CLINICAL PROTOCOL

A Randomized, Controlled, Single-Blind Clinical Study Assessing the Effects of an Experimental Dentifrice in Maintaining Tooth Color Following Tooth Bleaching

Protocol Number:	300109
Compound/Product Name:	Potassium Nitrate Dentifrice
United States (US) Investigational New Drug (IND) Number:	N/A
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Sponsor Information

Sponsor Name & Legal Registered Address	**Haleon (UK)** St Georges Avenue, Weybridge, Surrey, KT13 0DE, United Kingdom (UK)
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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	Change of the peroxide bleaching treatment from Captivate to Opalescence and update of associated application instructions. Removal of custom fitting of tray (no longer required with Opalescence peroxide trays). Addition of return of peroxide kit at Visit 3 Alignment of name of “Whitening history” and “Post-whitening” questionnaires throughout. Deletion of statement that questionnaire and diaries will be sourced by the study site.

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

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PROTOCOL SUMMARY

1.1 Synopsis

Short Title:

Randomised, Controlled Clinical Study Assessing the Effects of an Experimental Dentifrice in Maintaining Tooth Color Following Tooth Bleaching

Background and Rationale:

The main aim of this study is to investigate the ability of an experimental dentifrice containing 5% potassium nitrate (KNO_3), 1% alumina and 5% sodium tripolyphosphate (STP), to maintain tooth color and reduce extrinsic dental stain accumulation following peroxide tooth bleaching compared to a regular fluoride dentifrice. Additionally, the ability of the test dentifrice to reduce tooth sensitivity concurrent with peroxide tooth bleaching will be explored.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To compare tooth color after 24 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice following peroxide tooth bleaching as measured by VITA Bleachedguide 3D-Master.	Mean VITA shade score at 24 weeks after tooth bleaching.
Secondary	
To compare tooth color after 12 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice following peroxide tooth bleaching as measured by VITA Bleachedguide 3D-Master.	Mean VITA shade score at 12 weeks after tooth bleaching.
To compare extrinsic dental stain after 12 and 24 weeks, twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice following peroxide tooth bleaching as measured by Modified Lobene Stain Index.	Mean MLSI at 12 and 24 weeks after tooth bleaching in: • Total MLSI (Area (A) x Intensity (I)) • Gingival sites (AxI) • Interproximal sites (AxI) • Body sites (AxI) • MLSI (A) • MLSI (I)
Exploratory	
To compare subject-perceived tooth sensitivity during peroxide tooth bleaching with twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice, as measured by subject-completed sensitivity questionnaire overall and within strata (clinically-diagnosed DH [Y/N]).	Mean sensitivity questionnaire scores pre and post peroxide tooth bleaching in: • Visual analogue scale (VAS) • Labelled Magnitude scales (Intensity, Duration. Tolerability, Description) - LMS • Bothersomeness score - NRS
To explore subject's experience of peroxide tooth bleaching when simultaneously using either a '5% KNO_3/1% alumina/5% STP' dentifrice or a regular fluoride dentifrice.	Post-whitening questionnaire

To confirm the tooth whitening efficacy of peroxide tooth bleaching with concurrent, twice daily use of '5% KNO3/1% alumina/5% STP' dentifrice and a regular fluoride dentifrice as measured by VITA Bleachedguide 3D Master.	Change in mean VITA shade score from pre to post tooth bleaching
Safety	
To assess the safety and tolerability of a '5% KNO_3/1% alumina/5% STP' dentifrice.	Treatment emergent adverse events

Abbreviations: MLSI: Modified Lobene Stain Index, VAS: Visual Analogue Scale, LMS: Labelled Magnitude Scales, NRS: Numerical Rating Scale.

Study Design:

This will be a randomized, single-blind, single-center, controlled, two arm, stratified (clinically diagnosed DH (Y/N)), parallel group study to evaluate the efficacy of an experimental dentifrice containing 5% potassium nitrate (KNO_3), 1% alumina and 5% sodium tripolyphosphate (STP), to maintain tooth color and reduce the accumulation of extrinsic tooth stain following peroxide tooth bleaching compared to a regular fluoride-containing dentifrice. The study will recruit generally healthy subjects who wish to undergo peroxide tooth bleaching.

Potential subjects will attend a screening visit (Visit 1) to determine their suitability to participate. Having obtained their written informed consent, relevant details of their demography, medical history and current medications will be recorded, followed by oral soft tissue (OST) and oral hard tissue (OHT) examinations. Subjects will undergo an assessment of the tooth color (shade) of the facial surfaces of the six maxillary anterior teeth (tooth numbers 6-11) [Universal tooth numbering system] using the VITA Bleachedguide 3D-MASTER (Gomez-Polo et al., 2015) and extrinsic tooth stain on the facial surfaces of the same teeth using the MacPherson modification (Macpherson et al., 2000) of the Lobene Stain Index(Lobene, 1968) (MLSI). Those subjects with a self-reported history of dentine hypersensitivity (DH) will be clinically-evaluated to confirm their DH status (including Erosion/Abrasion/Recession (EAR) assessment, gingival assessment, tooth mobility assessment and evaporative (air) sensitivity assessment (Schiff Sensitivity score)).

Subjects meeting all study criteria, will be considered as eligible to proceed, stratified (based upon their clinically-diagnosed DH status [Y/N]) and randomized to treatment group. Randomized subjects will then complete the tooth sensitivity questionnaire. Subjects will be dispensed their study products (including diary and sundry items) and undertake a supervised brushing with their allocated dentifrice at the clinical site and be scheduled to attend Visit 2 (2 weeks ± 2 days after Screening/Randomization). Subjects will continue to use their allocated study products (twice-daily) throughout the study and will record this usage in their study diary.

At Visit 2 (2 weeks after Screening/randomization) subjects will undergo a review of their diary and current medications and will then undergo an OST examination. Tooth color and extrinsic tooth stain will be assessed for the same teeth in the same way as at Visit 1. Subjects who fulfil all inclusion/exclusion criteria will continue in the study and will complete the tooth sensitivity questionnaire and the whitening history questionnaire. Subjects will have their tooth bleaching tray custom made per manufacturer's instructions (at the examiner's discretion this can be performed at Visit 1 instead). Subjects will then be dispensed a commercially available 15% peroxide tooth bleaching kit for use at home for 7 days, once per day, as per pack instructions Subjects will undergo a supervised tooth brushing (with their study dentifrice) and will floss their teeth and have their first application of the peroxide bleaching at the study site under supervision in accordance with the manufacturer's instructions. Subjects will be instructed in the correct use of the peroxide product for at home use in accordance with the manufacturer's instructions. Subjects will continue to use their assigned dentifrice twice daily and perform

their peroxide bleaching daily per instructions, and to record this usage in their supplied diary. Subjects will be scheduled to return to the study site for Visit 3 (after the completion of their 7 -days tooth bleaching period).

After the completion of the tooth bleaching period at Visit 3 [7 days after the commencement of tooth bleaching, with an acceptable range of 7-9 days] subjects will return to the clinical site and undergo a review of their diary and current medications and undergo an OST examination. Tooth color and extrinsic tooth stain will be assessed for the same teeth in the same way as at Visit 1. Subjects will then complete the tooth sensitivity questionnaire and the post-whitening questionnaire and scheduled to return for Visit 4 (12 weeks [±1 week] after completion of the peroxide tooth bleaching).

At Visit 4 subjects will return to the clinical site and undergo a review of their diary and current medications and an OST examination. Tooth color and extrinsic tooth stain will be assessed for the same teeth in the same way as at Visit 1. Subjects will then be scheduled to return for Visit 5 (24 weeks [±1 week] after completion of the peroxide tooth bleaching).

At Visit 5 subjects will return to the clinical site and return their study products and undergo a review of their diary and current medications and an OST and OHT examination. Tooth color and extrinsic tooth stain will be assessed for the same teeth in the same way as at Visit 1. Subjects will then exit the study.

Safety and oral tolerability of the study products will be monitored over the duration of the study by review of reported AEs and through Oral Soft Tissue examinations. Medical device incidents will also be monitored for the device in this study which is the study toothbrushes.

Study Products:

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

Type and Planned Number of Subjects:

Study subjects will be of either sex and any gender, aged 18-65 years, in good general and oral health, with the required level of tooth color and who are willing and able to undergo peroxide tooth bleaching.

Sufficient subjects will be screened to randomize approximately 160 subjects to study treatment (approximately 80 per treatment group) to ensure approximately 128 evaluable subjects complete the study with an assumed dropout rate of 20%. Subjects will be stratified according to their clinically-diagnosed DH status [Clinically diagnosed DH (Y/N)].

