CLINICAL PROTOCOL

A Randomized, Controlled, Examiner-Blind Clinical Study Investigating the Effects of a Dentifrice Containing 67% Sodium Bicarbonate When Used Twice Daily for 12 Weeks on Gingivitis Treatment and Plaque Removal

Protocol Number:	300029
Compound/Product Name:	Dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	N/A
Other Regulatory Agency Identified Number:	N/A
Phase:	N/A

This document contains confidentiality statements that are not relevant for this publicly available version

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** St Georges Avenue, Weybridge, Surrey, KT13 0DE, United Kingdom (UK)
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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	• Updated the AE reporting mailbox • Removed appendix (15.1)-Product Usage Instruction • Section 5.2 (AT BASELINE (Visit 2)): updated the order number (a,b,c) to (d,e,f), which helps to differentiate the items in "AT SCREENING (Visit 1)" • Correction of typos
Amendment 2	3.0	• Clarified compliance guidelines by adding ISO 14155 in 1) principal investigator Protocol Agreement page; 2) section 6.1.1; 3) 10.10; 4) 13.3.2; 5) 13.3.3 • Clarified Schedule of Activities table • Clarified “number of bleeding sites” calculation in section 9.2.2 • Section 12.2 and 12.3: Clarified that the mITT will be used for efficacy analyses. • Section 12.1, 12.3, 12.3.1 and 12.3.2: Clarification added with respect to statistical analysis model and control of multiplicity

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

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines and applicable portions of EU MDR 2017/745 and European Nation International Organisation for Standardisation (ISO) 14155:2011 and ISO 14155:2020
- 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:	PPD
Investigator Qualifications:	PPD
Investigator Signature:	PPD
Date of Signature/Agreement:	PPD DD-Mmm-YYYY

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1 PROTOCOL SUMMARY

1.1 Synopsis

Background and Rationale:

The sponsor markets dentifrices containing 62-67% w/w sodium bicarbonate as a specialist gum health toothpaste by facilitating the removal of plaque bacteria, thereby reducing gingivitis. The sponsor has sponsored a series of clinical studies, per current international guidelines, assessing the gingival health benefits of twice daily use of sodium bicarbonate-containing dentifrices (Kakar et al 2014, Newby et al 2014, Lomax et al 2017, Jose et al 2018, Akwagyiram et al 2018.). The results consistently demonstrated that sodium bicarbonate-containing dentifrices significantly reduced plaque and improved clinical measures associated with gingivitis compared to the negative control fluoride toothpaste. Among these studies, only one study (sponsor clinical study CCI 2012) didn't include professional tooth cleaning at screening or baseline visits (pre-prophylaxis process). This study is designed to add more data on measuring gingivitis progression in subjects that do not receive a professional dental cleaning.

The definition of periodontal health and wellness has evolved since 1999, and the Classification of Periodontal and Peri-Implant Diseases and Condition was updated in 2017 (Chapple et al., 2018). The new classification, for the first time, clearly defines periodontal health and gingivitis for patients with intact periodontium, and patients with reduced periodontium due to periodontitis or other cause. Under the new classification, the bleeding on probing (BOP) and pocket depth become critical factors in determining patients' gingival health status, which therefore affect the inclusion and exclusion criteria for gingivitis clinical studies.

This clinical study will investigate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.31% w/w sodium fluoride, without pre-prophylaxis process, in gum health and plaque clinical indices, and compare it to a marketed regular fluoride dentifrice after 12 weeks twice daily brushing for subjects with gingivitis as defined by the updated classification of periodontal health (Chapple et al., 2018).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride, compared to its baseline, for the assessment of gingivitis, as measured by the number of bleeding sites, after 12 weeks twice daily toothbrushing.	Number (no.) of bleeding sites at 12 weeks, compared to baseline
Secondary	
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride, compared to negative control, for the assessment of gingivitis, as measured by the number of bleeding sites after 12 weeks twice daily toothbrushing.	Number (no.) of bleeding sites at 12 weeks, compared to negative control
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride for the assessment of gingivitis, as measured by the number of bleeding sites after 3 and 6 weeks twice daily toothbrushing.	Number (no.) of bleeding sites at 3 and 6 weeks, compared to baseline and negative control

To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride for the assessment of gingivitis, as measured by the Bleeding Index (BI) after 3, 6 and 12 weeks twice daily toothbrushing.	Mean Bleeding Index (BI) at 3, 6 and 12 weeks, compared to baseline and negative control
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride for the assessment of gingivitis, as measured by the Modified Gingival Index (MGI) after 3, 6 and 12 weeks twice daily toothbrushing	Mean MGI at 3, 6 and 12 weeks, compared to baseline and negative control
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride for the assessment of plaque accumulation, as measured by the Turesky Plaque Index (TPI, overall and interproximal) after 3, 6, and 12 weeks twice daily brushing.	Mean TPI (overall and interproximal) at 3, 6 and 12 weeks, compared to baseline and negative control
Safety	
To assess the oral tolerability of dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride, over 12 weeks twice daily use.	Treatment-emergent adverse events over 12 weeks

Study Design:

This will be a single center, controlled, single blind (examiner blind), randomized, two-treatment arm, parallel study in volunteers with clinically measurable levels of gingivitis, defined as those with 10-30 % bleeding sites on probing (Chapple et al., 2018). Study subjects will be over 18 years old, non-smokers, in good general health that meet all study criteria at the Screening and Baseline visits.

Approximately 200 subjects (n=100 per group) will be randomized to ensure 188 evaluable subjects (94 per group) complete the study.

This study will consist of 5 study visits (Screening, Baseline, Week 3, 6, and 12). At Visit 1, Screening, after signing informed consent, subjects will undergo an Oral Soft Tissue (OST) examination, an Oral Hard Tissue (OHT) examination and a gross assessment of gingival health, in addition to the standard procedures (inclusion, exclusion, medical history, demographics, prior/current medications) to assess eligibility for the study. Subjects will return to site 14±3 days after the Screening Visit, for Visit 2, Baseline.

At the Baseline Visit, subjects will undergo, in the following order, a full OST/ OHT examination followed by assessments of gingival inflammation (MGI), gingival bleeding (BI) including BOP (bleeding on probing) which is derived from BI assessment, periodontitis status (pocket depth), and supra-gingival plaque using the Turesky Plaque Index (TPI). Subjects with BOP, pocket depth or TPI score 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 for all clinical assessments (MGI, TPI, BI).

After all clinical assessments, subjects will be instructed to brush for at least a minute, in their usual manner, with their assigned study product and then instructed to continue using their assigned product twice daily (morning and evening), for 3 ,6 and 12 weeks after which they will return for their Visits 3, 4 and 5 assessments respectively. Subjects will record all brushing events in the diary provided (paper or electronic), and this will be reviewed by the site at each study visit.

After the Week 12 visit, study closeout procedures (return of study product etc.) will take place and subjects may undergo a prophylaxis if it is deemed necessary by the examiner. Safety and oral tolerability of the study products will be monitored over the 12 -week treatment period by review of reported Adverse Events and Incidents.

Study Products:

	Washout Dentifrice	Test Dentifrice	Reference Dentifrice
Product Name	Colgate Cavity Protection Dentifrice containing 0.76% w/w Sodium Monofluorophosphate (1000 ppm F) and 0.1% w/w Sodium Fluoride (450 ppm F)	Corsodyl Original Dentifrice containing 67% w/w Sodium Bicarbonate + 0.310% w/w Sodium Fluoride (1400 ppm F)	Colgate Cavity Protection Dentifrice containing 0.76% w/w Sodium Monofluorophosphate (1000 ppm F) and 0.1% w/w Sodium Fluoride (450 ppm F)
Product Master Formulation Code (MFC)	N/A	CCI	N/A
Dose/Application	Subjects will use the provided washout product during the washout period. Subjects will use their allocated study product for 12 weeks. Subjects will dose the toothbrush provided with a ribbon of paste to cover the brush head (a full brush head) on each brushing occasion. Each brushing occasion will be recorded by the subject in their diary to enable assessment of treatment compliance. • Washout period (Visit 1-2): Subjects will brush their teeth according to their normal brushing habits twice a day (morning and evening) with the washout product. • Visit 2 – Visit 5: Subjects will brush twice daily (morning and evening) for at least a (timed) minute with their allocated product.		
Route of Administration	Oral topical		
Return Requirements	All used/unused samples to be returned		

Type and Planned Number of Subjects:

Sufficient subjects will be screened to randomize approximately 200 subjects to study treatment (approximately 100 per treatment group) to ensure 188 evaluable subjects complete the study.

1.2 Schedule of Activities

The schedule of activities table provides an overview of the subject visits and study procedures. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening		Study Visits			
	Visit 1		Visit 2 Day 0 Baseline[1]	Visit 3 Day 21±3 (Week 3)[1]	Visit 4 Day 42±4 (Week 6)[1]	Visit 5 Day 84±4 (Week 12)[1]
Informed consent	X	Washout period 14 days				
Medical history	X					
Demographics	X					
Current/prior/concomitant medication review	X		X	X	X	X
OST Examination	X		X	X	X	X
OHT Examination	X		X			X
Gross gingival assessment[2]	X					
Review of Inclusion/exclusion Criteria	X		X			
Subject eligibility	X		X			
Subject continuance				X	X	X
Dispense washout toothpaste, toothbrush and washout diary[3]	X					
Return Washout Toothpaste/Toothbrush			X			
Modified Gingival Index (MGI) assessment			X	X	X	X
MGI repeat assessment[4]			X	X	X	X
Bleeding Index (BI) assessment[5]			X	X	X	X
Pocket Depth Assessment			X			
Plaque disclosure and plaque index (TPI) assessments			X	X	X	X
TPI repeat assessment[6]			X	X	X	X
Randomization			X			
Dispense study products, new toothbrush and timer			X			
Dispense study diary & instructions on how to complete			X			
Oral hygiene instruction[7] & supervised brushing with study dentifrice			X	X	X	
Review diary completion[8]			X	X	X	X
Collect study products, assess compliance, and return to subject				X	X	
Return study products (end of study)[9]						X
End of study dental prophylaxis (optional)						X

Adverse events review[10]	X		X	X	X	X
Medical device incidents review[8]			X	X	X	X
Study conclusion						X

Abbreviations: OST: Oral Soft Tissue, OHT: Oral Hard Tissue, MGI: Modified Gingivitis Index, TPI: Turesky Plaque Index, BOP: bleeding on probing

Footnotes:

1: Subjects will abstain from overnight toothbrushing for a minimum of 12hrs (+6hr, -2hr) immediately prior to the assessment visits (Visits 2, 3, 4 and 5)

2: In relation to the general dentition inclusion/ exclusion criteria

3: An electronic study diary will be installed on the personal mobile phones of subjects who consent to use it during the study period. A paper diary will be dispensed to subjects who are unable to adhere to completing their electronic diary.

4: One MGI repeat assessments during each clinical assessment day.

5: BOP and number of bleeding sites are derived from BI assessment

6: One TPI repeat assessments during each clinical assessment day

7: Instruction

8: Electronic or paper diary, depend on the type of diary that subject receives.

9: If installed at screening the electronic study diary will be deactivated at the last visit. Diaries (paper or electronic diary) will be reviewed for completion and then collected.

10: Adverse Events (AEs), Serious Adverse Events (SAEs) and medical device incidents collected immediately after subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF). Medical device in this study is the test product.

