CLINICAL PROTOCOL

A Randomized, Controlled Clinical Study Assessing the Effects of a Marketed Dentifrice Compared to a Regular Fluoride Dentifrice and a Positive Control Dentifrice on Tooth Sensitivity While Undergoing Tooth Bleaching

Protocol Number:	300106
Compound/Product Name:	Dentifrice containing NovaMin (5% w/w Calcium Sodium Phosphosilicate)
Phase:	IV

Sponsor Information

Sponsor Name & Legal Registered Address	**Haleon (UK)** Building 5, First Floor, The Heights, Weybridge, Surrey, KT13 0NY.
Sponsor Contact Details	**Haleon** 184 Liberty Corner Road, Warren, NJ, USA

Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
New Version		
Amendment 1	2.0	Change from an expectation that 30-50% of randomized subjects have clinically-confirmed DH to 40-50% of the randomized subjects have to have clinically-confirmed DH. Modification of Exc 6b to allow a min of 11 of the anterior 12 teeth to be allowable from requirement that all 12 be evaluable.
Amendment 2		

New versions incorporate all revisions to date prior to submission to institutional review boards/ethics committees (IRBs/ECs), etc.

Amendments incorporate all revisions to date, including amendments made at the request of 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 principles of Good Clinical Practice guidelines (GCP).
- 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

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1 INTRODUCTION

Tooth bleaching is a widely performed procedure 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 teeth and making them appear whiter.

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, many dentifrices advised by dental professionals to reduce tooth sensitivity whilst patients are undergoing tooth bleaching contain potassium ions, rather than occluding agents, likely because the number of published studies in support of occluding agents are few (Alexandrino et al., 2017, Malik et al., 2016, Shivaprasad et al., 2014). Therefore, conclusions from these published studies are difficult to interpret with any certainty and further studies are needed to demonstrate efficacy of dentifrices for tooth sensitivity reduction whilst patients are undergoing tooth bleaching and inform on potential treatment strategies relevant to dental professionals.

NovaMin (Calcium Sodium Phosphosilicate) is an occluding agent employed in dentifrices indicated for tooth sensitivity relief that is clinically proven to provide relief (Gendreau et al., 2011) by forming a calcium rich layer in and over the surface of exposed dentine following 5 days of twice daily use (Jones et al., 2015). The efficacy of NovaMin has been shown in a number of clinical trials where patients undergoing tooth whitening treatment were excluded (Litkowski and Greenspan, 2010, Narongdej et al., 2010, de Freitas et al., 2021). Given that it is now common practice for many patients to undergo tooth bleaching to achieve whiter teeth, it is of interest to understand if patients can benefit from using NovaMin to provide tooth sensitivity relief whilst undergoing tooth bleaching.

The aim of this exploratory study is to investigate the efficacy of a marketed dentifrice containing 5% NovaMin to reduce tooth sensitivity during and post tooth bleaching compared to a marketed dentifrice containing 5% potassium nitrate (KNO_3) and a marketed regular fluoride-containing dentifrice.

1.1 Background & Study Rationale

This is an exploratory, proof-of-principle study. The study will be a randomized, examiner-blind, single-center, controlled, three arm, parallel group proof-of-principal exploratory study to evaluate tooth sensitivity during and following at-home tooth bleaching. This study will compare the efficacy of a dentifrice containing NovaMin, a dentine tubule occluding agent to a positive control (containing 5% KNO_3) and a standard fluoride-containing reference dentifrice.

The tooth sensitivity benefit associated with the use of NovaMin containing dentifrices (the Test product in this study) is extensive (Gendreau et al., 2011, Arantes et al., 2019, Rajesh et al., 2012, Neuhaus et al., 2013). NovaMin is reported to function by adhering to exposed dentin surfaces, reacting with it to form a mineralized layer that is resistant to acid challenges and is mechanically strong (Burwell et al., 2010). This layer thus occludes patent dentine tubules with a hydroxyapatite-like layer (Earl et al., 2011) and thereby reducing pulpal nerve excitation by preventing the flow of dentinal fluid initiated by thermal/osmotic/tactile stimuli (Addy, 2002). However, the ability of NovaMin to reduce tooth sensitivity whilst patients are

undergoing tooth bleaching is less extensively reported in the literature. In one study on the effect of a dentifrice containing a bioactive glass similar to NovaMin, a statistically significant reduction in tooth sensitivity (evaluated by a VAS) was observed compared to a placebo dentifrice (Bizreh and Milly, 2022)

The ability for calcium-containing bioactive glasses when combined with the peroxide whitening agent to reduce tooth sensitivity whilst patients are undergoing tooth bleaching has been reviewed (Favoreto et al., 2023), concluding that there is a small but positive impact on these agents to reduce tooth sensitivity whilst patients are undergoing tooth bleaching. However, this review specifically excluded any analysis of studies with bioglass-containing dentifrices. The evidence specifically for NovaMin dentifrices is therefore minimal and thus, this study is required to investigate the potential for NovaMin to provide tooth sensitivity relief whilst patients are undergoing tooth bleaching.

The tooth sensitivity benefits of KNO_3 containing dentifrices are well established (Sharma et al., 2012, Hu et al., 2018). Additionally, there is clinical evidence to support the role of potassium ions at reducing tooth sensitivity while patients undergoing tooth bleaching. 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 compared to a standard dentifrice (Haywood et al., 2005). 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 KNO_3 and sodium fluoride 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) lead to the same tooth color at 4 and 24 weeks after bleaching. A separate study by the same authors concluded that a potassium ion-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 KNO_3 / 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 lead 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 [redacted] 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).

