CLINICAL PROTOCOL

A Randomized, Single-Blind Clinical Study Assessing the Effects of an Experimental Dentifrice Compared to a Regular Fluoride Dentifrice on Breath Odor When Used Twice Daily for 3 Weeks in a Population With Clinically Diagnosed Gingivitis

Protocol Number:	300025
Compound/Product Name:	0.454% Stannous Fluoride and 0.3% Zinc Chloride
United States (US) Investigational New Drug (IND) Number:	N/A
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Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (UK)
Sponsor Contact Details	**GlaxoSmithKline Consumer Healthcare (GSK CH)** 184 Liberty Corner Road, Warren, NJ

Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	Clarification throughout of 2 diaries being used, now labelled “washout diary” and “subject diary”. Amendment of Inclusion Criterion 5d to clarify that the less than 500ppb difference between samples requirement is between the 2 samples collected at any timepoint. Correction to Table 6-3 on pack for toothbrush. Correction in section 6.5 from “three study products” to “two study products”. Addition to section 6.7,3rd bullet point to clarify that subjects will have compliance investigated at visit 2 as well as visit 3. Deletion of range of OralChroma instrument in Section 9.2.1
Amendment 2		

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.
- 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:	
Investigator Signature:	PPD
Date of Signature/Agreement:	PPD DD-Mmm-YYYY

Table of Contents

List of in text tables

1 PROTOCOL SUMMARY

1.1 Synopsis

Background and Rationale:

This study will investigate the efficacy of an experimental dentifrice, containing 0.454% stannous fluoride and 0.3% zinc chloride, to reduce oral malodor, compared to a marketed regular fluoride dentifrice after 3 weeks twice daily brushing in a population of clinically diagnosed gingivitis. Oral malodor will be evaluated using a hedonic scale assessed by a panel of calibrated organoleptic assessors who will sniff the subject's breath, and through the instrumental measurement of the concentration of volatile sulfur compounds (VSCs) of a sample of the subject's breath.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate and compare the change in morning oral malodor by an organoleptic assessment following 3 weeks of twice-daily tooth brushing using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice.	Change in mean organoleptic score from Baseline (pre-brushing) to 3 weeks (pre-brushing)
Secondary	
To evaluate and compare the change in morning oral malodor by VSC determination following 3 weeks of twice-daily tooth brushing using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice.	Change from Baseline (pre-brushing) to 3 weeks (pre-brushing) in:- • Mean total VSC concentration in breath. • Mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath.
To evaluate and compare the change in oral malodor post brushing following 3 weeks of twice-daily tooth brushing using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice.	Change from Baseline (pre-brushing) to 3 weeks (1 hour post-brushing) in: • Mean total VSC concentration in breath. • Mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath. • Mean breath organoleptic scores.
To evaluate and compare the change in oral malodor 1 hour post brushing at Baseline, and 1 hour post brushing following 3 weeks twice-daily use using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice.	Change from pre-brushing to 1 hour post brushing at Baseline and after 3 weeks in:- • Mean total VSC concentration in breath. • Mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath. • Mean breath organoleptic scores.
Safety	
To assess the tolerability of an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride	Treatment emergent adverse events

Study Design:

This will be a single center, single blind (to the examiners undertaking the oral malodor assessments), randomized (stratified by subject's sex), controlled, two arm parallel study in volunteers with clinically diagnosed gingivitis. The study will evaluate the clinical efficacy of an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride to reduce oral malodor after 3 weeks of twice-daily use compared to a regular reference dentifrice.

Potential subjects will attend a screening visit to determine their suitability to participate. Having obtained their written informed consent, relevant details of their medical history and current medications will be recorded. Subjects will then undergo the screening assessment of their oral malodor followed by oral soft tissue (OST) and oral hard tissue (OHT) examinations and an assessments of gingivitis (Bleeding on probing examination). Subjects with gingivitis and oral malodor per the inclusion criteria, as well as meeting all other study criteria, will be considered as eligible to proceed, appointed for baseline assessments and dispensed a washout dentifrice and toothbrush to use instead of their regular oral hygiene products until they return for Visit 2 (1-3 weeks after screening).

At the Baseline visit (Visit 2), subjects, having abstained from oral hygiene procedures and food consumption for at least 8 hours, will undergo baseline breath VSC and organoleptic assessments. Qualifying subjects will be stratified by the subject's sex and randomized to one of the two study treatments. Subjects will then be instructed on the use of their study products and will brush their teeth, under supervision, for 1 minute with their assigned dentifrice. One hour (±5 minutes) post brushing, subjects will have their post-brushing breath VSC and organoleptic assessments. Subjects will then undergo an OST examination and instructed to brush twice daily (for 1 minute, morning and evening) with their assigned study dentifrice for the next 3 weeks until their next visit (Visit 3).

At Visit 3, subjects, having abstained from oral hygiene procedures and food consumption for at least 8 hours will undergo pre- and post-brushing evaluation of breath VSCs and organoleptic scores in the same manner as performed at the Baseline visit. Subjects will then undergo OST and OHT examinations and exit the study.

Study Products:

Experimental Dentifrice	Reference Dentifrice
Dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride.	Standard Fluoride Dentifrice [0.243% sodium fluoride] (Crest Cavity Protection, US market)

Both dentifrices will be brushed on to the teeth, twice daily (morning and evening) for 1 timed minute in line with the usage instructions in Appendix 15.1.

Type and Planned Number of Subjects:

Study subjects of either sex and any gender, aged of 18-65 years, will be in good general health with clinically diagnosed gingivitis and with the level of oral malodor required at baseline to participate in the study.

Sufficient subjects will be screened to randomize approximately 106 subjects to study treatment (approximately 53 per treatment group) to ensure approximately 100 evaluable subjects complete the study.

Statistical Analysis:

For the primary endpoint analyses, an ANCOVA model will be used to analyze the change in mean breath organoleptic score from Baseline (pre-brushing) to 3 weeks (pre-brushing) with study product and gender as fixed effects and the mean Baseline (pre-brushing) breath organoleptic score as a covariate. The difference between least square means for the Experimental Dentifrice compared to the Reference Dentifrice will be used to test for a difference between products at the two-sided 5% significance level. The assumption of normality and homogeneity of variance in the ANCOVA will be investigated. In case of violation of these assumptions, a suitable nonparametric test (adjusted for gender) will be performed, and results will be provided to support the ANCOVA results.

For secondary endpoint change from Baseline analyses, a similar ANCOVA model as used for the primary analysis will be applied but with the appropriate pre-brushing and post-baseline result used accordingly. For VSC endpoints, data will be log (base 10) transformed prior to analysis. There will be no adjustment for multiplicity for secondary endpoints.

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 Period			
	Visit 1		Visit 2 Baseline		Visit 3 Week 3
Informed consent	X	Wash-out period of at least 7 days.(maximum 21 days)		3 Weeks (+2 days)	
Demographics	X				
Medical history	X				
Current/prior/concomitant medication review	X		X		X
Screening assessment of oral malodor	X				
OST examination	X		X		X
OHT examination	X				X
Bleeding on probing assessment	X				
Review of inclusion/exclusion criteria	X		X		
Subject eligibility	X		X		
Dispense wash-out dentifrice, toothbrush and washout diary	X				
Subject returns wash-out dentifrice and toothbrush and washout diary			X		
Pre-brushing assessment of oral malodor[2]			X		X
Subject continuance					X
Stratification and randomization			X		
Dispense study products, subject diary and sundry items with instruction in proper use			X		
Supervised brushing			X		X
Post-brushing assessment of oral malodor[3]			X		X
Return study products and subject diary					X
Adverse events review[1]	X		X		X
Medical device incidents review[1]			X		X
Study conclusion					X

Abbreviations: OST: Oral Soft Tissue, OHT: Oral Hard Tissue, VSC: Volatile Sulfur Compound

Footnotes:

1. 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 supplied toothbrush.
2. At Visits 2&3, pre-brushing breath VSC-determination (by OralChroma) and organoleptic assessments will be performed with subjects having not brushed their teeth and not eaten for at least 8 hours.
3. Post-brushing breath VSC-determination (by OralChroma) and organoleptic assessments will be performed 1 hour (±5 minutes) after supervised brushing.

