CLINICAL PROTOCOL

An 8-week, randomised, controlled, examiner-blind, proof of principle study investigating the ability of a 3% methyl vinyl ether/maleic anhydride co-polymer (PVM/MA) + 5% potassium nitrate (KNO_3) combination toothpaste to protect from dentine hypersensitivity

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

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Document History

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Amendment 1	2.0	• Addition of Supervised Brushing with Study Toothpaste for all the Visits (2-6) in the schedule of activities • Change of toothbrush in the sundry items table (Aquafresh, flat trim, medium toothbrush (Germany)) • Amendment of Schiff score units in the Samples Size section
Amendment 2		

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, research ethics committees (RECs), etc.

Principal Investigator Protocol Agreement Page

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

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

Short Title:

A proof of principle (PoP) study to evaluate the ability of an experimental combination toothpaste formulation to protect sensitive teeth from dentine hypersensitivity.

Background and Rationale:

GlaxoSmithKline Consumer Healthcare (GSK CH) has developed a new combination toothpaste containing 3% poly vinyl methyl ether/maleic anhydride (PVM/MA) co-polymer and 5% potassium nitrate (KNO_3). It is hypothesised that the combination of these 2 ingredients with different modes of action (PVM/MA: dentin tubule occlusion; KNO_3: nerve desensitisation) will deliver superior protection for sensitive teeth from dentine hypersensitivity, compared to toothpastes containing either PVM/MA or KNO_3 alone.

Toothpastes containing co-polymers such as PVM/MA are reported to alleviate tooth sensitivity. None of the studies reported to date investigated PVM/MA+KNO_3 formulations compared to the single ingredients. This PoP will evaluate and compare the ability of the three products - a PVM/MA+KNO_3 combination toothpaste, a PVM/MA only toothpaste and a KNO_3 only toothpaste to provide sensitivity protection across an 8-week usage period. A regular fluoride toothpaste will be included as negative control.

Objectives and Endpoints:

Objectives	Endpoints
Product performance	
Primary	
To characterise the sensitivity protection profile of an experimental 3% PVM/MA + 5% KNO_3 combination toothpaste, a 3% PVM/MA only toothpaste, a 5% KNO_3 and a regular fluoride toothpaste (negative control) over 8 weeks (with twice daily use).	*At Day 0 (Baseline), Day 3 and Weeks 2, 4 & 8:* - Schiff sensitivity score - Tactile threshold (grams [g]) - Number of sensitive teeth (Schiff sensitivity score ≥ 1)

Secondary	
To investigate the ability of an experimental 3% PVM/MA + 5% KNO_3 combination toothpaste to provide sensitivity protection , in response to an evaporative (air) stimulus (Schiff sensitivity score), compared to a 3% PVM/MA only toothpaste, a 5% KNO_3 only toothpaste and a regular fluoride toothpaste (negative control), after 3 days and 2, 4 and 8 weeks twice daily use.	*At Day 3 and Weeks 2, 4 & 8:* Change from Baseline in Schiff sensitivity score
To investigate the ability of an experimental 3% PVM/MA + 5% KNO_3 combination toothpaste to provide sensitivity protection, in response to a tactile stimulus (tactile threshold), compared to a 3% PVM/MA only toothpaste, a 5% KNO_3 only toothpaste and regular fluoride toothpaste (negative control), after 3 days and 2, 4 and 8 weeks twice daily use.	*At Day 3 and Weeks 2, 4 & 8:* Change from Baseline in tactile threshold (g)
To monitor Oral Health Related Quality of Life (OHRQoL), as measured by the Dentine Hypersensitivity Experience Questionnaire (DHEQ), after 3 days and 2, 4 and 8 weeks twice daily use of a 3% PVM/MA + 5% KNO_3 combination toothpaste, a 3% PVM/MA only toothpaste, a 5% KNO_3 only toothpaste and a regular fluoride toothpaste (negative control).	*At Day 3 and Weeks 2, 4 & 8:* Change from Baseline in - Responses to DHEQ Section 1, Questions 7-9 - Total Score; responses to DHEQ Section 2, Questions 1-15 - Restrictions, Adaptation, Social Impact, Emotional Impact & Identity Domains
To explore changes in self-perceived discomfort associated with tooth sensitivity, as measured by a numeric rating scale (NRS), after 3 days and 2, 4 and 8 weeks twice daily use of a 3% PVM/MA + 5% KNO_3 combination toothpaste, a 3% PVM/MA only toothpaste, a 5% KNO_3 only toothpaste and a regular fluoride toothpaste (negative control).	*At Baseline, Day 3 and Weeks 2, 4 & 8:* - NRS score *At Day 3 and Weeks 2, 4 & 8:* - Change from Baseline in NRS score
Safety	
To assess the safety and tolerability of study products with twice daily use for 8 weeks.	Treatment emergent adverse events

Study Design:

This will be a PoP, single centre, 8-week, randomised, controlled, examiner blind, parallel design, stratified (by maximum Baseline Schiff sensitivity score of the two selected test teeth) clinical study, investigating the ability of a 3% PVM/MA + 5% KNO_3 combination toothpaste to protect sensitive teeth from dentine hypersensitivity.

In line with widely recommended oral hygiene practice and typical consumer habit, study subjects will be requested to brush their teeth twice daily (morning and evening) with their assigned study toothpaste for the duration of the 8-week study period.

Tooth sensitivity will be assessed at Screening (Visit 1), Baseline (Day 0), Day 3 and Weeks 2, 4 and 8 using two independent stimulus-based (tactile and evaporative (air)) measures will be employed, in line with published recommendations for the design and conduct of sensitivity clinical studies.

Oral Health Related Quality of Life (OHRQoL) will be evaluated using the validated Dentine Hypersensitivity Experience Questionnaire (DHEQ-15), completed by study subjects after 3 days and 2-, 4- and 8-weeks product use. In addition, a Numeric Rating Scale (NRS) will be also used to explore changes in self-perceived discomfort associated to tooth sensitivity after 3 days and 2-, 4- and 8-weeks product use.

Safety and oral tolerability of the study products will be monitored over the 8-week usage period by review of reported AEs.

Study Products:

Product Description	**Acclimatisation Product**	**Test Product**	**Comparator 1**	**Comparator 2**	**Negative control**
	Regular fluoride toothpaste	3% PVM/MA + 5% KNO_3 combination toothpaste	3% PVM/MA only toothpaste	5% KNO_3 only toothpaste	Regular fluoride toothpaste
Fluoride Content	1450 parts per million (ppm) fluoride as sodium fluoride (NaF)	1450 ppm fluoride as NaF	1450 ppm fluoride as NaF	1450 ppm fluoride as NaF	1450 ppm fluoride as NaF
Product Name	Colgate Cavity Protection	Not applicable (N/A)	N/A	N/A	Colgate Cavity Protection

Type and Planned Number of Subjects:

The study will be conducted in male and female subjects in good general health, aged 18-65 years inclusive, with pre-existing self-reported tooth sensitivity and at least two sensitive teeth (confirmed clinically) that meet all study criteria at both the Screening (Visit 1) and Baseline (Visit 2) visits.

Sufficient subjects will be screened to ensure approximately 120 subjects are randomised to study product (approximately 30 subjects per product arm); approximately 30 evaluable subjects per product group is considered sufficient to provide reliable estimates of performance for the purposes of this study and to aid in the design of future clinical studies.

Statistical Analyses:

A modified Intent-To-Treat population (mITT) (all randomised subjects who complete at least one use of study product and have at least one post baseline clinical performance assessment) will be used for product performance analyses. The primary statistical analyses will descriptively and visually present the performance of the study products over time. Summary statistics (mean, median, standard error (SE), standard deviation (SD), minimum, maximum) will be presented for each primary end point at each assessment time point. Raw means (average score of the two test teeth) ± SE will be plotted for Schiff sensitivity score and tactile threshold (g) at each timepoint by product group; the number of sensitive teeth will also be plotted at each timepoint by product group.

Secondary end points include change from Baseline in Schiff sensitivity score and tactile threshold (g). Change from Baseline will be analysed at each assessment time point using use of Analysis of Covariance (ANCOVA), comparing the Test Product to Comparator 1, Comparator 2 and the negative control. Adjusted mean change from Baseline, along with 95% confidence intervals (CIs) will be reported by product; p-values testing for non-zero change from Baseline will be presented for all products.

Summary of statistics (mean, median, SE, SD, minimum, maximum) will be presented for each secondary endpoint by product group and assessment time point. Significance testing will be conducted at the two-sided 5% significance level with no adjustments for multiple testing.

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 Day -28 to -14		Visit 2 **Baseline** Day 0	Visit 3 **Day 3** (± 1 day)	Visit 4 **Week 2** Day 14 (± 1 day)	Visit 5 **Week 4** Day 28 (± 2 day)	Visit 6 **Week 8** Day 56 (± 2 day)
Informed Consent	X	Acclimatisation Period (2-4 weeks)					
Demographics	X						
Medical History & Current/Prior Concomitant Medication/Treatment Review	X						
Changes in Health & Medications/ Treatments			X	X	X	X	X
Urine Pregnancy Test (UPT)[1]	X						X
Oral Soft Tissue (OST) Examination	X		X	X	X	X	X
Oral Hard Tissue (OHT) Examination	X						X
Eligible Teeth Assessments (Dentition Exclusions, Erosion/Abrasion/Recession [EAR], Modified Gingival Index [MGI], Tooth Mobility)	X						
Qualifying Tactile Sensitivity Assessment (Tactile Threshold) [2]	X		X				
Qualifying Evaporative (Air) Sensitivity Assessment (Schiff sensitivity score)[3]	X		X				
Inclusion / Exclusion Criteria	X		X				
Subject Eligibility	X		X				
Dispense Acclimatisation Toothpaste, Toothbrush, Timer & Diary	X						
Supervised Brushing with Acclimatisation Toothpaste	X						
Return Acclimatisation Toothpaste, Toothbrush & Diary[4]			X				
Stratification/Randomisation			X				
Dispense Study Toothpaste, Toothbrush & Diary			X				

Procedure/Assessment	Screening		Study Visits				
	Visit 1 Day -28 to -14		Visit 2 **Baseline** Day 0	Visit 3 **Day 3** (± 1 day)	Visit 4 **Week 2** Day 14 (± 1 day)	Visit 5 **Week 4** Day 28 (± 2 day)	Visit 6 **Week 8** Day 56 (± 2 day)
Supervised Brushing with Study Toothpaste			X	X	X	X	X
Return Study Toothpaste, Toothbrush & Diary[4]							X
Compliance Checks[5]			X	X	X	X	X
Clinical Examiner Selects Two 'Test Teeth' (Eligible Subjects Only)			X				
Tactile Sensitivity Assessment (Yeaple Probe): Two Test Teeth Only[2]				X	X	X	X
Evaporative (Air) Sensitivity (Schiff sensitivity score): Two Test Teeth Only[3]				X	X	X	X
Evaporative (Air) Sensitivity (Schiff sensitivity score): *All Remaining Eligible Teeth Identified at Screening*[3]				X	X	X	X
DHEQ [6]			X[6]	X[6]	X[6]	X[6]	X[6]
NSR Self- Perceived Discomfort Questions			X	X	X	X	X
Study Conclusion							X
Monitor Adverse Events (AEs)[7]			X	X	X	X	X

