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Clinical Protocol

207872

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SUMMARY INFORMATION

Title:	A Proof of Principal Study to Investigate the Stain Control of Two Stannous Fluoride Dentifrices
Protocol Number:	207872
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) St Georges Avenue, Weybridge, Surrey, KT13 0DE, United Kingdom (UK) • Tel: PPD
Product Names:	<ul style="list-style-type: none"> • 0.454% stannous fluoride (SnF₂) / 5% sodium tripolyphosphate (STP) containing dentifrice; 2.0% abrasive silica • 0.454% SnF₂ / 5% STP containing dentifrice; 3.5% abrasive silica
Development Phase:	N/A

Expert Advice Outside of Normal Working Hours:	PPD
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PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

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

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PROCESS FOR AMENDING THE PROTOCOL

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

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

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

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

Schedule of Events

Procedure	Pre-screening	Visit 1 Screening		Visit 2 Baseline Day 0	Visit 3 Week 2 Day 14 ± 2 days	Visit 4 Week 4 Day 28 ± 2 days
Telephone Screening of Subjects	✓					
Informed Consent		✓				
Demographics, Medical History, Smoking Status		✓				
Current / Concomitant Medication		✓		✓	✓	✓
Oral Soft Tissue (OST) Examination		✓		✓		
Full Oral Hard Tissue (OHT) Examination		✓		✓		
Visual MLSI Stain Assessment		✓				
Inclusion / Exclusion Criteria		✓		✓		
Eligibility		✓		✓		
Brush Anterior Teeth for 30 Seconds with Tap Water Prior to Stain Assessment				✓	✓	✓
Pre-prophylaxis Full MLSI Stain Assessment of the Anterior Teeth ¹				✓		
Stratification / Randomisation				✓		
Dental Prophylaxis ²				✓		
Post-prophylaxis Visual MLSI Stain Assessment				✓		
Full MLSI Stain Assessment ¹					✓	✓
Dispense Study Dentifrice, Timer, Toothbrush and Diary/Instructions Card				✓		
Supervised Brushing on Site				✓ ³	✓	
Adverse Events				✓	✓	✓
Incidents				✓ ⁴	✓	✓
Subject Adherence and Continuance					✓	✓
Diary Compliance Check ⁵					✓	✓
Return Dentifrice, Toothbrush and Diary Card					✓	✓
Post Treatment Dental Prophylaxis						✓ ⁶
Study End						✓

Minimum 24 hours, up to a maximum of 2 weeks

1. Ten subjects will be randomly selected for repeat examinations across each assessment window (a total of 30 repeat examinations over the duration of the study).
2. AEs will be recorded from and including dental prophylaxis onwards.
3. Time of first brushing will be captured to distinguish dentifrice AEs from prophylaxis AEs.
4. Incidents will be collected from first use of the tooth brush, prior to stain assessment.
5. Time of each brushing occasion in addition to missed/additional brushings, and changes to smoking status will be captured in the subject diary.
6. Once all efficacy assessments have been completed randomised subjects who request so will be given a full dental prophylaxis, and will be recorded in the eCRF.

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PROTOCOL SYNOPSIS FOR STUDY 207872

Brief Summary

This proof of principal (PoP) single centre, randomised, examiner blind, four-treatment arm, parallel design study will be used to evaluate and compare the stain build up of two 0.454% stannous fluoride (SnF₂) / 5% sodium tripolyphosphate (STP) dentifrices of differing abrasivity levels, with a marketed standard fluoride dentifrice and a marketed SnF₂ dentifrice.

Stain will be assessed following a full professional dental prophylaxis, at intervals over a 4 week treatment period, using an established clinical measure of extrinsic dental stain - the MacPherson modification [Macpherson, 2000] of the Lobene stain index [Lobene, 1968] (MLSI). Subjects will be stratified by pre-prophylaxis MLSI score (total MLSI Area x Intensity (A×I) for the facial surfaces of the 12 anterior teeth) and smoking status.

The study will be conducted in healthy subjects with a propensity for extrinsic dental stain (in the opinion of the examiner) on the facial surfaces of the anterior teeth.

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Objectives and Endpoints

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of two experimental 0.454% SnF₂ / 5% STP dentifrices with that of a marketed standard fluoride dentifrice, after 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI at week 4.
Secondary	
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of two experimental 0.454% SnF₂ / 5% STP dentifrices with that of a marketed SnF₂ dentifrice, after 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI at week 4.
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of a marketed SnF₂ dentifrice with that of a marketed standard fluoride dentifrice, after 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI at week 4.
Exploratory	
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of an experimental 0.454% SnF₂ / 5% STP, 2.0% abrasive silica dentifrice with that of an experimental 0.454% SnF₂ / 5% STP, 3.5% abrasive silica dentifrice, after 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI at week 4.

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<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of two experimental 0.454% SnF₂ / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF₂ dentifrice, after 2 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI at week 2.
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall Interproximal (Distal + Mesial) MLSI, of two experimental 0.454% SnF₂ / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF₂ dentifrice, after 2 and 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall Interproximal (Distal + Mesial) MLSI at weeks 2 and 4.
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI Area (A), of two experimental moderate abrasivity 0.454% SnF₂ / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF₂ dentifrice, after 2 and 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI Area at weeks 2 and 4.
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI Intensity (I), of two experimental moderate abrasivity 0.454% SnF₂ / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF₂ dentifrice, after 2 and 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI Intensity at weeks 2 and 4.

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Study Design

Overall Design

This is a single-centre, examiner-blind, randomised, four treatment, parallel group study, stratified by baseline total MLSI (A×I) score for the facial surfaces of at least 11 of the 12 anterior teeth (<45 (low); ≥45 (high)) and smoking status (smoker; non smoker). A single dental examiner will perform a full MLSI assessment of the area and intensity of extrinsic dental stain on the facial surfaces of the 6 maxillary and 6 mandibular anterior teeth (universal numbering: 6-11 and 22-27), and the lingual surfaces of the 6 mandibular anterior teeth (universal numbering: 22-27), at baseline (Visit 2), and following 2 and 4 weeks twice daily brushing (Visits 3 and 4).

Potential subjects will be pre-screened via telephone and later attend a screening visit during which they will give their written informed consent to participate in the study. Demography, medical history and concomitant medications will be recorded, followed by an oral examination. This will include an oral soft tissue (OST) examination, a full oral hard tissue (OHT) examination and a visual MLSI stain assessment. Subjects deemed (in the opinion of the examiner) to have a sufficient level of extrinsic dental staining (assessed to be formed due to ingestion of food or drinks, or use of tobacco products) on the facial surfaces of the scorable anterior (maxillary and mandibular) teeth, as well as meeting all other study criteria, will be considered as eligible to proceed with the study. Eligible subjects will continue to use their own dentifrice at home until their baseline visit. Prior to the baseline visit, subjects will be asked to abstain from oral hygiene for at least 6 hours.

