GlaxoSmithKline
Consumer Healthcare

CLINICAL PROTOCOL

A Randomized, Examiner-blind, Proof of Principal Study to Investigate the Stain and Plaque Removal Capability of Two Experimental 5% Potassium Nitrate Dentifrices in Healthy Subjects with the Propensity for Extrinsic Dental Stain

Compound Name:	5% Potassium Nitrate (KNO_3) / Sodium Fluoride (NaF)
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	N/A
Other Regulatory Agency Identified Number:	N/A
Protocol Number:	208078
Phase:	II

Sponsor information

Sponsor Legal Registered Address	**GlaxoSmithKline Research & Development Limited** 980 Great West Road Brentford Middlesex, TW8 9GS UK
Sponsor Contact Address	**GlaxoSmithKline Consumer Healthcare (GSK CH)** 184 Liberty Corner Rd. Warren, NJ 07059 USA Tel: PPD

Document History

Document	Version Date	Summary of Changes
Original protocol	26-Jul-2017	Not applicable (N/A)

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

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:	Jeffrey Milleman
Investigator Qualifications:	DDS, MPA
Investigator Signature:	PPD
Date of Signature/ Agreement:	PPD DD/MMM/YYYY

Table of contents

List of tables

SCHEDULE OF ACTIVITIES

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

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

Table 13-1 Schedule of Activities

Procedure/Assessment	Screening		Study Period				End of Treatment	
	Visit 1		Visit 2 Baseline (MLSI) Day 1	Visit 3 Baseline (TPI) Day 2	Visit 4 Week 2 Day 15 ± 1 days	Visit 5 Week 4 Day 29 ± 2 days	Visit 6 Week 8 Day 57 ± 3 days	Visit 7 Week 8 Day 58 ± 3 days
Informed Consent	X	Minimum 24 hours, maximum of 2 weeks						
Demographics, Ethnicity	X							
Medical History and Current Medication	X							
OST Examination	X		X	X	X	X	X	X
OHT Examination	X		X					
Visual MLSI Stain Assessment of the 12 Anterior Teeth	X							
Review Inclusion / Exclusion Criteria[1]	X		X	X				
Concomitant Medication			X	X	X	X	X	X
Eligibility	X		X					
Instruct Subjects on the Lifestyle Guidelines and Concomitant Treatment(s) Sections of the Protocol	X							
Brush Anterior Teeth for 30 Seconds with Tap Water Prior to Stain Assessment			X		X	X	X	

Procedure/Assessment	Screening		Study Period				End of Treatment	
	Visit 1		Visit 2 Baseline (MLSI) Day 1	Visit 3 Baseline (TPI) Day 2	Visit 4 Week 2 Day 15 ± 1 days	Visit 5 Week 4 Day 29 ± 2 days	Visit 6 Week 8 Day 57 ± 3 days	Visit 7 Week 8 Day 58 ± 3 days
Full MLSI Stain Assessment of the Anterior Teeth[2]			X		X	X	X	
Repeat MLSI Stain Assessment[3]			X		X	X	X	
Selection of 4 Assessment Teeth			X					
Stratification		Minimum 24 hours, maximum of 2 weeks	X					
Unsupervised Brushing on Site[4]			X	X				X
Plaque Disclosing Followed by Pre-brushing TPI Assessment[5]				X				X
Randomization and Dispense Study Dentifrice, Timer, Toothbrush and Diary/Instructions Card				X				
Supervised Brushing on Site[6]				X	X	X	X	X
Plaque Disclosing Followed by Post-brushing TPI Assessment[4]				X				X
Repeat TPI Assessment[3]				X				X
Adverse Events[7]			X	X	X	X	X	X
Incidents[8]			X	X	X	X	X	X
Subjects Return Dentifrice, Toothbrush and Diary Card					X	X	X	X
Subject Adherence and Continuance[9]				X	X	X	X	X
Diary Compliance Check					X	X	X	X

Procedure/Assessment	Screening		Study Period				End of Treatment	
	Visit 1		Visit 2 Baseline (MLSI) Day 1	Visit 3 Baseline (TPI) Day 2	Visit 4 Week 2 Day 15 ± 1 days	Visit 5 Week 4 Day 29 ± 2 days	Visit 6 Week 8 Day 57 ± 3 days	Visit 7 Week 8 Day 58 ± 3 days
Study Conclusion								X

Abbreviations: OST= Oral Soft Tissue; OHT = Oral Hard Tissue; MLSI = Macpherson Modification of the Lobene Stain Index; TPI = Turesky Plaque Index.

[1] At Visit 2 a review of Inclusion Criteria 10 and Exclusion Criteria 12.b and e will be conducted, and at Visit 3 a review of Inclusion Criteria 11 will be conducted.

[2] At Visit 2 a full MLSI assessment of the 12 anterior teeth will be conducted, at Visits 4, 5 and 6 a full MLSI assessment of the 4 assessment teeth will be conducted

[3] Five subjects will be randomly selected for repeat MLSI and TPI examinations across each assessment window (a total of 20 repeat MLSI and 10 repeat TPI examinations over the duration of the study).

[4] This will be with a standard fluoride dentifrice administered by the site. Once all efficacy assessments have been completed, subjects will be allowed to brush unsupervised prior to leaving the clinical study site.

[5] Two disclosing rinses with the plaque disclosing solution will be conducted, one prior to the pre-brushing TPI assessment and one prior to the post-brushing TPI assessment.

[6] The supervised brushing at Visits 4, 5, and 6 will be conducted following the MLSI stain assessments.

[7] Any serious adverse event assessed as related to study participation that occurs subsequent to the signing of informed consent and any adverse event subsequent to brushing with the standard fluoride dentifrice at Visit 2. For those subjects that don't brush with the standard fluoride dentifrice at Visit 2 adverse events will be collected from first use of the plaque disclosure solution at Visit 3.

[8] Incidents will be collected from first use of the tooth brush, prior to stain assessment.

[9] Time of each brushing occasion in addition to missed/additional brushings will be captured in the subject diary.

1 INTRODUCTION

Dentifrices are often recommended by dentists to help remove oral debris and dental plaque [Pader, 2012]. Dental plaque is a soft, sticky, colourless deposit of bacteria which collects on the teeth and along the gingival margin. Bacterial by-products from dental plaque can affect the health of the gingiva by causing inflammation of the gingival tissue [Davies, 2008]. Gingivitis and periodontal disease can develop when dental plaque accumulates above levels compatible with oral health [Marsh, 1992]. Mechanical plaque removal by toothbrushing is the most effective way to reduce plaque, and whilst the proper use of a toothbrush is effective in removing dental plaque [Pader, 2012], it is understood that the general population will brush using an inadequate technique, and for significantly less time than the recommended and accepted 2 minutes [Gallagher, 2009]. Clinical data support that brushing with a dentifrice that has been formulated with chemical and/or abrasive agents to help remove plaque, will facilitate, or enhance plaque removal efficacy [Davies, 2008; Parkinson, 2014; Ayad, 2015; Parkinson 2015; Feng, 2016].

