

CLINICAL PROTOCOL

Clinical Study to Investigate the Ability of a Stannous Fluoride Toothpaste to Protect from Dentine Hypersensitivity

Protocol Number:	300212
Compound/Product Name:	0.454% weight/weight (w/w) stannous fluoride (SnF ₂) toothpaste
Phase:	Not Applicable (N/A)

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Sponsor Information

Sponsor Name & Legal Registered Address	Haleon (UK) Building 5, First Floor, The Heights, Weybridge, Surrey, KT13 0NY
Sponsor Contact Details	Haleon St Georges Avenue, Weybridge, Surrey, KT13 0DE, UK

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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	Correction to Table 1-1
Amendment 2	3.0	Change in Acclimatisation toothpaste
Amendment 3	4.0	Updates to reflect: - Clarification as to purpose of study - Removal of pregnancy follow up requirements post withdrawal. - Descriptive statistical analysis terminology - CCI [REDACTED]
Amendment 4	5.0	Update to reflect: - Change in wording from 'Subject to 'Participant'

New versions incorporate all revisions to date prior to submission to the Research Ethics Committee (REC).

Amendments incorporate all revisions to date, including amendments made at the request of the REC.

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HALEON**Principal Investigator Protocol Agreement Page**

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure the investigator staff receive 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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Table of Contents

	Sponsor Information	2
	Document History	3
	Principal Investigator Protocol Agreement Page	4
	Table of Contents	5
1	INTRODUCTION	9
1.1	Background & Study Rationale	9
2	STUDY OBJECTIVES AND ENDPOINTS	10
3	STUDY DESIGN	11
4	STUDY POPULATION	14
4.1	Type and Planned Number of Participants	14
4.2	Inclusion Criteria	15
4.3	Exclusion Criteria	16
4.4	Lifestyle Considerations	18
4.4.1	Oral Hygiene Restrictions	18
4.4.2	Dietary Restrictions	18
4.4.3	Alcohol Restrictions	19
4.5	Concomitant Medications/Treatments	19
5	STUDY PROCEDURES	19
5.1	Schedule of Activities	20
5.2	SCREENING (Visit 1)	24
5.2.1	Informed Consent	24
5.2.2	Demographics	24
5.2.3	Review of Oral Care Products	24
5.2.4	Medical History and Prior Medication/Treatment	24
5.2.5	CCI	25
5.2.6	Clinical Examinations and Dentine Hypersensitivity Assessments	25
5.2.7	Inclusion/Exclusion Criteria	25
5.2.8	Participant Eligibility	25
5.2.9	Enrolled Participants and Screen Failures	26
5.2.10	Supervised Brushing with Acclimatisation Toothpaste	26
5.3	BASELINE (Visit 2, Day 1)	26
5.3.1	Product Usage Compliance Checks	27
5.3.2	Changes in Medical History and Concomitant Medications/ Treatments	27
5.3.3	Participant Adherence and Continuance	27

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CCI Abbreviated Clinical Protocol Template v1.0

