CLINICAL PROTOCOL

A 12-Week, Randomised, Controlled, Examiner-blind, Clinical Study to Evaluate the Efficacy of a Stannous Fluoride Toothpaste for the Relief of Dentine Hypersensitivity in a Chinese Population

Protocol Number:	300026
Compound/Product Name:	Stannous fluoride (SnF_2)
United States (US) Investigational New Drug (IND) Number:	Not Applicable (N/A)
European Clinical Trials Database (EudraCT) Number:	N/A
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Phase:	N/A

This document contains confidentiality statements that are not relevant for this publicly available version

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** St Georges Avenue, Weybridge, Surrey, KT13 0DE, United Kingdom (UK)
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Document History

Document	Version	Summary of Changes
Original protocol	1.0	N/A
Amendment 1	2.0	Minor amendment: In section 6.5, clarification on the blinding has been added as following: "As a matter of study conduct, including emergency unblinding events, only the investigator may learn the contents of one or more of the product codes used to allocate study product, not the clinical examiners. Given the application of IRT within this study, any such knowledge will not affect the decision to enroll a subject or influence the order in which subjects are enrolled"
Amendment 2	3.0	Minor amendments: 1) Sponsor address in China has been updated 2) Section 5.1 Type and planned number of subjects, the sentence "their use would not be expected to cause harm to the mother, the foetus or baby" has been deleted for clarification 3) In section 10, the safety email inbox has been amended from PPD to PPD

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:	PPD
Investigator Signature:	PPD
Date of Signature/Agreement:	PPD

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1 PROTOCOL SUMMARY

1.1 Synopsis

Short Title:

Randomized Controlled Clinical Study to Evaluate the Efficacy of a Stannous Fluoride Toothpaste for the Relief of Dentine Hypersensitivity in a Chinese Population.

Background and Rationale:

The sponsor markets 0.454% weight/weight (w/w) stannous fluoride (SnF_2) toothpastes for the relief of dentine hypersensitivity (DH) globally; clinical efficacy is supported by two 8-week DH studies conducted outside China. Chinese Ministry of Health (MoH) guidelines require two clinical studies to support the efficacy of a functional toothpaste; at least one of these studies (for each claimed benefit) must be conducted on a local Chinese population (Ministry of Health China, 2010). Thus, a clinical study conducted in the Chinese population is required to support long-term DH relief claims for 0.454% w/w stannous fluoride (SnF_2) toothpastes in China.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to an evaporative (air) stimulus (as measured by Schiff sensitivity score), compared to a negative control toothpaste, after 12 weeks twice daily use.	Change from Baseline in Schiff sensitivity score at Week 12.
Secondary	
To determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to a tactile stimulus (as measured by tactile threshold), compared to a negative control toothpaste, after 12 weeks twice daily use.	Change from Baseline in tactile threshold (grams [g]) at Week 12.
To determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to an evaporative (air) stimulus (as measured by Visual Analogue Scale [VAS]), compared to a negative control toothpaste, after 12 weeks twice daily use.	Change from Baseline in VAS (millimeters [mm]) at Week 12.
To determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to evaporative (air) and tactile stimuli (as measured by Schiff sensitivity score/VAS and tactile threshold, respectively), compared to a negative control toothpaste, after 6 weeks twice daily use.	Change from Baseline in Schiff sensitivity score, tactile threshold (g) and VAS (mm) at Week 6.
To determine the clinical efficacy of a 5.0% w/w calcium sodium phosphosilicate (CSPS) toothpaste (positive control) in reducing DH to evaporative (air) and tactile stimuli (as measured by Schiff sensitivity score/VAS and tactile threshold, respectively), compared to a negative control toothpaste, after 6 and 12 weeks twice daily use.	Change from Baseline in Schiff sensitivity score and tactile threshold (g) and VAS (mm) at Week 6 and Week 12.

Safety	
To evaluate the safety and oral tolerability of the study toothpastes when used twice daily for 12 weeks.	Treatment emergent adverse events (TEAEs)

Study Design:

This will be a single centre, 12-week, randomized, controlled, examiner-blind, 3 treatment arm, parallel group design, stratified (by maximum Baseline Schiff sensitivity score of the two selected 'test teeth') clinical study, investigating the clinical efficacy of a 0.454% SnF_2 toothpaste for the relief of DH in a Chinese population.

Randomized subjects will be requested to brush their teeth twice daily (morning and evening) with their assigned study toothpaste for the duration of the 12-week study period. DH will be assessed at Screening, Baseline (Day 1), Week 6 and Week 12 using three clinical measures (an evaporative (air) stimulus with Schiff sensitivity score; a tactile stimulus with tactile threshold [g]; an evaporative (air) stimulus with VAS [mm]). Safety and oral tolerability of the study products will be monitored over the 12-week usage period by review of reported adverse events (AEs).

A 5.0% w/w CSPS toothpaste with clinically proven longer term DH efficacy in the Chinese population will be included in the study as a positive control. The clinical efficacy of both anti-sensitivity toothpastes (test and positive control) will be compared with that of a regular fluoride toothpaste (negative control), with no known anti-sensitivity properties.

Study Products:

Product Description	Test Toothpaste	Reference Toothpaste (Positive Control)	Reference Toothpaste (Negative Control)
Product Name	0.454% w/w SnF_2 toothpaste (Sensodyne Sensitivity & Gum*)	5.0% w/w CSPS toothpaste (Sensodyne Repair & Protect*)	Regular fluoride toothpaste (Crest Cavity Protection Fresh Lime*)
Master Formulation Code	CCI	CCI	Not applicable (N/A)
Fluoride Content	1100 parts per million (ppm) fluoride as SnF_2	1150 ppm fluoride as sodium fluoride (NaF)	1150 ppm fluoride as NaF

* Chinese commercial product

Type and Planned Number of Subjects:

Male and female subjects aged 18-70 years (inclusive), in good general and oral health, with no clinically relevant abnormalities in medical history, or upon oral examination, that could impact subject safety or well-being, or the outcomes of the study. Female subjects who are pregnant, or intending to become pregnant during the study, or breast-feeding, will not be included.

Eligible subjects will have a minimum of 20 natural teeth, a self-reported history of tooth sensitivity and at least two teeth with clinical examiner-confirmed DH (tactile threshold ≤ 20 g; Schiff sensitivity score ≥ 2) at both Screening and Baseline and VAS ≥ 40 mm at Baseline; in addition, the selected test teeth must demonstrate a consistent response to the evaporative (air) stimulus at the Screening and Baseline visits (i.e., Schiff sensitivity score = 2 at Screening and Baseline, **or** Schiff sensitivity score = 3 at Screening and Baseline; Table 4-1).

Sufficient subjects will be screened to randomize approximately 240 subjects to study treatment to ensure approximately 235 subjects complete the study (approximately 94 each for test toothpaste and negative control, and 47 for positive control), allowing for approximately 2% dropouts after randomization, as observed in previous clinical studies conducted in China.

Statistical Analysis Summary:

A modified Intent-To-Treat (mITT) population will be used for the efficacy analyses (all randomized subjects who complete at least one use of study product and have at least one post Baseline clinical efficacy assessment).

Schiff sensitivity score, tactile threshold (g) and VAS (mm) will be derived as the average score or value, respectively, of the 2 test teeth (identified at Baseline). Change from Baseline will be derived for the individual teeth first before calculating the average change of the 2 test teeth.

Significance testing will be conducted at the two-sided 5% significance level.

Change from Baseline in Schiff sensitivity score will be analysed using a Mixed Model with Repeated Measures (MMRM) with study product, visit and study product x visit interaction as fixed effects and Baseline Schiff sensitivity score as a covariate. Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied.

For the primary endpoint (change from Baseline in Schiff sensitivity score at Week 12), the difference between least square means for the test toothpaste compared to the negative control at Week 12 from the MMRM will be presented along with the two-sided p-value and 95% confidence intervals (CIs) to test the primary hypothesis of the study.

Change from Baseline in tactile threshold (g) will be analysed using the same MMRM as the primary endpoint but with Baseline tactile threshold as a covariate, rather than Baseline Schiff sensitivity score. In addition, the maximum Baseline Schiff sensitivity score across test teeth (2 or 3) will be fitted as a fixed effect. The difference between least square means for the test toothpaste compared to the negative control at Week 12 from the MMRM will be presented, along with the two-sided p-value and 95% CIs.

Change from Baseline in VAS (mm) will be analysed using the same MMRM as for the change from Baseline in tactile threshold (g) but with Baseline VAS (mm) as a covariate, rather than the Baseline tactile threshold (g). The difference between least square means for the test toothpaste vs. negative control at Week 12 will be presented, along with the two-sided p-value and 95% CIs.

For the other secondary endpoints, the differences between least square mean change from Baseline from the respective MMRM (test toothpaste vs. negative control at Week 6, positive vs. negative control at Weeks 6 and 12) will be presented with two-sided p-values and 95% CIs.

The assumption of normality and homogeneity of variance in each MMRM will be investigated. In case of violation of these assumptions, a suitable non-parametric test (adjusted for the randomisation stratification) will be performed to assess the change from Baseline comparisons (test toothpaste vs. negative control and positive control vs. negative control at Week 6 and Week 12) and results will be provided to support the MMRM results; the non-parametric results will be considered to supersede the MMRM results under the observation of strong violations of the above assumptions.

1.2 Schedule of Activities

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

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening		Study Visits		
	Visit 1		Visit 2 Baseline (Day 1)	Visit 3 Week 6 (Day 43±4)	Visit 4 Week 12 (Day 85±4)
Informed consent[1]	X				
Demographics	X				
Confirm WeChat application available on subject's mobile phone[2]	X				
DH screening questionnaire	X				
Confirm absence of anti-sensitivity ingredients & DH claims from subject's own oral care products	X				
Review subject's normal oral hygiene routine, specifically their rinsing habits	X				
Medical history and prior/current medication/treatment review	X				
Changes in health and medications/treatments		**Acclimatization Period** (14-28 Days)	X	X	X
Compliance checks - Check returned study supplies, review diary & evaluate compliance with twice daily use. - Check compliance with Lifestyle Guidelines/ Medication requirements.			X	X	X
Check brushing videos to confirm compliance with acclimatisation toothpaste usage instructions			X		
Oral soft tissue (OST) examination	X		X	X	X
Oral hard tissue (OHT) examination	X				X
Eligible teeth assessments (dentition exclusions, Erosion/Abrasion/Recession [EAR], Modified Gingival Index [MGI], clinical mobility)	X				
Qualifying tactile sensitivity assessment (tactile threshold (g)) for all eligible teeth [3,4]	X		X		
Qualifying evaporative (air) sensitivity assessments (Schiff sensitivity score, VAS) for all eligible teeth with a tactile threshold ≤ 20g [3,4]	X		X		
Identify all **eligible teeth which qualify for Baseline sensitivity assessments**: - No dentition exclusions - Presence of EAR - MGI = 0 adjacent to the test area only - Clinical mobility = 0 - Tactile threshold ≤ 20g - Schiff sensitivity score ≥ 2	X				

Select two test teeth [5]			X		
Inclusion/exclusion criteria	X		X		
Subject eligibility	X		X		
Subject continuance				X	X
Dispense acclimatisation toothpaste, toothbrush, rinsing cups, timer and diary	X				
Supervised brushing with acclimatisation toothpaste [6]	X				
Return to site with acclimatisation toothpaste, toothbrush and completed diary			X		
Stratification and randomisation			X		
Dispense study toothpaste, toothbrush, rinsing cups and diary			X		
Dispense toothbrush only				X	
Supervised brushing with study toothpaste and reminder of product usage instructions [6,7]			X	X	
Return to site with study toothpaste, toothbrush and completed diary				X	X
Tactile sensitivity assessment (tactile threshold): Two test teeth only [5]				X	X
Evaporative (air) sensitivity assessment (Schiff sensitivity score, VAS): Two test teeth only [5]				X	X
Study conclusion					X
Monitor adverse events (AEs) [8]	X		X	X	X

Footnotes:

1. Study information will be communicated to the subjects by the investigator, or designee, and by interactive video. After signing the ICF, subjects will be asked to complete a knowledge check (a quiz).
   Subjects will also be shown a list of the ingredients contained in the test products to confirm they have no known allergies or hypersensitivity to any of the ingredients.
2. Send study information video (at Screening) and brushing instruction video (at Baseline) to subjects using WeChat.
3. Qualifying tactile threshold (g) and Schiff sensitivity scores can be recorded on paper source documents for later transcription into the electronic case report form (eCRF).
4. Prior to clinical examinations and assessments, subjects will be shown or reminded how to complete a VAS. Evaporative (air) assessments follow the tactile assessments, with minimum 5 minutes between last tactile assessment and first evaporative (air) assessment (to allow tooth recovery).
   - **Visits 1 and 2:** maximum force for tactile assessments = 20g
   - **Visits 3 and-4:** maximum force for tactile assessments = 80g

   The clinical examiner should communicate their Schiff sensitivity score to the scribe (non-verbally) before the subject completes the VAS. Examiner and subject should be blinded to each other's scores.
   VAS is a qualifying assessment at Baseline ONLY.
5. Test teeth must only be selected from eligible teeth (no dentition exclusions, presence of EAR, MGI = 0 adjacent to the test area only, clinical mobility = 0) with a tactile threshold ≤ 20 g and a Schiff sensitivity score ≥ 2 at both Screening and Baseline, and VAS ≥ 40 mm at Baseline.
   Test teeth must have the same Schiff sensitivity score at Screening and Baseline (i.e., Schiff sensitivity score = 2 at Screening and Baseline, **or** Schiff sensitivity score = 3 at Screening and Baseline**)**
6. Return study supplies to subject after supervised brushing.
7. **Subjects randomized to test toothpaste only:** Dispensing staff will show the subject the location of their two test teeth prior to supervised brushing.
8. Record AEs from signing of the informed consent form (ICF) until 5 days after last use of study product (or the last study procedure).

