Document Name	209723-Clinical Protocol-209723_Clinical Protocol
Scope	Studies
Document Type	003 Study protocol and Amendment
Document Subtype	Clinical Protocol

209723_Clinical Protocol

Author(s) PPD

APPROVALS

Name	Reason for Approval	Approval Date CET*(MM/DD/YYYY)
PPD		10/14/2018 3:01:09 PM
PPD		10/15/2018 8:15:15 AM
PPD		10/15/2018 10:45:57 AM
		10/16/2018 9:34:18 AM

Document ID	Version	Approved Date in CET*	Pages
0900c35380fa4d66	2.0	Oct 16,2018 9:34:00 AM	98

*CET: Central European Time

CLINICAL PROTOCOL

RANDOMIZED CONTROLLED EXAMINER-BLIND PHASE II EXPLORATORY CLINICAL STUDY TO CHARACTERIZE THE EFFICACY PROFILE OF AN EXPERIMENTAL DUAL ACTIVE COMBINATION DENTIFRICE FOR THE RELIEF OF DENTIN HYPERSENSITIVITY, IN SUBJECTS WITH CLINICALLY DIAGNOSED DENTIN HYPERSENSITIVITY

Protocol Number:	209723
Compound/Product Name:	Potassium nitrate 5% weight/weight (w/w) and stannous fluoride 0.454% (w/w) dentifrice
United States (US) Investigational New Drug (IND) Number:	Not applicable (N/A)
European Clinical Trials Database (EudraCT) Number:	N/A
Phase:	II

Sponsor Information

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Document Name	209723-Clinical Protocol Administrative Change Letter-209723_Clinical Protocol Administrative Change Letter_02
Scope	Studies
Document Type	003 Study protocol and Amendment
Document Subtype	Clinical Protocol Administrative Change Letter

209723_Clinical Protocol Administrative Change Letter_02

Author(s) PPD

APPROVALS

Name	Reason for Approval	Approval Date CET*(MM/DD/YYYY)
PPD		3/18/2019 1:21:25 PM

Document ID	Version	Approved Date in CET*	Pages
PPD	1.0	Mar 18,2019 1:21:00 PM	4

*CET: Central European Time

GlaxoSmithKline Consumer Healthcare
184 Liberty Corner Road
Warren, NJ 07059
Unites States of America

March 18, 2019

RE: Protocol Administrative Changes #02 for Study 209723

RANDOMIZED CONTROLLED EXAMINER-BLIND PHASE II EXPLORATORY CLINICAL STUDY TO CHARACTERIZE THE EFFICACY PROFILE OF AN EXPERIMENTAL DUAL ACTIVE COMBINATION DENTIFRICE FOR THE RELIEF OF DENTIN HYPERSENSITIVITY, IN SUBJECTS WITH CLINICALLY DIAGNOSED DENTIN HYPERSENSITIVITY

Dear Investigator,

This letter is being sent to notify you of the following clarifications and administrative changes to the 209723 protocol; version 2.0, dated 16 Oct 2018.

Points of Clarification:

- **Section 6.7 Subject Compliance,** the following statement is added for clarification.

  As this is an exploratory study, no specific thresholds for compliance/non-compliance have been defined. Compliance will be assessed at the Blind Data Review Meeting (Section 12.2.2 Exclusion of Data from Analysis), prior to database lock, to identify subjects with protocol deviations which would warrant exclusion of data from the mITT analysis population.

- **Section 10.7.1 Sponsor's Reporting Requirements to Regulatory Authorities and Ethics Committees,** the following statement is added for clarification.

  SAEs and SUSARs will be reported in an expedited manner to Health Canada as per the NNHPD Clinical Trials for NHPs guidance document (https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/clinical-trials.html).

- **Section 12.1 Sample Size Determination**, the following statement

  Approximately 104 subjects will be randomized to study treatment (approximately 52 per treatment group)

  is changed to

  Approximately 104 subjects will be randomized to study treatment (approximately 52 per treatment group) to achieve approximately 50 evaluable subjects per treatment group, allowing for a dropout rate of approximately 4%.

  for clarification.

Minor Administrative Changes:

- Protocol Administrative Change Letter #01 for Study 209723 referenced Section 9.9.2 in error, this is corrected to Section 9.2.2; stated NJ 07094 as ZIP code for the sponsor address in error, this is corrected to NJ 07059.
- **Section 1.1 Schedule of Activities, Table 1-1, Procedure/Assessment at Visit 6, Day 28 (± 2 days)**, the following statement is removed.

  Provide Subject with New Diary

  The diary provided at Visit 2 (Day 0, Baseline) will cover the entire 8-week treatment period; subjects will not be re-supplied with a diary at Visit 6.
- **Section 8.2.1 Baseline: Day 0 (Visit 2)**, the following statement is removed.

  Clinical examiner completes an OHT examination. Record findings in the CRF.

  OHT (oral hard tissue) examinations will be completed at Visit 1 (Screening) and Visit 7 (Day 56) only, as per Table 1.1 Schedule of Activities.
- **Section 9.1.4 Qualifying Tactile Sensitivity**, the following statement

  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 feet PAIN or DISCOMFORT.

  is corrected to

  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 PAIN or DISCOMFORT.

NO ADDITIONAL CHANGES HAVE BEEN MADE TO THE STUDY DOCUMENTATION.

Sincerely,

PPD

PPD

PPD

Clinical Research

18 Mar 2019
Date

cc: Trial Master File, IRB/EC

Document History

Document	Version	Summary of Changes
Original protocol	2.0	N/A

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

Principal Investigator Protocol Agreement Page

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

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

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1 PROTOCOL SUMMARY

Background and Rationale

GlaxoSmithKline Consumer Healthcare (GSK CH) has developed an anhydrous 5% potassium nitrate (KNO_3) and 0.454% stannous fluoride (SnF_2) combination dentifrice for the relief of dentin hypersensitivity (DH). It is hypothesized that the combination of two anti-sensitivity active ingredients with complementary modes of action (KNO_3: nerve desensitization; SnF_2: dentin tubule occlusion) will deliver superior anti-sensitivity efficacy, compared to either active alone. Published clinical studies report DH efficacy for KNO_3/SnF_2 combination dentifrices and indicate greater clinical benefit for dual active formulations, compared to KNO_3 only formulations, with 4-8 weeks treatment. They do not provide any information regarding performance versus SnF_2 only formulations (no SnF_2 only dentifrices were evaluated). This exploratory study will characterize the efficacy profile of an experimental 5% KNO_3 and 0.454% SnF_2 combination dentifrice, compared to a 0.454% SnF_2 single active desensitizing dentifrice, across an 8-week treatment period.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To characterize the efficacy profiles of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice and a 0.454% w/w SnF_2 only dentifrice in reducing DH, with twice daily use for 8 weeks.	*At Baseline, Days 3, 7, 14, 28, 56;* Schiff sensitivity score Tactile threshold (grams [g]) Number of sensitive teeth (Schiff sensitivity score ≥ 1)
Secondary	
To investigate the clinical efficacy of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice in reducing DH to an evaporative air stimulus (Schiff sensitivity score), compared to a 0.454% w/w SnF_2 only dentifrice, after 8 weeks twice daily use.	Change from Baseline in Schiff sensitivity score at Day 56
To investigate the clinical efficacy of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice in reducing DH to a tactile stimulus (tactile threshold), compared to a 0.454% w/w SnF_2 only dentifrice, after 8 weeks twice daily use.	Change from Baseline in tactile threshold (g) at Day 56
Safety	
To assess the safety and tolerability of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice with twice daily use for 8 weeks.	Treatment emergent adverse events
Other	
To investigate the clinical efficacy of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination	*At Days 3, 7, 14 & 28;* Change from Baseline in Schiff

dentifrice in reducing DH to evaporative air (Schiff sensitivity score) and tactile (tactile threshold) stimuli, compared to a 0.454% w/w SnF_2 only dentifrice, after 3, 7, 14 & 28 days twice daily use.	sensitivity score 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 4 and 8 weeks treatment with an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice and a 0.454% w/w SnF_2 only dentifrice	*At Days 28 & Day 56;* Change from Baseline in – responses to Questions 7-9, DHEQ Section 1 – Total Score, Questions 1-15, DHEQ Section 2 – Restrictions, Adaptation, Social Impact, Emotional Impact & Identity Domains

Study Design

This will be a single center, 8-week, randomized, controlled, examiner-blind, two treatment arm, parallel design, stratified (by maximum Baseline Schiff sensitivity score of the two selected test teeth), Phase II, exploratory study to evaluate the DH efficacy of an experimental 5% KNO_3 and 0.454% SnF_2 combination dentifrice (Test), compared to a marketed 0.454% SnF_2 desensitizing dentifrice (Control). Study dentifrices will be applied twice daily, by toothbrushing, over the 8-week treatment period.