5.3.4	Clinical Examinations and Assessments	27
5.3.5	Selection of Test Teeth	28
5.3.6	Participant Qualification	28
5.3.7	Stratification and Randomisation	28
5.3.8	Supervised Brushing with Study Toothpaste	28
5.4	Day 2 (Visit 3) and Week 1 (Visit 4, Day 8 (± 1 day))	29
5.4.1	Product Usage Compliance Checks	29
5.4.2	Changes in Medical History and Concomitant Medications/Treatments	30
5.4.3	Participant Adherence and Continuance	30
5.4.4	Clinical Examinations and Assessments	30
5.5	Week 2 (Visit 5, Day 15 (± 1 day))	30
5.5.1	Product Usage Compliance Checks	31
5.5.2	Changes in Medical History and Concomitant Medications/ Treatments	31
5.5.3	Participant Adherence and Continuance	31
5.5.4	Clinical Examinations and Assessments	31
5.5.5	Participant-Reported Outcomes	32
5.6	Study Conclusion	32
5.7	Follow-Up Contact	32
6	STUDY ASSESSMENTS	32
6.1	Screening Assessments (Visit 1)	32
6.1.1	Erosion, Abrasion and Recession (EAR)	33
6.1.2	Modified Gingival Index (MGI)	33
6.1.3	Clinical Mobility	34
6.1.4	Screening Tactile Sensitivity Assessment	34
6.1.5	Screening Evaporative (Air) Sensitivity Assessment	35
6.2	Dentine Hypersensitivity Assessments (Visits 2-5)	36
6.2.1	Tactile Sensitivity Assessment (Visits 2-5)	36
6.2.2	Evaporative (Air) Sensitivity Assessment (Visits 2-5)	37
6.2.3	CCI	37
6.2.4	CCI	38
6.3	Safety Assessments	40
6.3.1	Oral Soft Tissue (OST) Examination	40
6.3.2	Oral Hard Tissue (OHT) Examination	40
7	STUDY PRODUCTS	40
7.1	Study Product Supplies	41

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7.2	Study Product Storage, Accountability, Returns and Destruction	42
7.3	Randomisation and Blinding	43
7.4	Breaking the Blind	44
8	STATISTICAL CONSIDERATIONS AND DATA ANALYSES	44
8.1	Sample Size Determination	44
8.2	Populations for Analysis	45
8.2.1	Definitions of Analysis Populations	45
8.2.2	Exclusions of Data from Analysis	45
8.3	Statistical Analyses	46
8.3.1	Primary Endpoint Analyses	46
8.3.2	Secondary Endpoint Analyses	47
8.3.3	CCI	47
8.3.4	Safety Analyses	48
8.3.5	Other Analyses	48
8.3.6	Demographic and Baseline Characteristics	49
8.3.7	Study Product Compliance and Use of Other Therapies	49
8.3.8	Handling of Dropouts and Missing Data	49
8.3.9	Interim Analysis	50
9	APPENDICES	50
9.1	ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS	50
9.1.1	Definition of an Adverse Event (AE)	50
9.1.2	Definition of a Serious Adverse Event	51
9.1.3	Time Period and Frequency for Collecting AE and SAE Information	52
9.1.4	Reporting Procedures	52
9.1.5	Reporting an AE	53
9.1.6	Reporting an SAE	53
9.1.7	Evaluating AEs	54
9.1.8	Follow-up of AEs and SAEs	55
9.1.9	Withdrawal Due to an Adverse Event	56
9.1.10	Regulatory Reporting Requirements for SAEs	56
9.2	PREGNANCY	56
9.2.1	Time Period for Collecting Pregnancy Information	56
9.2.2	Action to be Taken if Pregnancy Occurs	56
9.3	DISCONTINUATION OF STUDY PRODUCT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL	57
9.3.1	Discontinuation of Study Product	57

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CCI Abbreviated Clinical Protocol Template v1.0

9.3.2	Participant Discontinuation/Withdrawal	57
9.3.3	Lost to Follow Up	58
9.4	DATA MANAGEMENT	58
9.4.1	Case Report Form	58
9.4.2	Data Handling	59
9.4.3	Data Queries	59
9.5	PROCESSING PARTICIPANT REPORTED OUTCOMES	59
9.6	STUDY GOVERNANCE CONSIDERATIONS	60
9.6.1	Quality Control	60
9.6.2	Quality Assurance	60
9.6.3	Regulatory and Ethical Considerations	61
9.7	Records Retention	62
9.8	Disclosure and Publication Policy	62
9.9	Conditions for Terminating the Study	63
9.10	CCI	63
9.11		64
10	ABBREVIATIONS	78
11	REFERENCES	80

List of In Text Tables

Table 2-1	Study Objectives and Endpoints	10
Table 5-1	Schedule of Activities	21
Table 7-1	Study Products	41
Table 7-2	Sundry Items	42
Table 11-1	Abbreviations	78

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1 INTRODUCTION

1.1 Background & Study Rationale

Dentine Hypersensitivity (DH) is described as '*a short sharp arresting pain when exposed dentine on crown and/or root of a healthy, vital tooth is stimulated by a naturally occurring stimulus. The pain ceases on stimulus withdrawal, is rarely associated with one tooth, can be episodic as the dentine tubules change from occluded to partially or un-occluded status and negatively effects quality of life*' (Pollard, 2023). Stimuli for DH are '*typically thermal, evaporative, tactile, osmotic or chemical*' in nature (Addy, 2002). Twice daily use of a desensitising toothpaste is generally recommended to help protect hypersensitive teeth (Pereira, 2015).