2 INTRODUCTION

It is generally accepted that oral malodor primarily originates from bacterial putrefaction of proteinaceous and other compounds within the oral cavity particularly by anaerobic bacteria including *Bacteroides forsythus, Actinobacillus actinomycetemcomitans and Prevotella intermedia (*Awano et al., 2002*)*. These bacteria are located throughout the oral cavity, and are found in particularly high numbers in saliva (Awano et al., 2002) and on the tongue, especially towards the tongue posterior (Allaker et al., 2008). These bacterial species are also associated and present in higher numbers in those with gingivitis and periodontal disease (Abusleme et al., 2021)

The odors that these bacteria produce include amines such as putrescine and cadaverine and fatty acids such as butyrate and valerate (Van den Broek et al., 2007). However, a significant contributor to oral malodor are the volatile sulfur compounds (VSCs) such as hydrogen sulfide, methanethiol and dimethyl sulfide, with hydrogen sulfide the most concentrated odor on the breath of oral malodor sufferers (Washio et al., 2005).

Although management of oral malodor is an active area of research, objective, clinical measurement of oral malodor, and thereby determination of the efficacy of condition management, is currently not possible. Organoleptic/hedonic assessment is often employed and clearly has the benefit of simplicity and relevancy to patients, however the human nose is not linear in response to malodor concentration and measurement is often complicated by the flavors that are routinely added to healthcare products. Measurement of VSC concentration in breath is therefore routinely used as a quantifiable surrogate measurement and given the prevalence of VSCs in breath this would appear to be appropriate. Indeed, clinical measurement of VSCs by techniques such as the Halimeter, the OralChroma and gas chromatography (GC) have been used to provide clinical evidence of efficacy of treatments (Vandekerckhove et al., 2009, Oho et al., 2001). Moreover, Rosenberg *et al.* have demonstrated a correlation between organoleptic assessment of oral malodor and clinically measured VSC concentrations (Rosenberg et al., 1991a).

Whilst not yet conclusive, there is evidence that periodontal diseases may be a factor in the etiology of oral malodor (De Geest et al., 2016). Oral malodor has been significantly related to periodontal pocket depth (Chen et al., 2016) and analysis of periodontal pockets has shown the presence of high concentrations of VSCs (Rizzo, 1967). Additionally the bacterial species associated with gingivitis and periodontal disease are also implicated in oral malodor (Abusleme et al., 2021).

Effective treatments to control oral malodor include mechanical removal of oral bacteria and dental plaque, such as tongue scraping and tongue/tooth brushing, and adjunctive use of antimicrobials such as chlorhexidine, cetylpyridinium chloride, essential oils and zinc ions (De Geest et al., 2016).

This study aims to assess the oral malodor of subjects with clinically diagnosed gingivitis who use an experimental dentifrice containing both stannous fluoride and zinc ions compared to use of a standard sodium fluoride dentifrice.

2.1 Study Rationale

This 3-week, randomized, controlled, parallel-design, stratified clinical study has been designed to evaluate the ability of an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride to reduce oral malodor, compared to a regular fluoride dentifrice in a population with clinically diagnosed gingivitis.

The anti-gingivitis benefits of stannous fluoride dentifrices similar to the test product is well established (see Section 2.2). Additionally, the oral malodor benefits through use of a single application of zinc-containing dentifrices has also been demonstrated in a non-gingivitis population. However, additional data are required to confirm the oral malodor reduction benefit of the experimental dentifrice in a population of subjects with clinically diagnosed gingivitis. The study will inform on the efficacy of the experimental dentifrice to reduce oral malodor through usage over 3 weeks (in line with ADA guidelines for the testing of products used in the management of oral malodor (ADA, 2016)).

2.2 Background

The experimental dentifrice being tested contains stannous fluoride, an active with an extensive history of gum-health efficacy (Makin, 2013, Paraskevas and Van der Weijden, 2006, Twetman et al., 2003, Rølla and Ellingsen, 1994). Formulations containing the same concentration of stannous fluoride as in the experimental dentifrice being evaluated in this study (although not containing zinc ions), have been evaluated previously both for dentine hypersensitivity relief (Parkinson et al., 2013, Parkinson et al., 2015, Parkinson et al., 2016) and improvements in gingivitis (Parkinson et al., 2018b, Parkinson et al., 2018a). Additionally this formulation has been shown not to exhibit dental staining that has previously been observed with stannous fluoride-based dentifrices (Nehme et al., 2013). Stannous fluoride has been recognized as safe and effective for the treatment of gingivitis by the US Food and Drug Administration (FDA) (FDA, 2003). Additionally a 0.45% stannous fluoride dentifrice has been shown to reduce oral malodor using both VSC measurement and organoleptic assessment in a non-gingivitis healthy population (Gerlach et al., 1998).

Given the association between gum disease and oral malodor (see Introduction) it is expected that treatment of gingivitis (through stannous fluoride) will additionally show benefits in oral malodor. Additionally, zinc-containing products are highly effective at reducing oral malodor (Young et al., 2001, Schmidt and Tarbet, 1978, Newby et al., 2008, Payne et al., 2011), possibly because they are dual active, being both antimicrobial, and chemically reactive to VSCs resulting in non-volatile (and therefore non-odorous) sulfur species (Burnett et al., 2011).

In summary, existing clinical data provide evidence of oral malodor efficacy for zinc-containing dentifrice formulations. However there appears to be little published evidence on the efficacy of these formulations for those with gingivitis. This study will therefore evaluate the efficacy of an experimental dentifrice containing stannous fluoride and zinc chloride in reducing oral malodor in a population of subjects with clinically diagnosed gingivitis.

2.3 Benefit/Risk Assessment

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

Whilst the exact formulation of the experimental dentifrice under investigation has not been previously clinically tested, similar products containing stannous fluoride and zinc chloride have been evaluated in clinical studies (see Background Section 2.2). These studies demonstrated the anti-gingivitis and/or anti oral malodor efficacy and safety of similar formulations. The active ingredients and formulation excipients contained in the study dentifrices have a history of safe use in oral care products and are currently used in marketed daily use dentifrices.

The experimental dentifrice is considered generally safe for topical oral use, with twice daily brushing, under the controlled conditions of a clinical trial.

2.4 Mechanism of Action/Indication

This study will be conducted in generally healthy subjects with clinically diagnosed gingivitis and with a minimum level of clinically-measured oral malodor as described in the inclusion criteria. The dentifrice being evaluated contains zinc ions which are effective at reducing oral malodor through their antimicrobial activity coupled with their ability to chemically react with VSCs resulting in non-volatile (and therefore non-odorous) sulfur species (Burnett et al., 2011). Additionally, the stannous fluoride in the formulation is expected to provide oral malodor benefits through its antimicrobial/ antiplaque benefits (Bosma et al., 1997, Mankodi et al., 2005, Mallatt et al., 2007) leading to improvements in gingivitis (Parkinson et al., 2018a, Parkinson et al., 2018b).

