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# Clinical Protocol

## 207014

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## SUMMARY INFORMATION

<b>Title:</b>	A Clinical Study Investigating the Gingivitis Efficacy of a Stannous Fluoride Dentifrice in a Chinese Population.
<b>Protocol Number:</b>	207014
<b>Sponsor:</b>	GlaxoSmithKline Consumer Healthcare (GSKCH; China) Co., Ltd 23F, The Headquarters building, No. 168 Tibet Road (M), Shanghai, 200001 China Tel: PPD
<b>Product Name:</b>	Dentifrice containing 0.454% w/w stannous fluoride and 0.0721% w/w sodium fluoride
<b>Development Phase:</b>	N/A

<b>Expert Advice Outside of Normal Working Hours:</b>	PPD, DDS, PhD Tel: PPD
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<b>Study Site Telephone Number:</b>	86-21-23271699
<b>Study Examiner:</b>	Dr CR Goyal, BDS


<b>IND/ EUDRACT No:</b>	N/A
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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:	Professor Feng Xiping
Investigator Qualifications:	DDS, MSc
Investigator Signature:	PPD
Date of Signature/ Agreement:	PPD DD/MMM/YYYY


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## PROCESS FOR AMENDING THE PROTOCOL

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

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

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

All non-substantial/ minor/ administrative amendments should be submitted to the IRB/ 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.

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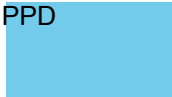
## PROTOCOL AMENDMENT PAGE


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.: 1	Non-Substantial/Minor <input type="checkbox"/>	This is Protocol amendment 1 (Protocol version 5.0) as previous amendments (2.0, 3.0 and 4.0) were made prior to Ethics submission.	Informed Consent <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Summary Information.	Signature: PPD 
Protocol Version No.: 5.0	Substantial/ Major <input checked="" type="checkbox"/>	Ethics committee meeting 28Mar17 “approval after modification” requesting dental fluorosis addition and clarification regarding substance/ drug abuse within the exclusion criteria.  Change of Clinical Study Manager details.	Safety Statement <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No CRF <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	4.2 Exclusion Criteria	Date: PPD 


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<b>Amendment No.:</b>	Non-Substantial/Minor <input type="checkbox"/>		Informed Consent <input type="checkbox"/> Yes <input type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input type="checkbox"/> No CRF <input type="checkbox"/> Yes <input type="checkbox"/> No		Signature: PPD 
<b>Protocol Version No.:</b>	Substantial/ Major <input type="checkbox"/>				Date: PPD 

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## SCHEDULE OF EVENTS

Procedure/Assessment	Visit 1 (Day -28 to -1)		Visit 2 Week 0 (Day 0) <sup>1</sup>	Visit 3 Week 6 (Day 42+/-3) <sup>1</sup>	Visit 4 Week 12 (Day 84+/-3) <sup>1</sup>
	Screening		Baseline <sup>1</sup>	Week 6	Week 12
Informed consent	X	1 – 28 days between Visit 1 and Visit 2 <sup>5</sup>			
Demographics	X				
Medical History <sup>2</sup>	X				
Current / Concomitant medication	X		X	X	X
Urine pregnancy test <sup>6</sup>	X		X	X	X
Oral soft and hard tissue (OST/OHT) examination <sup>3</sup>	X				
Gross gingival assessment	X				
Inclusion/ Exclusion Criteria	X		X		
Subject Eligibility/ Continuance	X		X	X	X
Full OST examination			X	X	X
Modified Gingival Index (MGI), Bleeding Index (BI) & Plaque Index (PI; disclosing)			X	X	X
Stratification/ randomization			X		
Sub- & supra-gingival prophylaxis and flossing (with second clinician check after disclosing & residual plaque removal, if applicable i.e. confirmed plaque score of zero)			X		
Dispense study dentifrice, toothbrush, study instructions, diary & timer <sup>4</sup>			X	X	
Oral hygiene instruction review/ compliance checks including diary completion review			X	X	X
Supervised subject brushing at site			X	X	
Collect study dentifrice, toothbrush & diary				X	X

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Compliance checks including diary review				X	X
Optional dental prophylaxis					X
Adverse Events			X	X	X
Study Conclusion					X

<sup>1</sup>. Subjects will abstain from overnight toothbrushing for a minimum of 12hrs (+6hr, - 2hr) immediately prior to the assessment visits (Visits 2, 3 & 4).


<sup>2</sup>. Including smoking status.

<sup>3</sup>. In relation to the general dentition exclusion criteria.

<sup>4</sup>. Timer only dispensed once, at visit 2 only.

<sup>5</sup>. Subjects will be instructed to brush using their normal toothpaste and following their normal routine between screening and baseline visits.

<sup>6</sup>. Female subjects of child bearing potential only.

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## PROTOCOL SYNOPSIS FOR STUDY 207014


### Brief Summary

This will be a single-centre, examiner-blind, randomized, stratified, two-treatment, parallel group, clinical study in healthy adult volunteers with moderate gingivitis. Treatment effect will be determined by evaluating the efficacy, in a Chinese population, of a dentifrice containing 0.454% w/w stannous fluoride to control gingivitis and supra-gingival plaque following 6 and 12 weeks twice daily brushing, compared to a fluoride control dentifrice. During the 12 week treatment period, subjects will brush with their allocated study product twice daily.


This clinical study will be conducted in China (Shanghai Ninth People's Hospital Affiliated to Shanghai Jiaotong University School of Medicine) and will be funded by GlaxoSmithKline Consumer Healthcare (GSKCH).

### Objectives and Endpoints

Objectives	Endpoints
<b>Primary</b>	
To compare gingivitis, as measured by BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12 weeks twice daily use.	Mean BI at 12 weeks.
<b>Secondary</b>	
To compare gingivitis, as measured by the number of bleeding sites using BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12 weeks twice daily use.	Number of bleeding sites at 12 weeks.
To compare gingivitis, as measured by MGI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12 weeks twice daily use.	Mean MGI at 12 weeks.
To compare dental plaque scores (PI; overall and interproximal) following twice daily use of an experimental 0.454% w/w stannous	Mean PI (overall and interproximal) at 12 weeks.

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fluoride dentifrice to a fluoride control dentifrice after 12 weeks twice daily use.	
<b>Other</b>	
To compare gingivitis, as measured by BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 6 weeks twice daily use.	Mean BI at 6 weeks.
To compare gingivitis, as measured by the number of bleeding sites using BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 6 weeks twice daily use.	Number of bleeding sites at 6 weeks.
To compare gingivitis, as measured by MGI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 6 weeks twice daily use.	Mean MGI at 6 weeks.
To compare dental plaque scores (PI; overall and interproximal) following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice to a fluoride control dentifrice after 6 weeks twice daily use.	Mean PI (overall and interproximal) at 6 weeks.
To evaluate and compare MGI and BI in low ( $\leq 2.00$ ) and high ( $> 2.00$ ) MGI subgroups following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice after 6 and 12 weeks twice daily use.	Mean MGI & BI at 6 & 12 weeks (in subgroups).
To evaluate examiner MGI & PI measurement reproducibility for a random subset of the study population.	Kappa coefficient for MGI & PI

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## Study Design

### Overall Design

This will be a single-centre, examiner-blind, randomized, stratified, two-treatment, parallel group, clinical study in healthy adult volunteers with moderate gingivitis. There will be four visits to the study site: Screening, Baseline, 6 Week and 12 Week. Gingivitis will be assessed using a Modified Gingival Index (MGI; Lobene, 1986) and a Bleeding Index (BI; Saxton, 1989). Plaque will be assessed by the Turesky modification of the Quigley & Hein Plaque Index (PI; Lobene, 1982).