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 dental erosion or abrasion), both result in exposure of dentine with patent dentinal tubules (Orchardson, 2000). The hydrodynamic theory of DH hypothesises that an external stimulus (e.g., a temperature/osmotic differential) applied to exposed dentine disrupts the movement of fluid within dentinal tubules (Brännström, 1962). This disruption may stimulate nerve processes in the pulpal area of the dentine including irritation of odontoblasts, pulpal neurons, and even subodontoblastic blood vessels (Hall, 2000), resulting in the characteristic short, sharp pain of DH.

Currently there are two approaches to the management of DH: nerve depolarisation or dentine tubule occlusion. Nerve depolarising agents, typically potassium salts, generally require a period of use (e.g., 14 to 28 days) before their benefit is established. The delivery of potassium ions to the dentine-pulp junction (odontoblastic layer) *via* exposed dentine tubules is believed to result in depolarisation of the afferent nerve membrane thereby interrupting the pain response (Orchardson, 2000). The second approach uses occluding agents which act to physically block or narrow the exposed end of dentinal tubules (by the precipitation of insoluble materials onto the dentine surface and/or within dentinal tubules), thus reducing disruption to dentinal fluid movement in response to an external stimulus (Pashley, 1986).

Stannous fluoride (SnF_2) has been incorporated into oral hygiene products indicated for the reduction of DH since the 1990s (Schiff, 2006); it provides relief from DH by the occlusion of the dentine tubules through chemical precipitation of stannous oxides and hydroxides. Proctor and Gamble (P&G), Colgate and the sponsor market 0.454% SnF_2 toothpastes indicated for DH relief, with published evidence demonstrating longitudinal clinical efficacy (Ni, 2010; Parkinson, 2011; Makin, 2013).

2.1 Study Rationale and Background

The longer-term clinical efficacy of sponsor's 0.454% SnF_2 toothpastes is currently supported by two 8-week DH studies conducted outside China (Parkinson et al, 2013; Parkinson et al, 2015). The Chinese MoH guidelines (Ministry of Health China, 2010) require two clinical studies to support the efficacy of a functional toothpaste, with at least one of these studies (for each claimed benefit) to be conducted in a local Chinese population. Thus, a clinical study in the Chinese population which meets the additional requirements described above is required to support longer-term DH relief claims for the sponsor's 0.454% SnF_2 toothpastes in China.

2.2 Benefit/Risk Assessment

Study products are commercially available daily use toothpastes which contain only ingredients with a history of safe use in oral healthcare products. Summary safety information for the acclimatization and study products will be provided on the product labels.

2.3 Mechanism of Action/Indication

Occlusion agents act to physically block or narrow dentinal tubules where they open on to the surface of exposed dentine, thereby preventing or reducing disruption to the movement of fluid within the tubule in response to an external stimulus (Addy, 2002). SnF_2 is one of the most

commonly employed tubule-occluding agents included in anti-sensitivity toothpastes. The stannous (tin [II]) ion reacts with water and phosphate minerals found in saliva and dentine tubule fluid to form insoluble deposits (a 'protective' layer) over the surface of the dentine (Parkinson 2011; Parkinson 2013)

3 STUDY OBJECTIVES AND ENDPOINTS.

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to an evaporative (air) stimulus (as measured by Schiff sensitivity score), compared to a negative control toothpaste, after 12 weeks twice daily use.	Change from Baseline in Schiff sensitivity score at Week 12.
Secondary	
To determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to a tactile stimulus (as measured by tactile threshold), compared to a negative control toothpaste, after 12 weeks twice daily use.	Change from Baseline in tactile threshold (grams [g]) at Week 12.
To determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to an evaporative (air) stimulus (as measured by Visual Analogue Scale [VAS]), compared to a negative control toothpaste, after 12 weeks twice daily use.	Change from Baseline in VAS (millimeters [mm]) at Week 12.
To determine the clinical efficacy of a 0.454% w/w SnF_2 toothpaste in reducing DH to evaporative (air) and tactile stimuli (as measured by Schiff sensitivity score/VAS and tactile threshold, respectively), compared to a negative control toothpaste, after 6 weeks twice daily use.	Change from Baseline in Schiff sensitivity score, tactile threshold (g) and VAS (mm) at Week 6.
To determine the clinical efficacy of a 5.0% w/w calcium sodium phosphosilicate (CSPS) toothpaste (positive control) in reducing DH to evaporative (air) and tactile stimuli (as measured by Schiff sensitivity score/VAS and tactile threshold, respectively), compared to a negative control toothpaste, after 6 and 12 weeks twice daily use.	Change from Baseline in Schiff sensitivity score and tactile threshold (g) and VAS (mm) at Week 6 and Week 12.
Safety	
To evaluate the safety and oral tolerability of the study toothpastes when used twice daily for 12 weeks.	Treatment emergent adverse events (TEAEs)

The study will be considered successful if the 0.454% SnF_2 toothpaste demonstrates statistically significant, superior anti-hypersensitivity efficacy, compared to negative control, as measured by Schiff sensitivity score at Week 12.

4 STUDY DESIGN

4.1 Overall Design

This will be a single centre, 12-week, randomised, controlled, examiner-blind, 3-treatment arm, parallel group design, stratified (by maximum Baseline Schiff sensitivity score of the 2 selected test teeth) clinical study investigating the clinical efficacy of a 0.454% SnF_2 toothpaste for the relief of DH in a Chinese population. A 5.0% CSPS toothpaste with clinically proven longer-term DH efficacy in the Chinese population will be included in the study as a positive control. The clinical efficacy of both anti-sensitivity toothpastes will be compared with that of a regular fluoride toothpaste (negative control), with no known anti-sensitivity properties.

Two stimuli will be employed to evaluate the DH efficacy of the test toothpaste. A tactile stimulus will be administered using a constant pressure probe (Yeaple Probe (Polson, 1980)); subject response to the stimulus determines the tactile threshold in grams (g). An evaporative (air) stimulus will be administered using a dental air syringe; subject response to the stimulus will be evaluated by a dental examiner using the Schiff sensitivity scale (Schiff, 1994) and a subject-completed VAS (mm). DH will be assessed at Screening, Baseline (Day 1), Week 6 and Week 12.

- At Screening, tactile sensitivity will be assessed **for all eligible teeth identified by oral examination** (i.e. no dentition exclusions, presence of EAR, MGI = 0 adjacent to the test area only, clinical mobility = 0), followed by evaporative (air) sensitivity (with Schiff sensitivity score and VAS) for eligible teeth with tactile threshold ≤ 20g.
- At Baseline, tactile sensitivity will be assessed **for all eligible teeth identified at Screening** (i.e. no dentition exclusions, presence of EAR, MGI = 0 adjacent to the test area only, clinical mobility = 0, tactile threshold ≤ 20g at Screening, Schiff sensitivity score ≥ 2 at Screening); followed by evaporative (air) sensitivity (with Schiff sensitivity score and VAS) **for all eligible teeth identified at Screening with Baseline tactile threshold ≤ 20g**.

On completion of the Baseline assessments, **two test teeth** will be selected for continued assessment of tactile and evaporative (air) sensitivity at subsequent visits. **Each test tooth** must comply with the following selection criteria:

- No dentition exclusions, presence of EAR, MGI = 0 adjacent to the test area only and clinical mobility = 0
- Tactile threshold ≤ 20g at Screening and Baseline
- Schiff sensitivity score ≥ 2 at Screening and Baseline
- VAS ≥ 40 mm at Baseline only
- **Test teeth must have the same Schiff sensitivity score at Screening and Baseline**
  Schiff sensitivity score = 2 at Screening and Baseline, OR
  Schiff sensitivity score = 3 at Screening and Baseline

Qualifying subjects will be stratified according to the maximum Baseline Schiff sensitivity score of their two test teeth and randomised to one of the 3 study toothpastes. Randomised subjects will brush their teeth twice daily (morning and evening) with their assigned study toothpaste for the duration of the 12-week treatment period.

Safety and oral tolerability of the study products will be monitored throughout the study by review of subject- and examiner-reported AEs.

4.2 Scientific Rationale for Study Design

A randomised, controlled, examiner-blind, parallel group design is a recognised approach for investigating the clinical efficacy of a product for the relief of DH (Holland, 1997).

The longer-term clinical efficacy of the sponsor's 0.454% SnF_2 toothpastes is currently supported by two 8-week DH studies conducted outside China (Parkinson et al, 2013; Parkinson et al, 2015). Longer-term DH studies evaluating an alternative occlusion technology (CSPS) in China employed a longer treatment period (Hall et al, 2017 11 weeks; CCI In order to establish longitudinal performance for the test toothpaste, with greater opportunity for its clinical benefits to be observed, a 12 week treatment period will be employed here (Murray, 1994; Irwin, 1997). To comply with Chinese MoH guidelines for the testing of functional (desensitising) toothpastes, a single interim assessment timepoint will be included after 6 weeks' treatment ('*Sensitivity levels are to be examined and recorded at the baseline, mid-trial and end-trial stages*'; Ministry of Health (China), 2010).

In line with published recommendations for the design and conduct of DH studies (Holland, 1997) and the requirements of the Chinese MoH guidelines for the testing of functional (desensitising) toothpastes (Ministry of Health (China), 2010), two independent stimuli will be employed (tactile and thermal (evaporative air) stimuli) to evaluate the efficacy of the 0.454% SnF_2 toothpaste. To avoid inter-assessor variability, the same clinical examiner should be responsible for the administration of a given stimulus (tactile or evaporative (air)) and the conduct of the associated examiner-assessed DH measure from Screening until the end of the study. DH will be assessed at Screening, Baseline (pre-treatment) and following 6 and 12 weeks of treatment.

The age range over which an individual can experience DH is wide (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 both dentine permeability and the tooth's response to external triggers of DH (Pashley, 2008; Seltzer and Bender, 1975). The dental pain experienced by much older members of the population is less likely to be diagnosed as DH (Rees, 2000), thus an age range of 18-70 years has been selected for this study to target individuals with tooth sensitivity due to DH.

While there is no published evidence to indicate that gender impacts the pathophysiology of DH, a national DH survey conducted in rural China in 2009 reported a greater proportion of females with DH compared to males (female 35.8%; male 23.4%) (Liang, 2017). To ensure the current study population is representative of the Chinese population being studied, the study site will aim to recruit a female:male ratio of approximately 3:2.

According to ICH guidelines (ICH E6 (R2) Good clinical practice | European Medicines Agency (europa.eu), for a study to be classed as double blind, the subject, investigator, clinical examiners, monitors, data analysts, and staff involved in determining subject eligibility/ assessing compliance should be blinded to the treatment a subject receives. However, given it will not be possible to ensure identical appearance, flavour and packaging for the three commercial toothpastes to be evaluated in this study, the study is described as 'examiner blind'.

In line with the Chinese MOH guidelines (Ministry of Health (China), 2010) for the testing of functional (desensitising) toothpastes, a regular fluoride toothpaste with no known (or claimed) anti-sensitivity efficacy will be included as the negative control (Crest Cavity Protection Fresh Lime; China commercial product). In addition, a 5.0% CSPS toothpaste (Sensodyne Repair & Protect; China commercial product) with proven DH efficacy in the Chinese population (in

clinical studies that satisfied current (at time of writing) Chinese MoH guidelines: sponsor clinical studies Hall et al, 2017 and CCI will be included in the study as a positive control (i.e., as a benchmark of performance in the Chinese population for 'study validation'). Given the primary objective is to demonstrate statistical superiority for the test toothpaste compared to negative control in change from Baseline in Schiff sensitivity score at Week 12, qualifying subjects will be randomised to study treatment using a 2:2:1 allocation ratio (Test: Negative Control: Positive Control).

Subjects using anti-sensitivity products as part of their normal oral hygiene routine will be excluded (their own oral hygiene products will be checked for presence of known anti-sensitivity ingredients at Screening); if they are continuing to experience DH, they are unlikely to respond to use of a sensitivity toothpaste in the current study.