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To characterize the subject-perceived sensitivity protection profile of a 5% NovaMin-containing dentifrice, a 5% KNO_3-containing dentifrice and a reference fluoride dentifrice during and for 2 weeks post tooth bleaching.	Daily responses from the tooth sensitivity questionnaire through the study in:- • Visual analogue scale (VAS) • Labelled Magnitude scales (Intensity, Duration. Tolerability, Description) - LMS • Bothersomeness score – NRS • Number of subjects who experience tooth sensitivity • Number of subjects who used analgesics to alleviate tooth sensitivity
Secondary	
To investigate the ability of a 5% NovaMin-containing dentifrice to reduce self-perceived tooth sensitivity as measured by a subject-completed tooth sensitivity questionnaire compared to a 5% KNO_3-containing dentifrice and a reference fluoride dentifrice during tooth bleaching.	Responses from the tooth sensitivity questionnaire completed during tooth bleaching (Visit 2-3) in:- • Mean VAS • Mean LMS • Mean Bothersomeness • % tooth sensitivity-free days • % days analgesics used to alleviate tooth sensitivity
To investigate the ability of a 5% NovaMin-containing dentifrice to reduce self-perceived tooth sensitivity as measured by a subject-completed tooth sensitivity questionnaire compared to a 5% KNO_3-containing-dentifrice and a reference fluoride dentifrice for 2 weeks from the end of tooth bleaching.	Responses from the tooth sensitivity questionnaire completed during the 2 weeks post completion of tooth bleaching (Visit 3-4) in:- • Mean VAS • Mean LMS • Mean Bothersomeness • % tooth sensitivity-free days • % days analgesics used to alleviate tooth sensitivity.
To confirm the tooth whitening efficacy of peroxide tooth bleaching with concurrent, twice daily use of a 5% NovaMin-containing dentifrice, a 5% KNO_3-containing dentifrice and a reference fluoride dentifrice as measured by VITA Bleachedguide 3D Master.	Change in mean VITA shade score from pre- to post-tooth bleaching (Visit 2-3)
Exploratory	
To explore subject's oral-health related quality of life during peroxide tooth bleaching when simultaneously using either a 5% NovaMin-containing dentifrice, a 5% KNO_3-containing dentifrice or a regular fluoride dentifrice.	Change from screening in responses from the Dentine Hypersensitivity Experience Questionnaire (DHEQ) during the tooth bleaching period (Visit 2-3) and for the two weeks post tooth bleaching (Visit 3-4)
To investigate the ability of a 5% NovaMin-containing dentifrice to reduce self-perceived tooth sensitivity as measured by a subject-completed tooth sensitivity questionnaire compared to a 5% KNO_3-containing-dentifrice and a reference dentifrice for 2 weeks from the	Responses from the DHEQ and tooth sensitivity questionnaire during the tooth bleaching period (Visit 2-3) and separately for the 2 weeks post tooth bleaching (Visit 3-4) in:- • Mean VAS

end of tooth bleaching separately for those subjects with and without clinically-confirmed dentine hypersensitivity (DH).	• Mean LMS • Mean Bothersomeness • % tooth sensitivity-free days • % days analgesics used to alleviate tooth sensitivity • Change from screening in DHEQ
To explore subject's experience of peroxide tooth bleaching when simultaneously using either a 5% NovaMin-containing dentifrice, a 5% KNO_3-containing dentifrice or a regular fluoride dentifrice.	Post-whitening questionnaire

No formal success criterion has been defined for this exploratory study; however, if the NovaMin dentifrice provides sensitivity protection during tooth bleaching, it would be expected that subject perceived tooth sensitivity (measured by the subject completed sensitivity questionnaires) for the NovaMin dentifrice would be directionally superior to the reference dentifrice during the study period.

3 STUDY DESIGN

This is a randomized, examiner blind, single-center, controlled, three arm, parallel group, proof-of-principal study to evaluate tooth sensitivity during and following a course of tooth bleaching in subjects with and without clinically-confirmed dentine hypersensitivity. 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 3-1.

Sufficient subjects will be screened to randomize approximately 90 subjects to study treatment (approximately 30 per treatment group).

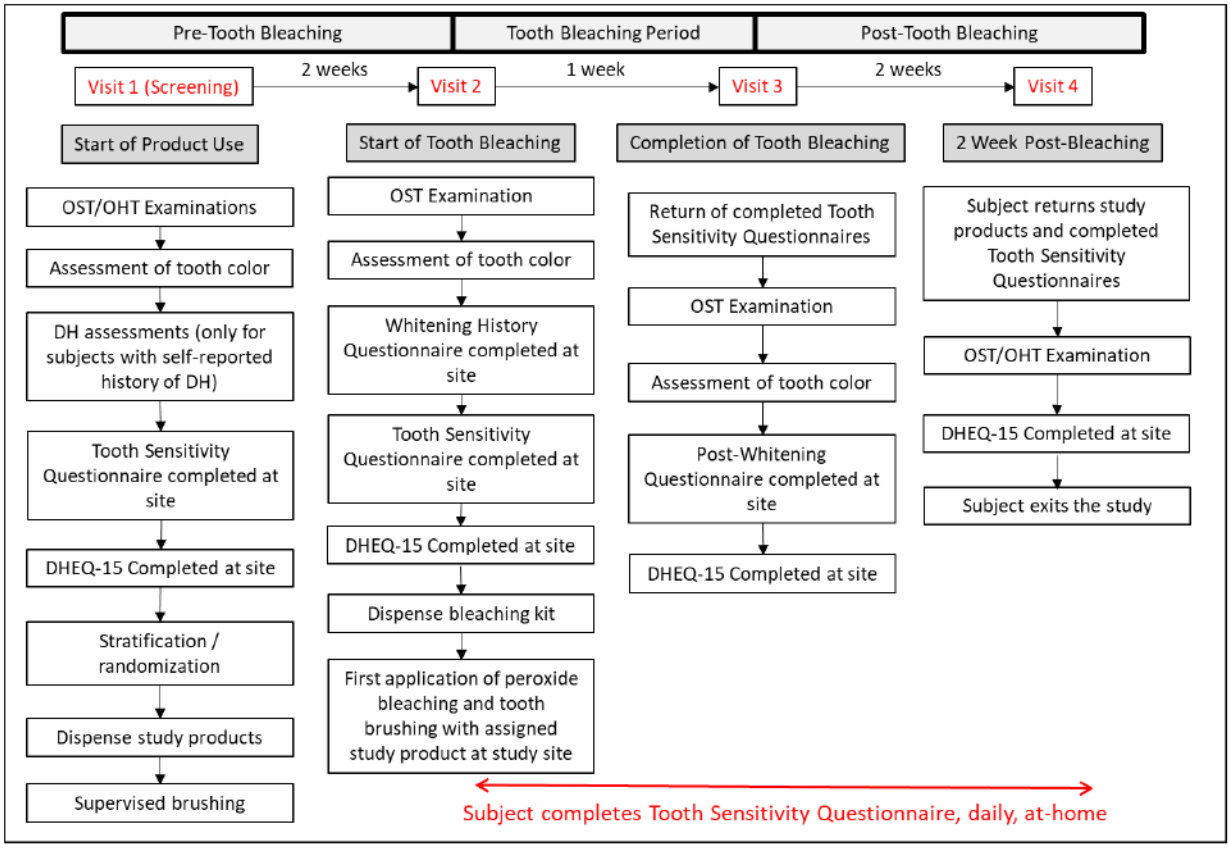
Subjects will attend a Screening visit (Visit 1) where, having obtained their written informed consent, relevant details of their medical history, demography and current medications will be recorded. Subjects will then undergo oral soft tissue (OST) and oral hard tissue (OHT) examinations. The shade (color) of the facial surfaces of the anterior 6 maxillary and mandibular teeth (tooth numbers 6-11 and 22-27) will then be assessed clinically using the VITA Bleachedguide 3D-MASTER (Gómez - Polo et al., 2015).