Footnotes:

1. Female subjects of child-bearing potential only.
2. **Visits 1-2:** maximum force 20g (Screening and Baseline); **Visits 3-6:** maximum force 80g.
3. Evaporative (air) assessment will follow tactile assessment, with minimum 5 minutes between last tactile assessment and first evaporative (air) assessment (to allow tooth recovery).
   Visit 1: assess the evaporative (air) sensitivity of teeth with tactile threshold ≤ 20 g.
   Visit 2: assess the evaporative (air) sensitivity of all eligible teeth identified at Screening.
   Visits 3-6: assess the evaporative (air) sensitivity of the 2 test teeth first, then assess the evaporative (air) sensitivity of all other eligible teeth identified at Screening.
4. Subject will be required to bring their study supplies (minus timer) to every visit.
5. Perform visual check of returned study supplies, review diary & evaluate compliance.
   Visit 2: check compliance with use of acclimatisation toothpaste.
   Visits 3-6: check compliance with use of study product.
   Visits 2-6: check compliance with Lifestyle Guidelines/Medication requirements.
6. DHEQ must be completed before the NRS question is asked; DHEQ & NRS question must be completed prior to OST examination/clinical assessments.
   DHEQ **Visit 2:** complete all questions
   DHEQ **Visits 3-6:** complete Section 1 Q7-9 & Section 2 all questions.
7. Record AEs from signing of informed consent until 5 days after last use of study product

2 INTRODUCTION

2.1 Study Rationale

GlaxoSmithKline Consumer Healthcare (GSK CH) has developed a new combination toothpaste containing 3% PVM/MA and 5% KNO_3 with potential to protect sensitive teeth from dentine hypersensitivity. It is hypothesised that the combination of these 2 ingredients with different modes of action (PVM/MA: dentin tubule occlusion; KNO_3: nerve desensitisation) will deliver superior protection from sensitive teeth, compared to the toothpastes containing either PVM/MA or KNO_3 alone.

Several clinical studies evaluating the ability of PVM/MA toothpaste to protect teeth from sensitivity are reported in the scientific literature (Schiff et al., 1994, Ayad et al., 1994, Chaknis et al., 2011), however, none of the studies reported to date investigated the performance of a toothpaste formulated with PVM/MA+KNO_3 in comparison with the single ingredients.

This PoP clinical study will evaluate and compare the ability of a daily use 3% PVM/MA+ 5% KNO_3 combination toothpaste, a 3% PVM/MA only toothpaste, a 5% KNO_3 only toothpaste and regular fluoride toothpaste (negative control) to provide sensitivity protection over 8 weeks, with twice daily brushing. Data generated will aid in the design of future clinical studies investigating this combination toothpaste.

2.2 Background

Dentine hypersensitivity (DH) is a common oral condition (Addy, 2000, West et al., 2014), with the peak incidence occurring at the end of the third decade and decreasing during the fourth and fifth decades of life (Irwin and McCusker, 1997, Bartold, 2006, West et al., 2014).

Reduced levels of DH in older individuals are most likely a result of reparative processes, such as the formation of reparative dentine, which decrease permeability and reduce hydraulic conductance (West, 2006). But, as individuals retain their teeth and complete functionality for longer (due to caries and periodontal disease prevention) and as diets change (with an increased consumption of acidic drinks and foods) it is reasonable to expect a higher incidence of oral discomfort related to DH (Drisko, 2002, West et al., 2014)

and with that an increase in use of oral care products which can help protect sensitive teeth from DH.

Epidemiological studies on the prevalence of DH in the general population have shown conflicting results and it is not simple to estimate a precise percentage (%) of incidence. This is likely due to several factors such as different sample populations, different diagnostic approaches, and whether the source data is based on clinical evaluation or patient-based questionnaires (West et al., 2014, Favaro Zeola et al., 2019, Splieth and Tachou, 2013). It is noted that individuals who have received periodontal therapy are four times more at risk for developing DH than the general population (Drisko, 2002).

In a normal tooth, dentine is covered by enamel over the crown, and by cementum (connective tissue) and the periodontal tissues over the root. Aetiologic factors such as gingival recession, tooth erosion and/or abrasion that result in loss of enamel or cementum and exposure of underlying dentine with patent dentinal tubules (Orchardson and Collins, 1987) are believed to be responsible for DH onset.

Once the dentine is exposed, the most common triggers of DH are evaporative (such as cold air), thermal (hot and cold drinks/foods), tactile (adding pressure e.g. from toothbrushing) and osmotic (sugary foods and drinks) stimuli. It is hypothesised that these stimuli can cause movement in the fluid within patent dentine tubules, triggering the intra-dental nerves (Brännström, 1963).

There are currently two ways to protect against DH. The first is to use desensitising agents, such as KNO_3. It is postulated that potassium ions, delivered into exposed dentine tubules, are able to depolarise the intra-dental nerves, thereby reducing the discomfort from tooth sensitivity (Addy and Smith, 2010). Numerous longer-term studies (typically 4-12 weeks) have been published demonstrating the clinical efficacy of KNO_3 in protecting sensitive teeth from DH (Silverman, 1985, Nagata et al., 1994, Gillam, 1996, West et al., 1997, Wara-aswapati et al., 2005, Kakar and Kakar, 2013, Bae et al., 2015).

The second approach, with more rapid effects (Gillam et al., 1996), is to use an occlusion technology. Occluding agents (such as strontium/stannous salts, bioglasses, arginine/calcium carbonate, silicas) act to seal or narrow the dentine tubules, thereby reducing fluid movement, pulpal irritation and the subsequent sensitivity response.

It has been reported that co-polymers such as PVM/MA, already extensively employed as excipients in oral care formulations such as toothpastes, denture adhesives and mouthwashes, may also act to occlude exposed dentine and help protect sensitive teeth (Schiff et al., 1994, Ayad et al., 1994, Chaknis et al., 2011). A 12-week clinical study demonstrated the ability of a combination toothpaste containing PVM/MA to alleviate sensitivity, compared to a placebo toothpaste (Schiff et al., 1994). In addition, Chaknis et al., showed the greater ability of a PVM/MA toothpaste, compared to a stannous fluoride only toothpaste, to protect sensitive teeth (Chaknis et al., 2011). None of the clinical DH studies reported to date investigated the combination of PVM/MA+KNO_3 compared to the single ingredients.

This PoP clinical study will evaluate and compare the ability of a daily use 3% PVM/MA+ 5% KNO_3 combination toothpaste, a 3% PVM/MA only toothpaste, a 5% KNO_3 only toothpaste and regular fluoride toothpaste (negative control) to protect sensitive teeth from DH over 8 weeks, with twice daily brushing. Given occluding toothpastes are reported to provide fast protection from the discomfort of DH, the clinical study will include clinical assessments at a range of time points across the 8-week usage period.

Safety and tolerability of the study toothpastes will be assessed by review of treatment emergent adverse events.

Data generated from this study will provide an initial indication of the clinical benefits of the new combination toothpaste, compared to its' individual components alone, and will be used to direct any future clinical evaluations.

2.3 Benefit/Risk Assessment

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

Three clinical studies evaluating the ability of a toothpaste formulated with PVM/MA polymer (in combination with various other ingredients) to protect sensitive teeth are reported in the scientific literature. In these studies, subjects brushed twice daily with their assigned study toothpaste for the duration of the treatment period. No adverse events which could be ascribed to use of the combination toothpaste were reported.

- **8-Week Study**: Toothpaste containing 2.0% PVM/MA copolymer, 0.3 % triclosan, 0.243% NaF (Chaknis et al., 2011).
- **12-Week Study**: Toothpaste containing 1.5% PVM/MA+ 5% KNO_3 (Ayad et al., 1994, Schiff et al., 1994).
- **12-Week Study**: Toothpaste containing 1.5% PVM/MA+ 5% KNO_3 (Ayad et al., 1994, Schiff et al., 1994).

The combination of 3% PVM/MA+ 5% KNO_3 is considered generally safe for topical oral use, when delivered from a toothpaste with twice daily brushing, under the controlled conditions of a clinical trial.

2.4 Mechanism of Action/Indication

Potassium nitrate has been found to be an effective desensitising ingredient. It is postulated that after each brushing with a potassium ion (K^+) containing toothpaste, the concentration of K^+ ions at the tooth surface is raised. K^+ ions move into the dentine through the tubules, gradually desensitising the nerves inside the tooth and thereby providing protection from DH. Potassium salts generally require a period of use (for example, 14 to 28 days) before their benefit is established (Parkinson et al., 2017, West et al., 1997, Jeandot et al., 2007, Schiff et al., 2000).

Occlusion agents act by physically blocking or narrowing the exposed ends of the dentine tubules, thereby reducing dentinal fluid movement and decreasing the effect of external stimuli and consequent discomfort. Tubule occlusion can be favored over nerve desensitisation, due to the more rapid onset of relief from DH (Gillam, 1996).

PVM/MA is an occluding polymer that has been shown to be effective in protecting sensitive teeth when delivered from a daily use toothpaste (Chaknis et al., 2011, Schiff et al., 1994).