Subjects will be asked to describe their typical daily oral care regimen at Screening. To help maintain study product in the oral cavity for the duration of each timed brushing, any subject who habitually rinses with water during toothbrushing (self-reported) will be excluded from the study. Similarly, at Baseline, following review of the brushing videos, any subjects who rinsed during brushing with the acclimatisation toothpaste will be excluded.

Clinical trials evaluating pain-related end points can be prone to 'placebo effects' (Addy, 1985; West, 1997); such effects are frequently observed in DH studies. A study conducted to evaluate the natural history of the DH condition also highlighted the existence of a 'no treatment' effect, characterised by an improvement in sensitivity simply as a result of study participation (Leight, 2008). Analyses of sponsor data from earlier DH efficacy studies indicate (i) subjects with a lower frequency of DH symptoms may exhibit greater 'placebo'/ 'no treatment' effects (sponsor clinical study: 216953) and (ii) subjects with different qualifying Schiff sensitivity scores at Screening and Baseline for one or both test teeth may also exhibit greater 'placebo'/ 'no treatment' effects (sponsor clinical study: 216954) .

To help minimise the potential impact of such effects:

- An acclimatisation period (2-4 weeks) will precede the Baseline visits. During this period, study subjects will brush twice daily with the regular fluoride toothpaste and toothbrush provided (in place of their normal oral hygiene products) and record each timed brushing occasion in a diary. The acclimatisation period will also help standardise oral hygiene practice across the study population prior to treatment.
- Subjects will complete a Screening Questionnaire (Appendix 15.2) at Visit 1; those who report experiencing DH symptoms only 'several times a month', 'once a month' or 'less than once a month' will be excluded from the study.
- Each selected test tooth must have the same qualifying Schiff sensitivity score at the Screening and Baseline visits (i.e., Schiff sensitivity score = 2 at Screening and Baseline, **or** Schiff sensitivity score = 3 at Screening and Baseline).

On completion of the Baseline assessments, the clinical examiner will select two test teeth from those that qualified at Screening (Visit 1) and Baseline (Visit 2) for assessment of tactile and evaporative (air) sensitivity at all subsequent visits (Table 4-1). The selection of two 'test teeth' to evaluate changes in DH is common practice in sensitivity studies (Schiff, 1994). Qualifying subjects will be stratified according to the maximum Schiff sensitivity score of their two selected test teeth to ensure treatment groups are balanced for DH severity.

DH is an episodic condition; symptoms are known to vary spontaneously (West, 2008, West et al., 2013). Baseline clinical values that would support enrolment may represent random highs

that could be followed by regression to the mean, leaving the subject or selected test tooth without the condition under investigation during the treatment period. To help minimise the potential for this to occur on the current study, randomised subjects will be required to demonstrate consistency in DH response at both the Screening and Baseline visits.

- Randomised subjects must have a minimum of two eligible teeth (no dentition exclusions, presence of EAR, MGI = 0 adjacent to the test area only, clinical mobility = 0) with a tactile threshold ≤ 20 g and a Schiff sensitivity score ≥ 2 at both Screening and Baseline.
- Test teeth can only be selected from eligible teeth identified at Screening (no dentition exclusions, presence of EAR, MGI = 0 adjacent to the test area only, clinical mobility = 0), with a tactile threshold ≤ 20 g and a Schiff sensitivity score ≥ 2 at both Screening and Baseline and with VAS ≥ 40 mm at Baseline only.
- **Test teeth must have the same Schiff sensitivity score at Screening and Baseline**.

Table 4-1 Eligibility Checks for Test Tooth Selection

Screening Assessments (Visit 1)							Baseline Assessments (Visit 2)			
Dentition Exclusions	EAR	MGI*	Clinical Mobility	Tactile Threshold	Schiff Sensitivity Score	**Eligible Tooth**	Tactile Threshold	Schiff Sensitivity Score	**VAS**	**Test Tooth**
None	Yes	0	0	≤ 20g	2	**Yes**	≤ 20g	2	≥ 40mm	**Yes**
None	Yes	0	0	≤ 20g	3	**Yes**	≤ 20g	3	≥ 40mm	**Yes**
None	Yes	0	0	≤ 20g	2	**Yes**	≤ 20g	3	≥ 40mm	**No**
None	Yes	0	0	≤20g	3	**Yes**	≤20g	2	≥ 40mm	**No**

Eligibility against each selection criterion is determined sequentially.

*Adjacent to the test area only

VAS is completed at Screening and Baseline, but is a qualifying measure for Test Tooth Selection at Baseline **ONLY**.

4.3 Justification for Dose

Study products are toothpastes, intended for topical oral use, and will be applied by toothbrushing using a manual toothbrush.

The usage regimen of twice daily brushing (morning and evening) will be the same for all subjects, based on widely recommended oral hygiene practice and typical consumer habit. Study subjects will brush for 1-timed minute with their assigned study toothpaste on each brushing occasion in line with typical brushing times specified for similar DH efficacy studies (Parkinson, 2011; Makin, 2013; Hall et al., 2017; Docimo et al., 2009). Subjects allocated to the test toothpaste will be instructed to brush their two test teeth first, to ensure their sensitive teeth are treated, then their whole mouth for 1-timed minute. The usage regimen specified for the negative and positive control products is aligned with the usage instructions provided on the commercial packaging of both toothpastes.

After 12 weeks (85 ± 4 days) twice daily usage, each subject should complete between 162-178 brushings with their randomized product. Subjects will complete a supervised brushing with their assigned study toothpaste at the end of each study visit (while still at the study site) to

enable staff to confirm correct usage and to encourage compliance with the required usage regimen for the duration of the study.

Tongue cleaning forms an integral part of typical oral hygiene practice for many Chinese consumers; it will be permitted during the current study (using the toothbrush provided), after completing each 1-minute toothbrushing with study toothpaste but before the 10ml water rinse. Tongue brushing is not permitted while toothbrushing.

To help ensure the study toothpaste is retained in the oral cavity for the 1-minute brushing time, subjects must not rinse with water or expectorate during toothbrushing.

A recent consumer study (sponsor data on file) observed rinsing with variable, often copious amounts of water following toothbrushing to be common practice in Chinese consumers. To standardise rinsing practice across the study population, all subjects will be instructed to rinse once with water (10 ml dispensed from a dosing cup) after each brushing occasion.

4.4 End of Study Definition

A subject will be considered to have completed the study if they have 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, as described in the Schedule of Activities (Table 1-1), for the last subject.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

The study will be conducted in a Chinese population (in China). Subjects will be male or female, with a minimum of 20 natural teeth, a self-reported history of tooth sensitivity and at least two teeth with clinical examiner-confirmed DH (tactile threshold ≤ 20 g and Schiff sensitivity score ≥ 2 at both Screening and Baseline; VAS ≥ 40 mm at Baseline). In addition, the selected test teeth must demonstrate a consistent response to the evaporative (air) stimulus at the Screening and Baseline visits (Schiff sensitivity score = 2 at Screening and Baseline, **or** Schiff sensitivity score = 3 at Screening and Baseline).

Sufficient subjects will be screened to randomize approximately 240 subjects to study treatment to ensure approximately 235 subjects complete the study (approximately 94 each for test toothpaste and negative control, and 47 for positive control), allowing for approximately 2% dropouts after randomization, as observed in previous clinical studies conducted in China.

Whilst the study products are not contra-indicated for pregnancy and breastfeeding, pregnant and/or lactating females will be excluded from this study due to the increased prevalence and severity of gingivitis and periodontal disease observed during pregnancy (Samant et al., 1976) and breastfeeding (Aghazadeh et al, 2019) which, together with the increased amounts of calculus and plaque observed during pregnancy, could impact DH assessments (Samant et al., 1976).

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 authorized representative) and successfully met the eligibility criteria to proceed beyond the screening visit as described in 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 study team before a subject is 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. 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 study procedures are performed.
2. Male or female who, at the time of screening, is between the ages of 18 to 70 years inclusive.
3. Subject who is willing and able to understand and comply with scheduled visits, product usage requirements and other study procedures.
4. Subject in good general, oral 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, that would impact the subject's safety or wellbeing, or the outcomes of the study, if they were to participate in the study, or affect the subject's ability to understand and follow study procedures and requirements.
5. Subject who owns a smartphone with WeChat application installed.
6. **At Screening (Visit 1)**

   Subject must have:

   a) Self-reported history of tooth sensitivity lasting more than 6 months but not more than 10 years and experience DH symptoms at least 'once a week' or more frequently (Screening Questionnaire, Appendix 15.2).

   b) Good general oral health, with a minimum of 20 natural teeth.

   c) Minimum of **two** accessible, non-adjacent teeth (incisors, canines, pre-molars), preferably in different quadrants, with clinically confirmed DH.

      Each eligible tooth must meet all the following criteria:

      i. Exposed dentine due to facial/cervical erosion, abrasion or gingival recession (EAR).

      ii. MGI = 0 directly adjacent to the exposed dentine (i.e., the test area) only.

      iii. Clinical mobility = 0.

      iv. DH as evidenced by qualifying levels of tactile and evaporative (air) sensitivity (tactile threshold ≤ 20g **and** Schiff sensitivity score ≥ 2).

7. **At Baseline (Visit 2)**:

   All teeth identified at Screening (Visit 1) as eligible for Baseline assessments will be re-assessed for tactile sensitivity first; eligible teeth with Baseline tactile threshold ≤ 20g will then be re-assessed for evaporative (air) sensitivity.

   Subjects must have:

   A minimum of two non-adjacent, accessible teeth (incisors, canines, pre-molars), preferably in different quadrants, with clinically confirmed DH as evidenced by qualifying levels of tactile and evaporative (air) sensitivity:

   a) Tactile threshold ≤ 20g at Screening and Baseline

   b) Schiff sensitivity score ≥ 2 at Screening and Baseline.

   c) VAS ≥ 40 mm at Baseline.

   The clinical examiner will select two 'test teeth' from those eligible teeth which meet the tactile threshold and Schiff sensitivity score criteria at both Screening and Baseline, and the VAS criterion at Baseline.

   Each test tooth must demonstrate a consistent DH response to the evaporative (air) stimulus at both Screening and Baseline:

Screening Schiff sensitivity score = 2 and **Baseline** Schiff sensitivity score = 2
OR
Screening Schiff sensitivity score = 3 and **Baseline** Schiff sensitivity score = 3

   The procedure for selecting test teeth is summarised in **Table 4-1**.

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will be excluded from the study:

1. Subject who is an employee of the study site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the study site otherwise supervised by the investigator; or a sponsor employee directly involved in the conduct of the study or a member of their immediate family.
2. Subject who is participating in, or has participated in, other studies (including non-medicinal studies) involving investigational product(s) within 30 days of Screening (Visit 1).
3. Subject who is participating in, has participated in, a study evaluating a tooth desensitising treatment within 8 weeks of Screening (Visit 1).
4. Subject who is using, or has used, an oral care product indicated for DH relief within 8 weeks of Screening (Visit 1). Subjects will be required to bring their current oral care products to Visit 1 for staff to verify the absence of known anti-sensitivity ingredients and DH claims.
5. Subject who has had a professional de-sensitising treatment within 8 weeks of Screening (Visit 1).
6. Subject who habitually rinses with water during toothbrushing (self-reported at Screening (Visit 1)).
7. Subject seen to rinse with water while brushing with the acclimatization toothpaste during

review of their brushing compliance videos at Baseline (Visit 2).

8. Subject with known or suspected intolerance or hypersensitivity to the study products or any of their stated ingredients (or closely related compounds).
9. Subject who is unwilling or unable to comply with product usage instructions (Section 4.3) or Lifestyle Considerations (Section 5.5) as described in the protocol.
10. Female subject who is pregnant or intending to become pregnant during the study (self-reported).
11. Female subject who is breastfeeding.
12. Subject with a recent history (within the last year) of alcohol and/or substance abuse.
13. Subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study 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.
14. Subject taking daily doses of medications or traditional herbal treatments which, in the opinion of the investigator or medically qualified designee, could interfere with their 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 treatments include clove oil, olive oil or other treatments directly applied to the oral cavity for the treatment of oral health conditions.
15. Subject taking daily doses of a medication which, in the opinion of the investigator or medically qualified designee, is causing xerostomia.
16. Subject who requires antibiotic prophylaxis for dental procedures.
17. **At Screening (Visit 1)**

    Subject who has taken antibiotics within 2 weeks of their Screening visit.
18. **At Baseline (Visit 2)**

    Subject who has taken antibiotics within 2 weeks of their Baseline visit (during the acclimatisation period).
19. Subject who has had a professional or self-applied tooth bleaching procedure within 8 weeks of Screening (Visit 1).
20. Subject who has had dental prophylaxis within 4 weeks of Screening (Visit 1).
21. Subject who has had treatment for periodontal disease (including surgery) within 12 months of Screening (Visit 1).
22. Subject who has had scaling or root planning within 3 months of Screening (Visit 1).
23. Subject with a tongue or lip piercing.
24. Subject with, in the opinion of the investigator or medically qualified designee, gross periodontal disease.