2 INTRODUCTION

Gingivitis is an inflammatory response to the presence of dental plaque (Kinane and Hodge 2001), which typically presents as redness, swelling (edema), and/or bleeding of the gums at the gingival margin surrounding the tooth. Gingivitis is a reversible condition but, if left untreated, can progress to the irreversible phase of periodontitis, where inflammation extends to the underlying tissues, periodontal ligament, and alveolar bone. The resulting loss of these structures can eventually lead to tooth loss through destruction of the periodontal tissues supporting the tooth. Periodontitis is reported to affect 5 to 20% of the world's population (Petersen and Ogawa 2012). The maintenance of good gingival health is therefore important in preventing gingivitis and the development of periodontal disease (Chapple et al., 2015).

Dental plaque is a soft, sticky, colorless deposit of bacteria which collects on the teeth and along the gingival margin. It is a causative agent of gingivitis and periodontitis (Silness and Loe 1964, Theilade et al 1966, Kinane and Hodge 2001, Davies 2008, Chapple et al 2015). Gingivitis develops when the plaque elicits a local inflammatory response in the gingivae at the site of its accumulation (Marsh 1992, Davies 2008). Gingivitis is prevented and resolved through effective plaque control, primarily via mechanical plaque removal i.e., toothbrushing (Marsh 1992, Brook 2003, Ower 2003, van der Weijden and Hioe 2005, Davies 2008, Chapple et al 2015).

Sodium bicarbonate in a dentifrice has been shown to enhance the removal of plaque biofilms which are the causative agent of gingivitis (Bosma et al 2018, Ghassemi et al 2008, Jose et al 2018, Newby et al 2014). The literature reports that the mode of action of sodium bicarbonate in toothpaste is:

- The large crystals of sodium bicarbonate may help the toothbrush to physically displace plaque from the tooth surface (Putt et al 2008).
- Sodium bicarbonate may reduce the viscosity of the polysaccharide matrix which helps bind the bacteria together and to the tooth surface, resulting in easier plaque removal (Putt et al 2008).

The primary objective of this study is to evaluate gingivitis treatment (number of bleeding sites) following twice-daily use of a 67% sodium bicarbonate toothpaste for 12 weeks. The study will also assess other indices, e.g., BI and MGI (for gingivitis treatment) and TPI (for dental plaque removal).

2.1 Study Rationale

Sodium bicarbonate has been incorporated into toothpaste formulas by several manufacturers, and a large number of clinical studies have been conducted to prove the efficacy of sodium bicarbonate-containing toothpaste in gingivitis treatment. Those studies could also be categorized depending on the formulas tested or the study's procedure, e.g., whether a professional tooth cleaning at Screening or Baseline Visit (pre-prophylaxis process) was included (Kakar et al 2014, Newby et al 2014, Lomax et al 2017, Jose et al 2018, Akwagyiram et al 2018) or not (Ghassemi et al, 2008, sponsor clinical study CCI 2012).

Most the sponsor's studies on high concentration (62%-67%) sodium bicarbonate formula included pre-prophylaxis, which have been summarized in a pooled analysis (sponsor clinical study 209509, 2020). More recently a randomized clinical study testing 67% sodium bicarbonate containing dentifrice (sponsor clinical study 208175, 2021) investigated bleeding (bleeding index (BI)), gingival inflammation (modified gingival index (MGI)), and plaque

(plaque index (TPI)) outcome measures. On the other hand, there was only one sodium bicarbonate gum-health study sponsored by the sponsor that excluded the pre-prophylaxis process. Study (sponsor clinical study CCI 2012) tested a 67% sodium bicarbonate dentifrice, a 62% sodium bicarbonate dentifrice compared to a toothpaste without sodium bicarbonate after 12 weeks use. The study assessed bleeding and plaque index (no gingival index), and the subject population included non-smokers and smokers.

The definition of periodontal health and wellness has evolved since 1999, and the Classification of Periodontal and Peri-Implant Diseases and Condition was updated in 2017. The new classification takes advantage of the knowledge from biological and clinical research (Dietrich, et al. 2019). For the first time, the new classification differentiates dental plaque-induced gingivitis on an intact and a reduced periodontium. BOP (%) and pocket depth, which are more accurate and objective than previously broadly used GI (gingival index) and BI (bleeding index), become critical in diagnosing patients' periodontium health. Localized and generalized, associated with BOP are also introduced to replace previously widely used "mild" and "moderate" to define the severity of gingivitis. The classification update potentially impacts the inclusion/exclusion criteria of the clinical studies. Recent studies testing dental floss and mouthwash have used some aspects of this updated classification to define inclusion and exclusion criteria (Rotella, et al 2022).

This study will also include the use of an electronic subject diary in order to capture subject reporting on compliance in real time. Historically paper diaries have been used, but in efforts to acquire reliable and real-time data e-diaries are being introduced in this study. The e-diary will work as a subject engagement tool in order to increase protocol compliance and adherence to the study requirements. Features such as reminder when brushings are missed and when visits are scheduled will be built into the diary application. In addition, subjects will be able to record Adverse Events and Concomitant medications allowing the investigator to complete safety reviews between visits if required. This will provide increased safety oversight on the study. In circumstances where subjects are unable to complete the e-diary e.g., they do not own a smart phone, paper diary will be provided which will capture same information. The learnings from using an electronic diary will help us digitalize further aspects of study execution and adopt a participant-centricity approach and promote engagement.

A first sponsor gum health study adopts the new classification for inclusion/exclusion criteria while excludes a professional tooth cleaning at screening or baseline visits (pre-prophylaxis process) to represent a broader population will be conducted to evaluate the efficacy of 67% w/w sodium bicarbonate toothpaste in reducing gingival inflammation, bleeding and plaque accumulation compared to a regular fluoride dentifrice. The results will help us better understand the benefit of 67% sodium bicarbonate toothpaste on improving patients' gingival health.

2.2 Background

The sponsor has sponsored a series of clinical studies, per current international guidelines, assessing the gingival health benefits of twice daily use of sodium bicarbonate-containing dentifrices (Kakar et al 2014, Newby et al 2014, Lomax et al 2017, Jose et al 2018, Akwagyiram et al 2018). The results consistently demonstrated that sodium bicarbonate-containing dentifrices significantly reduced plaque accumulation and improved clinical measures associated with gingivitis compared to the negative control fluoride toothpaste.

A pooled analysis of six sponsored clinical gingivitis studies was conducted to evaluate 67% w/w sodium bicarbonate dentifrice's benefit on gingival health improvements and plaque

accumulation reduction. (sponsor clinical study 209509, 2020). All studies (in the pooled analysis) had a pre-prophylaxis procedure at screening or baseline visits. In these studies, the sodium bicarbonate dentifrices showed significant benefits across all assessments (TPI, GI, BI, and the number of bleeding sites) at all main data points (week 6, 12, and 24) compared to the negative controls.

Most previous studies with no initial pre-prophylaxis were single brushing studies, which could only provide information on plaque removal (Bosma et al., 2018). Study CCI (completed in 2012), was the only sponsor sponsored sodium bicarbonate gum study that included pre-prophylaxis. It was a 12-week study to evaluate sodium fluoride toothpaste with 67% or 62% w/w sodium bicarbonate (negative control: sodium fluoride toothpaste with 0% sodium bicarbonate) on gingival health. The study assessed bleeding and plaque index but did not assess gingival index, and the subject population included non-smokers and smokers.

The 2017 World Workshop Classification system for periodontal and peri-implant diseases and conditions was updated from the previous 1999 International Classification of Periodontal Diseases. The new classification is expected to be more accurate and objective by introducing BOP (bleeding on probing, %) and pocket depth in diagnosing patients' periodontium health. The classification update potentially impacts the inclusion/exclusion criteria of the study population.

Traditionally, in a clinical study, subjects use paper diaries to record their compliance, and they often get reminders for the visits and activities associated with visits through phone calls or text messages from the clinical stie. The e-diary working as a subject engagement tool to increase protocol compliance and adherence to the study requirements is introduced to the study. Features such as reminders when brushings are missed and when visits are scheduled are built into the diary application. With the e-diary, subjects can also record Adverse Events and Concomitant medications on time, and the investigator can complete safety reviews between visits if required.

2.3 Benefit/Risk Assessment

Sodium bicarbonate dentifrice has a well-characterized safety profile to help stop and prevent gingivitis (bleeding gums) by the physical removal of plaque in adults and adolescents 12 years and above.

The sponsor has sponsored a series of clinical studies, per current international guidelines, assessing the gingival health benefits of twice daily use of 67% w/w sodium bicarbonate-containing dentifrices. The results consistently demonstrated that sodium bicarbonate-containing dentifrices significantly reduced plaque accumulation and improved clinical measures associated with gingivitis compared to negative control fluoride toothpaste.

2.4 Mechanism of Action/Indication

Sodium bicarbonate in a dentifrice has been shown to enhance the removal of plaque biofilms which are the causative agent of gingivitis (Bosma et al 2018, Ghassemi et al 2008, Jose et al 2018, Newby et al 2014). The literature reports that the mode of action of sodium bicarbonate in toothpaste is:

- The large crystals of sodium bicarbonate may help the toothbrush to physically displace plaque from the tooth surface (Putt et al 2008).

- Sodium bicarbonate may reduce the viscosity of the polysaccharide matrix which helps bind the bacteria together and to the tooth surface, resulting in easier plaque removal (Putt et al 2008).

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride, compared to its baseline, for the assessment of gingivitis, as measured by the number of bleeding sites after 12 weeks twice daily toothbrushing.	Number (no.) of bleeding sites at 12 weeks, compared to baseline
Secondary	
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride, compared to negative control, for the assessment of gingivitis, as measured by the number of bleeding sites after 12 weeks twice daily toothbrushing.	Number (no.) of bleeding sites at 12 weeks, compared to negative control
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride for the assessment of gingivitis, as measured by the number of bleeding sites after 3 and 6 weeks twice daily toothbrushing.	Number (no.) of bleeding sites at 3 and 6 weeks, compared to baseline and negative control
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride for the assessment of gingivitis, as measured by the Bleeding Index (BI) after 3, 6 and 12 weeks twice daily toothbrushing.	Mean Bleeding Index (BI) at 3, 6 and 12 weeks, compared to baseline and negative control
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride for the assessment of gingivitis, as measured by the Modified Gingival Index (MGI) after 3, 6 and 12 weeks twice daily toothbrushing	Mean MGI at 3, 6 and 12 weeks, compared to baseline and negative control
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride for the assessment of plaque accumulation, as measured by the Turesky Plaque Index (TPI, overall and interproximal) after 3, 6, and 12 weeks twice daily brushing.	Mean TPI (overall and interproximal) at 3, 6 and 12 weeks, compared to baseline and negative control
Safety	
To assess the oral tolerability of dentifrice containing 67% w/w sodium bicarbonate and 0.310% w/w sodium fluoride, over 12 weeks twice daily use.	Treatment-emergent adverse events over 12 weeks

4 STUDY DESIGN

4.1 Overall Design

This will be a single center, controlled, single blind (examiner blind), randomized, two-treatment arm, parallel study. Study subjects will be over 18 years old, non-smokers, in good general health with clinically measurable levels of gingivitis (defined as those with 10-30 % bleeding sites on probing (Chapple et al., 2018)) that meet all study criteria at the Screening and Baseline visits.

Approximately 200 subjects (n=100 per group) will be randomized to ensure 188 evaluable subjects (94 per group) complete the study.