At the Screening visit (Visit 1), subjects will give their written informed consent to participate in the study. Demographics, medical history, current and concomitant medications will be recorded, followed by an oral examination and a gingival assessment. Pregnancy testing will be carried out on all female subjects of child bearing potential at each visit. This will include full oral soft tissue (OST) and oral hard tissue (OHT) examinations, including dentition exclusions and gingival status. Subjects will be instructed to brush using their normal toothpaste and following their normal routine between screening and baseline.

Within 1-28 days of Screening (Visit 1), eligible subjects will return to the site for the Baseline visit (Visit 2) with overnight plaque (subjects will abstain from oral hygiene for 12hrs (+6hr, -2hr) i.e. overnight immediately before the visit). At the Baseline visit, subjects will undergo, in the following order, a full OST examination and assessments of gingival inflammation (MGI followed by BI), and supra-gingival plaque (PI).

Subjects with a suitable number of gradable teeth, with a mean overall MGI score between 1.75-2.30 and mean overall PI score  $\geq 1.5$  will continue in the study. Subjects with a mean overall MGI or PI scores outside the study range will be discontinued from the study at this visit. To control inter-examiner variability, the same suitably qualified examiner will be used throughout the study for each of the measures. The same examiner can perform more than one assessment but the same examiner must perform each of these assessments for all subjects throughout the study.

Subjects will be instructed to abstain from toothbrushing for a minimum of 12hrs (+6hr, -2hr) i.e. overnight immediately before each assessment visit. At the Baseline visit subjects will undergo a baseline oral soft tissue (OST) assessment, MGI followed by a BI followed by dental plaque (PI) assessment (assessments must occur in the order written) for all teeth meeting the inclusion criteria. Following the MGI & BI assessments, and after rinsing with 20ml of water, subjects will rinse their mouth



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with disclosing solution before receiving a dental plaque assessment.

Eligible subjects will be stratified based on gender (male/ female), smoking status (yes/ no) and baseline mean overall MGI score (low:  $\leq 2.00$ ; high  $> 2.00$ ) to ensure a balance in treatments across the strata, and then randomized into one of two treatment groups. Dental prophylaxis will be performed by a suitably qualified member of site staff for each subject using a standard dental prophylaxis paste followed by flossing by the examiner. Subject's teeth will be disclosed using a disclosing solution to check for residual plaque. A second clinician will check to ensure all plaque has been removed. Any residual plaque & calculus remaining will be removed by the second clinician by dental polishing with a standard dental prophylaxis paste, to bring the subject to a confirmed score of zero visible plaque (PI=0).

Following dental prophylaxis, subjects will receive their assigned study dentifrice, a diary, a toothbrush, a timer and instructions on product usage and diary completion. Subjects will brush their teeth with their allocated dentifrice, in their usual manner for one timed minute, under supervision. Subjects will continue to brush twice daily (morning and evening) for one timed minute recording each brushing on their study diary.

After using the study dentifrice twice daily for one timed minute at home for 6 and 12 weeks, subjects will return to the study site (Visits 3 and 4, respectively) having abstained from oral hygiene for 12hrs (+6hr, -2hr) i.e. from overnight immediately before each assessment visit, if possible at approximately the same time of day as the baseline visit. The study dentifrice will be collected and the diary reviewed for treatment compliance. Pregnancy testing will be carried out on all female subjects of child bearing potential at each visit. Subjects will have a full OST examination and then undergo, in the following order, MGI, BI followed by PI assessments after disclosing. At Visit 3, subjects will receive another supply of assigned study toothpaste, a new toothbrush and diary. At Visit 4, subjects will return all study materials and have a dental prophylaxis if deemed appropriate by the investigator or examiner.

At Visits 2, 3, 4, repeatability data will be generated for MGI & PI assessments from replicate examinations on the same subject. Depending on subject visit scheduling, every effort will be made to complete one repeatability examination for each clinical measure during each clinical session, 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. Replicate BI examinations will not be performed.

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### Visit 1 - Screening Visit

The following assessments will be conducted:

- Informed consent
- Demographics, medical history, current / concomitant medication, & smoking status.
- Urine pregnancy testing will be carried out on all female subjects of child bearing potential.
- Oral soft & hard tissue (OST/OHT) examination
- Gross gingival assessment
- Inclusion/exclusion criteria
- Subject eligibility / continuance
- Subjects will be instructed to brush using their normal toothpaste and following their normal routine between screening and baseline visits.

### Visit 2 - Baseline Visit; Day 0


The following assessments will be conducted:

- Review of current/concomitant medications, adverse events
- Urine pregnancy testing will be carried out on all female subjects of child bearing potential.
- Full OST examination
- MGI
- BI
- PI (following plaque disclosure)
- Inclusion/exclusion criteria
- Subject eligibility / continuance
- Stratification/randomization
- Sub- & supra-gingival prophylaxis & flossing (with second clinician check after disclosing & residual plaque removal, if applicable)
- Confirmed plaque score of 0 by second clinician following dental prophylaxis.
- Dispense study dentifrice, toothbrush, study instructions, diary & timer
- Oral hygiene instruction review / compliance checks including diary completion review with subject
- Supervised subject brushing at site
- Adverse events

### Visit 3 - Week 6; Day 42+/-3

The following assessments will be conducted:

- Review of current/concomitant medications, adverse events
- Compliance checks including diary review
- Urine pregnancy testing will be carried out on all female subjects of child bearing potential.


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<ul style="list-style-type: none"> <li>• Subject eligibility / continuance</li> <li>• Full OST examination</li> <li>• MGI</li> <li>• BI</li> <li>• PI (following plaque disclosure)</li> <li>• Collect study dentifrice, toothbrush &amp; diary</li> <li>• Dispense study dentifrice, toothbrush, study product usage instructions, diary &amp; timer</li> <li>• Oral hygiene instruction review / compliance checks including diary completion review with subject</li> <li>• Supervised subject brushing at site</li> <li>• Adverse events</li> </ul>
<b>Visit 4 – Week 12; Day 84+/-3</b>
<p>The following assessments will be conducted:</p> <ul style="list-style-type: none"> <li>• Review of current/concomitant medications, adverse events</li> <li>• Compliance checks including diary review</li> <li>• Urine pregnancy testing will be carried out on all female subjects of child bearing potential.</li> <li>• Subject eligibility / continuance</li> <li>• Full OST examination</li> <li>• MGI</li> <li>• BI</li> <li>• PI (following plaque disclosure)</li> <li>• Collect study dentifrice, toothbrush &amp; diary</li> <li>• Oral hygiene instruction review / compliance checks including diary completion review with subject</li> <li>• Complete optional second dental prophylaxis (if deemed necessary by the examiner)</li> <li>• Adverse events</li> <li>• Study conclusion</li> </ul>

### Type and Planned Number of Subjects

A sufficient number of subjects will be screened to randomize at least 120 subjects to ensure approximately 112 evaluable subjects complete the entire study (approximately 56 per treatment group).

With approximately 56 subjects per treatment group, the study has at least 80% power to detect a treatment difference of 0.08 in bleeding index over a period of 12 weeks

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treatment. The standard deviation used in calculation is 0.14. The difference of 0.08 represents more than 15% improvement in the test dentifrice compared to the fluoride control dentifrice reference product. CCI [REDACTED]

## Diagnosis and Main Criteria for Inclusion

Healthy adult subjects, aged 18 to 65 years, with moderate gingivitis at screening visit, with baseline overall mean MGI score between 1.75-2.30 and  $PI \geq 1.5$  (for all eligible teeth in agreement with the inclusion/ exclusion criteria), minimum 20 permanent natural teeth and with a minimum of 40 gradable surfaces free of irregularities and discoloration.

