Clinical Protocol

207656

CONFIDENTIAL

SUMMARY INFORMATION

Title:	A Method Development Clinical Study Investigating the Efficacy of an Experimental Oral Rinse in Providing Long Term Relief from Dentinal Hypersensitivity
Protocol Number:	207656
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) St Georges Avenue, Weybridge, Surrey, KT13 0DE, United Kingdom (UK) Tel: PPD
Product Name:	1.5% w/w dipotassium oxalate monohydrate (KOX) and 0 ppm fluoride oral rinse
Development Phase:	N/A

Expert Advice Outside of Normal Working Hours:	PPD

Key Protocol Authors:	
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Biostatistician:	PPD, PhD
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Clinical Supplies:	PPD

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Study Site Name & Address:	Salus Research, Inc 1220 Medical Park Drive Building No.4 Fort Wayne, IN 46825, USA
Study Site Telephone Number:	PPD
Study Examiner:	PPD, RDH, BSEd, MS

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

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

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PROCESS FOR AMENDING THE PROTOCOL

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

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

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

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

Schedule of Events

Procedure/Assessment	Screening Visit1	Acclimatisation Period – 2 to 3 weeks	Baseline Visit 2 (Day 0)	Week 1 Visit 3 (Day 7±1)	Week 2 Visit 4 (Day 14±1)	Week 3 Visit 5 (Day 21±2)	Week 4 Visit 6 (Day 28±2)	Week 5 Visit 7 (Day 35±2)	Week 6 Visit 8 (Day 42±3)	Week 7 Visit 9 (Day 49±3)	Week 8 Visit 10 (Day 56 ±3)
Informed Consent	X										
Demographics, Ethnicity, Medical History	X										
Current/Concomitant Medications	X		X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X		X								
Subject Eligibility	X		X								
Continued Eligibility			X	X	X	X	X	X	X	X	X
Oral Soft Tissue (OST) Assessment	X		X				X				X
Eligible Teeth Assessments (Full Oral Hard Tissue (OHT), Dentition Exclusions, EAR, MGI, Tooth Mobility)	X										
Qualifying Evaporative Air Sensitivity (Schiff Score 2/3)	X										
Dispense Acclimatisation Kit	X										
Supervised Acclimatisation Product Use	X										
Subjects Return Acclimatisation Kit			X								
Tactile Assessment (Yeaple Probe)[1]			X								
Evaporative Air Assessment (Schiff Sensitivity Score and VRS)[2]			X								
Select two test teeth			X								
Stratification / Randomisation			X								

Procedure/Assessment	Screening Visit1	ation Period 2	Baseline Visit 2 (Day 0)	Week 1 Visit 3 (Day 7±1)	Week 2 Visit 4 (Day 14±1)	Week 3 Visit 5 (Day 21±2)	Week 4 Visit 6 (Day 28±2)	Week 5 Visit 7 (Day 35±2)	Week 6 Visit 8 (Day 42±3)	Week 7 Visit 9 (Day 49±3)	Week 8 Visit 10 (Day 56 ±3)
Tactile Assessment (Yeaple Probe[2] – test teeth only							X				X
Evaporative Air Assessment (Schiff Sensitivity Score and VRS) – test teeth only							X				X
Dispense Study Kit / Redispense Oral Rinse and Assigned Dentifrice[3]			X				X				
Supervised Brushing/Rinsing with Allocated Treatment[4]			X	X	X	X	X	X	X	X	
Treatment Compliance[5]			X	X	X	X	X	X	X	X	X
Adverse Events	X[6]		X	X	X	X	X	X	X	X	X
Incidents	X[6]		X	X	X	X	X	X	X	X	X
Subjects Return Study Kit				X	X	X	X	X	X	X	X
Site Reissue Study Kit to Subjects				X	X	X	X	X	X	X	
Study Conclusion/ Medical Sign-off											X

1. At Baseline, maximum force applied = 20g, at all subsequent visits maximum force = 80g.
2. Evaporative air assessment to follow tactile assessment, minimum 5 mins between the two assessment types to allow for tooth recovery.
3. Subject Kit to include timer, rinsing cup, diary, dentifrice, toothbrush, and assigned oral rinse. At Visit 6 the dentifrice and assigned oral rinse will be re-dispensed.
4. Subject Kit to be returned to subject after supervised brushing/rinsing at all visits except for Visit 10.
5. Compliance with acclimatisation oral rinse at Visit 2 and with assigned treatment oral rinse at Visits 3, 4, 5, 6, 7, 8, 9 and 10 based on weight of oral rinse bottle and contents, and completed diaries.
6. After supervised use of acclimatisation products.

PROTOCOL SYNOPSIS FOR STUDY 207656

Brief Summary

This single centre, randomised, examiner blind, three-treatment arm, parallel design method development study will be used to investigate the efficacy of an experimental oral rinse, containing 1.5% potassium oxalate (KOX) and 0 ppm fluoride in relieving dentine hypersensitivity (DH) after 8 weeks use compared with a placebo oral rinse and a commercialised fluoride oral rinse.

The study will be conducted in healthy subjects with pre-existing self-reported and clinically diagnosed tooth sensitivity at screening.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by an evaporative air stimulus (with Schiff Sensitivity Scale), against a negative control oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 8 weeks.	• Change from baseline in Schiff sensitivity score at 8 weeks.
Secondary	
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by a tactile stimulus (Yeaple probe), against a negative control oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 8 weeks.	• Change from baseline in tactile threshold (Yeaple probe) at 8 weeks.

Exploratory	
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by an evaporative air stimulus (with Schiff Sensitivity Scale), against a placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 8 weeks.	• Change from baseline in Schiff sensitivity score at 8 weeks.
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by a tactile stimulus (Yeaple probe), against a placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 8 weeks.	• Change from baseline in tactile threshold (Yeaple probe) at 8 weeks.
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by an evaporative air stimulus (with Schiff Sensitivity Scale), against a marketed negative control oral rinse and a placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 4 weeks.	• Change from baseline in Schiff sensitivity score at 4 weeks.
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by a tactile	• Change from baseline in tactile threshold (Yeaple probe) at 4 weeks.

stimulus (Yeaple probe), against a marketed negative control oral rinse and a placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 4 weeks.	
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited an evaporative air stimulus (with VRS), against a marketed negative control oral rinse and a placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 4 and 8 weeks.	• Change from baseline in Visual Rating Score (VRS) at 4 and 8 weeks.
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by an evaporative air stimulus (with Schiff Sensitivity Scale), against the efficacy of the group obtained by combining the marketed negative control and the placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 4 and 8 weeks.	• Change from baseline in Schiff sensitivity score at 4 and 8 weeks.
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by a tactile stimulus (Yeaple probe), against	• Change from baseline in tactile threshold (Yeaple probe) at 4 and 8 weeks.

the efficacy of the group obtained by combining the marketed negative control and the placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 4 and 8 weeks.	
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited an evaporative air stimulus (with VRS), against the efficacy of the group obtained by combining the marketed negative control and the placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 4 and 8 weeks.	• Change from baseline in VRS at 4 and 8 weeks.

Study Design

Overall Design
This will be a single centre, eight week, randomised, examiner-blind, three treatment, parallel group design, stratified study in healthy subjects, with at least two sensitive teeth that meet all of the study criteria at the Screening and Baseline visits. DH will be assessed at Baseline, and after 4 and 8 weeks twice daily treatment. At the Screening visit, subjects will give their written informed consent to participate in the study. Demography, medical history and concomitant medications will be recorded, followed by an oral examination. This will include an oral soft tissue (OST) examination, an oral hard tissue examination (OHT), dentition exclusions, assessment of erosion, abrasion, recession (EAR), gingival status, tooth mobility and subject response to a qualifying air sensitivity assessment, subject response will be recorded as a numerical value (Schiff score 2/3). Eligible subjects will be supplied with a standard fluoride dentifrice and a fluoride oral rinse to use twice daily (morning and evening) during the acclimatisation period between the Screening and Baseline visits.

Each product use will be recorded in the diary provided. First use of the acclimatisation dentifrice and oral rinse will be carried out under supervision at the study site.

At the Baseline visit (2-3 weeks after Screening), eligibility to continue will be assessed. Subjects will undergo an OST examination, followed by tooth sensitivity assessments (a tactile stimulus [Yeaple probe, maximum 20g pressure], then an evaporative air stimulus [with Schiff Sensitivity Scale and VRS]), and a review of the inclusion/exclusion criteria. Two test teeth will then be identified and eligible subjects will be randomised to treatment (stratified by maximum baseline Schiff sensitivity score of the two selected test teeth). First use of allocated study product will be carried out under supervision at the study site, after the supervised brushing subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided. Subjects will continue to use their assigned study treatment twice daily (morning and evening) for the next 8 weeks, recording each brushing and rinsing occasion in the diary provided.