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 0-1 Schedule of Activities

Procedure/Assessment	Screening /Randomization	Study Period							
	Visit 1		Visit 2 (Start of tooth bleaching)		Visit 3 (End of tooth bleaching)		Visit 4 (12 weeks post tooth bleaching)		Visit 5 (24 weeks post tooth bleaching)
Informed consent	X	2 Weeks ±2days		7 days (acceptable range 7-9 days)		12 weeks ±1week		12 weeks ±1week	
Demographics	X								
Medical history	X								
Current/prior/concomitant medication review	X		X		X		X		X
OST Examination	X		X		X		X		X
OHT Examination	X								X
Assessment of tooth color and extrinsic tooth stain[1]	X		X		X		X		X
DH assessments (EAR, MGI, tooth mobility and evaporative air sensitivity)[2]	X								
Review of inclusion/exclusion criteria	X								
Subject eligibility	X								
Stratification followed by randomization to treatments[3]	X								
Subject completes tooth sensitivity questionnaire at site[4]	X		X		X				
Dispense study products, sundry items and diary	X								
Supervised toothbrushing at site	X		X						
Diary review			X		X		X		X

Procedure/Assessment	Screening /Randomization	Study Period							
	Visit 1		Visit 2 (Start of tooth bleaching)		Visit 3 (End of tooth bleaching)		Visit 4 (12 weeks post tooth bleaching)		Visit 5 (24 weeks post tooth bleaching)
Subject continuance			X						
Whitening History Questionnaire			X						
Subject returns used peroxide kit					X				
Subject dispensed bleaching treatment, petroleum jelly and floss for at home use with first application at study site under supervision[5]			X						
Post-Whitening Questionnaire					X				
Adverse events review[6]	X		X		X		X		X
Medical device incidents review[6]	X		X		X		X		X
Return study products, diary and sundry items									X
Study conclusion									X

Abbreviations: OST: Oral Soft Tissue, OHT: Oral Hard Tissue, MLSI: Modified Lobene Stain Index, LMS: Labelled Magnitude Scales, VAS: Visual analogue Scale, NRS: Numerical Rating Scale.

Footnotes:

1. Tooth color (Vita Bleachedguide 3D Master) and tooth stain (MLSI) assessed on facial surfaces of the maxillary anterior 6 teeth (tooth numbers 6-11).
2. Only subjects with a self-reported history of DH will be clinically assessed for DH.
3. Stratification will be based on clinically-diagnosed DH (Y/N) at screening.
4. The tooth sensitivity questionnaire will include Labelled Magnitude Scales (LMS) and a Visual Analogue Scale (VAS) to assess tooth sensitivity and a Numerical Rating Scale (NRS).
5. The supplied tooth bleaching treatment will be used once under supervision at the study site (for first application) and then daily, at home (for a total of 7 days) in accordance with the manufacturer's instructions.
6. Adverse Events (AEs), Serious Adverse Events (SAEs) and medical device incidents collected immediately after subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF). Medical device in this study is the supplied toothbrush.

2 INTRODUCTION

Tooth bleaching is a widely performed treatment that aims to improve the color (increase whiteness) of teeth to provide a cosmetic benefit. The most commonly used bleaching ingredient is hydrogen peroxide (or hydrogen peroxide-releasing ingredients such as carbamide peroxide), which functions by diffusing through the tooth enamel and oxidizing chromophores within the porous matrix of enamel and the underlying dentine. This has the effect of reducing the color within the tooth making the teeth appear whiter. The whitening benefit though is not permanent, with exposure to dietary chromogens eventually causing tooth color to return. The duration of the whitening benefit is therefore patient-specific with estimates ranging from a few months to 3 years (UK National Health Service, 2023). One study, however, found a reduction in the whitening benefit in as little as 7 days (Lunardi and Correr, 2014), and another after 10 months (Corcodel et al., 2017). It is therefore of interest to investigate whether a topical, daily-use dentifrice can help maintain tooth color following peroxide tooth bleaching.

Additionally, a common side effect of tooth bleaching is tooth sensitivity, the prevalence of which ranges from 10%-90% (West, 2023a), depending on the type, concentration and application method of the bleaching agent. Tooth sensitivity is most often reported for peroxide-based bleaching agents and usually occurs at the time of treatment and can last from several days up to 2 weeks. Peroxide has been shown to have the ability to diffuse through the enamel into the enamel-dentin junction and the dentin and induce localized reversible pulpitis.

Tooth sensitivity management works on the principle of either employing potassium-based agents aiming to stabilize pulpal nerve depolarization, or dentinal tubule occlusion agents aiming to occlude patent dentinal tubules (Pollard et al., 2023). However, the number of published studies in support of potassium-based dentifrices to reduce tooth sensitivity experienced during tooth bleaching are few (and the results have not been confirmed with follow-up studies) and the studies employed low numbers of subjects (Haywood et al., 2005, Pierote et al., 2019, CCI [redacted]). Therefore, conclusions from these published studies are difficult to interpret with any certainty and further studies are needed to explore the efficacy of potassium-containing dentifrice to reduce tooth sensitivity experienced during tooth bleaching.

The primary aim of this study is to evaluate whether an experimental dentifrice containing 5% potassium nitrate (KNO_3), 1% alumina and 5% sodium tripolyphosphate (STP) is able to better maintain tooth color after peroxide tooth bleaching.

2.1 Study Rationale

This 24-week, randomized, controlled, 2 arm, parallel-design, stratified (clinically diagnosed DH (Y/N)) clinical study has been designed to evaluate the ability of an experimental dentifrice containing 1% alumina, 5% STP and 5% KNO_3 to maintain tooth color and reduce extrinsic dental stain accumulation following peroxide tooth bleaching compared to a regular fluoride dentifrice. Additionally, the ability of the test dentifrice to reduce tooth sensitivity concurrent with peroxide tooth bleaching will be explored.

Whilst the dental stain removal and tooth whitening properties of dentifrices containing 1% alumina with 5% STP has been demonstrated (see Section 2.2); additional data are required to support new claims and benefits of the experimental dentifrice specifically when used concomitantly with and post peroxide tooth bleaching.

2.2 Background

Dentifrices containing 1% alumina and 5% STP have been evaluated previously in five unpublished clinical studies (Haleon Clinical Study 300024, 2023, CCI CCI , CCI). These studies, taken as a whole, demonstrate the ability of dentifrice containing 1% alumina and 5% STP to whiten teeth, reduce dental stain and help reduce further dental stain. None of these studies, however, evaluated the use of dentifrice containing 1% alumina and 5% STP concurrently with peroxide tooth bleaching.

The tooth sensitivity benefits of KNO_3 containing dentifrices are well established (Sharma et al., 2012, Hu et al., 2018). However, the evidence supporting the use of potassium ions to reduce tooth sensitivity associated with tooth bleaching is less clear. One study evaluated the twice-daily use of a 5% KNO_3 dentifrice for 2 weeks before, and during a 14 day treatment with a 9.5% hydrogen peroxide gel (Haywood et al., 2005) compared to a standard dentifrice. The study concluded that use of the potassium-containing dentifrice resulted in statistically significantly more sensitive-free days than the control dentifrice. Similar findings were found in another study (Pierote et al., 2020) where a variety of dentifrices were used during and after peroxide bleaching with a 26% hydrogen peroxide gel, concluding that dentifrices containing potassium nitrate were able to reduce tooth sensitivity during peroxide bleaching. The same study also evaluated tooth color finding that all of the tested dentifrices (including controls) led to the same tooth color at 4 and 24 weeks after bleaching, with teeth becoming darker with time. A separate study by the same authors concluded that a potassium-containing dentifrice was effective at helping to reduce tooth sensitivity when applied via a tray for 4 hours per night during the bleaching period (Pierote et al., 2019). In a further study (Adil et al., 2021), use of a potassium nitrate / sodium monofluophosphate gel post bleaching was found to be effective at reduction of tooth sensitivity when a 35% hydrogen peroxide bleaching treatment was used. Tooth sensitivity relief while using a KNO_3 dentifrice was also observed in a population with mild-to-moderate fluorosis following 35% hydrogen peroxide treatment (Nanjundasetty and Ashrafulla, 2016). Contrastingly, application of a KNO_3 gel immediately prior to bleaching with hydrogen peroxide was not found to reduce tooth sensitivity but also did not adversely affect the whitening efficacy of the bleaching treatment (de Lima et al., 2022). Further, an unpublished study found that use of a 5% KNO_3 dentifrice before, during and after a bleaching treatment led to a non-statistically significant reduction in tooth sensitivity during the 7 days post treatment, although statistically significant fewer subjects reported tooth sensitivity compared to the control dentifrice (CCI). A systematic review of tooth sensitivity associated with tooth bleaching, drawing on 13 publications, has concluded that 5% KNO_3 is effective at reducing tooth sensitivity at least up to 24 hours post conclusion of the bleaching treatment (Krishnakumar et al., 2022).

Therefore the aims of this study are to investigate the ability of an experimental dentifrice containing 5% potassium nitrate (KNO_3), 1% alumina and 5% sodium tripolyphosphate (STP), to maintain tooth color and reduce extrinsic dental stain accumulation following peroxide tooth bleaching compared to a regular fluoride-containing dentifrice. Additionally, the ability of the test dentifrice to reduce tooth sensitivity concurrent with peroxide tooth bleaching will be explored.

2.3 Benefit/Risk Assessment

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

Formulations containing 5% KNO_3, 1% alumina and 5% STP have been evaluated in clinical studies to evaluate their cleaning efficacy (see Background Section 2.2). These studies demonstrated the efficacy and safety of these formulations. The active ingredients and formulation excipients contained in the study dentifrices have a history of safe use in oral care products and are currently used in marketed daily-use dentifrices.

The experimental dentifrice under evaluation is therefore 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

The test dentifrice being investigated contains 1% alumina and 5% sodium tripolyphosphate (STP) which provide tooth whitening/stain removal benefits (CCI [redacted], CCI [redacted] CCI [redacted] Haleon Clinical Study 300024, 2023). Additionally, the test dentifrice contains 5% w/w KNO_3, which provides relief from tooth sensitivity through pulpal nerve depolarization (Sharma et al., 2012, Hu et al., 2018).