This study will consist of 5 study visits: Screening, Baseline, Week 3, 6 and 12. Gingivitis will be assessed using MGI (Lobene et al, 1986) and BI (Saxton and van der Ouderaa, 1989). Plaque will be assessed by the Turesky modification of the Quigley Hein Index (TPI) (Lobene et al, 1982). All evaluable teeth (in relation to the inclusion/ exclusion general dentition criteria) will be assessed.

At Screening visit (Visit 1; in relation to subject screening), subjects will provide their written informed consent to participate in the study. Demographics, medical history, and current medications will be recorded, followed by an oral examination (oral soft tissue (OST), oral hard tissue (OHT) examination and dentition exclusions) and a gross gingival assessment. Eligible subjects will be given washout toothpaste and toothbrush to use in between the Screening and Baseline Visits. They will also be issued with a study diary on product usage. For the subjects who consent to use the electronic study diary application during the study period, the e-diary app will be installed on the subject's own mobile device and the diary data will be collected remotely through the study app.

Within 14±3 days of Screening (Visit 1), eligible subjects will return to the site for the Baseline visit (Visit 2) with overnight plaque (subjects will be instructed to abstain from oral hygiene for 12 hours [+6 hours; -2 hours] i.e., overnight immediately before the visit). At the Baseline visit, subjects will undergo, in the following order, a full OST and OHT examination, assessments of gingival inflammation (MGI), gingival bleeding (BI), pocket depth and supra-gingival plaque (TPI). Subjects with BOP (derived from BI assessment), pocket depth or TPI score outside the study range will be discontinued from the study at this visit. Eligible subjects will then be randomized to study product and undergo a supervised brushing, where they will be instructed to brush for a least a minute at site with their assigned study product, after which they will be instructed to continue using their product twice daily (morning and evening until their next visit), at least a minute/each time.

After using the study dentifrice for 3, 6, and 12 weeks, subjects will return to the study site (Visits 3, 4, and 5, respectively) with overnight plaque (subjects will be instructed to abstain from overnight toothbrushing for 12 hours [+6 hours; -2 hours] immediately before each assessment visit), at approximately the same time of day as the Baseline visit. The study dentifrice and the diary will be reviewed to determine treatment compliance. Subjects will have a full OST examination and then undergo, in the following order, MGI, BI, and TPI assessments. At Visit 5, subjects will also have a full OHT examination, return all study supplies and have a dental prophylaxis if deemed appropriate by the investigator or examiner. The study diary app. will be deactivated at Visit 5 for those subjects who had the app. installed on their phones.

At Visits 2, 3, 4, and 5, repeatability data will be generated for MGI and TPI assessments from replicate examinations on the same subject (the subject for the MGI repeat assessment and the subject for the TPI assessment can be different). Depending on subject visit scheduling, every effort will be made to complete one repeatability examination for each clinical measure during each clinical assessment day, that is, at least one MGI and one TPI repeat assessment on each assessment day. Repeatability examinations will be separated by a minimum of 10 minutes and, where possible, separated by another subject. Due to the invasive nature of the BI assessment, it is not feasible to conduct an accurate repeatability assessment for this index.

Adverse events (AEs) and incidents will be recorded from informed consent and at the end of each study visit.

4.2 Scientific Rationale for Study Design

The main goal of this study is to evaluate and compare the efficacy of an on-market dentifrice containing 67% w/w sodium bicarbonate and 0.31% w/w sodium fluoride to a reference regular fluoride dentifrice on treating gingival bleeding and gingival inflammation as well as reducing plaque accumulation in population with gingivitis after 12 weeks use.

This design is typical of many studies conducted to evaluate the clinical efficacy of dentifrices in the treatment of gingivitis (FDA., 2005), except for excluding professional dental cleaning at the start of the study. Study subjects with a pre-specified level of gingivitis are randomized to the study product; efficacy is determined after a period of twice-daily brushing, compared to a control/comparator dentifrice.

For this non-pre-prophylaxis study, the 12 weeks timepoint will help ensure sufficient time to demonstrate a significant effect. (sponsor clinical study CCI 2012). Colgate Cavity Protection, which has been used in several plaque removal or gingivitis studies (Mankodi et al 1998, Triratana et al., 2015), is chosen as the negative control in this study. The earlier time points, 3 weeks and 6 weeks are considered to help obtain extra information on the progress.

The MGI and the BI are established clinical measures of gingival inflammation and gingival bleeding, respectively (i.e., gingival health, FDA., 2005); the TPI is an established clinical measure of supra gingival plaque accumulation (FDA., 2005). A single clinical examiner will be responsible for the conduct of the gingivitis and plaque accumulation measures (the same examiner being able to conduct all gingivitis/ plaque assessments) for the duration of the study for all subjects to eliminate the possibility of inter-examiner variability.

To assess examiner reproducibility across the treatment period, repeat MGI and TPI assessments will be performed on selected subjects throughout the study. Due to the invasive nature of the index, repeatability assessments are not feasible for the BI.

Based on widely recommended oral hygiene practices and typical consumer habits, all subjects will follow the same dosage regimen of twice-daily treatment (morning and evening) for the washout dentifrice and study products. To facilitate compliance with product usage throughout the study and to enable staff to confirm correct dosing, a supervised brushing will be performed on-site at the end of Visits 2-4. Subjects will also be required to record each brushing in the diary provided, including the time of the last brushing before returning for the site assessment visits. During the washout period for this study (14±3 days), eligible subjects will use a marketed, regular fluoride toothpaste and toothbrush (as provided). Using these products before the Baseline visit will help familiarize subjects with the dosing/diary completion requirements. It will also serve as a 'washout' from any anti-plaque ingredients contained in the subject's own oral hygiene products.

A parallel group design has been selected as most appropriate for this investigation. Anticipated differential changes in clinical variables among treatment groups could lead to carryover effects and an altered oral health state, which makes a crossover design inappropriate for this study. The dosage regimen of twice daily use (morning and evening) will be the same for each treatment group.

Healthy subjects with clinically measurable levels of gingivitis (10-30% bleeding site on probing) will be included in the study population. The gingivitis status inclusion and exclusion criteria follow the new classification (2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Condition (Chapple et al., 2018). This will help to minimize the risk of an atypical or potential lack of treatment response for subjects with sever gingival health conditions that may otherwise be managed professionally rather than solely via home use of a twice-daily dentifrice.

Smokers will be excluded from this investigation because of the masking effect of smoking on bleeding on probing. Based on the literature, smoking decreases the blood flow within the gingival microvasculature and interferes with neutrophil function, suppressing the inflammatory response to dental plaque and masking the clinical signs of periodontal disease (Machuca et al, 2000; Obeid and Bercy, 2000).

Hormonal changes during pregnancy may affect the response of the gingival tissue to plaque bacteria and could impact the gingivitis efficacy measurements (Figuero et al., 2010). Therefore, women who are pregnant at Screening will be excluded, and women who become pregnant during the study will be discontinued. It should be noted, however, that there are no safety concerns with pregnant women using any of the study products.

According to the International Conference on Harmonisation (ICH) guidelines (ICH, Nov 2016), 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 this oral care study, the level of blindness for this study is described as “examiner blind.”

4.3 Justification for Dose

The study products are dentifrices, intended for topical oral use, and will be applied by toothbrushing using a manual toothbrush. The dosage regimen of twice daily treatment (morning and evening) will be the same for all subjects and is based on Delivering better oral health guidance. Study subjects will be instructed to brush for at least a minute with their assigned study dentifrice on each brushing occasion. After 12 weeks (Day 84±4days) twice daily treatment, each subject should complete approximately 168 treatment applications. Each subject will complete a supervised brushing with their assigned study dentifrice at the end of each study visit (while still at the study site) except the last visit to enable staff to check correct dosing and encourage compliance with product usage throughout the study.

4.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (last subject last visit date).

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

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Sufficient subjects will be screened to randomize approximately 200 subjects to ensure 188 evaluable subjects complete the entire study.

An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process directly or via their legally authorized representative and successfully met eligibility criteria to proceed beyond the screening visit as applicable for the protocol design.

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

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

5.2 Inclusion Criteria

Eligible subjects are expected to meet the following inclusion criteria to be eligible for enrollment into the study:

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.

2. Subject is male or female who, at the time of screening, is at least 18 years old, inclusive.

3. A subject who is willing and able to comply with scheduled visits, treatment plan, and other study procedures.

4. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, no clinically significant/relevant abnormalities in medical history or upon oral examination, or condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.

5. Subject oral health that meets all the following:

AT SCREENING (Visit 1):

a. Subject with at least 20 natural, permanent teeth.

b. Subject with at least 40 evaluable surfaces for MGI, BI, and TPI.

An evaluable surface is defined as having 2/3rds of the natural tooth surface gradable for the selected clinical indices. The following should not be included in the evaluable surface count- third molars; fully crowned/extensively restored, grossly carious, orthodontically banded/bonded or abutment teeth; surfaces with calculus deposits which, in the opinion of the clinical examiner, would interfere with the baseline assessments of the selected clinical indices.

c. A subject with plaque-induced gingivitis, in the opinion of the clinical examiner, as confirmed by a gross visual examination at the Screening Visit.

AT BASELINE (Visit 2):

d. A subject with ongoing hard tissue eligibility and, in the opinion of the clinical examiner, at least 40 evaluable surfaces.
e. A subject with 10% < BOP < 30%.
f. A subject with mean whole mouth TPI score ≥1.5.

5.3 Exclusion Criteria

Subjects who meet any of the following exclusion criteria were not eligible for enrollment into the study:

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a sponsor's employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.
3. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
4. A subject who has any other clinical serious or unstable conditions (e.g., cardiovascular diseases, diabetes, liver disorders, and kidney disorders) which could have affected study out comes and/or subject safety.
5. A subject who is a pregnant female (self-reported) or is intending to become pregnant over the duration of the study.
6. A subject who is a breastfeeding female.
7. A subject who is known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
8. A subject who is unwilling or unable to comply with the lifestyle considerations
9. Subject who is a current smoker or an ex-smoker who stopped within 6 months of Screening.
10. Subject who is using smokeless forms of tobacco (e.g., chewing tobacco, gutkha, pan containing tobacco, nicotine-based e-cigarettes).
11. A subject who is diagnosed xerostomia or is taking any medication that in the view of the investigator is causing xerostomia.
12. A subject who has a medical condition which could have directly influenced gingival bleeding.
13. A subject who has a bleeding disorder that could have affected study outcomes and/or subject safety.
14. A subject who has a recent history (within the last year) of alcohol or other substance abuse.

15. A subject who has a severe oral condition (e.g., acute necrotizing ulcerative gingivitis or oral or peri-oral ulceration including herpetic lesions) that could, in the opinion of the investigator, compromise study outcomes or the oral health of the subject/examiner if they participate in the study.
16. Presence of a tongue or lip piercing, or any other oral feature that could interfere with the usage of a toothbrush.
17. **Medication exclusions:**

At screening (Visit 1):

a. A subject using any antibiotic medication within 14 days prior to screening or at any time during the study.

b. A subject currently taking an anti-inflammatory medication which, in the opinion of the Investigator, could affect gingival condition.

c. A subject currently taking a systemic medication (e.g., anti-inflammatory, anti-coagulant, immunosuppressants) or traditional/ herbal remedy which, in the opinion of the Investigator, could affect plaque/ gingival condition (e.g., ibuprofen, aspirin, warfarin, cyclosporin, phenytoin, calcium channel blockers).