At baseline, each subject will undergo an OST and a full OHT, and then brush their anterior teeth for 30 seconds using a wetted toothbrush (with tap water), prior to undergoing a full MLSI stain assessment. Subjects deemed (in the opinion of the examiner) to have a sufficient level of extrinsic dental stain on the facial surfaces of the scorable anterior (maxillary and mandibular) teeth, who continue to meet all study criteria, will be stratified (based on pre-prophylaxis baseline total MLSI (A×I) score and smoking status) and randomised to treatment. The stratification factor will give rise to four strata:

- MLSI Score High (≥45), Smoker
- MLSI Score Low (<45), Smoker
- MLSI Score High (≥45), Non Smoker
- MLSI Score Low (<45), Non Smoker

A dental hygienist will professionally clean each subject's teeth using a conventional

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dental prophylaxis paste followed by flossing (carried out by the hygienist) to remove all visible stain, plaque, debris, and all sub-and supra-gingival calculus from the anterior teeth. A second dental examiner will confirm all sub- and supra-gingival calculus, visible stain (Total MLSI (A×I) = 0), plaque and debris has been removed from the facial, palatal/lingual surfaces of the anterior teeth (visually and by tactile assessment using a dental explorer). Subjects will then be requested to brush twice daily (morning and evening) with their allocated study dentifrice for the next 4 weeks. They will receive verbal and written product usage instructions. First product use will be supervised on site, with a further supervised brushing at Visit 3. Subjects will be asked to record each product use in a diary, and note any significant changes to diet or smoking status, medications and health during the course of the study, and confirmed by the site at each visit.

Subjects will return to the site at Visits 3 and 4, having abstained from oral hygiene for at least 6 hours prior to their visit. Subjects will brush their anterior teeth for 30 seconds using a wetted toothbrush, prior to undergoing a full MLSI stain assessment. Subjects will be asked to bring their study dentifrice, toothbrush and completed diary to each visit to facilitate compliance checks.

Randomised subjects who request so will be offered a full mouth dental prophylaxis on completion of Visit 4 procedures, or on completion of the visit where they exit the study.

Repeat examinations will be performed by the dental examiner at each full MLSI assessment visit. Ten subjects will be randomly selected for repeat examinations across each assessment window (a total of 30 repeat examinations over the duration of the study) at Visits 2 (pre-prophylaxis), 3 and 4. There will be a minimum of 10 minutes, and a maximum of 30 minutes between repeatability examinations.

Pre-screening

Prior to the screening visit, telephone screening of interested subjects will be conducted by the site using a telephone script.

Visit 1 - Screening Visit

The following assessments will be conducted:

- Written informed consent.
- Review inclusion/exclusion criteria.
- Review of the oral care products the subject is currently using to confirm they do not contain any restricted ingredients.
- Demographics, current/concomitant medications, medical history and smoking status captured.

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- Oral examinations including an OST and a full OHT examination.
- Visual MLSI stain assessment of the facial (maxillary and mandibular) surfaces only.
- Confirmation of subject eligibility.

Visit 2 - Baseline Visit

The following assessments will be conducted:

- Review of current/concomitant medications.
- Review inclusion/ exclusion and confirmation of subject eligibility and continuance.
- Full OST examination.
- Full OHT examination.
- Supervised brushing of the anterior teeth for 30 seconds using a wetted toothbrush.
- Pre-prophylaxis full MLSI stain assessment of the facial (maxillary and mandibular) and lingual (mandibular) surfaces.
- Stratification (based on total MLSI score of the facial surfaces only) and randomisation.
- Full professional dental prophylaxis.
- Post-prophylaxis visual MLSI stain assessment of the facial (maxillary and mandibular) and lingual (mandibular) surfaces to confirm overall MLSI = 0.
- Dispensation of study dentifrice, toothbrush and diary/instructions card.
- Supervised brushing with subject's allocated dentifrice.
- AEs and Incidents following supervised brushing.

Visit 3 - Week 2

The following assessments will be conducted:

- Subjects return study dentifrice, toothbrush and diary card to the clinical site.
- Review of current/concomitant medications, AEs and incidents.
- Review of completed diary to confirm timing of each brushing occasion in addition to missed/additional brushings, and potential changes to smoking status.
- Confirmation of subject adherence and continuance.
- Supervised brushing of the anterior teeth for 30 seconds using a wetted toothbrush.
- Full MLSI stain assessment of the facial (maxillary and mandibular) and lingual (mandibular) surfaces.
- Supervised brushing with subject's allocated dentifrice.
- AEs and Incidents following supervised brushing.

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Visit 4 - Week 4 (LSLV)

The following assessments will be conducted:

- Subjects return study dentifrice, toothbrush and diary card to the clinical site.
- Review of current/concomitant medications, AEs and incidents.
- Review of completed diary to confirm timing of each brushing occasion in addition to missed/additional brushings, and potential changes to smoking status.
- Confirmation of subject adherence and continuance.
- Supervised brushing of the anterior teeth for 30 seconds using a wetted toothbrush.
- Full MLSI stain assessment of the facial (maxillary and mandibular) and lingual (mandibular) surfaces.
- Post assessment brushing with study dentifrice and tooth brush (if requested by the subject).
- Post treatment dental prophylaxis (if requested by the subject).
- AE's and incidents captured.
- Study end.

Type and Planned Number of Subjects

A sufficient number of subjects will be screened to randomise at least 220 subjects to ensure 200 evaluable subjects complete the study. This will ensure approximately 50 evaluable subjects per treatment arm.

This study has not been formally powered to make any claims, and is appropriately sized as a PoP study for the purpose of observing meaningful trends.

Diagnosis and Main Criteria for Inclusion

Subjects aged 18-65 years of age, with a minimum of 16 natural teeth (including the 12 anterior teeth) and in good general health with a propensity for extrinsic dental stain. At Screening and Baseline subjects must have the facial surfaces, and mandibular lingual surfaces, of at least 11 of the 12 anterior teeth, gradable for MLSI (four sites per tooth), with sufficient extrinsic dental stain (in the opinion of the examiner) on the facial surfaces of the scorable anterior (maxillary and mandibular) teeth.

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Product Information

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

	Test Product 1	Test Product 2	Reference Product 1	Reference Product 2
Product Name	Experimental dentifrice containing 0.454% SnF ₂ / 5% STP; 2.0% abrasive silica (RDA~58)	Experimental dentifrice containing 0.454% SnF ₂ / 5% STP; 3.5% abrasive silica (RDA~77)	Dentifrice containing 1000ppm fluoride as Sodium Monofluorophosphate (SMFP; Colgate Cavity Protection [®] , Canada Marketed dentifrice) moderate abrasivity (RDA~80)	Dentifrice containing 0.454% SnF ₂ (Sensodyne Complete Protection, Canada Marketed dentifrice) higher abrasivity (RDA~120)
Short Product Name	Test dentifrice (RDA~58)	Test dentifrice (RDA~77)	Reference dentifrice (RDA~80)	Reference dentifrice (RDA~120)
Product Formulation Code (MFC)	CCI [REDACTED]	CCI [REDACTED]	Commercially Available	Commercially Available
Dose	A ribbon of dentifrice, covering the length of the toothbrush head			
Route of Administration	Oral			
Dosing Instructions	Brush twice daily (morning and evening) with the allocated study dentifrice for 1 timed minute			

Statistical Methods

For the relevant stain variable, the various scores will be averaged over the regions under consideration. These include:

- Overall MLSI - calculated as the mean MLSI (A×I) score over all gingival, body, mesial and distal sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.
- Interproximal MLSI - calculated as the mean MLSI (A×I) score over all interproximal (mesial+distal) sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.

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- Overall MLSI Area - calculated as mean MLSI (A) score all gingival, body, mesial and distal sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.
- Overall MLSI Intensity - calculated as mean MLSI (I) score all gingival, body, mesial and distal sites on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.

Primary and Secondary Efficacy

The primary and secondary variables will be overall MLSI at Week 4. These variables will be analysed using analysis of covariance (ANCOVA) with treatment and smoking status as factor, and appropriate pre-prophylaxis baseline mean MLSI score as a covariate. Adjusted means and treatment differences between the test products and the marketed standard fluoride dentifrice will be provided together with their 95%CIs and p-values.