DH to tactile and evaporative air stimuli will be assessed at Screening (Visit 1) and Baseline (Visit 2), and after 3, 7, 14, 28 and 56 days treatment (Visits 3-7). Eligible subjects will complete an acclimatization phase (2-4 weeks) between the Screening and Baseline visits and will be randomized to study dentifrice following Baseline assessments. The safety and oral tolerability of the study products will be monitored over the treatment period by review of reported adverse events (AEs).

Study Products

	Acclimatization Dentifrice	**Test Dentifrice**	**Control Dentifrice**
Treatment Description	Dentifrice containing 1000 parts per million (ppm) fluoride as sodium monofluoro-phosphate (SMFP)	Dentifrice containing 5% w/w KNO_3 and 0.454% w/w SnF_2 (1100 ppm fluoride)	Dentifrice containing 0.454% SnF_2 (1100 ppm fluoride)
Product Name	Colgate Cavity Protection (Canadian market)	Experimental dentifrice	Sensodyne Rapid Relief Regular (registered as a Non-prescription Natural Health Product [NNHP] in Canada)

Type and Planned Number of Subjects

The study will be conducted in male and female subjects in good general health, aged 18-65 years, 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, pre-treatment) visits. Sufficient subjects will be screened (approximately 150 subjects) to enter approximately 125 subjects into the acclimatization phase to ensure approximately 104 subjects are randomized to study treatment (approximately 52 subjects per treatment arm).

Statistical Analyses

A modified Intent-To-Treat (mITT) population will be used for efficacy analyses.

The primary efficacy variables are Schiff sensitivity score and tactile threshold (g), both calculated as the average score of the two test teeth, and the number of sensitive teeth (Schiff sensitivity score ≥ 1) at Day 0 (Baseline), Day 3, Day 7, Day 14, Day 28 and Day 56. Summary statistics (mean, median, standard error (SE), standard deviation (SD), minimum, maximum) will be presented for each outcome variable at each assessment time point. Raw means (± SE) of Schiff sensitivity score, tactile threshold (g) and number of sensitive teeth at each timepoint will be plotted by treatment group.

The secondary efficacy variables are change from Baseline in Schiff sensitivity score and the change from Baseline in tactile threshold (g), at Day 56. Change from Baseline in Schiff sensitivity score will be analysed at Day 56 using an analysis of covariance (ANCOVA) model which will include treatment as a factor and Baseline Schiff sensitivity score as a covariate. Change from Baseline in tactile threshold (g) will be analysed at Day 56 using an ANCOVA model with treatment and Baseline Schiff stratification included as factors and Baseline tactile threshold included as a covariate. Adjusted mean change from Baseline, along with 95% confidence intervals (CIs) will be reported by treatment group. P-values testing for non-zero change from baseline will be presented for both treatment groups. The mean difference between treatment groups, 95% CIs and p-values will be provided. Significance testing will be conducted at the two-sided 5% significance level with no adjustments for multiple testing.

1.1 Schedule of Activities

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

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

Table 1-1 Schedule of Activities

Procedure/ Assessment	Visit 1 Day -28 to -14 Screening	Acclimatization Period (2-4 Weeks)	Visit 2 Day 0 Baseline	Visit 3 Day 3	Visit 4 Day 7 (+1day)	Visit 5 Day 14 (±1day)	Visit 6 Day 28 (±2days)	Visit 7 Day 56 (±2days)
Informed Consent	X							
Demographics	X							
Medical History	X							
Prior/Current Medications and Treatments	X							
Review Subject's Current Oral Care Products	X							
Subject Returns with Acclimatization Dentifrice, Toothbrush and Completed Diary[1]			X					
Subject Returns with Study Treatment, Toothbrush and Completed Diary[1]				X	X	X	X	X
Compliance Checks[2]			X	X	X	X	X	X
Concomitant Medications and Treatments			X	X	X	X	X	X
Urine Pregnancy Test (UPT)[3]	X		X					
Subject Continuance				X	X	X	X	X
Dentine Hypersensitivity Experience Questionnaire (DHEQ)[4]			X				X	X
Oral Soft Tissue (OST) Examination	X		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)[5]	X		X					
Qualifying Evaporative Air Sensitivity Assessment (Schiff sensitivity score)[6]	X		X					
Inclusion / Exclusion Criteria	X		X					

Procedure/ Assessment	Visit 1 Day -28 to -14 Screening		Visit 2 Day 0 Baseline	Visit 3 Day 3	Visit 4 Day 7 (+1day)	Visit 5 Day 14 (±1day)	Visit 6 Day 28 (±2days)	Visit 7 Day 56 (±2days)
Subject Eligibility	X		X					
Clinical Examiner Selects Two 'Test Teeth' *Eligible Subjects Only*			X					
Stratification/Randomization			X					
Dispense Acclimatization dentifrice, Toothbrush, Diary and Timer	X							
Supervised Brushing with Acclimatization Dentifrice	X							
Dispense Study Treatment, Toothbrush and Diary			X					
Tactile Sensitivity Assessment (Yeaple Probe)[5] *Test Teeth Only*				X	X	X	X	X
Evaporative Air Sensitivity (Schiff sensitivity score)[6] *Test Teeth Only*				X	X	X	X	X
Evaporative Air Sensitivity (Schiff sensitivity score)[6] *Remaining Eligible Teeth from Screening*			X	X	X	X	X	X
Supervised Brushing with Study Treatment			X	X	X	X	X	
Return Study Treatment/Toothbrush and Diary to Subject				X	X	X	X	
Provide Subject with New Diary							X	
Adverse Events/Incidents[7]	X		X	X	X	X	X	X
Study Conclusion								X

Footnotes:

1. Subject will be required to bring their study supplies (minus timer) to every visit.
2. Perform visual check of returned study supplies and review diary (Visit 2: compliance with use of acclimatization dentifrice; Visits 3-7: compliance with use of study treatment). Check compliance with Lifestyle Guidelines/Medication Requirements.
3. Female subjects of child bearing potential only.
4. DHEQ must be completed prior to OST examination/clinical assessments.
5. Visits 1-2: maximum force 20 g (Screening and Baseline); Visits 3-7: maximum force 80 g.
6. Evaporative air assessment will follow tactile assessment, with minimum 5 minutes between last tactile assessment and first evaporative (air) assessment (to allow tooth recovery). Visits 3-7: Complete evaporative (air) assessments for *2 test teeth* first, before assessing remaining eligible teeth from Screening.
7. AEs, and therefore all Serious Adverse Events (SAEs), and incidents will be recorded from immediately after a subject consents to participate in the study (by the completion of the Informed Consent Form [ICF]) until 5 days after last dose of study treatment.

2 INTRODUCTION

2.1 Study Rationale

GSK CH has developed a dual active dentifrice containing 5% KNO_3 and 0.454% SnF_2. Product development has been targeted at providing an effective dual active desensitizing formulation with improved efficacy compared to each single active ingredient, in an anhydrous toothpaste format.

A number of published clinical studies report DH efficacy for combination KNO_3/SnF_2 dentifrices, delivered from a dual chambered tube (Bae et al. 2015, Conforti et al. 2000, Schiff et al. 2000a, Schiff et al. 2000b, Sowinski et al. 2001, Sowinski et al. 2000a, Sowinski et al. 2000b). While the data would indicate greater clinical efficacy for the dual active formulations compared to KNO_3 alone (after 4 and 8 weeks treatment), they do not provide any information regarding performance of a combination dentifrice versus a SnF_2 only formulation. This exploratory study will investigate the efficacy profile of an experimental dual active KNO_3 and SnF_2 combination dentifrice (single chamber tube) for the relief of DH, compared to a SnF_2 only desensitizing dentifrice. Efficacy will be assessed at multiple time points over an 8-week treatment period, with a focus on Day 56 (primary time point). The data generated will provide an initial indication of the potential clinical benefit of a dual active formulation over a 'stannous only' formulation and will inform the design of future clinical studies investigating the efficacy of dual active anti-sensitivity dentifrices.

Complete information for the experimental KNO_3 and SnF_2 combination dentifrice may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB). Seven clinical studies evaluating the efficacy of a combination KNO_3/SnF_2 dentifrice (delivered from a dual chambered tube) are reported in the scientific literature. In each study, subjects brushed twice daily with their assigned study dentifrice for the duration of the treatment period [*Short Term (14 days):* (Conforti et al. 2000). *Longer Term (8 weeks):*(Schiff et al. 2000a, Schiff et al. 2000b, Sowinski et al. 2001, Sowinski et al. 2000a, Sowinski et al. 2000b). Only four of the seven studies reported safety outcomes (Conforti et al. 2000, Schiff et al. 2000a, Sowinski et al. 2000a, Sowinski et al. 2000b). There were no adverse events in the 2-week study (Conforti et al. 2000); there were no adverse events which could be ascribed to use of the combination dentifrice in the three 8-week studies (Schiff et al. 2000a, Sowinski et al. 2000a, Sowinski et al. 2000b). Based on the available non-clinical and clinical information, the combination of 5% KNO_3 and 0.454% SnF_2 is considered generally safe for topical oral use, when delivered from a dentifrice with twice daily brushing, under

controlled conditions of a clinical trial.

