Clinical Protocol

206886

CONFIDENTIAL

SUMMARY INFORMATION

Title:	Dose Response of Three Experimental Dentifrices in Plaque Removal in a Single Brushing Model
Protocol Number:	206886
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) St Georges Avenue, Weybridge, Surrey, KT13 0DE, United Kingdom (UK) Tel: PPD
Product Name:	• 67% w/w sodium bicarbonate dentifrice (parodontax® Classic) • 1450 ppm sodium fluoride dentifrice (Macleans® Fresh Mint Toothpaste) • 20% w/w sodium bicarbonate dentifrice • 35% w/w sodium bicarbonate dentifrice • 50% w/w sodium bicarbonate dentifrice
Development Phase:	N/A

Expert Advice Outside of Normal Working Hours:	Tel: PPD

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PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

Investigator Name:	
Investigator Qualifications:	
Investigator Signature:	PPD
Date of Signature/ Agreement:	

Table of Content

SUMMARY INFORMATION 2

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE 4

Table of Content 5

PROCESS FOR AMENDING THE PROTOCOL 9

PROTOCOL AMENDMENT PAGE 10

SCHEDULE OF EVENTS 11

PROTOCOL SYNOPSIS FOR STUDY 206886 12

1. INTRODUCTION 17

2. OBJECTIVE(S) AND ENDPOINT(S) 18

3. STUDY PLAN 18

- 3.1. Study Design 18
- 3.2. Subject Restrictions 21
- 3.3. Type and Planned Number of Subjects 22
- 3.4. Study Design and Dose Justification 22

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA 24

- 4.1. Inclusion Criteria 24
- 4.2. Exclusion Criteria 25
- 4.3. Screening/ Baseline Failures 27
- 4.4. Withdrawal/ Stopping Criteria 27
- 4.5. Subject Replacement 27
- 4.6. Subject and Study Completion 28

5. PRODUCT INFORMATION 29

5.1. Study Product....29
5.2. Dose Schedule....30
5.3. Dose Modification....30
5.4. Product Compliance....30
5.5. Precautions....30
5.6. Overdose....30
5.7. Rescue Therapy....31
5.8. Product Assignment....31
5.8.1 Randomization....31
5.8.2 Blinding....31
5.8.3 Code Breaks....32
5.9. Packaging and Labelling....32
5.9.1. Accountability of Product....33
5.9.2. Storage of Product....33
6. STUDY ASSESSMENTS AND PROCEDURES....33
6.1. Visit 1 - Screening Visit....34
6.1.1 Screening....34
6.1.2. Informed Consent....34
6.1.3. Demographics....34
6.1.4. Medical History and Concomitant Medication....34
6.1.5. Oral Soft Tissue (OST) Examination....34
6.1.6. Oral Hard Tissue (OHT) Examination....35
6.2. Visit 2, 3, 4 and 5 – Treatment 1, 2, 3 and 4....35
6.2.1. Oral Soft Tissue (OST) Examination....35
6.2.2. Oral Hard Tissue (OHT) Examination....35
6.2.3. Dental Plaque Assessment (Turesky Modification of Quigley Hein Index [TPI])....36
6.2.4. Repeatability of Plaque Assessment....36
6.3. Visit 6 – Treatment Visit 5 – Last Subject Last Visit....37

6.3.1. Oral Soft Tissue (OST) Examination 37
6.3.2. Oral Hard Tissue (OHT) Examination 37
6.3.3. Dental Plaque Assessment (Turesky Modification of Quigley Hein Index) 37
6.3.4. Repeatability of Plaque Assessment 37
6.3.6. Study Conclusion 37
7. SAFETY ASSESSMENTS 37
7.1. Definitions of an Adverse Event and Serious Adverse Event 37
7.1.1. Adverse Events 37
7.1.2. Serious Adverse Events 38
7.2. Recording Adverse Events and Serious Adverse Events 40
7.3. Evaluating Adverse Events and Serious Adverse Events 40
7.4. Reporting Adverse Events and Serious Adverse Events 41
7.5. Follow-up of Adverse Events and Serious Adverse Events 43
7.6. Collection of Pregnancy Information 44
7.6.1. Time Period for Collecting of Pregnancy Information 44
7.6.2. Action to be Taken if Pregnancy Occurs 44
8. DATA MANAGEMENT 45
8.1. Source Documents/ Data 45
8.2. Electronic Case Report Form 45
8.3. Data Handling 46
8.3.1. Data Queries 46
8.4. Processing Patient Reported Outcomes 46
8.5. External Data 47
9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES 47
9.1 Sample Size Determination 47

9.2. General Considerations 48
9.2.1. Definition of Analysis Populations 48
9.2.2. Exclusion of Data from Analysis 48
9.2.3. Criteria for Evaluation 49
9.2.4. Criteria for Assessing Efficacy 49
9.2.5. Criteria for Assessing Tolerability 49
9.2.6. Handling of Dropouts and Missing Data 49
9.3. Statistical Methods and Analytical Plan 49
9.3.1. Demographic and Baseline Characteristics 49
9.3.2. Primary Analysis 49
9.3.3. Secondary Analysis 50
9.3.4. Safety Analysis 51
9.3.5. Other Analysis 51
10. STUDY GOVERNANCE CONSIDERATIONS 51
10.1. Posting of Information on Publicly Available Clinical Trials Registers 51
10.2. Regulatory and Ethical Considerations, Including the Informed Consent 51
10.3. Quality Control (Study Monitoring) 52
10.4. Quality Assurance 53
10.5. Conditions for Terminating the Study 53
10.6. Records Retention 54
10.7. Provision of Study Results to Investigators, posting of Information on Publicly Available Clinical Trials Registers and Publication 55
11. REFERENCES 56
12. APPENDICES 57
12.1. Appendix 1 - Abbreviations and Trademarks 57

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.