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]. Therefore, plaque removal is considered to be an important feature in the prevention of stain build-up and thus careful selection of an appropriate abrasive and/or chemotherapeutic agents should be an important consideration when formulating dentifrices designed to enhance plaque removal.

The ability of a dentifrice to help control dental stain is also considered to be a key characteristic [Pader, 2012]. Extrinsic dental stain removal is typically achieved by the inclusion of dental grade abrasives such as silicas and chemical cleaning agents such as polyphosphates. A range of parameters have been shown *in vitro* to affect the stain removal and wear properties of abrasives including particle hardness, shape, size, distribution, and concentration [Joiner, 2010; Schemehorn, 2011]. Dental grade abrasive silicas are often relatively hard abrasives that are typically formulated in anti-sensitivity dentifrices within the range of 6-16% and, while effective at cleaning, often lend high abrasivity to dentifrices. CCI [redacted] It is currently hypothesized that the greater volume of smaller spherical silica particles offer a higher surface area of cleaning particles, and whilst further *in vitro* work should be conducted to elucidate the mode of action of spherical silica, it is prudent to explore if these results can also be replicated clinically.

Polyphosphates, such as sodium tripolyphosphate (STP), can also be included as chemical cleaning compounds, either on their own or 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, 1988; Rykke 1990], thereby helping to control stain build up.

CCI [redacted] Given that it is of importance that a dentifrice should clean and control extrinsic dental stain whilst minimising its abrasive effect [Schemehorn, 2011], particularly for people with tooth sensitivity where the softer dentin is exposed [Pickles, 2006] reduced abrasivity is considered to be advantageous in anti-sensitivity dentifrices.

This clinical study will compare an experimental low abrasivity 0.5% spherical silica dentifrice and a marketed low abrasivity 6% standard abrasive dentifrice, and an experimental moderate abrasivity 1% spherical silica / 5% STP dentifrice and a marketed high abrasivity 16% standard abrasive silica / 5% STP dentifrice. The main aims of this study are to determine whether spherical silica can achieve similar or greater extrinsic dental stain and plaque removal, in comparison to dentifrices containing higher concentrations of standard abrasive silica, and how the addition of 5% STP enhances cleaning capability. This study has not been designed to demonstrate the specific contribution that spherical silica or STP, are having on the overall reduction of stain and plaque.

1.1 Mechanism of Action

Micronized spherical silica is an abrasive cleaning agent and STP is a chelating stain removal agent that are currently being investigated in healthy subjects with a propensity for extrinsic dental stain.

1.2 Background and Rationale

1.2.1 Justification for Conducting the Study

Micronized spherical abrasive silica has shown significant potential *in vitro* for achieving stain and plaque removal. Given that no clinical data has been generated for this technology, it is prudent to explore if these results can also be replicated clinically.

1.2.2 Study and Dose Rationale

The test dentifrices have been designed to remove extrinsic dental stain and plaque caused by dietary and lifestyle habits, therefore a plaque and stain removal design has been assessed to be the most appropriate clinical model for this study.

Stain will be assessed 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 baseline MLSI score (total MLSI (A×I) for the facial surfaces of the 4 anterior assessment teeth). Plaque will be assessed using an established clinical measure of plaque - the Turesky Modification of the Quigley Hein Index, [Turesky, 1970] (TPI). A plaque disclosing solution will be used to temporarily stain the plaque, thus enabling a more accurate assessment.

Stain and plaque will be assessed at intervals over an 8 week treatment period. As stain is the primary focus in this study, in addition to the baseline and Week 8 assessments, MLSI assessments will also be conducted at Weeks 2 and 4. Plaque will be assessed at baseline and Week 8 only.

Plaque removal is expected to be achieved through the physical mode of action of the spherical or abrasive silica, as opposed to a chemotherapeutic action. Therefore, a pre- and post-brushing TPI assessment has been included in this study. It is expected to see greater effects in terms of plaque removal immediately after brushing.

Since the presence of overnight plaque could interfere with the conduct of accurate stain measurements, stain and plaque will be assessed on separate days (24 hours, +6 or -2 hours apart). Similarly, if stain assessments were to be conducted on the same day, but following plaque assessments, residual dye on the tooth surface could also prevent accurate stain scores from being measured.

Four of the anterior teeth will be selected for the purpose of stain assessment. Stain assessments will be made on the facial surfaces only as these surfaces are considered to be the most aesthetically important with respect to dental stain accumulation. The selection of 4 assessment teeth as opposed to 12, which is typically selected for this model, will allow teeth with a greater propensity for stain accumulation to be included in the total MLSI (A×I) scores thus enabling greater overall differences to be observed (if it exists) as teeth with low or zero stain scores will not be included in the overall total MLSI (A×I). Dental stain and plaque largely accumulate in the harder to reach interproximal areas, therefore in addition to analysis of the overall total MLSI (A×I) and overall TPI, 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, it is expected that little change in the total gingival MLSI (A×I) and total body MLSI (A×I) will be observed, therefore, these variables are not being analysed in this study.

Plaque reductions are normally seen in the hard to reach areas of the mouth, therefore, using only 4 test teeth may not provide sufficient data to observe trends for plaque removal. Therefore, a full mouth evaluation will be conducted, and all gradable teeth will be assessed for TPI.

A single examiner will perform the dental stain and plaque assessments for all subjects at each assessment visit to avoid inter-examiner variability. To assess the repeatability of the stain and

plaque assessments repeat examinations will be performed by the dental examiner at each assessment visit.

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.

Sensodyne Pronamel Daily Protection - Mint Essence has been selected as a reference dentifrice in this study as it is the lowest abrasive commercialised dentifrice in the Sensodyne range, without STP. Sensodyne Extra Whitening has been selected as a reference dentifrice as it is the highest abrasivity commercialized dentifrice in the Sensodyne range, with abrasive silica and STP.

