CLINICAL PROTOCOL

A Randomized, Controlled, Single-Blind Clinical Study to Investigate the Tooth Stain Removal Efficacy of Two Experimental Potassium Nitrate Dentifrices in Subjects with Extrinsic Dental Stain Compared to a Standard Dentifrice Control When Used Twice Daily for 8 Weeks

Protocol Number:	300024
Compound/Product Name:	Potassium Nitrate Dentifrices
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	N/A
Other Regulatory Agency Identified Number:	N/A
Phase:	N/A

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

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (UK)
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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	Section 9.2.3: Change from performing 3 assessments per tooth to a single assessment per tooth.
Amendment 2	3.0	Amalgamation of screening and baseline visits and correction of references associated with Table 12-1.

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

Background and Rationale:

This study will investigate the efficacy of two experimental 5% potassium nitrate (KNO_3) dentifrices, one containing alumina and sodium tripolyphosphate (STP), the other alumina, STP and high cleaning silica, to reduce extrinsic dental stain and thereby whiten the teeth, compared to a marketed regular fluoride dentifrice with 8 weeks twice daily brushing.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the change in extrinsic dental stain after 8 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice, a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice and a regular fluoride dentifrice, as measured by Total Modified Lobene Stain Index (Total MLSI (Area x Intensity)).	Change from baseline in mean Total MLSI (Area x Intensity) score at week 8.
Secondary	
To evaluate the change in extrinsic dental stain after 4 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice, a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice and a regular fluoride dentifrice, as measured by Total Modified Lobene Stain Index (Total MLSI (Area x Intensity)).	Change from baseline in mean Total MLSI (Area x Intensity) score at week 4.
To compare the change in extrinsic dental stain after 4 & 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured by Total MLSI (Area x Intensity).	Change from baseline in mean Total MLSI (Area x Intensity) score at weeks 4 & 8.
To evaluate and compare the change in tooth shade (color) after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured by the VITA Bleachedguide 3D-MASTER.	Change from baseline in mean VITA shade score (examiner assessed) at weeks 4 & 8.
To evaluate and compare the changes in dental stain at specific tooth sites (along gingival margin, inter-proximally and on the body of the tooth) after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured by Total MLSI (Area x Intensity).	Change from baseline in mean MLSI (Area x Intensity) in: • Gingival sites • Interproximal sites • Body sites
To evaluate and compare change in extrinsic dental stain after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured by MLSI (Area) and MLSI (Intensity).	Change from baseline in mean MLSI (Area) and MLSI (Intensity)
Exploratory	
To evaluate and compare the change in tooth color co-ordinates after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5%	Change from baseline in mean tooth shade, L*, a*, b*, WI_D and ΔE* determined using the VITA

STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured using the VITA EasyShade.	EasyShade instrument at weeks 4 & 8
Safety	
To assess the safety and tolerability of the two experimental KNO_3 dentifrices.	Treatment emergent adverse events

Mean MLSI values calculated for the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.

Mean tooth shade/color values are calculated for the facial surfaces of the 4 central and lateral maxillary incisors.

Study Design:

This will be a single-center, 8-week, randomized, controlled, single-blind (clinical examiner(s) and VITA EasyShade operator), three treatment-arm, parallel design, stratified clinical study in healthy volunteers with clinically confirmed dental stain (originating from the diet and/or smoking) on the surfaces of their anterior teeth.

Potential subjects will attend a screening visit (Visit 1, Day 0) to determine their suitability to participate. Having obtained their written informed consent, relevant details of their medical history and current medications will be recorded, followed by oral soft tissue (OST) and oral hard tissue (OHT) examinations. Subjects meeting the relevant study criteria, will be considered as eligible to proceed for baseline assessments on the same day.

At the baseline visit (Visit 2, Day 0), eligible subjects will undergo clinical and instrumental assessments of extrinsic dental stain (MLSI: facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth) and tooth color (VITA Bleachedguide 3D-MASTER and VITA EasyShade instrument: facial surfaces of the central and lateral maxillary incisors).

Qualifying subjects will be stratified by baseline Total MLSI $_{(A \times I)}$ (calculated for the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth only) and smoking status and randomized to one of the three study treatments. Randomized subjects will be instructed to brush twice daily (for 2 minutes, morning and evening) with their assigned study dentifrice for the next 8 weeks. Extrinsic dental stain and tooth color assessments will be repeated after 4- and 8-weeks treatment.

Study Products:

Experimental Dentifrices		**Reference Dentifrice**
5% KNO_3 dentifrice with 1% alumina and 5% STP	5% KNO_3 dentifrice with 1% alumina, 5% STP and 2% high cleaning silica	Regular Fluoride Dentifrice (Aquafresh Cavity Protection, US market)
Each study dentifrice will contain 0.2542% sodium fluoride (1100 parts per million (ppm) fluoride)		

All dentifrices will be applied in the same manner and will be brushed on to the teeth, twice daily (morning and evening) for 2 timed minutes.

Type and Planned Number of Subjects:

Study subjects of either sex and any gender, aged of 18-65 years, will be in good general and oral health, with the level of extrinsic tooth stain and color required at baseline to participate in the study.

Sufficient subjects will be screened to randomize approximately 300 subjects to study treatment (approximately 100 per treatment group) to ensure approximately 270 evaluable subjects complete the study.

Statistical Analysis Summary:

For the analysis of the change from baseline in the mean Total MLSI (Area x Intensity) and the change from baseline in the mean VITA shade score, separate Mixed Models with Repeated Measures will be used. Fixed effects will be included for smoking status, study product, visit and study product x visit interaction. The respective baseline score will be included as a covariate. Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied. The least square means for each Experimental Dentifrice at week 8 will be presented based on observed margins and used to test for a negative change from baseline. The differences between least square means for each Experimental Dentifrice compared to the Reference Dentifrice at week 8 will be presented and used to test for a difference between products.

The hypothesis testing of the of change from baseline in the mean Total MLSI (Area x Intensity) and the change from baseline in the mean VITA shade score will employ a graphical approach methodology, as per Bretz *et al* (Bretz et al., 2009) in order to maintain an overall two-sided familywise error rate of 5% within each Experimental Dentifrice (10% overall). The adjusted two-sided p-values and simultaneous 95% confidence intervals (following graphical testing approach) will be provided for all comparisons.