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate and compare the change in morning oral malodor by an organoleptic assessment following 3 weeks of twice-daily tooth brushing using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice.	Change in mean organoleptic score from Baseline (pre-brushing) to 3 weeks (pre-brushing)
Secondary	
To evaluate and compare the change in morning oral malodor by VSC determination following 3 weeks of twice-daily tooth brushing using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice.	Change from Baseline (pre-brushing) to 3 weeks (pre-brushing) in:- • Mean total VSC concentration in breath. • Mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath.
To evaluate and compare the change in oral malodor post brushing following 3 weeks of twice-daily tooth brushing using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice.	Change from Baseline (pre-brushing) to 3 weeks (1 hour post-brushing) in: • Mean total VSC concentration in breath. • Mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath. • Mean breath organoleptic scores.
To evaluate and compare the change in oral malodor 1 hour post brushing at Baseline, and 1 hour post brushing following 3 weeks twice-daily use using an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride compared to a standard fluoride dentifrice.	Change from pre-brushing to 1 hour post brushing at Baseline and after 3 weeks in:- • Mean total VSC concentration in breath. • Mean hydrogen sulfide, methanethiol and dimethyl sulfide concentration in breath. • Mean breath organoleptic scores.
Safety	
To assess the tolerability of an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride	Treatment emergent adverse events

This study will be considered successful if the experimental dentifrice containing stannous fluoride and zinc chloride demonstrates statistically significant greater reduction in total breath VSC compared to the reference dentifrice following 3 weeks of twice daily brushing.

4 STUDY DESIGN

4.1 Overall Design

This will be a single center, single blind (to the examiners undertaking the oral malodor assessments), randomized (stratified by the subject's sex), controlled, two arm parallel study in volunteers with clinically diagnosed gingivitis and oral malodor. The study will evaluate the clinical efficacy of an experimental dentifrice containing 0.454% stannous fluoride and 0.3% zinc chloride to reduce oral malodor after 3 weeks of twice-daily use compared to a regular reference dentifrice.

Potential subjects will attend a screening visit to determine their suitability to participate having abstained from oral hygiene procedures and food consumption for at least 8 hours. Having obtained their written informed consent, relevant details of their medical history and current medications will be recorded, followed by the screening assessment of their oral malodor. Subjects will then undergo oral soft tissue (OST) and oral hard tissue (OHT) examinations, and a gingivitis assessment (bleeding on probing examination). Subjects with sufficient gingivitis and sufficient concentration of hydrogen sulfide in their breath as per the inclusion criteria, as well as meeting all other study criteria, will be considered as eligible to proceed, appointed for baseline assessments and dispensed a washout dentifrice and toothbrush to use instead of their regular oral hygiene products until they return for Visit 2 (1-3 weeks after screening). A washout diary will also be dispensed for the subjects to record their washout product usage.

At the Baseline visit (Visit 2) subjects, having abstained from oral hygiene procedures and food consumption for at least 8 hours, will undergo baseline breath VSC (using the OralChroma instrument) and organoleptic assessments (judged by a panel of 3 assessors using the hedonic scale of Rosenberg (Rosenberg et al., 1991b). The organoleptic panel will have been recently calibrated and standardized (within the past year) with a kappa statistic of ≥0.6 per the American Dental Association guidelines (ADA, 2016).

Qualifying subjects, having a hedonic score ≥2 and a mean concentration of hydrogen sulfide (a major contributor to oral malodor) in their breath of at least 150ppb, will be stratified by the subject's sex and randomized to one of the 2 study treatments. Subjects will be instructed on the use of their study products and subject diary and will brush their teeth, under supervision, for 1 timed minute with their assigned dentifrice. One hour (±5 minutes) post brushing, subjects will have their post-brushing breath VSC and organoleptic assessments, followed by an OST examination. Subjects will be instructed to brush twice daily (for 1 minute, morning and evening) with their assigned study dentifrice for the next 3 weeks (+ 2 days) until their next visit (Visit 3).

At Visit 3, subjects, having abstained from oral hygiene procedures and food consumption for at least 8 hours will undergo pre- and post-brushing evaluation of breath VSCs and hedonic scores in the same manner as performed at the Baseline visit. Following all breath odor assessments subjects will undergo OST and OHT examinations and exit the study.

Safety and oral tolerability of the study products will be monitored over the 3-week usage period by review of reported AEs.

4.2 Scientific Rationale for Study Design

A parallel group experimental design was selected as carryover effects from the treatment groups would be anticipated.

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 blind to the treatment a subject receives, but the products under test must be identical in every way (color, flavor, appearance, packaging). Given the experimental dentifrices and the reference dentifrice will differ in appearance and flavor, the level of blindness for this study is described as 'examiner blind'. Study dentifrices will be supplied in overwrapped tubes. The blind will be maintained by staff involved in dispensing, brushing instruction and supervised brushings not being involved in the clinical examinations and study products being provided to subjects in blinded packs. Dental examiner(s) and organoleptic assessors will be blind to treatment allocation to ensure there is no bias in the assessments.

This is a single-center study. The same examiner(s) will perform the clinical assessments throughout the study to reduce the possibility of inter-examiner variability.

A regular fluoride dentifrice has been selected as reference dentifrice. For the purposes of this study, it was deemed more relevant to compare the efficacy of the experimental dentifrice against breath odor reducing performance of a typical daily-use dentifrice rather than a placebo.

The assessments used in this study (VSC determination and organoleptic assessment) are well established and recognized in the scientific literature for the evaluation of oral malodor (Rösing and Loesche, 2011, ADA, 2016). The odor judges performing the organoleptic assessment should have been recently calibrated and standardized with a kappa statistic of ≥0.6 per the ADA guidelines (ADA, 2016). VSC determination will be performed using the OralChroma instrument (Tangerman and Winkel, 2008), a methodology which has been previously well correlated with hedonic assessment (Dadamio et al., 2013) and Gas Chromatographic assessment of VSCs (Murata et al., 2006). In line with recommendations, the instrument will have been calibrated by the manufacturer prior to commencement of the study (Tangerman and Winkel, 2008). Organoleptic assessment of the hedonics of oral malodor will be performed using the scale devised by Rosenburg (Rosenberg et al., 1991b). This scale has been used in many previous clinical studies including demonstration of the efficacy of oral healthcare products in the reduction of oral malodor (Winkel et al., 2003).

A wash-out period where the subjects use a standardized dentifrice prior to baseline, is required to standardize oral hygiene procedures and products prior to oral malodor assessments since some oral hygiene products can affect oral malodor.

Oral malodor develops from the breakdown by micro-organisms of various proteins in the mouth. In order to for oral malodor of a sufficient level is present to be detected and treated, subjects will be asked to abstain from performing oral hygiene procedures and eating for at least 8 hours before any day on which oral malodor assessments are to be performed.

To detect differences in oral malodor following use of study products, it is necessary, at the baseline visit (pre-brushing), that subjects have a minimum level of oral malodor as measured by the organoleptic score, and the hydrogen sulfide concentration in their breath (both as defined in the inclusion criteria).

The experimental dentifrice being tested is intended to be indicated for users with gingivitis. This study will therefore assess oral malodor in subjects with clinically measurable levels of gingivitis, defined as those with 10-30 % bleeding sites on probing (Chapple et al., 2018).

Gingivitis symptoms are known to vary across the menstrual cycle (Machtei et al., 2004). Additionally, the production of breath VSC is influenced by menstrual cycle (Calil et al., 2008, Tonzetich et al., 1978). Subjects will therefore be stratified by the subject's sex prior to randomization to ensure equal balance of females in both treatment arms. Whilst this approach will not completely resolve within subject variation due to menstrual cycle, randomization will help ensure subjects at different stages of their menstrual cycle will be evenly distributed across the two treatment groups.

The testing duration of 3 weeks product use is aligned with recommendations provided by the American Dental Association for the testing of products for the management of oral malodor (ADA, 2016).

Whilst the study products are not contra-indicated for pregnancy (their use would not be expected to cause harm either to the mother or foetus), pregnant females will be excluded from this study due to the increased prevalence and severity of gingivitis (Samant et al., 1976) which could be a confounding factor for the objectives of this study. Pregnant females and those intending to become pregnant will be excluded. Pregnancy will be monitored by subject-reported pregnancy status.