Subjects will return to the study site each week (Visits 3, 4, 5, 6, 7, 8, 9 and 10) over the eight week study period and asked to return their study kit so that the oral rinse bottle and its contents can be weighed to verify study compliance. Diaries will also be checked at each visit. A supervised brushing and rinse will also be conducted at each visit (except Visit 10). Following supervised product use all products will be returned to the subject. The dentifrice and oral rinse will be re-dispensed at Visit 6 (week 4). Tooth sensitivity will be re-assessed after 4 and 8 weeks (Visits 6 and 10) of treatment, using first a tactile stimulus (Yeaple probe, maximum 80g pressure) and then an evaporative air stimulus (with Schiff Sensitivity Scale and VRS) on the two selected test teeth only. An OST examination will be completed at each of these visits, prior to the clinical assessments of sensitivity.

The study site will send twice daily (morning and evening) SMS reminders requesting that subjects remember to conduct their timed brush and rinse in the morning and evening.

Visit 1 - Screening Visit

The following assessments will be conducted:

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

- Demographics, current/concomitant medications and medical history.
- Oral examinations including an oral soft tissue (OST) and oral hard tissue (OHT) examinations, and assessments to determine eligible teeth.
- Qualifying evaporative air sensitivity assessment - record numerical value (Schiff score 2/3).
- Confirmation of subject eligibility.
- Dispensation of acclimatisation kit.
- Supervised brushing and rinse with acclimatisation dentifrice and oral rinse, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Adverse Events (AEs) and incidents will be documented from completion of the supervised use of the acclimatisation products.

Visit 2 - Baseline Visit

The following assessments will be conducted:

- Review of current/concomitant medications, AEs and incidents.
- Return of acclimatisation kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- Confirmation of subject eligibility and continuance.
- OST examination.
- Tactile sensitivity assessment of eligible teeth.
- Evaporative air sensitivity assessment of eligible teeth (Schiff sensitivity score and VRS)
- Inclusion criteria 4d (please see inclusion criteria table below).
- Selection of two test teeth.
- Stratification and Randomisation.
- Dispensation of study kit.
- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- AEs and Incidents following supervised brushing and rinse.

Visit 3 - Week 1

The following assessments will be conducted:

- Review of current/concomitant medications, AEs and incidents.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- A supervised brushing and rinse will be conducted, subjects will be requested

to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- AEs and Incidents following supervised brushing and rinse.
- Confirmation of subject continuance.

Visit 4 - Week 2

The following assessments will be conducted:
- Review of current/concomitant medications, AEs and incidents.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- AEs and Incidents following supervised brushing and rinse.
- Confirmation of subject continuance.

Visit 5 - Week 3

The following assessments will be conducted:
- Review of current/concomitant medications, AEs and incidents.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- AEs and Incidents following supervised brushing and rinse.
- Confirmation of subject continuance.

Visit 6 - Week 4

The following assessments will be conducted:
- Review of current/concomitant medications, AEs.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- Confirmation of subject continuance.
- OST examination.
- Tactile sensitivity assessment of two eligible test teeth.

- Evaporative air sensitivity assessment of two eligible test teeth (Schiff sensitivity score and VRS).
- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- Re-dispensation of study dentifrice and oral rinse with usage instructions and diary.
- AEs and Incidents following supervised brushing and rinse.

Visit 7 - Week 5

The following assessments will be conducted:

- Review of current/concomitant medications, AEs and incidents.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- AEs and Incidents following supervised brushing and rinse.
- Confirmation of subject continuance.

Visit 8 - Week 6

The following assessments will be conducted:

- Review of current/concomitant medications, AEs and incidents.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- AEs and Incidents following supervised brushing and rinse.
- Confirmation of subject continuance.

Visit 9 - Week 7

The following assessments will be conducted:

- Review of current/concomitant medications, AEs and incidents.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be

checked to determine usage compliance.

- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- AEs and incidents following supervised brushing and rinse.
- Confirmation of subject continuance.

Visit 10 - Week 8/ LSLV

The following assessments will be conducted:

- Review of current/concomitant medications, AEs and incidents.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- Confirmation of subject continuance.
- OST examination.
- Tactile sensitivity assessment of two eligible test teeth.
- Evaporative air sensitivity assessment of two eligible test teeth (Schiff sensitivity score and VRS).
- Subjects return all study products.
- Completion of compliance check.

Type and Planned Number of Subjects

A sufficient number of healthy subjects will be screened to randomise at least 100 subjects (approximately 50 to the experimental treatment, 25 to the negative control and 25 to placebo) to ensure 80 evaluable subjects complete the entire study. This will ensure approximately 40 evaluable subjects for the test treatment and 20 each for the negative control treatment and placebo.

With this 40/20/20 distribution of the subjects in the treatment arms, the study has less than 50% power to detect a mean treatment difference of 0.36 in the Schiff sensitivity score using a two-sided t-test of significance level 0.05 for the experimental product against the negative control. The standard deviation used in this calculation is 0.8; this estimate is obtained from the GSKCH study 204763. When the experimental treatment group is compared with the combined group comprising of the negative control group and the placebo group using the two-sided t-test with the same estimates of mean difference, significance level and standard deviation, the study will have 51.1% power.

Diagnosis and Main Criteria for Inclusion

Subjects aged 18-65 years of age, with a minimum of 20 natural teeth and in good general health who suffer from tooth sensitivity. At Screening, subjects must have a minimum of two accessible non adjacent teeth (incisors, canines, or pre-molars) with signs of erosion or abrasion or facial/cervical gingival recession (EAR), with a modified gingival index (MGI) =0 adjacent to the test area and a clinical mobility of ≤1, and with signs of sensitivity measured by qualifying evaporative air assessment. At Baseline subjects must have a minimum of two, non-adjacent accessible teeth (incisors, canines or pre-molars), with signs of sensitivity, measured by qualifying tactile stimulus (Yeaple ≤ 20g) and evaporative air assessment (Schiff Sensitivity Score ≥ 2).

Product Information

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

	Test Product	Negative Control	Placebo Product
Product Name	Experimental oral rinse containing 1.5% KOX, 0ppm fluoride, pH 7	Oral rinse containing 0.02% w/w NaF. Colgate Total Daily Repair® (USA marketed product)	Oral rinse containing 0% KOX and 0 ppm fluoride, pH 7
Product Formulation Code (MFC)	CCI [redacted]	Commercially Available	CCI [redacted]
Dose	10 ml	10 ml	10 ml
Route of Administration	Oral	Oral	Oral
Dosing Instructions	Rinse twice daily (morning and evening) with 10 ml of oral rinse for 60 timed seconds and expectorate. No further rinsing with water will be permitted after use of the oral rinse.	Rinse twice daily (morning and evening) with 10 ml of oral rinse for 60 timed seconds and expectorate. No further rinsing with water will be permitted after use of the oral rinse.	Rinse twice daily (morning and evening) with 10 ml of oral rinse for 60 timed seconds and expectorate. No further rinsing with water will be permitted after use of the oral rinse.

® Colgate and Total Daily Repair are registered trademarks of the Colgate-Palmolive group

Statistical Methods

Changes from baseline to Week 4 and Week 8 in Schiff Sensitivity Score will be analysed using an analysis of covariance (ANCOVA) model. The model will include treatment as a factor and baseline Schiff Sensitivity Score as a covariate.

Changes from baseline in tactile score and VRS score will be analysed for weeks 4 and 8 separately using ANCOVA analysis with treatment and baseline Schiff stratification as factors and the corresponding baseline scores as a covariate in the model.

The adjusted mean for each treatment, and the differences between each pair of treatments together with their corresponding 95% confidence intervals and the p-values for treatment comparisons, will be provided.

Assumptions of normality and homogeneity of residuals will be evaluated and if serious departures are observed transformations will be investigated. If suitable transformations cannot be found, non-parametric tests such as Wilcoxon Rank Sum test or the van Elteren test will be used.