Both the test and the reference dentifrice contain 0.254% w/w NaF, equivalent to 1150ppm fluoride. Sodium fluoride in both dentifrices provides an anti-caries benefit (Griffin et al., 2007, Marinho et al., 1996).

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare tooth color after 24 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice following peroxide tooth bleaching as measured by VITA Bleachedguide 3D-Master.	Mean VITA shade score at 24 weeks after tooth bleaching.
Secondary	
To compare tooth color after 12 weeks twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice following peroxide tooth bleaching as measured by VITA Bleachedguide 3D-Master.	Mean VITA shade score at 12 weeks after tooth bleaching.
To compare extrinsic dental stain after 12 and 24 weeks, twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice following peroxide tooth bleaching as measured by Modified Lobene Stain Index.	Mean MLSI at 12 and 24 weeks after tooth bleaching in: • Total MLSI (Area (A) x Intensity (I)) • Gingival sites (AxI) • Interproximal sites (AxI) • Body sites (AxI) • MLSI (A) • MLSI (I)
Exploratory	
To compare subject-perceived tooth sensitivity during peroxide tooth bleaching with twice daily use of a '5% KNO_3/1% alumina/5% STP' dentifrice compared to a regular fluoride dentifrice, as measured by subject-completed sensitivity questionnaire overall and within strata (clinically-diagnosed DH	Mean sensitivity questionnaire scores pre and post peroxide tooth bleaching in: • Visual analogue scale

[Y/N]).	(VAS) • Labelled Magnitude scales (Intensity, Duration. Tolerability, Description) - LMS • Bothersomeness score - NRS
To explore subject's experience of peroxide tooth bleaching when simultaneously using either a '5% KNO_3/1% alumina/5% STP' dentifrice or a regular fluoride dentifrice.	Post-whitening questionnaire
To confirm the tooth whitening efficacy of peroxide tooth bleaching with concurrent, twice daily use of '5% KNO3/1% alumina/5% STP' dentifrice and a regular fluoride dentifrice as measured by VITA Bleachedguide 3D Master.	Change in mean VITA shade score from pre to post tooth bleaching
Safety	
To assess the safety and tolerability of a '5% KNO_3/1% alumina/5% STP' dentifrice.	Treatment emergent adverse events

Abbreviations: MLSI: Modified Lobene Stain Index, VAS: Visual Analogue Scale, LMS: Labelled Magnitude Scales, NRS: Numerical Rating Scale.

This study will be considered successful if the Test dentifrice containing 5% KNO_3, 1% alumina and 5% STP demonstrates statistically significant whither teeth as measured by Vita Bleachedguide Shade in comparison with the reference dentifrice 24 weeks after peroxide tooth bleaching.

4 STUDY DESIGN

4.1 Overall Design

This will be a randomized, single-blind, single-center, controlled, two arm, stratified (clinically diagnosed DH (Y/N)), parallel group study to evaluate the efficacy of an experimental dentifrice containing 5% potassium nitrate (KNO_3), 1% alumina and 5% sodium tripolyphosphate (STP), to maintain tooth color and reduce the accumulation of extrinsic tooth stain following peroxide tooth bleaching compared to a regular fluoride-containing dentifrice. The study will recruit generally healthy subjects who wish to undergo peroxide tooth bleaching. A schematic of the principal study assessments and procedures is provided in Fig 4-1.

Potential subjects will attend a screening visit (Visit 1) to determine their suitability to participate. Having obtained their written informed consent, relevant details of their demography, medical history and current medications will be recorded, followed by oral soft tissue (OST) and oral hard tissue (OHT) examinations. Subjects will undergo an assessment of the tooth color (shade) of the facial surfaces of the six maxillary anterior teeth (tooth numbers 6-11) [Universal tooth numbering system] using the VITA Bleachedguide 3D-MASTER (Gomez-Polo et al., 2015) and extrinsic tooth stain on the facial surfaces of the same teeth using the MacPherson modification (Macpherson et al., 2000) of the Lobene Stain Index(Lobene, 1968) (MLSI). Those subjects with a self-reported history of dentine hypersensitivity (DH) will be clinically-evaluated to confirm their DH status (including Erosion/Abrasion/Recession (EAR) assessment, gingival assessment, tooth mobility assessment and evaporative (air) sensitivity assessment (Schiff Sensitivity score)).

Subjects meeting all study criteria, will be considered as eligible to proceed, stratified (based upon their clinically-diagnosed DH status [Y/N]) and randomized to treatment group.

Randomized subjects will then complete the tooth sensitivity questionnaire. Subjects will be dispensed their study products (including diary and sundry items) and undertake a supervised brushing with their allocated dentifrice at the clinical site and be scheduled to attend Visit 2 (2 weeks ± 2 days after Screening/Randomization). Subjects will continue to use their allocated study products (twice-daily) throughout the study and will record this usage in their study diary.

At Visit 2 (2 weeks after Screening/randomization) subjects will undergo a review of their diary and current medications and will then undergo an OST examination. Tooth color and extrinsic tooth stain will be assessed for the same teeth in the same way as at Visit 1. Subjects who fulfil all inclusion/exclusion criteria will continue in the study and will complete the tooth sensitivity questionnaire and the whitening history questionnaire. Subjects will then be dispensed a commercially available 15% peroxide tooth bleaching kit for use at home for 7 days, once per day, as per pack instructions and as detailed in Section 6.1.1.1. Subjects will undergo a supervised tooth brushing (with their study dentifrice) and will floss their teeth and have their first application of the peroxide bleaching at the study site under supervision in accordance with the manufacturer's instructions. Subjects will be instructed in the correct use of the peroxide product for at home use in accordance with the manufacturer's instructions. Subjects will continue to use their assigned dentifrice twice daily and perform their peroxide bleaching daily per instructions, and to record this usage in their supplied diary. Subjects will be scheduled to return to the study site for Visit 3 (after the completion of their 7 -days tooth bleaching period).

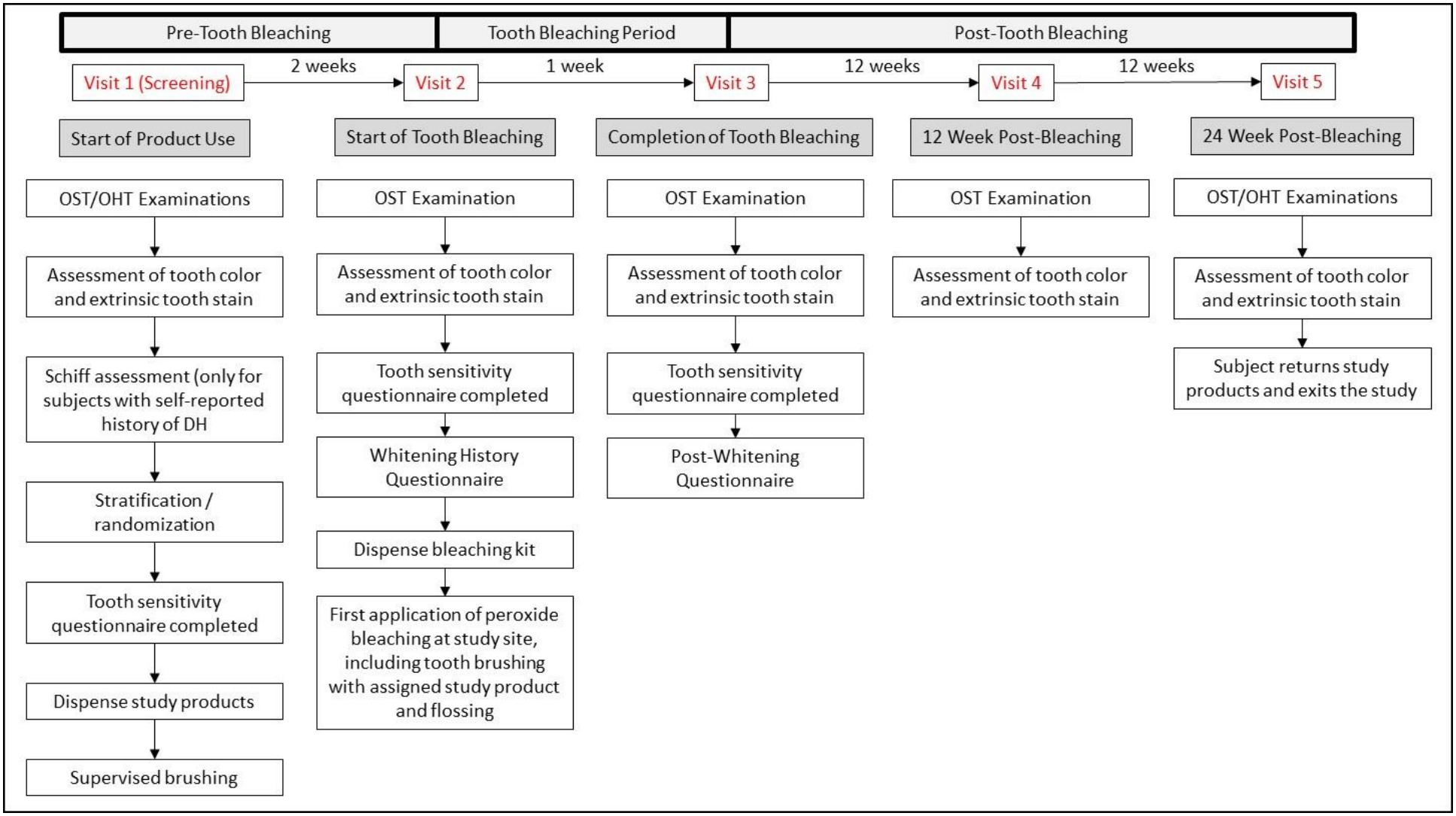
After the completion of the tooth bleaching period at Visit 3 [7 days after the commencement of tooth bleaching, with an acceptable range of 7-9 days] subjects will return to the clinical site and return their used bleaching kit and undergo a review of their diary and current medications and undergo an OST examination. Tooth color and extrinsic tooth stain will be assessed for the same teeth in the same way as at Visit 1. Subjects will then complete the tooth sensitivity questionnaire and the post-whitening questionnaire and scheduled to return for Visit 4 (12 weeks [±1 week] after completion of the peroxide tooth bleaching).