Those subjects with a self-reported history of dentine hypersensitivity (DH) will be clinically-evaluated to confirm their DH status [Y/N] (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 and will complete the tooth sensitivity questionnaire and the DHEQ-15 after being trained in the correct usage of these questionnaires. Eligible subjects will then be stratified (based upon their DH status [Y/N]) and randomized to treatment group. Subjects will then be dispensed their allocated dentifrice, timer and toothbrush and will undergo a supervised brushing with their allocated dentifrice at the clinical site and scheduled to attend visit 2 (2 weeks ± 2 days after Screening). Subjects will be instructed to use their assigned dentifrice twice daily (morning and evening) for 1 timed minute.

At Visit 2, subjects will undergo a review of their current medications and compliance to treatment and will then undergo an OST examination. The shade (color) of the facial surfaces of the anterior 6 maxillary and mandibular teeth (tooth numbers 6-11 and 22-27) will then be assessed in the same way as at Visit 1.

Figure 3-1 Schematic of Flow of Key Study Assessments/Procedures



Subjects will then complete the whitening history questionnaire, the tooth sensitivity questionnaire and the DHEQ after being given instruction in the completion of these questionnaires. Subjects will be dispensed their at-home Tooth Sensitivity Questionnaires for completion daily. Subjects will then be dispensed the tooth bleaching kits for use at home. Subjects will be instructed in the correct use of the tooth bleaching product, the first application of which will be undertaken at the study site under supervision followed by supervised toothbrushing with their allocated dentifrice. Subjects will be scheduled to return to the study site for Visit 3 (7 ±1 days) and will continue to use their assigned dentifrice twice daily and their tooth bleaching kit once daily per instructions and complete their Tooth Sensitivity Questionnaire at home, daily in the evening (including the evening of Visit 2).

At Visit 3, subjects will undergo a review of their current medications, and product compliance, return completed questionnaires and will then undergo an OST examination. The shade (color) of the facial surfaces of the anterior 6 maxillary and mandibular teeth (tooth numbers 6-11 and 22-27) will then be assessed in the same way as at Visit 1. Subjects will then complete the post whitening questionnaire and the DEHQ. Subjects will be scheduled to return to the study site for Visit 4 (2 weeks±2 days after the completion of peroxide tooth bleaching) and will continue to use their assigned dentifrice twice daily and complete their Tooth Sensitivity Questionnaire daily in the evening.

At Visit 4, subjects will undergo a review of their current medications and product compliance and return their completed Tooth Sensitivity Questionnaire and study products. Subjects will then undergo OST and OHT examinations and complete the DEHQ. Subjects will then exit the study.

Safety and oral tolerability of the study products will be monitored by review of reported AEs and medical device incidents collected at every study visit. Subjects of child-bearing potential shall confirm their pregnancy status at every site visit.

The study statistician and employees of the Sponsor who may influence study outcomes are blinded to the product allocation of subjects. The examiner(s) and outcome assessor(s) will be blinded to the treatment received. To ensure the examiner(s) and outcome assessor(s) remain blinded throughout the study, they are not permitted in the room while product is dispensed. All study products will be overwrapped to conceal any labelling. The dispensing staff will not be involved in any clinical assessments or administration of study questionnaires during the study, although they can be involved in the training of subjects in completing the questionnaires.

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 the possibility of inter-examiner variability.

The Schiff sensitivity scale, LMS, VAS and DHEQ have been previously used and validated for evaluating dentine hypersensitivity in clinical studies evaluating the effectiveness of dentifrices (Mason et al., 2019, Heaton et al., 2015, Holland et al., 1997, Gillam et al., 1997, Rocha et al., 2020, Schiff et al., 1994, Baker et al., 2015).

In this study tooth sensitivity will be evaluated during and for the 2 weeks post the completion of tooth bleaching. It is expected that tooth sensitivity will increase while tooth bleaching is underway and for a period of 1-10 days post bleaching. Evaluation of sensitivity for 2 weeks is therefore considered sufficient time post bleaching to enable tooth sensitivity to subside.

A regular fluoride dentifrice has been selected as reference dentifrice. For the purposes of this exploratory study, it was deemed more relevant to compare the efficacy of the Test dentifrice against a typical daily-use dentifrice rather than a placebo. Additionally, the reference dentifrice is representative of a standard family dentifrice commonly available in the country where the study will be performed (Canada). The positive control dentifrice contains 5% w/w potassium nitrate which have been previously shown to reduce tooth sensitivity experienced whilst patients are undergoing tooth bleaching (Krishnakumar et al., 2022).

The usage regimen of twice daily brushing (morning and evening) will be the same for all subjects and is based on widely recommended oral hygiene practice/typical consumer habit. Study subjects will be required to brush for 1 timed minute with their assigned study dentifrice on each brushing occasion. 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 product labelling for the study dentifrices.

The test dentifrice is indicated for DH. However, it is anticipated that it will be purchased both by consumers with DH and those who do not, but who are recommended (by a dental health care professional) to use a sensitivity dentifrice prior to, during and post peroxide dental bleaching treatment. A mixed population of those with clinically-diagnosed DH and those with no DH symptoms is therefore appropriate. Subjects will be stratified according to their DH status [DH positive or negative (DH positive defined as at least 1 tooth with a Schiff score ≥2)] to ensure a balanced population across treatment groups.

The subjects in this study who have self-diagnosed DH will be clinically evaluated to confirm their DH status. DH is prevalent at 30-50% of the population (West, 2023) and the enrollment

to this study is designed to mirror this with a requirement that approximately 45% [with a window of 40-50%] of the randomized subjects to have clinically confirmed DH.

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, rheology, 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' only. 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.

Whilst the products being tested in this study are not contra-indicated for pregnancy the precautions for the peroxide whitening gel state that "Pregnant or nursing women should not use teeth whitening products". Pregnant females and those intending to become pregnant are thus excluded in this study. Pregnancy status will be verbally confirmed by subjects at each site visit.

4 STUDY POPULATION

4.1 Type and Planned Number of Subjects

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

Sufficient subjects will be screened to randomize approximately 90 subjects (approximately 30 per treatment group) to ensure approximately 88 evaluable subjects complete the study (assuming a 2% dropout rate).

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.

4.2 Inclusion Criteria

An individual must meet all the following inclusion criteria to be eligible to be included into the study:

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is 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 wishes and is able to undergo at-home peroxide tooth bleaching.
6. Subject with generally good oral health that fulfil all of the following:
    a. Having no lesions of the teeth or oral cavity that could interfere with the study evaluations.
    b. At least a total of 11 of the facial surfaces of maxillary and mandibular anterior 6 teeth (tooth numbers 6-11 and 22-27) suitable for peroxide whitening and gradable for VITA Bleachedguide evaluation with no significant defects, calculus, restorations, crowns or veneers that could impact tooth bleaching performance or study evaluations as judged by the clinical examiner.
    c. a minimum of 16 natural teeth.