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

1.2.3 Safety Data

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

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
Efficacy	
Primary	
• To evaluate the ranking order in extrinsic dental stain removal, as measured by overall MLSI (A×I), of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 8 weeks twice daily brushing.	• Change from baseline in overall MLSI at 8 weeks.
Secondary	
• To compare the removal of extrinsic	• Change from baseline in overall MLSI

dental stain, as measured by overall MLSI (A×I), of a 0.5% spherical silica dentifrice and a marketed 6% abrasive silica dentifrice, after 8 weeks twice daily brushing.	at 8 weeks.
• To compare the removal of extrinsic dental stain, as measured by overall MLSI (A×I), of a moderate abrasivity 1% spherical silica / 5% STP dentifrice and a marketed higher abrasivity 5% STP whitening dentifrice, after 8 weeks twice daily brushing.	• Change from baseline in overall MLSI at 8 weeks.
Exploratory	
• To evaluate the ranking order of plaque removal, as measured by TPI, of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after a single use.	• Change from pre-brushing to post-brushing TPI after single use.
• To evaluate the ranking order of plaque removal, as measured by TPI, of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 8 weeks twice daily brushing.	• Change from baseline (pre-brushing) in overall post-brushing TPI at 8 weeks.
• To evaluate the ranking order of Interproximal plaque removal, as measured by TPI, of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 8 weeks twice daily brushing.	• Change from baseline (pre-brushing) in overall post-brushing interproximal TPI at 8 weeks.
• To compare the removal of extrinsic dental stain, as measured by	• Change from baseline in overall interproximal MLSI at 2, 4 and 8

interproximal (mesial + distal) MLSI (A×I), of a 0.5% spherical silica dentifrice and a marketed 6% abrasive silica dentifrice, after 2, 4 and 8 weeks twice daily brushing.	weeks.
• To compare the removal of extrinsic dental stain, as measured by interproximal (mesial + distal) MLSI (A×I), of a 1% spherical silica / 5% STP dentifrice and a marketed 16% abrasive silica / 5% STP whitening dentifrice, after 2, 4 and 8 weeks twice daily brushing.	• Change from baseline in overall interproximal MLSI at 2, 4 and 8 weeks.
• To evaluate the ranking order in extrinsic dental stain removal, as measured by interproximal (mesial + distal) MLSI (A×I), of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 2, 4 and 8 weeks twice daily brushing.	• Change from baseline in overall interproximal MLSI at 2, 4 and 8 weeks.
• To evaluate the ranking order in extrinsic dental stain removal, as measured by overall MLSI Area (A), of a 0.5% spherical silica dentifrice, a marketed 6% abrasive silica dentifrice, a 1% spherical silica / 5% STP dentifrice, and a marketed 16% abrasive silica / 5% STP dentifrice, after 2, 4 and 8 weeks twice daily brushing.	• Change from baseline in overall MLSI Area at 2, 4 and 8 weeks.
• To evaluate the ranking order in extrinsic dental stain removal, as measured by overall MLSI Intensity (I), of a low abrasivity 0.5% spherical silica dentifrice, a marketed low abrasivity dentifrice, a moderate abrasivity 1% spherical silica / 5% STP dentifrice, and a marketed higher	• Change from baseline in overall MLSI Intensity at 2, 4 and 8 weeks.

abrasivity 5% STP whitening dentifrice, after 2, 4 and 8 weeks twice daily brushing.	
Safety	
• To evaluate the safety and oral tolerability of the test dentifrices when used twice daily for 8 weeks.	• Adverse Events

This is a POP study designed to look at the relative extrinsic dental stain and plaque removal performance for all test dentifrices. However, we would expect the following rank order in overall MLSI (A×I) to be observed: the 1% spherical silica / 5% STP dentifrice ≥ 16% abrasive silica / 5% STP dentifrice ≥ 0.5% spherical silica dentifrice ≥ 6% abrasive silica dentifrice.

3 STUDY DESIGN AND SUBJECT POPULATION

This is an 8 week, single-centre, examiner-blind, randomized, four treatment, parallel group study conducted in healthy subjects with a propensity for extrinsic dental stain (based on the judgement of the examiner).

This PoP study will be used to evaluate and compare the extrinsic dental stain and plaque removal of an experimental low abrasivity 0.5% spherical silica dentifrice and a marketed low abrasivity 6% standard silica abrasive dentifrice, and an experimental moderate abrasivity 1% spherical silica / 5% STP dentifrice and a marketed high abrasivity 16% standard abrasive silica / 5% STP dentifrice. This study has not been designed to demonstrate the specific contribution that spherical silica or STP, are having on the overall reduction of stain and plaque.

Sensodyne Pronamel Daily Protection - Mint Essence has been selected as a low abrasivity reference dentifrice in this study as it is the lowest abrasive commercialised dentifrice in the Sensodyne range, without STP. Sensodyne Extra Whitening has been selected as a high abrasivity reference dentifrice as it is the highest abrasivity commercialised dentifrice in the Sensodyne range, with abrasive silica and STP.

A sufficient number of subjects will be screened to randomize at least 124 subjects to ensure 120 evaluable subjects complete the entire study. This will ensure approximately 30 evaluable subjects per treatment arm).

Subjects will be stratified by their baseline total MLSI (A×I) score of the facial surfaces of 4 of the 12 anterior teeth (<15 (low); ≥15 (high)). A single dental examiner will perform an assessment of the area and intensity of extrinsic dental stain on the facial surfaces of 4 qualifying teeth selected (based on the judgement of the examiner) from the 6 maxillary and 6 mandibular anterior teeth (universal numbering: 6-11 and 22-27), using the MLSI, at baseline (Visit 2), and following 2, 4 and 8 weeks (Visits 4, 5 and 6) twice daily brushing. Subjects

will return to the study site the day after baseline (MLSI) and Week 8 visits for pre- and post-brushing full mouth TPI plaque assessments (Visits 3 and 7) of the facial and lingual surfaces of all gradable teeth.

4 SUBJECT SELECTION

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

4.1 Inclusion Criteria

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

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

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Male and female subjects who, at the time of screening, are between the ages of 18 and 65 years, inclusive.
3. Subjects who are willing and able to comply with scheduled visits, treatment plan, and other study procedures.
4. 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.
5. Good general and mental health with, in the opinion of the investigator or medically qualified designee an 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.
6. In the opinion of the investigator or medically qualified designee, **at screening**, subjects must have good oral health.
7. In the opinion of the investigator or medically qualified designee, **at screening**, subjects must have at least 20 natural teeth including the 12 anterior teeth, gradable for TPI (Gradable teeth are those where restorative materials cover less than 25% of the tooth surface to be graded).
8. In the opinion of the investigator or medically qualified designee, **at screening**, subjects must have the facial surfaces of at least 4 of the anterior teeth, gradable for the MLSI.
9. In the opinion of the investigator or medically qualified designee, **at screening**, subjects must have the presence of extrinsic dental stain (judged to be formed due to dietary

factors) on the facial surfaces of the anterior teeth, as determined from a visual MLSI stain assessment.

10. In the opinion of the investigator, **at Visit 2,** subjects must have 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.
11. **At Visit 3,** a minimum overall pre-brushing plaque score (TPI) of ≥2.0.