Exploratory Efficacy

Exploratory variables include overall MLSI Intensity score at Week 2, and Interproximal MLSI score, overall MLSI Area score and overall MLSI Intensity score at Weeks 2 and 4. Each of these variables will be analysed using the same ANCOVA model as the primary analysis.

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1. INTRODUCTION

One of the main functions of a dentifrice is to help control extrinsic dental stain [Pader, 2012], typically achieved by the inclusion of dental grade abrasives such as silica's. Polyphosphates, such as sodium tripolyphosphate (STP), can also be included as chemical cleaning compounds, to supplement the physical stain removal offered by dental abrasives. Polyphosphates act as chelating ingredients and have been shown to bind strongly to the tooth surface, reducing the force of adhesion of adsorbed proteins [Shellis, 2005] and facilitating stain removal during toothbrushing. In addition, they have been shown to desorb salivary proteins from enamel, and inhibit protein adsorption [Rykke, 1997], thereby helping to control stain build up.

Extrinsic (surface) dental stain is primarily caused by chromagens (originating in the diet, or from smoking or medications) binding to proteinaceous compounds found in the salivary pellicle [Schuurs, 2013], and is a common finding in the adult population. The etiology of stain is multiple but is widely agreed to result from discoloration of plaque and pellicle on the surface of the tooth, with the main site for extrinsic stain build up generally accepted as the acquired salivary tooth pellicle [Shellis, 2005].

Stannous fluoride (SnF_2) has been incorporated into oral hygiene products indicated for the relief of dentinal hypersensitivity (DH) since the 1960s [Tinanoff, 1990; Thrash, 1994; Schiff, 2005; Baig, 2005; Paraskevas, 2006; Schiff, 2006]. The stannous salts found in dentifrice formulations have historically been associated with undesirable dental staining with long-term use [Tinanoff, 1995]. GSKCH currently markets a 0.454% SnF_2 dentifrice in Canada as Sensodyne Complete Protection. In order to control against the known staining effects of stannous salts, 5% STP was included in a moderate to high abrasivity formulation, as measured by a Relative Dentine Abrasivity (RDA) of ~120.

Two clinical studies were conducted on the now marketed dentifrice to evaluate the build up of extrinsic dental stain, following professional prophylaxis. In an 8 week study a marketed SnF_2 dentifrice; RDA~146 (Crest Pro-Health^{™*}) exhibited greater stain build up compared to the test SnF_2 dentifrice, and no statistically significant differences in dental stain build up were observed between the then test SnF_2 dentifrice and a standard fluoride dentifrice; RDA~80 (Colgate Cavity Protection[®]), after 8 weeks twice daily use [GSKCH study CCI [REDACTED]]. In a longer use 24 weeks study, a statistically significant difference in favour of the SnF_2 dentifrice versus the

^{™*} Crest Pro-Health is a registered trademark of Proctor and Gamble.

[®] Colgate is a registered trademark of the Colgate-Palmolive group.

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same standard fluoride dentifrice (Colgate Cavity Protection[®]) was observed after 24 weeks twice daily use [GSKCH study CCI [REDACTED]].

It is an important compromise that a dentifrice should be able to control extrinsic dental stain while minimising its abrasive effect [Schemehorn, 2011], particularly for people with tooth sensitivity where the softer dentin is exposed [Pickles, 2006].

Therefore, a lower abrasivity dentifrice is considered to be more appropriate for DH sufferers. GSKCH have therefore developed two experimental dentifrice formulations which have lower RDA values of ~52 and RDA of ~80, to support an overall lower abrasion/ enamel protection proposition.

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2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of two experimental 0.454% SnF₂ / 5% STP dentifrices with that of a marketed standard fluoride dentifrice, after 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI at week 4.
Secondary	
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of two experimental 0.454% SnF₂ / 5% STP dentifrices with that of a marketed SnF₂ dentifrice, after 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI at week 4.
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of a marketed SnF₂ dentifrice with that of a marketed standard fluoride dentifrice, after 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI at week 4.
Exploratory	
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of an experimental 0.454% SnF₂ / 5% STP, 2.0% abrasive silica dentifrice with that of an experimental 0.454% SnF₂ / 5% STP, 3.5% abrasive silica dentifrice, after 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI at week 4.

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<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI (A×I), of two experimental 0.454% SnF₂ / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF₂ dentifrice, after 2 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI at week 2.
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall Interproximal (Distal + Mesial) MLSI, of two experimental 0.454% SnF₂ / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF₂ dentifrice, after 2 and 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall Interproximal (Distal + Mesial) MLSI at weeks 2 and 4.
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI Area (A), of two experimental moderate abrasivity 0.454% SnF₂ / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF₂ dentifrice, after 2 and 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI Area at weeks 2 and 4.
<ul style="list-style-type: none"> To evaluate and compare the build up of extrinsic tooth stain, as measured by overall MLSI Intensity (I), of two experimental moderate abrasivity 0.454% SnF₂ / 5% STP dentifrices with that of a marketed standard fluoride dentifrice and a marketed SnF₂ dentifrice, after 2 and 4 weeks twice daily use. 	<ul style="list-style-type: none"> Overall MLSI Intensity at weeks 2 and 4.

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3. STUDY PLAN

3.1. Study Design

Overall Design

This is a single-centre, examiner-blind, randomised, four treatment, parallel group study, stratified by baseline total MLSI (A×I) score for the facial surfaces of at least 11 of the 12 anterior teeth (<45 (low); ≥45 (high)) and smoking status (smoker; non smoker). A single dental examiner will perform a full MLSI assessment of the area and intensity of extrinsic dental stain on the facial surfaces of the 6 maxillary and 6 mandibular anterior teeth (universal numbering: 6-11 and 22-27), and the lingual surfaces of the 6 mandibular anterior teeth (universal numbering: 22-27), at baseline (Visit 2), and following 2 and 4 weeks twice daily brushing (Visits 3 and 4).

Potential subjects will be pre-screened via telephone and later attend a screening visit during which they will give their written informed consent to participate in the study. Demography, medical history and concomitant medications will be recorded, followed by an oral examination. This will include an oral soft tissue (OST) examination, a full oral hard tissue (OHT) examination and a visual MLSI stain assessment. Subjects deemed to have a sufficient level of extrinsic dental staining (in the opinion of the examiner), assessed to be formed due to ingestion of food or drinks, or use of tobacco products) for the facial surfaces of the scorable anterior (maxillary and mandibular) teeth, as well as meeting all other study criteria, will be considered as eligible to proceed with the study. Eligible subjects will continue to use their own dentifrice at home until their baseline visit. Prior to the baseline visit, subjects will be asked to abstain from oral hygiene for at least 6 hours.

At baseline, each subject will undergo an OST and a full OHT, and then brush their anterior teeth for 30 seconds using a wetted toothbrush (with tap water), prior to undergoing a full MLSI stain assessment. Subjects with a sufficient level of extrinsic dental stain (in the opinion of the examiner) on the facial surfaces of the scorable anterior (maxillary and mandibular) teeth, who continue to meet all study criteria, will be stratified (based on pre-prophylaxis baseline total MLSI (A×I) score and smoking status) and randomised to treatment. The stratification factor will give rise to four strata:

- MLSI Score High (≥45), Smoker
- MLSI Score Low (<45), Smoker
- MLSI Score High (≥45), Non Smoker

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- MLSI Score Low (<45), Non Smoker

A dental hygienist will professionally clean each subject's teeth using a conventional dental prophylaxis paste followed by flossing (carried out by the hygienist) to remove all visible stain, plaque, debris, and all sub-and supra-gingival calculus from the anterior teeth. A second dental examiner will confirm all sub- and supra-gingival calculus, visible stain (Total MLSI (A×I) = 0), plaque and debris has been removed from the facial, palatal/lingual surfaces of the anterior teeth (visually and by tactile assessment using a dental explorer). Subjects will then be requested to brush twice daily (morning and evening) with their allocated study dentifrice for the next 4 weeks. They will receive verbal and written product usage instructions. First product use will be supervised on site, with a further supervised brushing at Visit 3. Subjects will be asked to record each product use in a diary, and note any significant changes to diet or smoking status, medications and health during the course of the study, and confirmed by the site at each visit.