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	Treatment Period				
	Visit 1 Screening (Day 0)[4]	Visit 2 Baseline (Day 0)[4]		Visit 3 Week 4 (Day 28 ±3 days)		Visit 4 Week 8 Day 56 ±3 days)
Informed consent	X		4 Weeks		4 Weeks	
Demographics	X					
Medical History / current oral care products / current and prior medication review	X					
Review changes in health and concomitant medications/treatments				X		X
OST Examination	X			X		X
OHT Examination	X					X
Clinical assessment of extrinsic dental stain (MLSI)[2]		X		X		X
Clinical assessment of tooth color (VITA Bleachedguide)		X		X		X
Instrumental assessment of tooth color (VITA EasyShade)		X		X		X
Repeatability assessments[3]		X		X		X
Inclusion/exclusion criteria review	X	X				
Subject eligibility	X	X				
Subject continuance				X		X
Randomization and stratification		X				
Dispense study products, diary and sundry items		X		X		
Supervised tooth brushing		X		X		
Return of study dentifrice, toothbrush and completed diary				X		X
Adverse events review[1]		X		X		X
Medical device incidents review[1]		X		X		X
Study conclusion						X

Abbreviations: OST: Oral Soft Tissue, OHT: Oral Hard Tissue, MLSI: Modified Lobene Stain Index

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) until 5 days after last use of the study dentifrice (or last procedure). Medical device in this study is the supplied toothbrush.
2. Brushing and/or flossing of the subject's assessment teeth will be performed prior to this assessment by the examiner if required (at the examiner's discretion).
3. Repeatability assessments for VITA Bleachedguide and MLSI assessments will be performed on a subset of subjects as described in Section 9.
4. Note Visits 1 & 2 will occur on the same day.

2 INTRODUCTION

Dental stain is common within the adult population. Extrinsic dental stain is primarily caused by chromogens (originating from the diet, smoking and medications) binding to proteinaceous compounds found in the salivary pellicle (Watts and Addy, 2001, Shellis et al., 2005). The etiology of stain is multiple, and while it is widely agreed to result from discoloration of plaque and pellicle on the surface of the tooth, the main site for extrinsic stain build up is generally accepted as the acquired salivary tooth pellicle (Shellis et al., 2005). One of the main functions of a dentifrice is to help control the build-up of dental stain (Pader, 2012). This is usually achieved by the inclusion of a common dental abrasive, such as silica, chalk or dicalcium phosphate dihydrate in the dentifrice formulation (Lippert, 2013). More recently alumina has been investigated for its enhanced stain removal and stain protection properties compared to silica (Milleman et al., 2017, Young et al., 2017) with lower dentine abrasivity (Seong et al., 2017).

Chemical cleaning compounds, such as polyphosphates are also commonly employed in dentifrices to supplement the physical cleaning provided by dental abrasives. Polyphosphates, such as sodium tripolyphosphate (STP), sodium pyrophosphate and hexametaphosphate, have been shown to bind strongly to the tooth surface and reduce the force of adhesion of adsorbed proteins (Shellis et al., 2005), thereby facilitating the removal of stain during toothbrushing. Polyphosphates have also been shown to desorb salivary proteins from enamel and inhibit protein adsorption (Ash et al., 2014) and thereby inhibit stain build up.

The aim of this study is to investigate the stain removal efficacy of 2 experimental anti-dentin hypersensitivity (DH) dentifrices:

- 5% potassium nitrate (KNO_3) dentifrice containing 1% alumina and 5% STP
- 5% KNO_3 dentifrice containing 1% alumina, 5% STP and 2% high cleaning silica

with four and eight weeks twice daily use. A daily use, regular fluoride dentifrice (US market) will be included as a reference dentifrice.

2.1 Study Rationale

This 8-week, randomized, controlled, parallel-design, stratified clinical study has been designed to evaluate the ability of two experimental dentifrices to reduce extrinsic dental stain (originating from the diet and/or smoking) and improve tooth color (whiten the teeth), compared to a regular fluoride dentifrice.

The dental stain removal and tooth whitening properties of 1% alumina with 5% STP has been demonstrated for similar dentifrice formulations (see Section 2.2); additional data are required to confirm the stain removal/whitening efficacy of a modified 1% alumina and 5% STP formulation and demonstrate efficacy for a novel 1% alumina, 5% STP and 2% high cleaning silica formulation.

2.2 Background

Both experimental dentifrices contain 5% KNO_3 and 0.2542% sodium fluoride (NaF). The efficacy of KNO_3-containing dentifrices for the relief of DH (Schiff et al., 1994, Gillam, 1996) and the anti-caries benefit associated with use of topical NaF (Featherstone, 1999, Marinho et al., 2003) are well-established.

The sponsor has completed four clinical studies evaluating the dental cleaning properties of dentifrices containing 1% alumina and 5% STP.

- Clinical study CCI evaluated the ability of 4 experimental dentifrices (including a 1% alumina and 5% STP dentifrice) to lighten tooth color (whiten teeth) compared to a regular fluoride dentifrice (Aquafresh Advanced), after 4 weeks twice daily brushing. A statistically significant improvement in tooth shade (1.48 units, VITA Classic shade guide), versus baseline, was observed for the 1% alumina and 5% STP dentifrice; there was no statistically significant difference between any of the test products and the regular fluoride dentifrice.
- Clinical study CCI evaluated the stain removal efficacy of 4 experimental dentifrices (including a 1% alumina and 5% STP dentifrice), compared to a regular fluoride dentifrice (Aquafresh Advanced), after 8 weeks twice daily brushing. The 1% alumina and 5% STP formulation demonstrated statistically significantly better stain removal (as measured by MLSI) versus the regular fluoride dentifrice after 8 weeks use.
- Clinical study CCI found that 8 weeks' twice daily brushing with 2 experimental dentifrice formulations, both containing 1% alumina and 5% STP, provided a statistically significant reduction of dental stain (as measured by MLSI) from baseline; no statistically significant differences were observed between the test products and a regular fluoride dentifrice.
- Clinical study CCI evaluated the stain prevention properties of an experimental dentifrice containing 1% alumina and 5% STP formulation. The study demonstrated statistically significantly less stain build-up (as measured by MLSI) after 8 weeks twice-daily use, compared to a regular fluoride dentifrice.

In all the above clinical studies, study treatments were found to be generally well tolerated.

In vitro evaluation of the experimental dentifrices to be investigated in this study has been performed using established models for dental stain removal (sponsor data on file). These studies show both experimental formulations to be effective at removing dental stain; the 1% alumina, 5% STP and 2% silica formulation (with the higher relative dentine abrasivity) outperforms the 1% alumina and 5% STP formulation.