4.2 Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are GSK employees directly involved in the conduct of the study.
2. Participation in another clinical study or receipt of an investigational drug(s) within 30 days prior to study entry and/or during study participation.
3. Subjects who have previously been enrolled in this study.
4. Acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
5. Any condition which, in the opinion of the investigator, causes xerostomia.
6. Pregnant female subjects.
7. Breastfeeding female subjects.
8. Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
9. Unwilling or unable to comply with the lifestyle guidelines described in this protocol.
10. Recent history (within the last year) of alcohol or other substance abuse.
11. Subject is unwilling to abstain from tobacco or nicotine-containing product use (including E-cigarettes) during the treatment evaluation period.
12. Subjects using the following mouth rinses, or taking the medications listed below:
    a) Regular use of mouthwashes containing ingredients that are known to impart staining. For example, chlorhexidine, essential oils or cetylpyridinium chloride (CPC).
    b) Use of a chlorhexidine, essential oil or CPC containing mouthwash within 14 days of Visit 2 or throughout the study.
    c) Current use of Listerine, or any antimicrobial mouth rinse.
    d) Use of minocycline, tetracycline or doxycycline within 30 days prior to screening.
    e) Use of minocycline, tetracycline or doxycycline between the screening and baseline visits.

f) 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.

13. Subjects who have the following dental exclusions:
    a) Received 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) Dental conditions / disease requiring immediate treatment.
    d) Used any professionally dispensed or over the counter bleaching/ whitening products (excluding daily use whitening dentifrices) within the past 3 months.
14. Subjects who have the following specific dental exclusions for assessment 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 hyperplasic areas which, in the opinion of the investigator, would prevent consistent grading of extrinsic dental stain.
    e) High levels of calculus deposits which might interfere with plaque assessments at the discretion of the investigator.
    f) Presence of orthodontic bands or appliances, extensive crowns, partial dentures, or fixed retainers.
15. Any subject who, in the judgment of the investigator, should not participate in the study.

4.3 Randomization Criteria

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

4.4 Lifestyle Guidelines

Eligible subjects will continue to use their current dentifrice (according to their normal habit) between the screening and baseline visits, and will return to the site for the baseline visit a minimum of 24 hours, or up to a maximum of 2 weeks after screening.

Following the supervised brushing with the standard fluoride dentifrice at the baseline (MLSI) visit up until completion of the study, subjects must only use the study products provided to them. Subjects will abstain from chewing gum and will not use any dental products, including home remedies for tooth whitening, other than the study products provided for the duration of the study. Subjects will be permitted to use non-antimicrobial dental floss for the removal of impacted food only.

On MLSI assessment days (Visits 2, 4, 5 and 6) subjects will attend the study site having refrained from all oral hygiene procedures for at least 6 hours.

On TPI assessment days (Visits 3 and 7) subjects will attend the study site having refrained from all oral hygiene procedures for 24 hours (+6, or -2 hours; including not brushing the evening before).

4.4.1 Meals and Dietary Restrictions

On MLSI assessment days (Visits 2, 4, 5 and 6) and TPI assessment days (Visits 3 and 7) subjects will attend the study site having refrained from eating and drinking for at least 2 hours (with the exception of water), prior to their scheduled visit.

4.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography, screen failure details (e.g., withdrawal of consent), eligibility criteria, and any serious adverse events (SAEs).

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

4.6 Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical/dental personnel for the study is documented in the study contact list in the study file.

The contact number can be used by investigational staff if they are seeking advice on medical/dental questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical/dental questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects are provided with a contact card. The contact

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

5 STUDY TREATMENTS

5.1 Blinding and Allocation to Treatment/Randomization

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 after they have left the clinical site. In addition, subjects should be treated in a separate area. The dispensing staff will not be involved in any efficacy assessments during the study.

The randomization list will be prepared using a randomization block design with an equal allocation to each of the strata. The clinical study site will be provided with two versions of the randomization 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 randomization numbers only and will not include any coded description, just a letter A, B, C or D.

The 'Emergency Use Only' randomization schedule will only be removed from the sealed envelope in an emergency situation. This schedule will have a randomization 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 four treatments arms. However, to maintain the blinding of the study as far as possible, all treatment allocations for all randomization numbers on this randomization schedule will be masked with scratch-off panels.

Qualified site personnel will be responsible for randomization and product dispensing. The investigational products will be dispensed in a blinded fashion to the subject. A second member of site personnel will verify that the correct dentifrice has been dispensed to each subject. Subjects will be stratified by their baseline total MLSI (A×I) score for the facial surfaces of 4 of the 12 anterior teeth (<15 (low); ≥15 (high)), and depending on which strata they fall under will be assigned their allocated test product from either the "low" or "high" randomization schedule. The strata will be identified as:

Strata 1: Low (MLSI <15)

Strata 2: High (MLSI ≥15)

In accordance with the randomization numbers, the subject will receive the study treatment assigned to the corresponding randomization number.

5.2 Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be a manual process, whereby only scratch-off panels will be removed for subjects that require unblinding. Blinding codes should be broken only in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator should consult with a member of the study team prior to breaking the blind unless the delay would endanger the subject's health. When the blinding code is broken, the reason must be fully documented and entered in the CRF.

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

5.3 Subject Compliance

Subjects will be asked to bring all tubes of study dentifrice to each study visit for a visual compliance check of each product. Any suspected product over use, or under use will be documented in the CRF and subjects will be re-educated on the correct dosing amount and instructions.

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 CRF.

5.4 Investigational Product Supplies

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

- **Test product 1:** 5% KNO_3 / 0.2542% NaF dentifrice with 0.5% spherical silica (RDA~38); CCI [redacted].
- **Test product 2:** 5% KNO_3 / 0.2542% NaF dentifrice with 1% spherical silica and 5% STP (RDA~58); CCI [redacted].
- **Reference Product 1:** 5% KNO_3 / 0.2542% NaF dentifrice with 6% abrasive silica (RDA~36); Sensodyne Pronamel Daily Protection - Mint Essence (CCI [redacted] - USA marketed dentifrice).
- **Reference Product 2:** 5% KNO_3 / 0.2543% NaF dentifrice with 16% abrasive silica and 5% STP (RDA~166); Sensodyne Extra Whitening (CCI [redacted] - USA marketed dentifrice).

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

- Oral-B Sensi Soft Manual Toothbrush (USA marketed)

- Colgate Cavity Protection (USA marketed) - standard fluoride dentifrice for post-baseline (MLSI) brushing and Week 7 post-assessment brushing
- Trace Disclosing Agent - Young Dental Manufacturing
- Countdown timers
- Rinsing cups

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. The site will also provide the dental floss.

5.4.1 Dosage Form and Packaging

All test and reference dentifrices are intended for oral use, and will be administered orally as detailed in Section 5.5.

The reference dentifrices will be sourced from the US market. The test dentifrices will be manufactured and filled into white ABL tubes and supplied by GSK CH.

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

All sundry items, including the Colgate Cavity Protection, 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.

5.4.2 Preparation and Dispensing

All investigational product will be dispensed by qualified blinded site personnel according to the dosage and administration instruction. The investigational products will be dispensed in a blinded fashion to the subject. A second member of site personnel will verify that the correct dentifrice has been dispensed to each subject. A record of the product dispensed to each subject will be recorded in a treatment dispensing log, and assigned against each subject number.