PROTOCOL AMENDMENT PAGE

Details of all amendments should be recorded in the table below. Affected sections should be listed in the table; the actual amendment/ change should be made in the relevant section of the main protocol.
To highlight the change, the following features will be used:
To **add** text: Use of **CAPITAL LETTERS, BOLD AND UNDERLINE**
To **delete** text: Use of Strikethrough e.g. ~~strikethrough~~

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.:	Non-Substantial/Minor ☐		Informed Consent ☐ Yes ☐ No Safety Statement ☐ Yes ☐ No CRF ☐ Yes ☐ No		Signature:
Protocol Version No.:	Substantial/ Major ☐				Date:
Amendment No.:	Non-Substantial/Minor ☐		Informed Consent ☐ Yes ☐ No Safety Statement ☐ Yes ☐ No CRF ☐ Yes ☐ No		Signature:
Protocol Version No.:	Substantial/ Major ☐				Date:

SCHEDULE OF EVENTS

Activity	Visit 1 Screening		Visit 2 Treatment Period 1		Visit 3 Treatment Period 2		Visit 4 Treatment Period 3		Visit 5 Treatment Period 4		Visit 6 Treatment Period 5
Informed Consent	X										
Demographics & Medical History	X										
Current/concomitant medication	X		X		X		X		X		X
Oral soft tissue examination	X		X		X		X		X		X
Oral hard tissue examination	X										
Plaque disclosure	X										
Plaque assessment	X										
Repeatability of plaque assessment in selection of subjects	X		X		X		X		X		X
Inclusion/Exclusion criteria	X[1]		X[1]								
Dispense wash-out toothpaste, toothbrush, countdown timer and diary card with verbal instructions	X										
Return wash-out toothpaste, toothbrush and diary card			X		X		X		X		X
Re-dispense wash-out toothpaste, toothbrush and diary card			X		X		X		X		
Pre-brushing plaque disclosure			X		X		X		X		X
Pre-brushing plaque assessment			X		X		X		X		X
Randomisation			X								
Supervised brushing with assigned toothpaste			X		X		X		X		X
Post brushing plaque disclosure			X		X		X		X		X
Post-brushing plaque assessment[2]			X		X		X		X		X
Brushing with washout toothpaste to remove stain from disclosing dye	X		X		X		X		X		X
Compliance check			X		X		X		X		X
Subject Adherence/Eligibility check			X		X		X		X		X
Adverse events	X		X		X		X		X		X
Study Conclusion											X

7 to 28 days wash-in | 4 to 6 days washout | 4 to 6 days washout | 4 to 6 days washout | 4 to 6 days washout

[1] Plaque (inclusion criteria 4 C) will be assessed at Visit 1 and Visit 2; use of antibiotics and Chlorhexidine mouthwashes (exclusion criteria 7 A and 8 K) at Visit 2 to determine eligibility to continue.

PROTOCOL SYNOPSIS FOR STUDY 206886

Brief Summary

This will be a single centre, , controlled, examiner blind, five treatment, five period, crossover design study in healthy volunteers. This study will evaluate the dose response of three experimental toothpastes containing 20%, 35% and 50% w/w sodium bicarbonate to remove plaque after a single brushing, compared to a positive control (67% w/w sodium bicarbonate) and negative control (0% w/w sodium bicarbonate) dentifrice.

This clinical study will be conducted at proDERM Institute, Germany and funded by GlaxoSmithKline Consumer Healthcare (GSK CH).

Objectives and Endpoints

Primary	**Endpoint**
• To evaluate and compare the plaque removal efficacy, as measured by Turesky modification of Quigley Hein Plaque Index (TPI), of 67% w/w sodium bicarbonate, versus a 0% sodium bicarbonate toothpaste.	• Change from Pre-brushing to Post-brushing TPI
Secondary	**Endpoint**
• To evaluate and compare the plaque removal efficacy, as measured by TPI, of three toothpastes containing 20%, 35% and 50% w/w sodium bicarbonate, versus a 0% sodium bicarbonate toothpaste.	• Change from Pre-brushing to Post-brushing TPI
• To evaluate and compare the plaque removal efficacy, as measured by TPI, of three toothpastes containing 20%, 35% and 50% w/w sodium bicarbonate, versus a 67% sodium bicarbonate toothpaste.	• Change from Pre-brushing to Post-brushing TPI

Study Design

Overall Design

This will be a single centre, , controlled, examiner blind, five treatment, five period, crossover design study in healthy volunteers. At the screening visit, following provision of written informed consent, all subjects will undergo an oral soft tissue (OST) examination and oral hard tissue (OHT) examination. Eligible subjects will be provided with a standard wash-out toothpaste and toothbrush to use at home during the study; and for at least 7 days (maximum 28 days) prior to the first treatment visit (Visit 2).

For each treatment visit, subjects must abstain from oral hygiene for a period of 22 - 30 hours, immediately preceding the pre-brushing dental plaque evaluation.

At Visit 2, all the subjects will undergo an OST examination followed by disclosing and a pre-brushing dental plaque assessment (TPI). Subjects meeting the entry criteria will be to one of the five study treatments. Subjects will then perform a supervised brushing as per directions with the assigned test product. This will be followed by re-disclosing and a post-brushing plaque assessment. Subjects will brush with the washout paste following the post brushing plaque assessments to remove stain from the disclosing dye.

A 4 – 6 days washout period will follow each treatment period during which subjects will brush with the standard washout toothpaste. Subjects will complete five treatment visits and will brush once with each of the five test toothpastes throughout the course of the study.

At Visits 3, 4, 5 and 6, subjects will undergo the same assessments as performed at Visit 2.

At Visits 1, 2, 3, 4, 5 and 6, repeatability data will be generated for plaque assessment from replicate examinations on the same subject. If deemed necessary by the examiner, plaque may be re-disclosed if the dye has faded. Depending on subject visit scheduling, every effort will be made to complete repeatability examination for two subjects, that is, one in the morning and one in the afternoon on each assessment day. Repeatability examinations will be separated by a minimum of 10 minutes and, where possible, separated by another subject.