In summary, existing clinical and laboratory data provide evidence of tooth cleaning efficacy for 1% alumina and 5% STP dentifrice formulations. However additional clinical 'cleaning' data is required to demonstrate dental stain removal/tooth whitening efficacy of the specific experimental formulations to be tested in this study to support the intended consumer claims for these products.

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 formulations of the experimental dentifrices under investigation have not been previously clinically tested, very similar products containing 5% KNO_3, 1% alumina and 5% STP have been evaluated in clinical studies of similar design (see Background Section 2.2). These studies demonstrated the 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 two experimental dentifrices are 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

One of the main functions of a dentifrice is to help control the build-up of dental stain (Pader, 2012). This can be achieved by inclusion of dental grade abrasives for the physical removal ('polishing') of stain from tooth surface during toothbrushing and/or by the addition of a chemically active cleaning compound to the formulation.

Polyphosphates (such as STP) are chemical cleaning compounds commonly employed in oral care products to supplement the physical stain removal properties of dental abrasives. Polyphosphates have been shown to bind strongly to the tooth surface and reduce the force of adhesion of adsorbed proteins (Shellis et al., 2005), facilitating the removal of stain during toothbrushing. Polyphosphates have also been shown to desorb salivary proteins from enamel, and inhibit protein adsorption (Ash et al., 2014). Combining such 'chelating' agents with effective abrasives, such as alumina and/or silica, can be more effective for the removal of dental stain compared to formulations with containing dental abrasive alone. CCI [redacted]

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the change in extrinsic dental stain after 8 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice, a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice or a regular fluoride dentifrice, as measured by Total Modified Lobene Stain Index (Total MLSI (Area x Intensity)).	Change from baseline in mean Total MLSI (Area x Intensity) score at week 8.
Secondary	
To evaluate the change in extrinsic dental stain after 4 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice, a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice or a regular fluoride dentifrice, as measured by Total Modified Lobene Stain Index (Total MLSI (Area x Intensity)).	Change from baseline in mean Total MLSI (Area x Intensity) score at week 4.
To compare the change in extrinsic dental stain after 4 & 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured by Total MLSI (Area x Intensity).	Change from baseline in mean Total MLSI (Area x Intensity) score at weeks 4 & 8.
To evaluate and compare the change in tooth shade (color) after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured by the VITA Bleachedguide 3D-MASTER.	Change from baseline in mean VITA shade score (examiner assessed) at weeks 4 & 8.
To evaluate and compare the changes in dental stain at specific tooth sites (along gingival margin, inter-proximally and on the body of the tooth) after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured by Total MLSI (Area x Intensity).	Change from baseline in mean MLSI (Area x Intensity) in: • Gingival sites • Interproximal sites • Body sites

To evaluate and compare change in extrinsic dental stain after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured by MLSI (Area) and MLSI (Intensity).	Change from baseline in mean MLSI (Area) and MLSI (Intensity)
Exploratory	
To evaluate and compare the change in tooth color co-ordinates after 4 and 8 weeks twice daily use of either a '5% KNO_3/1% alumina/5% STP' dentifrice or a '5% KNO_3/1% alumina/ 5% STP/2% silica' dentifrice, compared to a regular fluoride dentifrice, as measured using the VITA EasyShade.	Change from baseline in mean tooth shade, L*, a*, b*, WI_D and ΔE* determined using the VITA EasyShade instrument at weeks 4 & 8
Safety	
To assess the safety and tolerability of the two experimental KNO_3 dentifrices.	Treatment emergent adverse events

Mean MLSI values calculated for the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth, and the lingual surfaces of the six mandibular anterior teeth.

Mean tooth shade/color values are calculated for the facial surfaces of the 4 central and lateral maxillary incisors.

This study will be considered successful if either of the experimental dentifrices demonstrates statistically significant stain removal (as measured by mean Total MLSI (Area x Intensity) from baseline after 8 weeks twice daily use.

4 STUDY DESIGN

4.1 Overall Design

This will be a single-center, 8-week, randomized, controlled, single-blind (clinical examiner(s) and VITA EasyShade operator), three treatment-arm, parallel design, stratified clinical study in healthy volunteers with a propensity to form dental stain. It has been designed to investigate changes in tooth stain and color, following twice-daily use of two experimental dentifrices, after four- and eight-weeks twice daily use; a regular fluoride dentifrice will be included as reference dentifrice. Sufficient subjects will be screened to randomize approximately 300 subjects to study treatment to ensure approximately 270 subjects complete the study.

At screening (Visit 1, Day 0), subjects will give their written informed consent to participate in the study. Demography, relevant medical history and current medications/treatments will be recorded, followed by OST and OHT examinations. Subjects meeting the relevant study criteria, will be considered eligible to proceed for baseline assessments on the same day..

At baseline (Visit 2, Day 0) subjects, having refrained from oral hygiene procedures for at least 6 hours, will undergo clinical assessment of the stain on the facial surfaces of their six maxillary anterior teeth and six mandibular anterior teeth (tooth numbers 6-11 and 22-27) and the lingual surfaces of their six mandibular anterior teeth (tooth numbers 22-27) using the MacPherson modification (Macpherson et al., 2000) of the Lobene Stain Index (Lobene, 1968) (MLSI). The shade (color) of the facial surfaces of the central and lateral maxillary incisors (tooth numbers 7-10) will then be assessed clinically using the VITA Bleachedguide 3D-MASTER (Gómez-Polo et al., 2015) and the color of the same surfaces will be evaluated using the VITA

EasyShade instrument (Tung et al., 2002). Subjects who fulfil all inclusion/exclusion criteria will be enrolled into the study.

Qualifying subjects with a Total MLSI $_{(A \times I)} \geq 15$ for the facial surfaces of the 12 anterior teeth and a mean tooth shade ≥ 11 on the facial surfaces of the 4 maxillary incisors, who meet all other entry criteria, will be stratified according to their baseline Total MLSI $_{(A \times I)}$ (low < 45; high ≥ 45) and smoking status (smoker; non-smoker) and randomized to study treatment.

Randomized subjects will brush twice daily (morning and evening) with their assigned study dentifrice for the next 8 weeks and record each brushing in the diary provided; significant changes in diet or smoking status should also be noted in the diary. Subjects, having refrained from oral hygiene procedures for at least 6 hours, will return to the clinic after 4- and 8-weeks treatment (Visits 3 and 4, respectively) for clinical and instrumental assessments of dental stain and tooth shade/color.