2.2 Background

Dentin hypersensitivity (DH) has been defined as 'pain derived from exposed dentine in response to chemical, thermal, tactile, or osmotic stimuli which can't be explained as arising from any other dental defect or disease' (Addy et al. 1985, Canadian Advisory Board on Dentin Hypersensitivity 2003). The hydrodynamic theory of DH hypothesizes that a stimulus external to the tooth (for example, a temperature/osmotic differential, pressure) causes movement of the fluid resident within exposed dentinal tubules (Brännström 1963). This movement may stimulate nerve processes in the dental pulp (Addy 2002, Hall et al. 2000), resulting in the characteristic short, sharp pain of DH. Currently there are two approaches for the management of DH: nerve desensitization and the occlusion of exposed dentin tubules.

Nerve desensitizing agents, such as potassium nitrate (KNO_3), generally require a period of use (e.g. 2-4 weeks) before their benefit is established. Delivery of potassium ions into exposed dentin tubules is believed to result in desensitization of pulpal nerve fibers thereby blocking the pain response (Addy and Smith 2010). KNO_3 has been incorporated into oral hygiene products indicated for the relief of DH since the 1970s (Markowitz 2009). In the United States (US), the Monograph for Oral Health Care Drug Products for Over-the-Counter Human Use recognizes the cumulative clinical efficacy of KNO_3 in the relief of DH - '*potassium nitrate's effectiveness as a tooth desensitizer is cumulate...as it may take two or three weeks before significant therapeutic relief is obtained*' (Oral Health Care Drug Products for Over-the-Counter Human Use 1991). Many clinical studies (typically 4-12 weeks treatment) have been published demonstrating the efficacy of KNO_3 for the relief of DH [for example, (Acharya et al. 2013, Ayad et al. 1994, Gallob et al. 2017, Gillam et al. 1996, Hu et al. 2004, Jeandot et al. 2007, Jiang et al. 2009, Konekeri et al. 2015, Kumari et al. 2013, Kumari et al. 2016, Leight et al. 2008a, Li et al. 2013, Liang et al. 2011, Nagata et al. 1994, Orsini et al. 2010, Parkinson et al. 2017, Pradeep et al. 2012, Pradeep and Sharma 2010, Salian et al. 2010, Salvato et al. 1992, Satyapal et al. 2014, Schiff et al. 2000a, Schiff et al. 1994, Schiff et al. 2000b, Sharma et al. 2010, Shen et al. 2009, Silverman 1985, Silverman et al. 1996, Silverman et al. 1994, Sowinski et al. 2001, Sowinski et al. 2000a, Sowinski et al. 2000b, Surve et al. 2012, Wara-aswapati et al. 2005, West et al. 1997, Yates et al. 2005, Young et al. 2017, Zhuang and Cao 2011). Although one literature review of DH studies describes the effectiveness of potassium-containing treatments as unproven (West et al. 2015), numerous clinical studies and a meta-analysis of randomized controlled trials (RCTs) (Bae et al. 2015) report potassium-containing desensitizing dentifrices to be clinically effective in the treatment of DH.

Dentin tubule occluding agents, such as strontium salts, stannous salts, bioglasses or silicas serve to physically block or narrow the exposed ends of dentin tubules, reducing dentinal fluid movement, and thereby decreasing the effect of external stimuli. Tubule occlusion can be favored over nerve desensitization, due to the more rapid onset of relief from DH (Gillam et al. 1996). Stannous fluoride (SnF_2) has been incorporated into oral hygiene products indicated for the reduction of DH since the 1960s (Schiff et al. 2006). Its mechanism of action is thought to be via the chemical precipitation of tin salts which occlude exposed dentin tubules (Burnett 2013, Burnett et al. 2013, Earl and Langford 2013). Published clinical studies demonstrate the efficacy of stannous fluoride in providing both early onset (within days) and longer term (weeks) relief of DH [for example, *Short Term (typically 1-14 days treatment):* (Cepeda-Bravo et al. 2014, Creeth et al. 2017a, Creeth et al. 2017b, Goyal et al. 2017, He et al. 2014a, He et al. 2011a, He et al. 2011b, He et al. 2011c, He et al. 2011d, Parkinson et al. 2016, Seong et al. 2017, Sharma et al. 2011); *Longer Term (typically 4-12 weeks treatment):* (Chaknis et al. 2011, Day et al. 2010, Du et al. 2011, Gallob et al. 2017, Hazen et al. 1968, He et al. 2014b, Ni et al. 2011, Ni et al. 2010, Parkinson et al. 2013, Parkinson et al. 2015, Schiff et al. 2006, Schiff et al. 2005, Sharma et al. 2010, Vinaya et al. 2010)]. Review and meta-analyses of RCTs report desensitizing dentifrices containing stannous fluoride to be clinically effective in the treatment of DH (Bae et al. 2015, Gerlach and Sagel 2017, West et al. 2015, Yang et al. 2016).

It can be hypothesized that the combination of these two anti-sensitivity active ingredients with complementary modes of action (KNO_3 and SnF_2) will deliver superior anti-sensitivity efficacy, compared to either active alone.

- SnF_2 does not form a 'wholly protective' layer over the dentin (Mason et al. 2009), as evidenced by longer term clinical studies in the literature which at no time report complete resolution of DH.
- Occlusion is a dynamic process - occlusive deposits are formed, lost through acid dissolution/physical wear processes within the oral cavity (e.g. dietary acid challenge, tooth brushing, mastication), and then replaced/maintained with repeated, twice daily treatment (Markowitz 2009).
- With a dual active KNO_3/SnF_2 anti-sensitivity system, it can be envisaged that sensitivity arising from any un-occluded/re-exposed areas of the dentin could be treated by the ingress of potassium ions into patent tubules and subsequent desensitization of the intra-dental nerves.

Several clinical studies report DH efficacy for combination 5% KNO_3/0.454-0.590% SnF_2 dentifrices, delivered from a dual chambered tube [*Short Term (14 days):* (Conforti

et al. 2000). *Longer Term (8 weeks):* (Bae et al. 2015, Schiff et al. 2000a, Schiff et al. 2000b, Sowinski et al. 2001, Sowinski et al. 2000a, Sowinski et al. 2000b)]. While these studies are not directly comparable, due to differences in study design (differing assessment time points; differing control products, different marketed potassium nitrate formulations), they indicate greater clinical benefit for dual active anti-sensitivity formulations, compared to KNO_3 only formulations, with 4-8 weeks treatment. They do not provide any information regarding performance versus SnF_2 only formulations (no SnF_2 only dentifrices were evaluated).

The aim of the current exploratory clinical study is therefore to investigate the efficacy profile of an experimental dual active (KNO_3 and SnF_2) dentifrice for the relief of DH at multiple time points over an 8-week treatment period, compared to a single active (SnF_2 only) desensitizing dentifrice. Data generated will aid in the design of future clinical studies investigating the efficacy of dual active anti-sensitivity dentifrice formulations.

2.3 Mechanism of Action/Indication

Potassium ions (K^+) are thought to relieve DH by reducing the excitability of the intra-dental nerves. After each brushing with a K^+ containing toothpaste, the concentration of K^+ ions at the tooth surface is raised. K^+ ions move into the dentin through the tubules, gradually desensitizing the nerves at the center of the tooth and thereby providing relief from DH.

Occlusion agents act by physically blocking or narrowing the exposed ends of the dentin tubules, thereby reducing dentinal fluid movement and decreasing the effect of external stimuli. SnF_2 is known to rapidly oxidize (from Sn [II] to Sn[IV]) and hydrolyze in the presence of water (saliva) and saliva-derived ions to form insoluble tin compounds (hydroxides, oxides and phosphates) (Makin 2013, Miller et al. 1994). Stannous ions have been shown *in vitro* to form insoluble precipitates on the dentin surface and within dentin tubules (at the oral cavity end of the tubule) through combination with formulation excipients and saliva-derived ions (Ellingsen and Rolla 1987, Miller et al. 1994, Parkinson and Willson 2011, Shi et al. 2012, White et al. 2007, Zsiska et al. 2012, Zsiska et al. 2011), thereby providing relief from DH.