5.5 Administration

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

Subjects will be instructed to self-administer their investigational product according to the product use instructions provided to the subject (full toothbrush head for one timed minute, twice a day). 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. 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 TPI visit (Visit 3), and subjects will conduct a supervised brushing for one timed minute. This will be repeated again at Visits 4, 5, 6 and 7.

5.5.1 Medication Errors

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

- the wrong product,
- by the wrong subject,
- at the wrong time,
- or at the wrong dosage strength (other examples of concern may be added based on the investigational product administration, such as inadvertent exposure).

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

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

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not a medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page.

5.6 Investigational Product Storage

The investigator, or an approved representative, will ensure that all investigational products including any comparator and marketed products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and product label.

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

captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

Once an excursion is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

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

5.7 Investigational Product Accountability

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

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

The clinical study site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All study drugs will be accounted for using a drug accountability form/record.

At the end of the study subjects will return all study products back to the clinical study site, which 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 designated third party vendor.

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

5.7.1 Destruction of Investigational Product Supplies

All investigational study treatments and the Colgate Cavity Protection dentifrice shipped for this clinical study will be returned to the Sponsor at the termination of the study. At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH will inventory all used and unused investigational study treatment. The study treatment inventory record for returned study treatment will then be completed. All investigational product for this clinical study (empty containers), as well as all unused study product will be shipped to the designated vendor using the return instructions provided.

5.8 Concomitant Treatments

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

All concomitant and/or traditional/herbal ingredients taken during the study must be recorded in the CRF with indication, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 30 days before the first dose of study investigational product will be documented as a prior treatment. Treatments taken after the first dose of study investigational product will be documented as concomitant treatments.

Subjects will be asked not to have any non-emergency dental treatment during the study (including prophylaxis). Subjects will be withdrawn if they start a course of minocycline, tetracycline or doxycycline during the study period.

6 STUDY PROCEDURES

6.1 Study Period

6.1.1 Screening - Visit 1

Subjects will be admitted to the clinical site at least 24 hours prior to Day 1 dosing.

The following procedures/assessments will take place in the order listed below (where possible), and recorded in the CRF:

- Obtain written 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 GSK CH. 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.
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 will be provided with a copy of the signed and dated amended consent form. The date of consent will be recorded on the CRF.

- Collect demography and ethnicity.
- Collect medical history, including history of illegal drug, alcohol and tobacco use.
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 30 days prior to the planned first dose.
- Full oral soft tissue (OST) examination conducted by a qualified dental examiner.
- Full oral hard tissue (OHT) examination conducted by a qualified dental examiner.
- Visual MLSI stain assessment of the facial (maxillary and mandibular) surfaces by a qualified dental examiner.
- Review Inclusion and Exclusion criteria. Pregnancy status will be confirmed verbally by the subject.
- Confirmation of subject eligibility.
- To prepare for study participation, instruct subjects on the use of the Lifestyle Guidelines and Concomitant Treatment(s) sections of the protocol.

6.1.2 Baseline MLSI Visit (Day 1) - Visit 2

Subjects will be admitted to the clinical site at least 24 hours following the Screening visit. Subjects will attend the study site having refrained from all oral hygiene procedures for at least 6 hours, and from eating and drinking for at least 2 hours (with the exception of water), prior to their scheduled visit.

The following procedures will be completed in the following order (where possible), and recorded in the CRF:

- Review changes in the subject's medical history including concomitant medication since Screening.
- Review of Inclusion Criteria 10, and Exclusion Criteria 12.b and e.
- Full OHT and OST examinations conducted by a medically qualified examiner. Record any changes since the Screening visit in the CRF.
- Confirm subject eligibility and continuance.
- Supervised brushing of the anterior teeth for 30 seconds using a wetted toothbrush, followed by flossing.
- Full MLSI stain assessment of the facial (maxillary and mandibular) teeth conducted by a qualified dental examiner.

- 4 eligible assessment teeth selected by a qualified dental examiner.
- Repeat full MLSI stain assessment of the 4 assessment teeth for selected subjects.
- Stratification (based on total MLSI score of the 4 facial surfaces of the 4 eligible assessment teeth).
- Unsupervised brushing with standard fluoride dentifrice.
- AEs and incidents. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.1.3 Baseline TPI Visit (Day 2) - Visit 3

Subjects will be admitted to the clinical site 24 hours (+6, or -2 hours; including not brushing the evening before) after Visit 2, and will be requested to refrain from eating and drinking for at least 2 hours (with the exception of water), prior to their scheduled visit.

Prior to randomization the following procedures/assessments will be completed in the following order (where possible), and recorded in the CRF:

- Review changes in the subject's medical history including concomitant medication since the previous visit.
- Review of Inclusion Criteria 11.
- Confirmation of subject adherence and continuance. Full OST examination conducted by a medically qualified examiner.
- Subjects disclose plaque by rinsing with plaque disclosure solution.
- Pre-brushing full mouth TPI assessment of all gradable teeth, conducted by a qualified dental examiner.
- Randomization.

Following randomization, the following procedures/assessments will be completed in the following order (where possible), and recorded in the CRF:

- Dispense study dentifrice, toothbrush and diary/ instructions card.
- Supervised brushing with subject's allocated dentifrice. The time of brushing will be entered in the CRF.
- Subjects disclose plaque for a second time by rinsing with plaque disclosure solution.
- Post-brushing full mouth TPI assessment of all gradable teeth, conducted by a qualified dental examiner.
- Repeat TPI assessment conducted by a qualified dental examiner, for selected subjects.
- Post assessment brushing with standard fluoride dentifrice and toothbrush (if requested by the subject).

- AEs and incidents captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.1.4 Day 15 (MLSI) - Visit 4

Subjects will be admitted to the clinical site having refrained from all oral hygiene procedures for at least 6 hours, and from eating and drinking for at least 2 hours (with the exception of water), prior to their scheduled visit.

The following procedures/assessments will be completed in the following order (where possible), and recorded in the CRF:

- Subjects return study dentifrice, toothbrush, and diary card to the clinical site.
- Review changes in the subject's medical history including concomitant medication since the previous visit.
- Review of completed diary to confirm timing of each brushing occasion in addition to missed/additional brushings.
- AEs and incidents captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Confirmation of subject adherence and continuance.
- Full OST examination conducted by a medically qualified examiner.
- Supervised brushing of the anterior teeth for 30 seconds using a wetted toothbrush, followed by flossing.
- Full MLSI stain assessment of the 4 assessment teeth by a qualified dental examiner.
- Repeat full MLSI stain assessment of the 4 assessment teeth for selected subjects.
- Supervised brushing with subject's allocated dentifrice for 60 seconds.
- AEs and incidents captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.1.5 Day 29 (MLSI) - Visit 5

Subjects will be admitted to the clinical site having refrained from all oral hygiene procedures for at least 6 hours, and from eating and drinking for at least 2 hours (with the exception of water), prior to their scheduled visit.