25. Subject with evidence of gross intra-oral neglect or the need for extensive dental therapy.
26. Subject with a fixed or removable partial prosthesis which, in the opinion of the investigator or medically qualified designee, would impact study outcomes.
27. Subject with multiple dental implants which, in the opinion of the investigator or medically qualified designee, would impact study outcomes.
28. Subject with fixed or removable orthodontic braces/bands or a fixed orthodontic retainer.
29. **SPECIFIC DENTITION EXCLUSIONS FOR 'TEST TEETH':**
    a) Tooth with evidence of current or recent caries or reported treatment of decay within 12 months of Screening (Visit 1).
    b) Tooth with exposed dentin but with deep, defective or facial restorations.
    c) Tooth with full crown or veneer.
    d) Tooth adjacent to a bridge abutment or crown which, in the opinion of the investigator or medically qualified designee, would impact study outcomes.
    e) Sensitive tooth with contributing aetiologies other than erosion, abrasion or recession to exposed dentine.
    f) Sensitive tooth, in the opinion of the investigator or medically qualified designee, not expected to respond to treatment with an anti-sensitivity toothpaste.
30. Subject who has previously been enrolled in this study.
31. Any subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.

5.4 Randomization Criteria

Subjects who satisfy all selection criteria will be randomized into the study. Randomisation numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible.

Subjects will be stratified by the maximum Baseline Schiff sensitivity score of their two selected test teeth. The stratification factor will give rise to two strata.

- **Stratum 1:** Maximum Schiff sensitivity score = 2
- **Stratum 2:** Maximum Schiff sensitivity score = 3

Within each stratum, subjects will be randomized to test toothpaste, negative control or positive control with 2:2:1 allocation ratio using permuted randomised blocks (see Section 12.1).

5.5 Lifestyle Considerations

If, in the opinion of the investigator or medically qualified designee, a subject has not complied with a study restriction (oral hygiene, dietary or alcohol-related) prior to a study visit or cannot attend a study visit, every effort will be made to reappoint them within the permitted visit tolerances (see Schedule of Activities, Table 1-1). The reason for re-appointment will be documented in the electronic case report form (eCRF).

If re-appointment is not possible, the following visit specific actions should be taken:

- **Baseline (Visit 2):** if the subject cannot be reappointed (within the 2-4 week visit tolerance), they will be withdrawn from the study. No clinical efficacy assessments will be performed. The subject may be replaced.
- **Week 6 (Visit 3):** if the subject cannot be reappointed (within the visit tolerance) the subject will continue in the study. No clinical efficacy assessments will be performed.
- **Week 12 (Visit 4):** if the subject cannot be reappointed (within the visit tolerance), they will be withdrawn from the study. No clinical efficacy assessments will be performed. The subject will not be replaced.

5.5.1 Oral Care Restrictions

For the Duration of the Study: From Screening (Visit 1) to the Subject's Last Study Visit

- Subjects should stop using their own oral care products
- Subjects should not use any other oral care products (e.g., toothpastes, toothbrushes, oral rinses, tongue cleaners, whitening/bleaching products, interdental cleaning products) than those provided during the study.

  Note: *Dental floss can be used but only to remove impacted food.*
- Subjects should not chew gum.

Before a Clinical Assessment Visit: Baseline (Visit 2), Week 6 (Visit 3), Week 12 (Visit 4)

- Subjects will refrain from all oral hygiene procedures for at least 8 hours prior to their appointment (subjects will be sent a WeChat reminder the day before their appointment to remind them of this).

5.5.2 Dietary and Alcohol Restrictions

Before a Clinical Assessment Visit: **Baseline (Visit 2), Week 6 (Visit 3), Week 12 (Visit 4)**

- Subjects must not eat or drink for at least 2 hours before a clinical assessment visit.

  Note: *Small sips of room-temperature water are permitted to take medications or to relieve a dry mouth up to 1 hour before their appointment time*
- Subjects should refrain from excessive alcohol consumption for 24 hours before a clinical assessment visit.

5.5.3 Covid-19

Local Chinese guidelines and/or clinical site requirements will be followed.

5.5.4 Contraception

Given the study products are commercially available toothpastes, regulated as General Goods in China, and no drugs will be utilised in this clinical study, pregnancy testing and contraceptive requirements are not deemed necessary.

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 AEs, 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 and experienced medical/dental personnel or Clinical Research Scientist (CRS) for the study is documented in the Study Contact List located in the investigator site master file held at the study site.

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

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified sponsor 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 study site, and contact details in the event that the study site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Clinical Assessor Qualifications

The examiners responsible for the clinical efficacy measures will be qualified dentists, trained in the clinical assessment of DH (tactile and evaporative (air) sensitivity).

Additional qualified dentists, not trained in the clinical assessment of DH, will be permitted to conduct the oral (OST/OHT) examinations required at each study visit.

6 STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and sponsor 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 Study Product Supplies

The following study products will be supplied by the sponsor's Clinical Supplies Department:

Table 6-1 Study Product Supplies

Product Description	**Test Toothpaste**	**Reference Toothpaste (Positive Control)**	**Reference Toothpaste (Negative Control)**
Product Name**	0.454% w/w SnF_2 toothpaste (Sensodyne Sensitivity & Gum*)	5.0% w/w CSPS toothpaste (Sensodyne Repair & Protect*)	Regular Fluoride toothpaste (Crest Cavity Protection Fresh Lime*)
Fluoride Content	1100 ppm fluoride as SnF_2	1150 ppm fluoride as NaF	1150 ppm ppm fluoride as NaF
MFC	CCI	CCI	N/A
Pack Design	One carton containing 6 over-wrapped tubes of toothpaste		
Dispensing Details	Baseline (Visit 2): One carton		
Product Application	Dose the toothbrush with a strip of toothpaste (a ribbon of toothpaste across the full brush head) on each brushing occasion		
Route of Administration	Topical Oral Use		
Usage Instructions†	Brush the two test teeth first, then the whole mouth (all teeth) for 1-timed minute, twice daily (morning and evening). After brushing, rinse once with 10 ml water using the measuring cup provided.	Brush the whole mouth (all teeth) for 1-timed minute. After brushing, rinse once with 10 ml water using the measuring cup provided.	
Return Requirements	All used/unused samples to be returned		

*Chinese commercial product

† After completing each toothbrushing, subjects will be permitted to clean their tongue using the toothbrush provided (but this is not a study requirement). Tongue brushing must be completed after toothbrushing but before rinsing with 10 ml water.

Table 6-2 Acclimatization Product

Product Description	**Acclimatization Toothpaste**
Product Name	Regular fluoride toothpaste (Crest Cavity Protection Fresh Lime*)
Fluoride Content	1150ppm ppm fluoride as NaF
MFC	N/A
Pack Design	One carton containing 2 over-wrapped tubes of toothpaste
Dispensing Details	Screening (Visit 1): One carton
Product Application	Dose the toothbrush with a strip of toothpaste (a ribbon of toothpaste across the full brush head) on each brushing occasion
Route of Administration	Topical Oral Use
Usage Instructions†	Brush the whole mouth (all teeth) for 1-timed minute. After brushing, rinse once with 10 ml water using the measuring cup provided.
Return Requirements	All used/unused samples to be returned

*Chinese commercial product

† On completing each toothbrushing, subjects will be permitted to clean their tongue using the toothbrush provided (but this is not a study requirement). Tongue brushing must be completed after toothbrushing but before rinsing with 10 ml water.

Table 6-3 Sundry Items

Sundry Items to be supplied:

Item	**Supplied By**	**Pack Design**	**Dispensing Details**	**Return/Disposal Details**	
				Used Samples	**Unused Samples**
Lion Thin Bristle toothbrush (Chinese commercial product)	Sponsor or designated vendor	Commercial pack	**Screening (Visit 1):** One toothbrush **Baseline (Visit 2):** One toothbrush **Week 6 (Visit 3):** One toothbrush	Destroy at site using site disposal procedures	Return to sponsor
Countdown timer		Commercial pack containing 1 timer	**Screening (Visit 1)**	Subject to keep or destroy at site using site disposal procedures	
Measuring cups		N/A	**Screening (Visit 1):** 4 cups **Baseline (Visit 2):** 12 cups		
Opaque plastic bags		N/A	**Screening (Visit 1):** One bag **Baseline (Visit 2):** One bag		

For further information, please refer to the Global Clinical Supplies Packaging and Labelling Proposal. The sponsor will ensure copies of the diary (including toothpaste usage instructions), clinical assessment score sheets and Subject Contact Cards are provided to the study site.

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

6.1.1 Dosage Form and Packaging

All study products (test, negative control, positive control and acclimatization products) are toothpastes, intended for topical oral use, and will be applied using a manual toothbrush. All will be sourced in China.

All toothpastes will be provided to the clinical study site in their commercial packs, overwrapped in white vinyl (to mask their identity and obscure any branding) with a study label affixed. The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the sponsor's Global Clinical Supplies Department. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

Each subject will receive sufficient tubes of the acclimatization toothpaste and their assigned study toothpaste to cover usage during the acclimatization and treatment periods, respectively. 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 to ensure 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 over-wrapping or 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 Product Dispensing

Subjects will be assigned to study product in accordance with the randomization schedule generated by a sponsor-approved vendor, prior to the start of the study, using validated software.

The product dispensing area will be separate from the clinical examination area. Study toothpastes will be dispensed per protocol in blinded fashion to the subject, by trained study personnel. These staff members will not be involved in any safety or clinical efficacy assessments or any other aspect of the study that could be influenced by knowing which product a subject has been assigned to. An additional member of the study staff will verify the dispensing procedure has been completed accurately for each 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 eCRF.

6.2 Administration

Subjects will self-administer the acclimatization toothpaste (from Visit 1 to Visit 2) and their assigned study toothpaste (from Visit 2 to Visit 4) according to the usage instructions provided by study personnel at the study site and record each brushing in their diary.

To help ensure subjects fully understand the amount of toothpaste to use, the brushing instructions and how to complete the diary:

- **Screening (Visit 1):** Staff will demonstrate dispensing a full ribbon of toothpaste along the length of the toothbrush head to each qualifying subject and supervise their first brushing with the acclimatization toothpaste/diary completion at the end of the visit, after all clinical assessments have been completed.
- **Baseline (Visit 2):** Staff will check the dispensing of a full ribbon of toothpaste by each randomized subject and supervise the first brushing with their assigned study toothpaste/diary completion. Staff will clearly show subjects randomized to test toothpaste the location of their 2 test teeth prior to starting their supervised brushing.
- **Week 6 (Visit 3):** Staff will supervise each subject brushing with their assigned study toothpaste/completing their diary at the end of the visit, after all clinical assessments have been completed.

On-site administration of study products will be recorded in the dispensing log and the eCRF.

6.2.1 Product Dosing Errors

In this study, dosing errors may result from the administration or consumption of the wrong product, by the wrong subject, in the wrong way. Such dosing errors should be captured in the eCRF. Dosing errors are reportable irrespective of the presence of an associated AE, including:

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

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

6.2.2 Overdose

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

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

6.3 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 labels.

Site systems must be capable of measuring and documenting (e.g., via a log), at a minimum, the daily minimum and maximum temperatures for all site storage locations, as applicable (including frozen, refrigerated, and/or room-temperature products). This should be captured

from the time of first product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device/storage unit (e.g., 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 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 by authorized site staff only to subjects enrolled in the study in accordance with the protocol.

The 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 toothpaste to the study site at their Baseline visit (Visit 2). Subjects will bring the used and unused tubes of their assigned study toothpaste to each of their scheduled visits to the study site, per the Schedule of Activities (Table 1-1); all study products will be returned at study conclusion. Study product return will be documented using the 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 Study Product Supplies

At the end of the study, the investigator, or an appropriate designee, and a representative of the sponsor (study monitor) will inventory all used and unused study products and sundry items. The 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 sponsor's 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 the sponsor in time for study close out visit.

6.5 Blinding and Allocation/Randomization

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

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

This study is described as examiner-blind (clinical examiners will be blinded to product received). Subjects, site staff, study statistician(s), data management staff, other employees of the Sponsor (including the CRS) and vendors acting on behalf of the sponsor, who may influence study outcomes will also be blinded to product allocation. The monitors and the sponsor's Clinical Study Manager cannot be fully blinded as they will observe subjects brushing with their allocated study product while at the study site. As a matter of study conduct, including emergency unblinding events, only the investigator may learn the contents of one or more of the product codes used to allocate study product, not the clinical examiners. Given the application of IRT within this study, any such knowledge will not affect the decision to enroll a subject or influence the order in which subjects are enrolled.

To ensure the clinical examiners remain blinded throughout the study:

- Site staff involved in the dispensing of study products and supervision of on-site brushing will work in a separate area and will not be involved in any safety or product efficacy assessments.
- Clinical examiners will not be permitted in any area where study product or diaries are stored, dispensed, or in use.
- Subjects will be instructed not to remove their study product or diary from its opaque carrier bag outside of the dispensing room, while at the study site.
- Subjects will be instructed not to discuss which study product they have been assigned or usage instructions with the clinical examiners.