4.3 Justification for Dose

Subjects will use their assigned dentifrices twice daily in agreement with recommendations provided by the American Dental Association for effective toothbrushing (ADA, 2022). The brushing time has been standardized as 1 minute in line with normal consumer practice (Macgregor and Rugg - Gunn, 1985, Ganss et al., 2009) and to align with previous oral malodor studies performed by the sponsor CCI [redacted].

On each brushing occasion, the toothbrush will be dosed with a ribbon of dentifrice (covering the entire length of the toothbrush), in line with the proposed product labelling for the experimental dentifrices and the current product labelling for the marketed reference dentifrice.

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

4.4 End of Study Definition

A subject is considered to have completed the study if they have completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Activities.

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

Volunteers of either sex and any gender, aged 18 – 65 years will be recruited with sufficient levels of oral malodor (as defined in the inclusion criteria) to allow for evaluation of change

(reduction) in these parameters during the study. Subjects will be recruited from the study site's database.

Sufficient subjects will be screened to randomize approximately 106 subjects (equally distributed across the two treatment groups) to ensure approximately 100 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

An individual must meet all the following inclusion criteria to be eligible for enrollment into, and continuance in the study:

1. 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 of either sex and any gender who, at the time of screening, is between the ages of 18-65 years, inclusive.
3. Subject who is willing and able to comply with scheduled visits, product usage requirements, study procedures and lifestyle restrictions.
4. Subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, no clinically significant or relevant abnormalities in medical history (for example, a medical condition or medication confirmed to contribute to xerostomia),or upon oral examination, that would impact the subject's safety, wellbeing or the outcomes of the study, if they were to participate in the study, or affect the subject's ability to understand and follow study procedures and requirements.
5. Subject with generally good oral health that fulfil all of the following:
    a. Having at least 20 natural (vital) teeth.
    b. Good oral health without lesions in the oral cavity (including the tongue) that could interfere with the study evaluations.
    c. Having clinically diagnosed, plaque-induced gingivitis defined as having 10-30 % bleeding sites from the bleeding on probing assessment.
    d. At Screening (Visit 1) and prior to brushing with assigned dentifrice at Baseline (Visit 2) subjects must provide 2 samples of mouth air, which must have a mean hydrogen sulfide concentration greater than 150ppb. There must be ≤500ppb difference in hydrogen sulfide between the 2 samples collected at screening. Additionally, there must be ≤500ppb difference in hydrogen sulfide between the 2 samples collected at baseline (pre-brushing).
    e. At Baseline (Visit 2), prior to brushing with assigned dentifrice subjects must provide a breath sample with a mean organoleptic score ≥2.

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will be excluded from the study:

1) 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 an employee of the sponsor directly involved in the conduct of the study or a member of their immediate family.
2) Subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days of study entry and/or during study participation or who has previously been enrolled in this study.
3) 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 study 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 is pregnant (self-reported) or intending to become pregnant during the study
5) Subject who is breastfeeding.
6) Subject who habitually smokes, uses tobacco products or who vapes.
7) Subject with known or suspected intolerance or hypersensitivity to the study products or any of their stated ingredients (or closely related compounds).
8) Subject who is unwilling or, in the opinion of the investigator or medically qualified designee, unable to comply with the requirements and/or Lifestyle Considerations of the study.
9) Subject with a recent history (within the last year) of alcohol or other substance abuse.
10) General medical exclusions:
    a) Subject with a medical history that may prevent the subject from participating in the study until study conclusion.
    b) Subject with, or having recent history of, bronchitis, tonsillitis or sinusitis (within 6 weeks) or any other systemic condition that can cause oral malodor eg. xerostomia, chronic acid reflux, Type 1 diabetes, Crohn's disease, celiac disease or liver/kidney conditions.
    c) Subject with a significant infectious disease, such as hepatitis, COVID-19, flu, respiratory infection, tuberculosis, or any other condition which can be transmitted in saliva or salivary aerosols which, in the opinion of the examiner, could endanger the organoleptic assessors.
    d) Subject with any condition that impacts gum health (e.g. Type 2 Diabetes).
11) General medication exclusions:
    a. Subject using any antibiotic medication within 14 days prior to screening or at any time during the study.
    b. Subject using chlorhexidine, cetylpyridinium chloride (CPC) or stannous fluoride containing mouthwash or dentifrice within 14 days prior to Visit 2 or between Visit 2 & 3.

c. Subject taking medications which may impact oral mouth odour (e.g. Diazepam, Alprazolam, Lorazepam etc).

12) General oral exclusions:
   a. Subject with orthodontic or prosthetic appliances (fixed or removable), including dental implants.
   b. Subject having had professional dental cleaning (oral prophylaxis) within 3 months prior to the screening visit or at any time during the study.
   c. Subject with signs of active periodontal disease (with probing depth >3mm) or who is receiving or has received treatment for periodontal disease (including surgery) within 12 months of Screening.
   d. Subject who has had oral surgery or tooth extraction within 6 weeks of the screening visit.
   e. Subject who has dental conditions or disease under active dental treatment or requiring immediate treatment.
   f. Subject with tongue or lip piercing.
   g. Subject with OST examination findings at Screening which, in the opinion of the investigator, could interfere with the conduct of the study (for example, stomatitis, open sores, lesions, cavitied caries lesions, redness or swelling.
   h. Subject who does not practice daily oral care.

13) Subject with oral malodor which, in the opinion of the investigator, is not expected to respond to treatment with an over-the-counter dentifrice.

14) Subject who, in the opinion of the investigator, should not participate in the study.

5.4 Randomization Criteria

Subjects who satisfy the study selection criteria will be stratified according to their sex (male or female) and randomized to study treatment.

5.5 Lifestyle Considerations

The site may contact subjects to remind them of lifestyle restrictions and approaching scheduled visits.

5.5.1 Oral Hygiene Restrictions

- **Visits 1-3:**
  - Subjects will be asked to delay elective dental treatment (for example, dental prophylaxis) for the duration of the study. They will be required to inform site staff of any emergency treatment they receive during the study.
  - Subjects should not use any other oral care products (e.g. dentifrices, mouthwash, dental floss, interdental brushes, toothpicks, water picks, breath freshening products, e.g. chewing gums, breath mints, cough drops or breath sprays etc.) other than those provided during the study.
  - Subjects will not be permitted to use tongue brushes/scrapers and should refrain from brushing or debriding their tongue for the duration of the study.
- **Visits 2 & 3:** Subjects will abstain from all oral hygiene procedures for at **least 8 hours** prior to their visit to site.

5.5.2 Dietary Restrictions

- **Visits 2 & 3:**
  - Subjects will abstain from eating and drinking (with the exception of small amounts of water required for taking medication or to relieve thirst) for at **least 8 hours** prior to and during their clinical/instrumental assessment visits.
  - Subjects should refrain from eating heavily spiced food, garlic, and onion and drinking alcohol **for at least 24 hours** prior to the visit. Subjects who present with external odors (e.g., alcohol, garlic, smoke, candy, perfume etc.) which may interfere with the study evaluation may be withdrawn from the study or may be asked to return to the site on another occasion.

5.5.3 Use of Cosmetics

- **Visits 2 & 3:** Subjects will attend site without wearing cosmetic products that could affect the organoleptic assessments, e.g. perfume, lipstick etc.

5.5.4 Tobacco Product Restrictions

- **Visits 1-3:** Subjects will not be permitted to smoke, vape or use tobacco products from 11pm the evening prior to attending the study site till after all clinical procedures have been completed for that visit.

5.5.5 Medication and Treatment Restrictions

- **Visits 1-3:** Subjects will be asked to delay elective dental treatment (for example, dental prophylaxis) for the duration of the study. They will be required to inform site staff of any emergency treatment they receive during the study.
- **Visits 2 & 3:** Subjects will be asked to inform site staff of changes to their medications/treatments for the duration of the study. Should a subject commence a course of medication which, in the opinion of the investigator or medically qualified designee, could impact study outcomes, the subject may be withdrawn.