Type and Planned Number of Subjects

Sufficient healthy subjects will be screened by the study site so that a maximum of 56 subjects who fulfill all the entry criteria will be randomized, which should ensure that at least 50 evaluable subjects complete all study visits (thus allowing for at most a 10% drop-out).

With 50 subjects completing all study visits, the study has 90% power to detect a treatment difference of 0.15 in plaque index in a paired t-test of significance level 0.05. The standard deviation of difference (between treatments) is 0.32 as reviewed from the results of RH01455. As this is an exploratory study, multiplicity adjustment will not be applied.

Diagnosis and Main Criteria for Inclusion

Healthy subjects aged between 18 years and 65 years, having a minimum of 20 permanent gradable teeth. Subjects must have a mean Turesky plaque score of ≥ 2.00 at Visit 1 plaque assessment and Visit 2 pre-brushing plaque assessment.

Product Information

	Test Product 1	Test Product 2	Test Product 3	Reference product (Positive Control)	Reference Product (Negative Control)
Product Name	Experimental Dentifrice containing 20% w/w sodium bicarbonate	Experimental Dentifrice containing 35% w/w sodium bicarbonate	Experimental Dentifrice containing 50% w/w sodium bicarbonate	Dentifrice containing 67% w/w sodium bicarbonate (German marketed Parodontax Classic (non-fluoride) Toothpaste)	Dentifrice containing 0% w/w sodium bicarbonate (UK marketed Macleans Fresh Mint Toothpaste – 1450 ppm Fluoride)
Product Formulation Code (MFC)	CCI [redacted]	CCI [redacted]	CCI [redacted]	Commercially available	Commercially available
Dose	Single supervised use of a full brush head of toothpaste				
Route of Administration	Oral/ Topical	Oral/ Topical	Oral/ Topical	Oral/ Topical	Oral/ Topical
Dosing Instructions	***Supervised use:*** Subjects will apply a full ribbon of dentifrice to the study toothbrush.				

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

Name of Item	Purpose
Macleans® Fresh Mint Toothpaste (UK)	Wash-in and wash-out Toothpaste
Aquafresh® Clean Control Toothbrush (UK)	For toothpaste application
Countdown Timer	To time duration of brushing
Disclosing Solution	To disclose dental plaque for Plaque assessment
Dosing Cups	For dosing the disclosing solution

Statistical Methods

The change from pre-brushing Turesky modification of the Quigley Hein Index (post-brushing - pre-brushing) will be analysed using mixed effect Analysis of Covariance (ANCOVA). The ANCOVA model will include treatment group, study period as fixed effects, subject as a random effect and two baseline terms as covariates; (i) the subject-level baseline score calculated as the mean pre-brushing score across all periods within a subject, and (ii) the period level baseline minus the subject-level baseline. P-values for treatment comparisons, adjusted means of all treatments and treatment differences and their 95%CIs will be provided.

Only if the primary objective is met (comparison of 67% w/w sodium bicarbonate, versus a 0% sodium bicarbonate is significant), will the remaining secondary analyses be fully conducted. Otherwise no P-values will be provided for secondary comparisons. Only the estimations of treatment differences and confidence intervals will be provided.

To assess the dose-response relationship, linear and quadratic contrasts of treatment effects (in the above ANCOVA) will be tested for trends. When a trend is significant, a mixed effect regression (linear, quadratic etc) will be run to provide a dose-response curve.

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1. INTRODUCTION

Dental plaque is a soft sticky biofilm that forms on the surface of teeth. It is a film of salivary mucoproteins which is colonised by several different kinds of bacteria. Dental plaque begins forming on teeth just a few minutes after brushing. If not removed, plaque can cause dental caries and periodontal disease, such as gingivitis and periodontitis. In its earliest stages, periodontal disease begins as an inflammation of the gums (gingivitis). If left untreated this can progress to periodontitis, a serious form of periodontal gum disease, which is one of the major causes of tooth loss (Laudenbach and Simon., 2014; Petersen *et al.,* 2004).

Good oral hygiene which includes regular tooth brushing with a toothpaste and cleaning between teeth (e.g. by flossing) can affect the formation and control the build-up of plaque and as a result prevent gum disease.

Various levels of sodium bicarbonate have been demonstrated to be effective at plaque removal including 67%, 62 % and 45% sodium bicarbonate toothpastes; however the relative performance of lower levels of sodium bicarbonate in a toothpaste formulation compared to 67% sodium bicarbonate toothpaste has not been elucidated. Sodium bicarbonate can negatively impact on the desired organoleptics of the toothpaste, and therefore to maximise consumer acceptance, a lower level of sodium bicarbonate in the formulation is desired.

The mode of action of sodium bicarbonate on dental plaque and thus gingival health and sodium bicarbonate has been shown not to have significant biocidal activity. It is proposed that large crystals of sodium bicarbonate may facilitate physical disruption of plaque from the tooth surface, and that sodium bicarbonate may enhance plaque biofilm dispersion, contributing to more effective cleaning during tooth brushing (Pratten *et al.*, 2015). The removal of plaque by sodium bicarbonate toothpastes has been demonstrated clinically by GSKCH and others (Mankodi *et al.*, 1998; Putt *et al.*, 2008), and the effectiveness of 67% sodium bicarbonate toothpastes on gum health outcomes has been recently confirmed (RH02433, RH02434).

The aim of this study is to explore the potential plaque removal efficacy of sodium bicarbonate toothpastes at levels below 67%.