## Product Information

	Test Product	Reference Product
<b>Product Name</b>	Experimental dentifrice containing 0.454% w/w stannous fluoride & 0.0721% w/w sodium fluoride (1450ppm fluoride in total)	Regular fluoride dentifrice containing 0.14% w/w sodium monofluorophosphate – Colgate® Triple Protection Dentifrice (1400ppm fluoride as sodium monofluorophosphate; SMFP)
<b>Product Formulation Code (MFC)</b>	CCI [REDACTED]	Commercially available (Chinese marketplace)
<b>Dose</b>	Full ribbon of dentifrice to cover the head of the study toothbrush provided	Full ribbon of dentifrice to cover the head of the study toothbrush provided
<b>Route of Administration</b>	Oral topical	Oral topical
<b>Dosing Instructions</b>	Subjects will apply a full strip of dentifrice to cover the head of the toothbrush provided and brush their teeth with the assigned dentifrice twice daily (morning and evening) for one timed minute following their normal routine.	Subjects will apply a full strip of dentifrice to cover the head of the toothbrush provided and brush their teeth with the assigned dentifrice twice daily (morning and evening) for one timed minute following their normal routine.

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## Statistical Methods

BI score, MGI score and overall plaque score will be calculated as the average index values over all sites. Interproximal plaque score will be calculated as the average index values over all interproximal sites. Number of bleeding sites will be calculated as the number of sites with BI 1 or 2.

BI score, number of bleeding sites, overall plaque score and interproximal plaque score will be analysed using ANCOVA with treatment, gender, smoking status and baseline MGI stratification as factors and baseline score as covariate. Adjusted means of two treatments and treatment difference will be provided together with 95%CI and P-values.

MGI score will be analysed using ANCOVA with treatment, gender and smoking status as factors and baseline score as covariate. Baseline MGI stratification will not be included in the model since baseline MGI score is already included as covariate. Adjusted means of two treatments and treatment difference will be provided together with 95%CI and P-values.

Assumptions in ANCOVA analyses will be checked. If violated, data transformations or nonparametric methods will be used.

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## 1. INTRODUCTION


Gingivitis is a reversible inflammation of the periodontal tissues surrounding the tooth in response to the presence of dental plaque (Kinane *et al.* 2001). Gingivitis is reported to have a high prevalence worldwide as recognized by large population surveys (Albandar *et al.* 2002) and the World Health Organisation (Petersen & Ogawa 2012).

Plaque-induced gingivitis is a reversible condition that can be managed or prevented with regular effective oral hygiene (Brook *et al.* 2003; Ower *et al.* 2003) which is important not only in maintaining health and managing the signs and symptoms of gingivitis, but also to prevent the development of periodontitis (Kinane & Attström 2005). Approaches to the prevention and treatment of gingivitis are essentially two-fold including mechanical cleaning along with the use of an antibacterial mouthrinse (Chapple *et al.* 2015).

The addition of antimicrobial ingredients to a dentifrice will further complement the mechanical removal by helping to inhibit the growth of bacterial plaque from sites in the mouth that are less accessible to mechanical removal and/or prevent subsequent re-colonisation of dental plaque bacteria. Antimicrobial agents have been incorporated into dentifrices for many years with a view to delivering plaque control and periodontal benefits (Cummins *et al.* 1992). The stannous ion is a well known chemotherapeutic agent that has been used in dentifrices as stannous fluoride since the 1940's (van Loveren *et al.* 1990, 2001; Miller *et al.* 1994; Makin 2013). Stannous fluoride is a broad-spectrum antimicrobial agent that has been shown to inhibit and reduce bacterial biomass, virulence and metabolism (Tinanoff *et al.* 1990).

Clinically, the effects of stannous fluoride containing dentifrices (at a concentration of between 0.4-0.454% w/w) on gingivitis have been described in numerous clinical studies demonstrating that using a low water content, stabilized 0.454% w/w stannous fluoride dentifrice twice daily for 24 weeks resulted in 20.5% less gingivitis ( $P<0.05$ ) and 33.4% less bleeding ( $P<0.05$ ) when compared with a negative control (Perlich *et al.* 1995; Paraskevas *et al.* 2006). An additional study reported that subject's who used a low water content, stabilized stannous fluoride dentifrice twice daily for 24 weeks showed a statistically significant reduction in plaque when compared with a negative control dentifrice (Williams *et al.* 1997). In three other 24 week plaque/gingivitis clinical studies a 0.454% w/w low water content, stabilized stannous fluoride dentifrice exhibited statistically significant >20% plaque reduction compared with a negative control (Mankodi *et al.* 1997, 2005; Mallatt *et al.* 2007).


The literature reports that the largest reductions in gingivitis are observed following the use of "stabilized" stannous fluoride dentifrice formulations (Tinanoff *et al.* 1990). The stannous fluoride formulation to be evaluated in this study has been

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stabilized by employing non-aqueous excipients. CCI

Furthermore an additional study was currently reported (GSKCH 205045) investigating the efficacy of a 0.454% w/w stannous fluoride dentifrice to control gingivitis in subjects who demonstrate blood in toothpaste expectorate, showing significant improvements in measures of gingivitis (number of bleeding sites, BI and MGI) following 4 and 12 weeks of twice daily use compared to a reference control dentifrice. Whilst there is a well proven data package, GSK are investigating the effect of stannous fluoride in the wider worldwide population.


The aim of this clinical study is to evaluate the efficacy of a 0.454% w/w stannous fluoride dentifrice compared to a reference control to control gingivitis (gingival bleeding and visual signs of gingival inflammation) in dentally and periodontally healthy adult volunteers over 12 weeks' use in a Chinese population.

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## 2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary</b>	
To compare gingivitis, as measured by BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12 weeks twice daily use.	Mean BI at 12 weeks.
<b>Secondary</b>	
To compare gingivitis, as measured by the number of bleeding sites using BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12 weeks twice daily use.	Number of bleeding sites at 12 weeks.
To compare gingivitis, as measured by MGI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 12 weeks twice daily use.	Mean MGI at 12 weeks.
To compare dental plaque scores (PI; overall and interproximal) following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice to a fluoride control dentifrice after 12 weeks twice daily use.	Mean PI (overall and interproximal) at 12 weeks.
<b>Other</b>	
To compare gingivitis, as measured by BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 6 weeks twice daily use.	Mean BI at 6 weeks.
To compare gingivitis, as measured by the number of bleeding sites using BI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after 6 weeks twice daily use.	Number of bleeding sites at 6 weeks.
To compare gingivitis, as measured by MGI, following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice compared to a fluoride control dentifrice after	Mean MGI at 6 weeks.