At Visit 4 subjects will return to the clinical site and undergo a review of their diary and current medications and an OST examination. Tooth color and extrinsic tooth stain will be assessed for the same teeth in the same way as at Visit 1. Subjects will then be scheduled to return for Visit 5 (24 weeks [±1 week] after completion of the peroxide tooth bleaching).

At Visit 5 subjects will return to the clinical site and return their study products and undergo a review of their diary and current medications and an OST and OHT examination. Tooth color and extrinsic tooth stain will be assessed for the same teeth in the same way as at Visit 1. Subjects will then exit the study.

Safety and oral tolerability of the study products will be monitored over the duration of the study by review of reported AEs and through Oral Soft Tissue examinations. Medical device incidents will also be monitored for the device in this study which is the study toothbrushes.

Figure 4-1 Schematic of Flow of Key Study Assessments/Procedures



4.2 Scientific Rationale for Study Design

This is a randomized, controlled, single-blind (to the dental examiner(s) and outcome assessors), single-center, 2 treatment group, stratified (clinically diagnosed DH (Y/N)), parallel study in subjects who wish to undergo tooth bleaching treatment. This study has specifically been designed to investigate the efficacy of an experimental dentifrice containing KNO_3), STP and alumina to maintain tooth color and reduce extrinsic dental stain accumulation following peroxide tooth bleaching compared to a regular fluoride dentifrice. Additionally, the ability of the test dentifrice to reduce tooth sensitivity concurrent with peroxide tooth bleaching will be explored.

A parallel group experimental design was selected as subjects would not be expected to repeat peroxide tooth bleaching more than once per year, precluding the use of a cross-over design.

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

A 24 week treatment period is deemed sufficient to observe the anticipated effects in tooth color; a 12 week assessment is included should more rapid clinical effects occur. A regular fluoride dentifrice has been selected as the reference dentifrice. For the purposes of this study, it was deemed more relevant to compare the efficacy of the experimental dentifrice against a typical daily use, fluoride-containing dentifrice (which contains dental abrasive) rather than a placebo with no abrasive cleaning component. This reference dentifrice is representative of a standard family dentifrice commonly available in the country where the study will be performed (USA).

The subjects in this study who have self-reported DH will be clinically evaluated to confirm their DH status. Whilst there are no protocol requirements associated with this assessment, DH is prevalent at 30-50% of the population (West, 2023b) and the enrollment to this study is expected to mirror this. It is anticipated that the test dentifrice, will be marketed for consumers with DH. However, it is anticipated that it will be purchased both by consumers with DH and those without, but who are recommended to use an anti-sensitivity dentifrice prior to, during and post peroxide tooth bleaching. A mixed population of those with clinically-diagnosed DH and those without is therefore appropriate. Subjects will be stratified according to their clinically-diagnosed DH status [DH positive or negative] to ensure a balanced population across treatment groups.

Demography information will be recorded as part of this study, including age, race and gender. In accordance with the United States Food and Drug Administration (US FDA) guidelines (FDA, 2005) the ethnicity of subjects will also be captured.

According to the International Conference on Harmonisation (ICH) guidelines (ICH, Nov 2016), for a study to be classified as truly double-blind, not only does the examiner (and any appropriate member of staff who may be involved in the dispensing of products, analysis of data etc.) need to be blind to the treatment a subject receives, but the products under test must be identical in every way (color, flavor, appearance, packaging). Given the experimental dentifrices and the reference dentifrice will differ in appearance and flavor, the level of blindness for this study is described as ‘examiner blind’. The study will be blinded with respect to the dental examiner(s) and other outcome assessors to ensure there is no bias in the assessments. Study dentifrices will be supplied in overwrapped tubes. The blind will be maintained by staff involved in dispensing, brushing instruction and supervised brushings who will not be involved in any clinical examinations.

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 throughout the study by subject-reported pregnancy status.

Whilst evaluation of tooth color is the primary endpoint in this study, it is believed that surface tooth stain can lead to longer-term increase in tooth color. Measurement of extrinsic dental stain will therefore also be performed using the MacPherson modification (Macpherson et al., 2000) of the Lobene Stain Index (Lobene, 1968)(MLSI).

The clinical measures of tooth color and extrinsic tooth stain used in this study, VITA shade guide and MLSI respectively, 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). LMS and VAS (which in this study are components of the tooth sensitivity questionnaire) have been previously used and validated for measurement of tooth sensitivity in clinical studies evaluating the efficacy of dentifrices (Mason et al., 2019, Heaton et al., 2015, Holland et al., 1997, Gillam et al., 1997, Rocha et al., 2020).

4.3 Justification for Dose

Subjects will brush with their assigned dentifrices twice daily for 2 timed minutes as per the American Dental Association recommendations for effective toothbrushing (ADA, 2022) and the UK National Health Service teeth cleaning guide (NHS, 2019). Additionally this brushing time is consistent with that used in a recently completed study evaluating the test dentifrice (Haleon Clinical Study 300024, 2023).

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 dentifrice 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 he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Healthy volunteers of either sex and any gender, aged 18 – 65 years who wish to have their teeth whitened and meet all the inclusion/exclusion criteria will be recruited.

Sufficient subjects will be screened to randomize approximately 160 to ensure approximately 128 evaluable subjects complete the 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 and has been randomized to treatment group.

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

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

5.2 Inclusion Criteria

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

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is of either sex and any gender who, at the time of screening, is between the ages of 18-65 years, inclusive.
3. Subject is willing and able to comply with scheduled visits, and other study procedures and 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 who is willing and able to undergo at-home tooth bleaching with peroxide-containing treatment unsupervised.
6. Subject with generally good oral health that fulfil all of the following:
    a. Teeth suitable for peroxide bleaching and gradable for tooth color and suitable for MLSI evaluation with no significant defects, calculus, restorations, crowns or veneers that could impact peroxide tooth bleaching performance or study evaluations as judged by the clinical examiner.
    b. Facial surfaces of maxillary anterior 6 teeth (tooth numbers 6-11) [Universal tooth number system] with mean Vita Bleachedguide shade ≥13 at Visits 1 and 2
    c. Having no lesions of the teeth or oral cavity that could interfere with the study evaluations.

d. Having a minimum of 16 natural teeth.

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will not be eligible for enrolment into 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, a Haleon employee 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 60 days prior to study entry and/or during study participation.
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 investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
4. Subject who is pregnant (self-reported) or intending to become pregnant over the duration of the study or who is breastfeeding.
5. Subject with known or suspected intolerance or hypersensitivity to the study materials [including the peroxide bleaching treatment] (or closely related compounds) or any of their stated ingredients.
6. Subject who, in the opinion of the investigator or medically qualified designee, has a condition that would impact on their safety or wellbeing or affect their ability to understand and follow study procedures and requirements or who should not participate in the study for other reasons.
7. Subject unwilling or unable to comply with the Lifestyle Considerations described in this protocol.
8. Subject with a recent history (within the last year) of alcohol or other substance abuse.
9. Subject with gross periodontal disease or who has had treatment for periodontal disease (including surgery) within 12 months of Screening or who has had scaling or root planning within 3 months of Screening.
10. Subject who has had a peroxide tooth bleaching procedure (either professionally-dispensed or at-home [including peroxide-containing dentifrices]) within 12 months of Screening.
11. Subject who has had a dental prophylaxis within 8 weeks of screening.
12. Subject who has used tooth desensitizing treatment (eg dentifrice, mouthwash etc) within 2 weeks of screening.
13. Subject with a fixed or removable partial prosthesis, multiple dental implants or orthodontic braces/bands or fixed retainer or togue/lip piercing which, in the opinion of the investigator, could impact study outcomes.
14. During the study period, subject taking **daily doses** of medication/treatments which, in the opinion of the investigator or medically qualified designee, could interfere with their perception of tooth sensitivity (examples of such medications include analgesics, anticonvulsants, antihistamines that cause marked or moderate sedation, sedatives,

tranquillizers, antidepressants, mood-altering and anti-inflammatory drugs). Subjects will be allowed to use analgesics *ad hoc* to manage pain.

15. Subject who has tooth abnormalities such as cracking or gross caries lesions that may, in the opinion of the investigator, impact the ability to evaluate tooth sensitivity.
16. Subject who has previously been enrolled in this study.

5.4 Randomization Criteria

Subjects who have satisfied all subject selection criteria will be stratified according to their Clinical diagnosis of DH [Clinicall diagnosed DH (Y/N) (as defined in section 9.1.3)] and randomized to study treatment. Whilst there are no protocol requirements associated with this assessment, DH is prevalent at 30-50% of the population (West, 2023b) and the enrollment to this study is expected to mirror this.