Subjects will return to the site at Visits 3 and 4, having abstained from oral hygiene for at least 6 hours prior to their visit. Subjects will brush their anterior teeth for 30 seconds using a wetted toothbrush, prior to undergoing a full MLSI stain assessment. Subjects will be asked to bring their study dentifrice, toothbrush and completed diary card to each visit to facilitate compliance checks.

Randomised subjects who request so will be offered a full mouth dental prophylaxis on completion of Visit 4 procedures, or on completion of the visit where they exit the study.

Repeat examinations will be performed by the dental examiner at each full MLSI assessment visit. Ten subjects will be randomly selected for repeat examinations across each assessment window (a total of 30 repeat examinations over the duration of the study) at Visits 2 (pre-prophylaxis), 3 and 4. There will be a minimum of 10 minutes, and a maximum of 30 minutes between repeatability examinations.

Pre-screening

Prior to the screening visit, telephone screening of interested subjects will be conducted by the site using a telephone script.

Visit 1 - Screening Visit

The following assessments will be conducted:

- Written informed consent.
- Review inclusion/exclusion criteria.
- Review of the oral care products the subject is currently using to confirm they do not contain any restricted ingredients.

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- Demographics, current/concomitant medications, medical history and smoking status captured.
- Oral examinations including an OST and a full OHT examination.
- Visual MLSI stain assessment of the facial (maxillary and mandibular) surfaces.
- Confirmation of subject eligibility.

Visit 2 - Baseline Visit

The following assessments will be conducted:

- Review of current/concomitant medications.
- Confirmation of subject eligibility and continuance.
- Full OST examination.
- Full OHT examination.
- Supervised brushing of the anterior teeth for 30 seconds using a wetted toothbrush.
- Pre-prophylaxis full MLSI stain assessment of the facial (maxillary and mandibular) and lingual (mandibular) surfaces.
- Stratification (based on total MLSI score of the facial surfaces only) and randomisation.
- Full professional dental prophylaxis.
- Post-prophylaxis visual MLSI stain assessment of the facial (maxillary and mandibular) and lingual (mandibular) surfaces to confirm overall MLSI = 0.
- Dispensation of study dentifrice, toothbrush, timer and diary/instructions card.
- Supervised brushing with subject's allocated dentifrice.
- AEs and Incidents following supervised brushing.

Visit 3 - Week 2

The following assessments will be conducted:

- Subjects return study dentifrice, toothbrush, and diary card to the clinical site.
- Review of current/concomitant medications, AEs and incidents.
- Review of completed diary to confirm timing of each brushing occasion in addition to missed/additional brushings, and potential changes to smoking status.
- Confirmation of subject adherence and continuance. Supervised brushing of the anterior teeth for 30 seconds using a wetted toothbrush.
- Full MLSI stain assessment of the facial (maxillary and mandibular) and lingual (mandibular) surfaces.
- Supervised brushing with subject's allocated dentifrice.
- AEs and Incidents following supervised brushing.

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Visit 4 - Week 4 (LSLV)

The following assessments will be conducted:

- Subjects return study dentifrice, toothbrush, timer and diary card to the clinical site.
- Review of current/concomitant medications, AEs and incidents.
- Review of completed diary to confirm timing of each brushing occasion in addition to missed/additional brushings, and potential changes to smoking status.
- Confirmation of subject adherence and continuance.
- Supervised brushing of the anterior teeth for 30 seconds using a wetted toothbrush.
- Full MLSI stain assessment of the facial (maxillary and mandibular) and lingual (mandibular) surfaces.
- Post assessment brushing with study dentifrice and tooth brush (if requested by the subject).
- Post treatment dental prophylaxis (if requested by the subject).
- AE's and incidents captured.
- Study end.

3.2. Type and Planned Number of Subjects

A sufficient number of subjects will be screened to randomise at least 220 subjects to ensure 200 evaluable subjects complete the study. This will ensure approximately 50 evaluable subjects per treatment arm.

This study has not been formally powered to make any claims, and is appropriately sized as a PoP study for the purpose of observing meaningful trends.

3.3. Study Design and Dose Justification

This PoP single centre, randomised, examiner blind, four-treatment arm, parallel design study will be used to evaluate and compare the stain build up of two 0.454% SnF₂ / 5% STP dentifrices of differing abrasivity levels, with a marketed standard fluoride dentifrice and a marketed SnF₂ dentifrice.

• Stain will be assessed following a full professional dental prophylaxis, at intervals over a 4 week treatment period, using an established clinical measure of extrinsic dental stain - the MacPherson modification [Macpherson, 2000] of the Lobene stain index [Lobene, 1968] (MLSI). Subjects will be stratified by pre-prophylaxis MLSI

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score (total MLSI (A×I) for the facial surfaces of the 12 anterior teeth) and smoking status.

Since STP has been included in the test dentifrices to prevent SnF₂ from contributing to extrinsic dental stain, and not to directly reduce extrinsic stain caused by dietary and lifestyle habits, a stain build up design has been assessed to be the most appropriate clinical model for this study.

A 4 week treatment period has been selected for this study, as 4 weeks has been assessed to be a sufficient period of time to establish statistically significant between treatment differences for stain build up with this specific dentifrice technology. A previous 8 week study conducted by GSKCH demonstrated that although there was an increase in stain build up from Week 4 to 8, the between treatment differences observed at Week 4 were similar to those at Week 8 [GSKCH study CCI █████]. Stain assessments will also be conducted at Week 2, as this time-point was not included in earlier studies [GSKCH studies CCI █████ and CCI █████]. Therefore, it is of interest to assess the performance of the commercialised and experimental SnF₂ dentifrices at this time-point.

Stain assessments will be made on the facial and lingual surfaces of the anterior teeth as these surfaces are considered the most aesthetically important with respect to dental stain accumulation. Dental stain largely builds up in the harder to reach interproximal areas, therefore in addition to analysis of the total MLSI (A×I) the interproximal regions have also been given focus as an exploratory objective in this study. As most of the stain is removed from the body and gingival regions, we would expect to see little change in the total gingival MLSI (A×I) and total body MLSI (A×I), therefore, these variables are not being analysed in this study. Furthermore, separate analysis of the facial and lingual surfaces are not of focus in this study. As the facial teeth are the most brushed we would expect to see little stain build up on the facial surfaces in comparison to the lingual surfaces, with little difference expected between the total MLSI (A×I) and total lingual MLSI (A×I).

A single examiner will perform the dental stain assessments for all subjects at the baseline, Week 2 and 4 visits to avoid inter-examiner variability. To assess the repeatability of the stain assessments 30 repeat examinations will be performed by the dental examiner over the duration of the study.

The dosage regimen of twice daily use (morning and evening) will be the same for all subjects, and has been selected based on widely recommended oral hygiene practice, and typical consumer habit.