The conduct of randomised, controlled, examiner-blind, parallel group, clinical studies is the recommended approach for evaluating the performance of tooth sensitivity products (Holland, 1997). Dentine Hypersensitivity to two independent stimuli (typically tactile and thermal), is assessed at Baseline and after a period of twice daily brushing with the antihypersensitivity toothpaste. Appropriately trained and experienced clinical examiners administer the DH stimuli, evaluate participant responses, consistently and repeatedly.

The Clinical Trials Group (Periodontology) at Bristol Dental School have trained a new clinical examiner in the administration of tactile (Yeaple Probe (Polson, 1980)) and evaporative (air) stimuli, and the evaluation of participant response to those stimuli (Schiff sensitivity scale (Schiff, 1994)).

This is the first clinical study conducted by Haleon with the new DH examiner at this well-established investigator site. As such, the purpose of this study is to familiarise the new examiner with Haleon DH protocol requirements and endpoints.

This will be achieved by characterising the sensitivity protection performance of commercially available, daily use toothpastes.

A sensitivity toothpaste containing stannous fluoride (Sensodyne Rapid Relief – US product) will be compared to a regular fluoride toothpaste with no known DH benefits (Colgate Cavity Protection – US product); at intervals over a 2-week usage period as measured by Schiff sensitivity score and Tactile threshold (g).

Dentine hypersensitivity toothpastes typically act in one of two ways: nerve desensitisation or dentine tubule occlusion (Addy, 2002). Stannous fluoride (SnF_2) is one of the most commonly employed tubule-occluding ingredients; the stannous (tin [II]) ions react rapidly with the water and phosphate minerals found in saliva and dentine tubule fluid to form insoluble deposits over the surface of exposed dentine (Miller, 1994). Tubule occlusion is typically a fast process (Gillam, 1996), with protection from DH being reported after a single use of a 0.454% SnF_2 toothpaste (Creeth, 2019[a]; Creeth, 2019[b]). In this study, clinical assessments of DH will be completed at Screening and Baseline, and after 1 day, 1 week and 2 weeks twice daily brushing.

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Page 9 of 82

CCI

Therefore, this study will be considered successful if DH protection profile of the 0.454% SnF₂ toothpaste indicates improved tooth sensitivity protection compared to Baseline, at Week 2 and this will provide reassurance of the clinical examiner capabilities.

The safety and tolerability of the study toothpastes will be assessed by review of treatment emergent adverse events (TEAEs).

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To investigate the DH protection of a 0.454% SnF ₂ toothpaste and a regular fluoride toothpaste, in response to evaporative air (Schiff sensitivity score) and tactile (tactile threshold in grams (g)) stimuli, with twice daily brushing after 2 weeks.	At Week 2: Change from Baseline in Schiff sensitivity score. Change from Baseline in tactile threshold (g).
To characterise the DH protection profiles of a 0.454% SnF ₂ toothpaste and a regular fluoride toothpaste, in response to evaporative air (Schiff sensitivity score) and tactile (tactile threshold in grams (g)) stimuli, with twice daily brushing over 2 weeks.	At Baseline, Day 2, Week 1 and Week 2: Schiff sensitivity score. Tactile threshold (g). Change from Baseline in Schiff sensitivity score. Change from Baseline in tactile threshold (g).
Secondary	
To investigate the DH protection profiles of a 0.454% SnF ₂ toothpaste and a regular fluoride toothpaste, in response to evaporative air (Schiff sensitivity score) and tactile (tactile threshold in grams (g)) stimuli, with twice daily brushing at Day 2 and Week 1.	At Day 2 and Week 1: Change from Baseline in Schiff sensitivity score. Change from Baseline in tactile threshold (g).
To investigate the ability of a 0.454% SnF ₂ toothpaste to provide DH protection, in response to evaporative air (Schiff sensitivity score) and tactile (tactile threshold in g) stimuli, compared to a	At Day 2, Week 1 and Week 2 Change from Baseline in Schiff sensitivity score. Change from Baseline in tactile