In this exploratory study, it is hypothesised that the combination of these two ingredients (PVM/MA+KNO_3) with complementary modes of action should deliver greater protection for sensitive teeth, compared to either PVM/MA or KNO_3 alone.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Product performance	
Primary	
To characterise the sensitivity protection profile of an experimental 3% PVM/MA + 5% KNO_3 combination toothpaste, a 3% PVM/MA only toothpaste, a 5% KNO_3 and a regular fluoride toothpaste (negative control) over 8 weeks (with twice daily use).	*At Day 0 (Baseline), Day 3 and Weeks 2, 4 & 8:* - Schiff sensitivity score - Tactile threshold (grams [g]) - Number of sensitive teeth (Schiff sensitivity score ≥ 1)
Secondary	
To investigate the ability of an experimental 3% PVM/MA + 5% KNO_3 combination toothpaste to provide sensitivity protection, in response to an evaporative (air) stimulus (Schiff sensitivity score), compared to a 3% PVM/MA only toothpaste, a 5% KNO_3 only toothpaste and a regular fluoride toothpaste (negative control), after 3 days and 2, 4 and 8 weeks twice daily use.	*At Day 3 and Weeks 2, 4 & 8:* Change from Baseline in Schiff sensitivity score
To investigate the ability of an experimental 3% PVM/MA + 5% KNO_3 combination toothpaste to provide sensitivity protection, in response to a tactile stimulus (tactile threshold), compared to a 3% PVM/MA only toothpaste, a 5% KNO_3 only toothpaste and regular fluoride toothpaste (negative control), after 3 days and 2, 4 and 8 weeks twice daily use.	*At Day 3 and Weeks 2, 4 & 8:* Change from Baseline in tactile threshold (g)
To monitor Oral Health Related Quality of Life (OHRQoL), as measured by the Dentine Hypersensitivity Experience Questionnaire (DHEQ), after 3 days and 2, 4 and 8 weeks twice daily use of a 3% PVM/MA + 5% KNO_3 combination toothpaste, a 3% PVM/MA only toothpaste, a 5% KNO_3 only toothpaste and a regular fluoride toothpaste (negative control).	*At Day 3 and Weeks 2, 4 & 8:* Change from Baseline in - Responses to DHEQ Section 1, Questions 7-9 - Total Score; responses to DHEQ Section 2, Questions 1-15 - Restrictions, Adaptation, Social Impact, Emotional Impact & Identity Domains

To explore changes in self-perceived discomfort associated with tooth sensitivity, as measured by a numeric rating scale (NRS), after 3 days and 2, 4 and 8 weeks twice daily use of a 3% PVM/MA + 5% KNO_3 combination toothpaste, a 3% PVM/MA only toothpaste, a 5% KNO_3 only toothpaste and a regular fluoride toothpaste (negative control).	*At Baseline, Day 3 and Weeks 2, 4 & 8:* - NRS score *At Day 3 and Weeks 2, 4 & 8:* - Change from Baseline in NRS score
Safety	
To assess the safety and tolerability of study products with twice daily use for 8 weeks.	Treatment emergent adverse events

No formal success criterion has been defined for this exploratory study; however, if the combination toothpaste provides greater sensitivity protection, it would be expected that the performance profiles (plots of Schiff sensitivity score, tactile threshold (g) and number of sensitive teeth) for the 3% PVM/MA + 5% KNO_3 toothpaste would show a consistent improvement in sensitivity with 8 weeks twice-daily use, directionally superior to the respective component formulations (PVM/MA alone and KNO_3 alone) and the negative control.

4 STUDY DESIGN

4.1 Overall Design

This will be a PoP, single centre, 8-week, randomised, controlled, examiner blind, parallel design, stratified (by maximum Baseline Schiff sensitivity score of the two selected test teeth) clinical study in healthy subjects with sensitive teeth.

To help minimise the potential impact of 'placebo'/'no treatment' effects, and to standardise oral hygiene practices, an acclimatisation period (2-4 weeks) will be included between the Screening and Baseline assessments. Subjects who meet all study criteria at both Screening and Baseline visits will be randomised to one of the 4 study products.

In line with widely recommended oral hygiene practice and typical consumer habit, study subjects will be requested to brush their teeth for one timed minute twice daily (morning

and evening) with their assigned study toothpaste, covering the toothbrush head with full ribbon of toothpaste (approximately 1.5 g) on each brushing occasion.

Two independent stimulus-based (tactile and evaporative) measures of tooth sensitivity will be employed.

- A tactile stimulus will be administered using a constant pressure probe (Yeaple Probe (Polson et al., 1980)). Subject response will determine the tactile threshold in grams (g).
- An evaporative (air) stimulus will be administered using a dental air syringe. Subject response will be evaluated using the Schiff sensitivity scale (Schiff et al., 1994).

Sensitivity to tactile and evaporative (air) stimuli will be assessed at Screening (Visit 1) and then at various time points across the 8-week usage period - Baseline (Day 0), Day 3 and Weeks 2, 4 and 8. A single clinical examiner will assess both measures for the duration of the study for all study subjects. On completion of the Baseline assessments, the clinical examiner will select two 'test teeth' from those that qualified at Screening and Baseline, for assessment of tactile and evaporative (air) sensitivity at all subsequent visits. In addition, the remaining 'eligible teeth' identified as sensitive to both tactile and evaporative (air) stimuli at Screening will be assessed for evaporative (air) sensitivity only at Day 3 and Weeks 2, 4 and 8.

Oral Health Related Quality of Life (OHRQoL) will be evaluated using the validated Dentine Hypersensitivity Experience Questionnaire (short version DHEQ-15); this will be completed by study subjects at Baseline (Day 0), and after 3 days and 2, 4 and 8-weeks product use. A Numeric Rating Scale (NRS) will be also used to explore changes in self-perceived discomfort associated with tooth sensitivity after 3 days and 2-, 4- and 8-weeks product use.

Safety and oral tolerability of the study products will be monitored over the 8-week usage period by review of reported AEs.

4.2 Scientific Rationale for Study Design

The study will investigate the ability of an experimental combination toothpaste containing 3% weight/weight (w/w) PVM/MA + 5% w/w KNO_3 (Test Product), a 3% w/w PVM/MA only toothpaste (Comparator 1), a 5% w/w KNO_3 only toothpaste (Comparator 2) and a regular fluoride toothpaste with no known anti-sensitivity properties (negative control) to protect sensitive teeth from DH. Trends in sensitivity measures over time (from Baseline to 8 weeks) will be investigated for each product group as the primary objective. Inter-product comparisons will be investigated as secondary objectives; comparisons between the Test and Comparator toothpastes will be of particular interest to explore if the combination toothpaste provides enhanced sensitivity protection.

The randomised, controlled, examiner-blind, parallel design selected for this study follows the recommended approach for investigating the performance of sensitivity products.

Use of two independent stimulus-based (tactile and evaporative (air)) measures of tooth sensitivity is in line with published recommendations for the design and conduct of sensitivity clinical studies. The selection of two 'test teeth' to evaluate changes in DH is also common practice in sensitivity studies (Schiff et al., 1994). Eligible subjects will be stratified after the Baseline assessments according to the maximum Schiff sensitivity score of their two selected 'test teeth' to ensure product groups are balanced for sensitivity severity.

Study subjects will be aged between 18 and 65 years; DH most frequently occurs between the ages of 20 and 40 years and is known to decrease with age above 40 years (Bartold, 2006, West et al., 2014, Dababneh et al., 1999).

According to ICH guidelines, for a study to be classed as truly double blind, not only does the examiner (and any appropriate member of staff who may be involved in the dispensing of products, analysis of data etc.) need to be blinded as to the product the subject receives, but the products under test must be identical in every way (colour, flavour, appearance, packaging). Given it is almost impossible to ensure identical appearance, taste and packaging for the toothpastes evaluated in oral care studies, the level of product blinding for this study is described as 'examiner blind'. Study toothpastes will be supplied in over-wrapped tubes. The blind will be maintained by staff involved in dispensing, brushing

instruction and supervised brushings not being involved in the clinical examinations and study products being provided to subjects in blinded packs.

The DHEQ is a validated, condition-specific measure of the impacts of tooth sensitivity on everyday life; it has been shown to have good psychometric properties in both the general population and in a clinical sample of subjects with sensitive teeth (Boiko et al., 2010, Baker et al., 2014). A short form of the DHEQ (DHEQ-15) has also been developed and validated (Machuca et al., 2014) and will be included in this study to evaluate product performance in a clinically diagnosed DH population. In addition, an NRS will be used to monitor changes in the level of subject-perceived discomfort associated to tooth sensitivity at the same time points as the DHEQ.

4.3 Justification for Product Usage Regimen

The 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 and is based on widely recommended oral hygiene practice/typical consumer habit. Study subjects will be required to brush for at least 1 timed minute with their assigned study toothpaste on each brushing occasion. Subjects will brush their two selected sensitive 'test teeth' first, followed by their whole mouth. After 8 weeks (Day 56 ±2 days) twice daily usage, each subject should complete between 108-116 brushings.

Each subject 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 check correct usage and to encourage compliance with the required usage regimen for the duration of the study.

4.4 End of Study Definition

A subject is considered to have completed the study if they complete 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 shown in the Schedule of Activities for the last subject in the trial.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

The study will be conducted in male and female subjects in good general health, with pre-existing self-reported tooth sensitivity and at least two sensitive teeth (clinically confirmed DH) that meet all study criteria at both the Screening (Visit 1) and Baseline (Visit 2) visits. Sufficient subjects will be screened and entered into the acclimatisation phase to ensure approximately 120 subjects are randomised to study product (approximately 30 subjects per product arm). Subjects will be recruited primarily from the study site database.

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 or not a subject is suitable.

Eligibility to participate should be reviewed and documented by an appropriate member of the study site team before each subject is included in the study.

5.2 Inclusion Criteria

An individual must meet all the following inclusion criteria to be eligible to be included in the study:

1. Provision of a signed and dated informed consent indicating the subject has been informed of all pertinent aspects of the study before any study procedures are performed.
2. Male or female subject who, at the time of screening, is between the ages of 18 and 65 years inclusive.
3. Subject who is willing and able to 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. Female subject of child-bearing potential and at risk for pregnancy who agrees to use a highly effective method of contraception throughout the study and for at least 5 days after the last use of assigned study product.
6. **AT VISIT 1 (Screening):**

   Subject must have

   a) a self-reported history of tooth sensitivity lasting more than six months but not more than 10 years.

   b) a minimum of 20 natural teeth.

   c) a minimum of 2 accessible, non-adjacent teeth (incisors, canines, pre-molars), preferably in different quadrants, with clinically confirmed DH; each tooth must meet the following criteria:
      - exposed dentine due to facial/cervical erosion, abrasion or gingival recession (EAR).
      - MGI score = 0 adjacent to the test area (exposed dentine) only (Lobene et al., 1986)
      - clinical mobility = 0 (Laster et al., 1975)
      - DH as evidenced by qualifying levels of tactile and evaporative (air) sensitivity (tactile threshold ≤ 20 g; Schiff sensitivity score ≥ 2).
7. **AT VISIT 2 (Baseline):**

   Subject must have a minimum of two, non-adjacent accessible teeth (incisors, canines, pre molars) with DH, as evidenced by qualifying levels of tactile and evaporative (air) sensitivity (tactile threshold ≤ 20 g; Schiff sensitivity score ≥ 2) at the Screening and Baseline visits.

Note**: **All teeth which meet the eligibility criteria at Screening (Visit 1) should be assessed by tactile and evaporative (air) stimuli at Baseline (Visit 2).

The examiner will select two 'test teeth' from those which meet the tactile threshold and Schiff sensitivity score inclusion criteria at both Screening and Baseline. Test teeth should not be adjacent to each other and preferably in different quadrants.

5.3 Exclusion Criteria.

An individual who meets any of the following exclusion criteria will 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 GSK CH employee directly involved in the conduct of the study or a member of their immediate family.
2. Subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days of study entry and/or during study participation.
3. 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.
4. Female subject who is pregnant (as evidenced by a positive urine pregnancy test (UPT) at Screening) or intending to become pregnant during the study.
5. Female subject who is breastfeeding.
6. Subject with known or suspected intolerance or hypersensitivity to the study products or any of their stated ingredients (or closely related compounds).
7. Subject who is unwilling or unable to comply with the Lifestyle Considerations described in the protocol (Section 5.5).