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6 weeks twice daily use.	
To compare dental plaque scores (PI; overall and interproximal) following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice to a fluoride control dentifrice after 6 weeks twice daily use.	Mean PI (overall and interproximal) at 6 weeks.
To evaluate and compare MGI and BI in low ( $\leq 2.00$ ) and high ( $> 2.00$ ) MGI subgroups following twice daily use of an experimental 0.454% w/w stannous fluoride dentifrice after 6 and 12 weeks twice daily use.	Mean MGI & BI at 6 & 12 weeks (in subgroups).
To evaluate examiner MGI & PI measurement reproducibility for a random subset of the study population.	Kappa coefficient for MGI & PI

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### 3. STUDY PLAN

#### 3.1. Study Design

Overall Design
<p>This will be a single-centre, examiner-blind, randomized, stratified, two-treatment, parallel group, clinical study in healthy adult volunteers with moderate gingivitis. There will be four visits to the study site: Screening, Baseline, 6 Week and 12 Week. Gingivitis will be assessed using a Modified Gingival Index (MGI; Lobene, 1986) and a Bleeding Index (BI; Saxton, 1989). Plaque will be assessed by the Turesky modification of the Quigley &amp; Hein Plaque Index (PI; Lobene, 1982).</p> <p>At the Screening visit (Visit 1), subjects will give their written informed consent to participate in the study. Demographics, medical history, current and concomitant medications will be recorded, followed by an oral examination and a gingival assessment. Pregnancy testing will be carried out on all female subjects of child bearing potential at each visit. This will include full oral soft tissue (OST) and oral hard tissue (OHT) examinations, including dentition exclusions and gingival status. Subjects will be instructed to brush using their normal toothpaste and following their normal routine between screening and baseline.</p> <p>Within 1-28 days of Screening (Visit 1), eligible subjects will return to the site for the Baseline visit (Visit 2) with overnight plaque (subjects will abstain from oral hygiene for 12hrs (+6hr, -2hr) i.e. overnight immediately before the visit). At the Baseline visit, subjects will undergo, in the following order, a full OST examination and assessments of gingival inflammation (MGI followed by BI), and supra-gingival plaque (PI).</p> <p>Subjects with a suitable number of gradable teeth, with a mean overall MGI score between 1.75-2.30 and mean overall PI score <math>\geq 1.5</math> will continue in the study. Subjects with a mean overall MGI or PI scores outside the study range will be discontinued from the study at this visit. To control inter-examiner variability, the same suitably qualified examiner will be used throughout the study for each of the measures. The same examiner can perform more than one assessment but the same examiner must perform each of these assessments for all subjects throughout the study.</p> <p>Subjects will be instructed to abstain from toothbrushing for a minimum of 12hrs (+6hr, -2hr) i.e. overnight immediately before each assessment visit. At the Baseline visit subjects will undergo a baseline oral soft tissue (OST) assessment, MGI</p>

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followed by a BI followed by dental plaque (PI) assessment (assessments must occur in the order written) for all teeth meeting the inclusion criteria. Following the MGI & BI assessments, and after rinsing with 20ml of water, subjects will rinse their mouth with disclosing solution before receiving a dental plaque assessment.

Eligible subjects will be stratified based on gender (male/ female), smoking status (yes/ no) and baseline mean overall MGI score (low:  $\leq 2.00$ ; high  $> 2.00$ ) to ensure a balance in treatments across the strata, and then randomized into one of two treatment groups. Dental prophylaxis will be performed by a suitably qualified member of site staff for each subject using a standard dental prophylaxis paste followed by flossing by the examiner. Subject's teeth will be disclosed using a disclosing solution to check for residual plaque. A second clinician will check to ensure all plaque has been removed. Any residual plaque & calculus remaining will be removed by the second clinician by dental polishing with a standard dental prophylaxis paste, to bring the subject to a confirmed score of zero visible plaque (PI=0).

Following dental prophylaxis, subjects will receive their assigned study dentifrice, a diary, a toothbrush, a timer and instructions on product usage and diary completion. Subjects will brush their teeth with their allocated dentifrice, in their usual manner for one timed minute, under supervision. Subjects will continue to brush twice daily (morning and evening) for one timed minute recording each brushing on their study diary.

After using the study dentifrice twice daily for one timed minute at home for 6 and 12 weeks, subjects will return to the study site (Visits 3 and 4, respectively) having abstained from oral hygiene for 12hrs (+6hr, -2hr) i.e. from overnight immediately before each assessment visit, if possible at approximately the same time of day as the baseline visit. The study dentifrice will be collected and the diary reviewed for treatment compliance. Pregnancy testing will be carried out on all female subjects of child bearing potential at each visit. Subjects will have a full OST examination and then undergo, in the following order, MGI, BI followed by PI assessments after disclosing. At Visit 3, subjects will receive another supply of assigned study toothpaste, a new toothbrush and diary. At Visit 4, subjects will return all study materials and have a dental prophylaxis if deemed appropriate by the investigator or examiner.

At Visits 2, 3, 4, repeatability data will be generated for MGI & PI assessments from replicate examinations on the same subject. Depending on subject visit scheduling, every effort will be made to complete one repeatability examination for each clinical measure during each clinical session, that is, one in the morning and one in the

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afternoon on each assessment day. Repeatability examinations will be separated by a minimum of 10 minutes and, where possible, separated by another subject. Replicate BI examinations will not be performed.

### Visit 1 - Screening Visit

The following assessments will be conducted:

- Informed consent
- Demographics, medical history, current / concomitant medication, & smoking status.
- Urine pregnancy testing will be carried out on all female subjects of child bearing potential.
- Oral soft & hard tissue (OST/OHT) examination
- Gross gingival assessment
- Inclusion/exclusion criteria
- Subject eligibility / continuance
- Subjects will be instructed to brush using their normal toothpaste and following their normal routine between screening and baseline visits.


### Visit 2 - Baseline Visit; Day 0

The following assessments will be conducted:

- Review of current/concomitant medications, adverse events
- Urine pregnancy testing will be carried out on all female subjects of child bearing potential.
- Full OST examination
- MGI
- BI
- PI (following plaque disclosure)
- Inclusion/exclusion criteria
- Subject eligibility / continuance
- Stratification/randomization
- Sub- & supra-gingival prophylaxis & flossing (with second clinician check after disclosing & residual plaque removal, if applicable)
- Confirmed plaque score of 0 following dental prophylaxis.
- Dispense study dentifrice, toothbrush, study instructions, diary & timer
- Oral hygiene instruction review / compliance checks including diary completion review with subject
- Supervised subject brushing at site
- Adverse events

### Visit 3 - Week 6; Day 42+/-3

The following assessments will be conducted:

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- Review of current/concomitant medications, adverse events
- Compliance checks including diary review
- Urine pregnancy testing will be carried out on all female subjects of child bearing potential.
- Subject eligibility / continuance
- Full OST examination
- MGI
- BI
- PI (following plaque disclosure)
- Collect study dentifrice, toothbrush & diary
- Dispense study dentifrice, toothbrush, study instructions, diary & timer
- Oral hygiene instruction review / compliance checks including diary completion review with subject
- Supervised subject brushing at site
- Adverse events

#### Visit 4 - Week 12; Day 84+/-3


The following assessments will be conducted:

- Review of current/concomitant medications, adverse events
- Compliance checks including diary review
- Urine pregnancy testing will be carried out on all female subjects of child bearing potential.
- Subject eligibility / continuance
- Full OST examination
- MGI
- BI
- PI (following plaque disclosure)
- Collect study dentifrice, toothbrush & diary
- Oral hygiene instruction review / compliance checks including diary completion review with subject
- Complete optional second dental prophylaxis (as/ if deemed necessary by examiner)
- Adverse events
- Study conclusion

### 3.2. Subject Restrictions

#### Lifestyle/ Dietary

The following lifestyle restrictions apply for the duration of the study:

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#### **Screening to study completion:**

- 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 only.


#### **Baseline/Randomization, 6 and 12 week visits:**

- Subjects should only use the dentifrice and toothbrushes provided and must abstain from use of all other oral hygiene products including mouthwash from the baseline visit.
- Subjects must abstain from using oral hygiene products for 12hrs (+6hr, -2hr) i.e. overnight immediately before an assessment visit and until the visit is complete.
- Subjects must abstain from eating (and smoking where necessary) for at least 4 hours, and from drinking for at least 1 hour prior to all clinical assessments and until all assessments are complete.