18. **Medication exclusions**

At Baseline (Visit 2):

a. A subject who has taken (in the previous 14 days), any antibiotics.

b. A subject who has taken (in the previous 14 days) a systemic medication (e.g., anti-inflammatory, anti-coagulant, immunosuppressants) or traditional/ herbal remedy which, in the opinion of the Investigator, could affect plaque/ gingival condition (e.g., ibuprofen, aspirin, warfarin, cyclosporin, phenytoin, calcium channel blockers).

c. A subject who has used an antibacterial dentifrice or mouthwash (e.g., chlorhexidine) or any oral care product that in the view of the investigator could interfere with plaque formation or measures of gingivitis, in the period between Screening and the Baseline visit.

19. **Periodontal exclusions**

a. A subject who shows signs of periodontitis (one or more sites with probing pocket depths > 3 mm).

b. A subject who is receiving or has received treatment for periodontal disease (including surgery) within 12 months of Screening.

c. A subject who has gingivitis, which in the opinion of the investigator, is not expected to respond to treatment with an over the counter (OTC) dentifrice.

20. **Dental Exclusions**

a. A subject who has active caries that could, in the opinion of the investigator, compromise study outcomes or the oral health of the subject if they participate in the study.

b. A subject who has dentures (partial or full).

c. A subject who has an orthodontic appliance (bands, appliances, or fixed/ removable retainers).

d. A subject who received orthodontic therapy within 3 months of Screening.

e. A subject who has numerous restorations in a poor state of repair.

f. A subject who has any dental condition (e.g., overcrowding) that could, in the opinion of the investigator, compromise study outcomes or the oral health of the subject if they participate in the study.

g. A subject who has had dental prophylaxis within 12 weeks of Screening.

h. A subject who has had teeth bleaching within 12 weeks of Screening.

i. A subject who has high levels of extrinsic stain or calculus deposits, in the opinion of the investigator, that could have interfered with plaque assessments.

21. A subject who has previously been enrolled in this study.

22. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.

5.4 Randomization Criteria

Subjects who satisfy the study selection criteria will be randomized to study treatment.

5.5 Lifestyle Considerations

The site may contact subjects prior to study visits, as a reminder of the approaching scheduled visit and any applicable lifestyle restrictions.

5.5.1 Meals and Dietary Restrictions

From Screening (Visit 1) to the Subject's Last Study Visit

Subjects should not chew gum or consume any confectionery containing xylitol (e.g., mints).

Before Clinical Efficacy Assessment Visits: Baseline (Visit 2) to Last Study Visit

Subjects must abstain from all food and drink (except water) for at least 4hrs prior to their scheduled assessment visits and until all assessments are complete during visit days. Water is permitted until 1 hour prior to their scheduled study visits.

5.5.2 Alcohol, Caffeine and Tobacco

- Subjects will not be permitted to use chewing tobacco or chewing gum from screening to the end of the study.
- Subjects will not be permitted to smoke, vape or use tobacco (e.g., chewing tobacco, gutkha, pan containing tobacco, nicotine-based e-cigarettes) products during their scheduled visits to the study site.

5.5.3 Dental Product/Treatment and Oral Hygiene Restrictions

From Screening (Visit 1) to the Subject's Last Study Visit

- Subjects will not be permitted to use any oral care products (e.g., dentifrices, toothbrushes, mouth rinses) other than those provided during the study.

- Subjects will not be permitted to use any dental floss, toothpicks, waterpicks, or inter-dental brushes (except for the removal of impacted food with non-antimicrobial products only).
- Subjects will be instructed to delay any non-emergency dental treatment until after study completion (including dental prophylaxis).

Before Clinical Efficacy Assessment Visits:

Subjects should refrain from oral hygiene procedures for 12 hours (+6 hours, -2 hours) before their visit and attend the study site with overnight plaque growth.

5.5.4 Medication and Treatment Restriction

The following medication and treatment restrictions apply for the duration of the study:

- If current/ concomitant medications/ treatments or traditional herbal ingredients/ 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.

For more information on concomitant medications, please refer to Section 6.8.

5.5.5 Contraception

The are no contraception requirements for subjects entered into this study. Females of child-bearing potential should verbally confirm they are not currently pregnant or planning to become pregnant.

5.5.6 COVID-19

In accordance with the clinical site procedures, and at the investigator's discretion, subjects may be required to provide a negative COVID test (PCR or lateral flow test) and/or a temperature assessment prior to or while attending a study visit.

5.6 Screen Failures

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

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

5.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical/dental personnel for the study is documented in the Study Contact List located in the investigator study master file held at the study site.

The contact number is only to be used by investigational staff seeking advice on medical/ dental questions or problems in the event that the established communication pathways between the investigational site and the study team are not available.

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or

problems, subjects will be provided with a contact card. The contact card will provide, as a minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Rater/Clinical Assessor Qualifications

Clinical examiners involved in screening and efficacy assessment procedures will be qualified dental professionals, registered to practice in UK. Oral examinations to determine subject eligibility and all safety (OST and OHT) and efficacy (MGI, BI & TPI) assessments will be performed by an appropriately trained clinical examiner with a demonstrable recent history of use of these measures in clinical trials.

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and the sponsor's policy, study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

This includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

6.1 Investigational/Study Product Supplies

The following study products will be supplied by the sponsor Clinical Supplies Department.

Table 6-1 Investigational/Study Product Supplies

	Test Product	Reference Product
Product Name	Corsodyl Original Toothpaste	Colgate Cavity Protection Toothpaste
Pack Design	Carton of 6 over-wrapped tubes	Carton of 6 over-wrapped tubes
Dispensing Details	One carton – baseline visit	One carton – baseline visit
Product Master Formulation Code (MFC)	CCI [redacted] (Commercial Product)	Commercial Product
Dose/Application	Full ribbon of toothpaste on head of toothbrush provided	Full ribbon of toothpaste on head of toothbrush provided
Route of Administration	Oral	Oral

Usage Instructions	Subjects will brush their teeth for at least a minute twice a day (morning and evening)	Subjects will brush their teeth for at least a minute twice a day (morning and evening)
Return Requirements	All used/unused samples to be returned	All used/unused samples to be returned

Table 6-2 Washout/Acclimatization Product Supplies

	Washout Toothpaste
Product Name	Colgate Cavity Protection Toothpaste
Pack Design	Carton of 2 over-wrapped tubes
Dispensing Details	One carton – screening visit
Product Master Formulation Code (MFC)	N/A - commercial product
Dose/Application	Apply a full ribbon of toothpaste on the head of toothbrush provided
Route of Administration	Topical oral use
Usage Instructions	Subjects will brush their teeth according to their normal brushing habits twice a day (morning and evening).
Return Requirements	All used/unused samples to be returned

Table 6-3 Sundry Items

Sundry Items to be supplied:

Item	**Supplied By**	**Pack Design**	**Dispensing Details**	**Return/Disposal Details**	
				Used Samples	**Unused Samples**
Toothbrush (Sensodyne Daily Care, Soft)	Sponsor	Individual commercial pack – 2 per subject	1 at screening for use with washout product 1 at baseline for use with study product	Destroy at site using site disposal procedures	Return
Countdown Timer	Sponsor	Individual commercial	Baseline visit	Subject to keep or destroyed at	Return

		pack – 1 per subject		site using site disposal procedures	
Opaque Bags	Sponsor	Commercial Pack	Screening Visit and baseline visit	Subject to keep or destroyed at site using site disposal procedure	Return
Dosing Cups	Sponsor	Commercial Pack	For use with disclosing solution dosing procedures	Destroy at site using site disposal procedures	Return
Mira-2-ton Disclosing Solution	Sponsor	Commercial Pack	Baseline, week 3, 6 and 12	Destroy at site using site disposal procedures	Return

Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction which will be provided by the sponsor during the study in time for study close out visit.

6.1.1 Medical Devices

The definitions and procedures detailed are in accordance with ISO 14155:2020

- The sponsor manufactured medical devices provided for use in this study is the test product (Corsodyl Toothpaste (UK))

6.1.2 Dosage Form and Packaging

The washout and study products are dentifrices intended for topical oral use and will be applied by toothbrushing using a manual toothbrush.

The washout, test and reference dentifrices will be supplied in their commercial tubes but over-wrapped in white opaque vinyl in order to mask their identity as much as possible. All samples will have a study label affixed and will be provided in labelled product cartons containing sufficient samples for the duration of the use period.

The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the sponsor Global Clinical Supplies group. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

Sundry items will be supplied in their commercial packaging for dispensing by study staff as specified in Table 6-3.

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

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

6.1.3 Preparation and Dispensing

Subjects will be assigned to products in accordance with the randomization schedule generated by an approved sponsor's vendor, prior to the start of the study, using validated software.

Study product will be dispensed by qualified site personnel (unblinded) per the dosage/administration instructions. These staff members will not be involved in any safety, efficacy assessments or other aspects of the study that could be influenced by the knowledge of product a subject has been assigned to use. An additional member of site staff should ensure the dispensing procedures are completed accurately.

The study toothpastes will be dispensed in a blinded fashion to the subject. The study site will be provided with opaque bags in which the study products and product usage instructions will be placed in the bag prior to the subject leaving the dispensing area. Subjects should be advised as to correct product usage in accordance with the Product Usage Instructions at visit 2, 3, and 4. All randomized subjects should receive standard oral care advice at Visit 2 (section 8.2.1).

6.2 Administration

Only subjects enrolled in the study may receive study products and only authorized site staff may supply or administer study products. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the authorized site staff only.

After washout period, subjects will be instructed to self-administer their assigned product per the usage instructions provided to the subject. Subjects will receive a brushing instruction and study diary sheet (or an electronic study diary for the subjects who consented to use the e-diary app). This will outline the brushing instructions and will be used to record the date and time of each brushing occasion during the treatment period. Subjects will also be asked to note any missed brushings, and to use the diary to record any changes in medications, or new medications, or to diet. To ensure that subjects understand the dose of dentifrice to be used, staff will demonstrate what is meant by a 'full ribbon' (i.e. covering the length of the toothbrush head) and provide detailed oral hygiene instruction during the supervised toothbrushing in agreement with the study schedule and product usage instructions.

6.2.1 Medication/Dosing Errors

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

- the wrong product,
- by the wrong subject,
- at the wrong time,
- or at the wrong dosage.

Such medication/dosing errors occurring to a study subject are to be captured in the CRF. In the event of medication dosing error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours.**

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

- Medication/dosing errors involving subject exposure to any of the study products;

- Potential medication/dosing errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

If a medication/dosing error is accompanied by an AE, as determined by the investigator, the medication/dosing error and, any associated adverse event(s) are to be captured in the CRF AE form.

6.2.2 Overdose

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

Overdose is not likely to occur in this study.

Limited quantities of the study product(s) 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.

6.3 Investigational/Study Product Storage

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

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

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

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

Subjects will return used and unused tubes of the washout dentifrice to the study site at their Baseline visit (Visit 2). Subjects will return used and unused tubes of their assigned study dentifrice to the study site at their last visit (for most subjects this will be Visit 5).

Study product return will be documented using the investigational/study product accountability form/record.

6.4 Investigational/Study Product Accountability

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

All study products must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only the staff have access. Upon receipt, all study products should be stored according to the instructions specified on the product

labels. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

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

Subjects will return used and unused tubes of the washout dentifrice to the study site at their Baseline visit (Visit 2). Subjects will return used and unused tubes of their assigned study dentifrice to the study site at their last visits (for most subjects this will be Visit 5). Study product return will be documented using the investigational/study product accountability form/record.