8. Subject with a recent history (within the last year) of alcohol or other substance abuse.
9. Subject who has participated in another tooth sensitivity study within 8 weeks of Screening.
10. Subject who has used an oral care product indicated for the relief of DH or care of sensitive teeth within 8 weeks of Screening (subjects will be required to verbally confirm the name of their current oral care products to enable site staff to verify the absence of known sensitivity ingredients).
11. Subject who has had dental prophylaxis within 4 weeks of Screening.
12. Subject who has had a teeth bleaching procedure within 8 weeks of Screening.
13. Subject who has had treatment for periodontal disease (including surgery) within 12 months of Screening.
14. Subject who has had scaling or root planning within 3 months of Screening.
15. Subject with gross periodontal disease.
16. Subject with evidence of gross intra-oral neglect or the need for extensive dental therapy.
17. Subject with a tongue or lip piercing.
18. Subject with a fixed or removable partial prosthesis which, in the opinion of the investigator, would impact study outcomes.
19. Subject with multiple dental implants which, in the opinion of the investigator, would impact study outcomes.
20. Subject with fixed or removable orthodontic braces/bands or a fixed orthodontic retainer.
21. **SPECIFIC DENTITION EXCLUSIONS FOR 'TEST TEETH':**
    a) Tooth with evidence of current or recent caries or reported treatment of decay within 12 months of Screening.
    b) Tooth with exposed dentine but with deep, defective or facial restorations.
    c) Tooth with full crown or veneer.

d) Tooth adjacent to a bridge abutment or crown which, in the opinion of the investigator, would impact study outcomes.

e) Sensitive tooth with contributing etiologies other than erosion, abrasion or recession to exposed dentine.

f) Sensitive tooth not expected to benefit from use of a sensitivity toothpaste in the opinion of the investigator

22. Subject taking daily doses of medication/treatments which, in the opinion of the investigator or medically qualified designee, could interfere with their perception of tooth sensitivity (examples of such medications include analgesics, anticonvulsants, antihistamines that cause marked or moderate sedation, sedatives, tranquilisers, antidepressants, mood-altering and anti-inflammatory drugs).

23. AT VISIT 1 (Screening):

Subject who has taken antibiotics in the 2 weeks prior to the Screening visit.

24. AT VISIT 2 (Baseline):

Subject who has taken antibiotics in the 2 weeks prior to the Baseline visit, during the acclimatisation period.

25. Subject who is taking daily doses of a medication which, in the opinion of the investigator or medically qualified designee, is causing xerostomia.

26. Subject who requires antibiotic prophylaxis for dental procedures.

27. Subject who has previously been enrolled in this study.

28. Subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.

5.4 Randomisation Criteria

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

Subjects will be stratified (by 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.

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, 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 this is not possible, the following visit specific actions should be taken.

- **Screening (Visit 1):** if the subject cannot be reappointed, they will be withdrawn from the study (Section 7.1). No clinical assessments will be performed. The subject may be replaced.
- **Baseline (Visit 2):** if the subject cannot be reappointed, they will be withdrawn from the study (Section 7.1). No clinical assessments will be performed. The subject will not be replaced.
- **Day 3 (Visit 3):** the subject will continue in the study. No clinical assessments will be performed.
- **Weeks 2 and 4 (Visits 4-5):** if the subject cannot be reappointed (within the visit tolerance for Visits 4-6), they will continue in the study. No clinical assessments will be performed.
- **Week 8 (Visit 6)**: if the subject cannot be reappointed, they will be withdrawn from the study (Section 7.1). No clinical assessments will be performed. The subject will not be replaced.

5.5.1 Oral Hygiene Restrictions

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

- Subjects should not use any other oral care products (for example, toothpastes, toothbrushes, oral rinses, tongue cleaners, whitening/bleaching products, interdental cleaning products) than those provided during the study.

  Note: dental floss can be used to remove impacted food.

- Subjects should not use any other dental products intended for treating or caring for sensitive teeth (including herbal remedies) than those provided during the study.
- Subjects should not chew gum.

Before a Clinical Assessment Visit: Baseline (Visit 2) to Week 8 (Visit 6)

- Subjects will refrain from all oral hygiene procedures for at least 8 hours before a study visit.

5.5.2 Dietary and Alcohol, Restrictions

Before a Clinical Assessment Visit: Baseline (Visit 2) to Week 8 (Visit 6)

- Subjects should not eat or drink for at least 4 hours before a study visit.

  Small sips of room-temperature water will be permitted to take medications or to relieve a dry mouth up to 1 hour before attending the study site (but not within 1 hour of the visit).

- Subjects should refrain from excessive alcohol consumption for 24 hours before a study visit.

5.5.3 Contraception (Hatcher and Nelson, 2007)

All female subjects who are of child-bearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active study period and for at least 5 days after the last use of assigned study product.

Female subjects of non-child-bearing potential must meet at least one of the following criteria (subject-reported):

- female who has achieved post-menopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause;
- female who has undergone a documented hysterectomy and/or bilateral oophorectomy;
- female who has undergone one of the following procedures: bilateral tubal ligation or salpingectomy; hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion;
- female who has medically confirmed ovarian failure;
- female who is pre-menarcheal.

The investigator, or their designee, will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation. In addition, the investigator, or their designee, will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

The following is the all-inclusive list of the methods for avoiding pregnancy that meets the GSK definition of highly effective (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label)

The list does not apply to females of reproductive potential with same sex partners or to subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

- Contraceptive subdermal implant
- Intrauterine device (IUD) or intrauterine system
- Combined estrogen and progestogen oral contraceptive

- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches
- Male partner sterilisation with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject. The documentation on male sterility can come from site personnel review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator will confirm that subjects have had instruction in how to properly use these methods of contraception from an appropriately trained health care professional and will document such conversation.

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, and any adverse events as applicable.

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

5.7 Sponsor's Qualified Medical Personnel

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

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

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately experienced GSK CH 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

Examiners involved in screening and clinical assessment procedures will be qualified dentists, registered to practice in the UK. Oral examinations to determine subject eligibility and all safety/product performance (tactile threshold/ Schiff sensitivity scale) assessments will be performed by appropriately trained clinical examiners. No additional qualifications are required for the clinical examiners involved in this study.

6 STUDY PRODUCTS

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

This includes a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

6.1 Study Product Supplies

The following study products will be supplied by Clinical Supplies Department, GSK CH.

Table 6-1 Investigational/Study Product Supplies

Product Description	**Acclimatisation Product**	**Test Product**	**Comparator 1**	**Comparator 2**	**Negative control**
	Regular fluoride toothpaste	3% PVM/MA + 5% KNO_3 combination toothpaste	3% PVM/MA only toothpaste	5% KNO_3 only toothpaste	Regular fluoride toothpaste
Fluoride content	1450ppm fluoride as NaF	1450ppm fluoride as NaF	1450ppm fluoride as NaF	1450ppm fluoride as NaF	1450ppm fluoride as NaF
Product Name	Colgate Cavity Protection	N/A	N/A	N/A	Colgate Cavity Protection
Pack Design	One carton containing 2 overwrapped tubes of toothpaste				
Dispensing Details	Visit 1 (Screening): 1 carton	Visit 2 (Baseline): 2 cartons			
Product Master Formulation Code (MFC)	Commercial Product	CCI	CCI	CCI	Commercial Product
Product Application	Subjects will dose the toothbrush provided with a strip of dentifrice (a full brush head) on each brushing occasion				
Route of Administration	Topical Oral Use				
Usage Instructions	Subjects will brush for one timed minute, twice daily (morning and evening); subjects will be permitted to rinse with water post-brushing.	Subjects will brush their two selected 'test teeth' first, followed by the whole mouth for one timed minute, twice daily (morning and evening); subjects will be permitted to rinse with water post-brushing.			
Return Requirements	All used/unused product to be returned to GSK				

Table 6-2 Sundry Items

Item	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
Aquafresh, flat trim, medium toothbrush (Germany)	GSK CH	Individual toothbrush in commercial pack	One toothbrush at Screening for use with acclimatisation toothpaste One toothbrush at Baseline for use with assigned study toothpaste	Destroy at site using site disposal procedures	Return to GSK
Countdown Timer	GSK CH	Individual timer in commercial pack	One timer at Screening visit	Subject to keep or destroy at site using site disposal procedures	Return to GSK
Pregnancy Tests (UK Market)	GSK CH	Commercial pack	Use as per study schedule	Destroy at site using site disposal procedures	Return to GSK

For further information, please refer to the Global Clinical Supplies (GCS) Packaging and Labelling Proposal. GSK CH will ensure copies of the diary (which will also include toothpaste usage instructions), the clinical assessment score sheets, the DHEQ-15, the NRS question and the Subject Contact Cards are provided to the study site.

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

6.1.1 Product Form and Packaging

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

The test product and comparator toothpastes will be manufactured and filled into plain white tubes by GSK CH with a study label affixed; the acclimatisation and control toothpastes will be supplied in their commercial packs. All study toothpastes (including

the acclimatisation product) will be 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 GSK CH GCS group. 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 acclimatisation toothpaste and their assigned study toothpaste to cover usage during the acclimatisation and treatment periods, respectively. Acclimatisation toothpaste will be dispensed at Screening (Visit 1); study toothpaste will be dispensed at Baseline (Visit 2). 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 will be instructed to not remove or deface any part of a product 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 randomisation schedule generated by an approved GSK CH vendor, prior to the start of the study, using validated software.

The product dispensing area will be separate from the clinical examination area. Study toothpastes will be dispensed in blinded fashion to the subject, by trained site personnel. These staff members will not be involved in any safety/product performance assessments or other aspects of the study that could be influenced by the knowledge of product a subject has been assigned to. An additional member of the site 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 case report form (eCRF).

6.2 Administration

Subjects will be instructed to self-administer the acclimatisation toothpaste and their assigned study toothpaste according to the usage instructions provided at the study site and detailed in the diary. To help ensure subjects fully understand the amount of toothpaste to be used each time they brush and the usage instructions:

- staff will demonstrate dispensing a full ribbon of toothpaste along the length of the toothbrush head to each eligible subject and supervise their first brushing with the acclimatisation toothpaste/diary completion at the end of the Screening visit (Visit 1), after all clinical assessments have been completed;
- staff will supervise the first brushing with study toothpaste/diary completion at the end of the Baseline visit (Visit 2), after all clinical assessments have been completed;
- staff will supervise a brushing with study toothpaste/diary completion at the end of the Day 3, Week 2, 4 and 8 visits (Visits 3-6), 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 Usage Errors

Study product usage errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, in the wrong way.