#### **Medications and Treatments**

The following lifestyle restrictions apply for the duration of the study:

- 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 and recorded in the CRF. Should a randomized subject embark on a course of treatment during the study which includes a prohibited medication, the identity of that medication/treatment, dosage and frequency and start date will be recorded. The subject will not be withdrawn.
- Subjects may not take any of the medications prohibited in the exclusion criteria (as directed in the section). In addition, the subjects are to refrain from the use of any over-the-counter anti-inflammatory products or traditional Chinese medicines (TCM) which are not permitted within 2 weeks prior to any gingival examination and throughout the study following the baseline examination.
- Subjects will be requested to not have any elective dental procedures other than those performed within the study (excluding emergency dental treatment).
- Subjects will not be able to receive a dental prophylaxis (except that administered by the site), or use any professional or over-the-counter whiteners or antimicrobial mouthrinses during the course of the study.

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### 3.3. Type and Planned Number of Subjects

A sufficient number of subjects will be screened to randomize at least 120 subjects to ensure approximately 112 evaluable subjects complete the entire study (approximately 56 per treatment group).


### 3.4. Study Design and Dose Justification

This will be a single-center, examiner-blind, randomized, stratified (by gender, smoking status, baseline mean overall MGI value), two-treatment, parallel group, clinical study in healthy adult volunteers with moderate gingivitis. There will be four visits to the study site: Screening, Baseline, 6 Week, and 12 Week. Gingivitis will be assessed using a MGI (Lobene, 1986) and a BI (Saxton, 1989). Plaque will be assessed by the Turesky modification of the Quigley Hein PI (Lobene, 1982). All evaluable teeth (in relation to the inclusion/ exclusion general dentition criteria) will be assessed.

This clinical study design has been chosen as this is recommended by the dental research communities and is consistent with the “Efficacy evaluation of toothpaste guidelines” of Health Industrial Standard of the People’s Republic of China guidelines for such studies. The study will be blinded with respect to the dental examiner.

A parallel group design has been selected as more appropriate for this investigation. The dosage regimen of twice daily use (morning and evening) will be the same for each treatment and is based on consumer habit and common practice within oral care clinical trials.

According to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, for a study to be classified as truly double-blind, not only does the examiner (and any appropriate member of staff who may be involved in the dispensing of products, analysis of data etc.) need to be blinded as to the treatment the subject receives, but the products under test must be identical in every way (color, flavor, appearance, packaging). Given it is almost impossible to ensure identical appearance, taste and packaging for the dentifrices evaluated in oral care studies, the level of blindness for this study is described as ‘examiner blind’ only. The same examiner will be used

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throughout the study for each clinical index to eliminate the possibility of inter-examiner variability.

At the Screening visit (Visit 1), subjects will give their written informed consent to participate in the study. Demographics, medical history, current and concomitant medications will be recorded, followed by an oral examination and a gingival assessment. This will include an OST and OHT examination, dentition exclusions and gingival status.


Within 1 to 28 days of Screening (Visit 1), eligible subjects will return to the site for the Baseline visit (Visit 2) with overnight plaque (subjects will abstain from oral hygiene for 12hrs (+6hr, -2hr) i.e. overnight immediately before the visit). At the Baseline visit, subjects will undergo, in the following order, a full OST examination and assessments of gingival inflammation (MGI), gingival bleeding (BI) and supra-gingival plaque (PI). Subjects with a mean whole mouth MGI score between 1.75 – 2.30 and mean whole mouth PI score  $\geq 1.5$  will continue in the study. Subjects with mean MGI or PI scores outside the study range will be discontinued from the study at this visit. To control inter-examiner variability, the same examiner will be used throughout the study.

Eligible subjects will be stratified based on gender, smoking status and baseline mean whole mouth MGI score (Low:  $\leq 2.00$ /High  $> 2.00$ ), to ensure a balance of treatments within the strata, and then randomized into one of two treatment groups. Healthy subjects with moderate gingivitis will be stratified according to their gender, smoking status and baseline mean overall MGI to ensure a balance in gender, smoking status and gingival health across both treatment groups. Gender & smoking are known modifiers of the initiation and outcome of conditions related to gingival health (Alam, 2012). Stratifying by MGI will also facilitate evaluation of gingivitis (BI and MGI) in low and high MGI subgroups.

Dental prophylaxis will be performed for each subject using a conventional non-fluoride dental prophylaxis paste followed by flossing. Subject's teeth will be disclosed using a disclosing solution to check for residual plaque. A second clinician will check to ensure all plaque has been removed. Any residual plaque remaining will be removed by the second clinician by dental polishing with a standard polishing dental compound, to bring the subject to a confirmed zero plaque score (PI=0).

Following dental prophylaxis, subjects will receive their assigned study dentifrice, a diary, a toothbrush, a timer and instructions on product usage and diary completion. Subjects will brush their teeth with their allocated dentifrice, in their usual manner for




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one timed minute, under supervision. Subjects will continue to brush twice daily (morning and evening) for one timed minute and record on their study diary completed brushings.

After using the study dentifrice for 6 and 12 weeks, subjects will return to the study site (Visits 3 and 4, respectively) with overnight plaque (subjects will abstain from overnight toothbrushing for 12hrs (+6hr, -2hr) immediately before each assessment visit), if possible at approximately the same time of day as the baseline visit. The study dentifrice will be collected and the diary reviewed for treatment compliance. Subjects will have a full OST examination and then undergo, in the following order, MGI, BI and PI assessments. At Visit 3, subjects will receive another supply of assigned study toothpaste, a new toothbrush and diary. At Visit 4, subjects will return all study materials and have a dental prophylaxis if deemed appropriate by the investigator or examiner.

At Visits 2, 3, 4, repeatability data will be generated for MGI and PI assessments from replicate examinations on the same subject. Depending on subject visit scheduling, every effort will be made to complete one repeatability examination for each clinical measure during each clinical session, 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. Replicate BI examinations will not be carried out.

The dosing regimen of twice daily brushing with a brush length of toothpaste will be the same for each treatment and is based on consumer habit and common practice within oral care clinical trials. Subjects will apply a full ribbon of dentifrice to the study toothbrush and brush their teeth in their usual manner for one timed minute twice daily (morning and evening). Subjects will brush their teeth for one timed minute twice daily for 12 weeks, once in the morning and once in the evening. No dose modification is permitted in this study. Any variation from the brushing instructions should be communicated to study site personnel and recorded as a deviation on the CRF.

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## 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 jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

### 4.1. Inclusion Criteria


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

<b>1. CONSENT</b>
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.
<b>2. AGE</b>
Aged 18 to 65 years.
<b>3. COMPLIANCE</b>
Understands and is willing, able and likely to comply with all study procedures and restrictions.
<b>4. GENERAL HEALTH</b>
<p>Good general and mental health with, in the opinion of the investigator or medically qualified designee:</p> <ul style="list-style-type: none"> <li>a. No clinically significant and relevant abnormalities in medical history or upon oral examination.</li> <li>b. Absence of any condition that would impact on the subject's safety or wellbeing or affect the individual's ability to understand and follow study procedures and requirements.</li> </ul>

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## 5. DENTAL HEALTH

- a. A minimum of 20 natural teeth (all teeth; incisors, canines, pre-molars & molars), and a minimum of 40 gradable surfaces for MGI, BI and PI. A scorable surface is defined as a surface that has 50% of the surface gradable for each clinical index. Third molars, orthodontically banded/bonded, fully crowned or extensively restored or grossly carious teeth are not included in the tooth count.
- b. Moderate gingivitis present at the screening visit (in the opinion of the clinical examiner from a gross visual examination).
- c. Mean whole mouth MGI between 1.75 and 2.30 and a mean overall PI score  $\geq 1.5$  at Baseline visit.