1. INTRODUCTION

Dentine hypersensitivity (DH) has been defined as 'pain derived from exposed dentine in response to chemical, thermal, tactile, or osmotic stimuli which can't be explained as arising from any other dental defect or disease' [Addy, 1985; Canadian Advisory Board on Dentin Hypersensitivity, 2003]. The primary aetiological factors associated with the onset of DH include gingival recession and/or enamel loss (e.g. through erosion or abrasion) that result in exposure of dentine with patent dentinal tubules [Orchardson, 1987]. The hydrodynamic theory of DH hypothesises that a stimulus external to the tooth (e.g. a temperature/osmotic differential) causes transport of the fluid resident within dentinal tubules [Brännström, 1962]. This fluid movement may stimulate nerve processes in the pulpal area of the dentine including irritation of odontoblasts, pulpal neurons, and even subodontonblastic blood vessels [Hall, 2000], resulting in the characteristic short, sharp pain of DH.

Currently there are two approaches to the management of DH using home use oral care products: either nerve depolarisation or dentinal tubule occlusion. Nerve depolarising agents, typically potassium salts, generally require a period of use (for example, 14 to 28 days) before their benefit is established. The delivery of potassium ions to the dentine-pulp junction (odontoblastic layer) *via* dentinal tubules is believed to result in depolarisation of the afferent nerve membrane thereby blocking the pain response. The second approach uses tubule occluding agents which physically block the exposed end of the dentinal tubules, thus reducing dentinal fluid movement and pulpal irritation. Tubule occluding agents such as strontium and stannous salts, bioglasses, silicas or oxalates serve to seal or block the dentine tubules and thereby reduce the effect of external stimuli. Such agents are believed to function by precipitating insoluble materials onto the dentine surface and/or within the dentinal tubules to reduce dentinal fluid transport.

Tubule occluding agents have been formulated in a number of commercialised over-the-counter (OTC) DH dentifrices, and more recently in DH oral rinses. A number of successful clinical studies have been conducted on oral rinses containing occluding agents 8% Arginine [Boneta, 2013; Hu, 2013; Markowitz, 2013], and 1.4% KOX [Sharma, 2013[a]; Sharma, 2013[b]], these products are marketed as Colgate® Sensitive Pro-relief™ Mouthwash and Listerine®** Advanced Defence Sensitive Mouthwash, respectively.

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™ Pro-relief is a registered trademark of the Colgate-Palmolive group
®** Listerine is a registered trademark of Johnson & Johnson Limited

GSKCH has evaluated the DH efficacy of two different technologies in rinse format, potassium nitrate (KNO_3) and KOX.

Three studies of a similar design have been conducted to evaluate the DH efficacy of three different 1.5-2.0 % KOX containing oral rinses [GSKCH studies: 204762; 204763; 204773]. When evaluated in randomised double-blind, placebo-controlled studies, similar statistically significant improvements were measured from baseline in favour of all test oral rinses versus the placebo [GSKCH study 204763], but statistical differentiation versus placebo treatment was not reported for two of these studies [GSKCH studies: 204762 and 204773]. The reason for the lack of statistical differentiation in these studies is unclear as KOX has been shown to be effective in reducing DH in other published clinical studies [Sharma, 2013[a]; Sharma, 2013[b]].

The mixed results that have been observed in GSKCH DH mouthrinse studies has prompted a piece of method development work to be completed. The aim of this method development study is to explore some of the areas of clinical design in an 8 week DH clinical study that could be used for existing and future DH oral rinse technologies.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by an evaporative air stimulus (with Schiff Sensitivity Scale), against a negative control oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 8 weeks.	• Change from baseline in Schiff sensitivity score at 8 weeks.
Secondary	
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by a tactile stimulus (Yeaple probe), against a negative control oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 8 weeks.	• Change from baseline in tactile threshold (Yeaple probe) at 8 weeks.
Exploratory	
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by an evaporative air stimulus (with Schiff Sensitivity Scale), against a placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 8 weeks.	• Change from baseline in Schiff sensitivity score at 8 weeks.
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by a tactile stimulus (Yeaple probe), against a placebo oral rinse,	• Change from baseline in tactile threshold (Yeaple probe) at 8 weeks.

following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 8 weeks.	
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by an evaporative air stimulus (with Schiff Sensitivity Scale), against a marketed negative control oral rinse and a placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 4 weeks.	• Change from baseline in Schiff sensitivity score at 4 weeks.
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by a tactile stimulus (Yeaple probe), against a marketed negative control oral rinse and a placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 4 weeks.	• Change from baseline in tactile threshold (Yeaple probe) at 4 weeks.
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• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by an evaporative air stimulus (with Schiff Sensitivity Scale), against	• Change from baseline in Schiff sensitivity score at 4 and 8 weeks.

the efficacy of the group obtained by combining the marketed negative control and the placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 4 and 8 weeks.	
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited by a tactile stimulus (Yeaple probe), against the efficacy of the group obtained by combining the marketed negative control and the placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 4 and 8 weeks.	• Change from baseline in tactile threshold (Yeaple probe) at 4 and 8 weeks.
• To evaluate and compare the clinical efficacy of a 1.5% KOX containing oral rinse for the relief of DH, as elicited an evaporative air stimulus (with VRS), against the efficacy of the group obtained by combining the marketed negative control and the placebo oral rinse, following use as an adjunct to twice daily brushing with a standard fluoride dentifrice, after 4 and 8 weeks.	• Change from baseline in VRS at 4 and 8 weeks.

3. STUDY PLAN

3.1. Study Design

Overall Design

This will be a single centre, eight week, randomised, examiner-blind, three treatment, parallel group design, stratified study in healthy subjects, with at least two sensitive teeth that meet all of the study criteria at the Screening and Baseline visits. DH will be assessed at Baseline, and after 4 and 8 weeks twice daily treatment.

At the Screening visit, subjects will give their written informed consent to participate in the study. Demography, medical history and concomitant medications will be recorded, followed by an oral examination. This will include an oral soft tissue (OST) examination, an oral hard tissue examination (OHT), dentition exclusions, assessment of erosion, abrasion, recession (EAR), gingival status, tooth mobility and subject response to a qualifying air sensitivity assessment, subject response will be recorded as a numerical value (Schiff score 2/3). Eligible subjects will be supplied with a standard fluoride dentifrice and a fluoride oral rinse to use twice daily (morning and evening) during the acclimatisation period between the Screening and Baseline visits. Each product use will be recorded in the diary provided. First use of the acclimatisation dentifrice and oral rinse will be carried out under supervision at the study site.

At the Baseline visit (2-3 weeks after Screening), eligibility to continue will be assessed. Subjects will undergo an OST examination, followed by tooth sensitivity assessments (a tactile stimulus [Yeaple probe, maximum 20g pressure], then an evaporative air stimulus [with Schiff Sensitivity Scale and VRS]), and a review of the inclusion/exclusion criteria. Two test teeth will then be identified and eligible subjects will be randomised to treatment (stratified by maximum baseline Schiff sensitivity score of the two selected test teeth). First use of allocated study product will be carried out under supervision at the study site, after the supervised brushing subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided. Subjects will continue to use their assigned study treatment twice daily (morning and evening) for the next 8 weeks, recording each brushing and rinsing occasion in the diary provided.

Subjects will return to the study site each week (Visits 3, 4, 5, 6, 7, 8, 9 and 10) over the eight week study period and asked to return their study kit so that the oral rinse bottle and its contents can be weighed to verify study compliance. Diaries will also be

checked at each visit. A supervised brushing and rinse will also be conducted at each visit (except Visit 10). Following supervised product use all products will be returned to the subject. The dentifrice and oral rinse will be re-dispensed at Visit 6 (week 4). Tooth sensitivity will be re-assessed after 4 and 8 weeks (Visits 6 and 10) of treatment, using first a tactile stimulus (Yeaple probe, maximum 80g pressure) and then an evaporative air stimulus (with Schiff Sensitivity Scale and VRS) on the two selected test teeth only. An OST examination will be completed at each of these visits, prior to the clinical assessments of sensitivity.

The study site will send twice daily (morning and evening) SMS reminders requesting that subjects remember to conduct their timed brush and rinse in the morning and evening.

Visit 1 - Screening Visit

The following assessments will be conducted:

- Written informed consent.
- Review inclusion/exclusion criteria.
- Review of the oral care products the subject is currently using to confirm they do not contain any ingredients intended for treating sensitive teeth.
- Demographics, current/concomitant medications and medical history.
- Oral examinations including an oral soft tissue (OST) and full oral hard tissue (OHT) examinations, and assessments to determine eligible teeth.
- Qualifying evaporative air sensitivity assessment - record numerical value (Schiff score 2/3).
- Confirmation of subject eligibility.
- Dispensation of acclimatisation kit.
- Supervised brushing and rinse with acclimatisation dentifrice and oral rinse, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Adverse Events (AEs) and incidents will be documented from completion of the supervised use of the acclimatisation products.