6.4.1 Destruction of Investigational/Study Product Supplies

At the end of the study, the Principal Investigator or an appropriate designee, and a representative of the sponsor (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study (including empty containers), will be returned for destruction to the sponsor Clinical Supplies Department or designated vendor using the return instructions provided. Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction will be provided by sponsor during the study in time for study close out visit.

Return and destruction instructions for sundry items are provided in Table 6-3.

6.5 Blinding and Allocation/Randomization

All subjects will be centrally randomized to one of the two study products using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided to the study site. Study products will be dispensed according to the instruction received through the IRT at the appropriate study visits. Returned study products should not be re-dispensed to any subject. This study is described as examiner-blind (the investigator, clinical examiner and monitor will be blinded to product received). Site staff, the study statistician, data management staff, other employees of the Sponsor and vendors acting on behalf of the sponsor, who may influence study outcomes will also be blinded to the product allocation. To ensure the clinical examiner remains blinded throughout the study:

- site staff involved in the dispensing of study product and the supervision of onsite product usage will work in a separate area;
- the examiner will not be permitted in any area where study product is stored, dispensed, or in use;
- study subjects will be instructed not to remove study product from the opaque bags provided outside of the dispensing room, while at the study site;
- dispensing staff and on-site brushing supervisors will not be involved in any safety/product performance assessments during the study.

6.6 Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be an electronic process.

The electronic system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's product assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a subject's product assignment unless this could delay emergency treatment of the subject.

If a subject's product assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

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

6.7 Compliance

Study products will be administered under the supervision of investigator site personnel.

A diary (paper or electronic) will be supplied to promote compliance and to capture details of product use throughout the study period. Subjects may also record additional information such as any missed/ additional brushings, the reasons for any missed/ additional brushings, any issues with the dentifrice used, oral problems, illnesses, AEs, and any new medications/ treatments. Any additional details relevant to efficacy or safety should be reviewed by the investigator (or suitably qualified designee) with the subjects and transcribed to the CRF as appropriate. Additionally, all subjects active on the study will receive an SMS (text message) reminder from the study site (subjects with e-diary will also get a reminder from the app.) prior to a scheduled visit (Visits 2-5) to remind them of the requirement for no oral hygiene and meal restriction on the morning prior to their visit. Subjects will also attend each study visit with all tubes of dentifrice provided (used and unused) for a visual check of product usage, and with their completed diary for review by study staff. Additionally, a timer will be provided to the subjects to aid compliance with the product usage instructions through visit 2 to the end of the study.

The number of any missed or additional applications or doses will be captured as protocol deviations and transcribed from the diary into the CRF. Subjects will be re-instructed in the correct usage requirements and diary completion as needed.

Supervised brushings will be carried out at the study site in agreement with the Schedule of Activities, to facilitate subject compliance with dosing and brushing instructions.

A threshold of compliance with allocated study treatment has been set as 80% of the recommended doses.

6.8 Concomitant Medication/Treatment(s)

Any medications, treatments, or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) taken during the study, from signing the informed consent, must be recorded in the CRF with indication, reason for use, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about medications/treatments at each site visit.

Medication/treatments taken within 30 days of signing the informed consent form will be documented as a prior medication/treatment. Medications/treatments taken after first treatment dose will be documented as concomitant medication/treatments.

Subjects will abstain from all concomitant treatments, except for contraceptives and those used for the treatment of adverse events

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

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

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

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

7.2 Lost to Follow up

If a subject fails to return to the site for a required study visit the site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all products that they had been dispensed and if appropriate request that the subject return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs).

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion, which could include the following: an oral examination.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow up.

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

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

8 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study visit. The timing of each procedure is listed in the Schedule of Activities section.

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

8.1 Visit 1/Screening

Screening procedures will be conducted by the Investigator, or suitably qualified designee.

Subjects will be screened within 14±3 days prior to administration of the investigational/study product to confirm that they meet the subject selection criteria for the study.

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

1. Informed consent
2. Demographics, medical history (including smoking) and prior/concomitant medication/treatment
3. Oral soft tissue (OST) examination (Section 9.3.1)
4. Oral hard tissue (OHT) examination (Section 9.3.2)
5. Gross gingival assessment (Section 9.1.1)
6. Review of inclusion/exclusion criteria
7. Subject eligibility
8. Dispense washout products/ dentifrice, toothbrush and diary* (including instruction on diary completion)
    - *For subjects who consent to use the e-diary during the study period:
        - The diary App will be installed in their own devices.
        - The training for the e-diary App will be provided
9. Adverse events & Incidents (Section 10)

8.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Two copies of the informed consent form (ICF) will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

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 signed and dated consent will be provided by either the investigator or by the sponsor.

The investigator, or designee, should sign and date each copy of the ICF to confirm that the consent process was completed correctly after the subject has signed.

The time the subject signed the informed consent form will be captured as this is the point at which all Adverse Events will be captured from. The date and time of consent will be captured in the CRF.

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. Each subject should be provided with a copy of the signed and dated amended consent form. The date of re-consent will be recorded on the CRF.

After signing the ICF, subjects will undergo the screening assessments to confirm that they meet all the inclusion criteria and none of the exclusion criteria. If the subject is confirmed eligible by the investigator (or designee) to participate in the study the subject is considered enrolled in the study.

A copy of the consent will be printed and given to the subject and the consent documents will be retained by the site.

8.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, gender and race.

Ethnicity and race of subjects will be recorded in accordance with FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials, 2005.

8.1.3 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history (in the past one year) including allergies or drug sensitivity, will be documented in the CRF.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days and prior to signing the informed consent form, will be documented in the CRF.

8.1.4 Oral Examination/Assessment

The following procedures will be completed, and data recorded in the CRF. The following screening procedures should be carried out by a qualified dental professional:

- Oral soft tissue (OST) examination as described (Section 9.3.1)
- Oral hard tissue (OHT) examination as described in (Section 9.3.2.)
- Gross assessment of gingival health (Section 9.1.2).

The oral examinations/assessments should be carried out as described in Section 9. All findings will be recorded in the CRF.

Findings from this examination performed at the Screening Visit will be used to determine subject eligibility.

8.1.5 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be documented in the CRF.

8.1.6 Subject Eligibility

The investigator and/or medically qualified designee will review inclusion/exclusion criteria, medical history, prior medications to confirm subject eligibility to participate in the clinical trial. This will be documented in the CRF.

To prepare for study participation, subjects will be instructed in the Lifestyle Guidelines and any Concomitant Medication/Treatment(s) requirements of the protocol.

8.1.7 Dispense Washout Products

Eligible subjects will be provided with the washout toothpaste, toothbrush and diary (paper or e-diary) to use during the washout period (14±3 days). Subjects will be instructed to use only their supplied oral care products (washout products) according to their normal habit until their next appointment. Completion of all procedures will be documented in the CRF.

8.2 Study Period

8.2.1 Visit 2/Day 0 - Baseline

Subjects will visit the clinical study site 14±3 days after the Screening visit. The following procedures/ assessments will take place in the order listed below as much as possible and be recorded in the CRF:

1. Return washout products/ compliance checks including diary review
2. Review of current/ prior medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions
3. Full oral soft tissue (OST) examination (Section 9.3.1)
4. Full oral hard tissue (OHT) examination (Section 9.3.2)
5. MGI assessment (& repeatability assessment, where applicable) (Section 9.2.1)
6. Gingival bleeding and pocket depth assessment
    - BI assessment (Section 9.2.2) (including BOP which is derived from BI assessment (section 9.1.2))
    - Pocket depth assessment (section 9.1.3)
7. Plaque disclosure (Section 9.2.3)
8. TPI assessment (& repeatability assessment, where applicable) (Section 9.2.4)
9. Inclusion/exclusion criteria
10. Subject eligibility
11. Randomization
12. Dispense study dentifrice, toothbrush, study instructions & diary and timer*
    - *For subjects who consent to use the e-diary during the study period
        - The built-in timer will be activated

13. Oral hygiene instruction review / compliance checks including diary completion review with subject
14. Supervised subject brushing at site
15. Concomitant medications/ treatments will be collected as per Section 6.8.
16. Adverse events & Incidents (Section 10)

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

8.2.2 Visit 3 and 4 / Day 21 and 42 (Week 3 and 6)

The following procedures/ assessments will take place in the order listed below and be recorded in the CRF:

1. Collect study dentifrice, toothbrush & diary from subject
2. Review of concomitant medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions
3. Compliance checks including diary review
4. Subject continuance
5. Full OST examination (Section 9.3.1)
6. MGI assessment (& repeatability assessment, where applicable) (Section 9.2.1)
7. BI assessment (Section 9.2.2)
8. Plaque disclosure (Section 9.2.3)
9. TPI assessment (& repeatability assessment, where applicable) (Section 9.2.4)
10. Return study dentifrice, toothbrush, study instructions and diary to subject
11. Oral hygiene instruction review / compliance checks including diary completion review with subject
12. Supervised subject brushing at site
13. Adverse events & Incidents (Section 10)

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

8.2.3 Visit 5 / Day 84 (Week 12)

The following procedures/ assessments will take place in the order listed below and be recorded in the CRF:

1. Collect study dentifrice, toothbrush, diary & timer (all study supplies) from subject

2. Review of concomitant medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions
3. Compliance checks including diary review
4. Subject continuance
5. Oral soft tissue (OST) examination (Section 9.3.1)
6. Oral hard tissue (OHT) examination (Section 9.3.2)
7. MGI assessment (& repeatability assessment, where applicable) (Section 9.2.1)
8. BI assessment (Section 9.2.2)
9. Plaque disclosure (Section 9.2.3)
10. TPI assessment (& repeatability assessment, where applicable) (Section 9.2.4)
11. Complete optional dental prophylaxis (as/ if deemed necessary by examiner) (Section 8.4)
12. Adverse events & Incidents (Section 10)
13. Study conclusion (Section 8.5)

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

8.3 Diary Review

The diary (both paper and electronic diary) should be reviewed at every visit by the investigator, or suitably qualified designee, and the subject. Any subject comment captured in the diary which is considered an adverse event or Incident will be assessed and reported as per the defined procedure in this protocol. Adverse event reporting procedures are summarized in Adverse Event and Serious Adverse Events. Incident reporting procedures are summarized in Definition of and Procedure for Reporting Medical Device Incidents (Section 10.10).

Any additional comments relating to medications/treatments provided in the diary will be reviewed by the investigator or medically qualified designee with the subject and entered into the CRF as appropriate. Where the subject has consented to use the electronic diary, the investigator can review the entered data periodically and may receive alerts of any concomitant medications or adverse event of concern.

Additional and missed product applications will be considered deviations from the protocol and will be recorded on the Deviations Log.

8.4 End of Study Optional Prophylaxis

Subjects who, in the opinion of the clinical examiner, would benefit from dental prophylaxis following their participation in the study will be offered full mouth dental prophylaxis (using conventional prophylaxis paste and periodontal instruments as required) on completion of all clinical assessments. Prophylaxis may be carried out by different, appropriately qualified clinicians to facilitate subject flow.

8.5 Study Conclusion

The Study Conclusion page of the CRF will be completed for all subjects whether they completed all study procedures or if they were discontinued from the study early. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page.

If a subject has any clinically significant, study-related abnormalities or AEs at the end of the study, the sponsor's medical monitor (or designated representative) should be notified and, the subject may be asked to remain at the clinical site or be asked to return for a follow-up visit to ensure any issue is resolved or deemed not clinically significant.