4.3 Exclusion Criteria

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

1. Subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, 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 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 whitening gel] (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 tooth bleaching procedure (either professionally-dispensed or at-home) within 12 months of Screening.
11. 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.
12. During the period from screening till 2 weeks post completion of tooth bleaching, 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, tranquilizers, antidepressants, mood-altering and anti-inflammatory drugs).
13. Subject who has previously been enrolled in this study.
14. Subject who has used an oral care product indicated for the relief of DH or care of sensitive teeth within 8 weeks of Screening (subjects will be required to verbally confirm the name of their current oral care products to enable site staff to verify the absence of known sensitivity ingredients).
15. Subject who is taking daily doses of a medication which, in the opinion of the investigator or medically qualified designee, is causing xerostomia.
16. Subject who has had dental prophylaxis within 4 weeks of Screening or who requires antibiotic prophylaxis for dental procedures.

4.4 Lifestyle Considerations

4.4.1 Oral Hygiene Restrictions

For the Duration of the Study

- Subjects should not use any oral care products (for example, toothpastes, toothbrushes, oral rinses, tongue cleaners, whitening/bleaching products, interdental cleaning products, tooth sensitivity products) other than those provided during the study.

4.4.2 Dietary and Alcohol, Restrictions

Before a Clinical Assessment Visits: Visits 2-3

- 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.
- Subjects should refrain from excessive alcohol consumption for 24 hours before a study visit.

4.4.3 Use of Cosmetics

- **Visits 1, 2 & 3:** Subjects will refrain from applying lipstick or colored lip coverings prior to and during their clinical tooth color assessment visits.

4.4.4 Tobacco Product Restrictions

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

4.4.5 Medication and Treatment Restrictions

- **Visits 1-4:** Subjects will be asked to delay elective dental treatment (for example, dental prophylaxis) for the duration of the study. They will be required to inform site staff of any emergency treatment they receive during the study.
- **Visits 1-4:** Subjects will be asked to inform site staff of changes to their medications/treatments for the duration of the study. Should a subject commence a course of medication which, in the opinion of the investigator or medically qualified designee, could impact study outcomes, the subject may be withdrawn.
- **Visits 1-4:** Subjects who use *ad hoc,* temporary medication to relieve tooth sensitivity should note this in their tooth sensitivity questionnaire.

5 STUDY PROCEDURES

All study procedures for each visit and the order in which they should be performed (where practically feasible) should be completed in accordance with **Table 5-1 Schedule of Activities.**

Adherence to the study design requirements, including all procedures are essential and required for study conduct. All procedures will be conducted by the Investigator (or suitably qualified designee) and all information and data collected will be documented in the CRF. Clinical examiner(s) involved in the screening, safety and efficacy assessments will be appropriately qualified dental professionals, registered to practice in Canada.

5.1 Schedule of Activities

Table 5-1 Schedule of Activities

Procedure/Assessment	Screening	Study Period				
	Visit 1 (Day 1)		Visit 2 [start of tooth bleaching] (Day 15)		Visit 3 [completion of tooth bleaching] (Day 22)		Visit 4 [2 weeks post completion of tooth bleaching) (Day 36)
Informed consent	X	14 days ±2days		7 days (+1 day)		14 days ±2day	
Medical history	X						
Demographics	X						
Current/prior/concomitant medication review	X		X		X		X
Review of product compliance			X		X		X
Return of completed Tooth Sensitivity Questionnaires					X		X
Return study products							X
OST Examination	X		X		X		X
OHT Examination	X						X
Assessment of tooth color[2]	X		X		X		
DH assessments (EAR, MGI, tooth mobility and evaporative air sensitivity)[6]	X						
Review of inclusion/exclusion criteria	X						
Subject eligibility	X						
Subject completed the Whitening History questionnaire at site			X				
Subject completes tooth sensitivity questionnaire at site	X		X				
Subject completes the Post-Whitening questionnaire at site					X		
Subject completes the DHEQ at site[8]	X		X		X		X
Stratification and Randomization to treatments[7]	X						
Dispense study products	X						
Supervised toothbrushing	X						
Subject dispensed tooth sensitivity questionnaire for at home completion[3]			X				
Subject dispensed tooth bleaching kit for at home use with first application followed by tooth brushing at study site under supervision[4]			X				
Adverse events review[1]	X		X		X		X
Medical device incidents review[1]	X		X		X		X
Study conclusion							X

Abbreviations: OST: Oral Soft Tissue, OHT: Oral Hard Tissue, DH: Dentine Hypersensitivty
Footnotes:

1. Adverse Events (AEs), Serious Adverse Events (SAEs) 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 and medical device incidents will be recorded from first use of a medical device.
2. Tooth color assessed on the facial surfaces of the anterior 6 maxillary and mandibular teeth (tooth numbers 6-11 and 22-27) using the VITA Bleachedguide 3D Master.
3. The tooth sensitivity questionnaire will evaluate overall tooth sensitivity with LMS and VAS assessments. The questionnaire will be completed for the duration of tooth bleaching treatment and for 2 weeks post completion of tooth bleaching.
4. The supplied tooth bleaching kit will be used once under supervision at the study site and then once per day at home (for a total of 7 days) in accordance with the manufacturer's instructions.
5. Female subjects of child-bearing potential only.
6. DH assessments to be administered only to subjects with self-diagnosed DH.
7. Stratification will be based on clinically-diagnosed DH (Y/N) at screening.
8. Sections 1&2 to be completed at V2. Section 1 (questions 7-9 only) and Section 2 to be completed at V3&4. DHEQ to be completed at the study site.

6 STUDY PROCEDURES and ASSESSMENTS

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

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 Schiff Sensitivity scale for determination of tooth sensitivity.

6.1.1 Screening Procedures

6.1.1.1 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, potential hazards of the study and their rights to refuse to enter the study or to withdraw from it at any time.

Informed consent must be obtained before any study-specific activity is performed. Two copies of the informed consent form (ICF) will be signed and dated by the subject, and the subject will be provided with one copy and the other will be kept at site.

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.

6.1.1.2 Demographics

The following demographic information will be collected: year of birth, sex at birth, race and ethnicity.

6.1.1.3 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria as per Section 4.2 and 4.3.

6.1.1.4 Medical History and Prior Medication/Treatment

Relevant medical and/or surgical history (in the last year), including allergies or drug sensitivity and prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 28 days, that began before obtaining informed consent will be recorded as the Medical History/Current Medical Conditions.

6.1.1.5 Subject Eligibility

The investigator and/or medically qualified designee will review inclusion/exclusion criteria, medical history and prior medications to confirm subject eligibility to participate in the study.

6.1.2 Enrolled Subjects and Screen Failures

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

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.

6.2 Screening Assessments

6.2.1 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.

6.2.1.1 Erosion, Abrasion and Recession (EAR)

Teeth that will be peroxide bleached and that exhibit none of the dentition exclusion criteria for tooth DH, 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.

6.2.1.2 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 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 color, little change in color; little change in texture of any portion of the marginal or papillary gingival unit.
2	Mild inflammation; criteria as above but involving the entire marginal or 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.

6.2.1.3 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, 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.