The clinical examiner will perform replicate MLSI and tooth shade assessments (as described in Sections 9.2.1.1 and 9.2.2.1, respectively) at Visits 2-4. The clinical examiner may brush the subject's anterior teeth with water and/or floss between the anterior teeth prior to MLSI assessments, if required, to remove any debris on the teeth.

Safety and oral tolerability of the study products will be monitored over the 8-week usage period by review of reported AEs.

4.2 Scientific Rationale for Study Design

Subjects will be stratified according to their smoking status and their baseline tooth stain score to ensure a balance in all treatment groups.

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, rheology, appearance, packaging). Given it is almost impossible to ensure identical appearance, taste and packaging for the dentifrices evaluated in oral care studies, the level of product blinding 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 VITA EasyShade operator(s) will be blind to treatment allocation to ensure there is no bias in the assessments.

This is a single-center study. The same examiner will perform the clinical assessments and instrumental measures throughout the study to eliminate 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 dentifrices against the stain removal/tooth whitening performance of a typical daily use dentifrice (which contains dental abrasive) rather than a placebo with no abrasive cleaning component.

The experimental dentifrices, when marketed, will be indicated for DH. It is anticipated they will be purchased by consumers with DH who desire whiter teeth (less dental stain). However, the study objectives relate solely to dental stain and tooth color, both of which are independent of DH; thus, study subjects are not specifically required to experience DH nor do the exclusion criteria exclude subjects with DH. Subjects will be stratified according to their baseline tooth stain score and smoking status to ensure balance across the three treatment groups.

An 8-week treatment period is deemed sufficient to observe the anticipated clinical benefits; 4-week assessments are included should more rapid clinical effects occur.

The clinical measures used in this study, MLSI and VITA shade guide, are well established in the scientific literature for the evaluation of dental stain and tooth color respectively (Joiner and Luo, 2017). VITA shade guides are routinely used by dentists in practice to assess the color of natural teeth to enable accurate matching of prosthetic devices (e.g. crowns, partial dentures) to the natural dentition. The VITA shade guide selected for use in this study (VITA Bleachedguide 3D-MASTER) has the advantage over the classic VITA shade guide in providing a linear presentation of tooth shade which will enable more accurate assessment of shade changes (Paravina, 2008). Furthermore, it is accepted by the American Dental Association for use in determining the efficacy of tooth whitening products (ADA, 2020).

The VITA EasyShade instrument, whilst being a more recent approach to the assessment of tooth color, has been shown to provide precise measurement of tooth color in a previous clinical study (Dozić et al., 2007) and offers the potential for objective, examiner-independent evaluation of tooth color (Knezovic Zlataric et al., 2016). It is included in this study is to provide further information on tooth color-specific variables (e.g. L*, a*, b*, WI_D and ΔE) that could provide greater understanding on the tooth-cleaning properties of the experimental dentifrices.

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 and periodontal disease along with increased amounts of calculus and oral debris observed with pregnancy, both of which could impact dental stain and tooth color (Samant et al., 1976). The severity of these conditions is known to vary during the course of pregnancy (Samant et al., 1977), thus pregnancy would 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 brush with their assigned dentifrices twice daily for 2 minutes as per the American Dental Association recommendations for effective toothbrushing (ADA, 2022) and the UK National Health Service teeth cleaning guide (NHS, 2019).

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

Healthy volunteers of either sex and any gender, aged 18 – 65 years will be recruited with sufficient levels of dental stain and appropriate tooth color 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 300 subjects (equally distributed across the three treatment groups) to ensure approximately 270 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 to be included into 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 confirmed to be causing 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 with:
    a. At least 16 natural (vital) teeth including 11 of the 12 anterior teeth.

b. Facial surfaces of all anterior teeth (maxillary and mandibular) and lingual surfaces of anterior teeth (mandibular only) gradable for MLSI with no significant calculus or large restorations as judged by the clinical examiner.

c. Presence of extrinsic dental stain (formed on the surface of the teeth) which, in the opinion of the clinical examiner, originates from the diet and/or use of tobacco products.

d. Facial surfaces of central and lateral maxillary incisors gradable for tooth shade (free of cervical margin defects and restorations which could impact assessment), as judged by the clinical examiner.

e. Baseline Total MLSI $_{(A \times I)} \geq 15$ for the facial surfaces of the 12 anterior teeth.

f. Baseline mean tooth shade (VITA Bleachedguide 3D-MASTER) ≥ 11 on the facial surfaces of the 4 maxillary incisors.

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. Subject who is pregnant (self-reported) or intending to become pregnant during the study.
5. Subject who is breastfeeding.
6. Subject with known or suspected intolerance or hypersensitivity to the study products or any of their stated ingredients (or closely related compounds).
7. Subject who is unwilling or, in the opinion of the investigator or medically qualified designee, unable to comply with the requirements and/or lifestyle restrictions of the study.
8. Subject with a recent history (within the last year) of alcohol or other substance abuse.
9. 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.
10. Subject using daily oral care products and/or taking daily doses of medications/treatments which, in the opinion of the investigator or medically qualified designee, could interfere with study outcomes, specifically:

    a) currently daily use of mouthwashes containing ingredients known to cause tooth stain (for example, chlorhexidine or cetylpyridinium chloride),

b) past or current use of minocycline,

c) use of tetracycline or doxycycline within 30days of screening and/or during the study,

d) medications known to cause tooth stain (for example, drugs or supplements containing metal ions known to increase enamel staining).

11. Subject who has used any professionally-dispensed tooth whitening products 6 months prior to baseline or any over-the-counter products (including peroxide- or covarine blue-containing dentifrice, but not other daily use whitening dentifrices) 3 months prior to baseline.

12. Specific exclusions for assessment teeth:
    a. Non-vital tooth.
    b. Tooth with evidence of current or recent carious lesions.
    c. Tooth used as an abutment for fixed or partial dentures
    d. Tooth adjacent to fixed retainers and fixed or removable orthodontic appliances.
    e. Tooth with surface irregularities, cracked enamel, discoloration due to trauma or orthodontic treatment, tetracycline stain, restorations or hyper-/hypoplastic areas, which, in the opinion of the clinical examiner, grading of extrinsic dental stain and tooth shade.
    f. Tooth with a crown or veneer.
    g. Tooth with exposed dentine which, in the opinion of the investigator, could impact grading of extrinsic dental stain and tooth shade.