Visit 2 - Baseline Visit

The following assessments will be conducted:

- Review of current/concomitant medications, AEs and incidents.
- Return of acclimatisation kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- Confirmation of subject eligibility and continuance.
- OST examination.

- Tactile sensitivity assessment of eligible teeth.
- Evaporative air sensitivity assessment of eligible teeth (Schiff sensitivity score and VRS)
- Inclusion criteria 4d (please see inclusion criteria table below).
- Selection of two test teeth.
- Stratification and Randomisation.
- Dispensation of study kit.
- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- AEs and Incidents following supervised brushing and rinse.

Visit 3 - Week 1

The following assessments will be conducted:

- Review of current/concomitant medications, AEs and incidents.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- AEs and Incidents following supervised brushing and rinse.
- Confirmation of subject continuance.

Visit 4 - Week 2

The following assessments will be conducted:

- Review of current/concomitant medications, AEs and incidents.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- AEs and Incidents following supervised brushing and rinse.
- Confirmation of subject continuance.

Visit 5 - Week 3

The following assessments will be conducted:

- Review of current/concomitant medications, AEs and incidents.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be

checked to determine usage compliance.

- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- AEs and Incidents following supervised brushing and rinse.
- Confirmation of subject continuance.

Visit 6 - Week 4

The following assessments will be conducted:

- Review of current/concomitant medications, AEs.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- Confirmation of subject continuance.
- OST examination.
- Tactile sensitivity assessment of two eligible test teeth.
- Evaporative air sensitivity assessment of two eligible test teeth (Schiff sensitivity score and VRS).
- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- Re-dispensation of study dentifrice and oral rinse with usage instructions and diary.
- AEs and Incidents following supervised brushing and rinse.

Visit 7 - Week 5

The following assessments will be conducted:

- Review of current/concomitant medications, AEs and incidents.
- Return of study kit.
- Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance.
- A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided.
- Study kit returned to subject.
- AEs and Incidents following supervised brushing and rinse.
- Confirmation of subject continuance.

Visit 8 - Week 6
The following assessments will be conducted: • Review of current/concomitant medications, AEs and incidents. • Return of study kit. • Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance. • A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided. • Study kit returned to subject. • AEs and Incidents following supervised brushing and rinse. • Confirmation of subject continuance.
Visit 9 - Week 7
The following assessments will be conducted: • Review of current/concomitant medications, AEs and incidents. • Return of study kit. • Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance. • A supervised brushing and rinse will be conducted, subjects will be requested to measure out the dose of the oral rinse using the dosing cup provided. • Study kit returned to subject. • AEs and incidents following supervised brushing and rinse. • Confirmation of subject continuance.
Visit 10 - Week 8/ LSLV
The following assessments will be conducted: • Review of current/concomitant medications, AEs and incidents. • Return of study kit. • Review of completed diary and weight of oral rinse bottle and contents will be checked to determine usage compliance. • Confirmation of subject continuance. • OST examination. • Tactile sensitivity assessment of two eligible test teeth. • Evaporative air sensitivity assessment of two eligible test teeth (Schiff sensitivity score and VRS). • Subjects return all study products. • Completion of compliance check.

3.3. Type and Planned Number of Subjects

A sufficient number of healthy subjects will be screened to randomise at least 100 subjects (approximately 50 to the experimental treatment, 25 to the negative control and 25 to placebo) to ensure 80 evaluable subjects complete the entire study. This will ensure approximately 40 evaluable subjects for the test treatment and 20 each for the negative control treatment and placebo.

With this 40/20/20 distribution of the subjects in the treatment arms, the study has less than 50% power to detect a mean treatment difference of 0.36 in the Schiff sensitivity score using a two-sided t-test of significance level 0.05 for the experimental product against the negative control. The standard deviation used in this calculation is 0.8; this estimate is obtained from the GSKCH study 204763. When the experimental treatment group is compared with the combined group comprising of the negative control group and the placebo group using the two-sided t-test with the same estimates of mean difference, significance level and standard deviation, the study will have 51.1% power.

3.4. Study Design and Dose Justification

This study will be a randomised, examiner blind, three treatment parallel group design. Subjects will apply a full brush head of the standard fluoride dentifrice, brush for one timed minute (in their usual manner) and expectorate; rinse with 10ml of tap water for 5 seconds and expectorate; and then rinse with 10 ml of their randomly assigned oral rinse for 60 timed seconds and expectorate. No further rinsing with water will be permitted after use of the oral rinse, and subjects will be asked to refrain from eating or drinking within 30 minutes of using the oral rinse. The dosage regimen of twice daily treatment (morning and evening) will be the same for all subjects, and has been selected based on widely recommended oral hygiene practice, and typical consumer habit.

An experimental 1.5% w/w KOX rinse will be included in the study (1.5% w/w KOX / 0 ppm fluoride, pH 7) as it has previously shown statistically significant DH efficacy compared to a placebo oral rinse [GSKCH study 204763]. KOX has also been selected as the DH active as it has been shown to be effective in reducing DH in other published studies [Sharma, 2013[a]; Sharma, 2013[b]]. Efficacy will be compared to that of a placebo oral rinse and a US marketed rinse, with no known anti-sensitivity activity.

All subjects will receive the same regular fluoride dentifrice and a US marketed oral rinse during the acclimatisation period to familiarise themselves with the required brushing and rinsing regimen, and standardise oral hygiene practices. The sodium monofluorophosphate (SMFP) control paste and sodium fluoride (NaF) oral rinse have been selected for use in this study as they do not contain any known anti-sensitivity ingredients

The control products will be a placebo oral rinse and a US marketed, twice daily use fluoride rinse. 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 the oral rinses evaluated in this study, the level of blindness for this study is described as 'examiner blind' only.

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

An acclimatisation period of 2 weeks is often utilised in DH oral rinse studies [Boneta, 2013; Hu, 2013; Markowitz, 2013; Sharma, 2013a, 2013b]. Therefore, an acclimatisation period of 2-3 weeks will be included in this study.

A weekly supervised rinsing at the study site and twice daily SMS reminders to subjects participating in the study will be conducted to aid compliance. During study site visits subjects will be asked to measure out their own dose of oral rinse using the cups provided, so that dose amount compliance can be monitored by the study staff. Subjects will also be asked to return their assigned oral rinse at each visit, so that the bottle and its contents can be weighed and compliance assessments made. Furthermore, only regular (twice daily) oral rinse users will be recruited for this study.

Other causes of dental pain can present with the same symptoms as DH, for example cracked tooth syndrome, fractured restorations, chipped tooth, dental caries, post-restorative sensitivity and teeth in acute hyperfunction [Dababneh, 1999]. While the

age range over which an individual can experience DH is wide (from early teens to 70s) [Fischer, 1992], peak incidence is known to occur between the ages of 20-40 years [Graf, 1977; Flynn, 1985]. The fall in prevalence observed in later decades reflects age related changes in the dentine and pulp of the tooth which act to reduce dentine permeability and the tooth's response to the external triggers of DH [Seltzer, 1975; Pashley, 2008]. Given that the dental pain experienced by older members of the population is less likely to be diagnosed as DH [Rees, 2000], the age range of 18-65 selected for this study targets individuals suffering from tooth sensitivity which is most likely due to DH. This will facilitate recruitment and minimise inconvenience to older participants who are more likely to be rejected at screening.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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

4.1. Inclusion Criteria

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

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

2. AGE
Aged between18-65 years.

3. GENERAL HEALTH
Good general and mental health with, in the opinion of the investigator or medically qualified designee: a) No clinically significant and relevant abnormalities in medical history or oral examination. b) Absence of any condition that would impact on the subject's safety or wellbeing or affect the individual's ability to understand and follow study procedures and requirements.