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## 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 (including women who have a positive urine pregnancy test; pregnancy testing will be carried out for all female subjects who are of child bearing potential).

### 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. CONCURRENT MEDICATION

#### Screening:

- Currently taking antibiotics or requiring antibiotic use prior to dental prophylaxis or other dental procedures.
- Currently taking an anti-inflammatory medication or traditional Chinese medicines (TCM) which, in the opinion of the Investigator, could affect gingival condition.
- Currently taking a systemic medication which, in the opinion of the Investigator, could affect gingival condition (e.g. calcium channel blockers, or aspirin therapy).

#### Baseline (Visit 2):

- Has taken, or currently taking, antibiotics in the previous 14 days.
- Has taken, or currently taking, an anti-inflammatory medication which, in the opinion of the Investigator, could affect gingival condition in the previous 14 days.
- Has taken, or currently taking, a systemic medication which, in the opinion of the Investigator, could affect gingival condition in the previous 14 days (e.g. calcium channel blockers, or aspirin therapy).

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#### 5. GENERAL DENTITION EXCLUSIONS

- a. 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.
- b. Restorations in a poor state of repair.
- c. Partial dentures or orthodontic appliances.
- d. Teeth bleaching within 12 weeks of screening.
- e. Use of an antibacterial mouthwash (e.g. chlorhexidine) currently, or within 14 days of baseline.
- f. **EVIDENCE OF DENTAL FLUOROSIS, AS DETERMINED BY THE INVESTIGATOR.**

#### 6. CLINICAL STUDY/ EXPERIMENTAL PRODUCT

- a. Participation in another clinical study or receipt of an investigational drug or investigational oral care product within 30 days of Baseline (Visit2).
- b. Previous participation in this study.

#### 7. SUBSTANCE/ DRUG ABUSE


Recent history (within the last year) of alcohol or other substance **(E.G. ILLICIT DRUG)** abuse.

#### 8. PERSONNEL

- a. An employee of the sponsor or the study site or members of their immediate family.
- b. Employed by any dentifrice manufacturer or their immediate family.

### 4.3. Screening/ Baseline Failures

Screen failures are defined as subjects who consent to participate in the study but are never subsequently randomized. 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.

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#### 4.4. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons.

If the reason for removal of a subject from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the electronic case report form (CRF). 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 stabilizes, 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-randomization will not be replaced.

#### 4.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the date of the last subject's last visit.

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## 5. PRODUCT INFORMATION


### 5.1. Study Product

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

	<b>Test Product</b>	<b>Reference Product</b>
<b>Product Name</b>	Experimental dentifrice containing 0.454% w/w stannous fluoride & 0.0721% w/w sodium fluoride (1450ppm fluoride in total)	Regular fluoride dentifrice containing 0.14% w/w sodium monofluorophosphate – Colgate® Triple Protection Dentifrice (1400ppm fluoride as sodium monofluorophosphate; SMFP)
<b>Product Formulation Code (MFC)</b>	CCI	Commercially available (Chinese marketplace)
<b>Dose</b>	Full ribbon of dentifrice to cover the head of the study toothbrush provided	Full ribbon of dentifrice to cover the head of the study toothbrush provided
<b>Route of Administration</b>	Oral topical	Oral topical
<b>Dosing Instructions</b>	Subjects will apply a full strip of dentifrice to cover the head of the toothbrush provided and brush their teeth with the assigned dentifrice twice daily (morning and evening) for one timed minute following their normal routine.	Subjects will apply a full strip of dentifrice to cover the head of the toothbrush provided and brush their teeth with the assigned dentifrice twice daily (morning and evening) for one timed minute following their normal routine.

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

<b>Name of Item</b>	<b>Purpose</b>
Aquafresh® Clean Control (Everyday Clean) toothbrushes (UK market place)	To apply dentifrice to the teeth and facilitate toothbrushing
Countdown Timers	To accurately measure toothbrushing for one timed minute and assist subject compliance for brushing time.
Plaque disclosing solution CCI	To disclose the presence of dental plaque

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Opaque Bags	To carry study supplies

Subject diaries (including product usage instructions) will be supplied by GSKCH, China.

Urine pregnancy test kits (to test for pregnancy on female subjects of child bearing potential) will be provided by the site.

## 5.2. Dose Schedule

Subjects will brush their teeth for one timed minute twice daily for 12 weeks, once in the morning and once in the evening.

## 5.3. Dose Modification

No dose modification is permitted in this study. Any variation from brushing instructions should be communicated to study site personnel and recorded as a deviation on the CRF.

## 5.4. Product Compliance


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

At Visits 2 and 3, site staff will review the study instructions with the subjects to ensure subjects understand how to use the study products, complete the diary and operate the timer. Subjects will complete their first brushing at the study site under the supervision of trained study personnel who will assess the subject's understanding of study procedures and stress the importance of completing the study diary each time they brush their teeth. The diary will have a place to note when daily the brushings were completed and the date/time of the first and last brushings which will be recorded on the CRF.

## 5.5. Precautions

No special precautions are necessary provided the study is carried out in accordance with this protocol. Study products will be labelled "For Clinical Trial Use Only".



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## 5.6. Overdose

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

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

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

## 5.7. Rescue Therapy

No rescue therapy is required in this study.

## 5.8. Product Assignment

Subjects will be assigned to study product in accordance with the 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.

There will be eight strata according to gender, smoking status and baseline mean whole mouth MGI score (Low $\leq$ 2.0/High $>$ 2.0):

- Stratum 1: Male, Smoker, Baseline MGI  $\leq$ 2.00
- Stratum 2: Male, Smoker, Baseline MGI  $>$ 2.00
- Stratum 3: Male, Non-smoker, Baseline MGI  $\leq$ 2.00
- Stratum 4: Male, Non-smoker, Baseline MGI  $>$ 2.00
- Stratum 5: Female, Smoker, Baseline MGI  $\leq$ 2.00
- Stratum 6: Female, Smoker, Baseline MGI  $>$ 2.00
- Stratum 7: Female, Non-smoker, Baseline MGI  $\leq$ 2.00
- Stratum 8: Female, Non-smoker, Baseline MGI  $>$ 2.00

Subjects will be allocated to one of the eight strata and within each stratum, randomization numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible.

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### 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.

### 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

The study dentifrice tubes [Experimental dentifrice containing 0.454%w/w stannous fluoride and 0.0721% w/w sodium fluoride CCI and Colgate Triple Protection fluoride dentifrice (China market place product)] will be overwrapped in opaque white vinyl to obscure any branding on the commercial tube pack. Each tube will have a study label affixed. Each subject will receive a sufficient number of tubes to cover usage during the treatment phase.

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

Care should be taken with the supplied study 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.

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.

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All sundry items will be supplied in commercial packaging to be distributed by site staff as required throughout the study duration.

### 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. The exact timing of each assessment is listed in the Schedule of Events section.

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

### 6.1. Visit 1 - Screening Visit

#### 6.1.1 Telephone Screening

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

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### 6.1.2. Informed Consent

The investigator, or designee, must obtain written (signed and dated by the subject) informed consent from each subject before starting any study specific procedures 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 should 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.


### 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. Smoking status will also be detailed. Details of any relevant medical or surgical history, 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. Urine Pregnancy Test

Urine pregnancy testing will be performed on females of child bearing potential at every visit according to the test kit manufacturer's instructions. Urine collected for urine pregnancy testing will be disposed of as appropriate immediately following the test result.