6.2.1.4 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, 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, behavioral 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

6.3 Efficacy Assessments

The following efficacy assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Schedule of Events 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.

6.3.1 Tooth Sensitivity Questionnaire

The tooth sensitivity questionnaire [including VAS and LMS] will be completed by the subject at the screening visit, at Visit 2 (prior to bleaching) to describe the overall tooth sensitivity experienced by the subject on that day. The questionnaire should then be dispensed to the subject to complete at home, in the evening, every day until they complete the study. Thus on the day of Visit 2 the subject should complete 2 questionnaires, one at site and one in the home. Thereafter the subject should complete 1 questionnaire per day at home.

Subjects will indicate whether they have felt tooth sensitivity during the previous 24 hours. 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 CRF.

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.

All questionnaire data shall be recorded in the CRF.

6.3.2 Whitening History and Post-Whitening Questionnaires

Subjects will be dispensed the Whitening History and Post-Whitening Questionnaires to complete at . Subjects should complete these individually at the study site without reference to other subjects. Site staff should ensure the questionnaires are correctly completed before the subject leaves the site.

6.3.3 Dentine Hypersensitivity Experience Questionnaire (DHEQ)

A 'short form' DHEQ-15 will be completed by each eligible subject at Visits 1, 2 (prior to first application of tooth bleaching), 3 and 4.

The DHEQ-15 is divided into two sections - Section 1 asks questions about 'your sensitive teeth and the impact it has on your everyday life'; Section 2 asks questions about 'the ways in which the sensations in your teeth affect you in your daily life' grouped into the following domains.

- Restrictions (Section 2, Q1-3)
- Adaptation (Section 2, Q4-6)
- Social Impact (Section 2, Q7-9)
- Emotional Impact (Section 2, Q10-12)
- Identity (Section 2, Q13-15)

At Visit 1 all questions will be answered - Section 1 (Q1-9) and Section 2 (Q1-15)

At Visits 2, 3 and 4 Section 1 (Q7-9 only) and Section 2 (Q1-15) will be answered.

6.3.4 Tooth Shade (Color) Assessment

Tooth shade (color) of the facial surfaces of the facial surfaces of the anterior 6 maxillary and mandibular teeth (tooth numbers 6-11 and 22-27) 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.

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 color assessment.

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

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

6.4 Safety and Other Assessments

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

6.4.1 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.

6.4.2 Oral Hard Tissue (OHT) Examination

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

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

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

7 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.

7.1 Investigational/Study Product Supplies

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

Table 7-1 Investigational/Study Product Supplies

	Test Dentifrice	Positive Control Dentifrice	Reference Dentifrice
Product Description	Dentifrice containing 5% w/w NovaMin and 1040ppm fluoride as sodium fluoride	Dentifrice containing 5% w/w KNO_3 and 1150ppm fluoride as sodium fluoride	Dentifrice containing 1100ppm fluoride as sodium fluoride
Product Name	Sensodyne Repair and Protect Original Mint	Sensodyne Fresh Mint	Crest Cavity Protection Regular
Product Master Formulation Code	Commercial product – Canada marketplace CCI [redacted]	Commercial product – Canada marketplace CCI [redacted]	Commercial product – Canada marketplace
Pack Design	Carton of overwrapped tubes		
Dispensing Details	Dentifrice kit dispensed at Screening Visit		
Return Requirements	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 one timed minute twice daily (morning and evening); subjects will be permitted to rinse with water post-brushing.		
Route of Administration	Oral topical		

Table 7-2 Sundry Items

Sundry Items to be supplied:

Item	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
Sensodyne Sensitive Care soft bristle toothbrushes [Canada Marketplace]	Haleon	Twin Pack	One pack at Screening (Visit 1)	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 [Canada Marketplace]	Study Site	Commercial pack	First use at site, dispensed for at-home use at Visit 2	Destroy at site using site disposal procedures	Destroy at site using site disposal procedures
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

The toothbrush is a marketed medical device and will be used in accordance with the label instructions.

7.1.1 Application of the Peroxide Bleaching

The peroxide bleaching should be performed at-home (except for the first application which will be performed under supervision at the study site). Subjects should apply their peroxide-containing trays to their teeth (both maxillary and mandibular) once per day for 15 timed minutes in accordance with the manufacturer's instructions. Subjects should then brush their teeth in accordance with the tooth brushing instructions. Subjects should attempt to perform the tooth bleaching at 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.

7.2 Product Supplies Product Storage, Accountability, Returns and Destruction

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

Guidance will be provided to the Investigator and site staff for the receipt, storage and management of products for the duration of the trial by Haleon Clinical Supplies during the Site Initiation Visit and with further instructions included with the shipping documentation.

The site should ensure that the room or area set aside for storage is able to maintain the correct temperature to meet the product label storage conditions, is sufficient to store all products and is secure and access controlled.

Any temperature excursions or discrepancies during transit or whilst study products are stored at site require the affected products to be quarantined and this must be communicated immediately to the Sponsor who will provide documentation to approve further usage.

Use of any of the affected product(s) prior to sponsor approval will be considered a protocol deviation.

Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff. Subjects will be informed on product usage, storage, return and what to do in the event of product loss when they are first dispensed after enrolment.

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.

Detailed instructions for the return of study product/study supplies will be provided by Haleon during the study in time for study close out. Investigational products can only be destroyed at site in agreement with and after approval from the Sponsor.

7.3 Blinding and Randomization

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

Subjects will be randomized to one of the study products with a 1:1:1 allocation ratio using an Interactive Response Technology (IRT). The randomization schedule will use a stratified randomly permuted block design. Stratification will be based on the clinically diagnosis of DH at -Screening (Yes/No). Approximately 45% (40-50%) of randomized subjects should have clinically-confirmed DH.

Study products will be provided to subjects in individual packs (cartons); each carton will contain overwrapped tubes of study product. The carton and tubes of study product will be labelled with the same unique container number. Subjects will be assigned to container numbers associated with cartons containing only their randomized study product using an Interactive Response Technology (IRT); product codes will not be used.

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

This study is described as examiner-blind (the clinical examiner will be blinded to the product received).

To ensure the examiner remains blinded throughout the study, staff involved in the preparation and dispensing of study products will work in a separate area.

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.

7.4 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.

8 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

8.1 Sample Size Determination

No formal sample size calculation was performed for this study. The sample size requirement of approximately 30 randomized subjects per arm is based on feasibility due to the exploratory (proof-of-principal) nature of the study, whilst ensuring an adequate number of subjects to address the study objectives (Kieser and Wassmer, 1996).

8.2 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 VAS score for tooth sensitivity recorded during the tooth-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.

8.2.1 Exclusions of Data from Analysis

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

8.3 Statistical Analyses

This section describes the planned statistical analyses of the study endpoints. Any amendments or clarifications to the details here will be documented in the blinded data review documentation prior to database lock and unblinding.