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 the eCRF, 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 Institutional Review Board (IRB) if the blind is broken.

6.7 Compliance

To facilitate compliance with product usage, subjects will be provided with a diary at Screening (Visit 1), at Baseline (Visit 2) and Week 6 (Visit 3) to record each brushing with the acclimatization toothpaste and their assigned study product, respectively.

- The diaries will provide detailed usage instructions for the subject to refer to throughout their participation in the study.
- Subjects will be instructed to note any missed/additional brushings, the reasons for any missed/additional brushings, any issues with the toothpaste used, oral problems, illnesses and any new medications/treatments in their diaries.
- Completed diaries will be reviewed by study staff at the start of each study visit. Any missed or additional brushings will be captured in the eCRF as protocol deviations. Subjects will be re-instructed in correct product usage requirements/diary completion, as needed.

Information recorded in the diary relating to changes in health and medications/ treatments will be reviewed by the investigator, or medically qualified designee, with the subject and transcribed into the eCRF, as appropriate (e.g., as an AE). Information related to product use should also transcribed into the eCRF, as appropriate, taking care to maintain the blind.

Subjects will be instructed to bring all tubes of toothpaste provided (used and unused) to each study visit. Study staff will perform a visual check of product usage. Any suspected over or under use will be documented in the eCRF and the subject will be re-instructed in the correct usage requirements.

To confirm subjects understood the usage instructions provided at Screening (Visit 1), they will be asked to record 2-4 brushings (one per week) during the 2-4 week acclimatisation period using their smartphone video. At Baseline (Visit 2), a designated member of the study team will check these videos to confirm compliance with the usage requirements against a checklist (Appendix 15.3). Any subjects who rinse with water during brushing with the acclimatisation toothpaste will be excluded; subjects deemed non-compliant with any other aspect of study usage requirements will be re-instructed in correct product usage.

Supervised brushings will be carried out at the study site at the end of each study visit to facilitate compliance with usage instructions. If any deviations from per protocol product usage are observed, the subject will be re-instructed of correct product usage.

Subjects will be sent reminders on WeChat to adhere to study lifestyle restrictions every 2 weeks for the duration of the study.

6.8 Concomitant Medications/Treatments

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

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

For the Duration of the Study: Screening (Visit 1) to Subject's Last Study Visit

- Subjects should delay any non-emergency, elective dental treatments until after study completion (including dental prophylaxis).
- Should a randomized subject start a course of treatment which includes daily, regular or intermittent use of any medication, details of that medication/treatment will be recorded in the eCRF. The investigator, or their medically qualified designee, will decide if the subject can continue on the study or should be withdrawn.
- Should a subject take a medication which, in the opinion of the investigator or their medically qualified designee, could impact the subject's perception of DH (e.g., an analgesic) within 8 hours of a scheduled study visit, the medication should be recorded in the eCRF and every effort will be made to reappoint them within permitted visit tolerances (see Schedule of Activities, Table 1-1). The reason for re-appointment will be documented in the eCRF.

If re-appointment is not possible, the following visit specific actions should be taken:

- **Screening (Visit 1):** the subject will be withdrawn from the study. No tooth sensitivity assessments will be performed. The subject may be replaced.
- **Baseline (Visit 2):** the subject will be withdrawn from the study. No tooth sensitivity assessments will be performed. The subject will not be replaced.
- **Weeks 6 & 12 (Visits 3 & 4):** the subject will continue in the study. Tooth sensitivity assessments will be performed.

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

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

- Protocol violation that may impact the subject's safety
- Inability of the subject to comply with the protocol-required schedule of study visits, procedures or lifestyle considerations
- Withdrawal of informed consent
- Subject lost to follow-up
- Unblinding of the subject
- Pregnancy

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

7.2 Lost to Follow up

If a subject fails to return to the site for a required study visit, the site must attempt to contact the subject and reschedule the missed visit as soon as possible, 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 they repeatedly fail to return for scheduled visits and cannot 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). All contact attempts should be documented in the eCRF. If contact is made, the investigator or designee should inquire about the reason for withdrawal, request that the subject return all study products provided and, if appropriate, request the subject return for a final visit and follow-up with the subject regarding any unresolved AEs.

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion, which may include an oral examination.

Should the subject be unreachable, they 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 provided 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 (Table 1-1).

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

8.1 Visit 1/Screening

The following procedures and assessments will be completed by the investigator, or a suitably qualified/experienced designee, and the clinical examiners, 14-28 days prior to randomisation to study product. Where practically feasible, they should be completed in the order listed below. Data collected will be recorded in the eCRF.

8.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in the study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Study information will be communicated to the subjects by the investigator, or designee, and by interactive video which will also be sent to the subjects via WeChat for their own reference. After signing the ICF, subjects will be asked to complete a knowledge check (a quiz) to ensure key information and study expectations are understood. If the subject answers one or more questions incorrectly, the study information will be re-explained and the subject

will be asked to complete knowledge check again. If subjects are not able to understand the study information, they will be excluded.

A list of ingredients in the toothpastes to be used during the study will be provided to each subject during the consent process to enable them to confirm they are not aware of any allergy or hypersensitivity to any of the ingredients listed.

The investigator, or designee, must 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 consent will be provided by either the investigator or the sponsor. Two copies of the ICF will be signed and dated by the subject; the subject will retain one copy, the other will be kept at site. The time the ICF was signed by the subject will be recorded on the ICF; AEs will be captured from that time. The investigator, or designee, will sign and date each copy of the ICF after the subject has signed to confirm that the consent process was completed correctly. The date and time subject received the ICF and signed the ICF will be recorded in the eCRF.

If new information becomes available during the course of the study that could affect willingness to participate, each participating subject will receive a copy of the new information and be re-consented into the study (2 copies as before). Each subject will be provided with a copy of the signed and dated amended consent form. The date and time of re-consent will be recorded in the eCRF.

After signing the ICF, subjects will undergo the screening assessments to confirm they meet the subject selection criteria for the study. If the subject is confirmed eligible by the investigator or designee to participate, the subject will be considered enrolled in the study.

8.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, sex (male or female) and race.

8.1.3 Check of the WeChat Application

Subjects will be also asked to show study staff their mobile phone to confirm the WeChat application is installed. Subjects who do not have WeChat and are not willing to install it while at the study site will be excluded.

8.1.4 DH Screening Questionnaire

Subjects will complete a screening questionnaire (Appendix 15-2) to confirm self-reported DH symptoms. Subjects who report experiencing DH symptoms only ‘several times a month’, ‘once a month’ or ‘less than once a month’ will be excluded from the study.

8.1.5 Review of Oral Care Products

Subjects will be required to bring their current oral care products to the Screening visit for study staff to confirm the absence of known anti-sensitivity ingredients and DH relief claims on the packaging. Presence/absence of fluoride will also be documented in the eCRF.

Subjects who are currently using anti-sensitivity oral care product(s) will be excluded.

Subjects will also be asked about the oral care products they have been using in the last 8 weeks; those who report using anti-sensitivity product(s) in the previous 8 weeks will also be excluded.

8.1.6 Review of Brushing Habits

Subjects will be asked to describe their typical oral care routine. Subjects who habitually rinse with water during toothbrushing will be excluded.

8.1.7 Medical History and Prior Medication/Treatment

The following will be documented in the eCRF:

- Details of relevant medical history and recent surgery (within the last year), including allergies and drug sensitivities.
- Pregnancy status (self-reported by female subjects only).
- Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days.

8.1.8 Clinical Examinations and Assessments

Prior to commencing the clinical examinations and assessments, subjects will be shown how to complete a VAS (Section 9.1.3).

The following clinical examinations will be completed as described in Study Assessments and the findings recorded in the eCRF. To facilitate subject flow, source documents can be used to record the eligible teeth and DH assessments for later transcription into the eCRF (transcription from source documents must be completed within 5 days of recording the data for each subject).

- OST examination
- OHT examination
- Clinical assessment of incisors, canines and pre-molars for dentition exclusions, EAR, MGI (adjacent to the test area only) and clinical mobility to identify eligible teeth for DH assessment (as described in Section 9.1).
- Clinical assessment of tactile sensitivity (tactile threshold (g)) for each eligible tooth (no dentition exclusions, presence of EAR, MGI = 0 adjacent to the test area only, clinical mobility = 0).
- Clinical assessment of evaporative (air) sensitivity (Schiff sensitivity score [examiner assessed], followed by VAS [subject completed]) for each eligible tooth with a tactile threshold of ≤ 20g.

  There should be at least a 5-minute break between completing the tactile assessments and starting the evaporative (air) assessments.

To prepare for the Baseline visit, the clinical examiners will confirm those teeth which are eligible for ongoing DH assessment at Baseline (Visit 2).

- **'Eligible teeth identified at Screening' (Table 4-1):** incisors, canines and pre-molars with none of the study-specific dentition exclusions, which meet EAR, MGI adjacent to the test area only and mobility inclusion criteria, and record a qualifying tactile threshold of ≤ 20 g and a qualifying Schiff sensitivity score of ≥ 2 at Screening (Visit 1).

8.1.9 Inclusion/Exclusion Criteria

Information relating to all inclusion and exclusion criteria will be completed in the eCRF.

8.1.10 Subject Eligibility

The investigator, or medically qualified designee, will review the inclusion/exclusion criteria to confirm subject eligibility to participate in the study; this will be documented in the eCRF.

Note: In addition to meeting all other study requirements, only those subjects with a minimum of two eligible teeth with a qualifying tactile threshold ≤ 20 g and a qualifying Schiff sensitivity score ≥ 2 can continue on the study.

To prepare for study participation, enrolled subjects will be instructed in the Lifestyle Guidelines and Concomitant Medications/Treatments requirements of the study (as already detailed in the ICF and described during the consent process). Adherence to the requirements of the study protocol is essential for successful study conduct.

8.1.11 Supervised Brushing with Acclimatization Toothpaste

Enrolled subjects will be provided with the acclimatization toothpaste, a toothbrush, a timer, rinsing cups and a diary to use during the acclimatization period.

Staff will describe the toothpaste usage instructions to the subject and demonstrate covering the full brush head with a ribbon of toothpaste. Staff will then supervise the subject carrying out first their first brushing with the acclimatization toothpaste and recording the first use in their diary.

Any deviation from the product usage instructions will be captured as a protocol deviation in the eCRF and the subject will be reminded of the correct directions for use. Dispensing of the acclimatization toothpaste and completion of the supervised first brushing will also be documented in the eCRF.

Spontaneously reported AEs, and any AEs elicited by asking subjects to respond to a non-leading question, such as 'How do you feel?', on completion of the supervised brushing with the acclimatization toothpaste will be recorded in the eCRF.

Staff will remind subjects to bring their acclimatisation products to their next study visit and to note any changes in health, medications or treatments in their diary (or report such changes to study staff between visits using the contact numbers provided or inform the staff at their next visit, if preferred).

8.2 Study Period

8.2.1 Visit 2 (Baseline/Day 1)

The following procedures and assessments will be completed by the investigator, or a suitably qualified/experienced designee and the clinical examiners. Where practically feasible, they should be completed in the order listed below. All data collected should be recorded in the eCRF.

8.2.1.1 Compliance Checks

Complete visual checks of returned acclimatization toothpaste, review completed diary and watch the brushing videos (using the Video Compliance Checklist (Appendix 15.3) to help determine compliance). Subjects seen to rinse with water while brushing with the acclimatization toothpaste during review of their brushing compliance videos will be excluded.

Record any suspected over or under use and the number of any missed or additional brushings in the eCRF. Any deviation from the product usage instructions or missed brushing videos will be captured as protocol deviations in the eCRF and subjects will be re-instructed in the correct directions for use.

Do not return the acclimatization toothpaste, toothbrush or completed diary to the subject.

8.2.1.2 Changes in Medical History and Concomitant Medications/Treatments

Staff will ask subjects if there have been any changes in their health, concomitant medications and non-drug treatments/procedures. All changes will be documented in the eCRF.

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 eCRF.

Any AEs and/or changes in medications/treatments identified during review of the completed diary will also be recorded in the eCRF.

8.2.1.3 Subject Adherence and Continuance

Confirm subject adherence to the requirements of the protocol and document their continuance in the eCRF. Record any deviations from study requirements in the eCRF.

8.2.1.4 Clinical Examinations and Assessments

Prior to commencing the clinical examinations and assessments, subjects will be reminded how to complete a VAS (Section 9.1.3).

The following clinical examinations will be completed as described in Study Assessments and the findings recorded in the eCRF. To facilitate subject flow, source documents can be used to record the DH assessments for later transcription into the eCRF (transcription from source documents must be completed within 5 days of recording the data for each subject).