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Sensodyne Complete Protection has been selected as a reference dentifrice in this study as it is a commercialised SnF₂ containing dentifrice. Colgate Cavity Protection® has been selected as a reference comparator as it is marketed globally, does not contain any ingredients known to impart extrinsic dental stain, and is considered to be representative of a moderate abrasivity standard, daily use fluoride dentifrice. Two recent stain build up studies have been conducted by GSKCH, which contain both the commercialised SnF₂ dentifrice and Colgate Cavity Protection®, providing us with a recent benchmark of relative and expected performance at the Week 4 time-point.

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

The study statistician and other employees of the Sponsor who may influence study outcomes are blinded to the product allocation of subjects. The examiner will be blinded to the treatment received. To ensure the examiner remains blinded throughout the study, the examiner is not permitted in the room whilst product is dispensed. All study products will be overwrapped to conceal any labelling. In addition, subjects will be treated in a separate area and instructed not to share their allocated treatment with the examiner. The dispensing staff will not be involved in any clinical assessments during the study.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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

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4.1. Inclusion Criteria

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

1. CONSENT

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

2. AGE

Aged between 18 and 65 years inclusive.

3. COMPLIANCE

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

4. GENERAL HEALTH

Good general and mental health with, in the opinion of the investigator or medically qualified designee:

- No clinically significant and relevant abnormalities of medical history or oral examination which could impact study outcomes.
- Absence of any condition that would impact on subject safety or wellbeing, or affect the subject's ability to understand and follow study procedures and requirements.

5. DENTAL HEALTH

In the opinion of the investigator or medically qualified designee

At screening:

- Good oral health.
- At least 16 natural teeth including the 12 anterior teeth.
- The facial surfaces, and mandibular lingual surfaces, of at least 11 of the 12 anterior teeth, gradable for the MLSI.
- Presence of extrinsic dental stain (judged to be formed due to dietary factors, or use of tobacco products) on the facial surfaces of the anterior teeth, as determined from a visual stain assessment.

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At baseline:

- e) A sufficient level of extrinsic dental stain (in the opinion of the examiner) on the **facial surfaces** of the scorable anterior (maxillary and mandibular) teeth.

4.2. Exclusion Criteria

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

1. PREGNANCY

Women who are known to be pregnant, or who are intending to become pregnant over the duration of the study. Since this study is not being conducted under an IND this information will be self-reported, and not diagnosed through the conduct of urinary pregnancy testing.

2. BREAST-FEEDING

Women who are breast-feeding.

3. SUBSTANCE ABUSE

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

4. CONCURRENT MEDICATION

- a) Current regular use of mouthwashes containing ingredients that are known to impart staining. For example, chlorhexidine or cetylpyridinium chloride (CPC).
- b) Use of minocycline, tetracycline or doxycycline within 30 days prior to screening.
- c) Use of minocycline, tetracycline or doxycycline between the screening and baseline visit.
- d) Daily doses of a medication and/or traditional/herbal ingredients which, in the opinion of the investigator, may affect study outcomes. For example, drugs or supplements containing metal ions known to impart staining to the enamel.

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5. DISEASE

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

6. ALLERGY/ INTOLERANCE

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

7. CLINICAL STUDY/ EXPERIMENTAL PRODUCT

- a) Participation in another clinical study or receipt of an investigational drug within 30 days of the screening visit.
- b) Previous participation in this study.

8. GENERAL DENTITION EXCLUSIONS

- a) Dental prophylaxis within 8 weeks of screening.
- b) Gross periodontal disease, treatment of periodontal disease (including surgery) within 12 months of screening, scaling or root planning within 3 months of screening.
- c) Use of any professionally dispensed or over the counter bleaching/ whitening products (excluding daily use whitening dentifrices) within the past 3 months.

9. SPECIFIC DENTITION EXCLUSIONS FOR TEST TEETH

- a) Any tooth which, in the opinion of the investigator, appears to be non vital based on changes in the intrinsic colour.
- b) Tooth with evidence of current or recent caries, or reported treatment of decay in 12 months of screening.
- c) Tooth with exposed dentine which, in the opinion of the investigator, could impact grading of extrinsic dental stain; tooth with deep, defective or facial restorations; tooth used as an abutment for fixed or removable partial dentures; tooth with full crown or veneer, orthodontic bands or cracked enamel.
- d) Tooth with surface irregularities, discoloration due to trauma, tetracycline stain, restorations, or hypo or hyperplastic areas which, in the opinion of the investigator, would prevent consistent grading of extrinsic dental stain.

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10. PERSONEL

An employee of the sponsor or the study site or members of their immediate family.

11. OTHER

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

4.3. Screening/ Baseline Failures

Screen failures are defined as subjects who consent to participate in the study but are never subsequently randomised. In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information is required to be entered into the electronic case report form (eCRF):

- Consent
- Demography
- Study conclusion form (reason must include documentation of inclusion/exclusion criteria that was failed)
- AE forms (Yes/No and specifics if Yes)

Re-screening of subjects will not be allowed in this study.

4.4. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If the reason for removal of a subject from the study is an AE, the principal specific event or test will be recorded in the eCRF. If a subject is withdrawn from the study because of a product limiting AE, thorough efforts should be clearly made to document the outcome. Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilises, is otherwise explained, or the subject is lost to follow-up. Should there be any subject circumstances, which in the opinion of the investigator could affect study outcomes (e.g. excessive alcohol consumption), every attempt will be made to reschedule the subject. If they cannot be reappointed they will be withdrawn from the study.

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

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.

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- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, at least 2 telephone calls). The contact attempt should be documented in the subject's record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

Should a situation arise for a randomised subject, which in the opinion of the investigator could affect study outcomes (e.g. excessive alcohol consumption), the following actions must be taken:

- Baseline visit: every attempt will be made to reschedule the subject. If they cannot be reappointed they will be withdrawn from the study. No clinical efficacy measures will be performed. The subject should not be replaced.
- Week 2 visit: every attempt will be made to reschedule the subject. If they cannot be reappointed they will continue in the study. No stain assessments will be performed at this visit.
- Week 4 visit: every attempt will be made to reschedule the subject. If they cannot be reappointed they will be withdrawn from the study. No stain assessments will be performed. The subject should not be replaced.

4.5. Subject Replacement

Subjects who withdraw from the study post-randomisation will not be replaced.

4.6. Subject and Study Completion

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

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5. PRODUCT INFORMATION

5.1. Study Product

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

	Test Product 1	Test Product 2	Reference Product 1	Reference Product 2
Product Name	Experimental dentifrice containing 0.454% SnF ₂ / 5% STP; 2.0% abrasive silica (RDA~58)	Experimental dentifrice containing 0.454% SnF ₂ / 5% STP; 3.5% abrasive silica (RDA~77)	Dentifrice containing 1000ppm fluoride as Sodium Monofluorophosphate (SMFP; Colgate Cavity Protection [®] , Canada Marketed dentifrice) moderate abrasivity (RDA~80)	Dentifrice containing 0.454% SnF ₂ (Sensodyne Complete Protection, Canada Marketed dentifrice) higher abrasivity (RDA~120)
Short Product Name	Test dentifrice (RDA~58)	Test dentifrice (RDA~77)	Reference dentifrice (RDA~80)	Reference dentifrice (RDA~120)
Product Formulation Code (MFC)	CCI	CCI	Commercially Available	Commercially Available
Dose	A ribbon of dentifrice, covering the length of the toothbrush head			
Route of Administration	Oral			
Dosing Instructions	Brush twice daily (morning and evening) with the allocated study dentifrice for 1 timed minute			

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

Name of Item	Purpose
Oral-B Sensi Soft Manual Toothbrush	Dentifrice application by tooth brushing.
Countdown timers	To ensure accurate brushing.

In addition to the test dentifrice, toothbrush and countdown timer all subjects will be supplied with a diary card/instructions. The diary card/instructions will be printed by the study site.