The following procedures/assessments will be completed in the following order and recorded in the CRF:

- Subjects return study dentifrice, toothbrush, and diary card to the clinical site.
- Review changes in the subject's medical history including concomitant medication since the previous visit.

- Review of completed diary to confirm timing of each brushing occasion in addition to missed/additional brushings.
- AEs and incidents captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Confirmation of subject adherence and continuance.
- Full OST examination conducted by a medically qualified examiner.
- Supervised brushing of the anterior teeth for 30 seconds using a wetted toothbrush, followed by flossing.
- Full MLSI stain assessment of the 4 assessment teeth by a qualified dental examiner.
- Repeat full MLSI stain assessment of the 4 assessment teeth for selected subjects.
- Supervised brushing with subject's allocated dentifrice for 60 seconds.
- AEs and incidents captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.1.6 Day 57 (MLSI) - Visit 6

Subjects will be admitted to the clinical site having refrained from all oral hygiene procedures for at least 6 hours, and from eating and drinking for at least 2 hours (with the exception of water), prior to their scheduled visit.

The following procedures/assessments will be completed in the following order and recorded in the CRF:

- Subjects return study dentifrice, toothbrush, and diary card to the clinical site.
- Review changes in the subject's medical history including concomitant medication since the previous visit.
- Review of completed diary to confirm timing of each brushing occasion in addition to missed/additional brushings.
- AEs and incidents captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Confirmation of subject adherence and continuance.
- Full OST examination conducted by a medically qualified examiner.
- Supervised brushing of the anterior teeth for 30 seconds using a wetted toothbrush, followed by flossing.
- Full MLSI stain assessment of the 4 assessment teeth by a qualified dental examiner.
- Repeat full MLSI stain assessment of the 4 assessment teeth for selected subjects.
- Supervised brushing with subject's allocated dentifrice for 60 seconds.

- AEs and incidents captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.1.7 Day 58 (TPI) - Visit 7

Subjects will be admitted to the clinical site 24 hours (+6, or -2 hours; including not brushing the evening before) after Visit 2, and will be requested to refrain from eating and drinking for at least 2 hours (with the exception of water), prior to their scheduled visit.

The following procedures/assessments will be completed in the following order and recorded in the CRF:

- Subjects return study dentifrice, toothbrush, and diary card to the clinical site.
- Review changes in the subject's medical history including concomitant medication since the previous visit.
- Review of completed diary to confirm timing of each brushing occasion in addition to missed/additional brushings.
- AEs and incidents captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Confirmation of subject adherence and continuance.
- Full OST conducted by a qualified dental examiner.
- Subjects disclose plaque by rinsing with plaque disclosure solution.
- Pre-brushing full mouth TPI assessment of all gradable teeth, conducted by a qualified dental examiner.
- Supervised brushing with subject's allocated dentifrice.
- AEs and incidents captured following supervised brushing.
- Subjects disclose plaque for a second time by rinsing with plaque disclosure solution.
- Post-brushing full mouth TPI assessment of all gradable teeth, conducted by a qualified dental examiner.
- Repeat TPI assessment conducted by a qualified dental examiner.
- Post assessment brushing with standard fluoride dentifrice and toothbrush (if requested by the subject).
- AEs and incidents captured. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Study conclusion.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the GSK CH medical monitor (or designated representative) should be notified and depending on the abnormality, the subject may be asked

to remain at the clinical site until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain at the clinical site and/or when outpatient follow-up is deemed appropriate, the GSK CH medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.2 Subject Withdrawal

At the end of the study 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 CRF by selecting one of the options below.

1. Subject did not meet study criteria
2. Adverse event
3. Subject lost to follow up
4. Protocol Violation
5. Withdrawal of informed consent
6. Other

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

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

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

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

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The Investigator or site staff should attempt to contact the subject twice. After two attempts, clinical site staff must send a registered letter. If no response is received from the subject, the subject will be considered lost to follow up. All attempts to contact the subject and information received during contact attempts must be documented in the CRF. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all study products (used and unused), and follow-up with the subject regarding any unresolved AEs.

It may be appropriate for the subject to return to the clinical site for final safety assessments. Subjects should be questioned regarding their reason for withdrawal. An OST may be conducted at the investigator's discretion.

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

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

7 ASSESSMENTS

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

7.1 Efficacy

The following efficacy assessments will be performed at times defined in the Study Procedures section of this protocol.

7.1.1 Macpherson Modification of the Lobene Stain Index (MLSI)

Stain assessments will be performed by a single clinical examiner, in the same room with consistent light levels, throughout the study to facilitate standardization 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 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

Extrinsic dental stain will be scored in each area using the MSLI [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

7.1.1.1 Repeatability of the MLSI Assessment

To assess the repeatability of the stain assessments, replicate examinations will be performed by the same qualified dental examiner at each assessment visit. Five subjects will be randomly selected for repeat MLSI assessments across each assessment window (a total of 20 repeat MLSI assessments over the duration of the study). Every effort should be made to ensure the examiner does not refer to the results of the assessment completed prior to the repeat assessment. The results of the initial assessment will not be visible to the examiner or scribe when the repeat assessment is carried out.

7.1.2 Turesky Modification of the Quigley Hein Index Dental Plaque Assessment (TPI)

The qualified dental examiner must ensure that the subjects taking part in this exercise have been appropriately informed and have consented to take part to this activity.

The dental examiner will use the Turesky Modification of the Quigley Hein Index [Turesky 1970], to assess plaque on all gradable teeth for the full mouth. Only natural teeth devoid of restorations which would prevent plaque grading can be assessed. This means no crowns, bridges, and teeth with restorations which, in the investigator's judgment would prevent an accurate grading. Wisdom teeth are not to be assessed.

The plaque will first be disclosed using a dye solution (provided by site). Subjects will then rinse with 5 millilitres (mL) of Trace Disclosing Agentfor 10 seconds to disclose any residual plaque. They will expectorate and rinse with 10 mL of water for 10 seconds and expectorate again. Plaque will be assessed with each tooth being divided into 6 areas including the mesiofacial, facial, distofacial, mesiolingual, lingual and distolingual surfaces.

Disclosed plaque will be scored as follows and recorded in the CRF:

Score		Description
0		No plaque
1		Slight flecks of plaque at the cervical margin of the tooth
2		A thin continuous band of plaque (1 mm or smaller) at the cervical margin of the tooth
3		A band of plaque wider than 1 mm but covering less than 1/3 of the crown of the tooth
4		Plaque covering at least 1/3 but less than 2/3 of the crown of the tooth
5		Plaque covering 2/3 or more of the crown of the tooth

7.1.2.1 Repeatability of the Plaque Assessment

To assess the repeatability of the TPI assessments, replicate examinations will be performed by the same qualified dental examiner at each assessment visit. Five subjects will be randomly selected for repeat TPI examinations across each assessment window (a total of 10 repeat TPI examinations over the duration of the study). Repeatability assessments will be a minimum of 10 minutes between repeat plaque assessments of the same subject. The results of the initial assessment will not be visible to the examiner or scribe when the repeat assessment is carried out.