- OST examination
- Clinical assessment of tactile sensitivity (tactile threshold (g)) for each ***eligible tooth identified at Screening*** (eligibility criteria described in Section 8.1.8 and Table 4-1).
- Clinical assessment of evaporative (air) sensitivity (Schiff sensitivity score [examiner assessed], followed by VAS [subject completed]) for each eligible tooth identified at Screening with a Baseline tactile threshold of ≤ 20g.

  There should be at least a 5-minute break between completing the tactile assessments and starting the evaporative (air) assessments.

Subjects must have at least two eligible teeth with the qualifying tactile threshold ≤ 20 g and qualifying Schiff sensitivity score ≥ 2 at both Screening and Baseline, and VAS ≥ 40 mm at Baseline to continue.

8.2.1.5 Selection of Test Teeth

The procedure for selecting test teeth is summarised in Table 4-1

The clinical examiner responsible for 'Schiff' assessments will examine all qualifying teeth both at Screening and Baseline to identify two 'test teeth' for DH assessment at subsequent study visits. The identity of the two test teeth will be recorded in the eCRF. Subjects with fewer than two suitable test teeth will be discontinued.

- Test teeth can only be selected from eligible teeth with the 'qualifying' levels of DH:
  - Tactile threshold ≤ 20 g at Screening (Visit 1) and Baseline (Visit 2).
  - Schiff sensitivity score ≥ 2 at Screening (Visit 1) and Baseline (Visit 2).
  - VAS ≥ 40 mm at Baseline (Visit 2).
- Each test tooth must have the same Schiff sensitivity score at Screening and Baseline.

Screening Schiff sensitivity score = 2 and **Baseline** Schiff sensitivity score = 2
OR
Screening Schiff sensitivity score = 3 and **Baseline** Schiff sensitivity score = 3

8.2.1.6 Subject Eligibility

The investigator, or medically qualified designee, will review the inclusion/exclusion criteria and verify the presence of two test teeth which meet all study criteria before confirming each subject's suitability to continue in the study; eligibility will be documented in the eCRF.

8.2.1.7 Stratification and Randomization

Eligible subjects will be stratified to one of two strata as described in Section 5.4. Subject stratum will be entered directly into the eCRF. 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. The randomized toothpaste code will be entered directly into the eCRF.

8.2.1.8 Supervised Brushing with Study Toothpaste

Randomised subjects will be provided with their allocated study toothpaste, a new toothbrush, more rinsing cups and a new diary.

Toothpaste usage instructions will be re-described, and those subjects randomized to the test toothpaste will be shown the location of their two 'test teeth' within the mouth (using a tooth diagram/model and a mirror, as appropriate). Staff will then supervise the subject carrying out first the first brushing with their study toothpaste and recording the first use in their diary. A brushing video will be also shared with the subjects via WeChat according to their allocated study toothpaste.

Any deviation from the product usage instructions will be captured as a protocol deviation in the eCRF and the subject will be reminded of the correct directions for use. Dispensing of study toothpaste and completion of the supervised first brushing will also be documented in the eCRF.

Spontaneously reported AEs, and any AEs elicited by asking subjects to respond to a non-leading question, such as 'How do you feel?', on completion of the supervised brushing with the study toothpaste will be recorded in the eCRF.

Randomized subjects will be re-instructed of the Lifestyle Guidelines and Concomitant Medications/Treatments requirements of the study. Staff will remind them to bring their study products to their next study visit and to note any changes in health, medications or treatments in their diary (or report such changes to study staff between visits using the contact numbers provided or inform the staff at their next visit, if preferred).

8.2.2 Visit 3 (Week 6/Day 43 ± 4) and Visit 4 (Week 12/Day 85 ± 4)

The following procedures and assessments will be completed by the investigator, or a suitably qualified/experienced designee and the clinical examiners. Where practically feasible, they should be completed in the order listed below. All data collected should be recorded in the eCRF.

8.2.2.1 Compliance Checks

Complete visual checks of returned study toothpaste and review completed diary. Record any suspected over or under use and the number of any missed or additional brushings in the eCRF.

Any deviation from the product usage instructions will be captured as protocol deviations in the eCRF and subjects will be re-instructed in the correct directions for use.

Week 6 (Visit 3): *Return the study toothpaste to the subject; retain the used toothbrush and completed 'Week 6' diary at site. Dispense new diary card and new toothbrush.*

Week 12 (Visit 4): *Retain the study toothpaste, toothbrush and completed 'Week 12' diary.*

8.2.2.2 Changes in Medical History and Concomitant Medications/Treatments

Staff will ask subjects if there have been any changes in their health, concomitant medications and non-drug treatments/procedures. All changes will be documented in the eCRF.

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 eCRF.

Any AEs and/or changes in medications/treatments identified during review of the completed diary will also be recorded in the eCRF.

8.2.2.3 Subject Adherence and Continuance

Confirm subject adherence to the requirements of the protocol and document their continuance in the eCRF. Record any deviations from study requirements in the eCRF.

8.2.2.4 Clinical Examinations and Assessments

Prior to commencing the clinical examinations and assessments, subjects will be reminded how to complete a VAS (Section 9.1.3).

The following clinical examinations will be completed as described in Study Assessments and the findings recorded in the eCRF. To facilitate subject flow, source documents can be used to record the DH assessments for later transcription into the eCRF (transcription from source documents must be completed within 5 days of recording the data for each subject).

- OST examination
- **Week 12 (Visit 4) only:** OHT examination
- Clinical assessment of tactile sensitivity (tactile threshold (g)) **for the two test teeth only**.
- Clinical assessment of evaporative (air) sensitivity (Schiff sensitivity score, followed by VAS) **for the two test teeth only**.

There should be at least a 5-minute break between completing the tactile assessments and starting the evaporative (air) assessments.

8.2.2.5 Supervised Brushing with Study Toothpaste

Week 6 (Visit 3) only:

Subjects will be provided with a new toothbrush and a new diary; staff will supervise each subject completing another on-site brushing with their study toothpaste and recording this use in their diary.

Any deviation from the product usage instructions will be captured as a protocol deviation in the eCRF and the subject will be reminded of the correct directions for use. Completion of the 'Week 6' supervised brushing will also be documented in the eCRF.

Spontaneously reported AEs, and any AEs elicited by asking subjects to respond to a non-leading question, such as 'How do you feel?', on completion of the supervised brushing with the study toothpaste will be recorded in the eCRF.

Subjects will be re-instructed of the Lifestyle Guidelines and Concomitant Medications/ Treatments requirements of the study. Staff will remind them to bring their study products to their next study visit and to note any changes in health, medications or treatments in their diary (or report such changes to study staff between visits using the contact numbers provided or inform the staff at their next visit, if preferred).

Week 12 (Visit 4) only:

No supervised brushing.

8.3 Study Conclusion

The Study Conclusion page of the eCRF will be completed for all subjects whether or not they complete all study procedures (e.g., if they are discontinued from the study early). If the subject is discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page.

For subjects who attend all study visits, the Study Conclusion page of the eCRF will be completed at Visit 4. Staff will remind each subject to inform the site if they experience any change in health, medications or treatments in the next 5 days (i.e., in the 5 days following their last use of study product).

If a subject has any clinically significant, study-related abnormalities or AEs at the end of the study, the sponsor's 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.

8.4 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). At the discretion of the investigator, or medically qualified designee, additional oral examinations may be carried out at such visits.

9 STUDY ASSESSMENTS

Every effort should be made to ensure the protocol-required examinations and assessments are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the investigator's control, that may make it unfeasible to complete an

examination or 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 examination or assessment cannot be performed, the investigator (or designee) will document the reason for the missed procedure as a protocol deviation and any corrective and preventative actions they have taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed examinations or assessments in a timely manner.

9.1 Screening Assessments

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

The eligibility of each tooth will be assessed against the inclusion/exclusion criteria and recorded in the eCRF.

9.1.1.1 Erosion, Abrasion and Recession (EAR)

The facial surfaces of all incisor, canine and pre-molar teeth (Figure 9-1) that do not present any of the general dentition exclusion criteria, or specific dentition exclusion criteria for eligible teeth, will be examined for signs of cervical EAR (Addy, 2000).

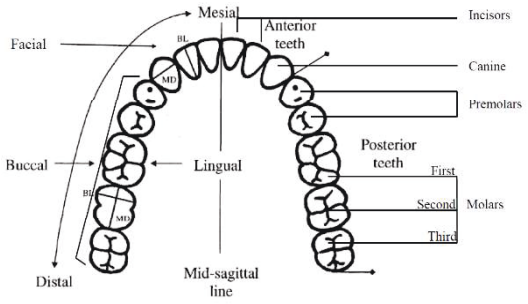

Figure 9-1 Dental Nomenclature. (Dempsey and Townsend, 2001)

9.1.1.2 Modified Gingival Index (MGI)

The MGI is a non-invasive visual assessment of gingival health (Lobene, 1986). MGI will be assessed for incisor, canine and pre-molar teeth exhibiting none of the dentition exclusions and facial/cervical EAR. MGI should be scored for the facial gingiva, directly adjacent to the area of exposed dentine (i.e., the test area) only.

Eligible teeth will have a MGI of zero (0) directly adjacent to the test area.

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, oedema, and/or hypertrophy of the marginal or papillary gingival unit.
4	Severe inflammation; marked redness, oedema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

9.1.1.3 Clinical Mobility

Clinical mobility will be assessed for incisor, canine and pre-molar teeth exhibiting none of the dentition exclusions, with facial/cervical EAR and a MGI = 0 adjacent to the test area only, using a modification of the Miller Index (Laster, 1975).

Eligible teeth will have clinical mobility = 0.

Degree	Description
0	No movement or mobility of the crown of the tooth < 0.2mm in a horizontal direction
1	Mobility of the crown of the tooth 0.2 - 1mm in a horizontal direction
2	Mobility of the crown of the tooth exceeding 1mm in a horizontal direction
3	Mobility of the crown of the tooth in a vertical direction as well.

9.1.2 Qualifying Tactile Sensitivity

The tactile sensitivity of incisor, canine and pre-molar teeth (Figure 9-1) exhibiting none of the dentition exclusions, and meeting the EAR, MGI (adjacent to the test area only) and clinical mobility criteria, will be assessed using a constant pressure probe (Yeaple probe (Polson et al., 1980). 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 of the tactile stimulus, the subject will be asked to indicate whether they experienced any pain or discomfort. The examiner will tell the subject to only respond 'yes' if they feel PAIN or DISCOMFORT when the probe is applied to their tooth. 'Yes' and 'no' are the only acceptable answers. The subject may respond 'yes' if they feel pressure. The examiner will remind them, as needed, that they will feel pressure each time the probe is in contact with the tooth but they should only respond 'yes' if they feel pain or discomfort. The gram setting which elicits the two consecutive 'yes' responses will be recorded as the tactile threshold (g) in the source document. At Screening, the upper force setting will be 20g.

- **For a tooth to qualify at Screening, it must have a tactile threshold ≤ 20g.**
- **If no sensitivity is found at the upper force setting, the tactile threshold will be recorded as > 20g and the tooth will be disqualified from further testing.**

If a subject fails to give a definite answer, the examiner will re-prompt them to provide a 'yes' or 'no' response. If their uncertainty continues, this should be recorded on the source document. and the next stimulus should be at the next step in the upward direction. If the subject continues to be unsure, or the examiner is unsure of the reliability of their response, the examiner may opt to re-probe at the same force setting (indicated to the scribe by a non-verbal signal, e.g., a hand gesture) or move to the next force setting (10g increase). If the examiner considers the subject's 'yes' response may be between gram settings, a conservative approach should always be adopted, and the lower (more 'severe') tactile threshold (g) recorded.

The examiner will generally make the force setting adjustments (this can also be done by an assistant/scribe); the scribe will record the micro-amperage setting and subject's responses in the source document.

Calibration of the Yeaple Probe:

The Yeaple probe will be calibrated by an appropriately trained member of the study staff (typically the clinical examiner or their assistant/scribe) before use on each day subjects are

assessed. The microamp settings may vary from day to day (partly due to battery power consumption), but the difference should not be significant. Thus, previous probe settings can serve as a guide. Calibration should start at the lowest microamp setting and then increase. Either calibration method described below is acceptable.

- **Method 1 ('Water Cup'):** The Yeaple probe is fixed to a clamp attached to a ring stand so that the probe tip is vertical. A small paper cup attached with cotton thread is balanced over the end of the Yeaple probe, without the probe tripping. The probe dial is set to the microamp setting and water is fed into the paper cup using a dropper until the probe trips. The gram setting is recorded and the Yeaple probe reset to the next microamp value. The procedure is repeated until data has been collected to more than 80 g.
- **Method 2:** The Yeaple probe is fixed to a clamp attached to a ring stand so that the top is perpendicular to the pan of an ohaus dial-o-gram® balance or equivalent. The probe tip is positioned to just touch the pan when the balance is set at zero grams. The probe dial is set to the microamp setting and the gram setting is increased on the balance until the probe trips. The gram setting is recorded and the Yeaple probe reset to the next microamp value.