The combination of these two active ingredients (KNO_3 and SnF_2) in a dentifrice format will be investigated in subjects with DH.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To characterize the efficacy profiles of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice and a 0.454% w/w SnF_2 only dentifrice in reducing DH, with twice daily use for 8 weeks.	*At Baseline, Days 3, 7, 14, 28, 56;* Schiff sensitivity score Tactile threshold (grams [g]) Number of sensitive teeth (Schiff sensitivity score ≥ 1)
Secondary	
To investigate the clinical efficacy of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice in reducing DH to an evaporative air stimulus (Schiff sensitivity score), compared to a 0.454% w/w SnF_2 only dentifrice, after 8 weeks twice daily use.	Change from Baseline in Schiff sensitivity score at Day 56
To investigate the clinical efficacy of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice in reducing DH to a tactile stimulus (tactile threshold), compared to a 0.454% w/w SnF_2 only dentifrice, after 8 weeks twice daily use.	Change from Baseline in tactile threshold (g) at Day 56
Safety	
To assess the safety and tolerability of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice with twice daily use for 8 weeks.	Treatment emergent adverse events
Other	
To investigate the clinical efficacy of an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice in reducing DH to evaporative air (Schiff sensitivity score) and tactile (tactile threshold) stimuli, compared to a	*At Days 3, 7, 14 & 28;* Change from Baseline in Schiff sensitivity score Change from Baseline in tactile threshold (g)

0.454% w/w SnF_2 only dentifrice, after 3, 7, 14 & 28 days twice daily use.	
To monitor Oral Health Related Quality of Life (OHRQoL) as measured by the Dentine Hypersensitivity Experience Questionnaire (DHEQ) after 4 and 8 weeks treatment with an experimental 5% w/w KNO_3 and 0.454% w/w SnF_2 combination dentifrice and a 0.454% w/w SnF_2 only dentifrice	*At Days 28 & Day 56;* Change from Baseline in – responses to Questions 7-9, DHEQ Section 1 – Total Score, Questions 1-15, DHEQ Section 2 – Restrictions, Adaptation, Social Impact, Emotional Impact & Identity Domains

This exploratory study will be considered successful if the efficacy profiles of both study products indicate a reduction in sensitivity. In addition to this reduction, a statistically significant difference in change from Baseline in Schiff sensitivity score at Day 56 between the Test and Control dentifrices, in favour of the Test dentifrice would be viewed as success.

4 STUDY DESIGN

4.1 Overall Design

This will be a single center, 8-week, randomized, controlled, examiner-blind, two treatment arm, parallel design, stratified (by maximum Baseline Schiff sensitivity score of the two selected test teeth), Phase II, exploratory clinical study in healthy subjects with DH. Eligible subjects will enter a 2-4 week acclimatization phase between the Screening and Baseline assessments. Subjects who meet all study criteria at both Screening and Baseline visits will be randomized to study treatment.

DH to tactile and evaporative air stimuli will be assessed at Screening (Visit 1) and then at multiple time points across the 8-week treatment period - for all qualifying teeth at Baseline (Day 0) and then for two ‘test teeth’ only from Day 3 onwards (Days 3, 7, 14, 28 and 56). In addition, the remaining qualifying teeth identified at Screening will be assessed for evaporative air sensitivity from Day 3 onwards (Days 3, 7, 14, 28 and 56). A single clinical examiner will be responsible for the conduct of both clinical measures of DH for the duration of the study for all study subjects.

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

4.2 Rationale for Study Design

In line with published recommendations for the design and conduct of DH clinical trials (Holland et al. 1997), two independent stimulus-based efficacy measures will be employed (tactile and thermal [evaporative air] sensitivity) to assess the efficacy of the study dentifrices.

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

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. The selection of two 'test teeth' to evaluate changes in DH is 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 treatment groups are balanced for sensitivity severity.

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

The Investigational Product (IP) is an experimental dual active (KNO_3/SnF_2) dentifrice. The Control is a single active (SnF_2 only) dentifrice, selected as a representative 0.454% SnF_2 desensitizing formulation, and is registered as a Non-prescription Natural Health Product (NNHP) in Canada. The two dentifrices will be identical in visual appearance (white pastes, packaged in plain white laminate tubes) and flavour, but may differ in rheology. The level of blindness for this study is therefore described as 'examiner-blind'. For a study to be classed as truly double blind, not only does the examiner (and any member of staff involved in the dispensing of products, analysis of data etc.) need to be blind to the treatment received, but the products under test should be identical (in color, flavor, rheology, appearance and packaging). Study dentifrices will be dispensed in a blinded fashion to the subject, by trained site personnel who are not involved in clinical efficacy assessment procedures, in a separate area from the clinical examination area.

Clinical trials evaluating clinical end points relating to pain can be prone to 'placebo effects' (Addy et al. 1985, West et al. 1997). Such effects are frequently observed in DH

studies. A clinical study conducted to evaluate the natural history of the DH condition also highlighted the existence of a 'no treatment' effect, characterized by an improvement in sensitivity simply as a result of study participation (Leight et al. 2008b). To help minimize the potential impact of such effects, it is relatively common to include a lead-in (acclimatization) period prior to Baseline assessments, and to randomize only subjects whose signs or symptoms remain above a pre-specified entry level value. This helps to ensure that subjects who would show improvement for reasons other than a response to study treatment (spontaneous improvement, 'placebo effect', their own expectations or clinical observation) are not randomized (i.e. subjects incapable of showing a treatment response). During the acclimatization period subjects will be provided with a marketed, regular fluoride toothpaste and toothbrush to use in place of their own oral hygiene products. Use of these products will also help provide the study population with a standardized oral hygiene regimen prior to the Baseline visit and familiarize them with completion of a product usage diary after each brushing.

DH is an episodic condition; symptoms are known to vary spontaneously (West 2008, West et al. 2013). Baseline clinical values that would support enrolment may represent *random highs* in the condition that will be followed by regression to the mean, leaving the subject or a particular sensitive tooth without the condition under investigation during the treatment period. To help minimize the potential for this to occur on the current study, subjects will be required to demonstrate consistency in response at both the Screening and the Baseline visits (qualifying responses to tactile and evaporative air stimuli must be met at Screening and Baseline).

With the growing acknowledgment of the value of information gleaned directly from the subject, self-reported outcome measures have become increasingly important barometers of the benefit of medical interventions. The dentine hypersensitivity questionnaire (DHEQ) is a validated, condition specific measure of impacts on everyday life for DH sufferers which has been shown to have good psychometric properties in both the general population and in a clinical sample of DH sufferers (Baker et al. 2014, Boiko et al. 2010). A short form of the DHEQ has also been developed and validated (Machuca et al. 2014), and will be included in this study to evaluate treatment impacts in a clinically diagnosed DH population.

4.3 Justification for Dose

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

The dosage regimen of twice daily treatment (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 dentifrice on each brushing occasion. To align with the usage instructions of the marketed, stannous-only dentifrice, subjects will brush their two selected sensitive 'test teeth' first, followed by their whole mouth. After 8 weeks (Day 56 ±2 days) twice-daily treatment, each subject should complete between 108-116 treatments.

Each subject will complete a supervised brushing with their assigned study dentifrice at the end of each study visit (while still at the study site) to enable staff to check correct dosing and encourage compliance with product usage throughout the study.

4.4 End of Study Definition

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

The end of this study is defined as the date of the last scheduled procedure 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 (DH confirmed clinically) that meet all study criteria at both the Screening (Visit 1) and Baseline (Visit 2 - pre-treatment) visits. Sufficient subjects will be screened (approximately 150 subjects) to enter approximately 125 subjects into the acclimatization phase to ensure approximately 104 subjects are randomized to study treatment (approximately 52 subjects per treatment arm). Subjects will be recruited primarily from the study site's 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 a subject is suitable for this protocol.

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

5.2 Inclusion Criteria

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

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. 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, treatment plan, 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/relevant abnormalities in medical history, or upon oral examination, or condition that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.
5. Male subject able to father children or female subject of child-bearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 5 days after the last dose of assigned treatment. A female subject who is of child-bearing potential must meet requirements in Section 5.5.3.
6. **AT VISIT 1 (Screening):**

   Subject must have

   a) a self-reported history of DH 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 diagnosed DH; each tooth must meet the following criteria:

      - exposed dentin due to facial/cervical erosion, abrasion or gingival recession (EAR).
      - MGI score = 0 adjacent to the test area (exposed dentin) only (Lobene et al. 1986)

- clinical mobility ≤ 1 (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), preferably in different quadrants, with DH, as evidenced by qualifying tactile and evaporative air sensitivity (each tooth must have a tactile threshold ≤ 20 g and a Schiff sensitivity score ≥ 2) at the Screening and Baseline visits.

   Note: *All teeth which meet the sensitivity criteria (tactile threshold ≤ 20g; Schiff sensitivity score ≥ 2) 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 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 not be eligible for enrollment into the study.

1. Subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or a GSK CH employee directly involved in the conduct of the study or a member of their immediate family.
2. Subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.
3. Subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical, oral, psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
4. Subject with any condition which, in the opinion of the investigator or medically qualified designee, causes xerostomia.