Such study product usage errors occurring to a study subject are to be captured in the eCRF. In the event of study product usage error, the sponsor should be notified immediately.

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

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

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

6.2.2 Overdose

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

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

6.3 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, the product label and Clinical Study Supplies Checklist.

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

Any excursions from the product-label storage conditions 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 secure location to which only permitted staff have access. Upon receipt, all study products should be stored according to the instructions specified on the product labels. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorised site staff.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the 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 return used and unused tubes of their assigned study toothpaste to the study site at their last visit (for most subjects this will be Visit 6). 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 conclusion of the study, the investigator or an appropriate designee, and a representative of GSK CH (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 (including empty containers), will be returned for destruction to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided.

Return and destruction instructions for sundry items are provided in Table 6-2.

6.5 Blinding and Allocation/Randomisation

All subjects will be centrally randomised to one of the four study products 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 (the subjects, investigator, clinical examiner and monitor will be blinded to product received). Site staff, the study statistician, data management staff, other employees of the Sponsor and vendors acting on behalf of the sponsor, who may influence study outcomes will also be blinded to the product allocation.

To ensure the clinical examiner remains blinded throughout the study:

- site staff involved in the dispensing of study product and the supervision of onsite product usage will work in a separate area;
- the examiner will not be permitted in any area where study product is stored, dispensed, or in use;
- study subjects will be instructed not to remove study product from the opaque bags it is provided in outside of the dispensing room, while at the study site;
- dispensing staff and on-site brushing supervisors will not be involved in any safety/product performance assessments during the study.

6.6 Breaking the Blind

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

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

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

Any AE associated with breaking the blind must be recorded and reported as specified in this protocol. The study site may also be required be required to inform the REC 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) and at Baseline (Visit 2) to record each brushing with the acclimatisation toothpaste and their assigned study product throughout their study participation. They will also use the diary 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.

Subjects will attend each study visit with all tubes of toothpaste provided (used and unused) for a visual check of product usage, and with their completed diary for review by study staff.

Any suspected over or under use, and the number of any missed or additional brushings, will be documented in the eCRF. Subjects will be re-instructed in the correct product usage requirements and diary completion as needed.

Supervised brushings will be carried out at the study site at the end of Visits 2-5 to facilitate subject compliance with product usage instructions.

6.8 Concomitant Medication/Treatment(s)

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

Medications taken and treatments within 30 days of signing the informed consent form will be documented as a prior medication/treatment. Medications taken and treatments started 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 treatment until after study completion (including dental prophylaxis).
- Should a randomised subject start a course of treatment which includes daily or intermittent use of an analgesic, details of that medication/treatment will be recorded as outlined above. The investigator or designee will decide if the subject should continue on the study or be withdrawn.
- Should a subject take a medication which, in the opinion of the investigator or their medically qualified designee, could impact their perception of sensitivity (for example, an analgesic) within 8 hours of a scheduled study visit, 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 this is not possible, the following visit specific actions should be taken.

  Screening (Visit 1): if the subject cannot be reappointed, they will be withdrawn from the study (Section 7.1). No tooth sensitivity assessments will be performed. The subject may be replaced.

Baseline (Visit 2): if the subject cannot be reappointed, they will be withdrawn from the study (Section 7.1). No tooth sensitivity assessments will be performed. The subject will not be replaced.

Day 3 (Visit 3): the subject will continue in the study. Tooth sensitivity assessments will be performed.

Week 2, 4 & 8 (Visits 4-6): if the subject cannot be reappointed (within the visit tolerance for Visits 4-6), they will continue in the study. Tooth sensitivity assessments will be performed.

- Subjects should not participate in any other clinical study (including cosmetic studies) or be in receipt of another IP.

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, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

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

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

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

7.2 Lost to Follow up

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

A subject will be considered lost to follow up if 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). These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all study products provided and, if appropriate, request the subject return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs).

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

Should the subject continue to 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 so long as the subject's safety was preserved.

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

8 STUDY PROCEDURES

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

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

8.1 Screening: Day -28 to Day -14 (Visit 1)

Screening procedures will be conducted by the investigator, or suitably qualified designee.

8.1.1 Informed Consent

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

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

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

The time the subject signed the informed consent form will be captured as this is the point from which all Adverse Events will be captured. The date and time of consent will be captured in the eCRF.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study (2 copies

as before). Each subject should be provided with a copy of the signed and dated amended consent form. The date of re-consent will be recorded on the eCRF.

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

e-Consent is a tool that assists in the consent process by using multimedia components delivered by an electronic system (e.g. iPad/tablet). The multimedia components consist of video, audio, knowledge review, dictionary and electronic signature The site staff can use the system to consent the subject with the benefit of helping the subject understand the research they are taking part in and to control the consent process. The system will allow for a copy of the consent to be printed and given to the subject and for consent documents to be retained by the site in PDF format. A GSK CH approved vendor will be used to provide the system and training and help desk will be provided as needed. If the country and/or site does not have approval to use the e-Consent system, or the subject does not want to use the e-Consent system, then the conventional paper process will be followed. It is possible to use the e-Consent system to educate the subject while using paper to obtain signatures.

8.1.2 Demographics

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

Ethnicity and race of subjects will be recorded in accordance with FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials, 2005.

8.1.3 Inclusion/Exclusion Criteria

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

8.1.4 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history, including allergies and drug sensitivities, will be documented in the eCRF.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days will be documented in the eCRF.

8.1.5 Subject Eligibility

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

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

8.1.6 Screening Procedures

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

- Review the oral care products the subject is currently using (subject will provide the names of their current oral care products) to confirm they do not contain any ingredients intended for treating sensitive teeth.
- Female subjects of child-bearing potential only complete a UPT.
- Clinical examiner completes an OST examination as described in Section 9.3.1.
- Clinical examiner completes as OHT examination as described in Section 9.3.2.
- Clinical examiner completes eligible teeth assessments for incisors, canines and pre-molars, including dentition exclusions and assessments of EAR, MGI and tooth mobility as described in Section 5.3, Section 9.1.1, Section 9.1.2 and Section 9.1.3 respectively.
- Clinical examiner assesses the sensitivity of each tooth that meets the above eligibility criteria, first to a tactile stimulus and then to an evaporative (air) stimulus, as described in Section 9.1.4 and Section 9.1.5 respectively. Evaporative (air) sensitivity will only be assessed for teeth with a qualifying tactile threshold of ≤ 20 g. The examiner will allow at least 5 minutes between the completion of the tactile assessments and the start the evaporative (air) assessments.

To facilitate subject flow, clinical assessments may be recorded on a paper score sheet (source document) and later transcribed into the eCRF.

The same examiner will be responsible for completing both sensitivity measures (tactile and evaporative (air) sensitivity) for the duration of the study.

8.1.7 Supervised Use of Acclimatisation Toothpaste

Eligible subjects will be provided with the acclimatisation toothpaste, a toothbrush, diary and timer to use during the acclimatisation period (2-4 weeks). Toothpaste usage instructions will be described to the subject and covering the full brush head with toothpaste will be demonstrated. Staff will supervise the subject carrying out first their first use of acclimatisation toothpaste and recording first use in their diary.

Completion of all procedures 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. Any AEs reported on completion of the supervised brushing with the acclimatisation toothpaste will be recorded in the eCRF.

8.2 Study Period

8.2.1 Baseline: Visit 2 (Day 0)

Changes in concomitant medication or non-drug treatments/procedures 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.

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

- Complete visual checks of returned acclimatisation toothpaste tubes and review completed diary. Record any suspected over or under use and the number of any missed or additional brushings.

  Do not return acclimatisation toothpaste/toothbrush/diary to subject.

- Confirm subject adherence to the requirements of the protocol and continuance.

- Female subjects of child-bearing potential only to self-report pregnancy status.
- Subject completes a DHEQ Sections 1 and 2 (source document) for later transcription into the eCRF.
- Subject completes the NRS question (source document) for later transcription into the eCRF
- Clinical examiner completes an OST examination.
- Clinical examiner completes sensitivity assessments for each eligible tooth identified at Screening, first to a tactile stimulus and then to an evaporative (air) stimulus.

  Eligible teeth are defined as incisors, canines and pre-molars with none of the study-specific dentition exclusions (Section 5.3) which meet the EAR, MGI and mobility inclusion criteria (Section 5.2) and had a tactile threshold ≤ 20 g and a Schiff sensitivity score ≥ 2 at Screening (Visit 1).

  The examiner will allow at least 5 minutes between the completion of the tactile assessments and the start the evaporative (air) assessments for tooth recovery. To facilitate subject flow, assessments may be recorded on a paper score sheet (source document) and later transcribed into the eCRF.
- Clinical examiner reviews inclusion and exclusion criteria and confirms subject eligibility. Subjects who meet all the inclusion criteria and none of the exclusion criteria with at least 2 eligible sensitive teeth (tactile threshold ≤ 20 g and Schiff sensitivity score ≥ 2 at Screening and Baseline) will continue.
- Clinical examiner selects the two 'test teeth'.
- Complete stratification and randomisation.
- Dispense allocated study toothpaste, toothbrush and diary.
- Describe toothpaste usage instructions and diary completion to subject; supervise their first use of study toothpaste and recording of brushing in the diary.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed.

Any AEs reported on completion of the supervised brushing with the assigned study toothpaste will be recorded.

- Remind the subject of the Lifestyle Guidelines (Section 5.5) and any Concomitant Medication/Treatment(s) requirements (Section 6.8) of the protocol.

8.2.2 Visits 3-5 (Day 3±1 day, Week 2±1 day and Week 4 ±2 days)

Changes in health, concomitant medication or non-drug treatments/procedures 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.

The following procedures will then be completed at each visit, and data recorded in the eCRF.

- Complete visual checks of returned study toothpaste tubes and review completed diary. Record any suspected over or under use and the number of any missed or additional brushings. Re-instruct the subject in the correct dosing, usage requirements and diary completion as needed.

  Return toothpaste/toothbrush/diary to subject.
- Confirm subject adherence to the requirements of the protocol and continuance.
- Female subjects of child-bearing potential only to self-report pregnancy status.
- Subject completes a DHEQ Section 1 Questions 7-9 only and Section 2 all questions (source document) for later transcription into the eCRF.
- Subject completes the NRS question (source document) for later transcription into the eCRF
- Clinical examiner completes an OST examination.
- Clinical examiner completes sensitivity assessments for the two 'test teeth' selected at Baseline, first to a tactile stimulus and then to an evaporative (air) stimulus.

  The examiner will allow at least 5 minutes between the completion of the tactile assessments and the start the evaporative (air) assessments for tooth recovery.

Record clinical assessment scores using source documentation for later transfer to the eCRF.

- Clinical examiner then assesses the evaporative (air) sensitivity (Schiff Sensitivity Scale only) of all remaining eligible teeth identified at Screening.

  Record clinical assessment scores using source documentation for later transfer to the eCRF.

