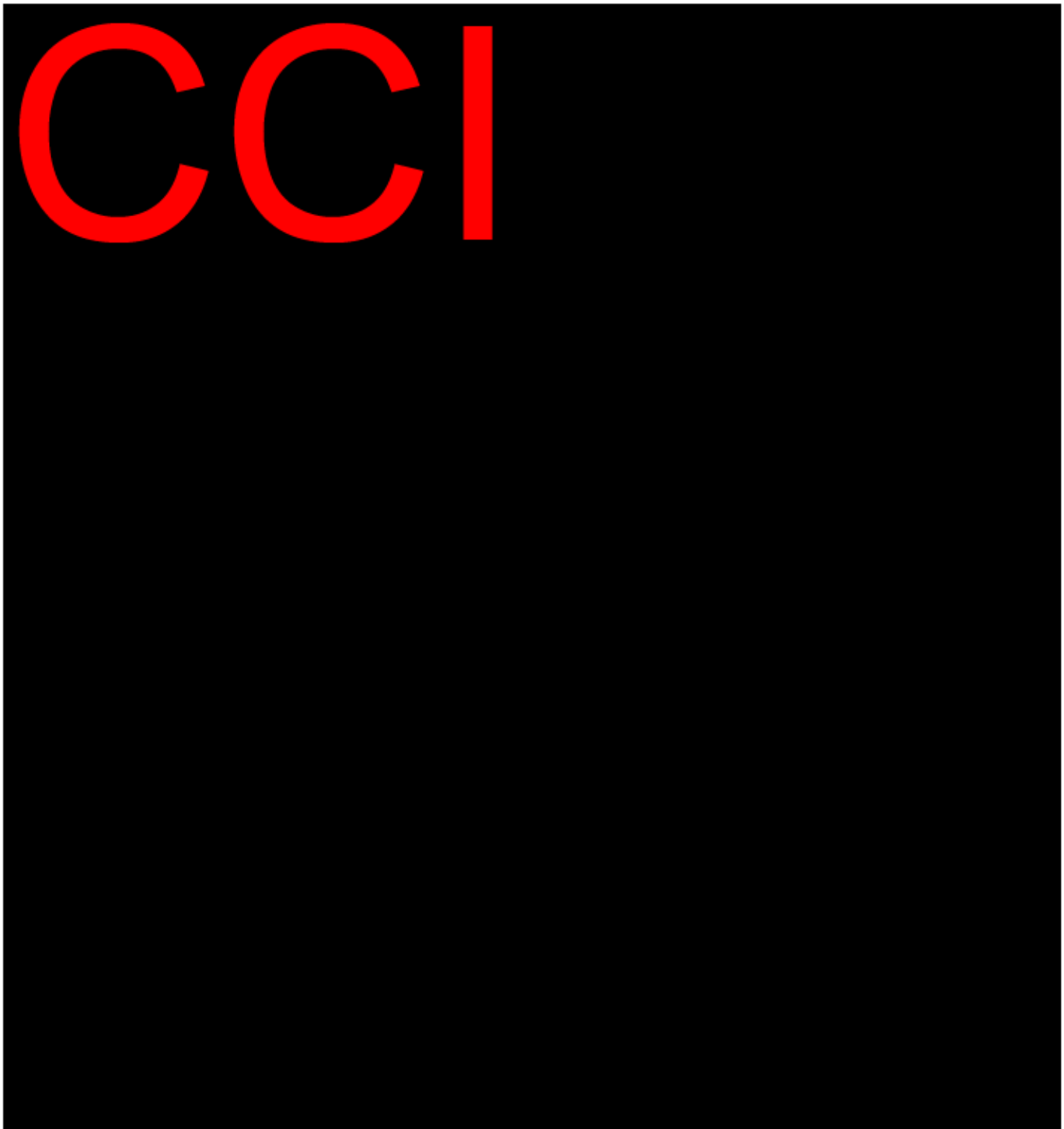
15.1 ABBREVIATIONS

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

Table 15-1 Abbreviations

Abbreviation	Term
AE	Adverse event
ANCOVA	Analysis of covariance
BDM	Biostatistics and Data Management
BDR	Blinded data review
CRF	Case report form
CRS	Clinical Research Scientist
DH	Dentin Hypersensitivity
DHEQ	Dentin Hypersensitivity Experience Questionnaire
DMS	Document Management System