13. General oral exclusions:
    a. Generalized severe gingivitis or advanced periodontal disease; treatment of periodontal disease (including surgery) within 12 months of screening; scaling or root planning within 3 months of screening.
    b. Any oral condition requiring immediate care.
    c. Having received a dental prophylaxis within 8 weeks of screening.

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 will be stratified according to their baseline Total MLSI $_{(A \times I)}$ (low < 45; high ≥ 45) and smoking status (smoker; non-smoker) and randomized to study treatment.

The two stratification factors will give rise to four strata.

- **Stratum 1:** Baseline Total MLSI $_{(A \times I)}$ < 45, Smoker
- **Stratum 2:** Baseline Total MLSI $_{(A \times I)}$ < 45, Non-smoker
- **Stratum 3:** Baseline Total MLSI $_{(A \times I)}$ ≥ 45, Smoker
- **Stratum 4:** Baseline Total MLSI $_{(A \times I)}$ ≥45, Non-smoker

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

- **Visit 1 onwards:** Eligible subjects will not be permitted to use chewing gum from screening to the end of the study.
- **Visits 2, 3 & 4:** Subjects will abstain from all oral hygiene procedures (including tooth brushing) for at **least 6 hours** prior to and during their clinical/instrumental assessment visits.
- **Visit 1 onwards:** Subjects should not use any other oral care products (for example, dentifrices, toothbrushes, oral rinses, tongue cleaners, whitening/bleaching products, interdental cleaning products) than those provided during the study.

  Dental floss can be used to remove impacted food from the anterior teeth; subjects may floss posterior teeth provided they do not abut an assessment tooth.

5.5.2 Dietary Restrictions

- **Visits 2, 3 & 4:** Subjects will abstain from eating and drinking (with the exception of small amounts of water required for taking medication) for at **least 2 hours** prior to and during their clinical/instrumental assessment visits.

5.5.3 Use of Cosmetics

- **Visits 2, 3 & 4:** Subjects will refrain from applying lipstick or colored lip coverings prior to and during their clinical/instrumental assessment visits.

5.5.4 Tobacco Product Restrictions

- **Visit 1 onwards:** Subjects will not be permitted to use chewing tobacco from screening to the end of the study.
- **Visits 1-4:** Subjects will not be permitted to smoke, vape or use tobacco products during their scheduled visits to the study site.

5.5.5 Medication and Treatment Restrictions

- **Visits 1-4:** 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 3 & 4:** 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.

5.6 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 Examiner 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 examiner(s) will also be experienced in use of the VITA EasyShade instrument for intra-oral measurement of tooth shade.

6 INVESTIGATIONAL/STUDY PRODUCTS

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 Dentifrices		Reference Dentifrice
	5% KNO_3 dentifrice with 1% alumina and 5% STP	5% KNO_3 dentifrice with 1% alumina, 5% STP and 2% high cleaning silica	Regular Fluoride Dentifrice
Product Name	N/A	N/A	Aquafresh Cavity Protection (US market)
Fluoride Content	0.2542% NaF (1100 ppm fluoride)		
Pack Design	One carton containing 2 tubes of dentifrice		
Dispensing Details	Visit 2 (Baseline): 2 cartons; Visit 3 (Week 4): 2 cartons		
Product Master Formulation Code (MFC)	CCI	CCI	CCI
Dose/Product Application	Subjects will dose the toothbrush provided with a strip of dentifrice (a full brush head) on each brushing occasion		
Route of Administration	Topical oral use		
Usage Instructions	Subjects will brush twice daily (morning and evening) for 2 timed minutes 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 Sundry Items

Item	Pack Design	Dispensing Details	Return/Disposal Details	
			Used Samples	Unused Samples
Parodontax Complete Protection Soft-Bristled Toothbrush (US market)	Individual toothbrush in commercial pack	Visit 2: 1 brush Visit 3: 1 brush	Destroy at site using site disposal procedures	Return to sponsor
Countdown Timer	Individual toothbrush 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 8-week treatment period. Sundry items will be supplied in their commercial packaging for dispensing by study staff as specified in Table 6.2.

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 2-4 to ensure compliance with brushing instructions. The reference dentifrice

is commercially available and the application instructions described in this protocol are consistent with it's label instructions. The two experimental dentifrices are 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 at the end of the baseline visit (Visit 2), after all clinical assessments have been completed.
- staff will supervise a brushing with study dentifrice and diary completion at the end of the Week 4 visit (Visit 3), after all clinical assessments have been completed.

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 6 hours prior to attending site at Visits 2-4.

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 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 3 and 4 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 Department or designated vendor using the return instructions provided. Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction will be provided by 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 three 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.

While this study is described as examiner-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 baseline MLSI score and smoking status 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 end of 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 2-minute brushing time. A further supervised brushing will be carried out at the study site at the end of Week 4 procedures (Visit 3).
- Subjects will be provided with a diary at baseline (Visit 2) and Week 4 (Visit 3) to record each completed brushing with study product.
- Subjects will attend each study visit with all tubes of dentifrice provided (used and unused) for a visual check of product usage, and with their completed diary for review by study staff. 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.

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. Full OST and OHT examinations
5. Review of the inclusion/exclusion criteria
6. Subject eligibility

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 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.
- Confirm eligibility of the anterior teeth against the dentition exclusions described in Section 5.3.

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.

8.1.1.5 Inclusion/Exclusion Criteria

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

8.1.1.6 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.

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. MLSI is assessed on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth (tooth numbers 6-11 and 22-27), and the lingual surfaces of the six mandibular anterior teeth (tooth numbers 22-27), including a repeat assessment if required. At the examiner's discretion, the examiner my use floss and/or a wetted toothbrush to remove debris from the teeth prior to the assessment if required.
2. Clinical assessment of tooth shade is performed on the facial surfaces of the central and lateral maxillary incisors (tooth numbers 7-10) through use of the VITA Bleachedguide 3D-MASTER instrument including a repeat assessment if required.
3. Tooth color is assessed through use of the VITA EasyShade instrument.
4. Review of the inclusion/exclusion criteria.
5. Subject eligibility assessed. Subjects who do not meet the criteria for participation will be discontinued.
6. Qualifying subjects will be stratified and randomized to treatment groups.
7. Study products will be dispensed, including sundry items, and diary.
8. 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.
9. AEs and incidents recorded.