5.5 Lifestyle Considerations

5.5.1 Oral Hygiene Restrictions

- **On Study Days, Visits 1-5:** Subjects will abstain from all oral hygiene procedures (including tooth brushing) for at **least 6 hours** prior to and during their clinical assessment visits.
- **From Visit 1 to end of study:** Subjects should not use any other oral care products (for example, toothpastes, toothbrushes, oral rinses, tongue cleaners, whitening/bleaching products, interdental cleaning products) other than those provided during the study.
- **From Visit 1 to end of study:** Subjects should not use any product intended for treating or caring for sensitive teeth (including herbal remedies) other than those provided during the study.

5.5.2 Dietary Restrictions

On study days, for the Duration of the Study: Visit 1-5

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 assessment visits.

5.5.3 Use of Cosmetics

On study days, Visit 1-5

Subjects will refrain from applying lipstick or colored lip coverings prior to and during their clinical assessment visits.

5.5.4 Medication and Treatment Restrictions

- **From Visit 1 to end of study:** 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.
- **From Visit 3 to end of study:** Subjects must 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.

- **From Visit 2 to end of study:** Subjects who use ***ad hoc*** medication to relieve tooth sensitivity should note this in their tooth sensitivity questionnaire.

5.5.5 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 include demography, screen failure details (e.g. withdrawal of consent), eligibility criteria, any protocol deviations and any adverse events or incidents as applicable.

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

5.7 Sponsor's Qualified Medical Personnel

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

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

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects will be provided with a contact card. The contact card will provide, as a minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 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 USA.

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 Bleachedguide (or equivalent) for measurement of tooth color, the MLSI (or similar) for measurement of dental stain and the evaporative (air) stimulus measured by Schiff sensitivity score for determination of DH status.

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and Haleon policy, study intervention is defined as any investigational intervention(s), marketed

product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

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

6.1 Investigational/Study Product Supplies

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

Table 6-1 Investigational/Study Product Supplies

	Test Dentifrice	Reference Dentifrice
Product Description	Dentifrice containing 5% w/w KNO_3, 1% alumina, 5% STP and 1150ppm fluoride as sodium fluoride	Dentifrice containing 1150ppm fluoride as sodium fluoride
Product Name	Experimental Dentifrice	Aquafresh Cavity Protection
Product Master Formulation Code	CCI [redacted]	Commercial product – US marketplace (CCI [redacted])
Pack Design	Carton of overwrapped tubes	Carton of overwrapped tubes
Dispensing Details	Dentifrice kit dispensed at Screening Visit	Dentifrice kit dispensed at Screening Visit
Return Requirements	All used/unused samples to be returned	All used/unused samples to be returned
Dose/Application	Subjects will dose the toothbrush provided with a strip of dentifrice (a full brush head) on each brushing occasion. Subjects will brush for two timed minutes twice daily (morning and evening); subjects will be permitted to rinse with water post-brushing.	
Route of Administration	Oral topical	

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

Table 6-2 Sundry Items

Sundry Items to be supplied:

Item	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
parodontax Complete Protection Soft-Bristled Toothbrush (US market)	Haleon	Twin Pack	Two packs at Screening (visit 1) Subjects will be instructed by site staff to start using a new brush at V3 and at V4.	Destroy at site using site disposal procedures	Return
Countdown Timer	Haleon	Individual commercial pack	At Screening (visit 1)	To be kept by subject or disposed of.	Return
Opalescence Go 15% Peroxide Kit [USA Marketplace]	Study Site	Commercial pack	First use at site, dispensed for at-home use at visit 2	Return	Return
Petroleum Jelly	Haleon	Commercial pack	First use at site, dispensed for at-home use at visit 2	Destroy at site using site disposal procedures	Return
Dental Floss	Haleon	Commercial pack	First use at site, dispensed for at-home use at Visit 2	Destroy at site using site disposal procedures	Return

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

The toothbrushes are marketed medical devices and will be used in accordance with the label instructions.

6.1.1.1 Application of the Peroxide Bleaching

The peroxide tooth bleaching procedure should be performed at-home (except for the first application which will be performed under supervision at the study site) following manufacturer instructions. Subjects should brush their teeth with the study dentifrice and floss their teeth prior to applying the peroxide gel. Subjects will apply the supplied gel-containing tray to their maxillary teeth per the product instructions. Subjects should apply their peroxide-containing

tray to their maxillary teeth once per day for 15 timed minutes immediately after either their morning or evening tooth brushing with their assigned study dentifrice. Subjects should attempt to perform the tooth bleaching at approximately the same time of day wherever possible. Subjects should perform peroxide bleaching for 7 consecutive days. Should subjects experience gum sensitivity/irritation due to the peroxide, they should apply a thin layer of the supplied petroleum jelly to the affected gum tissue prior to applying the peroxide, taking care not to contact the teeth with the petroleum jelly.

Subjects should note every bleaching event in their diaries to help monitor compliance.

6.1.2 Medical Devices

The definitions and procedures detailed are in accordance with ISO 14155.

- The Haleon manufactured medical devices (provided for use in this study) are the study toothbrushes.
- All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 10.10) and appropriately managed by the sponsor.

6.1.3 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 dentifrice will be manufactured and filled into plain white tubes by the sponsor; the reference dentifrice will be supplied in its commercial pack and sourced from the market the study is performed in (USA). 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 24-week treatment period. Sundry items (including the peroxide bleaching treatment) 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.

6.1.4 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 and peroxide bleaching treatment 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 interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the authorized site staff only.

Subjects will be instructed to self-administer their assigned study dentifrice and tooth bleaching treatment according to the usage instructions provided to the subject. Additionally, subjects will undergo supervised brushing with dentifrice at Visit 1 and 2 and application of the tooth bleaching treatment at Visit 2 to ensure compliance with application instructions. The reference dentifrice and the tooth bleaching treatment are commercially available, and the application instructions described in this protocol are consistent with their label instructions. The experimental dentifrice is intended for commercialization and the application instructions here are consistent with the intended label instructions.

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

- Staff will demonstrate dispensing a full ribbon of dentifrice along the length of the toothbrush head to each randomized subject and supervise their first brushing with study dentifrice (Visit 1&2) and diary completion at the screening visit (Visit 1).
- Staff will demonstrate and aid subjects for their first application of the peroxide tooth bleaching procedure at Visit 2.
- staff will review diary completion and subject's study products at Visits 2-5.

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

Instructions on usage of the study products are detailed in the Appendices.

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 area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and the product label.

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

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

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

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

6.4 Investigational/Study Product Accountability

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

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

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the

investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

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

Subjects should return their used and unused study products to the clinical site at Visit 5 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.

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 Haleon (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study (including empty containers), will be returned for destruction to the Haleon 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 Haleon during the study in time for study close out visit.

6.5 Blinding and Allocation/Randomization

All subjects will be centrally randomized to one of the two study products using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided. Study products will be dispensed according to the instruction received through the IRT at the appropriate study visits.

Returned study products should not be re-dispensed to any subject.

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

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

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

Prior to randomization, subjects will be stratified on their DH 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 screening visit (Visit 1) and additionally at 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. Subjects will be provided with a diary at Screening (Visit 1) to record each completed brushing.
- First use of the peroxide tooth bleaching procedure will be carried out under supervision at the study site at Visit 2; study staff will demonstrate the application of the bleaching gel according to manufacturer's instructions. Subjects will be provided with a diary to record each completed tooth bleaching treatment.
- 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 his or her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

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

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

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

7.2 Lost to Follow up

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

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

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion, which could include OST and OHT examinations.

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

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

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

8 STUDY PROCEDURES

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

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

8.1 Visit 1/Screening

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

The following screening procedures will be completed, in the following order (wherever possible), and the findings recorded in the CRF. To facilitate subject flow, clinical assessments may be recorded on a paper source document and later transcribed into the CRF.

1. Informed Consent.
2. Demographics.
3. Review of medical history (including smoking/tobacco use status) and prior/concomitant medication/treatment.
4. OST and OHT examinations.
5. Assessment of tooth color and extrinsic tooth stain.
6. For subjects with a self-reported history of DH, assessment of DH, including EAR, MGI and tooth mobility assessments and Evaporative (Air) Sensitivity Assessment (Schiff sensitivity score).
7. Review of the inclusion/exclusion criteria.
8. Subject eligibility assessed. Subjects who do not meet the criteria for participation will be discontinued.
9. Qualifying subjects will be stratified and randomized to treatment groups.
10. Subject completes the tooth sensitivity questionnaire at site.
11. Study products will be dispensed, including sundry items, and diary.
12. 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.
13. AEs and incidents recorded.

8.1.1 Screening Procedures

8.1.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of

the study. An ingredients listing for the study dentifrices and peroxide tooth beaching kit 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, ethnicity and race. Ethnicity and race of subjects will be recorded in accordance with FDA Guidance (US FDA, 2005).

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

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

The clinical examiner(s) will perform the following examinations/assessments.

- OST examination.
- OHT examination.
- Assessment of tooth color and extrinsic tooth stain.
- Clinical assessment of incisors, canines and pre-molars for dentition exclusions, erosion abrasion and attrition (EAR), Modified Gingival Index (MGI) adjacent to the test area only, and clinical mobility to clinically diagnose DH for those subjects with a self-reported history of DH.