5.5.6 Contraception

There are no contraception requirements for subjects participating in this study. At each visit, female subjects of child-bearing potential should verbally confirm they are not currently pregnant or planning to become pregnant.

5.5.7 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 be collected, including demography, reason for screen failure (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 site staff seeking advice on medical/ dental questions or problems in the event that the established communication pathways between the study site and the sponsor's 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 study site, and contact details in the event that the study site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Clinical Assessor Qualifications

Clinical examiner(s) involved in the screening, safety and efficacy assessments will be appropriately qualified dental professionals, registered to practice in the US.

Oral examinations to determine subject eligibility and to monitor the safety/performance of study products will be performed by appropriately trained clinical examiner(s), with prior relevant clinical experience. Clinical examiners performing the organoleptic assessments will have been recently calibrated and standardized with a kappa statistic of ≥0.6.

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's Clinical Supplies Group.

Table 6-1 Investigational/Study Product Supplies

Product Description	**Experimental Dentifrice**	**Reference Dentifrice**
	0.454% Stannous Fluoride dentifrice with 0.3% Zinc Chloride	Regular Fluoride Dentifrice
Product Name	N/A	Crest Cavity Protection (US Market Product)
Pack Design	One carton containing 2 overwrapped tubes of dentifrice	
Dispensing Details	Visit 2 (Baseline): 1 carton	
Product Master Formulation Code (MFC)	CCI [redacted]	N/A
Dose/Product Application	Subjects will dose the toothbrush provided with a ribbon of paste to cover the brush head (a full brush head) on each brushing occasion	
Route of Administration	Oral topical use	
Usage Instructions	Subjects will brush twice daily (morning and evening) for 1 timed minute with their allocated product.	
Return Requirements	Used and unused study product to be returned to the sponsor.	

The following sundry items will be supplied by the sponsor's Global Clinical Supplies Group.

Table 6-2 Washout Product Supplies

	Washout Dentifrice
Product Name	Aquafresh Cavity Protection (US Marketplace)
Pack Design	One carton containing 2 over-wrapped tubes
Dispensing Details	One carton at Screening Visit
Product Master Formulation Code (MFC)	CCI [redacted]
Dose/Application	Full ribbon of toothpaste on 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

Item	Pack Design	Dispensing Details	Return/Disposal Details	
			Used Samples	Unused Samples
Sensodyne Sensitive Care soft-bristled Toothbrushes (US marketplace)	Individual toothbrush	Visit 1: 1 brush Visit 2: 1 brush	Destroy at site using site disposal procedures	Return to sponsor
Countdown Timer	Individual supplied in commercial pack	At Visit 2: 1 timer	Subject to keep or destroy at site using site disposal procedures	Return to sponsor

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 toothbrushes to be used in this study are medical devices.

6.1.2 Dosage Form and Packaging

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

The experimental dentifrices will be manufactured and filled into plain white tubes by the sponsor; the reference dentifrice will be supplied in its commercial pack. All study dentifrices will be overwrapped in white vinyl (to mask their identity and obscure the branding of the marketed product) with a study label affixed. The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the sponsor's Global Clinical Supplies Group. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

Each subject will receive sufficient tubes of their assigned study dentifrice for usage during the 3-week treatment period. Washout dentifrice and sundry items will be supplied in their commercial packaging for dispensing by study staff as specified in Table 6.2 and Table 6.3 respectively.

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

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 study treatment in accordance with the randomization schedule generated by an approved sponsor vendor, prior to the start of the study, using validated software.

The product dispensing area will be separate from the clinical examination area. Study dentifrices will be dispensed to the subject, by trained site personnel. These staff members will not be involved in any safety/product performance assessments or any other aspect of the study that could be influenced by the knowledge of product a subject has been assigned to. An additional member of the site staff will verify the dispensing procedure has been completed accurately for each subject.

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 products 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.

Subjects will be instructed to self-administer their assigned study dentifrice according to the usage instructions provided to the subject. Additionally, subjects will undergo supervised brushing at Visits 2&3 to ensure compliance with brushing instructions. The reference dentifrice is commercially available and the application instructions described in this protocol are consistent with its label instructions. The experimental dentifrice is intended for commercialization and the application instructions here are consistent with the intended label instructions.

To help ensure subjects understand the amount of dentifrice they should use each time they brush, brushing instructions and diary completion requirements:

- staff will demonstrate dispensing a full ribbon of dentifrice along the length of the toothbrush head to each randomized subject and supervise their first brushing with study dentifrice and diary completion.

On-site administration of study products will also be recorded in the CRF.

Instructions on usage of the study products are detailed in the Section 15.1.

Subjects should ensure they do not brush their teeth for at least 8 hours prior to attending site at Visits 2&3.

6.2.1 Product Usage Errors

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

Product usage errors are reportable irrespective of the presence of an associated AE, including:

- Usage errors involving subject exposure to any of the study products;
- Potential product errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

If a study product usage error is accompanied by an AE, as determined by the investigator, the usage 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.

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

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study products received and any discrepancies are reported and resolved before use according to the supplied shipping documentation.

The investigator, or designee, will ensure that all study products are stored in a secured, environmentally monitored (manual or automated) area with controlled access (authorized site staff only) in accordance with the labeled storage conditions and Clinical Study Supplies Checklist, and in accordance with applicable regulatory requirements.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of first product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product-label storage conditions should be reported to appropriate site staff upon discovery and communicated to sponsor as soon as possible. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Excursions from the storage requirements, including any actions taken, must be documented as a protocol deviation and reported to the sponsor.

Once an excursion is identified, the affected product (or products) must be quarantined and not used until the sponsor provides documentation of permission to use. Use of any of the affected product(s) prior to sponsor approval will be considered a protocol deviation.

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

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 authorized site 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 study 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.

Subjects should return their used and unused study products to the clinical site at Visits 2 and 3 in accordance with the study schedule. Study product return will be documented. Subjects will complete diaries to detail their usage of study products which will be used to monitor usage compliance.

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.

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 study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study will be returned for destruction to the sponsor's Clinical Supplies Group 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 the sponsor during the study in time for study close out visit.

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. 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.

The investigator's knowledge of the product allocation should not influence the decision to enroll a subject or affect the order in which subjects are enrolled.

This study is described as single-blind (the clinical examiner(s) performing the efficacy assessments will be blinded to the product received). To ensure the examiner(s) remains blinded throughout the study, the examiner(s) will not be permitted in any area where study product is stored, dispensed, or in use; staff involved in the preparation and dispensing of study products will work in a separate area, and subjects will be instructed not to remove study products from the opaque bags provided/cartons outside of the dispensing room, while at the study site. Dispensing staff will not be involved in any efficacy/safety assessment procedures during the study.

Site staff, study statistician(s), data management staff and other employees of the sponsor and vendors acting on behalf of the sponsor, who may influence study outcomes will be blinded to the product allocation.

Prior to randomization, subjects will be stratified on their sex as detailed in Section 5.4.

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 be required to inform the Institutional Review Board (IRB) if the blind is broken.

6.7 Compliance

To facilitate subject compliance with product usage requirements:

- First use of their assigned study dentifrice will be carried out under supervision at the study site at the baseline visit (Visit 2); study staff will demonstrate the correct amount of dentifrice to dispense and how to use the timer to ensure a 1-minute brushing time. A further supervised brushing will be carried out at the study site at Visit 3.
- Subjects will be provided with a diary at screening (Visit 1) to record each completed brushing with washout and study products.
- Subjects will attend Visits 2&3 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. Any suspected over or under use, the number of any missed or additional brushings will be documented as deviations in the CRF; subjects will be re-instructed in the correct use of product and diary completion, as required.
- Subjects will also use the diary to note any issues with their study product, any oral problems, illnesses and new medications/ treatments. Details relevant to safety or efficacy should be reviewed by the investigator (or suitably qualified designee) and transcribed to the CRF, as appropriate; AEs must be documented in the CRF.