Female subjects of non-childbearing potential must meet at least one of the following criteria:

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- a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause;
- b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- c. Have medically confirmed ovarian failure.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

#### **6.1.6. Oral Soft & Hard Tissue Examination**

The screening clinician will perform an initial oral soft tissue examination in order to capture any abnormalities, in agreement with section 6.2.1.

The screening dentist will also perform a visual examination of the oral hard tissues to confirm that the subject has a minimum of 20 natural teeth and to evaluate the dentition for exclusions.

The examinations will be performed by direct observation.

#### **6.1.7. Gross Gingival Health Assessment**

The screening dentist will determine gingival health by visual examination of the subject's oral soft tissue. Subjects considered to have generalized moderate gingivitis will continue in the study.


### **6.2. Visits 2, 3 & 4**

#### **6.2.1. Urine Pregnancy Test**

Complete as described in Section 6.1.5.

#### **6.2.2. Oral Soft Tissue Examination (OST)**

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee. The examination will be accomplished throughout the study 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, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands.

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The results of the examination will be recorded in the CRF 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.

### 6.2.3. Modified Gingival Index (MGI) Assessment (Lobene, 1986)

The MGI assessment is a non-invasive evaluation which focuses on the visual symptoms of gingivitis (for example, redness, texture, edema). The MGI will be assessed on the facial and lingual surfaces of each scorable tooth (7-7 in each arch). Two scores will be recorded buccally/labially (papilla and margin) and two scores lingually/palatally (papilla and margin). The scoring of the MGI will be performed under dental office conditions using a standard dental light for illuminating the oral cavity.

The MGI scoring system will be as follows:

0 = absence of inflammation

1 = mild inflammation; slight change in color, little change in color; little change in texture of any portion of the marginal or papillary gingival unit.

2 = mild inflammation; criteria as above but involving the entire marginal or papillary gingival unit.


3 = moderate inflammation; glazing, redness, edema, and/or hypertrophy of the marginal or papillary gingival unit.

4 = severe inflammation; marked redness, edema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

The MGI will be assessed by the same examiner on all evaluable teeth at Baseline/Visit 2, Visit 3 and Visit 4.

### Repeatability Exercise

Data for MGI assessments will be taken from replicate examinations performed by the Examiner during the study. Depending on subject visit scheduling, every effort

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will be made to do repeatability examinations during each session, that is, one in the morning and one in afternoon every day examinations are carried out.

Repeatability examinations will have a minimum of 10 minutes between and, where possible, will be separated by another subject.

#### **6.2.4. Bleeding Index (BI) Assessment (Saxton, 1989)**

The BI assesses the number of bleeding points elicited on probing as a measure of gingival condition. The gingivae will be air dried and then the examiner will use an Oulix color coded periodontal PCPII 5B Hufreidy or blunt-ended CPI probe to assess bleeding. The probe will be gently inserted into the gingival crevice to a depth of approximately 1 millimeter (mm) and then run around the tooth (at angle of ~ 60° to the long axis of the tooth), gently stretching the epithelium while sweeping from interproximal to interproximal along the sulcular epithelium. Minimum force should be used to avoid damage to the gingival tissue. The BI will be assessed on the facial and lingual gingival surfaces of each scorable tooth (7-7 in each arch). Three scores (according to the scale below) should be recorded buccally/labially (distal, body, mesial sites) and three scores lingually/palatally. All scorable teeth in one quadrant should be probed first (approximately 30 seconds) before recording the number of gingival units which bleed.

The BI scoring system will be as follows:

0 = no bleeding after 30 seconds

1 = bleeding upon probing after 30 seconds


2 = immediate bleeding observed

The BI will be assessed by the same examiner on all evaluable teeth at Baseline/Visit 2, Visit 3 and Visit 4.

**Repeatability exercise will not be performed for BI. Due to the invasive nature of the BI assessment it is not feasible to conduct a repeatability exercise.**

#### **6.2.5. Plaque Index (PI) Assessment (Lobene, 1982)**

The Turesky Modification of the Quigley Hein Plaque Index (Lobene, 1982) will be used to assess plaque on all gradable teeth meeting the inclusion/ exclusion criteria.

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Only natural teeth can be assessed. This means no crowns, bridges, and teeth with fillings (surface that has 50% of the surface gradable or no more than 50% of the surface filled) which, in the examiner's judgment, would prevent an accurate grading should be assessed. Third molars should not to be assessed.

The plaque will first be disclosed using a dye solution (Plaque disclosing solution

CCI

, in agreement with the manufacturer's instructions. The PI will be assessed on the facial and lingual surfaces of each scorable tooth. (7-7 in each arch). Three scores should be recorded buccally/ labially (distal, body, mesial sites) and three scores lingually/ palatally (distal, body, mesial sites).

Disclosed plaque will be scored as follows:

0 = No plaque

1 = Slight flecks of plaque at the cervical margin of the tooth

2 = A thin continuous band of plaque (1mm or smaller) at the cervical margin of the tooth

3 = A band of plaque wider than 1mm but covering less than 1/3 of the area

4 = Plaque covering at least 1/3 but less than 2/3 of the area

5 = Plaque covering 2/3 or more of the crown of the tooth


The PI will be assessed by the same examiner on all evaluable teeth at Baseline/Visit 2, Visit 3 and Visit 4.

### Repeatability Exercise

Data for plaque assessments will be taken from replicate examinations performed by the examiner during the study. Depending on subject visit scheduling, every effort will be made to do repeatability examinations during each session, that is, one in the morning and one in afternoon every day examinations are carried out.

Repeatability examinations will have a minimum of 10 minutes between (where possible separated by another subject).



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### 6.2.6. Dental Prophylaxis

A suitable qualified member of clinical staff will provide professional dental prophylaxis for each subject using a standard prophylaxis polishing paste followed by flossing to ensure teeth are free of all supra and gingival calculus and plaque, both visually and by tactile assessment using a dental explorer. A second suitable qualified examiner will then visually check that all plaque has been removed following plaque disclosure. Subjects will have their plaque disclosed and any residual plaque remaining will be removed by the second clinician by dental polishing with a standard prophylaxis polishing paste to bring the subject to zero plaque.

In addition, at the final study visit, subjects will be offered a dental prophylaxis if determined appropriate in the opinion of the investigator or suitably clinically qualified designee.


### 6.2.7. 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

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### 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.

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### 7.1.2. Serious Adverse Events

<b>Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:</b>	
<b>A. Results in death</b>	
<b>B. Is life-threatening</b> 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.	
<b>C. Requires hospitalization or prolongation of existing hospitalization</b> 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.	
<b>D. Results in disability/incapacity</b> 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.	
<b>E. Is a congenital anomaly/birth defect</b>	
<b>F. Other Situations</b> <ul style="list-style-type: none"> <li>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 jeopardize 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.</li> <li>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</li> </ul>	

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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 assigned treatment product 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 utilized for rating the intensity of an event; and both AEs and SAEs can be

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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-characterized 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***

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*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.

### Fax Serious Adverse Events to:

China: PPD

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

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

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## 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 stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- 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, IRB/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 IRB or IEC, if appropriate according to local requirements.