8.6 Followup Visit/Phone Call

The study site may contact a subject to follow up an AE post-study completion/withdrawal and, in some circumstances, request they return to the site for additional follow-up visits (final safety assessments). If needed, additional examinations may be carried out at such visits.

9 STUDY ASSESSMENTS

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

9.1 Screening and Inclusion/Exclusion Assessments

Screening and inclusion/exclusion assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the Study Procedures section of this protocol. A single examiner will be responsible for the conduct of the clinical measures of gingivitis/ plaque accumulation for the duration of the study.

Eligible tooth assessments will be accomplished by oral examination and will evaluate dentition exclusions along with a gross gingival assessment in relation to the general dentition inclusion/ exclusion criteria.

Assessments will be carried out by the investigator, or qualified designee, against the inclusion/ exclusion criteria. Ineligible subjects will not be re-screened.

Findings from these examinations will be used to determine subject eligibility.

9.1.1 Gross Assessment of Gingival Health

Visual assessment of gingival health will be performed to record the presence/absence of plaque-induced gingivitis as per the inclusion criteria during Screening visit (Visit 1). (MGI/BI will not be recorded for this assessment).

9.1.2 Bleeding on Probing

To assess the inclusion requirement for gingivitis, the examiner should evaluate the number of bleeding sites elicited on probing as a measure of gingival condition at Baseline visit (Visit 2). The gingivae will be air dried and then the examiner will use UNC15 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 ~ 60º 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 bleeding will be assessed on the facial and lingual gingival surfaces of each scorable tooth (7-7 in each arch). Three sites for each tooth should be evaluated buccally/labially (distal, body, mesial sites) and three sites 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 percentage of bleeding sites will be recorded in the CRF.

9.1.3 Pocket Depth Measurement

UNC15 probe will be used as a "sensing" instrument to determine pocket depth. The probe tip will be inserted gently into the gingival sulcus or pocket and the total extent of the sulcus or pocket will be assessed.

9.2 Efficacy Assessments

The following efficacy assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol

If in the opinion of the examiner a subject is between defined grades/scores, a conservative approach should be used to provide the final score. The same approach should be applied throughout the study to ensure consistency in the grading of the scores at all timepoints.

The same examiner will be used throughout the study for each clinical index to eliminate the possibility of inter-examiner variability.

9.2.1 Modified Gingival Index (MGI) Assessment (Lobene et al, 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 (second permanent molar to second permanent molar in each arch) by an appropriately qualified examiner. 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:

Table 9-1 Modified Gingival Index Scoring System

Score	Description
0	Absence of inflammation
1	Mild inflammation; slight change in colour, little change in colour; little change in texture of any portion of the marginal or papillary gingival unit

2	Mild inflammation; criteria as above but involving the entire marginal or 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 from Baseline onwards as indicated in the Schedule of Activities.

9.2.2 Bleeding Index (BI) Assessment (Saxton and van der Ouderaa, 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 UNC15 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 ~ 60º 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:

Table 9-2 Bleeding Index scoring system

Score	Description
0	No bleeding after 30 seconds
1	Bleeding observed within 30 seconds of probing
2	Bleeding observed immediately on probing

The BI will be assessed by the same examiner on all evaluable teeth from Baseline onwards as indicated in the Schedule of Activities.

The number of bleeding sites for each subject at each visit is calculated as the number of evaluable tooth sites with a BI score of either 1 or 2.

Repeatability exercise will not be performed for BI.

9.2.3 Plaque Disclosure

Dental plaque is colorless and so is usually disclosed ('stained') prior to assessment. The disclosing solution will be used according to the manufacturer's instructions.

- At the request of the subject, the clinician may apply a thin layer of petroleum jelly to the subject's lips, as a barrier to help minimize staining by the disclosing solution. Care should be taken to ensure no petroleum jelly comes into contact with the labial surfaces of the anterior teeth as this could impact clinical assessments in this region.

- The subject will rinse their mouth with 10 mL tap water for 10 seconds to remove any food debris and expectorate.
- The clinician will then apply the plaque disclosing solution as per the label instructions. Care will be taken not to dislodge the plaque during this process. The subject will then rinse with 10 mL tap water for 10 seconds and expectorate to remove excess solution.

Plaque may be redisclosed between the TPI and repeat assessments at the discretion of the clinical examiner.

9.2.4 Plaque Index (TPI) Assessment (Lobene et al, 1982)

The Turesky Modification of the Quigley Hein Plaque Index (Lobene et al, 1982) will be used to assess plaque on all gradable teeth meeting the inclusion/ exclusion criteria, and will be performed by an appropriately qualified examiner. 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 be assessed.

The plaque will first be disclosed using a plaque disclosing dye solution, in agreement with the manufacturer's instructions. The TPI 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:

Table 9-3 Turesky Plaque Index Scoring System

Score	Description
0	No plaque
1	Separate flecks of plaque at the cervical margin
2	Thin continuous band of plaque (up to 1 mm) at the cervical margin
3	Band of plaque wider than 1 mm but covering < 1/3 of the tooth surface
4	Plaque covering ≥ 1/3 but < 2/3 of the tooth surface
5	Plaque covering ≥ 2/3 of the tooth surface

The TPI will be assessed by the same examiner on all evaluable teeth from Baseline onwards as indicated in the Schedule of Activities.

9.2.5 Repeatability Assessments

The clinical examiner selected for this study will have demonstrated their ability to replicate their own scores (intra-examiner repeatability/reliability) on a tooth site-by-tooth site basis in previous studies and/or calibration exercises. Repeat MGI and TPI assessments will be performed by the clinical examiner at Visits 2 - 5. At least 1 repeat assessment should be performed for each index on each clinical assessment day, that is, at least one MGI and one TPI repeat assessment on each assessment day. 'Repeat' subjects will be selected at random from those in attendance. Different subjects can be used for repeat MGI and TPI assessments.

There should be a delay of at least 10 minutes between original and repeat assessments for a given subject and ideally separated by another subject. No other procedure on the subject should

be carried out between the first and the repeat assessment. Where possible, the clinical examiner should assess a different subject in the intervening period.

Scores from the first assessment must not be visible to the examiner/scribe when the repeat assessment is carried out.

9.3 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol.

9.3.1 Oral Soft Tissue Examination (OST)

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee. The OST 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.

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 a pre-existing condition observed by the clinical examiner or reported by the subject from the OST examination carried out at Screening will be recorded as an AE.

During the oral examination, if any abnormalities on the oral soft tissues are detected, the subject will be advised to seek further medical/ dental advice from their dentist or general medical practitioner as deemed appropriate in the opinion of the clinical examiner.

Findings from this examination at Screening will be used to determine subject eligibility.

9.3.2 Oral Hard Tissue Examination (OHT)

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

The OHT examination will assess grossly carious lesions or signs of erosive wear, enamel irregularities, tooth fracture, gross decay, decalcification, faulty restorations and implants. The examination will be performed by direct observation

During the oral examination, if any abnormalities on the oral hard tissues are detected, the subject will be advised to seek further medical/ dental advice from their dentist or general medical practitioner.

Observations will be listed as “Absent” or “Present” and conditions noted as present will be described. Examination findings will be described and documented in the CRF. Any abnormalities or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject from the OHT examination carried out at Screening will be recorded as an AE.

Findings from this examination at Screening will be used to determine subject eligibility.

9.3.3 Pregnancy Testing

For this study, the individual products being tested are not contra-indicated for pregnancy or intended to be contra-indicated for pregnancy and use of them would not be expected to cause harm either to the mother or fetus. A pregnancy test is therefore not required. However, subjects of child-bearing potential will be asked to provide verbal confirmation of pregnancy status at screening (Visit 1) and to inform site staff if they find they are pregnant while participating in the study. In case of a positive confirmed pregnancy, the subject will be withdrawn from the study.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

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

10.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product (or medical device), whether or not considered related to the study product, including any washout or lead-in product (or medical device).

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

Events Meeting the AE Definition:

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

Events NOT meeting the AE definition:

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

10.2 Definition of a Serious Adverse Event (SAE)

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

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

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - 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 outpatient 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.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption

- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Note: Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements.

10.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs, and therefore all SAEs will be collected immediately after a subject provides consent to participate in the study by the completion (signature) of the ICF and until 5 days following last administration of the study product (or last procedure).

Medical occurrences that began before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF not the AE section.

Details recorded by the subject on a diary or similar document that meet the definition of an AE must also be discussed with the subjects and transcribed in the AE section of the CRF.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study product or study participation, the investigator must promptly notify the sponsor.

10.4 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up on AEs that are serious, considered related to the study product(s), participation in the study, or a study procedure, or that caused the subject to discontinue the study product or study.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to non-leading such as "How do you feel" will be assessed and any AE's recorded in the CRF and reported appropriately.

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

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

When an AE occurs, it is the responsibility of the investigator (or medically qualified designee) to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE in the CRF and all details relating to an SAE in the paper SAE Form provided.

It is **not** acceptable for the investigator (or medically qualified designee) to send photocopies of the subject's medical records to the sponsor in lieu of completion of the AE CRF page/SAE form.

There may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records prior to submission to the sponsor.

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be the documented as the AE/SAE where known and not the individual signs/symptoms. (e.g. upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

AEs elicited by the investigator (or medically qualified designee) in a standard manner at the study visits should also be recorded in the AE section of the CRF and/or using the SAE form (subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

10.4.1 Reporting of an Adverse Event

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

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE CRF page, an SAE form should be completed, as fully as possible. Hard copies of the 'paper' SAE form will be provided in the investigator study master file. Original SAE forms will be retained in the investigator study master file.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (or study procedure, if appropriate)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and the sponsor's 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 in relation to the study product
- Outcome if known

The SAE form, completed as fully as possible, must be scanned and e-mailed to the Case Management Group mailbox PPD with copy to the appropriate sponsor Study Manager, with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. The investigator will submit any updated SAE data to the sponsor, **immediately and under no circumstance should this exceed 24 hours** of it being available.

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

The sponsor Study Manager will be responsible for forwarding the SAE form to other sponsor personnel as appropriate.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.5.2 Assessment of Causality

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE CRF page and the SAE form (subject to the

classification of the AE). The investigator will also document in the medical notes that he/she has reviewed the AE and assessed causality, where applicable.

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

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

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. **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 the sponsor.** The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.6 Follow-up of AEs and SAEs

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

All AEs (serious and non-serious) 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 the sponsor to elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded on the AE CRF page and on the SAE form (subject to the classification of the AE).

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

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the investigator will promptly notify the sponsor by emailing the information to the Case Management Group mailbox at the sponsor PPD with copy to the appropriate sponsor Study Manager.

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

10.7 Withdrawal Due to an Adverse Event

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

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

10.8 Regulatory Reporting Requirements for SAEs

The sponsor 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 the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Both the investigator and the sponsor will comply with all local medical device reporting requirements

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

An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure in the investigator study master file, and will notify the IRB/IEC, if appropriate according to local requirements.

10.9 Pregnancy

10.9.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the signing of informed consent until 5 days after last administration of study product.

10.9.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the Case Management Group mailbox PPD), with copy to the appropriate sponsor Study Manager within 24 hours of learning of the subject becoming pregnant. Original pregnancy information forms will be retained in the investigator study master file.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the investigator to the Case Management Group mailbox at the sponsor PPD with copy to the appropriate sponsor Study Manager. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

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

Any female subject who becomes pregnant while participating will be withdrawn from the study.