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Protocol Number: 300212

regular fluoride toothpaste, after 1 day, 1 week and 2 weeks twice daily use.	threshold (g).
Exploratory	
	
Safety	
To monitor the safety and tolerability of the study toothpastes with twice daily brushing over 2 weeks.	Treatment emergent adverse events (TEAEs).

This study will be considered successful if DH protection profile of the 0.454% SnF₂ toothpaste indicates improved tooth sensitivity protection (as measured by Schiff sensitivity score and tactile threshold (g), compared to Baseline, at Week 2.

3 STUDY DESIGN

This will be a single centre, randomised, controlled, examiner-blind, 2-arm, stratified, parallel design clinical study in healthy male and female participants, aged 18-70, with self-reported and clinically confirmed DH.

Participants who meet the required study criteria at Screening and Baseline will be randomised to one of two study toothpastes: 0.454% SnF₂ toothpaste (Test) or a regular fluoride toothpaste (Negative Control).

Enrolled participants will complete an acclimatisation period (2 weeks duration) between the Screening and Baseline visits during which they will brush twice daily (morning and evening) with the acclimatisation toothpaste (commercially available regular fluoride toothpaste).

As per Holland (1997) for the evaluation of DH products, two independent stimulus-based

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Protocol Number: 300212

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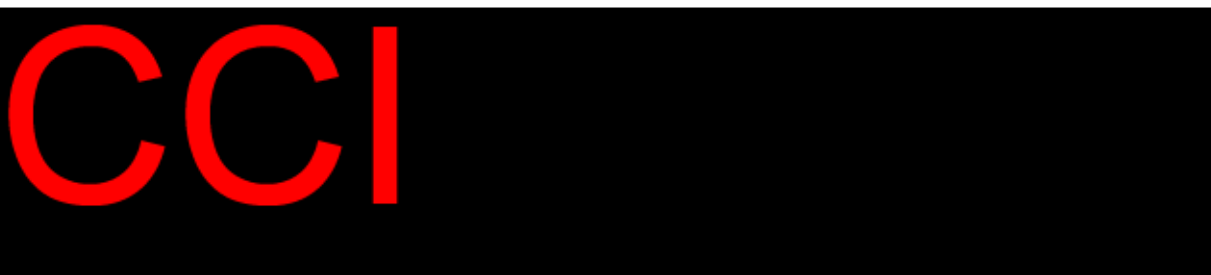
clinical measures will be employed to assess DH.

- A tactile stimulus will be administered using a constant pressure probe - Yeaple Probe (Polson, 1980); participant response to the stimulus determines the tactile threshold (g).
- An evaporative (air) stimulus (i.e., a thermal stimulus) will be administered using a dental air syringe; participant response to the stimulus will be examiner-evaluated using the Schiff sensitivity scale (Schiff, 1994).

DH will be assessed at Screening and Baseline, and after 1 day, 1 week and 2 weeks toothpaste usage. The same clinical examiner will administer both stimuli and assess their associated DH measures (tactile threshold (g) and Schiff sensitivity score) for all study participants for the duration of the study.

On completion of the Baseline assessments, the clinical examiner will select two 'test teeth' for assessment of tactile and evaporative (air) sensitivity at all subsequent visits. To qualify for selection as a 'test tooth', the tooth must meet the protocol-specific inclusion/exclusion criteria, specifically a tactile threshold ≤ 20 g and a Schiff sensitivity score ≥ 2 at both Screening and Baseline visits.