5. Subject who is a pregnant female (as evidenced by a positive UPT at Screening).
6. Subject who is a breast-feeding female.
7. Subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
8. Subject who is unwilling or unable to comply with the Lifestyle Considerations described in this protocol (Section 5.5).
9. Subject with a recent history (within the last year) of alcohol or other substance abuse.
10. Subject who has participated in another tooth desensitizing treatment study within 8 weeks Screening.
11. Subject who has used an oral care product indicated for the relief of DH within 8 weeks of Screening (subject will be required to bring their current oral care products to the site in order to verify the absence of known anti-sensitivity ingredients).
12. Subject who has had dental prophylaxis within 4 weeks of Screening.
13. Subject who has had a teeth bleaching procedure within 8 weeks of Screening.
14. Subject who has had treatment for periodontal disease (including surgery) within 12 months of Screening
15. Subject who has had scaling or root planning within 3 months of Screening.
16. Subject with gross periodontal disease
17. Subject with evidence of gross intra-oral neglect or the need for extensive dental therapy.
18. Subject with a tongue or lip piercing or presence of multiple dental implants.
19. Subject with fixed or removable partial dentures.
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 dentin but with deep, defective or facial restorations.
    c) Tooth with full crown or veneer.

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

e) Sensitive tooth not expected to respond to treatment with an over-the-counter dentifrice 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 the perception of pain (examples of such medications include analgesics, anticonvulsants, antihistamines that cause marked or moderate sedation, sedatives, tranquilizers, anti-depressants, 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 acclimatization period.
25. Subject 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 Randomization Criteria

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

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

- **Stratum 1:** maximum Schiff sensitivity score = 2.
- **Stratum 2:** maximum Schiff sensitivity score = 3.

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 CRF. 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 efficacy 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 efficacy assessments will be performed. The subject will not be replaced.
- **Day 3 (Visit 3):** the subject will continue in the study. No clinical efficacy assessments will be performed.
- **Days 7, 14 & 28 (Visits 4-6):** if the subject cannot be reappointed (within the visit tolerance for Visits 4-6), they will continue in the study. No clinical efficacy assessments will be performed.
- **Day 56 (Visit 7):** if the subject cannot be reappointed, they will be withdrawn from the study (Section 7.1). No clinical efficacy 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, dentifrices, toothbrushes, oral rinses, tongue cleaners, whitening/bleaching products, inter-dental 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 sensitive teeth (including herbal remedies) than those provided during the study.
- Subjects should not chew gum.

Before a Clinical Efficacy Assessment Visit: Baseline (Visit 2) to Day 56 (Visit 7)

- 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 Efficacy Assessment Visit: Baseline (Visit 2) to Day 56 (Visit 7)

- 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

All male subjects able to father children and 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 dose of assigned treatment.

Female subjects of non-childbearing 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 highly effective methods for avoiding pregnancy that meets the GSK definition (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) (Guidance on Reproductive Issues in Clinical Studies GSK Cross-Business CCI).

The list does not apply to females of reproductive potential with same sex partners or for 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 acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device (IUD) or intrauterine system
3. Combined estrogen and progestogen oral contraceptive
4. Injectable progestogen
5. Contraceptive vaginal ring
6. Percutaneous contraceptive patches
7. Male partner sterilization 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. Male subjects with female partners of child-bearing potential must comply with the following contraception requirements from the time of first dose of study medication until at least 5 days after the last dose of assigned treatment [Guidance on Reproductive Issues in Clinical Studies GSK Cross-Business CCI

1. Vasectomy with documentation of azoospermia. 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.
2. Male condom plus partner use of one of the contraceptive options below that meets the effectiveness criteria including a less than 1% rate of failure per year, as stated in the product label:

- Contraceptive subdermal implant
- IUD or intrauterine system
- Combined estrogen and progestogen oral contraceptive
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches

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 randomized. 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 or incidents as applicable.

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

5.7 Sponsor's Qualified Medical Personnel

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

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

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects will be provided with a contact card. The contact card will provide, as a minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Rater/Clinical Assessor Qualifications

Clinical examiners involved in screening and efficacy assessment procedures will be qualified dentists, registered to practice in Canada. Oral examinations to determine subject eligibility and all safety/efficacy (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 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and GSK policy, investigational product is defined as a pharmaceutical form of an active ingredient, a non-medicinal product (marketed or investigational), or a placebo, being tested or used as a reference (positive or negative control), in a clinical trial. This includes a product with a marketing authorization 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 Investigational/Study Product Supplies

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

Table 6-1 Investigational/Study Product Supplies

	Acclimatization Dentifrice	Test Dentifrice	Control Dentifrice
Treatment Description	Dentifrice containing 1000 ppm fluoride as SMFP	Dentifrice containing 5% w/w potassium nitrate and 0.454% w/w stannous fluoride (1100 ppm fluoride)	Dentifrice containing 0.454% stannous fluoride (1100 ppm fluoride)
Product Name	Colgate Cavity Protection (Canadian market)	Experimental dentifrice	Sensodyne Rapid Relief Regular (registered as NNHP in Canada)
Pack Design	One carton containing two tubes	One carton containing two tubes	One carton containing two tubes
Dispensing Details	One carton (two tubes) at Screening	Two cartons (four tubes) at Baseline	Two cartons (four tubes) at Baseline

Product Master Formulation Code (MFC)	Commercial Product	CCI [redacted]	CCI [redacted]
Dose/Application	Subjects will dose the toothbrush provided with a strip of dentifrice (a full brush head) on each brushing occasion	Subjects will dose the toothbrush provided with a strip of dentifrice (a full brush head) on each brushing occasion	Subjects will dose the toothbrush provided with a strip of dentifrice (a full brush head) on each brushing occasion
Route of Administration	Oral topical use	Oral topical use	Oral topical use
Usage Instructions	Subjects will brush for at least 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 at least 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 at least one timed minute, twice daily (morning and evening); subjects will be permitted to rinse with water post-brushing.
Return Requirements	All used/unused samples to be returned	All used/unused samples to be returned	All used/unused samples to be returned

Table 6-2 Sundry Items

Item	**Supplied By**	**Pack Design**	**Dispensing Details**	**Return/Disposal Details**	
				Used Samples	**Unused Samples**
Oral B Sensi-soft toothbrush (Canadian market)	GSK CH	Individual toothbrush in commercial pack	One toothbrush at Screening for use with acclimatization product One toothbrush at Baseline for use with assigned study dentifrice	Destroy at site using site disposal procedures	Return to 3rd party vendor
Countdown Timer	GSK CH	Individual timer in commercial pack	One timer at Screening	Subject to keep or destroy at site using site disposal procedures	Return to 3rd party vendor

Pregnancy Tests (Canadian market)	GSK CH	Commercial pack	Use as per study schedule	Destroy at site using site disposal procedures	Return to 3rd party vendor

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 dentifrice usage instructions), the clinical assessment score sheets, the DHEQ 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 during the course of the study in time for study close out visit.

6.1.1 Dosage Form and Packaging

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

The IP and the Control dentifrice will be manufactured and filled into plain white tubes by GSK CH with a study label affixed. The acclimatization dentifrice will be supplied in its' commercial pack and overwrapped in white vinyl (to mask its' 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 acclimatization dentifrice and their assigned study dentifrice to cover usage during the acclimatization and treatment periods, respectively. Acclimatization dentifrice will be dispensed at Screening (Visit 1); study dentifrice 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 so that they are maintained in good condition; it is important that all labels remain intact and legible for the duration of the study. Subjects 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 Preparation and Dispensing

Subjects will be assigned to products in accordance with the randomization 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 dentifrices will be dispensed in blinded fashion to the subject, by trained site personnel. These staff members will not be involved in any safety/efficacy assessments or other aspects of the study that could be influenced by the knowledge of product a subject has been assigned to. 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 (CRF).

6.2 Administration

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

- staff will demonstrate dispensing a full ribbon of dentifrice along the length of the toothbrush head to each eligible subject and supervise their first brushing with the acclimatization dentifrice/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 dentifrice/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 dentifrice/diary completion at the end of the Day 3, Day 7, Day 14 and Day 28 visits (Visits 2-6), after all clinical assessments have been completed.

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

6.2.1 Medication/Dosing Errors

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

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

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

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

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

6.3 Investigational/Study Product Storage

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily 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 until product is returned to the 3rd party vendor. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

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

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

6.4 Investigational/Study Product Accountability

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

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

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

Subjects will return used and unused tubes of the acclimatization dentifrice to the investigator site at their Baseline visit (Visit 2). Subjects will return used and unused tubes of their assigned study dentifrice to the investigator site at their last visit (for most subjects this will be Visit 7). Study product return will be documented using the investigational/study product accountability form/record.

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

6.4.1 Destruction of Investigational/Study Product Supplies

At the conclusion of the study, the Principal Investigator (PI) or an appropriate designee, and a representative of GSK CH (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study (including empty containers) will be returned for destruction to the GSK CH 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/Randomization

All subjects will be centrally randomized to one of the two study treatments using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided to each 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(s) 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 examiner remains blinded throughout the study:

- site staff involved in the dispensing of study treatment 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/efficacy assessment procedure during the study.

6.6 Breaking the Blind

At the initiation of the study, the study site will be instructed in 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 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 would delay emergency treatment of the subject.