4. DENTAL HEALTH
At Screening: a) Self-reported history of DH lasting more than six months but not more than 10 years. b) Minimum of 20 natural teeth. c) Minimum of 4 accessible non-adjacent teeth (incisors, canines, premolars), preferably in different quadrants, that meet all of the following criteria: - Signs of facial/cervical gingival recession and/or signs of erosion or abrasion (EAR). - Tooth with MGI score =0 adjacent to the test area (exposed dentine) only [Lobene, 1986] and a clinical mobility of ≤1. - Tooth with signs of sensitivity measured by qualifying evaporative air assessment (Schiff sensitivity score ≥ 2). ***At Baseline***: d) Minimum of two, non-adjacent accessible teeth (incisors, canines, premolars), that meet all of the following criteria: - Tooth with signs of sensitivity, measured by qualifying tactile stimulus (Yeaple ≤ 20g) and evaporative air assessment (Schiff sensitivity score ≥ 2) Note: Teeth which meet the EAR, MGI and mobility inclusion criteria and none of the dentition exclusion criteria at Screening should be assessed by tactile stimulus at Visit 2. Those teeth which meet the required tactile threshold (Yeaple ≤ 20g) should then be assessed by evaporative air stimulus. When two teeth that meet the study criteria are identified, no further testing is necessary. The examiner will select two Test Teeth from those which meet both the tactile threshold and Schiff sensitivity score criteria. Test Teeth should not be adjacent to each other and preferably in different quadrants.

5. CONTRACEPTION
Females of childbearing potential who are, in the opinion of the investigator, practicing a reliable method of contraception. Adequate contraception is defined as abstinence, oral contraceptive, either combined or progestogen alone OR injectable progestogen OR implants of levonorgestrel OR estrogenic vaginal ring OR percutaneous contraceptive patches OR intrauterine device or intrauterine system OR double barrier method (condom or occlusive cap [diaphragm or cervical vault caps] plus spermicidal agent [foam, gel, film, cream, suppository]) OR male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject.

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

7. ORAL RINSE USERS
Subjects will be current and regular (twice daily), users of an OTC Monograph or cosmetic oral rinse.

8. CELL PHONE OWNERS
Subjects will be cell phone owners so that they can contactable by SMS.

4.2. Exclusion Criteria

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

1. PREGNANCY
A woman who is known to be pregnant or who is intending to become pregnant over the duration of the study.

2. BREAST-FEEDING
A woman who is breast-feeding.

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

4. CLINICAL STUDY/ INVESTIGATIONAL PRODUCT
a) Participation in another clinical study (including cosmetic studies) or receipt of an investigational drug within 30 days of the screening visit. b) Previous participation in this study.

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

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

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

8. GENERAL DENTITION EXCLUSIONS
a) Dental prophylaxis within 4 weeks of Screening. b) Tongue or lip piercing. c) Desensitising treatment within 8 weeks of Screening (professional sensitivity treatments and non-dentifrice sensitivity treatments). d) Gross periodontal disease, treatment of periodontal disease (including surgery) within 12 months of Screening, scaling or root planning within 3 months of Screening. e) Teeth bleaching and any teeth whitening procedures within 8 weeks of Screening.

9. SPECIFIC DENTITION EXCLUSIONS FOR *TEST TEETH*
a) Tooth with evidence of current or recent caries, or reported treatment of decay within 12 months of Screening. b) Tooth with exposed dentine but with deep, defective or facial restorations, teeth used as abutments for fixed or removable partial dentures, dental implants, teeth with full crowns or veneers, orthodontic bands or cracked enamel. Sensitive teeth with contributing aetiologies other than erosion, abrasion or recession of exposed dentine. c) Sensitive tooth not expected to respond to treatment with an over-the-counter dentifrice in the opinion of the investigator.

10. PRODUCT USE
Use of an oral care product indicated for the relief of dentine hypersensitivity within 8 weeks of screening (subjects will be required to bring their current oral care products to the site in order to verify the absence of known anti-sensitivity ingredients).

11. CONCOMITANT MEDICATION/MEDICAL HISTORY
a) Daily doses of medication/treatments which, in the opinion of the investigator, could interfere with the perception of pain. Examples of such medications include analgesics, anticonvulsants, antihistamines that cause marked or moderate sedation, sedatives, tranquilisers, anti-depressants, mood-altering and anti-inflammatory drugs. b) Currently taking antibiotics or has taken antibiotics within two weeks of Baseline. c) Daily dose of a medication which, in the opinion of the investigator, is causing xerostomia. d) Presence of kidney disease, hyperoxaluria, or any other condition that may be exacerbated by oxalic acid or oxalate salts. e) Presence of chronic debilitating disease which, in the opinion of the investigator, could affect study outcomes.

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

4.3. Screening/ Baseline Failures

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

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

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

4.4. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If the reason for removal of a subject from the study is an AE, the principal specific event or test will be recorded in the eCRF. If a subject is withdrawn from the study because of a product limiting AE, thorough efforts should be clearly made to document the outcome. Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilises, is otherwise explained, or the subject is lost to follow-up. Should a subject take an analgesic medication within 8 hours of an assessment visit, or should any other factor, in the opinion of the investigator, be thought to affect study outcomes (e.g. analgesic or excessive alcohol consumption), every attempt will be made to reschedule the subject. If they cannot be reappointed they will be withdrawn from the study.

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

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

Should a randomised subject take an analgesic medication within 8 hours of an assessment visit, or should any other factor, in the opinion of the investigator, be thought to affect study outcomes (e.g. excessive alcohol consumption), the following actions must be taken:

- Baseline visit: every attempt will be made to reschedule the subject. If they cannot be reappointed they will be withdrawn from the study. No clinical efficacy measures will be performed. The subject should not be replaced.

- Week 4 visit: every attempt will be made to reschedule the subject. If they cannot be reappointed they will continue in the study. No clinical efficacy measures will be performed at this visit.
- Week 8 visit: every attempt will be made to reschedule the subject. If they cannot be reappointed they will be withdrawn from the study. No clinical efficacy measures will be performed. The subject should not be replaced.

4.5. Subject Replacement

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

4.6. Subject and Study Completion

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

5. PRODUCT INFORMATION

5.1. Study Product

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

	Test Product	Negative Control	Placebo Product
Product Name	Experimental oral rinse containing 1.5% KOX, 0ppm fluoride, pH 7	Oral rinse containing 0.02% w/w NaF. Colgate Total Daily Repair® (USA marketed product)	Oral rinse containing 0% KOX and 0 ppm fluoride, pH 7
Product Formulation Code (MFC)	CCI [redacted]	Commercially Available	CCI [redacted]
Dose	10 ml	10 ml	10 ml
Route of Administration	Oral	Oral	Oral
Dosing Instructions	Rinse twice daily (morning and evening) with 10 ml of oral rinse for 60	Rinse twice daily (morning and evening) with 10 ml of oral rinse for 60 timed	Rinse twice daily (morning and evening) with 10 ml of oral rinse for 60

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	timed seconds and expectorate. No further rinsing with water will be permitted after use of the oral rinse.	seconds and expectorate. No further rinsing with water will be permitted after use of the oral rinse.	timed seconds and expectorate. No further rinsing with water will be permitted after use of the oral rinse.

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

Name of Item	Purpose
Dentifrice containing 0.76% w/w SMFP (1000ppm fluoride). Colgate® Cavity Protection (USA marketed product).	Acclimatisation and daily use dentifrice - to standardise oral hygiene practice prior to treatment phase and use prior to rinsing with oral rinse during the treatment phase.
Oral rinse containing 0.02% w/w NaF. Crest Pro-Health Advanced with Extra Deep Clean mouthwash (USA marketed product).	Acclimatisation oral rinse - to standardise oral hygiene practice prior to treatment phase.
Oral-B Sensi Soft Manual Toothbrush	Dentifrice application by tooth brushing.
Countdown timers	To ensure accurate brushing.
Dosing cups	For accurately measuring out the oral rinse and rinsing with water after brushing.

The acclimatisation kit will include the following items: acclimatisation dentifrice, oral rinse, toothbrush, dosing cup, usage instructions, diary and timer.

The study kit will include the following items: study dentifrice, assigned oral rinse, toothbrush, dosing cup, usage instructions, timer and diary.

5.2. Dose Schedule

During the acclimatistion period, subjects will apply a full brush head of the standard fluoride dentifrice, brush for one timed minute (in their usual manner) and expectorate; rinse with 10 ml of tap water for 5 seconds and expectorate; and then rinse with 10 ml of the acclimatisation oral rinse for 60 timed seconds and expectorate.

During the treatment period, subjects will apply a full brush head of the standard fluoride dentifrice, brush for one timed minute (in their usual manner) and expectorate; rinse with 10 ml of tap water for 5 seconds and expectorate; and then

rinse with 10 ml of the allocated treatment oral rinse for 60 timed seconds and expectorate.

No further rinsing with water will be permitted after use of the oral rinse during the acclimatisation phase or treatment period, and subjects will be asked to refrain from eating or drinking within 30 minutes of using the oral rinse.