Approximately 80 qualifying participants will be stratified by the maximum Baseline Schiff sensitivity score of their two selected 'test teeth' and randomised to study toothpaste (approximately 40 participants each to the test toothpaste and negative control groups). Randomised participants will be instructed to brush twice daily (morning and evening) with their allocated study toothpaste for the next 2 weeks. First use of study toothpaste will be completed under supervision at the investigator site.



The safety and oral tolerability of the study toothpastes will be monitored over the 2-week usage period by review of TEAEs.

Scientific Rationale for Study Design

Conduct of a DH study designed in accordance with recommended guidelines for the evaluation of DH products (Holland, 1997), with two independent stimuli for DH and a test toothpaste with a wealth of published evidence to support its ability to provide DH protection is considered appropriate to familiarise a DH examiner with the conduct of Haleon DH studies.

There is no established, objective method for evaluating the performance of a new DH clinical examiner against an experienced examiner (as would be the case for clinical measures of plaque accumulation and gingival health where kappa values can be used to assess inter-examiner reproducibility).

The trends in DH protection over time anticipated for this study are expected to be broadly aligned with those observed in previous similar DH studies involving daily use of a

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Protocol Number: 300212

 0.454% w/w SnF₂ toothpaste and will provide reassurance of clinical examiner capability.

The etiology of DH requires tooth wear (loss of enamel) and/or gingival recession (with loss of cementum) to expose the underlying dentine (Addy, 1987). In the absence of an underlying condition or pathology, these processes are slow and progressive, leading to dentine exposure in early adulthood; thus, DH is rarely seen in children (West, 2022). While the age range over which an individual can experience DH is wide (early teens to 70s), peak incidence is known to occur between the ages of 20-40 years and decline thereafter (Bartold, 2006; Dababneh, 1999; Fischer, 1992; Flynn, 1985; West, 2014). The fall in prevalence observed in later decades reflects age-related changes in the dentine and pulp of the tooth which act to reduce both dentine permeability and the tooth's response to external triggers of DH (Seltzer, 1975; Splieth, 2013). Dental pain experienced by older members of the population is less likely to be diagnosed as DH (Rees, 2000), thus an age range of 18-70 years has been selected for this study to target individuals with tooth sensitivity due to DH.

Female participant participants who are pregnant (or intending to become pregnant during the study) or breast-feeding will be excluded from participation in the study. The study toothpastes are not contra-indicated for pregnancy or breastfeeding (their use would not be expected to cause harm to the mother, the foetus or a baby), however, pregnant and lactating females will be excluded due to the increased prevalence/severity of gingivitis and periodontal disease reported during pregnancy and breastfeeding which, together with the increased amounts of calculus and plaque observed on the teeth during pregnancy, could affect the DH clinical assessments (Aghazadeh, 2019; Samant, 1976).

DH is an episodic condition; symptoms are known to vary spontaneously (West, 2008, West, 2013). Baseline clinical values that would support enrolment may represent random highs that could be followed by regression to the mean, leaving the participant or selected test tooth without the condition of interest (i.e., DH) during the 2-week investigational period. To help minimise the potential for this to occur in this study, qualifying participants will be required to demonstrate a minimum level of response to both DH stimuli (tactile and evaporative (air)) at Screening (Visit 1) and Baseline (Visit 2).

- Randomised participants must have a minimum of two eligible teeth of which each have a tactile threshold $\leq 20\text{g}$ and a Schiff sensitivity score ≥ 2 at both Screening and Baseline.

Clinical trials evaluating pain-related endpoints, such as tooth sensitivity, can be prone to 'placebo effects' (Addy, 1985; West, 1997); such effects are frequently observed in DH studies.

A study conducted to evaluate the natural history of DH also highlighted the existence of a 'no treatment' effect, characterised by an improvement in sensitivity simply as a result of study participation (Leight, 2008).