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

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

6.7 Subject 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 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 dentifrice used, oral problems, illnesses and any new medications/treatments. Subjects will attend each study visit with all tubes of dentifrice 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 CRF. Subjects will be re-instructed in the correct dosing, usage requirements and diary completion as needed.

Supervised brushings will be carried out at the study site at the end of Visits 2-6 to facilitate subject compliance with dosing and brushing 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 CRF 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.

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

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 subject perception of pain (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 CRF. 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 efficacy 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 efficacy assessments will be performed. The subject will not be replaced.

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

  Days 7, 14, 28 & 56 (Visits 4-7): if the subject cannot be reappointed (within the visit tolerance for Visits 4-7), they will continue in the study. Clinical efficacy 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 his/her own request, or may be withdrawn at any time at the discretion of either the investigator or the sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

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

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

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

7.2 Lost to Follow up

A subject will be considered lost to follow up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

If a subject fails to return to the site for a required study visit, the site must attempt to contact the subject to reschedule the missed visit as soon as possible, to counsel the subject on the importance of maintaining the assigned visit schedule and to ascertain whether or not the subject wishes to and/or should continue in the study.

Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all products dispensed to them and, if appropriate, request that the subject return for a final visit and follow-up with the subject regarding any unresolved AEs.

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

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

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

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

8 STUDY PROCEDURES

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

Adherence to the study design requirements, including all procedures, is 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 dentifrices 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 also be captured on the ICF as this is the point from which all AEs will be captured. The date and time of consent will be transcribed to the CRF.

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

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

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 CRF: year of birth, gender, ethnicity and race.

Data from this study may be submitted to the US Food and Drug Administration (FDA) at a later date as part of a New Drug Application (NDA) for a dual active DH dentifrice; the FDA require ethnicity and race to be reported in clinical studies submitted in support of an NDA. Ethnicity and race of subjects will be recorded in accordance with FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials (FDA 2016).

8.1.3 Medical History and Prior Medication/Treatment

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

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

8.1.4 Screening Procedures

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

- The oral care products the subject is currently using will be reviewed to confirm that they do not contain any ingredients intended for treating sensitive teeth.

Subjects will be required to bring the products to the study site to enable study staff to check ingredient listings.

- Female subjects of child-bearing potential *only* will complete a UPT.
- An OST examination will be completed by a clinical examiner as described in Section 9.3.1.
- An OHT examination will be completed by a clinical examiner as described in Section 9.3.2.
- Eligible teeth assessments for incisors, canines and pre-molars, including dentition exclusions and assessments of EAR, MGI (gingiva adjacent to the exposed dentin only) and tooth mobility will be completed by a clinical examiner as described in Section 5.3, Section 9.1.1, Section 9.1.2 and Section 9.1.3 respectively.
- The sensitivity of each tooth that meets the eligibility criteria, first to a tactile stimulus and then to an evaporative air stimulus will be evaluated by the clinical examiner 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 ease subject flow, assessments may be recorded on a score sheet and later transcribed into the CRF. The same examiner will be responsible for completing both clinical measures of DH (tactile and evaporative air sensitivity) for the duration of the study.

8.1.5 Inclusion/Exclusion Criteria

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

8.1.6 Subject Eligibility

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

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

8.1.7 Supervised Use of Acclimatization Dentifrice

Eligible subjects will be provided with the acclimatization dentifrice, toothbrush, diary and timer to use during the acclimatization period (2-4 weeks). Dentifrice usage instructions will be described to the subject and dosing of a full brush head with dentifrice will be demonstrated. Staff will supervise the subject carrying out first dosing/brushing with acclimatization dentifrice and recording first use in their diary. Completion of all procedures will be documented in the CRF.

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/incidents reported on completion of the supervised brushing with the acclimatization dentifrice will be recorded in the CRF.

8.2 Study Period

8.2.1 Baseline: Day 0 (Visit 2)

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

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 and any AEs recorded in the CRF.

The following procedures will then be completed.

- Complete visual checks of returned acclimatization dentifrice tubes and review completed diary. Record any suspected over or under use, and the number of any missed or additional brushings, in the CRF.
  Do not return acclimatization dentifrice/toothbrush/diary to subject.
- Female subjects of child-bearing potential *only c*omplete a UPT. Record the result in the CRF.
- Subject completes a DHEQ (source document), for later transcription into the CRF.
- Clinical examiner completes an OST examination. Record findings in the CRF.
- Clinical examiner completes an OHT examination. Record findings in the CRF.
- Clinical examiner completes sensitivity assessments for each eligible tooth identified at Screening (eligible incisors, canines, pre-molars, with a tactile threshold of ≤ 20 g and a Schiff sensitivity score ≥ 2), 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 CRF or using source documentation for later transfer to the CRF. The same examiner will be responsible for completing both clinical measures of DH (tactile and evaporative air sensitivity) for the duration of the study.

- Clinical examiner reviews inclusion and exclusion criteria and confirms subject eligibility in the CRF. Subjects with at least 2 sensitive teeth (tactile threshold ≤ 20 g; Schiff sensitivity score ≥ 2 at Screening and Baseline) will continue.
- Clinical examiner selects the two 'test teeth' for sensitivity assessment at subsequent study visits. Record in the CRF.
- Complete stratification and randomization.
- Dispense allocated study dentifrice, toothbrush and diary. Record in the CRF.
- Describe dentifrice usage instructions and diary completion to subject; supervise their first dosing and brushing with study dentifrice and recording of brushing in the diary. Record in the CRF.
- 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/incidents reported on completion of the supervised brushing with the assigned study dentifrice will be recorded in the CRF.
- Remind the subject of the Lifestyle Guidelines (Section 5.5) and any Concomitant Medication/Treatment(s) requirements (Section 6.8) of the protocol. Record in the CRF.

8.2.2 Day 3, Day 7 (+1 day), Day 14 (±1 day) and Day 28 (±2 days) (Visits 3-6)

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

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 and any AEs recorded in the CRF.

The following procedures will then be completed at each visit.

- Complete visual checks of returned study dentifrice tubes and review completed diary. Record any suspected over or under use, and the number of any missed or additional brushings, in the CRF. Re-instruct the subject in the correct dosing, usage requirements and diary completion as needed.
  Return dentifrice/toothbrush/diary to subject.
- Confirm subject adherence to the requirements of the protocol and continuance. Record in the CRF.
- ***Day 28 (Visit 6) only:*** Subject completes a DHEQ (source document), for later transcription into the CRF.
- Clinical examiner completes an OST examination. Record findings in the CRF.
- 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 CRF or using source documentation for later transfer to the CRF.

  Clinical examiner completes evaporative air sensitivity assessments (Schiff Sensitivity Scale only) on remaining eligible teeth identified at Screening. Record clinical assessment scores in the CRF or using source documentation for later transfer to the CRF.

  The same examiner will be responsible for completing both clinical measures of DH (tactile and evaporative air sensitivity) for the duration of the study.
- Remind subject of dentifrice usage instructions; supervise dosing and brushing with study dentifrice and recording of brushing in the diary. Record in the CRF.
- 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/incidents reported on completion of the supervised brushing with the assigned study dentifrice will be recorded in the CRF.
- Remind the subject of the Lifestyle Guidelines (Section 5.5) and any Concomitant Medication/Treatment(s) requirements (Section 6.8) of the protocol. Record in the CRF.

8.2.3 Day 56 (±2 days) (Visit 7)

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

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 and any AEs recorded in the CRF.

The following procedures will then be completed at each visit.

- Complete visual checks of returned study dentifrice tubes and review completed diary. Record any suspected over or under use, and the number of any missed or additional brushings, in the CRF. *Do not return dentifrice/toothbrush/diary to subject.*
- Confirm subject adherence to the requirements of the protocol and continuance. Record in the CRF.
- Subject completes a DHEQ (source document), for later transcription into the CRF.
- Clinical examiner completes an OST examination. Record findings in the CRF.
- Clinical examiner completes an OHT examination. Record findings in the CRF.
- 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 CRF or using source documentation for later transfer to the CRF.

  Clinical examiner completes evaporative air sensitivity assessments (Schiff Sensitivity Scale only) on remaining eligible teeth identified at Screening. Record clinical assessment scores in the CRF or using source documentation for later transfer to the CRF.

  The same examiner will be responsible for completing both clinical measures of DH (tactile and evaporative air sensitivity) for the duration of the study.
- 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 dose of study treatment).
- 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 comment captured in the diary which is considered an adverse event or incident will be assessed and reported as per the defined procedures in this protocol. Adverse event reporting procedures are summarized in Adverse Event and Serious Adverse Events (Section 10). Incident reporting procedures are summarized in Definition of and Procedure for Reporting Medical Device Incidents (Section 10.9).

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

Additional and missed product applications will be considered deviations from the protocol and will be recorded on the Deviations Log.

8.4 Study Conclusion

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

If a subject has any clinically significant, study-related abnormalities, AEs or incidents at the conclusion of the study, the GSK CH medical monitor (or designated representative) should be notified and, 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 oral examinations may be carried out at such visits.