2. OBJECTIVE(S) AND ENDPOINT(S)

Primary	Endpoint
• To evaluate and compare the plaque removal efficacy, as measured by Turesky modification of Quigley Hein Plaque Index (TPI), of 67% w/w sodium bicarbonate, versus a 0% sodium bicarbonate toothpaste.	• Change from Pre-brushing to Post-brushing TPI
Secondary	**Endpoint**
• To evaluate and compare the plaque removal efficacy, as measured by TPI, of three toothpastes containing 20%, 35% and 50% w/w sodium bicarbonate, versus a 0% sodium bicarbonate toothpaste.	• Change from Pre-brushing to Post-brushing TPI
• To evaluate and compare the plaque removal efficacy, as measured by TPI, of three toothpastes containing 20%, 35% and 50% w/w sodium bicarbonate, versus a 67% sodium bicarbonate toothpaste.	• Change from Pre-brushing to Post-brushing TPI

3. STUDY PLAN

3.1. Study Design

Overall Design
This will be a single centre, , controlled, examiner blind, five treatment, five period, crossover design study in healthy volunteers. At the screening visit, following provision of written informed consent, all subjects will undergo an oral soft tissue (OST) examination and oral hard tissue (OHT) examination. Eligible subjects will be provided with a standard wash-out toothpaste and toothbrush to use at home during the study; and for at least 7 days (maximum 28 days) prior to the first treatment visit (Visit 2).

For each treatment visit, subjects must abstain from oral hygiene for a period of 22 - 30 hours, immediately preceding the pre-brushing dental plaque evaluation.

At Visit 2, all the subjects will undergo an OST examination followed by disclosing and a pre-brushing dental plaque assessment (TPI). Subjects meeting the entry criteria will be to one of the five study treatments. Subjects will then perform a supervised brushing as per directions with the assigned test product. This will be followed by re-disclosing and a post-brushing plaque assessment. Subjects will brush with the washout paste following the post brushing plaque assessments to remove stain from the disclosing dye.

A 4 – 6 days washout period will follow each treatment period during which subjects will brush with the standard washout toothpaste. Subjects will complete five treatment visits and will brush once with each of the five test toothpastes throughout the course of the study.

At Visits 3, 4, 5 and 6, subjects will undergo the same assessments as performed at Visit 2.

At Visits 1, 2, 3, 4, 5 and 6, repeatability data will be generated for plaque assessment from replicate examinations on the same subject. If deemed necessary by the examiner, plaque may be re-disclosed if the dye has faded. Depending on subject visit scheduling, every effort will be made to complete repeatability examination for two subjects, that is, one in the morning and one in the afternoon on each assessment day. Repeatability examinations will be separated by a minimum of 10 minutes and, where possible, separated by another subject.

Visit 1 - Screening Visit

The following assessments will be conducted:

- Written informed consent
- Demographics
- Medical history
- Current and concomitant medications
- Oral Soft Tissue Examination (OST)
- Oral Hard Tissue Examination (OHT)
- Plaque disclosure
- Plaque assessment
- Plaque assessment repeatability- randomly for selection of subjects
- Inclusion/ Exclusion Criteria
- Subject Eligibility
- Dispense washout toothpaste, toothbrush, countdown timer and diary card

- Brushing with washout toothpaste to remove stain from disclosing dye
- Adverse events

Wash-in Period: 7 to 28 days

Visit 2 - Treatment 1

The following assessments will be conducted:

- Current and concomitant medications
- Return washout toothpaste, toothbrush and diary card
- Washout toothpaste compliance check (checking Diary and toothpaste tube)
- OST Examination
- Adverse events
- Pre-brushing plaque disclosure
- Pre-brushing plaque assessment
- Plaque assessment repeatability- randomly for a selection of 2 subjects in a day
- Inclusion Criteria 4 C; and Exclusion criteria 7 A and 8 K
- Subject eligibility/ continuance
- Randomisation
- Supervised brushing with assigned treatment toothpaste
- Post-brushing plaque disclosure
- Post-brushing plaque assessment
- Plaque assessment repeatability- randomly for a selection of 2 subjects in a day
- Brushing with washout toothpaste to remove stain from disclosing dye
- Re-dispense washout toothpaste, toothbrush and diary card

Wash-out Period: 4 to 6 days

Visit 3, 4 and 5 – Treatment 2, 3 and 4

The following assessments will be conducted:

- Current and concomitant medications
- Return washout toothpaste, toothbrush and diary card
- Washout toothpaste compliance check (checking Diary and toothpaste tube)
- OST Examination
- Adverse events
- Subject continuance
- Pre-brushing plaque disclosure
- Pre-brushing plaque assessment
- Plaque assessment repeatability- randomly for a selection of 2 subjects in a day
- Supervised brushing with assigned toothpaste

- Post-brushing plaque disclosure
- Post-brushing plaque assessment
- Plaque assessment repeatability- randomly for a selection of 2 subjects in a day
- Brushing with washout toothpaste to remove stain from disclosing dye
- Re-dispense washout toothpaste, toothbrush and diary card

Wash-out Period: 4 to 6 days between treatments

Visit 6 – Treatment 5

The following assessments will be conducted:

- Current and concomitant medications
- Return washout toothpaste, toothbrush and diary card
- Washout toothpaste compliance check (checking Diary and toothpaste tube)
- OST Examination
- Adverse events
- Subject continuance
- Pre-brushing plaque disclosure
- Pre-brushing plaque assessment
- Plaque assessment repeatability- randomly for a selection of 2 subjects in a day
- Supervised brushing with assigned treatment toothpaste
- Post-brushing plaque disclosure
- Post-brushing plaque assessment
- Plaque assessment repeatability- randomly for a selection of 2 subjects in a day
- Brushing with washout toothpaste to remove stain from disclosing dye
- Study Conclusion

3.2. Subject Restrictions

Lifestyle/ Dietary

During the entire study (Screening – LSLV):

- Subjects will be requested not to have any elective dental procedures including teeth professionally cleaned other than those performed within the study (excluding emergency dental treatment).
- Subjects should only use the dentifrice and toothbrushes provided and must abstain from use of all other oral hygiene products including mouthwash from Visit 1.
- Subjects should abstain from chewing gum and consuming confectionery containing xylitol (e.g. mints).