Randomized subjects will be appointed to attend the study site for their Week 4 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 4 (Day 28 ± 3)

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

Subjects will undergo, in the following order (wherever possible), and findings recorded in the CRF:

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 will return study products and diary for visual inspection to evaluate product compliance and adherence to protocol. Subject continuance in the study confirmed.
4. Subject undergoes an OST examination.

5. MLSI is assessed on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth (tooth numbers 6-11 and 22-27), and the lingual surfaces of the six mandibular anterior teeth (tooth numbers 22-27), including a repeat assessment if required. At the examiner's discretion, the examiner my use floss and/or a wetted toothbrush to remove debris from the teeth prior to the assessment if required.
6. Clinical assessment of tooth shade is performed on the facial surfaces of the central and lateral maxillary incisors (tooth numbers 7-10) through use of the VITA Bleachedguide 3D-MASTER instrument including a repeat assessment if required.
7. Tooth color is assessed through use of the VITA EasyShade instrument.
8. Resupply of allocated study products will be dispensed, including sundry items, and diary.
9. Re-instruct subject in product usage requirements/diary completion; supervise on-site brushing and diary entry.
10. AEs and incidents recorded.

Subjects will be appointed to attend the study site for their Week 8 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.

8.2.3 Visit 4 /Week 8 (Day 56 ± 3)

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 and/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 will return study products and diary for visual inspection to evaluate product compliance and adherence to protocol. Subject continuance in the study confirmed.
4. Subject undergoes OST and OHT examinations.
5. MLSI is assessed on the facial surfaces of the six maxillary anterior teeth and six mandibular anterior teeth (tooth numbers 6-11 and 22-27), and the lingual surfaces of the six mandibular anterior teeth (tooth numbers 22-27), including a repeat assessment if required. At the examiner's discretion, the examiner my use floss and/or a wetted toothbrush to remove debris from the teeth prior to the assessment if required.
6. Clinical assessment of tooth shade is performed on the facial surfaces of the central and lateral maxillary incisors (tooth numbers 7-10) through use of the VITA Bleachedguide 3D-MASTER instrument including a repeat assessment if required.
7. Tooth color is assessed through use of the VITA EasyShade instrument.
8. AEs and incidents recorded.
9. Study conclusion.

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

8.2.4 Study Procedures

8.2.4.1 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.

8.2.4.2 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.

8.2.4.3 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 well-being 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 Macpherson Modification of the Lobene Stain Index (MLSI)

Extrinsic dental stain will be assessed on the facial surfaces of the 6 maxillary and 6 mandibular anterior teeth (6-11 and 22-27), and the lingual surfaces of the 6 mandibular anterior teeth (22-27) at baseline, Week 4 and Week 8 (Visits 2-4), using the MacPherson modification (Macpherson et al., 2000) of the Lobene stain index (Lobene, 1968) (MLSI).

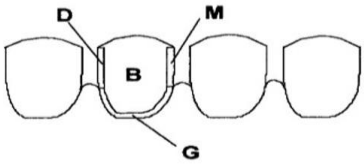
All assessments should be performed by a single, trained clinical examiner, with consistent lighting to standardize of the assessment conditions. If required the examiner will brush the subject's anterior teeth with a wetted toothbrush and/or floss to remove any debris which could impact the accuracy of the stain assessment. Teeth will be air dried prior to and during the assessment as needed.

The facial surfaces of each assessable tooth is divided into four regions. The 'gingival' region is defined as a crescent-shaped band, approximately 2 mm wide, adjacent to the free margin of the gingiva and extending to the crest of the interdental papillae of the adjacent teeth. The 'body' of the tooth is then sub-divided into three regions on the facial surfaces.

The facial and lingual surfaces of each assessable tooth will be divided into 2 regions, with a total of 4 sites per tooth surface (Figure 9-1).

- **Gingival Region**: Defined as a crescent-shaped band (~ 2 mm wide) adjacent to the free margin of the gingiva and extending to the crest of the inter-dental papillae of the adjacent teeth (1 site).
- **Body Region**: The remainder of the tooth surface (the body) is further sub-divided into 3 sites.
  - Distal facial, body facial, mesial facial sites
  - Distal lingual, body lingual, mesial lingual sites

Figure 9-1 MLSI Assessment Sites: Body (B), Gingival (G), Mesial (M), Distal (D)



Area (A) and intensity (I) of extrinsic dental stain is scored separately for the four 'gingival' and 'body' sites, as follows.

Score	Area	Intensity
0	No stain	No stain
1	Stain covering up to one third of region	Light stain
2	Stain covering up to two thirds of region	Moderate stain
3	Stain covering more than two thirds of region	Heavy stain

9.2.1.1 Repeatability of the MLSI Assessment

To assess the repeatability of the MLSI assessments, replicate examinations will be performed by the same clinical examiner. Ten subjects will be randomly selected for repeat MLSI assessments at each assessment time point (Visits 2, 3 and 4), a total of 30 repeat assessments over the duration of the study. Replicate assessments will be separated by a minimum of 10 minutes (maximum 60 minutes) from the original assessment for a given subject and, where possible, separated by at least one subject.

The scores of the initial assessment will not be visible to the examiner or scribe when the repeat assessment is carried out.

9.2.2 Tooth Shade (Color) Assessment

Tooth shade (color) of the facial surfaces of the four central and lateral maxillary incisors (tooth numbers 7-10) will be assessed by a single, trained clinical examiner using the VITA Bleachedguide 3D-MASTER. The arch tooth position will be parallel to the floor.

Assessment conditions should be standardized: color corrected lighting in the range of 5000° Kelvin; a grey bib will be placed over the subject's clothing; subjects will be asked not to wear lipstick; assessments will be performed in the same room (necessary) at approximately the same time of day (if possible); outside light will be controlled by covering the windows or using a windowless room. Color determination should be made within 5-7 seconds of starting an assessment to avoid eye fatigue.

The VITA Bleachedguide 3D-MASTER (Paravina, 2008) uses a value-ranked ordered scale from 1 (the lightest) to 29 (the darkest). The shade level of each tooth surface is scored visually by the clinical examiner with reference to the Bleachedguide.

A single VITA Bleachedguide will be used for all assessments throughout the study wherever possible.

9.2.2.1 Repeatability of the Tooth Color Shade Assessment

To assess the repeatability of the tooth shade assessments, replicate examinations will be performed by the same clinical examiner using the same VITA Bleachedguide instrument. Ten subjects will be randomly selected for repeat shade assessments at each assessment time point (Visits 2, 3 & 4), a total of 30 repeat shade assessments over the duration of the study. Replicate assessments will be separated by a minimum of 10 minutes (maximum 60 minutes) from the original assessment for a given subject and, where possible, separated by at least one subject.