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

A record of the number of dentifrice tubes dispensed to and taken by each subject must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

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 28 days prior to signing the informed consent form and until first study product application will be documented as a prior medication/treatment. Medications/treatments taken after first study product application will be documented as concomitant medication/treatments.

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 their 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 they repeatedly fail 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 provided 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 an oral examination.

Should the subject continue to be unreachable, they 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 is 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 7-21 days prior to randomization to confirm they meet the selection criteria for the study.

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

1. Informed Consent.
2. Demographics.
3. Review of medical history (including smoking/tobacco use status) and prior/concomitant medication/treatment.
4. Screening assessment of oral malodor.
5. OST and OHT examinations.
6. Gingivitis (bleeding on probing) assessment.
7. Review of the inclusion/exclusion criteria.
8. Subject eligibility.
9. Dispense washout products toothbrush and diary. Instruct subjects in diary completion.
10. AEs recorded.

8.1.1 Screening Procedures

8.1.1.1 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. An ingredients listing for the study dentifrices will be provided to each subject during the consent process to enable them to confirm they are not aware of any allergy or

hypersensitivity to any of the ingredients listed. 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 ICF will be captured as this is the point from which all AEs will be captured. The date and time of consent will be recorded 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.

8.1.1.2 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 (US FDA, 2005).

8.1.1.3 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history (in the last 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 28 days and prior to signing the informed consent form, will be documented in the CRF.

8.1.1.4 Screening Assessment of Gingivitis (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. The gingivae will be air dried and then the examiner will use an Oulix color coded periodontal PCPII 5B Hu-Freidy or blunt-ended CPI probe to assess bleeding. The probe will be gently inserted into the gingival crevice to a depth of approximately 1 millimeter (mm) and then run around the tooth (at angle of ~ 60^{o} 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 tooth. Three sites for each tooth should be evaluated buccally/labially (distal, body, mesial sites) and three sites lingually/palatally. The percentage of bleeding sites shall be recorded in the CRF.

8.1.1.5 Screening Assessment of Oral Malodor

At screening, subjects having abstained from oral hygiene procedures and food consumption for at least 8 hours, will have 2 samples of mouth air taken by syringe which will be analyzed by the OralChroma instrument per the procedure described in Section 9.2.1.

Subjects with insufficient mean hydrogen sulfide concentration in their mouth air per the inclusion criteria will be discontinued from the study.

8.1.1.6 Oral Examinations

Following review of the oral care products the subject is currently using (subject-reported product names) to confirm they do not contain any ingredients that could interfere with study outcomes, the clinical examiner(s) will perform the following examinations/assessments.

- OST examination.
- OHT examination.

Oral examinations/assessments should only be performed by suitably qualified examiner(s) as described in Section 5.8.

To facilitate subject flow, clinical assessments may be recorded on a paper source document and later transcribed into the CRF.

8.1.1.7 Inclusion/Exclusion Criteria

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

8.1.1.8 Subject Eligibility

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

Eligible subjects will be appointed to attend the study site for baseline assessments (Visit 2) a minimum of 7 days, and a maximum of 21 days, after their screening visit and will be instructed to use only their supplied oral care products [washout products] (according to their normal habit) until their next appointment.

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

8.2 Study Period

8.2.1 Visit 2/Day 0 - Baseline

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

Subjects will undergo, in the following order (wherever possible).

1. Subject returns washout dentifrice and toothbrush.
2. Changes in concomitant medication or non-drug treatments/procedures will be documented.

3. 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.
4. Pre-brushing assessment of oral malodor (organoleptic assessment directly from subject’s breath and VSC determination via OralChroma analysis of 2 samples of subject breath obtained through a syringe).
5. Review of the inclusion/exclusion criteria.
6. Subject eligibility assessed. Subjects who do not meet the criteria for participation will be discontinued.
7. Qualifying subjects will be stratified and randomized to treatment groups.
8. Study products will be dispensed, including sundry items.
9. Instruct subject in product usage requirements/diary completion and demonstrate dispensing ribbon of dentifrice on to toothbrush head; supervise first brushing and first diary entry.
10. 1 hour (±5 minutes) post brushing perform the post-brushing assessment of oral malodor (organoleptic assessment directly from subject’s breath and VSC determination via OralChroma analysis of 2 samples of subject breath obtained through a syringe).
11. Subject undergoes an OST examination.
12. AEs and incidents recorded.

Randomized subjects will be appointed to attend the study site for their Week 3 assessments and reminded of the Lifestyle Guidelines and to bring their study product and completed diary with them to the next visit.

To facilitate subject flow, clinical and instrumental assessments may be recorded on a paper source document and later transcribed into the CRF.

8.2.2 Visit 3/Week 3 (Day 21 +2)

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

Subjects will undergo, in the following order (wherever possible).

1. Changes in concomitant medication or non-drug treatments/procedures will be documented.
2. 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.
3. Subject’s study products and diary will be visual inspected to evaluate product compliance and adherence to protocol. Subject continuance in the study confirmed.
4. Pre-brushing assessment of oral malodor (organoleptic assessment directly from subject’s breath and VSC determination via OralChroma analysis of 2 samples of subject breath obtained through a syringe).
5. Supervised tooth brushing with study product.
6. Return of study products.
7. 1 hour (±5 minutes) post brushing perform the post-brushing assessment of oral malodor (organoleptic assessment directly from subject’s breath and VSC determination via OralChroma analysis of 2 samples of subject breath obtained through a syringe).
8. Subject undergoes an OST and OHT examination.

9. AEs and incidents recorded.
10. Study conclusion.

To facilitate subject flow, clinical and instrumental assessments may be recorded on a paper source document and later transcribed into the CRF.

8.2.3 Study Procedures

8.2.3.1 Diary Review

The 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 will be assessed and reported as defined in the Adverse Event and Serious Adverse Events section of this protocol.

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.

Additional and missed product applications will be considered deviations from the protocol and will be recorded on the Deviations Log and as a deviation in the CRF.

8.2.3.2 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 was 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.

8.2.3.3 Follow-up 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 clinical examinations may be carried out at such visits.

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol required examinations and assessments are completed as described. However, it is anticipated that 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 they have taken to ensure the required processes are adhered to as soon as possible. The sponsor must be informed of any missed assessments in a timely manner. The outcome of all examinations and assessments should be recorded in the CRF.

9.1 Screening Assessments

Screening examinations and assessments will be performed by appropriately trained clinical examiners at the times, and in the order, defined in the Study Procedures section of this protocol.

9.1.1 OST Examination

The screening clinician will perform an initial oral soft tissue examination in agreement with Section 9.3.1 in order to record any abnormalities and assess the subject's suitability and eligibility for enrollment into the study.

9.1.2 OHT Examination

The screening clinician will perform a visual examination of the oral hard tissues in agreement with Section 9.3.2 in order to record any abnormalities and assess the subject's suitability and eligibility for enrollment into the study.

9.2 Efficacy Assessments

The following efficacy assessments will be performed by appropriately trained clinical examiner(s), 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.

9.2.1 Mouth Air VSC Determination

Mouth air VSC determination will be performed pre- and 1 hour (±5 minutes) post-brushing at Visits 2&3.

The mouth air sample will be evaluated using the OralChroma Halitosis Measuring instrument (Model CHM-2 [Nissha FIS, Inc.; Osaka, Japan]) in agreement with the manufacturer's instructions. The OralChroma is a portable gas chromatograph with a highly sensitive semiconductor gas detector which can determine the concentration of the three main VSCs in breath (hydrogen sulfide, methane thiol and dimethyl sulfide).