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

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

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

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

8.2.1 Visit 2/ start of peroxide tooth bleaching

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

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

1. Changes in concomitant medication or non-drug treatments/procedures will be documented.
2. Spontaneous reporting of AEs 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.
4. Subject undergoes an OST examination.
5. Subject undergoes assessment of tooth color (Vita Shade) and extrinsic tooth stain (MLSI).
6. Subject continuance in the study is assessed. Subjects who do not meet the criteria for participation will be discontinued.
7. Subject completes the tooth sensitivity questionnaire.
8. Subject completes the whitening history questionnaire.
9. Subject undergoes supervised tooth brushing using their study dentifrice. Subject flosses their teeth.

10. Subject is dispensed the peroxide tooth bleaching kit (including petroleum jelly and dental floss) and instructions for at home use.
11. Subject undergoes the first application of the peroxide tooth bleaching under supervision at the study site.
12. AEs and incidents recorded.

8.2.2 Visit 3/ End of tooth bleaching

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

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

1. Changes in concomitant medication or non-drug treatments/procedures will be documented.
2. Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed.
3. Subject will return study products and diary for visual inspection to evaluate product compliance and adherence to protocol.
4. Subject undergoes an OST examination.
5. Subject undergoes assessment of tooth color (Vita Shade) and extrinsic tooth stain (MLSI).
6. Subject completes the tooth sensitivity questionnaire.
7. Subject completes post-whitening questionnaire.
8. AEs and incidents recorded.

8.2.3 Visit 4 /12 weeks post tooth bleaching

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

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

1. Changes in concomitant medication or non-drug treatments/procedures will be documented.
2. Spontaneous reporting of AEs 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.
4. Subject undergoes an OST examination.
5. Subject undergoes assessment of tooth color (Vita Shade) and extrinsic tooth stain (MLSI).
6. AEs and incidents recorded.

8.2.4 Visit 5 /24 weeks post tooth bleaching

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

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

1. Changes in concomitant medication or non-drug treatments/procedures will be documented.
2. Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed.
3. Subject will return study products and diary for visual inspection to evaluate product compliance and adherence to protocol.
4. Subject undergoes OST and OHT examinations.
5. Subject undergoes assessment of tooth color (Vita Shade) and extrinsic tooth stain (MLSI).
6. AEs and incidents recorded.
7. Study conclusion.

8.2.5 Study Procedures

8.2.5.1 Diary Review

The diary should be reviewed at every visit by the investigator, or suitably qualified designee, with the subject. Any subject comment captured in the diary which is considered an AE 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.

8.2.5.2 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 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 Haleon 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.

8.2.5.3 Follow-up Visit / Phone Call

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

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required examinations and assessments are completed as described. However, it is anticipated that there may be circumstances outside the control of the investigator that may make it unfeasible to complete an assessment. In these

cases, the investigator must take all steps necessary to ensure the safety and wellbeing of the subject. When a protocol required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that they have taken to ensure the required processes are adhered to as soon as possible. The sponsor must be informed of any missed assessments in a timely manner. The outcome of all examinations and assessments should be recorded in the CRF. To facilitate subject flow, clinical assessments may be recorded on a paper source document and later transcribed into the CRF.

9.1 Screening Assessments

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

9.1.1 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.

9.1.3 Dentine Hypersensitivity Assessments

At Visit 1, prior to randomization, subjects with a self-reported history of DH should undergo further clinical assessments. For a subject to be clinically-diagnosed as having DH they must have **at least one of the teeth that will be peroxide bleached** to meet all of the following inclusion criteria and none of the following exclusion criteria:

Inclusion criteria for a tooth to be considered to have DH:

- Tooth with exposed dentine due to facial/cervical erosion, abrasion or gingival recession (EAR).
- Tooth with an MGI score=0 directly adjacent to the affected dentine.
- Tooth with a clinical tooth mobility score=0.
- Tooth demonstrating a positive response to the evaporative (air) sensitivity assessment [defined as those with a Schiff sensitivity score ≥2].

Exclusion criteria for a tooth to be considered to have DH:

- Tooth with evidence of current or recent caries or reported treatment of decay.
- Tooth with deep, defective or facial restorations, full crowns or veneers.
- Tooth with contributing aetiologies other than erosion, abrasion or recession to exposed dentine.

9.1.3.1 Erosion, Abrasion and Recession (EAR)

Teeth that will be peroxide bleached and that exhibit none of the dentition exclusion criteria for tooth DH (Section 9.1.3), will be examined for signs of cervical EAR (Addy et al., 2000). Only

teeth that demonstrate signs of EAR will be assessed further for DH.

9.1.3.2 Modified Gingival Index (MGI)

The MGI is a non-invasive visual assessment of gingival health (Lobene, 1986). MGI will be assessed for teeth that will be peroxide bleached and that exhibit none of the dentition exclusion criteria for tooth DH (Section 9.1.3) and which show signs of EAR. MGI should be scored for the facial gingiva, directly adjacent to the area of exposed dentine only, as described below.

Score	Description
0	Absence of inflammation
1	Mild inflammation; slight change in colour, little change in colour; little change in texture of any portion of the marginal or papillary gingival unit.
2	Mild inflammation; criteria as above but involving the entire marginal or papillar gingival unit.
3	Moderate inflammation; glazing, redness, oedema, and/or hypertrophy of the marginal or papillary gingival unit.
4	Severe inflammation; marked redness, oedema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

9.1.3.3 Clinical Mobility

Clinical tooth mobility will be assessed for teeth that will be peroxide bleached and that exhibit none of the dentition exclusion criteria for tooth DH (Section 9.1.3), which show signs of EAR and which have an MGI=0 directly adjacent to the exposed dentine only, using a modification of the Miller Index (Laster et al., 1975) as described below.

Degree	Description
0	No movement or mobility of the crown of the tooth < 0.2mm in a horizontal direction
1	Mobility of the crown of the tooth 0.2 - 1mm in a horizontal direction
2	Mobility of the crown of the tooth exceeding 1mm in a horizontal direction
3	Mobility of the crown of the tooth in a vertical direction as well.

9.1.3.4 Evaporative (Air) Sensitivity Assessment (Schiff sensitivity score)

The Evaporative (air) Sensitivity Assessment will be assessed for teeth that will be peroxide bleached and that exhibit none of the dentition exclusion criteria for tooth DH (Section 9.1.3), which show signs of EAR, which have an MGI=0 directly adjacent to the exposed dentine and which have clinical mobility = 0 only.

The examiner will apply an evaporative air stimulus by directing a maximum one second application of air from a dental air syringe to the exposed dentine surface from a distance of approximately 1 cm. The subject response will be scored using the Schiff Sensitivity scale immediately following the evaporative air stimulus. The Schiff Sensitivity scale is an examiner based index (Schiff et al., 1994) focusing on a combination of specific, observable, physical, behavioural and verbal responses from the subject as a result of the stimulation of exposed dentine, rather than solely an oral request from the subject to discontinue stimulation and may facilitate discrimination. The examiner will indicate the subject's response to the evaporative

air stimulus, after the stimulation of each individual tooth, using the Schiff Sensitivity scale as below.

Score	Subject Response
0	Subject does not respond to air stimulation
1	Subject responds to air stimulus but does not request discontinuation of stimulus
2	Subject responds to air stimulus and requests discontinuation or moves from stimulus
3	Subject responds to stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus

9.1.4 Assessment of Tooth Color and Extrinsic Tooth Stain

Tooth color will be assessed using the VITA Bleachedguide 3D Master shade guide as described in Section 9.2.2. Extrinsic tooth stain will be assessed using the MLSI as described in Section 9.2.1.

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 Tooth Color Assessment

Tooth color of the facial surfaces of the six anterior maxillary teeth (tooth numbers 6-11) [Universal tooth numbering system] 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 3D Master Shade guide will be used for all assessments throughout the study wherever possible.

Subjects should have abstained from all oral hygiene procedures (including tooth brushing) for at **least 6 hours** prior to and during this assessment. Additionally, subjects should have refrained from eating or drinking for at **least 2 hours** prior to and during this assessment, with the exception of small amounts of water required for taking medication.

9.2.1.1 Repeatability of the Tooth Color Assessment

To assess the repeatability of the tooth color assessments, replicate examinations will be performed by the same clinical examiner using the same VITA Bleachedguide 3D Master shade guide. Approximately ten subjects will be randomly selected for repeat shade assessments at each assessment time point (Visits 1-5), a total of 50 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.

9.2.2 Macpherson Modification of the Lobene Stain Index (MLSI)

Extrinsic dental stain will be assessed on the facial surfaces of the 6 maxillary anterior teeth (6-11) [Universal tooth numbering system] at Visits 1-5), using the MacPherson modification (Macpherson et al., 2000) of the Lobene stain index (Lobene, 1968) (MLSI).

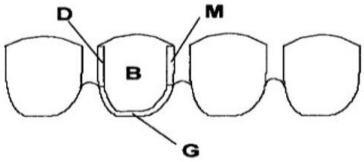
All assessments should be performed by a single, trained clinical examiner, with consistent lighting to standardize of the assessment conditions. If required, the examiner will brush the subject's anterior teeth with a wetted toothbrush and/or floss to remove any debris which could impact the accuracy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

Subjects should have abstained from all oral hygiene procedures (including tooth brushing) for at **least 6 hours** prior to and during this assessment. Additionally, subjects should have refrained from eating or drinking for at **least 2 hours** prior to and during this assessment, with the exception of small amounts of water required for taking medication.