• Subjects should abstain from interproximal cleaning (use of dental floss, waterpick and toothpicks). Use of toothpicks is permitted to remove impacted food.
At least 4 hours prior to Visits 1, 2, 3, 4, 5 and 6: • Subjects must abstain from eating for at least 4 hours and from drinking for at least 1 hour prior to all clinical assessments and until all assessments are complete.
At least 22 – 30 hours preceding Visits 1, 2, 3, 4, 5 and 6: • Subjects must abstain from **all** oral hygiene procedures including use of dental floss, waterpick and toothpicks. Use of toothpicks is permitted to remove impacted food only.
Medications and Treatments
During the entire study (Screening – LSLV): • If current/ concomitant medications and/ or treatments are used during the study, their identity, as well as their dosage and frequency, start and stop dates must be reported to the Investigator/ Examiner and recorded in the CRF. Should a randomized subject embark on a course of treatment during the study which included a prohibited medication (antibiotic treatment or any other treatment that [in the opinion of the investigator] would interfere with the study outcomes), the subject may be withdrawn. • Subjects who enter the study will be requested to delay having any non - emergency, elective dental treatment until after study completion (including dental prophylaxis).

3.3. Type and Planned Number of Subjects

Sufficient healthy subjects will be screened by the study site so that a maximum of 56 subjects who fulfill all the entry criteria will be randomized, which should ensure that at least 50 evaluable subjects complete all study visits (thus allowing for at most a 10% drop-out).

3.4. Study Design and Dose Justification

Sodium bicarbonate based toothpastes have previously shown superior cleaning efficacy against 'everyday' marketed toothpastes. Mankodi *et al* [1998] showed that a toothpaste containing 65% sodium bicarbonate removed significantly more plaque during a one minute single timed brushing than two conventional sodium bicarbonate -free toothpastes. More recently, Putt *et al* [2008] has also shown that sodium bicarbonate toothpastes ranging from 20 - 65% exerted a superior and significant cleaning effect following a single timed brushing compared to both sodium

fluoride/silica and triclosan/copolymer based toothpastes. Both of the aforementioned papers identified a potential dose dependent relationship whereby there appears to be a positive relationship between sodium bicarbonate concentration and enhanced plaque removal. In the current study a dose response of sodium bicarbonate toothpastes ranging from 20% to 50% will be tested against two marketed toothpastes (Positive control: 67% sodium bicarbonate toothpaste and Negative control: 0% sodium bicarbonate toothpaste) using a one minute single timed brushing model.

The design of the current study is based on the model previously used by Putt *et al* [2008] and parallels used in other GSK studies [E5931015, E5930966, RH01455] evaluating different commercially available formulations.

The cross-over design will help minimise inter-subject variability and allow greater sensitivity to analyze treatment differences. The current study will be performed at a single clinical site by a single dental examiner, thus eliminating the possibility of inter-examiner variability which will be confirmed by repeating assessments on the same subjects and formally tested. This allows for supervised control of brushing quantities and times, and clear identification of any differences in plaque removal by the different treatments.

Each subject will be randomly allocated to the order in which they receive the five study treatments in order to avoid any potential bias that may occur across multiple treatments. Additionally, the dental examiner study will remain blinded to the treatment regime to ensure there is no bias in the assessments.

The Turesky modification of the Quigley-Hein plaque index is recognised as industry standard for assessing plaque levels and will be performed by a trained examiner to accurately measure the level of plaque removed by brushing, both across different areas of the tooth, and on teeth in different areas of the mouth.

A 7 to 28 day wash-in period will be utilised between screening and the first of the five treatment visits. A wash-in is typically required in order to standardise oral hygiene procedures and products prior to treatment and to allow sufficient time to have passed since the subject last used any oral hygiene products that could interfere with the outcome of the study (e.g. triclosan containing toothpastes). The study will also employ a 4 to 7 day wash-out period between the treatments which is considered sufficient to avoid any carry over effects from the previous treatment.

The study will be blinded with respect to the dental examiner to ensure there is no bias in the assessments.

Subjects will brush their teeth under supervision with one full head of toothpaste (in line with the label instruction for the toothpaste). The full head of toothpaste would weigh approximately 1.5 grams which is the normal dose for a toothpaste.

The age range of the subjects in the clinical study is 18 – 65 as the target for this study is the adult population.

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.

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

4.1. Inclusion Criteria

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

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

2. AGE
Aged between 18- 65 years

3. GENERAL HEALTH
Good general health with (in the opinion of the investigator) no clinically significant and relevant abnormalities of medical history or oral/dental examination. 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
A. Good dental health based on medical history and oral soft tissue examination at screening. B. A minimum of 20 permanent gradable teeth. (Gradable teeth are those where restorative materials cover less than 25% of the tooth surface to be graded). C. Mean Turesky plaque score of ≥ 2.00 at Visit 1 and Visit 2 (pre-brushing plaque assessment).

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

4.2. Exclusion Criteria

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

1. PREGNANCY
Women who are known to be pregnant or who are intending to become pregnant over the duration of the study.

2. BREAST-FEEDING
Women who are 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/ EXPERMENTAL PRODUCT
A. Participation in another clinical study: cosmetic studies within 14 days of the screening visit 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
A. An employee of the sponsor or the study site or members of their immediate family. B. An employee of any toothpaste manufacturer or their immediate family.

7. MEDICAL HISTORY/ CURRENT MEDICATIONS
A. Antibiotic treatment within 14 days prior to Visit 2 or throughout the study. B. Any other treatment that would interfere with the study outcomes, at the discretion of the examiner or investigator.

8. DENTAL CONDITIONS
A. High levels of extrinsic stain or calculus deposits which might interfere with plaque assessments at the discretion of the investigator. B. Dental conditions / disease requiring immediate treatment. C. Pre-existing sensitivity to oral care products. D. Severe gingivitis that may, in the opinion of the investigator, compromise the study or the oral health of the subjects if they participate in the study. E. Presence of orthodontic bands or appliances, extensive crowns, partial dentures, or fixed retainers on the maxillary or mandibular teeth. F. Active carious lesions needing immediate care. G. Oral lesions/manifestations that would impact on the outcome of the study. H. Presence of oral or peri-oral ulceration including herpetic lesions at the time of screening. I. Have current active caries or periodontitis that may, in the opinion of the investigator, compromise the study or the oral health of the subjects if they participate in the study. J. Restorations in a poor state of repair that may, in the opinion of the investigator, compromise the study or the oral health of the subjects if they participate in the study. K. Use of a chlorhexidine mouthwash within 14 days of Visit 2 or through the study. L. Current use of Listerine, Corsodyl or any antimicrobial mouth rinse or throughout the study.