- Remind subject of toothpaste usage instructions; supervise brushing with study toothpaste and recording of brushing in the diary.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed. Any AEs reported on completion of the supervised brushing with the assigned study toothpaste will be recorded.
- Remind the subject of the Lifestyle Guidelines (Section 5.5) and any Concomitant Medication/Treatment(s) requirements (Section 6.8) of the protocol.

8.2.3 Visit 6 (Week 8 ±2 days)

Changes in health, concomitant medication or non-drug treatments/procedures 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.

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

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

  Do not return toothpaste/toothbrush/diary to subject.

- Confirm subject adherence to the requirements of the protocol and continuance.
- Female subjects of child-bearing potential only complete a UPT.

- Subject completes a DHEQ Section 1 Questions 7-9 only and Section 2 all questions (source document) for later transcription into the eCRF.
- Subject completes the NRS question (source document) for later transcription into the eCRF
- Clinical examiner completes an OST examination, then an OHT examination.
- Clinical examiner completes sensitivity assessments for the two 'test teeth' selected at Baseline, first to a tactile stimulus and then to an evaporative (air) stimulus.

  The examiner will allow at least 5 minutes between the completion of the tactile assessments and the start the evaporative (air) assessments for tooth recovery. Record clinical assessment scores in the eCRF or using source documentation for later transfer to the eCRF.
- Clinical examiner then assesses the evaporative (air) sensitivity (Schiff Sensitivity Scale only) of all remaining eligible teeth identified at Screening.

  Record clinical assessment scores in the eCRF or using source documentation for later transfer to the eCRF.
- Remind the subject to inform the site if they experience any untoward medical occurrence or use any medications in the next 5 days (that is, in the 5 days following their last use of study product).
- Study conclusion.

8.3 Diary Review

The diary should be reviewed at every visit by the investigator, or suitably qualified designee, and the subject. Any subject-recorded comment captured in the diary considered an AE will be assessed and reported as described in Section 10.

Any additional comments relating to medications/treatments captured in the diary will be reviewed by the investigator, or medically qualified designee, with the subject and recorded in the eCRF as appropriate. Additional and missed product applications will be considered deviations from the protocol and will be recorded on the Deviations Log and captured as a deviation in the eCRF.

8.4 Study Conclusion

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

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

8.5 Follow-up Visit/Phone Call

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

9 STUDY ASSESSMENTS

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

To ensure the clinical examiner/staff involved in safety/product performance assessments remain blind to product received throughout the study, site staff involved in the dispensing of study product and the supervision of on-site product usage will work in a separate area; the examiner will not be permitted in any area where study product is stored, dispensed or in use; study subjects will be instructed not to remove study product from the opaque bags

provided, outside of the dispensing room, while at the study site; dispensing staff will not be involved in any safety/product performance assessment procedures during the study.

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the Study Procedures section of this protocol (Section 8). Eligible tooth assessments will be accomplished by oral examination and will evaluate dentition exclusions, EAR, MGI, tooth mobility and sensitivity to tactile and evaporative (air) stimuli. Eligibility assessments will be carried out by the investigator, or qualified designee, against the inclusion/exclusion criteria. Ineligible subjects will not be re-screened.

9.1.1 Erosion, Abrasion and Recession (EAR)

The facial surfaces of all incisor, canine and pre-molar teeth 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, 2002).

9.1.2 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 will be scored for the facial gingiva only, adjacent to the test area (exposed dentine). Eligible teeth will have a MGI score of zero.

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

9.1.3 Tooth Mobility Assessment

Clinical mobility will be assessed for incisor, canine and pre-molar teeth exhibiting none of the dentition exclusions, facial/cervical EAR and MGI = 0, using a modification of the Miller Index (Laster et al., 1975). Eligible teeth will have clinical mobility = 0.

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

9.1.4 Qualifying Tactile Sensitivity (Visit 1)

The tactile sensitivity of incisor, canine and pre-molar teeth exhibiting none of the dentition exclusions, and meeting the EAR, MGI and clinical mobility criteria, will be assessed using a constant pressure probe (Yeaple probe (Polson 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, the subject will be asked to indicate whether they experienced any sensitivity or discomfort (yes/no response only). The subject may respond "yes" if they feel pressure as the probe is applied to their tooth. The examiner will remind them they should only respond 'yes' if they feel sensitivity or discomfort. The gram setting which elicits the two consecutive 'yes' responses will be recorded as the tactile threshold (g). At Screening, the upper force setting will be 20 g.

For a tooth to qualify at Screening, it must have a tactile threshold ≤ 20 g. If no sensitivity is found at the upper setting, the tactile threshold will be recorded as > 20 g 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 response. If uncertainty continues, this will be indicated on the clinical assessment score sheet/in the eCRF. 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 assistant by a non-verbal signal, i.e. a hand gesture), or move to the next force setting (10 g increase).

The examiner will generally make the pressure setting adjustments (may be carried out by an assistant/scribe); the scribe will record the micro-amperage setting and the subject's responses in a 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.

9.1.5 Qualifying Evaporative Air Sensitivity (Visit 1)

Evaporative (air) sensitivity will be assessed on the facial surfaces of incisor, canine and pre-molar teeth exhibiting none of the dentition exclusions, and meeting the EAR, MGI, clinical mobility criteria, with a tactile threshold (≤ 20 g) criteria; assessment will commence a minimum of 5 minutes after the tactile assessments have been completed. The assessment will be made by directing a one second application of air from a standard dental syringe held perpendicular to the tooth surface, approximately 1-2 mm coronal to the gingival margin, and from a distance of approximately 1 centimeter. The 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 et al., 1994). This is an examiner-based index, scored immediately following administration of the evaporative (air) stimulus. This scale focuses on a combination of specific, observable, physical, behavioural and verbal responses from the subject, which may facilitate discrimination.

For a tooth to qualify at screening, it must have a Schiff sensitivity score ≥ 2. If Schiff sensitivity score = 0 or 1, the tooth will be disqualified from further testing.

9.2 Product Performance Assessments

The following product performance assessments will be performed by appropriately trained staff/clinical examiners (who are blind to product received), at the times and in the order defined in the Study Procedures section of this protocol (Section 8).

9.2.1 Dentine Hypersensitivity Experience Questionnaire (DHEQ)

A 'short form' DHEQ (Appendix I: Example DHEQ-15) will be completed by each study subject at Baseline (Visit 2), Day 3 (Visit 3), Week 2 (Visit 4), Week 4 (Visit 5) and Week 8 (Visit 6), prior to the OST examination and clinical assessments.

The DHEQ is divided into two sections - Section 1 asks questions about 'your sensitive teeth and the impact it has on your everyday life'; Section 2 asks questions about 'the ways in which the sensations in your teeth affect you in your daily life' grouped into the following domains.

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

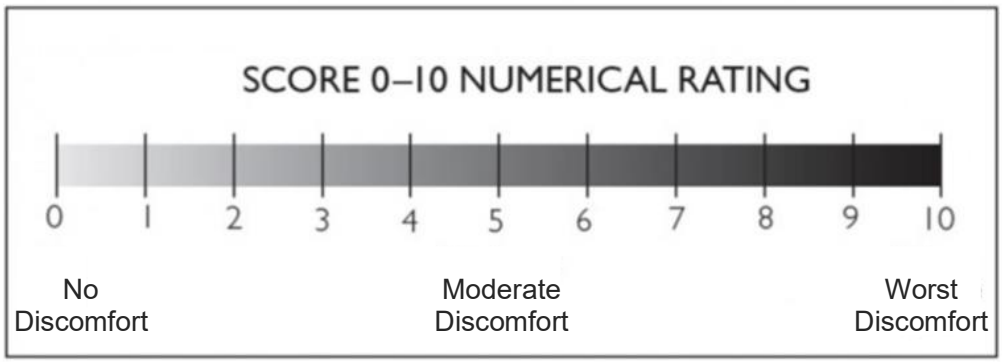
At Baseline, all questions will be answered - Section 1 (Q1-9) and Section 2 (Q1-15)

At Day 3, Week 2, Week 4 and Week 8, Section 1 (Q7-9 only) and Section 2 (Q1-15) will be answered.

9.2.2 Self-Perceived Sensitivity Discomfort Assessment

The 11-item Numeric Rating Scale (NRS) is a segmented numeric version of the visual analog scale (VAS) in which a respondent selects the number (0–10) that best reflects the intensity of the discomfort caused by their sensitivity (Hawker et al., 2011, Rocha et al., 2020). Similar to the VAS, the NRS is anchored by terms describing discomfort extremes and ranges from 0 = no discomfort to 10 = worst discomfort imaginable.

An NRS (example below) will be completed by each study subject at Baseline (Visit 2), Day 3 (Visit 3), Week 2 (Visit 4), Week 4 (Visit 5) and Week 8 (Visit 6), after the DHEQ but prior to the OST examination and clinical assessments.



9.2.3 Tactile Sensitivity Assessment

Visit 2: The tactile sensitivity of all qualifying teeth from Screening (i.e., teeth that exhibited none of the dentition exclusions, met the EAR, MGI, clinical mobility and qualifying tactile threshold/Schiff sensitivity score criteria) will be assessed at Baseline.

Visits 3-6: The tactile sensitivity of the two 'test teeth' selected by the clinical examiner at Baseline will be assessed for randomised subjects. The tactile stimulus will be administered and subject response recorded, as described in Section 9.1.4. The gram setting which elicits the two consecutive 'yes' responses will be recorded as the tactile threshold (g).

At Baseline (Visit 2), the upper force setting will be 20 g; at all subsequent visits (Visits 3-6), the upper force setting will be 80 g. If no sensitivity is found at the upper setting, the tactile threshold will be recorded as > 20 g at Baseline, and as > 80 g on Day 3, Week 2, 4 and 8.

9.2.4 Evaporative (Air) Sensitivity Assessment

Visit 2: The evaporative (air) sensitivity of all qualifying teeth from Screening will be assessed at Baseline.

Visits 3-6: The evaporative (air) sensitivity of the two 'test teeth' selected at Baseline will be assessed **first** for all randomised subjects; this will followed by the assessment of evaporative (air) sensitivity for all remaining eligible teeth identified at Screening.

The evaporative (air) stimulus will be administered, and subject response recorded, as described in Section 9.1.5. On every occasion, the evaporative (air) assessment of the two test teeth will begin a minimum of 5 minutes after the last tactile assessment has been completed (to allow tooth recovery time).

Score	Description
0	Subject does not respond to stimulus
1	Subject responds to stimulus but does not request discontinuation of stimulus
2	Subject responds to stimulus and requests discontinuation of, or moves from stimulus
3	Subject responds to stimulus, considers it uncomfortable and requests discontinuation of stimulus

9.2.5 Selection of Test Teeth

On completion of the Baseline clinical assessments, the clinical examiner will select two 'test teeth' for each eligible subject, to be evaluated first at all subsequent visits. The test teeth will exhibit none of the dentition exclusions and meet all the inclusion criteria for eligible teeth (including Screening and Baseline tactile threshold ≤ 20 g; Screening and Baseline Schiff sensitivity score ≥ 2). Test teeth should not be adjacent to each other and preferably in different quadrants.