The data are plotted, and the points connected with line segments in order to interpolate the micro-amp values equivalent to 10, 20, 30, 40, 50, 60, 70 and 80 g. This calibration should be repeated three times, and the average of the three used for the day's settings. The settings will be recorded on the Yeaple probe calibration record (along the probe's serial number) which will serve as the force setting guide for that day's examinations.

9.1.3 Qualifying Evaporative (Air) Sensitivity

Evaporative (air) sensitivity will be assessed on the facial surfaces of incisor, canine and pre-molar teeth (Figure 9-1) which exhibit none of the dentition exclusions, and meet the EAR, MGI (adjacent to the test area only), clinical mobility and tactile threshold (≤ 20g) criteria. Assessment will start a minimum of 5 minutes after the tactile assessments have completed. The assessment will be made by directing a 1-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.

Subject response to the 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. The scale focuses on a combination of specific, observable, physical, behavioural and verbal responses from the subject, which may facilitate discrimination.

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 the clinical examiner assesses the subject response to be between scores, a conservative approach should always be adopted, and the higher (more 'severe') score recorded.

After the clinical examiner has communicated each Schiff sensitivity score to the scribe (non-verbally), the subject will rate the intensity of their response to the evaporative (air) stimulus using a 100 mm VAS (example below). The clinical examiner and the subject should be blinded to their respective scores.

0
No discomfort

100mm (not to scale)
Extreme discomfort
(worst imaginable)

A trained member of staff will measure the distance (mm) from zero (0) to the left of the line marked by the subject and record this value in the eCRF.

- **For a tooth to qualify at Screening, it must have a tactile threshold ≤ 20g and a Schiff sensitivity score ≥ 2.**
- **If Schiff sensitivity score = 0 or 1, the tooth will be disqualified from further testing** (the subject's VAS response will still be recorded)**.**

9.2 Dentine Hypersensitivity Efficacy Assessments

The following product efficacy assessments will be performed by appropriately trained clinical examiners (who are blind to product received), at the times and in the order defined in the Study Procedures section of this protocol.

The same examiner will be responsible for a given DH assessment (tactile or evaporative (air) sensitivity) throughout the study (Visit 1 to Visit 4).

9.2.1 Tactile Sensitivity Assessment (Yeaple Probe)

Baseline (Visit 2):

The tactile sensitivity of all ***eligible teeth identified at Screening*** (Visit 1) will be assessed for all enrolled subjects. The tactile stimulus will be administered, and subject response recorded as described in Section 9.1.2. At Baseline, the upper force setting will be 20g.

- **For a tooth to 'qualify' at Baseline, it must have a tactile threshold ≤ 20g.**
- **If no sensitivity is found at the upper force setting, the tactile threshold will be recorded as > 20g and the tooth will be disqualified from further testing.**

Note: '*Eligible teeth identified at Screening*' are defined as incisors, canines and pre-molars with none of the study-specific dentition exclusions, which meet the EAR, MGI (adjacent to the test area only) and mobility inclusion criteria, and record a qualifying tactile threshold of ≤ 20g and a qualifying Schiff sensitivity score of ≥ 2 at Screening (Visit 1).

Week 6 (Visit 3) & Week 12 (Visit 4):

The tactile sensitivity of the two test teeth identified by the clinical examiners at Baseline (Visit 2) will be assessed for all randomized subjects. The tactile stimulus will be administered, and subject response recorded as described in Section 9.1.2.

At Week 6 and Week 12, the upper force setting will be 80g. The gram setting, which elicits two consecutive 'yes' responses, will be recorded as the tactile threshold (g). If no sensitivity is found, the tactile threshold should be recorded as >80g.

9.2.2 Evaporative (Air) Sensitivity Assessments

Baseline (Visit 2):

The evaporative (air) sensitivity of all ***eligible teeth identified at Screening*** (Visit 1), with a Baseline tactile threshold ≤ 20g, will be assessed for all enrolled subjects. The evaporative (air) stimulus will be administered, and subject response (Schiff sensitivity score, followed by VAS) recorded as described in Section 9.1.3. Assessment will start a minimum of 5 minutes after the tactile assessments have completed.

- **For a tooth to 'qualify' at Baseline, it must have a tactile threshold ≤ 20g, a Schiff sensitivity score of ≥ 2 and a VAS ≥ 40 mm.**
- **If Schiff sensitivity score is < 2, the tooth will be disqualified from further testing.**

Week 6 (Visit 3) & Week 12 (Visit 4):

The evaporative (air) sensitivity of the two test teeth identified by the clinical examiners at Baseline (Visit 2) will be assessed for all randomized subjects. The evaporative (air) stimulus will be administered, and subject response (Schiff sensitivity score, followed by VAS) recorded as described in Section 9.1.3 .

9.3 Safety and Other Assessments

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

9.3.1 Oral Soft Tissue (OST) Examination

The OST examination will be accomplished by direct observation and palpation, using retraction aids as appropriate, and will include examination of the labial mucosa (including lips), buccal mucosa, mucogingival folds, gingival mucosa, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands. The results of the examination will be recorded in the eCRF as either 'normal' or 'abnormal'; details of any abnormalities will be documented in the eCRF.

Any observation that changes from 'normal' to 'abnormal', or worsens, from the OST examination completed at Screening will be recorded as an AE.

9.3.2 Oral Hard Tissue (OHT) Examination

The OHT examination will be accomplished by direct observation, using retraction aids as appropriate, and will identify enamel irregularities, tooth fractures, 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 irregularities (e.g., hypo/hypermineralisation, decalcification) and significant tooth staining. Observations will be listed as 'absent' or 'present'; conditions noted as 'present' will be described in the eCRF. Any observation that changes from 'absent' to 'present', or worsens, from the OHT examination completed at Screening will be recorded as an AE.

The presence of any implants, fixed or removable dentures, fixed or removable orthodontic braces/bands, fixed orthodontic retainers, full crowns or veneers will be recorded, along with evidence of gross intra-oral neglect or the need for extensive dental therapy.

The OHT examination is also used to assess the dentition against the general and specific dentition exclusions described in Section 5.3 (Exclusion Criteria 25, 26, 27, 28 and 29 a) to f)).

9.3.3 Pregnancy

This clinical study will evaluate toothpastes classified as general goods in China. Sponsor studies in which no drug is utilized do not require pregnancy testing.

Female subjects will provide verbal confirmation of pregnancy status at Screening (Visit 1) and will be asked to inform study staff immediately should this change at any point during the study.

Female subjects who are pregnant or intending to become pregnant during the study (self-reported) will be excluded.

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

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

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

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

- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

10.3 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 study procedure).

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

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

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 they consider 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 AEs and those elicited by asking subjects to respond to non-leading question, such as 'How do you feel?', will be assessed and any AEs recorded in the eCRF 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 eCRF and all details relating to an SAE in the paper SAE Form provided.

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

There may be instances when copies of medical records for certain cases are requested by the sponsor. 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 the sponsor.

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, were known, and not the individual signs/symptoms. (e.g., upper respiratory tract infection, seasonal allergy, etc. not cough, runny nose).

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

10.4.1 Reporting of an Adverse Event

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

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE eCRF screen, an SAE form should be completed, as fully as possible. Hard copies of the paper SAE form will be provided in the investigator site master file. Original SAE forms will be retained in the investigator site 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 sponsor 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 Case Management Group mailbox PPD ,with copy to the appropriate sponsor Study Manager, 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 initial report will be followed up with more information as relevant, or as requested by the sponsor study manager. The sponsor's Study Manager will be responsible for forwarding the SAE form to other sponsor personnel as appropriate.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

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

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

10.5.2 Assessment of Causality

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

For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE eCRF screen and the paper SAE form (subject to the classification of the AE). The investigator will also document in the medical notes that they have 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 their 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 they have 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 eCRF, 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 the sponsor. **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 the sponsor.** The investigator may change their 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 the sponsor 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 eCRF screen and on the paper SAE form (subject to the classification of the AE).

The investigator will submit any updated SAE data to the sponsor 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 the sponsor by emailing the information to the Case Management Group mailbox PPD with copy to the

appropriate sponsor Study Manager.

The investigator will submit any updated SAE data to the sponsor 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 eCRF screen.

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

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

The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Good Clinical Practice (GCP) Office/Institutional Review Board (IRB) and the investigator.

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

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs from the sponsor) will review and then file it in the investigator site master file, and will notify the GCP office/IRB, 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 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 Case Management Group mailbox PPD with copy to the appropriate sponsor Study Manager. Original pregnancy information forms will be retained in the investigator site 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 Case Management Group mailbox PPD, with copy to the appropriate sponsor Study Manager. 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 in the study will be withdrawn.

11 DATA MANAGEMENT

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

For this study, subject data will be entered into an electronic CRF (eCRF), using a validated system. Data relating to clinical screening/efficacy assessments, SAEs and pregnancy 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 eCRF should be specified. The eCRF, paper forms 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 eCRF must be completed and signed by the investigator (or authorized designee) to certify the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

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 the sponsor 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 eCRF or as part of the query text.

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

The sponsor will obtain and retain all eCRFs 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, which 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.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medication terms (if applicable) using a validated medication dictionary, WHODrug.

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 eCRF 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 third-party vendor 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 eCRFs in accordance with the monitoring plan, to confirm that data entered into the eCRF 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 monitor can also run reports and listings on the eCRFs to raise manual queries, as needed, for site clarification or correction.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

Sufficient subjects will be screened to randomize approximately 240 subjects to study treatment to ensure approximately 235 complete the study (approximately 94 subjects each for test toothpaste and negative control, and 47 subjects for positive control), allowing for 2% dropouts after randomization, as observed in previous clinical studies conducted in China.

The study will be powered sufficiently to demonstrate statistical superiority of the test toothpaste compared to the negative control for the change from Baseline in the Schiff sensitivity score after 12 weeks of treatment.

The true effect size is expected to be 0.5 (effect size (ES) = mean difference [test toothpaste – negative control] / pooled standard deviation [SD]; mean difference = 0.3, SD=0.6). Such assumptions would also infer at least a 15% superior relative mean change from Baseline for the test toothpaste compared to the negative control (assuming mean change from a Baseline Schiff sensitivity score for negative control less than 2), a requirement of the Chinese MoH guidelines for the testing of functional (desensitising) toothpastes for at least one clinical DH measure (Ministry of Health (China), 2010).

With 94 subjects per group (for test toothpaste and negative control arms), there is 92.65% power to detect an effect size of 0.5 at the two-sided 5% significance level based on a two-sample t-test (using PASS software version 19.0.1).

Estimates of the above dropout rate and SD are based on results from three similar clinical studies (sponsor clinical studies: 205794, 208153, 216954).

The positive control has clinically proven longer-term DH efficacy in two clinical studies conducted in China on Chinese populations (sponsor clinical studies: CCI which satisfied the China MoH requirements (Ministry of Health (China), 2010). As such, it has been included in this study as a benchmark of performance in the Chinese population for 'study validation'; 47 subjects in the positive control group are deemed sufficient to demonstrate statistical superiority for positive vs. negative controls.

12.2 Populations for Analysis

12.2.1 Definitions of Analysis Populations

The Safety population will include all randomized subjects who complete at least one use of study product. This population will be based on the study product the subject received. All assessments of safety will be based on this analysis population.

The modified Intent-To-Treat (mITT) population will include all randomized subjects who complete at least one use of study product and have at least one post Baseline efficacy assessment. This population will be based on the study product to which the subject was randomized. All assessments of efficacy will be primarily based on this analysis population.

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

12.2.2 Exclusion of Data from Analysis

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

A PP analysis will be performed for each change from Baseline in Schiff sensitivity score and tactile threshold endpoints if there is more than 10% difference in the number of subjects between the PP and mITT populations. A decision to perform a PP analysis should be made prior to study unblinding (release of the randomization codes).

12.3 Statistical Analyses

This is a summary of the planned statistical analyses; the detail of the proposed statistical analyses will be documented in the statistical analysis plan (SAP), written following finalization of the protocol and prior to study unblinding.

Significance testing will be conducted at the two-sided 5% significance level.

Schiff sensitivity score, tactile threshold (g) and VAS (mm) will be derived as the average score or value, respectively, of the 2 test teeth (identified at Baseline). Change from Baseline will be derived for the individual teeth first before calculating the average change of the 2 test teeth.

12.3.1 Primary Analysis

The primary endpoint of this study is the change from Baseline in the Schiff sensitivity score at Week 12; the primary hypothesis test will be the comparison between the test toothpaste and the negative control in the mITT population.

Change from Baseline in Schiff sensitivity score will be analysed using a Mixed Model with Repeated Measures (MMRM), with study product, visit and study product by visit interaction as fixed effects, and Baseline Schiff sensitivity score as a covariate. Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied (Kenward and Roger, 1997). The difference between least square means for the test toothpaste compared to the negative control at Week 12 will be presented along with two-sided p-value and 95% CIs.