To help minimise the potential impact of both effects, an acclimatisation period (14 days duration) will precede the Baseline visit. During this period, study participants will brush twice daily with the regular fluoride toothpaste and toothbrush provided (in place of their own oral hygiene products). The acclimatisation period will also serve to standardise oral hygiene practice across the study population and familiarise study participants with several important study procedures (e.g., toothpaste dosage, timed brushings) prior to first use of their allocated study toothpaste.

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Protocol Number: 300212

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Per International Conference on Harmonization (ICH) GCP guidance ([ICH E6 \(R2\) Good Clinical Practice](#)), for a study to be classified as double blind, the participants, investigator(s) and staff involved in the treatment or clinical evaluation of participants should be unaware of study toothpaste received. In addition, the products under investigation should have the same appearance, smell and taste (i.e., study arms should not be distinguishable from each other). Given it will not be possible for the study toothpastes evaluated in this study (two commercially available toothpastes, (which will be provided overwrapped), the study is described as only ‘examiner-blind’

4 STUDY POPULATION

4.1 Type and Planned Number of Participants

The study will be conducted in male and female participants, aged 18-70 years (inclusive), in good general and oral health, with a self-reported history of tooth sensitivity and at least two sensitive teeth (with clinically confirmed DH) that meet study eligibility criteria at both Screening (Visit 1) and Baseline (Visit 2).

Sufficient participants will be screened and entered into the acclimatisation phase to ensure approximately 80 participants are randomised to study toothpaste (approximately 40 participants per group) and approximately 70 participants complete the study (approximately 35 participants per group, allowing for up to 10% dropouts).

This study can only fulfil its objectives if appropriate participants participate. Currently, there is no published evidence to indicate that gender, race or ethnicity impacts the pathophysiology of DH. Thus, every effort will be made to enrol participant’s representative of the adult population who would benefit from use of an antisensitivity toothpaste; the protocol inclusion/exclusion criteria will not unnecessarily preclude any participant from participation.

- Female participants who are pregnant (or intending to become pregnant during the study) or breast-feeding will be excluded from participation in the study. The study toothpastes are not contra-indicated for pregnancy or breastfeeding (their use would not be expected to cause harm to the mother, the foetus or a baby), however, pregnant and lactating females will be excluded due to the increased prevalence/severity of gingivitis and periodontal disease reported during pregnancy and breastfeeding which, together with the increased amounts of calculus and plaque observed on the teeth during pregnancy, could affect the DH clinical assessments (Aghazadeh, 2019; Samant, 1976). Pregnancy and breast-feeding status will be self-reported.
- Potential study participants will be asked to bring their current oral hygiene products to Screening (Visit 1). Individuals already using products for the treatment or protection of sensitive teeth as part of their oral hygiene routine will be excluded. If they are using such products and continuing to experience tooth sensitivity, they would be unlikely to respond to use of the test toothpaste in this study and will be advised to seek advice from their dental healthcare provider.

Participant eligibility to participate in the clinical study should be reviewed and documented by an appropriate member of the investigator’s study team before Participants are included in

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the study. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a Participant is suitable to participate in this study.

The following eligibility criteria are designed to select Participants for whom participation in the study is considered appropriate.

4.2 Inclusion Criteria

Each individual Participant must meet all the following inclusion criteria to be eligible to participate in the study.

1. Provision of signed and dated informed consent document confirming the Participant has been informed of all pertinent aspects of the study and has given their written consent for study participation before any study procedures are performed.
2. Participant is biologically male or female.
3. Participant is 18 to 70 years of age, inclusive, at the time of signing the consent form.
4. Participant is willing and able to comply with the study visit schedule, toothpaste usage instructions, lifestyle restrictions and other study procedures.
5. Participant is in good general, oral and mental health with, in the opinion of the investigator or medically qualified designee, with no clinically significant or relevant abnormalities in self-reported medical history, or upon oral examination that would impact their safety or wellbeing, or the outcomes of the study, if they were to participate in the study, or affect their ability to understand and follow study requirements.