9. TOBACCO USERS AND E-CIGARETTE USERS
A. Subject unwilling to abstain from using chewing tobacco (with or without tobacco). B. Subject unwilling to abstain from smoking tobacco or E-cigarettes for 4 hours prior to all visits and until all dental assessments are completed at each visit.

4.3. Screening/ Baseline Failures

Screen failures are defined as subjects who consent to participate in the study but are never subsequently . In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events. 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 Adverse Event (AE) or an abnormal laboratory test result, the principal specific event or test will be recorded on the electronic case report form (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.

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".

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 1	Test Product 2	Test Product 3	Reference product (Positive Control)	Reference Product (Negative Control)
Product Name	Experimental Dentifrice containing 20% w/w sodium bicarbonate	Experimental Dentifrice containing 35% w/w sodium bicarbonate	Experimental Dentifrice containing 50% w/w sodium bicarbonate	Dentifrice containing 67% w/w sodium bicarbonate (German marketed Parodontax Classic (non-fluoride) Toothpaste)	Dentifrice containing 0% w/w sodium bicarbonate (UK marketed Macleans Fresh Mint Toothpaste – 1450 ppm Fluoride)
Product Formulation Code (MFC)	CCI	CCI	CCI	Commercially available	Commercially available
Dose	Single supervised use of a full brush head of toothpaste				
Route of Administration	Oral/ Topical	Oral/ Topical	Oral/ Topical	Oral/ Topical	Oral/ Topical
Dosing Instructions	***Supervised use:*** Subjects will apply a full ribbon of dentifrice to the study toothbrush.				

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

Name of Item	Purpose
Macleans® Fresh Mint Toothpaste (UK)	Wash-in and wash-out Toothpaste
Aquafresh® Clean Control Toothbrush (UK)	For toothpaste application
Countdown Timer	To time duration of brushing
Disclosing Solution	To disclose dental plaque for Plaque assessment
Dosing Cups	For dosing the disclosing solution

5.2. Dose Schedule

Subjects will use each treatment once. Subjects will brush their teeth once for one timed minute supervised at site.

5.3. Dose Modification

No dose modification is permitted in this study.

5.4. Product Compliance

There is no treatment compliance measure as subjects will be required to use the product on site under staff supervision. However, subjects will record each wash-in and wash-out toothpaste use in the diary provided for compliance check for use at home. Completed diaries and the toothpaste tubes will be reviewed at Visits 2, 3, 4, 5 and 6 at the study site, and any changes to medical/dental history and concomitant medications will be confirmed. Any missed and additional brushings will be recorded in the CRF.

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.

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® Aquafresh is a registered trademark of GlaxoSmithKline Consumer Healthcare, LP.

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 randomization schedule generated by the Biostatistics Department, GSKCH, prior to the start of the study, using validated internal software.

5.8.1 Randomization

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 randomized according to the randomization schedule. Randomization numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible.

The randomisation schedule will be provided under the guidance of the Biostatistics Department, GSKCH.

5.8.2 Blinding

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 will not be permitted in the room where the test products are stored or dispensed. The product dispensing area will be separate from the subjects' examination area. The dispensing staff will not be involved in any study efficacy assessments.

The study site will receive two versions of the randomisation schedule, each in a sealed envelope and clearly marked as "For Dispensing" or "Emergency Use Only".

The dispensing schedule will be used by site for subject randomisation purposes and will not identify the treatments by name (treatments will be identified as A, B etc. corresponding to the labelled study supplies). The other randomisation schedule will only be removed from the sealed envelope in an emergency situation. This schedule however will be footnoted with a key identifying the content of treatments A, B etc. 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 subject unblinding should be removed.

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 study blind must be returned to GSKCH at the end of the study.

5.9. Packaging and Labelling

Packaging and labeling of all test products will be carried out according to ICH GCP guidelines and will be the responsibility of the Clinical Supplies Department, GSKCH.

The wash-out dentifrice will be supplied in its commercial packaging with a study label affixed to each sample. Sufficient product will be provided to last for the duration of all the washout periods.

All treatment products will be supplied in over-wrapped tubes with a study label affixed to each sample in order to mask their identity as much as possible.

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 use as required throughout the course of the study.

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.

Each study label will contain, but not be limited to, protocol number, product code letter (for treatment products only), directions for storage, emergency contact telephone number and "For Clinical Trial Use Only".

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.

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 date(s) and quantity of the study product dispensed to the subject.
- The date(s) 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. 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 Screening

Prior to the screening visit, telephone screening of interested subjects will be conducted. 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 or be provided with a copy of the signed and dated amended consent form. The date of consent will be recorded on the CRF.

6.1.3. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, gender and race. In accordance with FDA guidelines (Guidance for Industry: collection of Race and Ethnicity Data in Clinical Trials, 2005, FDA) the ethnicity of subjects will also be captured.

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 medical or surgical history (within the last year), including allergies or drug sensitivity, will be recorded on the CRF. 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 dental examiner or clinically qualified designee for all subjects for the duration of the study. 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, 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. Any post-treatment soft tissue abnormality, or worsening of a pre-existing condition, observed by the examiner or reported by the subject will be recorded on the CRF. Any abnormalities, or worsening of pre-existing conditions, that occur from Visit 2 onwards will be recorded as AEs.

6.1.6. Oral Hard Tissue (OHT) Examination

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee for all subjects. Subjects with evidence of gross intra-oral neglect or the need for extensive dental therapy will be excluded.
The OHT examination will assess grossly carious lesions or signs of erosive wear, enamel irregularities, tooth fracture, gross decay, decalcification and faulty restorations.