The dosage regimen of twice daily treatment (morning and evening) will be applied during the acclimatisation and treatment period.

5.3. Dose Modification

No dose modification is permitted in this study.

5.4. Product Compliance

A weekly supervised rinsing at the study site and twice daily (morning and evening) SMS reminders to subjects participating in the study will be conducted to aid compliance. During study site visits subjects will be asked to measure out their own dose of oral rinse using the cups provided, so that dose amount compliance can be monitored by the study staff. Subjects will also be asked to return their assigned oral rinse at each visit, so that the bottle and its contents can be weighed and compliance assessments made. Furthermore, only regular (twice daily) oral rinse users will be recruited for this study.

5.5. Precautions

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

5.6. Overdose

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

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

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

5.7. Rescue Therapy

No rescue therapy is required in this study.

5.8. Product Assignment

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

prior to the start of the study, using validated software.

5.8.1 Randomisation

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

Subjects will be stratified according to their maximum baseline Schiff of the two selected teeth (2/3). Randomisation numbers within each stratum will be assigned in ascending numerical order according to appearance at the study site on the day subjects are randomised. The stratification factor will give rise to two strata.

- **Stratum 1:** Subjects with maximum baseline Schiff sensitivity score of 2 for the two selected test teeth
- **Stratum 2:** Subjects with the maximum baseline Schiff sensitivity score of 3 for the two selected test teeth.

The randomisation list will be prepared using a randomisation block design with a 2:1:1 ratio. The study site will receive two versions of the randomisation schedule, each in a sealed envelope and clearly marked as either “For Dispensing” or “Emergency Use Only”.

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

The ‘Emergency Use Only’ randomisation schedule will only be removed from the sealed envelope in an emergency situation (see Section 5.8.3). This schedule will

have a randomisation number followed by the letter A, B or C. The schedule will be have a footnote with a key for A, B and C identifying the three treatments. However, to maintain the blinding of the study as far as possible, all treatment allocations for all randomisation numbers on this randomisation schedule will be masked with scratch-off panels. Only the panels required for the unblinding the particular subject should be removed.

5.8.2. Blinding

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

5.8.3. Code Breaks

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

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

5.9. Packaging and Labelling

The acclimatisation products, the study dentifrice and negative control oral rinse will be sourced from the US market. The test oral rinse and placebo oral rinse will be manufactured, filled and supplied by GSKCH.

All products, including the acclimatisation products, will be overwrapped in white vinyl to obscure any branding on the commercial packs. Each tube and bottle will have a study label affixed. Each subject will receive a sufficient number of tubes and bottles to cover usage during the treatment phase.

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

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

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

5.9.1. Accountability of Product

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

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

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

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

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

5.9.2. Storage of Product

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

6. STUDY ASSESSMENTS AND PROCEDURES

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

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

6.1. Visit 1 - Screening Visit

6.1.1 Telephone Screening

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

6.1.2. Informed Consent

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

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

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

6.1.3. Demographics

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

6.1.4. Medical History and Concomitant Medication

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

6.1.5. Oral Soft Tissue (OST) Examination

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

An OST examination will be conducted at every study 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.

6.1.6. Oral Hard Tissue (OHT) Visual Examination

A suitable qualified individual will perform an examination of the oral hard tissue to confirm that the subject has a minimum of 20 natural teeth and to evaluate dentition exclusions. The examination will be performed by direct observation.

6.1.7. Eligible Tooth Assessment

Eligible tooth assessment will include an oral hard tissue examination (visual assessment only to evaluate dentition exclusions - see Exclusion Criteria 8 and 9); erosion, abrasion and/or gingival recession; gingival index; tooth mobility and qualifying evaporative air assessment. Assessments will be carried out by the

Investigator or medically qualified designee against the inclusion/exclusion criteria and recorded in the eCRF.

6.1.7.1. Erosion, Abrasion and Recession (EAR) assessment

The presence of cervical erosion, abrasion and/or gingival recession [Addy, 2000] will be determined on the facial surfaces of individual teeth. Teeth exhibiting EAR will be assessed to ensure they do not meet any of the general dentition exclusion criteria and the specific dentition exclusion criteria for test teeth (see Exclusion Criteria 8 and 9).

6.1.7.2. Modified Gingival Index (MGI)Assessment

The MGI is a non-invasive visual evaluation of gingival health [Lobene, 1986] scored on a scale of 0-4. MGI will be assessed for the facial gingiva adjacent to the test area (exposed dentine) only of teeth exhibiting facial cervical erosion, abrasion and/or recession at the Screening visit. MGI = 0 is required for eligible teeth.

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

6.1.7.3. Tooth Mobility Assessment

The clinical mobility assessment will only be performed on teeth exhibiting facial cervical erosion, abrasion and/or recession and that have a MGI = 0. Clinical mobility will be classified in the following way (based on a modification to the Miller Index) [Laster, 1975] and the degree of mobility will be recorded. A clinical mobility of ≤1 is required for eligible teeth.

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

6.1.7.4. Qualifying Evaporative air Sensitivity

The screening dentist will assess sensitivity by a simple air blast on the facial surface of all teeth that meet the EAR, MGI and mobility criteria. This assessment is made by directing a one second application of air from a standard dental syringe perpendicular to the tooth surface approximately 1- 2 mm coronal to the free gingival margin and from a distance of approximately 1cm. Following the air blast, the dentist will ask the subject if they experienced sensitivity. In order to qualify, the subject should confirm they experienced sensitivity and a qualifying score of ≥2 will be recorded.

6.1.8. Acclimatisation Product Supervised Brushing

Subjects will apply a full brush head of the standard fluoride dentifrice, brush for one timed minute (in their usual manner) and expectorate; rinse with 10 ml of tap water for 5 seconds and expectorate; and then rinse with 10 ml of the acclimatisation oral rinse for 60 timed seconds and expectorate.

6.2. Visit 2 - Baseline Visit

6.2.1. Oral Soft Tissue (OST) Examination

Complete as described in Section 6.1.5.

6.2.2. Tactile Assessment (Yeaple probe)

Tactile assessments will be performed by a single trained examiner.

Testing shall begin at 10 g and increase by 10 g with each successive challenge until a "yes" response is recorded. The force setting which elicited the “yes” response will be repeated. If a second "yes" is not obtained, the force setting will be increased by 10 g

and continue until a force is found which elicits two consecutive "yes" responses. If no sensitivity is found below the session maximum, the tooth is disqualified from further testing. The gram setting, which elicits the two consecutive “yes” responses, will be recorded as the threshold.

At this visit (pre-treatment) the upper test limit is 20g. If no pain response is found, the threshold will be recorded as >20 g and the tooth will be disqualified from further tactile testing. Examiners discretion may be used to discontinue further tactile testing once they have determined the qualifying teeth.

The recording/calibration assistant or examiner will make adjustments and record the micro-amperage force setting and subject's responses onto the source document. The assistant will not give verbal cues to the examiner (the individual applying the probe tip to the tooth) other than when it is okay to proceed as this may bias the subject's response. For example, if the assistant feels that the subject did not give a true response, they may then elect to repeat the same force setting without telling the examiner. In this respect the examiner is also blinded, to avoid investigator bias. Since this places more responsibility on the assistant, it is imperative that the assistant be well trained in this procedure. It is also possible that the investigator may be unsure of the reliability of the subject's response. In this case, the investigator may then opt to re-probe at the same force setting. This can be indicated to the assistant by a non-verbal signal (i.e. a hand gesture).

The evaporative air stimulus (with Schiff Sensitivity Score) should follow the tactile assessment, with a minimum of five minutes in between each assessment type to allow recovery time.

6.2.2.1. Subject Response

The probe tip should be placed perpendicular to the buccal surface and moved in a slow motion while drawn across the tooth surface in order to ensure application of the stimulus across the sensitive area of the exposed dentine. After each challenge, subjects will be asked to indicate whether the sensation caused pain or discomfort. Only "yes" and "no" are acceptable answers. The examiner will tell the subject that they should indicate "yes" only if they feel PAIN or DISCOMFORT each time the probe is applied to their tooth. The subject may respond "yes" if they feel pressure, so it is important to remind them, as much as necessary, that they will feel pressure but to only respond "yes" if they feel pain or discomfort. If the subject fails to give a definite answer, the examiner should re-prompt them to provide a “yes” or “no” response. If they continue to be reluctant, their uncertainty should be indicated on the

score sheet and the next stimulus should be at the next step in the upward direction. The gram setting, which elicits the two consecutive "yes" responses, will be recorded as the threshold.