Categorical variables will be summarized by the number and percentage of subjects with each relevant characteristic in each study product group. Continuous variables will be summarized by mean, standard deviation (SD), standard error (SE), median, minimum and maximum values in each study product group. The number of missing and non-missing data will also be presented.

8.3.1 Primary Endpoint Analysis

The modified Intent-to-Treat (mITT) population will be used for the primary analyses.

The primary endpoints are:

- Daily VAS scores collected through the study
- Daily LMS scores collected through the study
- Daily Bothersomeness scores collected through the study
- Daily number and % of subjects with a tooth sensitivity-free day through the study
- Daily number and % of subjects with analgesic used to alleviate tooth sensitivity through the study

Each endpoint will be summarized descriptively at Screening and Visit 2 (pre-bleaching) as well as by each relative day within the tooth bleaching and post-tooth bleaching period.

Days within the tooth-bleaching period will be relative to the Visit 2 [at home] result (day 1) up to and including the result recorded on the day prior to Visit 3. Days within the post-tooth bleaching period will be relative to the result following Visit 3 (at home) (day 1) and include any results up to and including the day of Visit 4. The daily mean (± SE) profiles of VAS, LMS and Bothersomeness scores across the study (clearly denoting each period) will be plotted by study product group.

8.3.2 Secondary Endpoint Analyses

The VAS score for tooth sensitivity for the first 7 days during the tooth bleaching period will be analyzed using a Mixed Model with Repeated Measures (MMRM), with study product, DH diagnosis at screening (yes/no), days of bleaching and study product by days of bleaching interaction as fixed effects. The VAS score at screening will also be included as a covariate. Subject will be included as a repeated measure with compound symmetry covariance structure. Kenward Rogers degrees of freedom approach will be applied (Kenward and Roger, 1997). The overall (across all days) least square means (with SE and 95% confidence intervals [CI]) for each study product will be presented along with the difference (with SE and 95% CI).

A separate MMRM will be applied to evaluate the pairwise differences between products for each day. This will be identical to the above MMRM but subject will be included as a repeated measure with unstructured covariance matrix. In case of convergence issues, the Toeplitz, Autoregressive (1), Compound Symmetry covariance structures will be applied until convergence is attained (all heterogeneous versions first and then the same sequence of homogeneous versions). The least square means (with SE and 95% CI) for each study product will be presented along with the pairwise differences (with SE and 95% CI) between products for each day using the appropriate contrasts from the MMRM results.

As a further sensitivity analysis, the mean VAS score for tooth sensitivity over the tooth-bleaching period (Visit 2 [at home] to Visit 3) for a subject will be analyzed using an Analysis of Covariance (ANCOVA) model will be used with study product and DH diagnosis at screening (yes/no) as fixed effects and the VAS score at screening as a covariate. The least square means (with SE and 95% CI) for each study product will be presented along with the difference (with SE and 95% CI).

The LMS and the Botheredsomeness scores during the tooth-bleaching period will be analyzed and presented in identical fashion to the VAS scores endpoint using the same MMRMs and ANCOVA (replacing the respective screening result as a covariate).

For the % tooth sensitivity-free days and the % days analgesics used to alleviate tooth sensitivity during the tooth bleaching period, a negative binomial model will be applied to the number of days with the event. Study product and DH diagnosis at screening (yes/no) will be fitted as fixed effects. An offset variable for the number of days the daily question related to tooth sensitivity (Yes/No) was completed during the tooth bleaching period will be included to adjust for missing days in estimating the rates. The back transformed rates for each study product group and ratios between rates will be presented along with 95% CIs.

Each analysis assessing tooth sensitivity during the tooth bleaching period will also be applied to the same tooth sensitivity endpoints during the post-tooth bleaching period.

The tooth sensitivity scores at Visit 2 (prior to bleaching) will not be included in the analyses as a covariate because it is expected that the randomized product group at Screening will have

a causal effect on this outcome. Low tooth sensitivity following tooth bleaching should not be adjusted in the analysis for low tooth sensitivity at Visit 2, as this could be lower in general for subjects randomized to test and reference dentifrice groups at Visit 1.

An ANCOVA model will be applied to analyze the change in the mean VITA Shade score from pre- to post-tooth bleaching (Visit 2-3) with study product as a fixed effect and the mean VITA-Shade color score at screening fitted as a covariate. The least square means (with SE and 95% CI) for each study product will be presented along with the difference (with SE and 95% CI).

The assumption of normality and homogeneity of variance in each parametric test applied (i.e. ANCOVA / MMRM) 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.

8.3.3 Exploratory Analyses

Responses to the Post whitening questionnaire (separate questions and total score) will analyzed between product groups using an independent t-test.

The change from screening in DHEQ total and domain scores at Visit 3 and Visit 4 will be analyzed between groups using separate ANCOVA models with study product as a fixed effect and the respective DHEQ total or domain score at screening as a covariate. The least square means (with SE and 95% CI) for each study product will be presented along with the difference (with SE and 95% CI).

All tooth-sensitivity endpoints will be summarized further, split by the whether the subject had confirmed DH at the screening assessment. Additional statistical testing may be performed using similar methods to those performed on the full mITT dataset.

8.3.4 Safety Analyses

The Safety population will be used for safety analyses. Safety analyses will be presented by study product group (and overall) according to study product received.

Safety analyses will focus on:

- Exposure and compliance with study products
- Adverse Events (AEs)

All AEs will be reviewed by the safety examiner or PI to categorize them as Oral/Non-Oral. AEs will be regarded as ‘treatment’ emergent if they occur on or after the first use of study product at the Screening visit.

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

- Treatment Emergent AEs (TEAEs)
- Oral TEAEs
- Non-Oral TEAEs
- Treatment emergent treatment related AEs
- Oral Treatment emergent treatment related AEs
- Oral Treatment emergent bleaching related AEs
- Serious AEs

- Serious TEAEs
- Treatment emergent treatment related serious AEs
- Medical device incidents

A listing of all AEs will be presented for all subjects in the Safety population.

8.3.5 Demographic and Baseline Characteristics

Demographic data will be summarized descriptively by study product group and overall.

8.3.6 Study Product Compliance and Use of Other Therapies

8.3.6.1 Study Product Compliance

The number and percentage of subjects who are not compliant with study product usage instructions, as recorded at each study visit, will be summarized using descriptive statistics at each study visit (and any non-compliance overall). The percentage will be based on subjects who attended each visit.

8.3.6.2 Other Therapy

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

8.3.7 Prior and Concomitant Medications

Prior and Concomitant Medications will be listed only.

8.3.8 Handling of Dropouts and Missing Data

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

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

8.3.9 Interim Analysis

No interim analysis is planned for this study.

9 APPENDICES

9.1 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.

9.1.1 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.

9.1.2 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.

9.1.3 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.

9.1.4 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. AEs will be categorized as oral or non-oral by the examiner prior to database lock.

9.1.4.1 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.

9.1.4.2 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.

9.1.5 Evaluating Adverse Events

9.1.5.1 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.