The scores of the initial assessment will not be visible to the examiner or scribe when the repeat assessment is carried out.

9.2.3 VITA EasyShade Assessment

Tooth shade (Bleachedguide shade) and color coordinates (L*, a*, b*) will be measured instrumentally for the facial surfaces of the four central and lateral maxillary incisors (tooth numbers 7-10) using the VITA EasyShade instrument. The clinical examiner will take a single reading from the middle section of each assessable tooth, in accordance with the manufacturer's instructions. The spectrophotometer should be calibrated using the calibration block supplied, in accordance with the manufacturer's instructions.

The collected data will be used to calculate the ΔE* and WI_D (del Mar Pérez et al., 2016) values as:

$$\Delta E^* = \sqrt{\Delta L^{*2} + \Delta a^{*2} + \Delta b^{*2}}$$

$$WI_D = 0.511L^* - 2.324a^* - 1.100b^*$$

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 of the subjects may be utilized at any site visit at the examiner's discretion.

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 eCRF. 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 Investigator's Brochure in the investigator study master file, and will notify the IRB/IEC, if appropriate according to local requirements.

10.9 Pregnancy

10.9.1 Time Period for Collecting Pregnancy Information

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

10.9.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the Case Management Group mailbox PPD), with copy to the appropriate 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 BDM 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.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

The study will be powered sufficiently (>90%) to provide evidence of superiority for an Experimental Dentifrice compared to the Reference Dentifrice for both stain removal and whitening after 8 weeks under the graphical approach method (with initial two-sided alpha

allocation of 5% for testing within each Experimental Dentifrice) to adjust for multiple comparisons and preserve a two-sided 10% family wise error rate as described in section 12.3.

Table 12-1 Sample Size Power by Endpoint at 5% and 2.5% Significance Levels with 90 Subjects per Arm

Endpoint at Week 8	Assumptions		Independent power from 90 subjects per arm for each endpoint by two-sided significance level [3]		Power from graphical approach to achieve statistical significance at 5% level [4]
	Mean Difference	Standard Deviation (SD)	5%	2.5%	
Within Experimental Dentifrice change from baseline in mean Total MLSI (Area x Intensity) [1]	0.6	0.4	>99.9%	>99.9%	>99.9%
Comparison with Reference Dentifrice in change from baseline in mean Total MLSI (Area x Intensity) [1]	0.3	0.4	99.8%	99.7%	99.8%
Within change from baseline in the mean VITA shade score [2]	2	2	>99.9%	>99.9%	>99.9%
Comparison with Reference Dentifrice in change from baseline in the mean VITA shade score [2]	1	2	91.5%	86.1%	90.2%

1) Estimates of mean difference and SD were based on results from previous GSKCH studies of similar design [redacted]
2) Estimates of mean difference and SD were based on results from a previous GSKCH study of similar design [redacted] Within treatment study reductions in the mean VITA shade score are expected to be greater in this study due to greater baseline VITA shade scores and an 8 week primary assessment instead of 4 weeks. As such, the SD is also assumed to increase, so an effect size (mean difference/SD) of 0.5 is assumed.
3) Based on carrying out a two tailed one-sample (within Experimental Dentifrice) or two-sample (Comparison with Reference Dentifrice) t-test at the 5% significance level using PASS software version 19.0.1.
4) Simulation using SAS 9.4 software based on stated assumptions for all endpoints and graphical approach analysis detailed in section 12.3.

As detailed in the independent sample size calculations in Table 12-1, the minimum required sample size assessment depends almost entirely on the mean VITA shade score reduction comparison between Experimental and Reference Dentifrices. Simulation shows that under the graphical approach methodology (Section 12.3) and the above underlying assumptions for an Experimental Dentifrice, the power to show statistical significance in all 4 comparisons for that Experimental Dentifrice (reduction from baseline and superior reduction compared to Reference Dentifrice in both mean Total MLSI [Area x Intensity] and mean VITA shade score) is > 90%.

Approximately 100 subjects per group (approximately 300 in total) will be randomized to account for a drop-out rate of up to 10% prior to Week 8.

12.2 Populations for Analysis

12.2.1 Definitions 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 baseline 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 mean Total MLSI (Area x Intensity) and mean VITA shade score endpoints 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

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

12.3.1 Primary Analyses

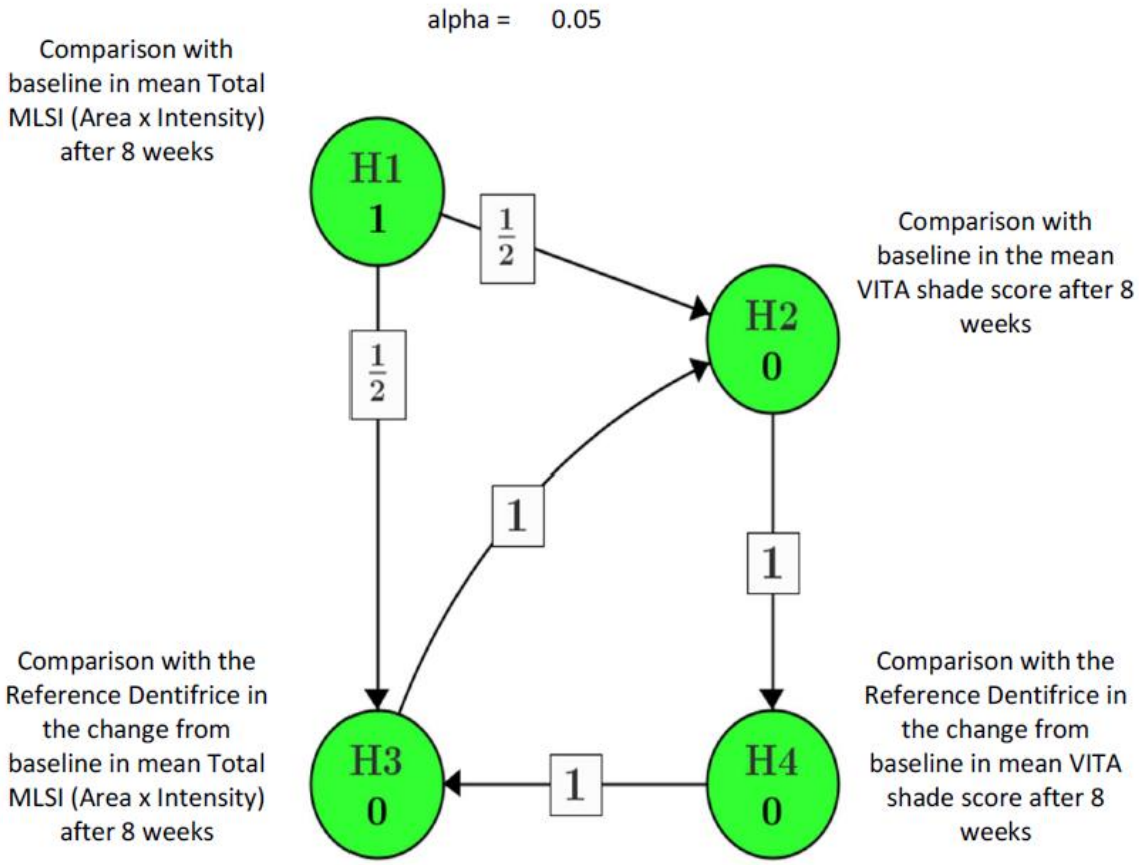
The hypothesis testing of the mean Total MLSI (Area x Intensity) and mean VITA shade score within each Experimental Dentifrice will employ the graphical approach shown in Figure 12.1, as per Bretz et al (Bretz et al., 2009) in order to maintain an overall two-sided familywise error rate at 5% within each Experimental Dentifrice (10% overall).