The evaporative air stimulus should follow the tactile assessment, with a minimum of five minutes in between each assessment type to allow recovery time.

6.2.2.2. Calibration of the Yeaple Probe

A digital video disc (DVD) demonstration of this procedure will be provided by GSKCH. Either of the two procedures described below are preferred; however other comparable procedures may be acceptable.

The microamp settings will vary from day to day (partly due to battery power consumption), but the difference should not be significant. Thus, previous probe settings will serve as a guide. Calibration should start at the lowest microamp setting and then increase.

1. The yeaple probe is fixed to a clamp attached to a ring stand so that the probe tip is vertical. A small paper cup attached with cotton thread is balanced over the end of the yeaple probe, without the probe tripping. The probe dial is set to the microamp setting and water is fed into the paper cup using a dropper until the probe trips. The gram setting is recorded and the yeaple probe reset to the next microamp value. The procedure is repeated until data has been collected to more than 80 grams.

2. The yeaple probe is fixed to a clamp attached to a ring stand so that the top is perpendicular to the pan of an ohaus dial-o-gram® balance or equivalent. The probe tip is positioned to just touch the pan when the balance is set at zero grams. The probe dial is set to the microamp setting and the gram setting is increased on the balance until the probe trips. The gram setting is recorded and the yeaple probe reset to the next microamp value.

The data are plotted and the points connected with line segments in order to interpolate the micro-amp values equivalent to 10, 20, 30, 40, 50, 60, 70, and 80 grams. This calibration should be repeated three times, and the average of the three used for the day's settings.

The settings will be recorded on the yeaple probe calibration record. This form must also be dated and initialed by whoever performs the calibration. For convenience a separate form should be used for each probe (record the unit's serial number on the

form). This record will serve as the guide for the force setting for that day's examinations.

6.2.3. Evaporative Air Sensitivity Assessment

This assessment will be conducted by a single examiner for all subjects at each visit by directing a maximum one second application of air from a dental air syringe to the exposed dentine surface from a distance of approximately 1 cm. The examiner should take appropriate measures to isolate the test tooth surface in order to prevent stimulus exposure to adjacent tooth or surrounding soft tissue. Response to this stimulus will be evaluated using the Schiff Sensitivity Scale.

The examiner will assess the evaporative air sensitivity of all clinically eligible teeth identified at Screening (teeth that qualified on EAR, MGI and tooth mobility criteria, and had none of the dentition exclusions), that qualified for the tactile assessment using the Schiff Sensitivity Scale. Two test teeth will be selected according to specific eligibility criteria in an individual subject.

6.2.3.1. Schiff Sensitivity Scale

This is an examiner based index [Schiff, 1994], scored immediately following administration of the evaporative air stimulus. This scale focuses on a combination of specific, observable, physical, behavioural and verbal responses from the subject as a result of the stimulation of exposed dentine, rather than solely an oral request from the subject to discontinue stimulation and may facilitate discrimination.

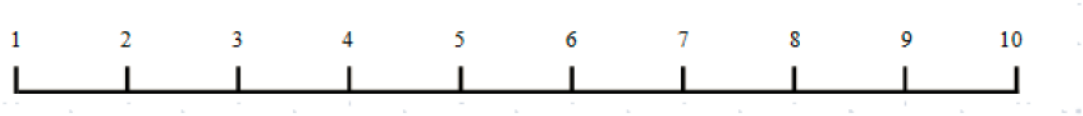
Those teeth which meet the tactile threshold inclusion criterion (tactile threshold ≤ 20g) will be assessed. The examiner will indicate the subject's response to the evaporative air stimulus, after the stimulation of each individual tooth, using the Schiff Sensitivity Scale as follows.

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

Those teeth which meet the required tactile threshold (Yeaple ≤ 20g) should then be assessed by evaporative air stimulus. When two teeth that meet the study criteria are identified, no further testing is necessary.

6.2.3.2. Visual Rating Scale (VRS)

Subjects will rate the intensity of their response to the stimulus using a VRS scale as shown below of 1 ("No Pain") to 10 ("Intense Pain"). A member of study staff will record this value in the eCRF.



No Pain Intense Pain

6.2.4. Selection of Two Test Teeth

Two test teeth will be selected by the examiner that meet the inclusion criteria.

6.2.5. Supervised Product Use

After stratification and randomisation subjects will perform a supervised brushing and rinsing. See Section 5.1 for dosing and instructions, subjects will be asked to measure out their own dose of oral rinse using the cups provided.

6.3. Visits 3, 4, 5, 7, 8 and 9

6.3.1. Supervised Product Use

See Section 5.1 for dosing and instructions, subjects will be asked to measure out their own dose of oral rinse using the cups provided.

6.4. Visits 6 and 10

6.4.1. OST Examination

Complete as described in section 6.1.5.

6.4.2. Tactile Assessment (Yeaple Probe)

Tactile assessment will be conducted as described in section 6.2.2, of the two selected test teeth only. The upper force setting will be 80g, if no sensitivity is found, the threshold will be recorded as >80g.

6.4.3. Evaporative Air Sensitivity Assessment

The evaporative air assessment should follow the tactile assessment with a minimum of 5 minutes between the last tactile assessment and the first evaporative air assessment to allow the teeth recovery time.

6.4.3.1. Schiff Sensitivity Scale

The examiner will record the subjects' response to each of the two selected test teeth immediately following administration of the evaporative air stimulus as described in section 6.2.3.

6.4.3.2. VRS

Subjects will rate the intensity of their response to the stimulus using a VRS scale as described in Section 6.2.3.2. A member of study staff will record this value in the eCRF.

6.4.4. Supervised Product Use

See Section 5.1 for dosing and instructions, subjects will be asked to measure out their own dose of oral rinse using the cups provided.

6.4.5. Study Conclusion

At Visit 10, subjects will be evaluated to determine if they completed all study procedures or if they were discontinued from the study early. If the subject discontinued at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page of the eCRF by selecting one of the options below.

1. Subject did not meet study criteria
2. Adverse Event
3. Lost to Follow Up
4. Protocol Violation
5. Withdrawal of Consent

6. Other

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

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

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of an investigational or washout product, whether or not considered related to the investigational or washout 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 an investigational or washout product.

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

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder/ condition being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition..

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

7.1.2. Serious Adverse Events

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

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

  Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in disability/incapacity**
  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Other Situations**
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or

hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:

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

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

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

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

Assessment of Causality:

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

7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

- AEs will be recorded in the AE section of the eCRF.
- Medical conditions recorded by the subject on a diary card or similar document that meet the definition of an AE must also be recorded in the AE section of the eCRF, if not previously well-characterised by the investigator in the subject's medical history.

- AEs elicited by the investigator in a standard manner at the study visits should also be recorded in the AE section of the eCRF. The investigator or designee must ask the subject the following question during each visit including any follow-up visits: ***"Have you felt unwell, experienced any symptoms or taken any medication (since your last visit) (today) (since your last dose) (since the last session)?"***
- The medically qualified investigator should review adverse events in a timely manner; this review should be documented in writing in the source document or in the eCRF.
- After the study is completed at a given site, and the site has received their study data on Compact Discs (CDs), the electronic data collection tool will be removed from the internet to prevent the entry of new data or changes to existing data.

SAE Reporting to GSKCH:

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.
It is essential to enter the following information:

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

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

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

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

Fax Serious Adverse Events to:
US: PPD
Email Serious Adverse Events to:
PPD

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

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

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

Follow-up of AEs and SAEs:

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

Regulatory and ethics reporting requirements for SAEs:

- The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.
- GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC and investigators.
- Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.

- An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the safety statement and will notify the IEC, if appropriate according to local requirements.

7.6. Definition of and Procedure for Reporting Medical Device Incidents

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

7.6.1. Definition of an Incident

Definition of an Incident:

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

7.6.2. Reporting of Incidents and Malfunctions

Incident Reporting to GSKCH:

- **All incidents must be reported to GSKCH, within 24 hours (or sooner if possible) of the investigator or designee becoming aware of the situation.**
- Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE or an SAE, the appropriate AE eCRF page or SAE form will be completed and reported as per the AE and SAE reporting sections.
- The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSKCH. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
- The completed Incident Report Form should be faxed or emailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE pages should be sent together with this report form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will remain

with the subject's records.

- The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax the Incident Report Forms to:
US: PPD

- The GSKCH Study Manager will be responsible for forwarding the Incident Report Form to the Case Management Group, Global Clinical Safety and Pharmacovigilance, the Medical Director responsible for the study and other GSKCH personnel as appropriate.