9.1.5.2 Assessment of Causality

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

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

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

The investigator will use clinical judgment to determine the relationship and will also consult the Safety Statement, in the determination of 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.

9.1.6 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.

9.1.7 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.

9.1.8 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.

9.1.9 Pregnancy

9.1.9.1 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.

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

9.1.10 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 supplied toothbrush.

9.1.10.1 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.

9.1.11 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).

9.1.12 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.

9.1.13 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.

9.2 DISCONTINUATION OF STUDY PRODUCT AND SUBJECT DISCONTINUATION/WITHDRAWAL

If a subject is discontinued early from the study product (Section 9.2.1) or discontinued or prematurely withdraws from the study (Section 9.2.2), the reason(s) for intervention discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the CRF. If a subject is discontinued early from the study product, the subject should stay in the study and complete the remaining assessments unless they need to be withdrawn (see Section 9.2.2).

9.2.1 Discontinuation of Study Product

A subject may be discontinued from the study product at any time whilst still in the study at the discretion of the investigator related to safety, subject consent or a potential worsening of the risk / benefit assessment from the subject of remaining on the intervention for the following reasons:

- Adverse Event
- Lack of efficacy from the intervention

- Subject request
- Subject to be withdrawn from the study (see Section 9.2.2)

9.2.2 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 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.

9.2.3 Lost to Follow up

If a subject fails to return to the site for a required study visit, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls or emails or local equivalent methods) 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 and withdrawn from the study if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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).

9.3 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.

The source documents which contain the source of data recorded in the CRF should be specified. The CRF 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.

9.3.1 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.

9.3.2 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 tracked and will include the rationale for the change. A complete record of the changes and corrections will be endorsed by the Investigator.

9.3.3 Data Queries

Reports and listings on the CRF data will be run and manual queries will be raised as needed for site clarification or correction.

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. For this study not all elements of ICH GCP will be applied.

9.4 Processing Patient Reported Outcomes

Paper based patient reported outcome (PRO) data (eg study questionnaires) will be entered into the CRF

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. 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 PRO will be reviewed and transcribed to the CRF 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 Data that will be forwarded to Haleon or Third-Party Vendor.

9.5 Regulatory and Ethical Considerations

9.5.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent document, 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.

9.5.2 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 ISO 14155:2011, and applicable local regulatory requirements and laws.

9.5.3 Subject Information

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

When study data are compiled for transfer to 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.

9.6 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.

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 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.

9.7 Disclosure and Publication Policy

Study information from this protocol may be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable Haleon policies.

Haleon intends to make anonymized subject-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical

science. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with sponsor policy and as per the country specific requirements for disclosure.

9.8 Abbreviations

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

Table 9-1 Abbreviations

Abbreviation	Term
AE	adverse event
ANOVA	analysis of variance
BDR	blinded data review
CI	confidence interval
CRF	case report form
DH	Dentine Hypersensitivity
EAR	Erosion, Abrasion, Recession (assessment of)
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
LMS	Labelled Magnitude Scale
LSLV	last subject last visit
MedDRA	medical Dictionary for Regulatory Activities
MGI	Modified Gingival Index
MMRM	Mixed model with repeated measures
N/A	not applicable
OST	Oral Soft Tissue (examination)
OHT	Oral Hard Tissue (examination)
PI	principal investigator
SAE	Serious Adverse Event
USA	United States of America
VAS	Visual Analogue Scale

9.9 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 1 minutes, and then brush your teeth in your usual manner for 1 timed minute.

- Bring your toothpaste, toothbrush and tooth bleaching kit to all study visits.

Peroxide bleaching usage

On days where the study staff have indicated you should use your peroxide tooth bleaching kit:

- Apply the peroxide-containing dental trays to your teeth according to the instructions provided by the study site. 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. You should place the tray on your teeth and keep the tray in place for 15 minutes (please use the supplied timer). After removing the trays please brush your teeth according to the brushing instructions above. Should you experience any gum soreness or irritation please apply a thin smear of the supplied petroleum jelly to your gums prior to next wearing your trays. Try to avoid getting the petroleum jelly in contact with your teeth.

9.10 Tooth Sensitivity Questionnaire (EXAMPLE)

Subject # Date:

When completing this form please consider your experience over the last 24 hours

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 24 hours**

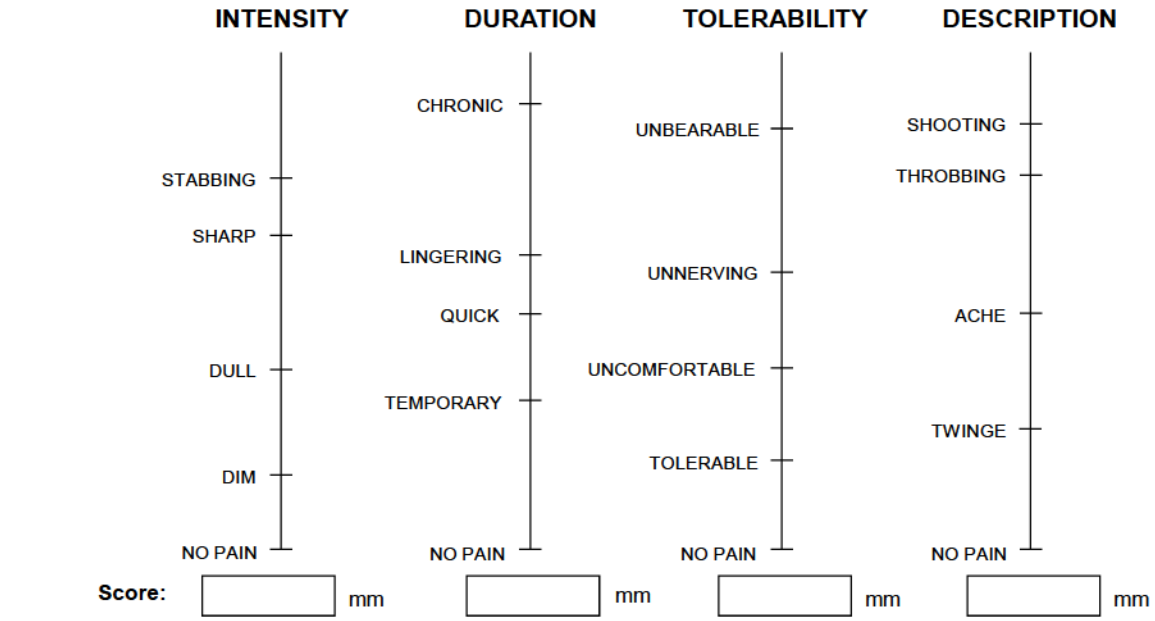
No Sensitivity _____ Extreme Sensitivity

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

In the last 24 hours, have you used any pain killing medications to relive tooth sensitivity/pain?

Yes ☐	No ☐

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 24 hours.** 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.



Final v1.0 16 Oct 15

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 24 hours** (please circle your answer)

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

9.11 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?		