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5.2. Dose Schedule

During the treatment period, subjects will apply a full brush head of their allocated dentifrice, brush for one timed minute (in their usual manner) and expectorate.

The dosage regimen of twice daily treatment (morning and evening) will be applied during the treatment period. Subjects will be offered the opportunity to brush unsupervised with their allocated dentifrice at Visit 4, after completing all visit procedures.

5.3. Dose Modification

No dose modification is permitted in this study.

5.4. Product Compliance

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

To ensure that subjects understand the dose of dentifrice to be used, staff will demonstrate what is meant by a 'full ribbon' (i.e. covering the length of the toothbrush head) at the baseline visit, and a supervised brushing will be carried out at Visit 3 (at the end of the visit procedures).

Subjects will receive a brushing instruction/diary sheet. This will outline the brushing instructions and will be used to record the date and time of each brushing occasion during the treatment period. Subjects will also be asked to note any missed brushings, and to use the diary to record any significant changes to diet or smoking status.

Subjects will be provided with a diary at baseline, which they will return at each visit to the study site. The number of missed or extra brushings will be recorded in the eCRF.

Subjects will also be asked to bring all tubes of study dentifrice to each study visit for a visual compliance check of each product.

5.5. Precautions

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

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5.6. Overdose

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

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

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

5.7. Rescue Therapy

No rescue therapy is required in this study.

5.8. Product Assignment

Subjects will be assigned to study product in accordance with the randomisation schedule generated by inVentiv Health prior to the start of the study, using validated software.

5.8.1 Randomisation

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

Subjects with a sufficient level of extrinsic dental stain (in the opinion of the examiner) on the facial surfaces of the scorable anterior (maxillary and mandibular) teeth, who continue to meet all study criteria, will be stratified (based on pre-prophylaxis baseline total MLSI (A×I) score and smoking status) and randomised to treatment. The stratification factor will give rise to four strata:

- MLSI Score High, Smoker
- MLSI Score Low, Smoker
- MLSI Score High, Non Smoker

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- MLSI Score Low, Non Smoker

The randomisation list will be prepared using a randomisation block design with an equal allocation to each of the strata. The study site will receive two versions of the randomisation schedule, each in a sealed envelope and clearly marked as either “For Dispensing” or “Emergency Use Only”.

The “For Dispensing” schedule will contain the list of randomisation numbers only and will not include any coded description, just a letter A, B, C or D.

The ‘Emergency Use Only’ randomisation schedule will only be removed from the sealed envelope in an emergency situation (see Section 5.8.3). This schedule will have a randomisation number followed by the letter A, B, C or D. The schedule will have a footnote with a key for A, B, C and D identifying the three treatments.

However, to maintain the blinding of the study as far as possible, all treatment allocations for all randomisation numbers on this randomisation schedule will be masked with scratch-off panels. Only the panels required for the unblinding the particular subject should be removed.

5.8.2. Blinding

The study statistician, other employees of the sponsor, and vendors acting on behalf of the sponsor, who may influence study outcomes are blinded to the product allocation of subjects. The examiner will be blinded to the treatment received. To ensure the examiner remains blinded throughout the study, the examiner is not permitted in the room whilst product is dispensed, and subjects will be asked not to remove study products from their bags outside of the dispensing room and until they are home. In addition, subjects should be treated in a separate area. The dispensing staff will not be involved in any efficacy assessments during the study.

5.8.3. Code Breaks

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

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

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5.9. Packaging and Labelling

The reference dentifrices (Colgate Cavity Protection® and Sensodyne Complete Protection) will be sourced from the Canadian market. The test dentifrices will be manufactured, filled and supplied by GSKCH.

All dentifrices, will be overwrapped in white vinyl to obscure any branding on the commercial packs. Each tube will have one English label and one French label affixed. Each subject will receive a sufficient number of tubes to cover usage during the treatment phase.

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

All sundry items will be supplied in their commercial packaging for dispensing by study staff as required.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. Subjects should be instructed to not remove or deface any part of the study label.

5.9.1. Accountability of Product

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

Completion of diaries will be the responsibility of subjects, after they have been dispensed subjects will be asked to take them home and bring them back to the clinical site for each study visit.

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

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

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The inventory must be available for inspection by the study monitor during the study. At the end of the study, study product supplies will be verified by the monitor. Study product supplies will then be either collected by the study monitor or returned by the investigator or designee to the GSKCH Clinical Supplies Department or designated vendor.

5.9.2. Storage of Product

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

6. STUDY ASSESSMENTS AND PROCEDURES

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

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

6.1. Visit 1 - Screening Visit

6.1.1. Telephone Screening

Prior to the screening visit, telephone screening of interested subjects will be conducted using a telephone script. This will be conducted by the site recruitment staff or designee.

6.1.2. Informed Consent

The investigator, or designee, must obtain written (signed and dated by the subject) informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent will be provided by the investigator or by GSKCH. The investigator, or designee, should sign and date the consent form to confirm that the consent process was completed correctly. The subject will be provided with a copy of their signed and dated consent form and any other written information which they should be instructed to retain.

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

6.1.3. Demographics

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

6.1.4. Medical History and Concomitant Medication

Medical history will be assessed as related to the inclusion/exclusion criteria by the Investigator or medically qualified designee. Details of any relevant dental, medical or surgical history (within the last year), including allergies or drug sensitivity, will be recorded on the eCRF. Any concomitant therapy taken in the 30 days prior to the Screening Visit and throughout the study will also be recorded.

6.1.5. Oral Soft Tissue (OST) Examination

Where possible, this procedure should be conducted by a single trained dental examiner. The examination will be accomplished by direct observation and palpation with retraction aids as appropriate. The examiner will include examination of the Labial Mucosa (including lips), Buccal Mucosa, and Mucogingival folds, Gingival Mucosa, Hard Palate, Soft Palate, Tonsilar Area, Pharyngeal Area, Tongue, Sublingual Area, Submandibular Area and Salivary Glands. The results of the examination will be recorded in the eCRF as either normal or abnormal with details of any abnormalities. A brief description of any abnormality observed by the examiner or reported by the subject at the application site following dental prophylaxis or administration of the treatment dentifrices will be recorded as an AE.

An OST examination will be conducted at Visits 1 and 2, prior to any clinical assessments. While it is preferable to use the same OST examiner throughout the study, to facilitate subject flow, OST examinations may be carried out by different examiners.

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6.1.6. Full Oral Hard Tissue (OHT) Visual Examination

A suitable qualified individual will perform an examination of the oral hard tissue to confirm that the subject has a minimum of 16 natural teeth and to evaluate dentition exclusions. The examination will be performed by direct observation.

6.1.7. Visual MLSI Stain Assessment

A visual assessment of the 12 anterior teeth for stain will be performed (individual tooth scores will not be recorded) to determine eligibility. Eligible subjects will be deemed to have a sufficient level of extrinsic dental stain (in the opinion of the examiner) on the scorable surfaces of the anterior (maxillary and mandibular) teeth.

6.2. Visit 2 - Baseline Visit

6.2.1. Oral Soft Tissue (OST) Examination

Complete as described in Section 6.1.5.

6.2.2. Full Oral Hard Tissue (OHT) Examination

Complete as described in Section 6.1.6.

6.2.3. Full MLSI Stain Assessment

Stain assessments will be performed by a single clinical examiner, in the same room with consistent light levels, throughout the study to facilitate standardisation of the assessments. Subjects will brush their anterior teeth with a wetted toothbrush for 30 seconds prior to each stain assessment. Teeth will be air dried prior to the assessment, and during the assessment as needed.