9.2.2.1 Repeatability of the MLSI Assessment

To assess the repeatability of the MLSI assessments, replicate examinations will be performed by the same clinical examiner. Approximately ten subjects will be randomly selected for repeat MLSI assessments at each assessment time point (Visits 1-5), a total of approximately 50 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.

9.2.3 Tooth Sensitivity Questionnaire

The tooth sensitivity questionnaire (see Appendix 15.4) will be completed by the subject at the study site at Visits 1-3, to evaluate the overall tooth sensitivity experienced by the subject over the previous week. Thus, the questionnaire should record the subject's overall experience of the preceding 7 days. The questionnaire will be completed at the study site without reference to other subjects and will be checked for completeness prior to the subject leaving the site. Study personnel should demonstrate to subjects the correct completion of this questionnaire prior to administering.

Subjects will indicate whether they have felt tooth sensitivity during the previous week. Those who indicate they have not felt tooth sensitivity will not be required to complete the rest of the questionnaire. Subjects who indicate they did feel tooth sensitivity will complete the remainder of the questionnaire comprising the VAS, LMS and Bothersomeness numerical rating scale (NRS).

Subjects will rate their overall tooth sensitivity using a 100mm VAS with end anchors of ' No Sensitivity' to 'Extreme Sensitivity'.

The LMS apply psychophysical procedures (magnitude estimation and cross-modality magnitude matching) to condition specific descriptive words relevant to the subject's response (Gracely et al., 1978). The descriptive words are then aligned along a Visual Analogue Scale (VAS) at distances that reflect the psychological distances between words. These scales have been piloted and validated in a previously reported dentine hypersensitivity trials (Heaton et al.,

2013, Mason et al., 2019). The LMS will be used to rate the intensity, duration, tolerability and descriptive quality of their tooth sensitivity using the four individual 100 millimetre (mm) LMS.

The study staff will measure the line segment marked-off in mm from bottom to top along the line (for LMS) and from left to right (for the VAS) and record this in the eCRF.

The subject will also complete a NRS for bothersomeness for which the subject should circle an appropriate number on the scale.

All questionnaire data shall be recorded in the CRF upon return of completed questionnaire.

9.2.4 Whitening History and Post-Whitening Questionnaires

Subjects will be dispensed the questionnaires to complete at Visits 2&3. Subjects should complete these individually at the study site without reference to other subjects. Site staff should ensure the questionnaires are fully completed before the subject leaves the site.

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 or other disease 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 he/she considers the event to be reasonably related to the study product or study participation, the investigator must promptly notify the sponsor.

10.4 Reporting Procedures

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

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

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

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

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

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

It is **not** acceptable for the investigator (or medically qualified designee) to send photocopies of the subject's medical records to Haleon 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 Haleon. 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 Haleon.

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 Haleon 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 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 study manager.

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

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

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

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

10.5.2 Assessment of Causality

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

For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE CRF page and the SAE form (subject to the classification of the AE). The investigator will also document in the medical notes that he/she has reviewed the AE and assessed causality, where applicable.

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

The investigator will use clinical judgment to determine the relationship and will also consult the Safety Statement and Product Information for marketed products, in the determination of

his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

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

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

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

10.6 Follow-up of AEs and SAEs

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

All AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by Haleon 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 Haleon 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 Haleon by emailing the information to the Case Management Group mailbox at Haleon PPD), with copy to the appropriate Study Manager.

The investigator will submit any updated SAE data to Haleon 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

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

Haleon 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 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 Haleon PPD, with copy to the appropriate 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 subject who becomes pregnant while participating will be withdrawn from the study.

10.10 Medical Device Incidents

The definitions and procedures detailed are in accordance with ISO 14155.

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

Medical devices are being provided by Haleon for use in this study; the medical device in this study is the study 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 his/her state of health.

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

It is sufficient that:

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

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

Examples of incidents:

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

10.11 Reporting of Incidents and Malfunctions

All incidents must be reported to Haleon **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 Haleon. 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 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 study manager.

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

- Notify Haleon 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 Haleon, 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 Haleon 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 Haleon to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

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

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

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

11.2 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.

Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using an internal 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 Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

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

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

11.3 Processing Patient Reported Outcomes

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

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

To protect the privacy of subjects, no Personal Information (PI) (including the subject's name or initials or birth date) is to be recorded on any PRO/ePRO/IoMT Devices Data that will be forwarded to Haleon or Third-Party Vendor.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

There were no previous directly comparable studies that have evaluated the effect of a dentifrice on maintaining tooth whiteness after peroxide bleaching upon which to base an estimate of sample size. However, based on a previous study evaluating the tooth whitening abilities of the test dentifrice (Haleon Clinical Study 300024, 2023), a mean change (SD) of VITA scores of 1 (±2) was assumed. Sufficient individuals will be screened to enroll approximately 160 subjects (approximately 80 per group) assuming an estimated 20% dropout rate; approximately 128 completed subjects (approximately 64 per group) are deemed sufficient to detect a difference between the Test and Reference Dentifrices at 24 weeks with 80% power,

12.2 Populations for Analysis

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

12.3 Statistical Analyses

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

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

12.3.1 Primary Analysis

The primary efficacy variable is mean Vita Bleachedguide shade at 24 weeks after tooth bleaching has completed, calculated at the subject level as the average Vita Bleachedguide shade over all sites assessed. The primary comparison will be the test dentifrice vs. the reference dentifrice. As there is only a single primary objective, no adjustment for multiple comparisons is required.

Mean Vita Bleached guide shade will be analyzed using a repeated measures ANOVA model with treatment group and time point as factors, and treatment group by time point as interaction. The adjusted mean treatment difference at 24 weeks will be obtained from the model and presented, along with 95% confidence intervals (CIs) and p-values. All p-values presented will be two-sided and assessed at the 5% significance level.

The assumption of normality and homogeneity of variance in the ANOVA will be investigated. In case of violation of these assumptions, a suitable nonparametric test will be performed; inferences drawn from non-parametric analysis will be considered as confirmatory results.

Summary statistics including mean, SD, standard error (SE), median, minimum, maximum will be provided by visit and randomized treatment group. Raw means and SE will also be plotted over time by treatment group.

12.3.2 Secondary Analyses

The secondary efficacy variables are as follows:

Mean Vita Shade score at 12 weeks

MLSI score at 12 and 24 weeks:

- Mean total MLSI (Area x Intensity)
- Mean MLSI (AxI) for gingival sites
- Mean MLSI (AxI) for interproximal sites)
- Mean MLSI (AxI) for body sites
- Mean total MLSI Area
- Mean Total MLSI Intensity

Secondary endpoints will be analyzed using the same model as used in the primary analysis. The comparisons of interest will be the test dentifrice vs. the reference dentifrice. Adjusted mean treatment differences will be provided, along with p-values and 95% CIs.

Summary statistics including mean, SD, standard error (SE), median, minimum, maximum will be provided by visit and randomized treatment group. Raw means and SE will also be plotted over time by treatment group. Summary statistics of the between-treatment results at each time point will also be obtained and tabulated.

12.3.3 Exploratory Analysis

Tooth sensitivity questionnaire

For the exploratory endpoints listed below, the mean scores of the responses to the sensitivity questionnaire scores will be summarized for each time point; screening (Visit 1), prior to the start of tooth bleaching (Visit 2) and at the completion of tooth bleaching (Visit 3) and analyzed.

- Visual analogue scale
- Labelled Magnitude scales
- Bothersomeness score

These analyses will be performed for the mITT population and by strata group (clinically diagnosed DH (Y/N) (where applicable) at screening.

Additionally, the following data from the questionnaires will be presented with summary statistics.

- Number of subjects who experienced tooth sensitivity by treatment group and stratum (Clinically-diagnosed DH [Y/N])

Whitening History Questionnaire

The data from this questionnaire will be presented with summary statistics.

Post-Whitening Questionnaire

The data from this questionnaire will be presented with summary statistics only by treatment group.

Tooth Whitening History Questionnaire

The data from this questionnaire will be presented with summary statistics.

Change in VITA shade from pre-to post to bleaching

The mean Vita shade will be summarized for prior to the start of tooth bleaching (Visit 2) and at the completion of tooth bleaching (Visit 3) and analyzed. An Analysis of Covariance (ANCOVA) model will be applied to analyze the Change from pre-to-post bleaching treatment in the mean VITA-Shade color score with study product as a fixed effect and the mean VITA-Shade color score prior to the start of tooth bleaching fitted as a covariate. The least square means for each study product will be presented along with the pairwise differences.

The assumption of normality and homogeneity of variance in will be investigated. In case of violation of these assumptions, a suitable non-parametric test will be performed, and results will be provided to support the parametric results.

Additional details of the proposed statistical analysis of the exploratory endpoints will be documented in the statistical analysis plan (SAP).

12.3.4 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.

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.

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.

12.3.5 Other Analyses

The repeat tooth 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.

12.3.6 Exclusion of Data from Analysis

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

12.3.7 Demographic and Baseline Characteristics

Demographic and randomized stratification data will be summarized descriptively.

12.3.8 Study Product Compliance

12.3.8.1 Study Product Compliance

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

12.3.8.2 Prior and Concomitant Medications

Prior and Concomitant Medications will be listed. Concomitant medications that have been taken to alleviate tooth sensitivity/pain will be summarized and listed separately.

12.3.8.3 Other Therapy

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

12.3.9 Handling of Dropouts and Missing Data

The use of ANOVA 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. Sensitivity analyses may be added to the SAP prior to unblinding in case of high drop-out rates and/or exclusion from PP population.