Please tick the box that best answers the statement:

	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 concerned about possible tooth pain during tooth whitening.	☐	☐	☐	☐	☐	☐	☐

9.12 Dentine Hypersensitivity Experience Questionnaire (Example)

SECTION ONE

The following questions are about your sensitive teeth, and the impact it has on your everyday life.

1) Which of the following best describe any sensations that you may have felt in your teeth (tick all that apply)

☐ Itchy (1)	☐ Aching (2)	☐ Shooting (3)
☐ Piercing (4)	☐ Tingling (5)	☐ Sharp (6)
☐ Dull (7)	☐ Flashing (8)	☐ Shivery (9)
☐ Lingering (10)	☐ Twinging (11)	☐ Flickering (12)
☐ Stabbing (13)	☐ Shattering (14)	☐ Freezing (15)
☐ Fleeting (16)	☐ Quivering (17)	☐ Pricking (18)
☐ Pain (19)	☐ Discomfort (20)	☐ Twinges (21)
☐ Sensitivity (22)	☐ Other (please specify) (23)	
☐ None of the Above (24)		

From now on in this questionnaire we are going to call what you feel as '***sensations in your teeth***' or **'sensations'**.

2) How long have you been experiencing any ***sensations in your teeth***? (tick only one response)

- ☐ Less than six months (1)
- ☐ More than six months but less than a year (2)
- ☐ More than a year but less than five years (3)
- ☐ More than five years but less than 20 years (4)
- ☐ More than 20 years (5)
- ☐ None (0)

3) Which parts of your mouth have been affected? (tick all that apply)

- ☐ Top front (1)
- ☐ Top back (2)
- ☐ Bottom front (3)
- ☐ Bottom back (4)
- ☐ None (5)

4) Which of the following cause you to have ***sensations***? (tick all that apply)

☐ Cold fluids (1)	☐ Salty foods (2)	☐ Cold foods (3)
☐ Tooth brushing (4)	☐ Hot fluids (5)	☐ Acidy fruits (e.g. oranges) (6)
☐ Hot foods (7)	☐ Sweet things (8)	☐ Having teeth cleaned at the dentist (9)
☐ Hard foods (10)	☐ Sticky foods (11)	☐ Tooth Whitening Products (12)
☐ Cold air (13)	☐ Ice Cream (14)	☐ Metals touching my teeth (15)
☐ Other (Please Specify) (16)		
☐ None (17)		

5) How often do you have any ***sensations***? (tick only one response)

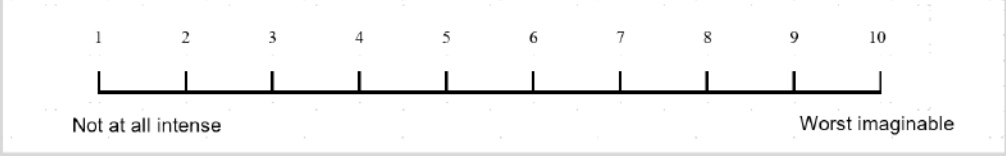
- ☐ Several times a day (7)
- ☐ Once a day (6)
- ☐ Several times a week (5)
- ☐ Once a week (4)
- ☐ Several times a month (3)
- ☐ Once a month (2)
- ☐ Less than once a month (1)
- ☐ Never (0)

6) If you have any ***sensations***, on average how long do these sensations last? (tick only one response)

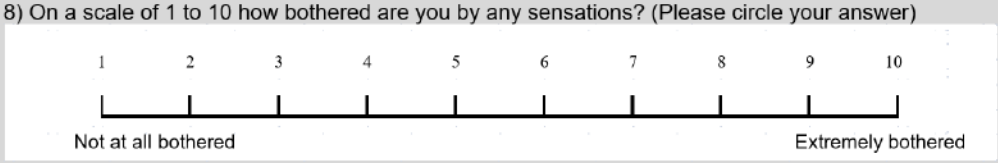
- ☐ A few seconds (5)
- ☐ About a minute (4)
- ☐ Several minutes (3)
- ☐ About half an hour (2)
- ☐ Longer than half an hour (Please specify) (1)
- ☐ Don't have them (0)

The following questions are about your sensitive teeth, and the impact it has on your everyday life.

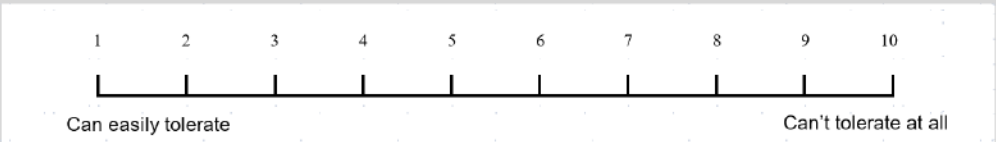
7) On a scale of 1 to 10 how intense are the sensations? (Please circle your answer)



8) On a scale of 1 to 10 how bothered are you by any sensations? (Please circle your answer)



9) On a scale of 1 to 10 how well can you tolerate sensations? (Please circle your answer)



SECTION TWO

The following questions are about ***the ways in which any sensations in your teeth affect you in your daily life***. Thinking about yourself ***over the last week*** to what extent would you agree or disagree with the following statements (Please tick only one response for each question)

	Strongly agree (7)	Agree (6)	Agree a little (5)	Neither agree nor disagree (4)	Disagree a little (3)	Disagree (2)	Strongly disagree (1)
1) Having sensations in my teeth takes a lot of the pleasure out of eating and drinking.	☐	☐	☐	☐	☐	☐	☐
2) It takes a long time to finish some foods and drinks because of sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
3) There have been times when I have had problems eating ice cream because of these sensations.	☐	☐	☐	☐	☐	☐	☐
4) I have to change the way I eat or drink certain things.	☐	☐	☐	☐	☐	☐	☐
5) I have to be careful how I breathe on a cold day.	☐	☐	☐	☐	☐	☐	☐

6) When eating some foods I have made sure they don't touch certain teeth.	☐	☐	☐	☐	☐	☐	☐
7) Because of the sensations I take longer than others to finish a meal.	☐	☐	☐	☐	☐	☐	☐
8) I have to be careful what I eat when I am with others because of the sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
9) Going to the dentist is hard for me because I know it is going to be painful as a result of sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
10) I've been anxious that something I eat or drink might cause sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
11) The sensations in my teeth have been irritating.	☐	☐	☐	☐	☐	☐	☐
12) The sensations in my teeth have been annoying.	☐	☐	☐	☐	☐	☐	☐
13) Having these sensations in my teeth makes me feel old.	☐	☐	☐	☐	☐	☐	☐
14) Having these sensations in my teeth makes me feel damaged.	☐	☐	☐	☐	☐	☐	☐
15) Having these sensations in my teeth makes me feels as though I am unhealthy.	☐	☐	☐	☐	☐	☐	☐

9.13 Post-Whitening Questionnaire.

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

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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