The facial and lingual surfaces of each assessable tooth is divided into four regions. The 'gingival' region is defined as a crescent-shaped band, approximately 2 mm wide, adjacent to the free margin of the gingiva and extending to the crest of the interdental papillae of the adjacent teeth. The 'body' of the tooth is then sub-divided into three regions on the facial surfaces.

- **Maxillary and mandibular facial surfaces:** distal facial area; body facial area; mesial facial area
- **Mandibular lingual surfaces:** distal lingual area; body lingual area; mesial lingual area

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Extrinsic dental stain will be scored in each area using the MLSI [MacPherson, 2000], with grades of 0-3 assigned for each category of intensity and area.

Stain Intensity: intensity will be scored separately for the 'gingival' and 'body' areas of each assessable tooth as follows.

- Score 0 = No stain
- Score 1 = Light stain
- Score 2 = Moderate stain
- Score 3 = Heavy stain

Stain Area: area will be scored separately for the 'gingival' and 'body' areas of each assessable tooth as follows.

- Score 0 = No stain
- Score 1 = Stain covering up to 1/3 of region
- Score 2 = Stain covering up to 1/3 of region, and no more than 2/3 of region
- Score 3 = Stain covering more than 2/3 of region

6.2.4. Dental Prophylaxis

Randomised subjects will receive full mouth professional dental cleaning (using conventional prophylaxis paste), followed by flossing carried out by the hygienist, to remove all sub- and supra-gingival calculus, plaque and debris from the teeth, with particular focus on the anterior teeth. A second dental professional will confirm all sub- and supra-gingival calculus, visible stain (MLSI = 0), plaque and debris has been removed from the facial, palatal/lingual surfaces of the anterior teeth (visually and by tactile assessment using a dental explorer). If necessary, additional dental cleaning will be carried out to achieve this.

Dental prophylaxis may be carried out by different dental hygienists to facilitate subject flow.

6.2.5. Visual MLSI Stain Assessment

A visual stain assessment will be performed to confirm the presence of no stain (MLSI = 0) on the eligible surfaces of the anterior (maxillary and mandibular) teeth.

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6.2.6 Supervised Product Use

After stratification and randomisation subjects will perform a supervised brushing. See Section 5.1 for dosing and instructions.

6.3. Visit 3 (Week 2)

6.3.1. Full MLSI Stain Assessment

See Section 6.2.3.

6.3.2. Supervised Product Use

See Section 5.1 for dosing and instructions.

6.4. Visit 4 (Week 4)

6.4.1. Full MLSI Stain Assessment

See Section 6.2.3.

6.4.2. Dental Prophylaxis (Optional)

Randomised subjects who request so will be offered a full mouth dental prophylaxis on completion of Visit 4 procedures, or on completion of the visit where they exit the study. See Section 6.2.4.

6.4.3. Brushing (Optional)

Following all study procedures, unsupervised brushing will be permitted with the study dentifrice and tooth brush (if requested by the subject).

6.4.4. Study Conclusion

At Visit 4, subjects will be evaluated to determine if they completed all study procedures or if they were discontinued from the study early. If the subject discontinued at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page of the eCRF by selecting one of the options below.

1. Subject did not meet study criteria
2. Adverse Event

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3. Lost to Follow Up
4. Protocol Violation
5. Withdrawal of Consent
6. Other

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

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

Adverse Event Definition:

- An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of an investigational product or clinical procedure, whether or not considered related to the investigational product or clinical procedure (eg. dental prophylaxis).
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational or clinical procedure (eg. dental prophylaxis).

Events meeting AE definition include:

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

Events NOT meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

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- The disease/disorder/ condition being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition..
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

7.1.2. Serious Adverse Events

Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

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

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

- **Results in disability/incapacity**
NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

- **Is a congenital anomaly/birth defect**

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- **Other Situations**
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:

- The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.
- The investigator or site staff will then record all relevant information regarding an AE/SAE in the eCRF.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).
- AEs will be collected from dental prophylaxis and until 5 days following last administration of the study product.
- SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

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7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality:

- The investigator is obligated to assess the relationship between study product and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.
- The investigator will also consult the Safety Assessment or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes (source document) or eCRF that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is **very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

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

SAE Reporting to GSKCH:

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (see section 8.3)
- Criterion for seriousness.

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

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken on study product
- Outcome if known

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The SAE form, completed as fully as possible, and SAE fax cover sheet must be faxed or e-mailed to the appropriate GSKCH Study Manager as soon as possible, but not later than 24 hours after study site personnel learn of the event. The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax Serious Adverse Events to:

US: PPD

Email Serious Adverse Events to:

PPD

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

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

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

Follow-up of AEs and SAEs:

- After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.
- All AEs/SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the subject is lost to follow-up.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- Investigators are not obliged to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including the death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify GSKCH.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Regulatory and ethics reporting requirements for SAEs:

- The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the

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investigator to GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

- GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC and investigators.
- Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.
- An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the safety statement and will notify the IEC, if appropriate according to local requirements.

7.6. Definition of and Procedure for Reporting Medical Device Incidents

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

7.6.1. Definition of an Incident

Definition of an Incident:

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

7.6.2. Reporting of Incidents and Malfunctions

Incident Reporting to GSKCH:

- All incidents must be reported to GSKCH within 24 hours (or sooner if possible) of the investigator or designee becoming aware of the situation.
- Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE or an SAE, the appropriate AE eCRF page or SAE form will be completed and reported as per the AE and SAE reporting sections.

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- The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSKCH. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
- The completed Incident Report Form should be faxed or emailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE pages should be sent together with this report form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will remain with the subject's records.
- The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax the Incident Report Forms to:

US: **PPD**

- The GSKCH Study Manager will be responsible for forwarding the Incident Report Form to the Case Management Group, Global Clinical Safety and Pharmacovigilance, the Medical Director responsible for the study and other GSKCH personnel as appropriate.
- The initial report will be followed up with more information as relevant, or as requested by the GSKCH study manager.

Reporting of Malfunctions to GSKCH:

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

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

7.6.3. Follow-up of Incidents

Follow-up of Incidents:

During the study:

- All incidents will be followed until resolution of the event, until the condition stabilises, until the condition is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature of the incident.

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

After the study:

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

Regulatory and Ethics Reporting Requirements for Incidents:

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

7.7. Collection of Pregnancy Information

7.7.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:

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

7.7.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:

- The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product. The investigator will record pregnancy information on the appropriate form and submit it to the following GSKCH mailbox:
PPD
- Pregnancy information must be submitted within 2 weeks of learning of the subject becoming pregnant.
- The subject will be followed to determine the outcome of the pregnancy.

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Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to GSKCH. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

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

8. DATA MANAGEMENT

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

8.1. Source Documents/ Data

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

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

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8.2. Electronic Case Report Form

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

For each subject who has given informed consent/assent and has been screened, eCRF must be completed and signed by the Principal Investigator (or authorised designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with applicable GSKCH standards and data cleaning procedures to ensure the integrity of the data e.g. removing errors and inconsistencies in the data.

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

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

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

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

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the GSKCH Principal Clinical Research Scientist, the Project Statistician and the Project Data Manager with the authorization from Head of Clinical Research.

Throughout the duration of the study, eCRFs (including queries, query responses and audit trails) will be retained by inVentiv Health. Following decommissioning of the study site data archived compact discs (CD(s)) prepared by inVentiv Health will be sent to the investigator and GSKCH.