9 STUDY ASSESSMENTS

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

complete an assessment. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments in a timely manner.

To ensure the clinical examiner/staff involved in efficacy and safety assessments remain blind to product received, throughout the study: site staff involved in the dispensing of study treatment 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/efficacy assessment procedure during the study.

9.1 Screening Assessments

Screening assessments to identify eligible teeth will be performed by appropriately trained clinical examiners at the times, and in the order, defined in the Study Procedures section of this protocol (Section 8). A single examiner will be responsible for the conduct of the clinical measures of DH (tactile and evaporative air sensitivity) for the duration of the study (at Screening and all subsequent visits).

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. 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 et al. 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 a MGI = 0, using a modification of the Miller Index (Laster et al. 1975). Eligible teeth will have clinical mobility ≤ 1.

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

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 pain 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 feet PAIN 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 CRF. 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 subject's responses.

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

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 and tactile threshold (≤ 20 g) criteria, a minimum of 5 minutes after the tactile assessments have been completed. The assessment will be made by directing a one second application of air from a standard dental syringe held perpendicular to the tooth surface, approximately 1-2 mm coronal to the gingival margin, and from a distance of approximately 1 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.

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

9.2 Efficacy Assessments

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

A single examiner will be responsible for the conduct of both clinical measures of DH (tactile and evaporative air sensitivity) for the duration of the study and the selection of the two 'test teeth' for all study subjects.

9.2.1 Dentine Hypersensitivity Experience Questionnaire (DHEQ-15)

A 'short form' DHEQ (Appendix I Example DHEQ) will be completed by each study subject at Baseline (Visit 2), Day 28 (Visit 3) and Day 56 (Visit 4), prior to the OST examination and the clinical efficacy 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 28 and Day 56, Section 1 (Q7-9 only) and Section 2 (Q1-15) will be answered.

9.2.2 Tactile Sensitivity

The tactile sensitivity of all teeth that exhibited none of the dentition exclusions, and met the EAR, MGI, clinical mobility and qualifying tactile threshold/Schiff sensitivity score criteria at Screening, will be assessed at Baseline (Visit 2). Teeth with a Baseline tactile threshold of ≤ 20 g will also be assessed for evaporative air sensitivity. The tactile sensitivity of the two 'test teeth' selected by the clinical examiner at Baseline will be assessed for randomised subjects at all subsequent visits (Visits 3-7).

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 3-7), 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 Days 3, 7, 14, 28 and 56.

9.2.3 Evaporative Air Sensitivity

The evaporative air sensitivity of all clinically eligible teeth from Screening will be assessed at Baseline (Visit 2). The evaporative air sensitivity of the two 'test teeth' selected at Baseline, followed by the remaining eligible teeth identified at Screening, will be assessed for all randomised subjects at subsequent visits (Visits 3-7).

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

9.2.4 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 at all subsequent visits. 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 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 CRF 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 CRF. 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 childbearing potential, a UPT will be performed at Screening (Visit 1) and Baseline, and the results obtained prior to first use of acclimatization dentifrice (Visit 1) and first use of study dentifrice (Visit 2) respectively.

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

A negative pregnancy result is required before the subject may receive study product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active study period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of the IRB/EC or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of 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 washout or lead-in product (or

medical device), whether or not considered related to the study product, including any washout or lead-in product (or medical device).

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

Events <u>Meeting</u> the AE Definition:

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

Events <u>NOT</u> 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. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

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

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

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

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

10.3 Reporting of Adverse Events

10.3.1 Reporting Period

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

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

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

10.4 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following

up on AEs that are serious, considered related to the study product(s), participation in the study, or a study procedure, or that caused the subject to discontinue the study product or study.

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

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

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

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

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

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

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be the documented as the AE/SAE where known and not the individual signs/symptoms. (e.g. upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

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

10.4.1 Reporting of an Adverse Event

All AEs will be reported on the AE page of the CRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the AE CRF page and the SAE form must

be completed in a consistent manner. For example, the same AE term should be used on both. AEs should be reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

10.4.2 Reporting of a Serious Adverse Event

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

It is essential to enter the following information:

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

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

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

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

Email Serious Adverse Events to:

PPD

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

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

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

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

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

10.5.2 Assessment of Causality

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

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

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

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

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

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

10.6 Follow-up of Adverse Events

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

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

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

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

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

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

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

10.7 Withdrawal Due to an Adverse Event

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

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

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

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

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

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

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

10.8 Pregnancy

10.8.1 Time Period for Collecting Pregnancy Information

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

10.8.2 Action to be Taken if Pregnancy Occurs

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

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

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

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

10.9 Definition of and Procedure for Reporting Medical Device Incidents

Medical devices are being provided by GSK CH for use in this study; the medical device in this study is the toothbrush Oral B Sensi-soft toothbrush (Canadian market).

10.9.1 Definition of an Incident

A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.

Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

An **incident** associated with a device happened and

- The incident was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include any of the following:
- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents:

- A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A subject's study treatment is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A subject's health deteriorates due to medical device failure.

10.9.2 Reporting of Incidents and Malfunctions

All incidents must be reported to GSK CH within 24 hours (or sooner if possible) of the investigator or designee becoming aware of the situation.

Any medical device incident occurring during the study will be documented in the subject's medical records, if in accordance with the investigator's normal clinical practice,

and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE (serious and non-serious), the appropriate AE CRF page and SAE form will be completed and reported as per the AE and SAE reporting sections.

The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK CH. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.

The completed Incident Report Form should be scanned and emailed to the GSK CH Clinical Operations Safety Reporting email box with the study number and subject number in the subject line of the email as soon as possible, **but not more than 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE form should be sent together with this report form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will be retained in the investigator study master file.

The GSK CH Study Manager should be notified of the situation by telephone or email.

Email the Incident Report Forms to:
PPD

The GSK CH Study Manager or designee will be responsible for forwarding the Incident Report Form to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox (PPD), responsible for the study and other GSK CH personnel as appropriate.

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

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

- Notify GSK CH immediately (by following the process described above).
- Schedule the subject to return to the site promptly to return the failed device.
- Record any incidents on the CRF and Incident Report Form following instructions given in the section above.
- Return the failed device to the sponsor as soon as possible, including documentation of the details of the failure

10.9.3 Follow-up of Medical Device Incidents

Medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all subjects, including those who discontinue study product or are withdrawn from the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed Incident Report form with all changes signed and dated by the investigator.

10.9.4 Regulatory and Ethics Reporting Requirements for Incidents

To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during all periods of the study in which the medical device is used.

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

11 DATA MANAGEMENT

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

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

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

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries, questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at

the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in Sections 8 and 9. The CRF and/or diary can be used as a source document at the discretion of data management.

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

11.1 Case Report Form

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

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

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

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

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

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

11.2 Data Handling

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

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

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

11.2.1 Data Queries

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

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

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

11.3 Processing Patient Reported Outcomes

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

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

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

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

11.4 External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSK CH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed quality control process will be performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSK CH.

Reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

No formal sample size has been produced for this exploratory clinical study to characterize the DH efficacy profile of the IP, as measured by Schiff sensitivity score and tactile threshold, over time. Based on previous GSK CH studies evaluating DH efficacy of 0.454% w/w SnF2 dentifrices (for example, (GSK CH Study 205794 2017, GSK CH Study RH01325 2013, GSK CH Study RH01685 2013), approximately 50 evaluable subjects per treatment group is considered sufficient to provide reliable estimates of treatment effect for the purposes of this study and to aid in the design of future clinical studies. Approximately 104 subjects will be randomized to study treatment (approximately 52 per treatment group).

12.2 Statistical Methods and Analytical Plan

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

Treatment differences in the study variables will be tested under the null hypothesis:

- H0: there is no treatment difference versus the alternate hypothesis;

- H1: there is a treatment difference.

12.2.1 Definition of Analysis Populations

The Safety population will include all randomized subjects who receive at least one dose of study product. This population will be based on the product the subject received.

The modified Intent-To-Treat (mITT) population will include all randomized subjects who receive at least one dose of study product and have at least one post baseline efficacy measurement. This population will be based on the study product to which the subject was randomized. Any subject who receives a randomization number will be considered to have been randomized.

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

12.2.2 Exclusion of Data from Analysis

Exclusion of any data from the analyses will be determined during a Blind Data Review Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable. A PP analysis will be performed only if 10% or more of the subjects from the mITT population are excluded from the PP population.

12.2.3 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 summarized by the number and percentage of subjects with each relevant characteristic in each treatment group. Age will be summarized by the mean, standard deviation, median, minimum and maximum values in each treatment group.

12.2.4 Study Drug/Product Compliance and Use of Other Therapies

12.2.4.1 Study Drug/Product Compliance

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

12.2.4.2 Prior and Concomitant Medications

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

12.2.5 Primary Analysis

The mITT population will be used for efficacy analyses.