For stratification purposes, the Total MLSI (Area x Intensity) will be derived as the sum of the MLSI (Area x Intensity) scores for each of evaluated regions (gingival and body) of the facial surfaces of each anterior tooth (4 values per assessed tooth surface).

For efficacy evaluation, the mean Total MLSI (Area x Intensity) for a subject will be derived as the mean of the Total MLSI (Area x Intensity) scores across all anterior teeth assessed (facial surfaces of the maxillary and mandibular anterior teeth and the lingual surfaces of the mandibular teeth, 4 values per assessed tooth surface).

The mean VITA shade score for a subject will be derived as the mean of the VITA shade scores across all teeth assessed.

Figure 12-1 Graphical Approach Showing Allocation and Propagation of Alpha Between Hypotheses Within Each Experimental Dentifrice



The above hypotheses tests will be conducted based on separate Mixed Models with Repeated Measures (MMRM) for the change from baseline in the mean Total MLSI (Area x Intensity) and mean VITA shade score. Fixed effects will be included for smoking status, study product, visit and study product x visit interaction. The respective baseline result will be included as a covariate. Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied. The least square means for each study product at week 8 will be presented based on observed margins and used to test for < 0 change from baseline. The differences between least square means for each Experimental Dentifrice compared to the Reference Dentifrice at week 8 will be presented and used to test for a difference between products. The adjusted two-sided p-values and simultaneous 95% confidence intervals (following graphical testing approach) will be provided for all comparisons.

The assumption of normality and homogeneity of variance in the MMRM will be investigated. In case of violation of these assumptions, a suitable nonparametric test (adjusted for the randomization stratification) will be performed for each comparison at week 8 and results will be provided to support the MMRM results.

The mean Total MLSI (Area x Intensity) and mean VITA shade score values across the study and change from baseline will be summarised descriptively.

12.3.2 Secondary and Exploratory Analyses

There will be no adjustment for multiplicity in the analyses described in this section.

The within and between study product comparisons for the mean Total MLSI (Area x Intensity) and mean VITA shade score after 4 weeks will be based on the same respective MMRM as used for the primary analyses but based on the least square means comparisons at week 4.

The within and between study product comparisons for the other secondary and exploratory efficacy endpoints (see Section 3) after 4 and 8 weeks will be based on the same MMRM as used for the primary analyses (replacing the respective baseline for the endpoint as a covariate) and the least square means comparisons at weeks 4 and 8. These other secondary and exploratory endpoint values across the study and change from baseline will also be summarised descriptively.

12.3.3 Safety Analyses

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

Safety analyses will focus on:

- Exposure and compliance with study product
- 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. During this review stage, AEs will be further categorized as oral or non-oral. 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
- Oral Hard Tissue and Examinations

A list of medical device incidents will also be included as part of the safety analyses. No specific risks or anticipated adverse device effects are expected to be observed within this study, however all AEs and medical device incidents will be assessed to evaluate the tolerability and safety of the treatments.

12.3.4 Other Analyses

The repeat stain and color assessments will be compared to the original assessments and will not be used in any efficacy analysis. The first and second assessments on each tooth site will be cross tabulated. A weighted Kappa coefficient (κ), along with the 95% CI will be calculated

to assess the intra-examiner reliability. Fleiss-Cohen weighted kappa will be calculated for the repeatability analysis. Reliability will be deemed

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

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

12.3.5 Demographic and Baseline Characteristics

Demographic and randomized stratification data will be summarized descriptively.

12.3.6 Study Product Compliance and Use of Other Therapies

12.3.6.1 Study Product Compliance

Number of brushings, brushing compliance (%), number of missed brushings, number of additional brushings will be summarized using descriptive statistics by cumulative visit.

Number of brushings is defined as: [(date of Visit N – 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 N – date of Visit 2) multiplied by 2].

12.3.6.2 Prior and Concomitant Medications

Prior and Concomitant Medications will be listed only.

12.3.6.3 Handling of Dropouts and Missing Data

The use of MMRM analyses account for missing data assuming a missing at random assumption, i.e., there is a systematic relationship between the propensity of missing values and the observed data, but not the missing data.

It is therefore assumed that a subject with missing data would have obtained a similar efficacy result compared to a subject using the same study product with the same smoking status and similar non-missing results at other timepoints (baseline and post-baseline). Sensitivity analyses may be added to the SAP prior to unblinding in case of high drop-out rates and/or exclusion from PP population.

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 dentifrices 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 2 minutes, and then brush your teeth in your usual manner for 2 timed minutes.

- 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
BDR	blinded data review
CI	confidence interval
CRF	case report form
EC	ethics committee
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IRB	institutional review board
LSLV	last subject last visit
KNO_3	Potassium nitrate
MedDRA	medical Dictionary for Regulatory Activities
MLSI	Modified Lobene Stain Index
MMRM	Mixed Models with Repeated Measures

Abbreviation	Term
N/A	not applicable
PI	principal investigator
PI	Personal information
SAE	serious adverse event
SOP	standard operating procedure
SRSD	single reference study document
SS	safety statement
STP	Sodium tripolyphosphate
US	United States

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