12.3.10 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 Haleon procedures, Haleon 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 Haleon 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.

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

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

The extent and nature of monitoring will be described in a written monitoring plan on file at Haleon. 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, Haleon 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 Haleon or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Haleon or its agents to prepare the study site for the inspection and will allow Haleon or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply copies of the inspection finding to Haleon or its agent. Before response submission to the regulatory authority, the investigator will provide Haleon or its agents with an opportunity to review and comment on responses to any such findings.

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent 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 Haleon 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 Haleon 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), guidelines for GCP (Council for International Organizations of Medical Sciences, 2016, ICH, 1996), 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

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 Haleon and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Haleon 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, Haleon 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.

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

13.3.4 Subject Recruitment

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

generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

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

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

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

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

In addition, the investigator will inform Haleon 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 Haleon processes.

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

13.5 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Haleon site or other mutually-agreeable location.

Haleon 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 Haleon 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 Haleon 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 Haleon, 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 Haleon, 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, Haleon standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between Haleon and the investigator. The investigator must notify Haleon 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, or study product safety problems, or at the discretion of Haleon. In addition, Haleon retains the right to discontinue development of potassium nitrate dentifrices at any time.

If a study is prematurely terminated, Haleon 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 Haleon, all study materials must be collected and all CRF's completed to the greatest extent possible. Where required by the applicable regulatory requirements, Haleon should inform the regulatory authority(ies) and the investigator should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.

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

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

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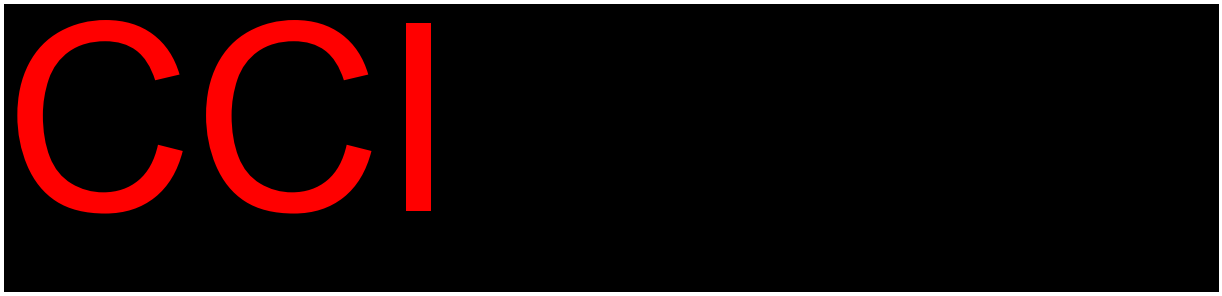

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15 APPENDICIES

15.1 ABBREVIATIONS

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

AE	adverse event
ANOVA	analysis of variance
BDR	blinded data review
CI	confidence interval
CRF	case report form
DH	Dentine Hypersensitivity

EAR	Erosion, Abrasion or Recession
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IRB	institutional review board
LSLV	last subject last visit
MedDRA	medical Dictionary for Regulatory Activities
MGI	Modified Gingival Index
MLSI	Modified Lobene Stain Index
MMRM	Mixed model with repeated measures
N/A	not applicable
PI	principal investigator
SS	safety statement
USA	United States of America

15.2 Study Product Usage Instructions Sheet

INSTRUCTIONS FOR PRODUCT USE

Brush your teeth 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, toothbrush and tooth bleaching treatment to all study visits.

Peroxide bleaching usage

On days where the study staff have indicated you should use your peroxide tooth bleaching kit after **either** your morning or evening toothbrushing:

- Having brushed your teeth with the supplied toothpaste, floss your teeth. Use the peroxide bleaching gel according to the supplied manufacturer's instructions. You should use the peroxide once-per-day for a total of 7 days. If possible, try to perform your tooth bleaching at roughly the same time each day (morning or evening after your tooth brushing). You should bleach your teeth for 15 minutes (please use the supplied timer). Should you experience any gum soreness or irritation please apply a thin smear of the supplied petroleum jelly to your gums prior to wearing your tray. Try to avoid getting the petroleum jelly in contact with your teeth.
- Record each use of the peroxide bleaching treatment on the diary card. Note any changes to these procedures and reasons for changes (e.g. missed bleaching, only bleached for 10 minutes etc) in the 'Comments' column.

15.3 Tooth Sensitivity Questionnaire (EXAMPLE)

Subject # Date:

When completing this form please consider your experience over the last week

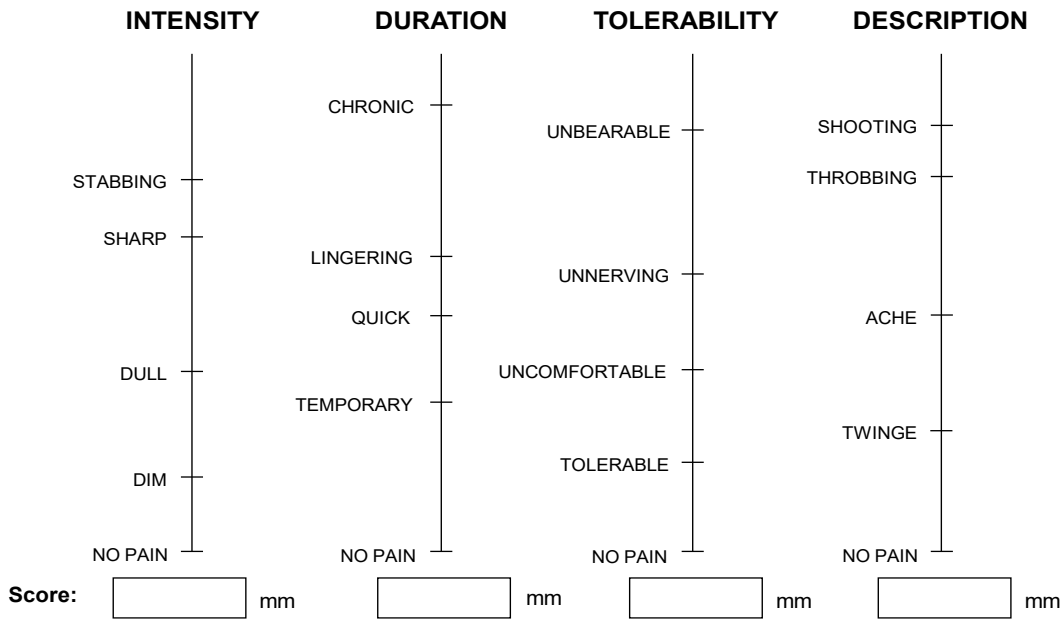
Have your teeth been sensitive ? Y/N **If NO do not complete any further questions.**

Please make a single vertical mark at the point on the line which represents the degree of overall tooth sensitivity (eg twinges, pain and other sensations in your teeth) that you have experienced **over the last week**

No Sensitivity _____ Extreme Sensitivity

For Site use only: ☐ **mm** ☐ **Initials**

Please rate the **INTENSITY/DURATION/TOLLERABILITY/DESCRIPTION** of your overall tooth sensitivity (eg twinges, pain and other sensations in your teeth) experienced **over the past week.** Mark the scales below with an **"x"** to indicate the best description of your sensitivity. Remember you can mark anywhere on the line, including between the descriptive words.



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NOT TO SCALE

Scorer initials (site staff):

On a scale of 1 to 10 **how bothered** have you been by any tooth sensitivity (eg twinges, pain, ache or other sensations in your teeth) that you have experienced **over the last week** (please circle your answer)

Not at all Bothered	1	2	3	4	5	6	7	8	9	10	Extremely Bothered

15.4 Whitening History Questionnaire.

To be completed at Visit 2 prior to first tooth whitening application

Have you ever had your teeth professionally whitened?	Yes ☐	No ☐
If you have had tooth whitening treatment previously, how many times?		
If you previously had your teeth whitened approximately how long ago was your last whitening treatment?		

15.5 Post-Whitening Questionnaire.

To be completed at Visit 3 after the completion of the peroxide tooth bleaching.

Please tick the boxes that best answers the statements:

	Strongly Agree	Agree	Agree a Little	Neither Agree nor Disagree	Disagree a Little	Disagree	Strongly Disagree
	(7)	(6)	(5)	(4)	(3)	(2)	(1)
1) I am **satisfied** with the results of my tooth whitening.	☐	☐	☐	☐	☐	☐	☐
2) I found it **inconvenient** to switch my toothpaste for this study.	☐	☐	☐	☐	☐	☐	☐
3) I found my teeth to be **painful** during the tooth whitening treatment.	☐	☐	☐	☐	☐	☐	☐
4) I would **recommend** tooth whitening to a friend or relative.	☐	☐	☐	☐	☐	☐	☐
5) I would consider further tooth whitening treatments in the future.	☐	☐	☐	☐	☐	☐	☐
6) I had to change the way I ate or drank certain things during the tooth whitening treatment.	☐	☐	☐	☐	☐	☐	☐
7) Having sensations in my teeth during tooth whitening took **pleasure out of eating and drinking.**	☐	☐	☐	☐	☐	☐	☐
8) Having sensations in my teeth during tooth whitening was **worrying** to me.	☐	☐	☐	☐	☐	☐	☐
9) Having sensations in my teeth during tooth whitening was **unpleasant** for me.	☐	☐	☐	☐	☐	☐	☐

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: PPD GMT+0000

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