The primary efficacy variables are:

- Schiff sensitivity score at Days 0 (Baseline), 3, 7, 14, 28 and 56;
- Tactile threshold (g) at Days 0 (Baseline), 3, 7, 14, 28 and 56;
- Number of sensitive teeth (Schiff sensitivity score ≥ 1) at Days 0 (Baseline), 3, 7, 14, 28 and 56.

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, standard error (SE), standard deviation (SD), minimum, maximum) will be presented for each outcome variable at each assessment time point. Raw means (± SE) of Schiff sensitivity score, tactile threshold (g) and number of sensitive teeth at each timepoint will be plotted by treatment group.

12.2.6 Secondary Analysis

The secondary efficacy variables are:

- change from Baseline in Schiff sensitivity score at Day 56;
- change from Baseline in tactile threshold (g) at Day 56.

The Schiff sensitivity score is derived as the average score of the two test teeth. The change from Baseline is derived from the individual teeth first before calculating the average change of the two test teeth. The change in Schiff sensitivity score will be analysed at Day 56 timepoint using an ANCOVA model which will include treatment as a factor and Baseline Schiff sensitivity score as a covariate. Note that since the Baseline Schiff sensitivity score will be included as a covariate, the Baseline Schiff stratification value will not be included in the model.

Tactile 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 Day 56 timepoint using an ANCOVA model with treatment and Baseline Schiff stratification included as factors and Baseline tactile threshold included as a covariate.

Using the above models, adjusted mean change from Baseline, along with 95% CIs will be reported by treatment group. P-values testing for non-zero change from baseline will also be presented for both treatment groups. Mean difference between treatment 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.

The assumption of normality and homogeneity of variance in the ANCOVA models will be investigated, and if violated, an appropriate data transformation or non-parametric method, for example, the van Elteren test, adjusting for the maximum baseline Schiff Sensitivity scores, will be performed.

12.2.7 Safety Analyses

The Safety population will be used for safety analyses. Safety analyses will be performed according to treatment 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 categorized as oral or non-oral. AEs will be listed and summarized by treatment received. SAEs will also be listed. AEs will be regarded as treatment emergent if they occur on or after the first treatment application at the Baseline visit. The following AEs tables will be produced, presented by treatment group:

- listing of all AEs (randomized subjects and non-randomized 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);
- listing of incidents (if there are no incidents, a null listing will be produced).

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

12.2.8 Other Analyses

Other efficacy variables include:

- Change from Baseline in Schiff sensitivity at Days 3, 7, 14 and 28;
- Change from Baseline in tactile threshold (g) at Days 3, 7, 14 and 28.

Change from Baseline in Schiff sensitivity score and tactile threshold at Days 3, 7, 14 and 28 will be analysed as per the secondary analyses: adjusted mean change from Baseline, along with 95% CIs will be reported by treatment group. Treatment differences and 95% CIs will also be presented. No p-values will be reported.

Change from Baseline in DHEQ (Short Form) at Day 28 (Week 4) and Day 56 (Week 8)

The following DHEQ 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 28 and Day 56 for each DHEQ endpoint.

Summary statistics (mean, median, SE, SD, minimum, maximum) will be presented for each DHEQ endpoint by treatment group.

12.2.9 Handling of Dropouts and Missing Data

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

12.2.10 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

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

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

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

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

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

13.2 Quality Assurance

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

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

The investigator(s) will notify GSK CH or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with GSK CH or its agents to prepare the study site for the inspection and will allow GSK CH or its agent, whenever feasible, to be present during the inspection. The

investigator will promptly apply copies of the inspection finding to GSK CH or its agent. Before response submission to the regulatory authority, the investigator will provide GSK CH or its agents with an opportunity to review and comment on responses to any such findings.

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

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

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

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with 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 2016), 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 authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by GSK CH in order to de-identify study subjects.

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

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

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

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

13.3.4 Subject Recruitment

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

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

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

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

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

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

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

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

13.5 Provision of Study Results to Investigators

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

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

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

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

13.6 Records Retention

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

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g. for a GSK CH audit or regulatory inspection) and must be

available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

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

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

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

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR) or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK CH standards/procedures, and/or institutional requirements.

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

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of the investigational product at any time. For multicenter studies (if applicable), this can occur at one or more or at all sites.

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

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

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

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15 APPENDICES

15.1 Abbreviations

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

Table 15-1 Abbreviations

Abbreviation	Term
AE	Adverse event
ANCOVA	Analysis of covariance
BDM	Biostatistics and Data Management
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
DH	Dentinal hypersensitivity
DHEQ	Dentinal hypersensitivity experience questionnaire
DMS	Data management system
EAR	Erosion abrasion recession
EC	Ethics committee
EDC	Electronic data capture
ECG	Electrocardiogram
eCRF	Electronic case report form
ePRO	Electronic patient reported outcome
FDA	Food and Drug Administration (United States)
FSH	Follicle-stimulating hormone
g	Gram
GCP	Good Clinical Practice
GCS	Global clinical supplies
GSK CH	GlaxoSmithKline Consumer Healthcare
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IND	Investigational new drug application
IP	Investigational product
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat

Abbreviation	Term
IUD	Intrauterine device
K^+	Potassium ion
KNO_3	Potassium nitrate
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Master formulation code
MGI	Modified gingival index
mITT	Modified intent-to-treat
N/A	Not applicable
NDA	New drug application
NNHP	Non-prescription natural health product
OHRQOL	Oral health related quality of life
OHT	Oral hard tissue
OST	Oral soft tissue
PI	Principal investigator
PII	Personally identifiable information
PP	Per protocol
ppm	Parts per million
PRO	Patient reported outcome
PT	Preferred term
RAP	Reporting and analysis plan
RCT	Randomized controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SOC	System organ class
SMFP	Sodium monofluorophosphate
SnF_2	Stannous fluoride
Sn	Tin
SRSD	Single reference study document
SUSAR	Suspected unexpected serious adverse reaction
UPT	Urine pregnancy test
US	United States
w/w	Weight/weight

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)

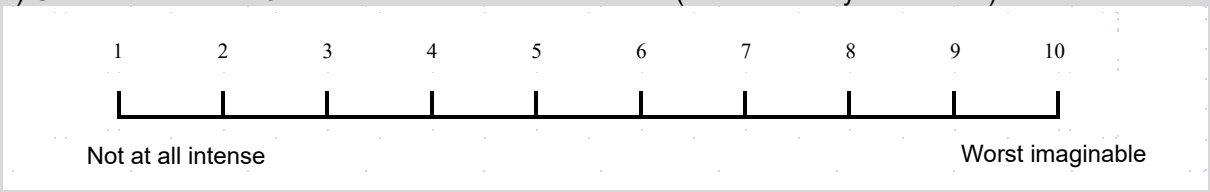
- ☐ Several times a day (7)
- ☐ Once a day (6)
- ☐ Several times a week (5)
- ☐ Once a week (4)
- ☐ Several times a month (3)
- ☐ Once a month (2)
- ☐ Less than once a month (1)
- ☐ Never (0)

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

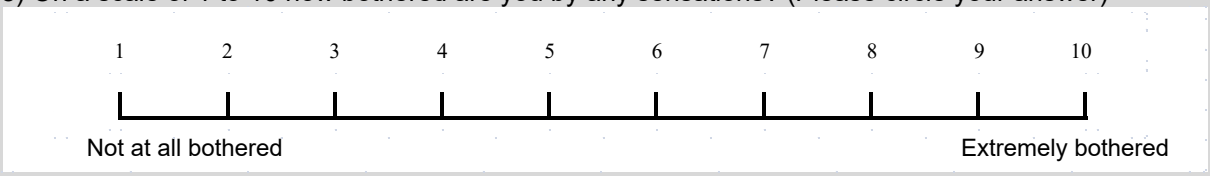
- ☐ A few seconds (5)
- ☐ About a minute (4)
- ☐ Several minutes (3)
- ☐ About half an hour (2)
- ☐ Longer than half an hour (Please specify) (1)
- ☐ Don't have them (0)

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

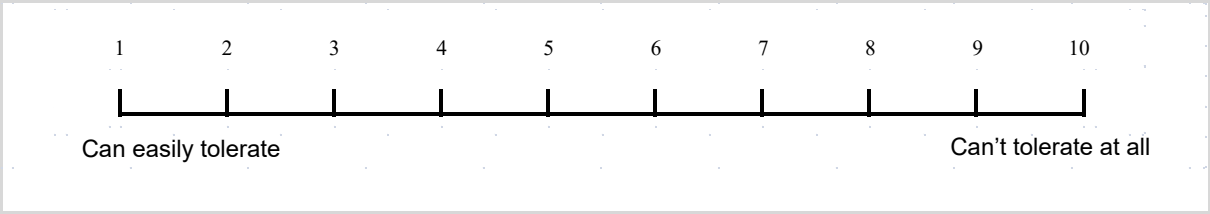
7) On a scale of 1 to 10 how intense are the sensations? (Please circle your answer)



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.	☐	☐	☐	☐	☐	☐	☐