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

Reporting of Malfunctions to GSKCH:

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

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

7.6.3. Follow-up of Incidents

Follow-up of Incidents:

During the study:

- All incidents will be followed until resolution of the event, until the condition stabilises, until the condition is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

After the study:

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

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

7.7. Collection of Pregnancy Information

7.7.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:
• Pregnancy information will be collected on all pregnancies reported following administration of any investigational product (or washout product). Information on pregnancy identified during the screening phase and prior to investigational product (or washout product) administration does not need to be collected.

7.7.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:
• The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product (or washout product). The investigator will record pregnancy information on the appropriate form and submit it to the following GSKCH mailbox: PPD • Pregnancy information must be submitted within 2 weeks of learning of the subject becoming pregnant. • The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to GSKCH. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported. • While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE.

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

8. DATA MANAGEMENT

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

8.1. Source Documents/ Data

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

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

8.2. Electronic Case Report Form

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

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

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

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

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

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

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

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

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

8.3. Data Handling

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

8.3.1. Data Queries

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

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

8.4. Processing Patient Reported Outcomes

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

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

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

9.1 Sample Size Determination

A sufficient number of healthy subjects will be screened to randomise at least 100 subjects (approximately 50 to the experimental treatment, 25 to the negative control and 25 to placebo) to ensure 80 evaluable subjects complete the entire study. This will ensure approximately 40 evaluable subjects for the test treatment and 20 each for the negative control treatment and placebo.

With this 40/20/20 distribution of the subjects in the treatment arms, the study has less than 50% power to detect a mean treatment difference of 0.36 in the Schiff sensitivity score using a two-sided t-test of significance level 0.05 for the experimental product against the negative control. The standard deviation used in this calculation is 0.8; this estimate is obtained from the GSKCH study 204763. When the experimental treatment group is compared with the combined group comprising of the negative control group and the placebo group using the two-sided t-test with the same estimates of mean difference, significance level and standard deviation, the study will have 51.1% power.

9.2. General Considerations

9.2.1. Definition of Analysis Populations

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

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

The Per Protocol (PP) population will include all subjects in the ITT population for whom all efficacy assessments are not deemed to be affected by protocol violations.

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

The primary population for assessment of efficacy will be the ITT population. A PP analysis will be performed on the primary variable only if more than 10% of the subjects in the ITT population have protocol deviations deemed to affect efficacy.

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

9.2.2. Exclusion of Data from Analysis

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

- Deviation from the inclusion/exclusion criteria likely to affect efficacy.

- The use of prohibited medication likely to affect efficacy.

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

9.2.3. Criteria for Evaluation

DH measures captured in the study will be used for efficacy evaluations of the study treatments. OST abnormalities, incidents and AEs reported in the study will be used for safety evaluations of the study treatments.

9.2.4. Criteria for Assessing Efficacy

The primary treatment comparison is between the experimental mouthwash and the negative control marketed mouthwash for the change from baseline in the Schiff Sensitivity score at 8 weeks. However a statistically significant difference is not expected as the study is not powered. The magnitude of the treatment difference is more important and is expected to be in favour of the experimental mouthwash.

9.2.5. Criteria for Assessing Tolerability

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

9.2.6. Handling of Dropouts and Missing Data

Dropouts and missing data are expected to be low (only 2.3% subjects were discontinued or had missing data after randomisation in the 8 week GSKCH study 204763). A robustness analysis based on worst case imputation might be elaborated in the SAP.

9.3. Statistical Methods and Analytical Plan

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

9.3.1. Demographic and Baseline Characteristics

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

9.3.2. Primary Analysis

The change from baseline to week 8 in the Schiff Sensitivity Score is the primary efficacy variable. This will be analysed using an analysis of covariance (ANCOVA) model. The model will include treatment as a factor and baseline Schiff Sensitivity Score as a covariate.

The primary treatment comparison is between the experimental oral rinse and the marketed oral rinse for the primary efficacy variable. The adjusted mean for each treatment, and the difference between the pair of treatments together with their corresponding 95% confidence intervals and the p-value for treatment comparison, will be provided.

Assumptions of normality and homogeneity of residuals will be evaluated and if serious departures are observed, data transformations will be investigated. If suitable transformations cannot be found, non-parametric tests such as Wilcoxon Rank Sum test or the van Elteren test will be used.

9.3.3. Secondary Analysis

The change from baseline to week 8 in tactile threshold is the secondary efficacy variable. This will be analysed using an ANCOVA with treatment and baseline Schiff stratification as factors and baseline tactile threshold as a covariate.

The secondary treatment comparison is between the experimental oral rinse and the marketed oral rinse for this variable. The adjusted mean for each treatment, and the difference between the pair of treatments together with their corresponding 95% confidence intervals and the p-value for treatment comparison, will be provided.

Assumptions of normality and homogeneity of residuals will be evaluated and if serious departures are observed, data transformations will be investigated. If suitable transformations cannot be found, non-parametric tests such as Wilcoxon Rank Sum test or the van Elteren test will be used.

9.3.4. Exploratory Analyses

Treatment comparisons other than the primary and secondary treatment comparisons mentioned above for the primary efficacy variable are exploratory. These will be performed in the similar way as the primary treatment comparison.

The change from baseline to week 4 in the Schiff Sensitivity Score will be analysed using the same ANCOVA model as mentioned for the change from baseline to week 8 for this measure.

The change from baseline to week 4 in the tactile threshold will be analysed using the same ANCOVA model as mentioned for the change from baseline to week 8 for this measure.

Changes from baseline to weeks 4 and 8 in VRS will be analysed separately using the similar ANCOVA model as mentioned for the changes from baseline in tactile threshold.

Changes from baseline to weeks 4 and 8 in Schiff Sensitivity Score will further be analysed separately using the same ANCOVA model as mentioned above for this measure but by combining the marketed oral rinse group and the placebo group as one treatment group.

Similar analyses for the combined control group will also be done for the changes from baseline to weeks 4 and 8 for the tactile threshold and VRS using the same ANCOVA model mentioned above for the analysis of the secondary variable.

The adjusted mean for each treatment, and the difference between the pairs of treatments together with their corresponding 95% confidence intervals and the p-values for treatment comparisons, will be provided.

Assumptions of normality and homogeneity of residuals will be evaluated and if serious departures are observed, data transformations will be investigated. If suitable transformations cannot be found, non-parametric tests such as Wilcoxon Rank Sum test or the van Elteren test will be used.

9.3.5. Safety Analyses

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

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

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

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

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

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

- Table of treatment emergent AEs by Oral/Non-Oral and Preferred Term
- Table of treatment emergent AEs by SOC and Preferred Term
- Table of Treatment emergent treatment related AEs by Oral/Non-Oral and Preferred Term
- Table of treatment emergent treatment related AEs by SOC and Preferred Term
- Listing of all AEs (including Non-treatment emergent from All Subjects)
- Listing of serious AEs
- Listing of incidents (if there are none a null listing will be produced)

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

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials Registers

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

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

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

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

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

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, the study monitor will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

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

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

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

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

10.4. Quality Assurance

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

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

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

10.5. Conditions for Terminating the Study

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

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

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

In addition:

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

10.6. Records Retention

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

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

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

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

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

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

No study document should be destroyed without a prior written agreement between GSKCH and the investigator. The investigator must notify GSKCH of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility

or transfer of ownership of the records in the event the investigator is no longer associated with the site.

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

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

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

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

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

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12. APPENDICES

12.1. Appendix 1

Abbreviations

AE	Adverse Event
CD	Compact Disc
CRO	Contract Research Organisation
CRF	Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GSKCH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention to Treat
KOX	Potassium Oxalate
NaF	Sodium Fluoride
PII	Personally Identifiable Information
PP	Per Protocol
SAE	Serious Adverse Event
SMFP	Sodium Monofluorophosphate
SOP	Standard Operating Procedure
PRO	Patient Reported Outcome

SIGNATURE PAGE

207656 Clinical Protocol

Date	Signed By
23-May-2017 09:12:08	PPD
Justification	Approved

Date	Signed By
23-May-2017 10:13:18	PPD
Justification	Biostatistics Approval

Date	Signed By
24-May-2017 03:05:29	PPD
Justification	Approved

Date	Signed By
25-May-2017 00:11:35	PPD
Justification	Clinical Operations Approval

Date	Signed By
Justification	

Date	Signed By
Justification	