EAR	Erosion, Abrasion, Recession
EDC	Electronic data capture
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSK CH	GlaxoSmithKline Consumer Healthcare
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
OHT	Oral hard tissue
OHRQoL	Oral Health Related Quality of Life
OST	Oral soft tissue
OTC	Over-the-counter
MFC	Manufacturing formulation code
MGI	Modified gingival index
MOH	Ministry of Health

Abbreviation	Term
NaF	Sodium fluoride
N/A	Not applicable
PI	Principal Investigator
PI	Personal information
PP	Per protocol
PRO	Patient Reported Outcome
QOL	Quality of Life
RAP	Reporting and analysis plan
SAE	Serious adverse event
SD	Standard deviation
SnF_2	Stannous fluoride
SRSD	Single reference safety document
SS	Safety statement
SUSAR	Suspected unexpected serious adverse reaction
UK	United Kingdom
US	United States
USA	United States of America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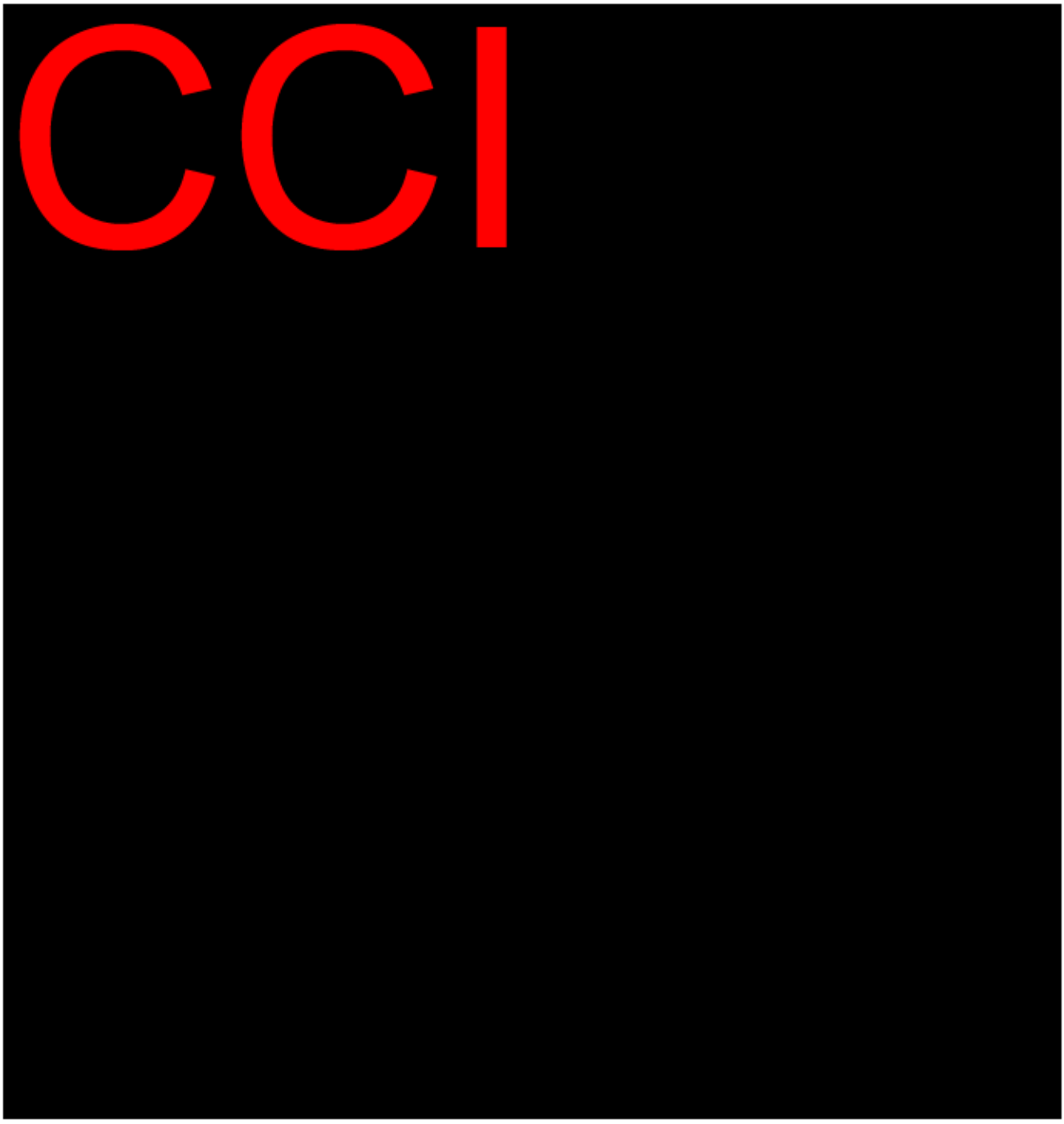
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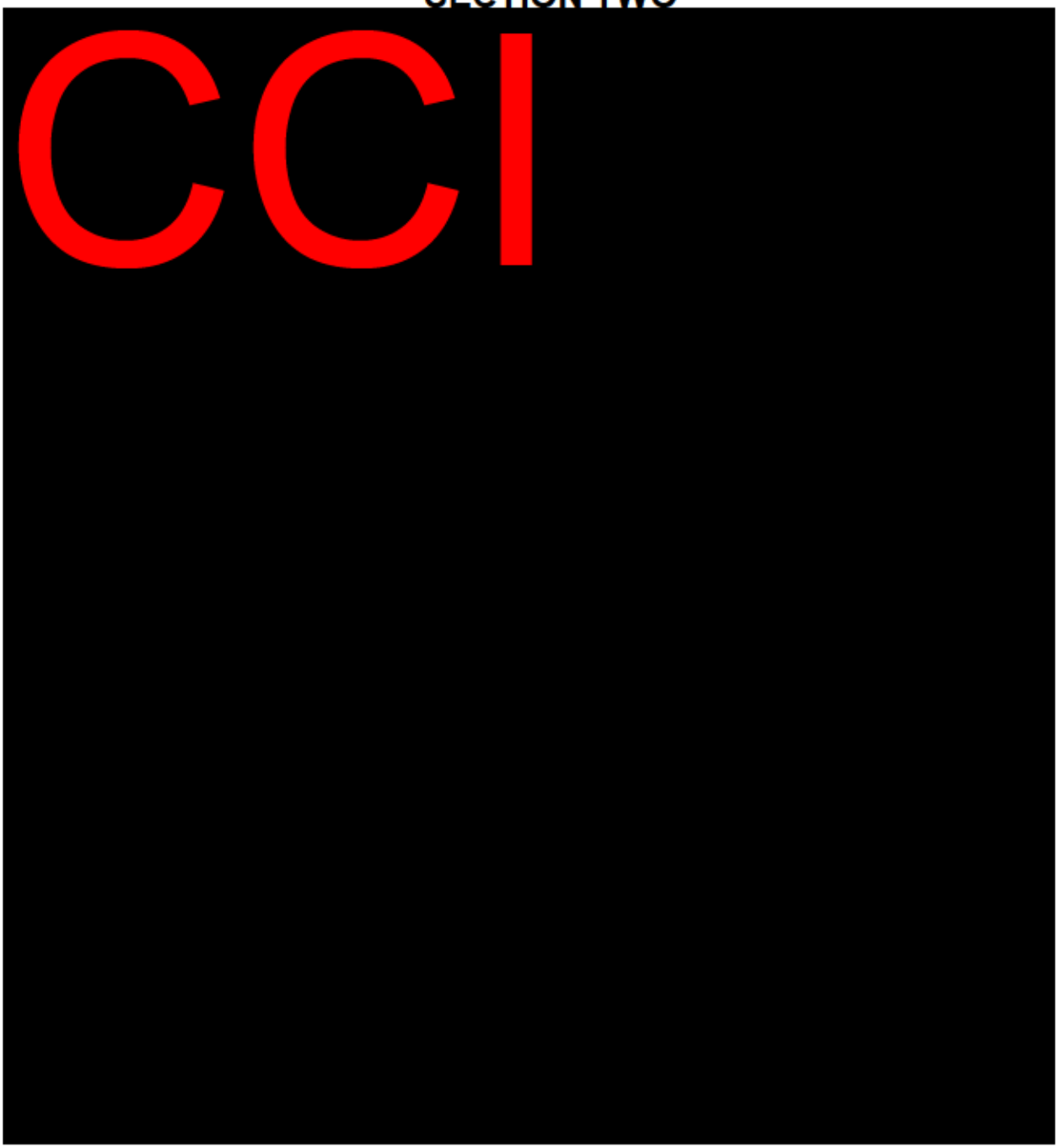
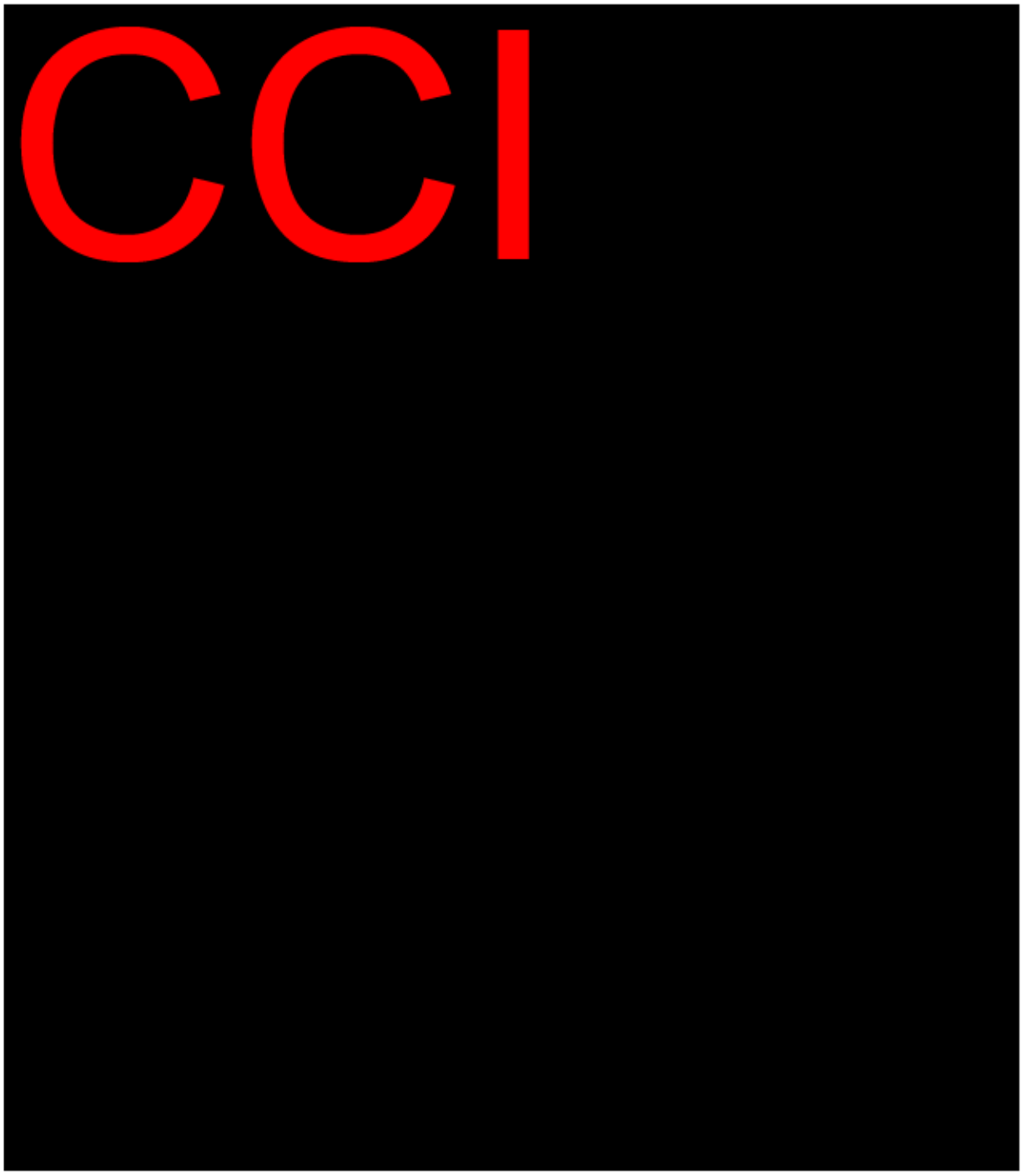
The following questions are about your sensitive teeth, and the impact it has on your everyday life.

SECTION TWO

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