10.10 Medical Device Incidents

The definitions and procedures detailed are in accordance with ISO 14155:2020

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

Medical devices are being provided by the sponsor for use in this study; the medical device in this study is the test product (Corsodyl Toothpaste (UK)).

10.10.1 Definition of an Incident

A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.

Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

An **incident** associated with a device happened and

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include any of the following:
- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents:

- A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A subject's study treatment is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A subject's health deteriorates due to medical device failure.

10.11 Reporting of Incidents and Malfunctions

All incidents must be reported to the sponsor **immediately and under no circumstance should this exceed 24 hours** of the investigator or designee becoming aware of the situation.

Any medical device incident occurring during the study will be documented in the subject's medical records, if 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 (serious and non-serious), the appropriate AE CRF page and SAE form will be completed and reported as per the AE and SAE reporting sections.

The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.

The completed Incident Report Form should be scanned and emailed to the Case Management Group mailbox PPD, with copy to the appropriate sponsor Study Manager, with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE form 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 be retained in the investigator study master file.

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

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

- Notify the sponsor immediately (by following the process described above).
- 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.
- For any incident/malfunction occurring with a medical device (including those that are part of combination products) supplied by the sponsor, return the failed device to the sponsor as soon as possible, including documentation of the details of the failure
- For any incident/malfunction occurring with a medical device (including those that are part of combination products) supplied by the Investigator site, report the incident to the device manufacturer and follow the manufacturer instructions for the return of the failed device (whilst keeping the sponsor informed).

10.12 Follow-up of Medical Device Incidents

Medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all subjects, including those who discontinue study product or are withdrawn from the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

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

10.13 Regulatory Reporting Requirements for Medical Device Incidents

To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during all periods of the study in which the medical device is used.

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

11 DATA MANAGEMENT

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

For this study, subject data will be entered into an electronic CRF (eCRF), using a validated system. Data relating to SAEs, pregnancy and incidents will also be collected on paper forms.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries, questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified. The CRF and/ or diary can be used as a source document at the discretion of data management.

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

11.1 Case Report Form

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

For each subject who has given informed consent/assent the CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Management of clinical data will be performed in accordance with Third Party Vendor applicable standards and data cleaning procedures with oversight by the sponsor to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

To protect the privacy of subjects, no Personal Information (PI) (including the subject's name or initials or full birth date) is to be recorded in the CRF or as part of the query text.

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

The sponsor will obtain and retain all CRFs and associated study data as applicable at the completion of the study.

11.2 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.

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

11.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The 3rd party data management vendor will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

The study monitor will perform ongoing review the of the CRFs in accordance with the monitoring plan, to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

11.3 Processing Patient Reported Outcomes and Data Collection from Internet of Medical Things

Paper based patient reported outcome (PRO) data may be recorded to a diary, questionnaire, or other specified document, etc. and entered into the data management system (DMS).

All PRO source data should be reviewed by the study staff and the study monitor to ensure accurate transcription of data and that any potential AEs or concomitant medications reported on these documents are discussed with the subject and transcribed accurately to the CRF and/or DMS. PROs that are classed as source data will be retained by the investigator and true/certified copies may be sent to a designated vendor or the sponsor as required. Any AEs or concomitant medications collected as ePRO will be reviewed and transcribed to the eCRF by the site.

To protect the privacy of subjects, no Personal Information (PI) (including the subject's name or initials or birth date) is to be recorded on any PRO/ePRO/IoMT (Internet of Medical Things)

Devices Data that will be forwarded to the sponsor or Third-Party Vendor. The main source of PROs from this study will be documented in the subject diaries.

11.4 External Data

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

An agreed quality control process will be performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to the sponsor.

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

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

A sample size of approximately 100 subjects per treatment group (before presumed 6% dropout rate) is needed to provide at least 90% power to achieve statistical significance (at the 5%, two-sided level) for the primary outcome (change from baseline at 12 weeks in the number of bleeding sites in the sodium bicarbonate group). The assumed treatment efficacy estimates for this calculation comes from the sponsor clinical study (CCI 2012) report where the change (SD) from baseline at 12 weeks (without pre-prophylaxis) was -14.7 (9.8) bleeding sites.

For the secondary objective (change from baseline at 12 weeks in the number of bleeding sites in the bicarbonate group compared to the negative control group), data from the sponsor clinical study (CCI 2012) focusing on the non-smoking strata and using a t-test comparing their respective mean changes (SD of change) of 15.5 (10.1) *vs.* 11.6 (9.1) indicates power will exceed 80%. (PASS 2019 Power Analysis and Sample Size Software (2019). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass). The assumed (from the sponsor clinical study CCI 2012) +0.7 correlation of the number of bleeding sites at baseline to week 12 helps attain that power.

12.2 Populations for Analysis

- The Safety population will comprise all randomized subjects who receive at least one dose of the study product. This population will be based on the product the subject actually received.
- The modified Intent-To-Treat (mITT) population will include all randomized subjects who complete at least one use of study product and have at least one post baseline clinical performance assessment. This population will be based on the study product to which the subject was randomized. Any subject who receives a randomization number will be considered to have been randomized.
- The Per-Protocol (PP) population will include all randomized subjects who do not have any protocol deviations that could confound the interpretation of analyses conducted on the mITT.

- The repeatability population for MGI is defined as all subjects who have at least one repeat MGI clinical assessment at any visit.
- The repeatability population for TPI is defined as all subjects who have at least one repeat TPI clinical assessment at any visit.

12.3 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical reporting and analysis plan (SAP), which will be written following finalization of the protocol and prior to study unblinding/analysis (as appropriate). This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

The mITT population will be used for all efficacy analyses. No repeat assessment data is to be used in any efficacy analyses.

Statistical analyses of the endpoints will be performed using the change from baseline, in order to easily present direct estimates for the within-treatment mean changes from baseline (e.g. the primary endpoint).

Descriptive summary statistics will be presented for the actual and change from baseline values at each time point.

All p-values presented will be two-sided and assessed at the 5% significance level. A sequential testing strategy will be used to adjust for multiplicity for the comparison between test and reference products in the number of bleeding sites at week 12. This will only be assessed for confirmatory evidence if the primary endpoint (change from baseline within the test product at week 12) achieves a statistically significance reduction. There will be no further adjustments for multiplicity for any other secondary endpoints.

12.3.1 Primary Analysis

A mixed model with repeated measures (MMRM) will be performed on the change from baseline in the number of bleeding sites with product (test or reference), time point (week 3, 6 and 12) and product by time point interaction as fixed effects, and baseline number of bleeding sites as a covariate. Subject will be fitted as a repeated measure with unstructured covariance. Kenward-Roger degrees of freedom will be used.

To test the null hypothesis (H_0: There is no difference in the number of bleeding sites from baseline to week 12 in the test product group) *vs.* the alternative hypothesis (H_1: There is a treatment effect on the number of bleeding sites at 12 weeks), estimates of treatment effect at 12 weeks will be based on least squares means (LS means) generated with an appropriate contrast statement. P-values and 95% confidence intervals (CI) will be provided.

12.3.2 Secondary Analysis(es)

Other secondary timepoints (week 3 and 6) related to the number of bleeding sites will be analyzed using the results from the MMRM from the primary analysis. Estimates of treatment effect (changes from baseline at 3, 6 and 12 weeks) and treatment comparisons will be based on least squares means (LS means) generated by appropriate contrast statements. P-values and 95% confidence intervals (CI) will be provided.

The secondary endpoints include (in addition to the number of bleeding sites):

BI (Bleeding Index= Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites). The BI score has a range of 0 to 2; (see section 9.2.1)

Modified Gingival Index (MGI) Assessment= Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites. The MGI score has a range of 0 to 4; (see section 9.2.2)

Overall and interproximal TPI Score = Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites. The TPI score has a range of 0 to 5. (see section 9.2.4)

For the change from baseline for each endpoint above, the same MMRM as applied for the number of bleeding sites will also be applied but including the respective baseline as covariate instead of the baseline number of bleeding sites. Results within and between treatments at each time point will also be obtained and presented in a similar manner.

12.3.3 Safety Analysis(es)

The Safety population will be used for safety analyses. Safety analyses will be performed according to product received. All AEs will be reviewed by the Clinical Research Scientist, or designee, prior to database lock and unblinding and will be coded using the MedDRA. During this review stage, AEs will be further categorized as oral or non-oral. AEs will be listed and summarized by product received. SAEs will also be listed. AEs will be regarded as 'treatment' emergent if they occur on or after the first product use at the Baseline visit.

The following AEs tables will be produced, presented by product group:

- listing of all AEs (randomized subjects and non-randomized subjects);
- summary of AEs;
- treatment emergent AEs by Oral/Non-Oral and Preferred Term (PT);
- treatment emergent AEs by System Organ Class (SOC) and PT;
- treatment related AEs by Oral/Non-Oral and PT;
- listing of serious AEs (if there are no SAEs, a null listing will be produced; if there are more than 5 treatment emergent serious AEs (SAEs), a table will be produced in place of the listing by SOC and PT);
- non-serious treatment emergent AEs by SOC and PT (only produced if there are more than 5 AEs).

The results of the OST and OHT examinations will be listed and the results of the OST examinations will be tabulated.

12.3.4 Other Analysis(es)

For descriptive purposes only, the percent change from baseline at weeks 3, 6 and 12, in each arm separately, will be calculated and reported for each primary and secondary outcome variable. Additionally, the number and percent of patients improving, remaining the same, or worsening (compared to baseline) at weeks 3, 6 and 12, in each arm separately, will be calculated and reported for each primary and secondary outcome variable. These analyses will only use the observed data and not the LOCF imputed data.

Repeatability of the examiner

The repeatability of the examiner in conducting the MGI and TPI assessments will also be performed. The repeat plaque and MGI assessments will be compared to the original assessments. The repeat assessment is not to be used in any efficacy analysis. The first and second assessments of each index will be analyzed with a Fleiss-Cohen weighted kappa

coefficient (κ), along with the 95% CI, to assess the intra-examiner reliability. Reliability will be deemed: Excellent if $\kappa > 0.75$, Fair to good if $0.4 \leq \kappa \leq 0.75$ and Poor if $\kappa<0.4$.

This analysis will be conducted on each respective index repeatability population (MGI population and TPI population).

Missing data:

Experience in previous, similar studies suggest missing data will not be prevalent. For example, in the sponsor clinical study (CCI 2012) of the same product over the same 12-week period, only one patient was lost. The SAS Proc Mixed implementation of the repeated measures ANCOVA that will be used in almost all analyses, implicitly imputes any missing data based on the non-missing observations. The basic theory on which Proc Mixed is based holds even with missing data as long as the missing data are missing at random (MAR).

An additional analysis will explore the sensitivity of results to the effect of missing data on the primary and secondary efficacy endpoints. The sensitivity analysis will use the same MMRM model as described above, but with Last Observation Carried Forward (LOCF) for missing data. All analyses will use contrasts to show estimates of the treatment group response and treatment group differences at each time point, with corresponding standard errors of the mean, and 95% confidence intervals (and p-values for treatment differences).

12.3.5 Exclusion of Data from Analysis

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

12.3.6 Demographic and Baseline Characteristics

Age and other continuous variables will be summarized using descriptive statistics including mean, standard deviation, median, minimum, and maximum. Gender, race and other categorical variables will be summarized using frequency counts and percentages for the safety and mITT populations. Medical history and current medical conditions will be listed.