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## 7.6. Definition of and Procedure for Reporting Medical Device Incidents

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


### 7.6.1. Definition of an Incident

Definition of an Incident:
<ul style="list-style-type: none"> <li>Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient or user or of other persons or to a serious deterioration in their state of health.</li> </ul>

### 7.6.2. Reporting of Incidents and Malfunctions

Incident Reporting to GSKCH:
<ul style="list-style-type: none"> <li><b>All incidents must be reported to GSKCH within 24 hours (or sooner if possible) of the investigator or designee becoming aware of the situation.</b></li> <li>Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE or an SAE, the appropriate AE CRF page or SAE form will be completed and reported as per the AE and SAE reporting sections.</li> <li>The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSKCH. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.</li> <li>The completed Incident Report Form should be faxed or emailed to the appropriate GSKCH Study Manager as soon as possible, <b>but not later than 24 hours</b> after study site personnel learn of the event. If there is an SAE, the completed SAE pages should be sent together with this report form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will remain with the subject's records.</li> <li>The GSKCH Study Manager should be notified of the situation by telephone or email.</li> </ul> <p style="text-align: right;"> <b>Fax the Incident Report Forms to:</b>  <b>China:</b> PPD </p>



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

#### **Reporting of Malfunctions to GSKCH:**

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

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

### **7.6.3. Follow-up of Incidents**

#### **Follow-up of Incidents:**

During the study:


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

After the study:

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

#### **Regulatory and Ethics Reporting Requirements for Incidents:**

- The investigator will promptly report all incidents occurring with any GSKCH medical device provided for use in the study within 24 hours. GSKCH has a legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in

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clinical studies. Prompt notification of incidents by the investigator to GSKCH is essential in order to meet legal obligations and ethical responsibility towards the safety of subjects.

- The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB.


## 7.7. Collection of Pregnancy Information

### 7.7.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:
<ul style="list-style-type: none"> <li>• Pregnancy information will be collected on all pregnancies reported following administration of any investigational or washout product. Information on pregnancy identified during the screening phase and prior to investigational or washout product) administration does not need to be collected.</li> </ul>

### 7.7.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:
<ul style="list-style-type: none"> <li>• The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the 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.</li> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> <li>• 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</li> </ul>

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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, memoranda, subjects' diaries, subject files and records kept 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.

All PRO source data should be reviewed by the Study Staff/ Study Monitor (as appropriate) in order to ensure that any potential AEs reported on these documents are represented in the DMS, as detailed in section 8.4.


### 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.

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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


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## 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. 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.

All PRO source data should be reviewed by the Study Staff/ Study Monitor (as appropriate) in order to ensure that any potential AEs reported on these documents are represented in the DMS.

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## 9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

### 9.1 Sample Size Determination

A sufficient number of subjects will be screened to randomize at least 120 subjects to ensure approximately 112 evaluable subjects complete the entire study (approximately 56 per treatment group).

With 56 subjects per treatment group, the study has at least 80% power to detect a treatment difference of 0.08 in bleeding index over a period of 12 weeks treatment. The standard deviation used in calculation is 0.14. The difference of 0.08 represents more than 15% improvement in the test dentifrice compared to the fluoride control dentifrice reference product. CCI [REDACTED]

### 9.2. General Considerations


#### 9.2.1. Definition of Analysis Populations

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

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

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

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### 9.2.2. Exclusion of Data from Analysis

Data listings of protocol violations, including but not necessarily limited to those listed below will be reviewed. Those protocol violations considered to have had affected efficacy will lead to exclusion of either subject or data from PP analyses.

1. Major violation of inclusion or exclusion criteria.
2. Significant non-compliance with assigned product regimen (e.g., under- or over- use)
3. Significant non-compliance with the visit schedule
4. Use of prohibited treatment or medication before or during the study.

All protocol violations reported and their impact on efficacy analyses will be determined between the Biostatistician and Medical Director or designee, ahead of database lock and unblinding.

### 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 a statistically significant reduction in Bleeding Index in the test dentifrice group compared to the reference dentifrice group after 12 weeks of study treatments.

### 9.2.5. Criteria for Assessing Tolerability

No specific safety criteria are planned for this study. Adverse Events and OST abnormalities will be assessed in each treatment group.

### 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 imputed.

## 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.

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### 9.3.2. Primary Analysis

Primary efficacy endpoint will be the Bleeding Index (BI) score after 12 weeks of study treatments. BI score will be calculated as the average index over all tooth sites. ANCOVA model will be applied for primary analysis with treatment, gender, smoking status and baseline MGI stratification as factors and baseline score as covariate. Adjusted means of two treatments and treatment difference will be provided together with 95%CI and P-values.

The assumption of residual normality and variance homogeneity in ANCOVA analysis will be investigated. If violated, data transformation or a non-parametric method will be used.

### 9.3.3. Secondary Analyses

#### ***BI score at Week 6***

BI score at Week 6 will be analysed using the same ANCOVA model as used for primary analysis.

#### ***Number of bleeding sites at Week 6 and Week 12***

Number of bleeding sites will be calculated as the number of sites with a BI score of 1 or 2. At each post-baseline visit, number of bleeding sites will be analysed using ANCOVA model with treatment, gender, smoking status and baseline MGI stratification as factors and baseline score as covariate. Adjusted means of two treatments and treatment difference will be provided together with 95%CI and P-values.

#### ***MGI score at Week 6 and Week 12***


MGI score will be calculated as the average index over all tooth sites. At each post-baseline visit, MGI score will be analysed using ANCOVA model with treatment, gender, smoking status as factors and baseline score as covariate. As baseline MGI is included as covariate, baseline MGI stratification will not be included again. Adjusted means of two treatments and treatment difference will be provided together with 95%CI and P-values

#### ***Overall plaque score at Week 6 and Week 12***

Overall plaque score will be calculated as the average index over all tooth sites. At each post-baseline visit, overall plaque score will be analysed using ANCOVA model with treatment, gender, smoking status and baseline MGI stratification as factors and baseline score as covariate. Adjusted means of two treatments and treatment difference will be provided together with 95%CI and P-values.

#### ***Interproximal plaque score at Week 6 and Week 12***



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Interproximal plaque score will be calculated as the average index over interproximal sites. Interproximal plaque score will be analysed similarly as overall plaque score.

For all of the above secondary analyses, Normality assumptions in ANCOVA models will be checked and accounted for in the same way as for the primary variable.

#### 9.3.4. Safety Analysis

All AEs will be coded using MedDRA. AEs will be categorized as oral and non-oral by the Medical Director or designee prior to database lock. AEs and oral soft tissue abnormalities will be listed by treatment and reviewed. Only treatment emergent AEs (i.e. those occurring after first use of either of the study treatments) will be tabulated. AEs occurring prior to randomisation will be included in the AE listing.

#### 9.3.5. Repeatability Analysis

A number of subjects will have repeat gingivitis (MGI and TPI) 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 purpose of repeated assessments is to check the consistency of the examiner. As each subject will provide around 100 records for repeatability judgement, one subject on the morning and one subject in the afternoon in each visit day over the course of the study is sufficient for repeatability assessment. The first and second assessments on each tooth at a given visit will be cross-tabulated and a weighted Kappa coefficient ( $\kappa$ ) 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  $0.4 \leq \kappa \leq 0.75$
- 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.

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## 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 IRB/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 IRB/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.

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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 IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

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- If the GSKCH terminates or suspends a trial, the investigator should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.
- If the IRB/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.

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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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CCI [REDACTED]
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## 12. APPENDICES

### 12.1. Appendix 1 - Abbreviations and Trademarks


#### Abbreviations

AE	Adverse Event
CD	Compact Disc
CRF	Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GSKCH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention to Treat
PII	Personally Identifiable Information
PP	Per Protocol
SAE	Serious Adverse Event
PRO	Patient Reported Outcome

#### Trademark Information

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## SIGNATURE PAGE

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<b>Justification</b>	Biostatistics Approval

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