In line with recommendations, the OralChroma instrument will have been calibrated by the manufacturer recently before the study begins (Tangerman and Winkel, 2008). If more than one OralChroma device is used in this study, the same subject will be evaluated by the same device for every assessment at all visits. The concentration values (in parts per billion [ppb]) of hydrogen sulfide, methanethiol and dimethyl sulfide will be recorded in the CRF separately, and the total VSC concentration will be calculated as the sum of the 3 individual concentrations.

A clean and sterile OralChroma syringe will be used to obtain a sample of the mouth air of the subject. The syringe will be inserted into the subject's mouth until the lips reach the stopper (flange). Subjects will be instructed to seal their lips tightly around the syringe holding the syringe gently between their front teeth without touching the tip with the tongue or allowing saliva to enter the syringe. Subjects should hold this position for 30 seconds while breathing through their nose. The trained OralChroma technician will slowly pull the syringe piston (plunger) away from the mouth / to the end of the syringe and then push the piston in towards the mouth / returning the gas into the mouth; the technician will repeat this pull-out and pull-in process and the mouth air will sample be collected on the third pull-out. Should the sample not

be taken correctly (e.g. subject does not correctly seal their lips around the syringe) a further sample may be taken.

This process will be repeated so that two syringes full of mouth air will be collected for each subject at each time period and the average of the two readings of total VSCs, and the three gases will be captured for each measurement time period (Screening, Baseline and all post-product use assessments).

After the syringe is removed from the mouth, the trained technician will wipe the syringe tip with clean, dry tissue paper to remove saliva. The syringe will not be wiped with alcohol or an antiseptic solution or touched with a bare or gloved hand that has been exposed to an antiseptic solution. After wiping, the technician will adjust the volume of gas in the syringe to 1.0 mL and will then insert the syringe into the gas inlet of the OralChroma and inject the oral gas. The sampled gas will be injected within one minute after collection.

The same trained technician will conduct all OralChroma measurements. Measurement data will be printed for each subject, which will serve as a source document, and the data from the OralChroma printout of the two mouth samplings at each measurement timepoint will be recorded in the CRF.

9.2.2 Organoleptic Assessment of Oral Malodor

At each oral odor evaluation (pre- and 1 hour (±5 minutes) post-brushing at Visits 2 and 3), the subjects will attend an odor grading station. They will place one end of a clean and sterile cylinder, about 1 3/4 inches long by 1 1/6 inches in diameter, through an opening in a privacy screen. The screen will be arranged so that the organoleptic assessors will not be able to observe the subject. Subjects will then place the cylinder in their mouth and, while the subject holds their breath, the assessors standing behind the screen will independently evaluate oral odor. During the evaluation, each subject will keep their tongue away from the palate of their mouth. Oral odor will be graded using the following scale (Rosenberg et al., 1991b):

0 = No appreciable odor
1 = Barely noticeable odor
2 = Slight but clearly noticeable odor
3 = Moderate odor
4 = Strong odor
5 = Extremely foul odor

The organoleptic assessors (using a panel of at least 3 assessors) will be blinded to the subject's product allocation and will have a minimum of a two-minute interval between individual assessments to allow adequate recovery of the assessors' olfactory senses. Wherever possible the same assessors will be used throughout the study to aid consistency of evaluation, however assessors may be replaced with another calibrated judge(s) in the event of illness or availability issues.

Prior to undergoing this assessment, subjects will be trained in the appropriate technique to ensure familiarity with the procedure requirements.

Prior to this study, the organoleptic assessors will have been recently (within the past year) calibrated and standardized with a Kappa statistic >0.6 in accordance with the American

Dentistry Association guidelines for the testing of Products Used in the Management of Oral Malodor (ADA, 2016).

9.3 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained clinical examiner(s), at the times and in the order defined in the Study Procedures section of this protocol. Additionally, to help prevent COVID-19 transmission within the study, the measurement of the temperature of subjects and/or questioning and/or Covid testing (PCR or lateral flow) of the subjects may be utilized at any site visit at the examiner's discretion and per the clinical site's procedures.

9.3.1 Oral Soft Tissue (OST) Examination

This procedure will be conducted by a qualified, experienced clinical examiner. The OST examination will be accomplished by direct observation and palpation with retraction aids, as appropriate. The examination will cover the oral 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. Findings from the examination will be recorded in the CRF as either normal or abnormal, with details of any abnormalities. The results of the OST examination performed at screening will be used to determine subject eligibility. Any new OST abnormality or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject after the screening examination will be recorded as an AE.

Where possible, this procedure should be conducted by a single clinical examiner.

9.3.2 Oral Hard Tissue (OHT) Examination

This procedure should be conducted by a qualified, experienced clinical examiner. The OHT examination will be accomplished by direct observation, using retraction aids as appropriate and will identify any grossly carious lesions, signs of erosive wear, enamel irregularities, tooth fracture, gross generalized dental caries decay, decalcification and faulty restorations. The presence of any implants, fixed or removable dentures, fixed or removable orthodontic braces/bands, fixed orthodontic retainers, full crowns or veneers will be recorded. Observations will be listed as either absent or present, and conditions noted as present will be described in the CRF. Any change observed by the clinical examiner or reported by the subject after the screening examination will be recorded as an AE.

The results of the OHT examination performed at Screening will be used to determine subject eligibility.

Where possible, this procedure should be conducted by a single clinical examiner.

9.3.3 Pregnancy Testing

Urine pregnancy testing of subjects of child-bearing potential is not required for this study (see Section 4.2 for details). 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 they consider 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 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 CH 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 CH study manager.

The CH Study Manager will be responsible for forwarding the SAE form to other CH 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 they have 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 Safety Statement, in the determination of their 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 they have 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 their 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 (PPD), with copy to the appropriate CH 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 Safety Statement 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 CH Study Manager. 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 (PPD), with copy to the appropriate CH 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

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 supplied toothbrush.

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 their 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 CH 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 the CH 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 correct 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 a validated medication dictionary, WHODrug.

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 sponsor's third party 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 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

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 sponsor as required.

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 that will be forwarded to the sponsor or Third-Party Vendor.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

Sufficient subjects will be enrolled to randomize approximately 106 subjects to have at least 100 complete the study (at least 50 subjects per treatment arm). It is considered sufficient to have 100 subjects complete in this study to meet the study's objectives. The subjects will be stratified by their sex prior to randomization.

Existing GSKCH studies were referred to for information and data to enable calculation of an appropriate power and sample size however no relevant information was observed for a 3-week study in a gingivitis population as planned for this study.

Data from a published study that evaluated halitosis in subjects with gingivitis and periodontitis (Pham et al., 2011) was taken into consideration to provide information regarding the variability and sample size for this endpoint. The sample size in this literature was N=116 for the gingivitis population and the variability estimate was observed to be 0.46 for the organoleptic score. The scoring was on a 5-point scale with very similar descriptors to those to be used in this study however only one assessor was used for organoleptic score assessment (as opposed to 3

assessors which will be used in this study). Considering the number of assessors in this study, the standard deviation was estimated to be 0.265 (0.46/sqrt(3)).

Using the standard deviation of 0.265, for 50 subjects per arm (100 subjects completing the study) the detectable mean difference is estimated to be 0.15 for 80% power and alpha=0.05.

12.2 Populations for Analysis

12.2.1 Definition of Analysis Populations

The Safety population will include all randomized subjects who complete at least one use of study product. This population will be based on the study product the subject received. All assessments of safety will be based on this analysis population.

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 treatment efficacy assessment. This population will be based on the study product to which the subject was randomized. All assessments of efficacy will be primarily based on this analysis population.

The per protocol (PP) population is defined as all subjects in the mITT population who have at least one assessment of efficacy considered unaffected by protocol violations.

12.2.2 Exclusions of Data from Analysis

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

A PP analysis will be performed on the primary endpoint if there is more than 10% difference in the number of subjects between the PP and mITT populations. A decision on whether a PP analysis will be performed will be made prior to study unblinding (release of the randomization codes).