Observations will be listed as "Absent" or "Present" and conditions noted as present will be described. Examination findings will be described and documented in the eCRF. Any observation that changes from "Absent" to "Present" from the screening assessment must be recorded as an AE.

6.2. Visit 2, 3, 4 and 5 – Treatment 1, 2, 3 and 4

6.2.1. Oral Soft Tissue (OST) Examination

See Section 6.1.5.

6.2.2. Oral Hard Tissue (OHT) Examination

See Section 6.1.6.

6.2.3. Dental Plaque Assessment (Turesky Modification of Quigley Hein Index [TPI])

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

The lips of the subjects will first be applied with Vaseline (supplied by the site). Then plaque will be disclosed using 5 millilitre (ML) of the dye solution (Gum Red Cote®) according to instructions. Subjects will rinse for 30 seconds with the dye and expectorate and then rinse with 10 ml of water for 10 seconds and expectorate again. Plaque will be assessed with each tooth being divided into 6 areas including the mesiofacial, facial, distofacial, mesiolingual, lingual and distolingual surfaces.

Disclosed plaque will be scored as follows for each tooth surface separately and recorded in the CRF:

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

Clinical assessments should be performed using a standard dental light to illuminate the oral cavity. Compressed air, water and mirrors should be available to the dental examiner.

6.2.4. Repeatability of Plaque Assessment

The repeatability of the examiner in conducting the plaque assessments either pre or post-brushing during the study will be performed. Depending on subject visit scheduling, every effort will be made to complete repeatability examination for two subjects, that is, one in the morning and one in the afternoon on each assessment day. Repeatability examinations will be separated by a minimum of 10 minutes and, where possible, separated by another subject. Every effort should be made to ensure the examiner does not refer to the results of the assessment completed prior to the repeat assessment. A weighted kappa coefficient will be calculated.

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6.3. Visit 6 – Treatment Visit 5 – Last Subject Last Visit

6.3.1. Oral Soft Tissue (OST) Examination

See Section 6.1.5.

6.3.2. Oral Hard Tissue (OHT) Examination

See Section 6.1.6.

6.3.3. Dental Plaque Assessment (Turesky Modification of Quigley Hein Index)

See Section 6.2.3.

6.3.4. Repeatability of Plaque Assessment

See Section 6.2.4.

6.3.6. Study Conclusion

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

1. Subject did not meet study criteria
2. Adverse Event
3. 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:

A. Results in death

B. 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.

C. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

D. 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.

E. Is a congenital anomaly/birth defect

F. 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 hospitalization 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 hospitalization 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 CRF.
- 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 of 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 wash-in product at Visit 1 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 Investigator Brochure (IB) and/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 CRF 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 CRF.
- 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 CRF, 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 CRF. 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 CRF.
- 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.

Email Serious Adverse Events to: PPD
Fax Serious Adverse Events to: UK: 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 Investigator Brochure (or safety statement) and will notify the IEC, if appropriate according to local requirements.

7.6. Collection of Pregnancy Information

7.6.1. 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.

7.6.2. 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 GSKCH 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 CRF."

8. DATA MANAGEMENT

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

8.1. Source Documents/ Data

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, 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 CRF should be specified in the Source Document Designation Form. In some cases the CRF 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, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with 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 CRF 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 CRFs and transmitted electronically to GSKCH in a validated (21 CFR Part 11 compliant) web-based electronic data capture system (InForm™).

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

The CRFs (including queries, query responses and audit trails) will be retained by GSKCH. Site data archived compact discs (CD(s)) prepared by a third party will be sent to the investigator to maintain as the investigator copy following the decommissioning of the study.

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 CRF data, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (Adverse Events and Drugs) are reported appropriately.

The study monitor at the study site will review the CRFs in accordance with the monitoring plan, and any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. Monitor can also run reports and listings on the CRFs, 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. The site staff should ensure that any potential AEs recorded in the diary cards should be reported in the DMS. In instances where the PRO data is entered into the DMS by GSKCH, the

PROs will be anonymised, and forwarded to GSKCH for entry, as agreed and documented ahead of the study starting. PROs that are source will be retained by the investigator and certified copies will be sent to GSKCH.

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

8.5. External Data

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

An agreed upon quality control process is performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSKCH via secured web portal or CD/DVD via mail carrier with tracking capabilities.

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Sample Size Determination

Sufficient healthy subjects will be screened by the study site so that a maximum of 56 subjects who fulfill all the entry criteria will be randomized, which should ensure that at least 50 evaluable subjects complete all study visits (thus allowing for at most a 10% drop-out).

With 50 subjects completing all study visits, the study has 90% power to detect a treatment difference of 0.15 in plaque index in a paired t-test of significance level 0.05. The standard deviation of difference (between treatments) is 0.32 as reviewed from the results of RH01455. As this is an exploratory study, multiplicity adjustment (67%, 50%, 35%, 20% w/w sodium bicarbonate dentifrices vs. 0% w/w sodium bicarbonate dentifrice) will not be applied.

9.2. General Considerations

9.2.1. Definition of Analysis Populations

Safety population is defined as all subjects who are randomized and have received at least one dose of study products.

The intent to treat (ITT) population is defined as those subjects who are randomized, receive at least one dose of study product and have at least one post-baseline efficacy measurement.

The Per Protocol (PP) population will be a subset of the ITT population. Subjects with a protocol violation that is deemed to affect efficacy for all efficacy assessments will be excluded from the PP population. Subjects with a protocol violation that is deemed to affect efficacy for only some (but not all) of the efficacy assessments will be part of the PP population, but their data will be excluded from the assessment at which the protocol violation occurred. Efficacy analysis will be based on ITT population. A PP analysis will be performed only if 10% or more ITT subjects are excluded from PP population.

The repeatability population is defined as all subjects who have a repeat clinical assessment (TPI) at any visit.