As a sensitivity analysis, the change from Baseline in Schiff sensitivity score at Week 12 will be compared between study products (test toothpaste vs. negative control) using an Analysis of Covariance (ANCOVA) model with study product as a fixed effect and Baseline Schiff sensitivity score as a covariate.

The assumption of normality and homogeneity of variance in each MMRM will be investigated. In case of violation of these assumptions, a suitable non-parametric test (adjusted for the randomisation stratification) will be performed to assess change from Baseline comparisons (test toothpaste vs. negative control at Week 12) and the results will be provided to support the MMRM results; the non-parametric results will be considered confirmatory under the observation of strong violations of the assumptions.

12.3.2 Secondary Analyses

Change from Baseline in Tactile Threshold (g) at Week 12:

Change from Baseline in tactile threshold (g) will be analysed using the same MMRM as the primary endpoint but with Baseline tactile threshold (g) as a covariate, rather than Baseline Schiff sensitivity score. In addition, the maximum Baseline Schiff sensitivity score of the two test teeth (2 or 3) will be fitted as a fixed effect. The difference between least square means for the test toothpaste vs. negative control at Week 12 will be presented, along with the two-sided p-value and 95% CIs.

As a sensitivity analysis, the change from Baseline in tactile threshold (g) at Week 12 will be compared between study products (test toothpaste vs. negative control) using an Analysis of Covariance (ANCOVA) model with study product and the maximum Baseline Schiff sensitivity score of the two test teeth (2 or 3) as fixed effects and the Baseline tactile threshold (g) as a covariate.

Change from Baseline in VAS (mm) at Week 12:

Change from Baseline in VAS (mm) will be analysed using the same MMRM and ANCOVA (as a sensitivity analysis) as for the change from Baseline in tactile threshold (g) but with Baseline VAS (mm) as a covariate, rather than the Baseline tactile threshold (g). The difference between least square means for the test toothpaste vs. negative control at Week 12 will be presented, along with the two-sided p-value and 95% CIs.

Other Secondary Endpoints:

- Test toothpaste vs. negative control
  - Change from Baseline in Schiff sensitivity score, tactile threshold (g) and VAS (mm) at Week 6
- Positive control vs. negative control
  - Change from Baseline in Schiff sensitivity score, tactile threshold (g) and VAS (mm) at Week 6 and Week 12.

These other secondary endpoint analyses will utilise the results at Week 6 (test toothpaste vs. negative control and positive vs. negative control) and Week 12 (positive vs. negative control) from the same respective MMRM model applied for the change from Baseline in Schiff sensitivity score, tactile threshold (g) and VAS (mm) described above.

The results from each MMRM will be tabulated together, presenting the following information, in addition to the results already specified for the primary and secondary analyses above.

- Least square mean change from Baseline for each study product at Week 6 and Week 12 (based on the observed stratification margins for tactile threshold model) and used to test for any change from Baseline with two-sided p-values and 95% CIs.
- Differences between least square mean change from Baseline (test toothpaste vs. negative control at Week 6, positive control vs. negative control at Week 6 and Week 12) with two-sided p-values and 95% CIs.

The assumption of normality and homogeneity of variance in each MMRM will be investigated. In case of violation of these assumptions, a suitable non-parametric test (adjusted for the randomisation stratification) will be performed for each required secondary endpoint comparison between study products at each time point and results will be provided to support the MMRM results; the non-parametric results will be considered to supersede the MMRM results under the observation of strong violations of the assumptions.

The ANCOVA sensitivity analysis results at Week 12 for positive vs. negative control for each endpoint will be obtained from the same ANCOVA models using Week 12 data as described above for the test toothpaste vs. negative control comparisons. As additional sensitivity analyses, the change from Baseline in Schiff sensitivity score, tactile threshold (g) and VAS (mm) at Week 6 will be analysed using the same ANCOVA model as for the Week 12 sensitivity analyses detailed above.

12.3.3 Safety Analyses

Safety analyses will be performed on the Safety population, according to study product received. AEs will be regarded as 'treatment emergent' if they occur on or after the first study product use at Baseline (Visit 1). In case of misallocation, compared to the randomisation schedule, TEAEs will be associated with the most recent study product received.

Each AE will be categorized as oral or non-oral by the investigator, or medically qualified designee. All will be reviewed by the CRS prior to database lock and unblinding, and coded using the MedDRA.

A listing of all AEs will be presented for all subjects in the Safety population with the following AEs summaries (number of distinct AEs and frequency/proportion of subjects affected) will be presented by product group and overall:

- Treatment emergent AEs
- Treatment emergent AEs by System Organ Class (SOC) and Preferred Term (PT)
- Treatment emergent AEs by Oral/Non-Oral and PT
- Treatment emergent treatment related AEs by Oral/Non-Oral and PT
- Treatment emergent treatment related serious AEs by SOC and PT

Separate listings will be presented for:

- Deaths, SAEs and any AEs leading to product or study discontinuation.
- OST findings (with a summary of abnormalities by visit)
- OHT findings (with a summary of changes by visit)
- Exposure to study product Section 12.3.5.1.

12.3.4 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized by treatment group for the Safety and mITT populations, and the PP population if a PP analysis is performed.

Categorical variables (such as sex, race and Baseline Schiff stratification score) will be summarized by the number and percentage of subjects with each relevant characteristic in each product group. Continuous variables such as (age) will be summarized by mean, SD, median, minimum and maximum values in each product group.

12.3.5 Study Product Compliance and Use of Other Therapies

12.3.5.1 Study Product Compliance

Compliance with product use (number of brushings) will be listed and summarized for the mITT population at each visit, and cumulatively for the overall treatment period (for most subjects this will be 12 weeks) by product group.

Number of expected brushings = 2 × Number of days between Visit X and Visit (X+1)

Number of actual brushings = (Number of expected brushings) – (Number of missed brushings) + (Number of additional brushings)

% Compliance at 'Visit X' = $\frac{\text{(Number of actual brushings prior to Visit X)}}{\text{(Number of expected brushings prior to Visit X)}} \times 100$

12.3.5.2 Prior and Concomitant Medications and Treatments

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

12.3.6 Handling of Dropouts and Missing Data

MMRM analyses account for missing data using 'a missing at random' assumption, i.e., there is a systematic relationship between the propensity for missing values and the observed data, but not the missing data. Under such assumptions, MMRM is shown to provide unbiased estimates of the treatment effect, whilst the analysis of only complete cases using ANCOVA are biased (Baron et al, 2008; Ashbeck et al, 2016). Such complete case analysis requires a 'missing completely at random' assumption to remain unbiased and this is unlikely to hold, i.e., the fact that the data are missing is independent of the observed and unobserved data.

Using an MMRM, it will therefore be assumed that a subject with missing data at one post-Baseline visit would have obtained a similar efficacy result at that visit compared to a subject using the same study product with similar non-missing results at other timepoints (Baseline and the other post-Baseline visit).

Sensitivity analyses will present results from the separate ANCOVA models using only non-missing values at each single time point. Additional sensitivity analyses may be added to the SAP prior to unblinding in case of high drop-out rates and/or exclusion from PP population.

12.3.7 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 the sponsor's procedures, the sponsor or designee (i.e., third-party vendor monitors) will contact the site to review the protocol, study requirements, and staff responsibilities with study personnel prior to the start of the study to satisfy regulatory, ethical, and sponsor requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The sponsor or designee will monitor the study and site activity to verify:

- 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 the sponsor. The investigator (or designee) agrees to allow the monitor(s) direct access to all relevant documents and agrees to co-operate with the monitor(s) to ensure that any problems detected during these monitoring visits are resolved.

13.2 Quality Assurance

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

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

The investigator will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor 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 supply copies of the inspection finding to the sponsor or its agent. Before response submission

to the regulatory authority, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any findings.

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board

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

The only circumstance in which an amendment may be initiated prior to GCP Office/IRB approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the GCP Office/IRB and sponsor 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 the sponsor and other authorised parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by the sponsor 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, the sponsor 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 GCP Office/IRB 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 GCP Office/IRB and investigator databases may be used to recruit study subjects. Use of a GCP Office/IRB approved, generic, pre-screening questionnaire to determine general eligibility for this study is allowed. This pre-screening questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects. The sponsor 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

The investigator will inform the sponsor 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 the investigator becomes aware of.

The sponsor defines a serious breach 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 sponsored human subject research studies.

In the event of any prohibition or restriction imposed (i.e., clinical hold) or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, the sponsor should be informed immediately.

13.4 Posting of Information on Publicly Available Clinical Trial Registers

Study-related information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable sponsor's processes. The sponsor intends to make anonymized subject-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

13.5 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures and relevant reports, and will have the opportunity to review the complete study results. The sponsor 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.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge. The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with the sponsor's policy.

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 sponsor 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 the sponsor, 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 the sponsor (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, sponsor standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between the sponsor and the investigator. The investigator must notify the sponsor 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 GCP Office/IRB, or study product safety problems, or at the discretion of the sponsor.

If a study is prematurely terminated, the sponsor 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 the sponsor, all study materials must be collected and all CRF's completed to the greatest extent possible. Where required by the applicable regulatory requirements, the sponsor should inform the regulatory authority(ies) and the investigator should promptly inform the GCP Office/IRB and provide the GCP Office/IRB with a detailed written explanation of the termination or suspension.

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

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

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15 APPENDICES

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
CI	Confidence interval
CRF	Case report form
CRS	Clinical Research Scientist
CSPS	calcium sodium phosphosilicate
DH	Dentine hypersensitivity
EAR	Erosion, Abrasion, Recession
ECs	Ethics committees
EDC	Electronic data capture
ECG	Electrocardiogram
eCRF	Electronic case report form
ES	Effect size
g	Gram
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IRT	Interactive Response Technology
OHT	Oral hard tissue
OST	Oral soft tissue
OTC	Over-the-counter
MFC	Manufacturing formulation code
MGI	Modified gingival index
mITT	Modified Intent to Treat
MMRM	Mixed model with repeated measures
MOH	Ministry of Health
NaF	Sodium fluoride
N/A	Not applicable
PI	Personal information
PP	Per protocol
P&G	Proctor and Gamble
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SnF_2	Stannous fluoride

Abbreviation	Term
SUSAR	Suspected unexpected serious adverse reaction
TEAEs	Treatment emergent adverse events
UK	United Kingdom
US	United States
vs	Versus

15.2 Screening questionnaire

1. Which of the following best describe any sensations that you may have felt in your teeth? (tick all that apply)

Itchy	Aching	Shooting
Piercing	Tingling	Sharp
Dull	Flashing	Shivery
Lingering	Twinging	Flickering
Stabbing	Shattering	Freezing
Fleeting	Quivering	Pricking
Pain	Discomfort	Twinges
Sensitivity	None of these	

If answer is 'None of these', EXCLUDE

From now on we are going to call what you feel, the 'sensations in your teeth' or 'sensations'.

2. How long have you been experiencing any sensations in your teeth? (tick only one response)

Less than six months	Exclude
More than six months but less than a year	Proceed
More than a year but less than five years	Proceed
More than five years but less than 10 years	Proceed
More than 10 years	Exclude
None	Exclude

3. Which parts of your mouth have been affected by these sensations? (tick all that apply)

Top front	Proceed
Top back	Proceed
Bottom front	Proceed
Bottom back	Proceed
None	Exclude

4. Which of the following cause you to have sensations in your teeth? (tick all that apply)

Cold fluids	Acidy fruits (e.g., oranges)	Having teeth cleaned at the dentist
Hot foods	Sweet things	Tooth Whitening Products
Hard foods	Sticky foods	Metals touching my teeth
Cold air	Ice Cream	flossing certain teeth
Salty foods	Cold foods	Tooth brushing
Hot fluids	None of these	

If answer is 'None of these', EXCLUDE

5. How often do you experience these sensations in your teeth?

Several times a day	Proceed
Once a day	Proceed
Several times a week	Proceed
Once a week	Proceed
Several times a month	Exclude
Once a month	Exclude
Less than once a month	Exclude
Never	Exclude

6. If you have any sensations, on average how long do these sensations last? (tick only one response)

A few seconds	Proceed
About a minute	Proceed
Several minutes	Proceed
About half an hour	Proceed
Longer than half an hour	Exclude
Don't have them	Exclude

15.3 Video Compliance Check-list

Did the subject only use the study products provided?	Yes	**No***
Did the subject use the correct amount of toothpaste (full toothbrush head)?	Yes	**No***
Did the subject brush according to the acclimatisation product usage instructions?	Yes	**No***
Did the subject rinse with water during tooth brushing?	**Yes****	No
Did the subject rinse with the correct amount of water after brushing?	Yes	**No***
If the subject brushed their tongue, did they do this after toothbrushing? **N/A** *(circle if subject did not brush their tongue)*	Yes	**No***

*Non-compliant response; re-instruct in correct product usage procedure

** Non-compliant response; exclude

Signature Page for 300026 TMF-238226 v3.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: PPD GMT+0000

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