9.3 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol (Section 8).

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, and mucogingival folds, gingival mucosa, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands. The results of the examination will be recorded in the eCRF as either normal or abnormal with details of any abnormalities. Any abnormality or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject from the OST examination carried out at Screening will be recorded as an AE.

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 any grossly carious lesions or signs of erosive wear, enamel irregularities, tooth fracture, gross decay, decalcification and faulty restorations.

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. Observations will be listed as either absent or present, and conditions noted as present will be described in the eCRF. Any change observed by the clinical examiner or reported by the subject from the OHT examination carried out at Screening will be recorded as an AE.

9.3.3 Pregnancy Testing

For female subjects of child-bearing potential, a UPT will be performed at Screening (Visit 1) and at Week 8 (Visit 6); the results must be obtained prior to first use of the acclimatisation toothpaste (Visit 1) and before the end of the study. They will also be asked to self-report their pregnancy status at the start of all other visits (Visits 2-5).

The investigator and site personnel will remind female subjects of child-bearing potential at each visit to inform site personnel if their menstrual cycle has changed or if they have any other reason to suspect they could be pregnant (e.g. had unprotected intercourse since the last visit).

A negative pregnancy test result is required before the subject receives the acclimatisation toothpaste. Pregnancy tests will also be done should one menstrual cycle be missed during the active study period (or when pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of the Research Ethics Committee (REC) or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of acclimatisation or study product and from the study.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

10.1 Definition of an Adverse Event (AE)

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

Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital sign measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of the 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" per se will not be reported as an AE. Such instances will be captured in the product performance assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of performance will be reported as AE if they fulfill the definition of an AE.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g. appendicitis).

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2 Definition of a Serious Adverse Event (SAE)

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

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

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

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

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

10.3 Time Period and Frequency for Collecting AE and SAE Information

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

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

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

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 considers the event to be reasonably related to the study product or study participation, the investigator must promptly notify the sponsor.

10.4 Reporting Procedures

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

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to non-leading such as “How do you feel” will be assessed and any 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 GSK CH in lieu of completion of the AE eCRF page/SAE form.

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

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be the documented as the AE/SAE, where known, and not the individual signs/symptoms (e.g., upper respiratory tract infection, seasonal allergy, 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. Where the same data are collected, the AE eCRF page 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 on the eCRF and the SAE form.

10.4.2 Reporting of a Serious Adverse Event

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

It is essential to enter the following information:

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

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

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken in relation to the study product
- Outcome if known

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

Email Serious Adverse Events to:

PPD

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

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

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

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

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above. An event is defined as 'serious' when it meets at least 1 of the pre-defined 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 page and the 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 Investigator Brochure (IB), Safety Statement and/or 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 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 GSK. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK CH.** The investigator may change 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 GSK CH to elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

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

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

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

10.7 Withdrawal Due to an Adverse Event

Withdrawal due to an AE 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 page.

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

10.8 Regulatory Reporting Requirements for SAEs

GSK CH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation.

Prompt notification of SAEs by the investigator to GSK CH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

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

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

An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure in the investigator study master file, and will notify the RIEC, 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 of child-bearing potential is participating in the study from the signing of informed consent until 5 days after last use of study product.

10.9.2 Action to be Taken if Pregnancy Occurs

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

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant/neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the investigator to the GSK CH Clinical Operations Safety Reporting email box and the GSK CH Study Manager or

designee will forward this information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK.

PPD

Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

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

Any female subject who becomes pregnant while participating will discontinue study product and/or be withdrawn from the study.

11 DATA MANAGEMENT

As used in this protocol, the term eCRF 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. To facilitate subject flow during Visits 1-6, clinical assessments (including tactile and evaporative (air) sensitivity) may be recorded on a paper score sheet (source document) and later transcribed into the eCRF; subjects will self-record each brushing occasion in paper diaries (source document); data relating to SAEs and pregnancy will also be collected on paper forms (source documents).

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

All 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 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 this unique number.

11.1 Case Report Form

An eCRF is a printed, optical, or electronic document designed to record the protocol required information to be reported to the sponsor on each study subject.

For each subject who has given informed consent the eCRF must be completed and signed by the investigator (or authorised designee) to certify the data are complete and correct. Where the eCRF is not the source document, the investigator must maintain accurate documentation (source data) to support information entered in the eCRF.

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

GSK CH 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, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the investigator.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using 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. A query should be issued to update the verbatim towards a codable description.

The study monitor will perform ongoing review 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 study monitor can also run reports and listings on the eCRFs, to raise manual queries as needed for site clarification or correction.

11.3 Processing Subject Reported Outcomes

Paper-based subject reported outcome (SRO) data will be collected from the product usage diary and DHEQ and entered into the eCRF.

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

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

11.4 External Data

Subject data generated externally to the eCRF from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSK CH is termed external data. No external data will be generated during the conduct of this study.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

No formal sample size has been produced for this PoP clinical study to investigate changes in sensitivity measures (Schiff sensitivity score, tactile threshold and number of sensitive teeth) over time with twice-daily use of a novel combination toothpaste. Based on previous, similar GSK CH studies evaluating the sensitivity protection provided by daily-use toothpastes, approximately 30 evaluable subjects per product group is considered sufficient to provide reliable estimates of performance for the purposes of this study and to aid in the design of future clinical studies. Approximately 120 subjects will be randomised to study product.

From a previous, similar GSK CH study (GSKCH Clinical Study 209723, 2020), change in Schiff sensitivity score at Week 8 had an SD of 0.7 units and the degree of variability (SD) in the test and control groups remained roughly consistent with each other over time. A similar trend was observed for the tactile threshold and number of sensitive teeth endpoints.

A sample size of 30 evaluable subjects per product group is expected to provide 95% CIs with a width of ± 0.261 units for the Schiff sensitivity score. This level of precision is considered sufficient for the purposes of this study. Approximately 120 subjects will be randomised to study treatment.

12.2 Populations for Analysis

The Safety population will include all randomised subjects who complete at least one use of study product. This population will be based on the product the subject received.

The modified Intent-To-Treat (mITT) population will include all randomised subjects who complete at least one use of study product and have at least one post baseline clinical performance assessment. This population will be based on the study product to which the subject was randomised. Any subject who receives a randomisation number will be considered to have been randomised.

The Per-Protocol (PP) population will include all randomised subjects who do not have any protocol deviations that could confound the interpretation of analyses conducted on the mITT.

12.3 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical reporting and analysis plan (RAP), which will be written following finalisation of the protocol and prior to study unblinding/analysis (as appropriate).

Where a hypothesis test between products is conducted, product differences in the study variables will be tested under the null hypothesis, H0: there is no product difference, versus the alternate hypothesis (H1) that there is a product difference.

12.3.1 Primary Analyses

The modified Intent-to-Treat (mITT) population will be used for the primary analyses.

The primary analysis variables are:

- Schiff sensitivity score at Day 0 (Baseline), Day 3, Weeks 2, 4 and 8;
- Tactile threshold (g) at Days 0 (Baseline), Day 3, Weeks 2, 4 and 8;
- Number of sensitive teeth (Schiff sensitivity score ≥ 1) at Day 0 (Baseline), Day 3, Weeks 2, 4 and 8.

Schiff sensitivity score is derived as the average score of the two test teeth; tactile threshold (g) is derived in the same way. Summary statistics (mean, median, SE, SD, minimum,

maximum) will be presented for each outcome variable at each assessment time point. Raw means (± SE) of Schiff sensitivity score and tactile threshold (g) and the number of sensitive teeth at each timepoint will be plotted by product group.

12.3.2 Secondary Analyses

Summary statistics (mean, median, SE, SD, minimum, maximum) will be presented for each secondary analysis variable by product group at each assessment time point, including Baseline assessments. Raw means (± SE) at each timepoint will be plotted by product group.

Change from Baseline in Schiff sensitivity score at Day 3, Weeks 2, 4 and 8

The Schiff sensitivity score is derived as the average score of the two test teeth. The change from Baseline is derived for the individual teeth first before calculating the average change of the two test teeth. The change in Schiff sensitivity score will be analysed at each time point using an ANCOVA model which will include product as a factor and Baseline Schiff sensitivity score as a covariate. Note that since the Baseline Schiff sensitivity score will be included as a covariate, the Baseline Schiff stratification value will not be included in the model.

Change from Baseline in tactile threshold (g) at Day 3, Weeks 2, 4 and 8

Tactile threshold (g) and change from Baseline will be derived as for the Schiff sensitivity score. The change in tactile threshold (g) will be analysed at each time point using an ANCOVA model with product and Baseline Schiff stratification included as factors and Baseline tactile threshold included as a covariate.

For both Change from Baseline in Schiff sensitivity score and Change from Baseline in tactile threshold, using the above models, adjusted mean change from Baseline, along with 95% CIs will be reported by product group. P-values testing for non-zero change from Baseline will also be presented for each product group. Mean difference between product groups, 95% CIs and p-values will also be provided. Significance testing will be conducted at the two-sided 5% significance level; no adjustment for multiple comparisons will be made.

In each case, the assumptions of the ANCOVA model will be investigated. An appropriate data transformation or non-parametric method may be performed in case of strong model violations.

Change from Baseline in DHEQ at Day 3, Weeks 2, 4 and 8

The following DHEQ-15 endpoints will be reported:

- Responses to Questions 7, 8 and 9, DHEQ Section 1 (as separate questions);
- Total Score for Questions 1 to 15, DHEQ Section 2;
- Restrictions Domain (total score for Questions 1 to 3, DHEQ Section 2);
- Adaptation Domain (total score for Questions 4 to 6, DHEQ Section 2);
- Social Impact Domain (total score for Questions 7 to 9, DHEQ Section 2);
- Emotional Impact Domain (total score for Questions 10 to 12, DHEQ Section 2);
- Identity Domain (total score for Questions 13 to 15, DHEQ Section 2);
- Change from Baseline at Day 3, and Week 2, 4 and 8 for each DHEQ endpoint.

Summary statistics (mean, median, SE, SD, minimum, maximum) will be presented for Change from Baseline for each DHEQ endpoint by product group at each assessment time point.

Change from Baseline in Numeric Rating Scale (NRS) at Day 3, Weeks 2, 4 and 8

Summary statistics (mean, median, SE, SD, minimum, maximum) will be presented for Change from Baseline in NRS by product group at each assessment time point.