9.2.2. Exclusion of Data from Analysis

Any of the following will be considered a protocol violation which will warrant exclusion from efficacy analysis:

- Violation of inclusion or exclusion criteria that are deemed to affect efficacy.
- Medical history which is deemed to affect efficacy.
- Use of prohibited treatment or medication before or during the study, which is felt to affect the assessment of efficacy. The assessments affected will be determined prior to database lock.
- Not receiving randomized treatment.
- Noncompliance on treatment washout

Further data listings will be included in the review of protocol violations but will be reviewed on a case-by-case basis to determine whether the data should be excluded from a PP. Full data listings will be provided in statistical analysis plan (SAP).

Protocol violations which warrant exclusion from efficacy analysis will be identified between the statistician and medical director or designee, ahead of database lock and breaking the study blind.

9.2.3. Criteria for Evaluation

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

9.2.4. Criteria for Assessing Efficacy

The success criterion of the study is to observe statistically significant reduction in TPI score in 67% w/w sodium bicarbonate dentifrice group compared to 0% sodium bicarbonate dentifrice group after a single brushing.

9.2.5. Criteria for Assessing Tolerability

No specific safety criteria are planned for this study. Adverse Events and OST abnormalities will be assessed for safety and tolerability.

9.2.6. Handling of Dropouts and Missing Data

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

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 finalization 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

Primary efficacy endpoint will be the TPI score change from pre-brushing after a single brushing treatment. TPI score will be calculated as the average index over all tooth sites. Mixed effect ANCOVA model will be applied with treatment, study

period as fixed effects, subject as a random effect and two baseline terms as covariates; (i) the subject-level baseline score calculated as the mean pre-brushing score across all periods within a subject, and (ii) the period level baseline minus the subject-level baseline. P-values for treatment comparisons, adjusted means of all treatments and treatment differences and their 95%CIs will be provided.

The primary analysis will be the comparison between the positive control and the negative control with null hypothesis H_0: there is no difference between two treatments, and alternative hypothesis H_a: there is a difference between two treatments.

Only if the primary objective is met (comparison of 67% w/w sodium bicarbonate, versus a 0% sodium bicarbonate is significant), will the remaining secondary analyses be fully conducted. Otherwise no P-values will be provided for secondary comparisons. Only the estimations of treatment differences and confidence intervals will be provided.

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

9.3.3. Secondary Analysis

Secondary analyses include the following treatment comparisons:

1. 50% sodium bicarbonate dentifrice versus a 0% sodium bicarbonate dentifrice;
2. 35% sodium bicarbonate dentifrice versus a 0% sodium bicarbonate dentifrice;
3. 20% sodium bicarbonate dentifrice versus a 0% sodium bicarbonate dentifrice;
4. 50% sodium bicarbonate dentifrice versus a 67% sodium bicarbonate dentifrice;
5. 35% sodium bicarbonate dentifrice versus a 67% sodium bicarbonate dentifrice;
6. 20% sodium bicarbonate dentifrice versus a 67% sodium bicarbonate dentifrice.

The analyses will be carried out by the same ANCOVA model in primary analysis. P-values for treatment comparisons, adjusted means of all treatments and treatment differences and their 95%CIs will be provided.

In the ANCOVA analysis of the effects of the five treatments with different contents of sodium bicarbonate (0%, 20%, 35%, 50%, 67%), the linear and quadratic contracts will be tested for dose-response trend. When a trend is significant, a mixed effect regression (linear, quadratic etc) will be run to provide dose-response curve. The regression curve will be plotted together with the dose-response data. If neither linear

model nor quadratic model appears to fit the data well, other nonlinear models may also be considered.

9.3.4. Safety Analysis

No specific safety criteria are planned for this study. Adverse Events and OST abnormalities will be collected and listed. Treatment emergent AEs (i.e. those occurring after the first usage of the study treatments) will be tabulated.

9.3.5. Other Analysis

A number of subjects will have repeat plaque (TPI) and assessments conducted by the examiner. The repeat assessments will be compared to the original assessments. The repeat assessments will not be used in any efficacy analysis. The first and second assessments on each tooth at a given visit will be cross-tabulated and a weighted Kappa coefficient (κ) will be calculated, along with the 95% confidence interval, to assess the intra-examiner repeatability. Repeatability will be deemed [Fleiss]:

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

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

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/institution should have written and dated approval/favorable opinion from the IEC for the trial protocol (including amendments), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), investigator brochure/ 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, GSK or designee (i.e. third party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

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

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

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

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

10.4. Quality Assurance

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

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

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

10.5. Conditions for Terminating the Study

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

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. For multicenter studies (if applicable), this can occur at one or more or at all sites.

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. Where required by the applicable regulatory requirements, GSKCH should inform the regulatory authority(ies).
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/favorable 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 CRFs or other documents submitted to GSKCH, 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 GSKCH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

GSK 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, GSK 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 GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

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.

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

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

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

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12. APPENDICES

12.1. Appendix 1 - Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
CI	Confidence Intervals
CRF	Case Report Form
CRO	Contract Research Organization
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GSKCH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Master Formula Code
mL	Miliilitre
OHT	Oral Hard Tissue Examination
OST	Oral Soft Tissue Examination
PI	Plaque Index
PII	Personally Identifiable Information
PP	Per Protocol
PRO	Patient Reported Outcome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
TPI	Turesky Modification of Quigley Hein Plaque Index
UK	United Kingdom
w/w	Weight/Weight
$\pm$	Plus or minus
$\geq$ / >	Greater than or equal to / greater than
$\leq$ / <	Less than or equal to / less than

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206886 Protocol

Date	Signed By
21-Oct-2016 10:51:39	PPD
Justification	Approved

Date	Signed By
24-Oct-2016 06:14:56	PPD
Justification	Biostatistics Approval

Date	Signed By
25-Oct-2016 04:50:29	PPD
Justification	Clinical Operations Approval

Date	Signed By
27-Oct-2016 12:48:27	PPD
Justification	Approved

Date	Signed By
Justification	

Date	Signed By
Justification	