7.2 Safety

The following safety assessments will be performed at times defined in the Study Procedures section of this protocol.

7.2.1 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 CRF 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 and study procedures or administration of the treatment dentifrices will be recorded as an AE.

An OST examination will be conducted at each visit 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.

7.2.2 Full Oral Hard Tissue (OHT) Examination

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee for all subjects. Subjects with evidence of gross intraoral neglect or the need for extensive dental therapy will be excluded.

The OHT examination will assess grossly carious lesions or signs of erosive wear, enamel irregularities, tooth fracture, gross decay, decalcification and faulty restorations. Observations will be listed as "Absent" or "Present" and conditions noted as present will be described. Examination findings will be described and documented in the CRF. Any observation that changes from "Absent" to "Present" from the screening assessment must be recorded as an AE.

8 ADVERSE EVENT AND OTHER EVENTS OF SPECIAL INTEREST REPORTING

8.1 Definitions of Adverse Events and Serious Adverse Events

8.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study product, whether or not considered related to the study product.

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

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

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

Events NOT meeting the AE definition:

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

8.1.2 Serious Adverse Event

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

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

- **Results in death**
- **Is life-threatening**

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Results in congenital anomaly/birth defect**
- **Other situations**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.2 Reporting Period

8.2.1 Adverse Event

AEs will be collected from first unsupervised brushing with the standard fluoride dentifrice at Visit 2, and until 5 days following last administration of the investigational product. For those subjects that don't brush with the standard fluoride dentifrice at Visit 2, AEs will be collected

from first use of the plaque disclosure solution, and until 5 days following last administration of the investigational product.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

8.2.2 Serious Adverse Event

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 provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product and until 5 days following last administration of the investigational product.

SAEs assessed as **not related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or not related to a GSK concomitant medication will be recorded from the time of signing the ICF and until 5 days following last administration of the investigational product.

8.3 Reporting Procedures

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

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

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

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.

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).

Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of 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 CRF. Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.1 Adverse Event

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

8.3.2 Serious Adverse Event

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
- Criterion for seriousness.

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

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

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

Email Serious Adverse Events to:

PPD

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

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

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

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

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

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

An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Safety Statement and will notify the IEC, if appropriate according to local requirements.

8.4 Evaluating Adverse Events and Serious Adverse Events

8.4.1 Severity Assessment

The investigator or designee will make an assessment of severity 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.

Note: An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4.2 Causality Assessment

The causality assessment is one of the criteria used when determining regulatory reporting requirements. For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

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

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

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 and send an SAE follow-up report with the updated causality assessment.

8.5 Withdrawal Due to an Adverse Event and Serious Adverse Events

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

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

8.6 Pregnancy

8.6.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported following administration of any study product and until 5 days after the last dose.

8.6.2 Action to be Taken if Pregnancy Occurs

The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product or washout product. The investigator will record pregnancy information on the appropriate form and e-mail it to the GSK CH Clinical Operations Safety Reporting email box PPD within 24 hours of learning of the subject becoming pregnant. The GSK CH Study Manager or designee will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox PPD

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

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

Any female participant who becomes pregnant while participating will discontinue study treatment.

8.7 Follow-up of Adverse Events and Serious Adverse Events

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

All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as

fully as possible the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed CRF.

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

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 GSK by emailing the information to the GSK CH Clinical Operations Safety Reporting email box PPD . The GSK CH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK PPD

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

9 DATA MANAGEMENT

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

For this study subject data will be entered into an electronic CRF using a validated data system.

9.1 Source Documents/ Data

The source documents (e.g., hospital records, clinical and office charts, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, microfiches, x-rays, subject files involved in the clinical study) which contain the source of data recorded in the CRF should be specified in Section 6. The CRF and diary can be used as a source document at the discretion of data management.

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

9.2 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, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with Third Party BDM Vendor applicable standards and data cleaning procedures with oversight by GSK CH to ensure 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 full birth date) is to be recorded in the CRF or as part of the query text.

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

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

9.3 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.

Any corrections to the entries made to the paper source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

9.3.1 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 CRF 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) appropriately.

The study monitor at the study site will review the CRFs 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 CRFs, to raise manual queries as needed for site clarification or correction.

9.4 Processing Patient Reported Outcomes

Patient reported outcome (PRO) data may be collected from diary cards, questionnaires, etc, and entered into the sponsor's clinical data management system (DMS). In instances where the PRO data is entered into the DMS by GSK CH, the PROs will be anonymized as agreed and documented prior to study initiation. PROs that are source will be retained by the investigator and certified copies will be sent to GSK CH.

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 GSK CH.

10 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1 Sample Size Determination

CCI

[redacted]

10.2 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 finalization of the protocol and prior to study unblinding as appropriate.

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

H0: there is no treatment difference versus the alternate hypothesis

H1: there is a treatment difference.

10.2.1 Demographic and Baseline Characteristics

Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for demographic baseline characteristics concomitant medication, medical history and compliance.

10.2.2 Primary Analysis(es)

The primary efficacy variable is the change from baseline in overall MLSI score. The primary time-point is 8 weeks.

The overall MLSI (AxI) for each subject is derived at a tooth site level first before averaging over all the teeth sites assessed. The change from baseline is derived from the individual sites first before calculating the average change across the sites assessed.

The change from baseline in overall MLSI will be analysed using analysis of covariance (ANCOVA) with treatment as a fixed effect and baseline overall MLSI as a covariate.

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated. Violation of this assumption will be overcome using a suitable data transformation or a non-parametric technique (eg Wilcoxon Rank Sum test or Van Elteren Test).

There are no comparisons for the primary objective as the main objective is to look at the rank order of the treatments in level of stain reduction after 8 weeks of treatment. This will be achieved via the adjusted means and confidence intervals for the means along with plots of MLSI over time. The hypothesis is that the test products will reduce stain to a greater extent than the reference products.

Two comparisons of interest will be done under secondary and exploratory objectives. These comparisons are: -

Test Product 1 vs Reference Product 1

Test Product 2 vs Reference Product 2.

Analyses at weeks 2 and 4 form part of the exploratory objectives.

10.2.3 Secondary Analysis(es)

Secondary analyses are covered in the primary analysis.