12.3.3 Safety Analyses

The Safety population will be used for safety analyses. Safety analyses will be performed according to product received. All AEs will be reviewed by the Clinical Research Scientist, or designee, prior to database lock and unblinding and will be coded using the MedDRA. During this review stage, AEs will be further categorised as oral or non-oral. AEs will be listed and summarised by product received. SAEs will also be listed. AEs will be regarded as 'treatment' emergent if they occur on or after the first product use at the Baseline visit.

The following AEs tables will be produced, presented by product group:

- listing of all AEs (randomised subjects and non-randomised subjects);
- summary of AEs;
- treatment emergent AEs by Oral/Non-Oral and Preferred Term (PT);
- treatment emergent AEs by System Organ Class (SOC) and PT;
- treatment emergent treatment related AEs by Oral/Non-Oral and PT;
- listing of serious AEs (if there are no SAEs, a null listing will be produced; if there are more than 5 treatment emergent serious AEs (SAEs), a table will be produced in place of the listing by SOC and PT);
- non-serious treatment emergent AEs by SOC and PT (only produced if there are more than 5 SAEs).

The results of the OST and OHT examinations will be listed and the results of the OST examinations will be tabulated.

12.3.4 Exclusion of Data from Analysis

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

12.3.5 Demographic and Baseline Characteristics

Demographic and Baseline characteristics summaries will be produced for the mITT and safety populations.

Categorical demographic variables include gender, race, ethnicity, Baseline Schiff stratification score. These variables will be summarised by the number and percentage of subjects with each relevant characteristic in each product group. Age will be summarised by the mean, standard deviation, median, minimum and maximum values in each product group.

12.3.6 Study Drug/Product Compliance and Use of Other Therapies

12.3.6.1 Study Drug/Product Compliance

Compliance with study product use (number of brushings) will be listed and summarised for the mITT population.

12.3.6.2 Prior and Concomitant Medications

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

12.3.6.3 Other Therapy/Rescue Medication (if applicable)

N/A

12.3.7 Handling of Dropouts and Missing Data

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

12.3.8 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

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

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document. Other documentation will be identified and agreed.

GSK CH, 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 being conducted in accordance with the currently approved protocol and any other study agreements, GCP and all applicable regulatory requirements.

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

13.2 Quality Assurance

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

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

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

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

13.3 Regulatory and Ethical Considerations

13.3.1 Research Ethics Committee (REC)

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

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

13.3.2 Ethical Conduct of the Study

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

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

13.3.3 Subject Information and Consent

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

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

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

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

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

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

13.3.4 Subject Recruitment

Advertisements approved by the REC and investigator databases may be used as recruitment procedures. Use of an REC approved, generic, pre-screening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by the site as a phone script and/or to review internal databases to identify potential study subjects.

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

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

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

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

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

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

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

13.5 Provision of Study Results to Investigators

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

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

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

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

13.6 Records Retention

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

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

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

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

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

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

institutional requirements or local laws or regulations, GSK CH standards/procedures, and/or institutional requirements.

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

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the REC, study product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of the test product at any time.

If the study is prematurely terminated, GSK CH will promptly notify the investigator. After notification, the investigator must promptly contact all participating subjects and should assure appropriate therapy/follow-up for the subjects. As directed by GSK CH, all study materials must be collected and all eCRFs completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authority and the investigator should promptly inform the REC and provide the REC a detailed written explanation of the termination or suspension.

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

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

14 REFERENCES

Available upon request

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15 APPENDICIES

15.1 ABBREVIATIONS

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

Table 15-1 Abbreviations

Abbreviation	Term
AE	Adverse event
ANCOVA	Analysis of covariance
BDR	Blinded data review
DH	Dentin Hypersensitivity
DHEQ	Dentin Hypersensitivity Experience Questionnaire
EAR	Erosion, Abrasion, Recession
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

Abbreviation	Term
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSK CH	GlaxoSmithKline Consumer Healthcare
ICF	Informed consent form
ICH	International Conference on Harmonisation
KNO_3	Potassium Nitrate
MFC	Manufacturing formulation code
MGI	Modified gingival index
mITT	Modified Intent-to-Treat
N/A	Not applicable
OHT	Oral hard tissue
OST	Oral soft tissue
PI	Principal investigator
PI	Personal information
POP	Proof of Principle
PVM/MA	methyl vinyl ether/maleic anhydride co-polymer
RAP	Reporting and analysis plan
REC	Research ethics committee
SAE	serious adverse event
SD	Standard deviation
SE	Standard error
SRSD	Single reference study document
SS	Safety statement
UPT	Urine Pregnancy Test

15.2 Dentine Hypersensitivity Experience Questionnaire (Example)

SECTION ONE

The following questions are about your sensitive teeth, and the impact it has on your everyday life.

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

☐ Itchy (1)	☐ Aching (2)	☐ Shooting (3)
☐ Piercing (4)	☐ Tingling (5)	☐ Sharp (6)
☐ Dull (7)	☐ Flashing (8)	☐ Shivery (9)
☐ Lingering (10)	☐ Twinging (11)	☐ Flickering (12)
☐ Stabbing (13)	☐ Shattering (14)	☐ Freezing (15)
☐ Fleeting (16)	☐ Quivering (17)	☐ Pricking (18)
☐ Pain (19)	☐ Discomfort (20)	☐ Twinges (21)
☐ Sensitivity (22)	☐ Other (please specify) (23)	
☐ None of the Above (24)		

From now on in this questionnaire we are going to call what you feel as '***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 (1)
- ☐ More than six months but less than a year (2)
- ☐ More than a year but less than five years (3)
- ☐ More than five years but less than 20 years (4)
- ☐ More than 20 years (5)
- ☐ None (0)

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

- ☐ Top front (1)
- ☐ Top back (2)
- ☐ Bottom front (3)
- ☐ Bottom back (4)
- ☐ None (5)

4) Which of the following cause you to have ***sensations***? (tick all that apply)

☐ Cold fluids (1)	☐ Salty foods (2)	☐ Cold foods (3)
☐ Tooth brushing (4)	☐ Hot fluids (5)	☐ Acidy fruits (e.g. oranges) (6)
☐ Hot foods (7)	☐ Sweet things (8)	☐ Having teeth cleaned at the dentist (9)
☐ Hard foods (10)	☐ Sticky foods (11)	☐ Tooth Whitening Products (12)
☐ Cold air (13)	☐ Ice Cream (14)	☐ Metals touching my teeth (15)
☐ Other (Please Specify) (16)		
☐ None (17)		

5) How often do you have any ***sensations***? (tick only one response)

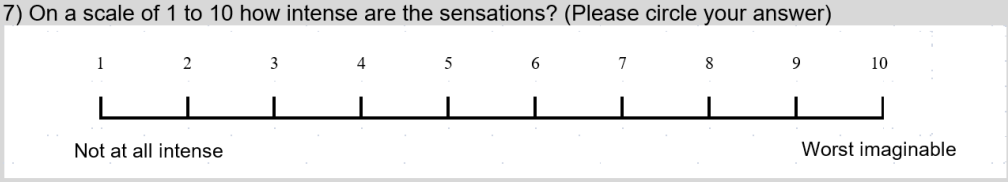
- ☐ Several times a day (7)
- ☐ Once a day (6)
- ☐ Several times a week (5)
- ☐ Once a week (4)
- ☐ Several times a month (3)
- ☐ Once a month (2)
- ☐ Less than once a month (1)
- ☐ Never (0)

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

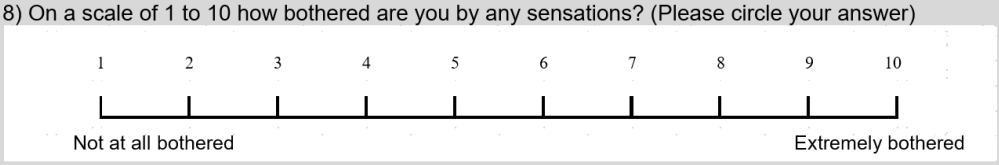
- ☐ A few seconds (5)
- ☐ About a minute (4)
- ☐ Several minutes (3)
- ☐ About half an hour (2)
- ☐ Longer than half an hour (Please specify) (1)
- ☐ Don't have them (0)

The following questions are about your sensitive teeth, and the impact it has on your everyday life.

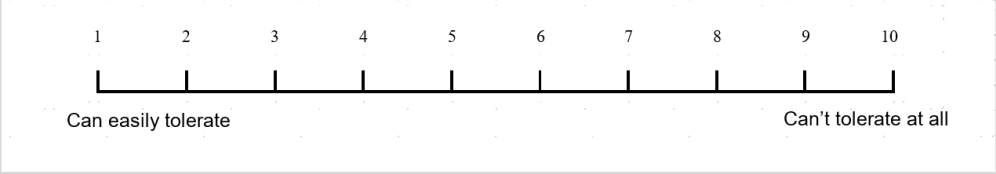
7) On a scale of 1 to 10 how intense are the sensations? (Please circle your answer)



8) On a scale of 1 to 10 how bothered are you by any sensations? (Please circle your answer)



9) On a scale of 1 to 10 how well can you tolerate sensations? (Please circle your answer)



SECTION TWO

The following questions are about ***the ways in which any sensations in your teeth affect you in your daily life***. Thinking about yourself ***over the last 4 weeks*** to what extent would you agree or disagree with the following statements (Please tick only one response for each question)

	Strongly agree (7)	**Agree (6)**	**Agree a little (5)**	**Neither agree nor disagree (4)**	**Disagree a little (3)**	**Disagree (2)**	**Strongly disagree (1)**
1) Having sensations in my teeth takes a lot of the pleasure out of eating and drinking.	☐	☐	☐	☐	☐	☐	☐
2) It takes a long time to finish some foods and drinks because of sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
3) There have been times when I have had problems eating ice	☐	☐	☐	☐	☐	☐	☐

cream because of these sensations.							
4) I have to change the way I eat or drink certain things.	☐	☐	☐	☐	☐	☐	☐
5) I have to be careful how I breathe on a cold day.	☐	☐	☐	☐	☐	☐	☐
6) When eating some foods I have made sure they don't touch certain teeth.	☐	☐	☐	☐	☐	☐	☐
7) Because of the sensations I take longer than others to finish a meal.	☐	☐	☐	☐	☐	☐	☐
8) I have to be careful what I eat when I am with others because of the sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
9) Going to the dentist is hard for me because I know it is going to be painful as a result of sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
10) I've been anxious that something I eat or drink might cause sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐

11) The sensations in my teeth have been irritating.	☐	☐	☐	☐	☐	☐	☐
12) The sensations in my teeth have been annoying.	☐	☐	☐	☐	☐	☐	☐
13) Having these sensations in my teeth makes me feel old.	☐	☐	☐	☐	☐	☐	☐
14) Having these sensations in my teeth makes me feel damaged.	☐	☐	☐	☐	☐	☐	☐
15) Having these sensations in my teeth makes me feels as though I am unhealthy.	☐	☐	☐	☐	☐	☐	☐

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

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