12.3.7 Study Drug/Product Compliance and Use of Other Therapies

12.3.7.1 Study Drug/Product Compliance

Compliance with study product use (based on number of brushings) will be summarized and listed for the mITT population.

Compliance is defined as: Compliance (%) = 100 x Actual number of brushings / Expected number of brushings. 'Expected number of brushings' is defined to exclude any brushings after a subject dropped out of the study.

A threshold of compliance with allocated study treatment has been set as 80% of the recommended doses. Subjects with overall compliance <80% will be considered protocol deviations and assessed at the time of Blinded Data Review for exclusion from the Per Protocol (PP) population.

12.3.7.2 Prior and Concomitant Medications

Prior medications, concomitant medications and significant non-drug therapies taken during treatment will be listed for all randomized subjects.

12.3.8 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 withdrawal. Subjects who withdraw will not be replaced. For the primary analyses, no data will be imputed in the case of dropouts or missing data. However, sensitivity analyses using LOCF are planned as detailed in section 12.3.4.

12.3.9 Interim Analysis

No interim analysis is planned for this study

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

In accordance with applicable regulations including GCP, and the sponsor procedures, the sponsor 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 the sponsor 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.

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

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

The extent and nature of monitoring will be described in a written monitoring plan on file at the sponsor. 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.

13.2 Quality Assurance

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

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

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

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

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

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

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (ICH, Nov 2016), guidelines for GCP (ICH, 1997) (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association, 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, applicable portion of EU MDR 2017/745, ISO 14155:2011 and ISO 14155:2020 and applicable local regulatory requirements and laws.

13.3.3 Subject Information and Consent

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

When study data are compiled for transfer to the sponsor and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by the sponsor in order to de-identify study subjects. (The use of initials should be avoided).

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

The informed consent documents must be in compliance with ICH GCP, applicable portion of ISO 14155, local regulatory requirements, and legal requirements, including applicable privacy laws.

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

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

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

13.3.4 Subject Recruitment

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

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

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

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

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

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

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

The sponsor intends to make anonymized subject-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

13.5 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided

reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a sponsor site or other mutually-agreeable location.

The sponsor 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 the sponsor Policy.

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

13.6 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 sponsor's 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 the sponsor, 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 the sponsor, e.g., subjects' written consent forms, should be maintained by the investigator in strict confidence.

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

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

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of the sponsor. In addition, the sponsor retains the right to discontinue development of the test product at any time.

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

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

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

14 REFERENCES

Available on request

Akwagyiram I, Amini P, Bosma ML, et al.] Efficacy and tolerability of sodium bicarbonate toothpaste in subjects with gingivitis: A 6-month randomized controlled study. Oral health & preventive dentistry. 2018;16(5):401-7.

Bosma M, Milleman KR, Akwagyiram I, et al. A randomised controlled trial to evaluate the plaque removal efficacy of sodium bicarbonate dentifrices in a single brushing clinical model. BDJ Open; 2018; 4: 17037.

Brook I. Microbiology and management of periodontal infections. General dentistry. 2003;51(5):424-8.

Chapple IL, Van der Weijden F, Doerfer C, et al. Primary prevention of periodontitis: Managing gingivitis. Journal of clinical periodontology. 2015;42

Chapple ILC, Mealey BL, Van Dyke TE, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. The Journal of periodontology. 2018;89

Davies RM. Toothpaste in the control of plaque/gingivitis and periodontitis. Periodontology 2000. 2008;48:23-30.

Delivering better oral health: https://www.gov.uk/government/publications/delivering-better-oral-health-an-evidence-based-toolkit-for-prevention

Dietrich T, Ower P., Tank M, West N, et al. Periodontal diagnosis in the context of the 2017 classification system of periodontal diseases and conditions – implementation in clinical practice. British dental journal. 2019;226 (1):16-22

FDA. Guidance for industry gingivitis: Development and evaluation of drugs for treatment or prevention (june 2005). 2005.

Figuero E, Carrillo-de-Albornoz A, Herrera D, et al. Gingival changes during pregnancy: I. Influence of hormonal variations on clinical and immunological parameters. Journal of clinical periodontology. 2010;37(3):220-9.

Ghassemi A, Vorwerk LM, Hooper WJ, et al. A four-week clinical study to evaluate and compare the effectiveness of a baking soda dentifrice and an antimicrobial dentifrice in reducing plaque. The Journal of clinical dentistry. 2008;19(4):120-6. GSK CH Clinical Study Report

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GSK CH Clinical Study Report 209509, A Post-hoc Pooled Analysis of GSK CH Clinical Data Investigating the Efficacy of a Dentifrice Containing 67% w/w Sodium Bicarbonate on Gingivitis and Plaque Accumulation.

GSK CH Clinical Study Report 208175, A Randomized, Controlled, Examiner-Blind, Phase II, Proof-Of-Principle, Clinical Study Investigating the Efficacy of an Experimental Dentifrice Containing Sodium Bicarbonate, High Molecular Weight Sodium Hyaluronate, and Sodium Fluoride on Gingivitis and Plaque Removal in a Population with Mild-Moderate Plaque-Induced Gingivitis

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CCI

CCI

GSK CH Clinical Study RH02433/ 202192, A six month clinical study based in the us to evaluate the efficacy and tolerability of sodium bicarbonate toothpaste. GSK Data Held on File; 2017.

GSK CH Clinical Study Report RH02434/ 202193, A six-month clinical study based in the US to evaluate the efficacy and tolerability of sodium bicarbonate toothpaste and its effect on opportunistic or resistant organisms. Data held on file 2017.ICH GENERAL CONSIDERATIONS FOR CLINICAL TRIALS E8. 1997

ICH Topic E6 (R2) Guideline for Good Clinical Practice, Nov 2016.

Jose A, Pratten J, Bosma ML, et al. Six-month evaluation of a sodium bicarbonate-containing toothpaste for reduction of established gingivitis: A randomized USA-based clinical trial. The Journal of clinical dentistry. 2018;29(1):33-9.

Kakar A, Lomax A, Siddiqi M, et al. Evaluate the efficacy of different concentrations of sodium bicarbonate toothpastes. (2014) IADR Cape Abstract No 754.

Kinane DF, Hodge PJ. Periodontal disease in children and adolescents: Introduction and classification. Periodontology 2000. 2001;26:7-15.

Lobene RR, Soparkar PM, Newman MB. Use of dental floss. Effect on plaque and gingivitis. Clinical preventive dentistry. 1982;4(1):5-8.

Lobene RR, Weatherford T, Ross NM, et al. A modified gingival index for use in clinical trials. Clinical preventive dentistry. 1986;8(1):3-6.

Lomax A, Patel S, Wang N, et al. A randomized controlled trial evaluating the efficacy of a 67% sodium bicarbonate toothpaste on gingivitis. Int J Dent Hyg; 2017; 15(4): e35-e41.

Machuca G, Rosales I, Lacalle JR, et al. Effect of cigarette smoking on periodontal status of healthy young adults. The Journal of periodontology. 2000;71(1):73-8.

Mankodi S, Berkowitz H, Durbin K, et al. Evaluation of the effects of brushing on the removal of dental plaque. J Clin Dent; 1998;9(3):57-60.

Marsh PD. Microbiological aspects of the chemical control of plaque and gingivitis. J Dent Res; 1992; 71(7): 1431-8.

Mason S, Karwal R, Bosma M. Two randomized clinical studies to confirm differential plaque removal by sodium bicarbonate dentifrices in a single timed brushing model. J Clin Dent; 2017; 28(3): 44-8.

Newby EE, Fu Y, Shaw D, et al. Efficacy of sodium bicarbonate toothpastes ongingivitis and plaque. (2014); IADR Cape Abstract No 1304.

Obeid P, Bercy P. Effects of smoking on periodontal health: A review. Advances in therapy. 2000;17(5):230-7.

Ower P. The role of self-administered plaque control in the management of periodontal diseases: I. A review of the evidence. Dental update. 2003;30(2):60-4, 6, 8.

Petersen PE, Ogawa H. The global burden of periodontal disease: Towards integration with chronic disease prevention and control. Periodontology 2000. 2012;60(1):15-39.

Pratten J, Wiecek J, Mordan N, et al. Physical disruption of oral biofilms by sodium bicarbonate: an in vitro study. Int J Dent Hyg; 2016; 14(3): 209-14.

Putt MS, Milleman KR, Ghassemi A, et al. Enhancement of plaque removal efficacy by tooth brushing with baking soda dentifrices: results of five clinical studies. J Clin Dent; 2008; 19(4):111-9.

Rotella K, Bosma M L, McGuire J A, Habits, Practices and Beliefs Regarding Floss and Mouthrinse among Habitual and Non-Habitual Users. Journal of Dental Hygiene, 2022; 96(3): 46-58

Samant A, Malik C, Chabra S, et al. Gingivitis and periodontal disease in pregnancy. 1976; 47(7): 415-8.

Saxton CA, van der Ouderaa FJ. The effect of a dentifrice containing zinc citrate and triclosan on developing gingivitis. Journal of periodontal research. 1989;24(1):75-80.

Silness J, Loe H Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand. 1964; 22: 121-35

Theilade E, Wright WH, Jensen SB, et al. Experimental gingivitis in man. II. A longitudinal clinical and bacteriological investigation. J Periodontal Res; 1966; 1: 1-13.

Triratana T, Kraivaphan P, Amornchat C, et al. Comparing three toothpastes in controlling plaque and gingivitis: A 6-month clinical study. Am J Dent. 2015 Apr;28(2):68-74

van der Weijden GA, Hioe KP A systematic review of the effectiveness of self-performed mechanical plaque removal in adults with gingivitis using a manual toothbrush. J Clin Periodontol; 2005; 32 (Suppl 6): 214-28.

World Medical Association. Declaration of Helsinki, 64th General Assembly, Fortaleza. 2013

15 APPENDICIES

15.1 ABBREVIATIONS

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

Table 15-1 Abbreviations

Abbreviation	Term
AE	Adverse event
ANCOVA	Analysis of covariance
BDM	Biostatistics and Data Management
BDR	Blinded data review
BI	Bleeding index
BOP	Bleeding on probing
CI	confidence interval
CRF	case report form
CRS	Clinical Research Scientist
CSR	Clinical study report
Da	Dalton
DMS	Data management system
EC	ethics committee
ECG	echocardiogram
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSFV	First subject first visit
GCP	Good Clinical Practice
GSK CH	GlaxoSmithKline Consumer Healthcare
GI	gingival index
hrs	hours
IB	investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IND	investigational new drug application
IRB	institutional review board
ITT	Intent to treat
IoMT	Internet of Medical Things
LLC	limited liability company
MedDRA	medical Dictionary for Regulatory Activities
MFC	Manufacturing formulation code
MGI	Modified gingival index
mITT	Modified Intent-to-Treat
mm	Millimeter

Abbreviation	Term
N/A	Not applicable
No.	Number
NNHP	Non-prescription Natural Health Product
OH	Oral health
OHT	Oral hard tissue
OST	Oral soft tissue
PI	Principal investigator
PI	Personal information
PP	Per protocol
PRO	Patient reported outcome
RAP	Reporting and analysis plan
REC	Research ethics committee
SAE	serious adverse event
SD	Standard deviation
SE	Standard error
SOP	standard operating procedure
SRSD	Single reference study document
SS	Safety statement
SUSAR	Suspected unexpected serious adverse reaction
TPI	Turesky modification of the Quigley Hein Plaque Index
UK	United Kingdom
w/w	Weight for weight

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