10.2.4 Safety Analysis(es)

Safety population will be used for safety assessments. Safety analyses will be performed according to the treatment that the subject received (using variable ATRT). All AEs will be reviewed by the Clinical Research Scientist or Designee prior to database lock and unblinding and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). During this review stage, AEs will be further categorized as oral or non-oral. AEs will be listed and summarized by treatment received. Serious AEs will also be listed. AEs will be regarded as treatment emergent if they occur on or after the first treatment application at the baseline visit. The following AEs tables split by treatment will be produced:

- Listing of all AEs (Randomized and Non-Randomized Subjects)

- Treatment emergent AEs by Oral/Non-Oral Preferred Term (PT)
- Treatment emergent AEs by System Organ Class (SOC) and PT
- Treatment emergent AEs by Intensity presented by System Organ Class (SOC) and PT
- Treatment emergent treatment related AEs by Oral/Non-Oral
- Listing of SAEs (if there are none a null listing will be produced; if there are more than 5 treatment emergent SAEs a table will be produced instead by SOC and PT)
- Non-serious treatment emergent AEs by SOC and PT (only produced if there are more than 5 SAEs).
- Listing of incidents (if there is none a null listing will be produced).

Further information related to safety also includes a table and listing of OST data. The table will show changes in abnormality pre and post treatment. A table of exposure not needed in this study as it is a single use study.

10.2.5 Other Analysis(es)

10.2.5.1 Exploratory variables

- Change from Baseline in interproximal MLSI (AxI) stain score at weeks 2, 4 and 8
- Change from Baseline in overall area (A) stain score at weeks 2, 4 and 8
- Change from Baseline in overall intensity (I) stain score at weeks 2, 4 and 8
- Change from Baseline (Pre-treatment) in overall TPI for day 2 post-treatment, week 8 pre-treatment and week 8-post treatment
- Change from Baseline (Pre-treatment) in interproximal TPI for day 2 post-treatment, week 8 pre-treatment and week 8 post-treatment
- Repeatability stain score
- Repeatability plaque score

10.2.5.2 Definition of exploratory variables

All stain variables will be derived in a similar way based on relevant tooth sites and analyzed as per the primary variable using the appropriate baseline value as a covariate. The interproximal stain sites are the mesial and distal tooth sites.

The overall TPI for each subject is derived at a tooth site level first before averaging over all the teeth sites assessed. The change from baseline is derived at the individual sites first before calculating the average change across the sites assessed.

The interproximal TPI is based on the mesial and distal tooth sites. The interproximal TPI score and change from baseline calculated in the same way as for the overall TPI.

10.2.5.3 Analysis of exploratory variables

The change from baseline in TPI variables will be analysed using analysis of covariance (ANCOVA) with treatment and MLSI stratification as fixed effects and appropriate baseline (pre-treatment) TPI as a covariate.

The repeat stain and plaque assessments will be compared to the original assessments and will not be used in any efficacy analysis. The first and second assessments on each tooth site will be cross tabulated. A weighted Kappa coefficient (κ), along with the 95% CI will be calculated to assess the intra-examiner reliability. Fleiss-Cohen weighted kappa will be calculated for the repeatability analysis. Reliability will be deemed

- Excellent if $\kappa > 0.75$
- Fair to good if $0.4 \leq \kappa \leq 0.75$
- Poor if $\kappa < 0.4$

All subjects who have repeatability data will be included in this analysis.

10.2.6 Definition of Analysis Populations

All assessments of safety will be based on the safety population, defined as all subjects who are randomized and receive at least one dose of study treatment during the study. Safety population summaries will be presented by treatment received.

The primary population for efficacy assessment will be the intent-to-treat (ITT) population, defined as all subjects who are randomized, receive the study treatment at least once and provide at least one post-baseline (post treatment) assessment of efficacy. All ITT population summaries and analyses will be presented by treatment randomized.

No Per Protocol population analysis will be performed for this study as it is purely an exploratory Proof of Principal study.

Repeatability population will be defined as any subject who has a repeat stain or plaque assessment. The repeat stain and plaque populations will be separate populations.

10.2.7 Exclusion of Data from Analysis

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

10.2.8 Handling of Dropouts and Missing Data

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

10.2.9 Interim Analysis

No interim analysis is planned for this study

11 STUDY GOVERNANCE CONSIDERATIONS

11.1 Quality Control

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

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

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

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

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

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

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

11.3 Regulatory and Ethical Considerations

11.3.1 Institutional Review Board

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

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

11.3.2 Ethical Conduct of the Study

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

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

11.3.3 Subject Information and Consent

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

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

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

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

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

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

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed informed consent document.

11.3.4 Subject Recruitment

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

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

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

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

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

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

11.4 Posting of Information on Publicly Available Clinical Trial Registers

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

11.5 Provision of Study Results to Investigators

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

GSK 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.

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

11.6 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.

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSK CH, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects'

codes, names and addresses. Documents not for submission to GSK CH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

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

No study document should be destroyed without a prior written agreement between GSK CH and the investigator. The investigator must notify GSK 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.

11.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB, or investigational product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of KNO_3 / NaF dentifrices at any time.

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

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

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

11.8 Definition of Study End/ End of Study

The end of the study will be the date of the Last Subject Last Visit (LSLV). For this study the LSLV will date will be the primary completion date (PCD).

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13 APPENDIX

13.1 Appendix I – Instructions Sheet

INSTRUCTIONS FOR PRODUCT USE

Brush twice a day (morning and evening).

Each time you brush:

- Dispense a ribbon of toothpaste covering the length of the toothbrush head (see below picture).
- Set your timer for 1 minute, and then brush your teeth in your usual manner for 1 timed minute.

- Record each brushing on the diary card. Note any changes to these brushing procedures and reasons for changes (e.g. missed brushings, extra brushings) in the 'Comments' column.
- Record any changes in your health and medications (prescription and over the counter medications), or treatments on the diary card.
- Bring your diary card (completed and not completed), toothpaste and toothbrush to the next study visit.

13.2 Appendix II - Abbreviations

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

Table 13-1 Abbreviations

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
CPC	cetylpyridinium chloride
CRF	case report form
DMS	data management system
EDC	electronic data capture
FSFV	first subject first visit
GCP	Good Clinical Practice
GSK CH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonisation
IND	investigational new drug application
IRB	institutional review board
ITT	intent-to-treat
KNO_3	potassium nitrate
LSLV	last subject last visit
MedDRA	medical Dictionary for Regulatory Activities
mL	milliliters
MLSI	Macpherson modification of the Lobene Stain Index
N/A	not applicable
NaF	sodium fluoride
OHT	oral hard tissue
OST	oral soft tissue
PI	principal investigator
PII	personally identifiable information
PT	preferred term
PRO	Patient reported outcome
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedure
SS	safety statement
STP	sodium tripolyphosphate
SUSAR	suspected unexpected serious adverse reactions
TPI	Turesky modification of the Quigley Hein Index
USA	United States of America

SIGNATURE PAGE

208078 Protocol

Date	Signed By
21-Aug-2017 10:22:00	PPD
Justification	Approved

Date	Signed By
21-Aug-2017 10:35:05	PPD
Justification	Clinical Operations Approval

Date	Signed By
24-Aug-2017 09:06:19	PPD
Justification	Biostatistics Approval

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	