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8.3. Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance. Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

8.3.1. Data Queries

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

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

8.4. Processing Patient Reported Outcomes

Patient reported outcome (PRO) data are collected directly from the subject PRO measures e.g. diary cards, questionnaires etc, and entered into the sponsor's clinical data management system (DMS) by the study site representative. PRO's that are source will be retained by the investigator and certified copies will be sent to GSKCH.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded on all PRO's that will be forwarded to GSKCH.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

All statistical activities will be conducted by inVentiv Health under the guidance of GSKCH.

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9.1 Sample Size Determination

A sufficient number of subjects will be screened to randomise at least 220 subjects to ensure 200 evaluable subjects complete the study. This will ensure approximately 50 evaluable subjects per treatment arm.

This study has not been formally powered to make any claims, and is appropriately sized as a PoP study for the purpose of observing meaningful trends.

9.2. General Considerations

9.2.1. Definition of Analysis Populations

The All Subjects population includes all subjects who enter the study and sign the informed consent form. This population includes screen failures as well as those that are randomised.

The Safety population will include all subjects who are randomised and receive at least one dose of investigational product and will be reported by treatment received.

The Intent-To-Treat (ITT) population will include all subjects who are randomised, receive at least one dose of investigational product and have at least one post-baseline efficacy evaluation and will be reported by randomised treatment.

The Per Protocol (PP) population will include all subjects in the ITT population who have at least one efficacy assessment considered unaffected by protocol violations. Efficacy assessments considered affected by protocol violations will be excluded from PP analysis.

Repeatability subjects are those subjects that have an initial and a repeat stain assessment.

The primary population for assessment of efficacy will be the ITT population. A PP analysis will be performed on the primary variable only if more than 20% of the subjects in the ITT population are excluded from the PP population.

The Safety population will be used for all safety and tolerability reporting.

9.2.2. Exclusion of Data from Analysis

The following will be considered as major protocol deviations leading to the exclusion of subjects / data for PP analysis:

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- Deviation from the inclusion/exclusion criteria likely to affect efficacy.
- The use of prohibited medication likely to affect efficacy.
- Not receiving randomised treatment

Other deviations likely to result in exclusion from the PP population will be detailed in the statistical analysis plan (SAP).

Protocol violations deemed to affect efficacy will be identified between the Biostatistician and Clinical Research Director or designee, ahead of breaking the study blind.

9.2.3. Criteria for Evaluation

Efficacy will be evaluated by the ITT or PP population. Safety will be assessed by the safety population.

9.2.4. Criteria for Assessing Efficacy

Efficacy will be evaluated based on the ranking performance of the study treatments on the stain variables. The minimum requirement will be similar, or lower levels of stain for at least one of the experimental products compared to the standard fluoride dentifrice (Colgate Cavity Protection®). The marketed SnF₂ dentifrice (Sensodyne Complete Protection) will be expected to demonstrate a comparable, or statistically significantly better performance on the stain parameters versus the experimental products and Colgate Cavity Protection®.

9.2.5. Criteria for Assessing Tolerability

The safety profile of the study treatments will be assessed with respect to adverse events (AEs) and oral soft tissue (OST) abnormalities.

9.2.6. Handling of Dropouts and Missing Data

Subjects who withdraw from the study early will be included in the statistical analysis up to the time point when they withdraw. Missing data will not be replaced.

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9.3. Statistical Methods and Analytical Plan

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

9.3.1. Demographic and Baseline Characteristics

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

9.3.2. Primary Analysis

The primary variable will be overall MLSI at Week 4. This variable will be analysed using analysis of covariance (ANCOVA) with treatment and smoking status as factor, and pre-prophylaxis baseline mean MLSI score as the covariate. Adjusted means and treatment differences between the two test products and the marketed standard fluoride dentifrice, and the treatment difference between the marketed SnF₂ dentifrice and the marketed standard fluoride dentifrice will be provided together with their 95% CIs and p-values.

The assumption of residual normality in ANCOVA analysis will be investigated. If violated, data transformation or a non-parametric method (e.g., the Wilcoxon rank sum test) will be applied.

9.3.3. Secondary Analysis

The secondary variables will be overall MLSI (A×I) at Week 4 for the treatment differences between the two test products and the marketed SnF₂ dentifrice, and the treatment difference between the marketed SnF₂ dentifrice and the marketed standard fluoride dentifrice.

These will be analysed and results summarised in the same way as per the primary variable but with the appropriate baseline term as the covariate.

9.3.4. Exploratory Analyses

Exploratory variables include overall MLSI Intensity score at Week 2, and Interproximal MLSI score, overall MLSI Area score and overall MLSI Intensity score at Weeks 2 and 4. Each of these variables will be analysed using the same ANCOVA

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model as in the primary analysis with the appropriate baseline term as the covariate. Adjusted means of all treatments and treatment differences will be provided together with their 95% CIs and p-values.

9.3.5. Safety Analyses

For the assessment of safety and tolerability, treatment emergent AEs will be summarised by treatment group. AEs and incidents will be listed. No inferential analyses will be performed to compare treatments with respect to safety data.

The safety profile of the study treatments will be assessed with respect to AEs. OST abnormalities are included as AEs if they appear or worsen after the initial assessment.

All safety data will be reported for the Safety population as per actual treatment received. All subjects screened will be included in the list of AEs.

All AEs will be reviewed by the Clinical Research Director or Designee prior to database freeze and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). During this review stage, AEs will be further categorised as oral or non-oral.

AEs will be regarded as treatment emergent if they occur on or after the start date and time of the first treatment usage (as determined by start date and time from the EXPOSURE/dispensing panel; if this date is missing a suitable alternative will be used eg date and time of randomisation). All other AEs prior to this will be considered non-treatment emergent.

The following summary tables and listings will be presented by treatment group.

- Table of treatment emergent AEs by Oral/Non-Oral and Preferred Term
- Table of treatment emergent AEs by SOC and Preferred Term
- Table of Treatment emergent treatment related AEs by Oral/Non-Oral and Preferred Term
- Table of treatment emergent treatment related AEs by SOC and Preferred Term
- Listing of all AEs (including Non-treatment emergent from All Subjects)
- Listing of SAEs
- Listing of incidents

In the event that there is nothing to report a null listing will be produced.

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No inferential analyses will be performed to compare treatments with respect to safety.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials Registers

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

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

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

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

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

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, the study monitor will contact the site prior to the start of the study to review with the site

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staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

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

The study monitor will monitor the study and site activity to verify that the:

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

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

10.4. Quality Assurance

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

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

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

10.5. Conditions for Terminating the Study

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

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Both GSKCH and the Investigator reserve the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance.

If the trial is prematurely terminated or suspended for any reason, the investigator site should promptly inform the trial subjects and should assure appropriate therapy/follow-up for the subjects.

In addition:

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

10.6. Records Retention

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

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

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

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

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The investigator must assure that the subject's anonymity will be maintained on eCRFs or other documents submitted to inVentiv Health, GSKCH, or any other GSKCH approved vendors. 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 inVentiv Health, GSKCH, or any other GSKCH approved vendors, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

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

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

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

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

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

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



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

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12. APPENDICES

12.1. Appendix 1

Abbreviations

AE	Adverse Event
CD	Compact Disc
CRO	Contract Research Organisation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GSKCH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention to Treat
MLSI	Macpherson Modification to the Lobene Stain Index
NaF	Sodium Fluoride
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PII	Personally Identifiable Information
PP	Per Protocol
RDA	Relative Dentin Abrasivity
SAE	Serious Adverse Event
SMFP	Sodium Monofluorophosphate
STP	Sodium Tripolyphosphate
SnF ₂	Stannous Fluoride
SOP	Standard Operating Procedure
PRO	Patient Reported Outcome

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