12.3 Statistical Analyses

This section is a summary of the planned statistical analyses focusing on the primary and secondary endpoints in detail with a brief overview for other endpoints. Additional details of all the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior to study unblinding.

12.3.1 Primary Analysis

The mean breath organoleptic score at a visit / time point will be derived across all of the recorded organoleptic scores recorded at the visit / time point.

The primary endpoint for the study is the change in mean breath organoleptic score from Baseline (pre-brushing) to 3 weeks (pre-brushing) and the comparison between the Experimental and Reference Dentifrices in the mITT population. This will be assessed at the two-sided 5% significance level.

An ANCOVA model will be used to analyze the change in mean breath organoleptic score from Baseline (pre-brushing) to 3 weeks (pre-brushing) with study product and gender as fixed effects and the mean Baseline (pre-brushing) breath organoleptic score as a covariate. The least square means for each study product will be presented based on observed margins and used to test for < 0 change from baseline. The difference between least square means for the

Experimental Dentifrice compared to the Reference Dentifrice will be presented and used to test for a difference between products. The two-sided p-values and 95% confidence intervals will be provided.

The assumption of normality and homogeneity of variance in the ANCOVA will be investigated. In case of violation of these assumptions, a suitable nonparametric test (adjusted for gender) will be performed, and results will be provided to support the ANCOVA results.

The mean pre-brushing breath organoleptic score values across the study and change from baseline will be summarised descriptively.

12.3.2 Secondary Analyses

All secondary endpoint analyses will be performed on the mITT population. There will be no adjustment for multiplicity in the analyses described in this section.

Volatile Sulfur Compounds (VSC)

There will be individual evaluations of hydrogen sulfide, methanethiol and dimethyl sulfide concentrations in breath taken at each visit (Baseline and Week 3) at each time point (pre-brushing /1-hour post- brushing). The Total VSC at a visit/time point will have two samples. This will be derived as the sum of the hydrogen sulfide, methanethiol and dimethyl sulfide concentrations in breath and then the mean over two samples to derive one value used for analysis per visit/timepoint. The sum and the average will be performed on the raw scale and final value will be transformed.

For each concentration (hydrogen sulfide, methanethiol, dimethyl sulfide, Total VSC), the result will be log (base 10) transformed. Details of handling zero values will be detailed in the SAP.

The ANCOVA models described below will be applied for each of the mean concentrations using a different definition of Baseline and post-baseline as follows:

- Baseline = Baseline (pre-brushing), Post-baseline = Week 3 (pre-brushing)
- Baseline = Baseline (pre-brushing), Post-baseline = Week 3 (1-hour post-brushing)
- Baseline = Baseline (pre-brushing), Post-baseline = Baseline (1-hour post-brushing)
- Baseline = Week 3 (pre-brushing), Post-baseline = Week 3 (1-hour post-brushing)

The appropriate change from Baseline in the logged value will be analyzed for each post-baseline concentration using an ANCOVA model with study product and gender as fixed effects and the respective logged mean Baseline concentration as a covariate. The least square means for each study product will be based on observed margins to test for < 0 change (on the logged scale) from baseline. The difference between least square means for the Experimental Dentifrice compared to the Reference Dentifrice will be used to test for a difference between products. As well as presenting the least square means and differences on the log scale, the corresponding back transformed values (antilog base 10) will be presented to represent percent reduction from baseline and percent difference from control relative to baseline. The two-sided p-values and 95% confidence intervals (logged and back-transformed) will be provided.

The raw and logged concentration (hydrogen sulfide, methanethiol, dimethyl sulfide, Total VSC) values across the study and changes from baseline (for each type of baseline detailed above) will also be summarised descriptively.

Organoleptic score

The primary analyses described in Section 12.3.1 will be repeated but will instead use the following as the Baseline and post-baseline mean breath organoleptic score definitions:

- Baseline = Baseline (pre-brushing), Post-baseline = Week 3 (1-hour post-brushing)
- Baseline = Baseline (pre-brushing), Post-baseline = Baseline (1-hour post-brushing)
- Baseline = Week 3 (pre-brushing), Post-baseline = Week 3 (1-hour post-brushing)

12.3.3 Safety Analysis

The Safety population will be used for safety analyses. Safety analyses will be performed according to study product received.

Safety analyses will focus on:

- Adverse Events (AEs)

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. AEs will be categorized as oral and non-oral by the examiner prior to database lock. AEs will be regarded as 'treatment' emergent if they occur on or after the first use of study product at the Baseline visit.

The following AEs summaries (number of distinct AEs and frequency/proportion of subjects affected will be presented by study product group and overall:

- Treatment emergent AEs
- Treatment emergent AEs by System Organ Class (SOC) and Preferred Term (PT);
- Treatment emergent AEs by Oral/Non-Oral and PT;
- Treatment emergent treatment related AEs by Oral/Non-Oral and PT;
- Treatment emergent treatment related serious AEs by SOC and PT;

A listing of all AEs will be presented for all subjects in the Safety population. Separate listings will be presented for any deaths, serious AEs and AEs leading to study or product discontinuation.

- Oral Soft Tissue and Examinations
  - Summary of abnormalities at each visit for each area examined
- Oral Hard Tissue and Examinations
  - Will be listed only.
- Exposure and compliance with study product
  - Detailed in section 12.3.6.1.

12.3.4 Demographic and Baseline Characteristics

Demographic and randomized stratification data will be summarized descriptively.

12.3.5 Study Drug/Product Compliance and Use of Other Therapies

12.3.5.1 Study Drug/Product Compliance

Number of brushings, brushing compliance (%), number of missed brushings, number of additional brushings over 3 weeks will be summarized using descriptive statistics.

Number of brushings is defined as: [(date of Visit 3 – date of Visit 2) multiplied by 2 – number of missing brushings + number of additional brushings].

Brushing compliance (%) is defined as: [100 x (Number of brushings / Expected number of brushings)], where expected number of brushings is defined as: [(date of Visit 3 – date of Visit 2) multiplied by 2].

12.3.5.2 Prior and Concomitant Medications

Prior and Concomitant Medications will be listed only.

12.3.6 Handling of Dropouts and Missing Data

All missing data for primary and secondary endpoints will be treated as missing data and not imputed. In the event that one of the hydrogen sulfide, methanethiol or dimethyl sulfide concentrations are missing then the Total VSC will also be treated as missing.

12.3.7 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's 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's 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 with 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 and informed consent documents, 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), and the Declaration of Helsinki (World Medical Association, 2013).

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

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 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, 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.

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

The sponsor defines a serious breach 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 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 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 the sponsor's 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's 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 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's 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 experimental dentifrice 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 the sponsor's Standard Operating Procedures.

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15 APPENDICIES

15.1 Product Usage Instructions Sheet

INSTRUCTIONS FOR PRODUCT USE

Brush twice a day (morning and evening).

Each time you brush:

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

- Record each brushing on the diary card. Note any changes to these brushing procedures and reasons for changes (e.g. missed brushings, extra brushings) in the ‘Comments’ column.

- Record any changes in your smoking habits, health, medications (prescription and over the counter medications), or treatments on the diary card.
- Bring your diary card (completed and not completed), toothpaste and toothbrush to the next study visit.

15.2 ABBREVIATIONS

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

Table 15-1 Abbreviations

Abbreviation	Term
AE	adverse event
ANOVA	analysis of variance
BDR	blinded data review
BOP	Bleeding on probing
CI	confidence interval
CRF	case report form
CSA	clinical study agreement
CTA	clinical trial application
DCT	data collection tool
EC	ethics committee
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ID	identification
IRB	institutional review board
IRC	internal review committee
LSLV	last subject last visit
MedDRA	medical Dictionary for Regulatory Activities
N/A	not applicable
PI	principal investigator
PI	Personal information
ppb	Parts per billion
QC	quality control
SAE	serious adverse event
SOP	standard operating procedure
SS	safety statement
US	United States

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