6. SCREENING (Visit 1)

Participant must have:

- a) History of tooth sensitivity lasting more than six months but not more than 10 years (self-reported).
- b) Good general oral health, with a minimum of 20 natural teeth.
- c) Minimum of 2 non-adjacent, accessible teeth (incisors, canines, premolars), in different quadrants, which meet all the following criteria:
 - Exposed dentine due to facial/cervical erosion or abrasion (i.e., tooth wear) or gingival recession (EAR).
 - MGI = 0 directly adjacent to the exposed dentine (i.e., the test area only).
 - Clinical mobility = 0.
 - Clinically confirmed DH to both tactile and evaporative (air) stimuli:
 - Tactile threshold $\leq 20\text{g}$
 - Schiff sensitivity score ≥ 2 .

7. BASELINE (Visit 2)

Participant must have a minimum of two non-adjacent, accessible teeth (incisors, canines, premolars), in different quadrants, with clinically confirmed DH to both tactile and evaporative (air) stimuli at both Screening (Visit 1) and Baseline (Visit 2).

- Tactile threshold $\leq 20\text{g}$ at Screening & Baseline

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- Schiff sensitivity score ≥ 2 at Screening & Baseline

The clinical examiner will select two ‘test teeth’ from those which meet the tactile threshold and Schiff sensitivity score inclusion criteria at both Screening and Baseline.

Notes: All teeth with clinically confirmed, qualifying levels of DH at Screening (i.e., a Screening tactile threshold ≤ 20 g and a Screening Schiff sensitivity score ≥ 2) will be assessed for tactile sensitivity at Baseline. Teeth with a Baseline tactile threshold ≤ 20 g will then be assessed for Baseline evaporative (air) sensitivity.

4.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will be excluded from participation in the study.

1. Participant is an employee of the investigator site directly involved in the conduct of the study, or an employee of the investigator site otherwise supervised by the investigator, or a member of their immediate family.
2. Participant is an employee of the sponsor directly involved in the conduct of the study or a member of their immediate family.
3. Female participant who is pregnant or intending to become pregnant during the study (self-reported).
4. Female participant who is breastfeeding (self-reported).
5. Participant with known or suspected intolerance or hypersensitivity to the study products, any of their stated ingredients or closely related compounds (self-reported).
6. Participant with a recent history (within the last year) of alcohol or other substance abuse (self-reported).
7. Participant is participating in or has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days of Screening (Visit 1) or plans to participate in other studies (including non-medicinal studies) during this study.
8. Participant has participated in a tooth sensitivity study within 8 weeks of Screening (Visit 1).
9. Participant is currently using an oral care product indicated for DH relief or care of sensitive teeth or has used such a product within 8 weeks of Screening (Visit 1)
Participants will be required to bring their current oral care products to Screening (Visit 1) for staff to verify the absence of antisensitivity ingredients and tooth sensitivity-related claims on the product packaging/label text.
10. Participant takes daily doses of medications/treatments which, in the opinion of the investigator or medically qualified designee, could interfere with their perception of tooth sensitivity (e.g., analgesics, anticonvulsants, antihistamines that cause marked or moderate sedation, sedatives, tranquilizers, antidepressants, mood-altering and anti-inflammatory drugs).

11. SCREENING (Visit 1)

Participant has taken antibiotics in the 2 weeks prior to Screening (Visit 1).

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HALEON**12. BASELINE (Visit 2)**

Participant has taken antibiotics in the 2 weeks prior to Baseline (Visit 2), i.e., during the acclimatisation period.

13. Participant takes daily doses of a medication which, in the opinion of the investigator or medically qualified designee, is causing xerostomia.
14. Participant requires antibiotic prophylaxis for dental procedures.
15. Participant has had professional tooth de-sensitising treatment within 8 weeks of Screening (Visit 1).
16. Participant has had a tooth bleaching procedure within 8 weeks of Screening (Visit 1).
17. Participant has had dental prophylaxis within 4 weeks of Screening (Visit 1).
18. Participant has had treatment for periodontal disease (including surgery) within 12 months of Screening (Visit 1).
19. Participant has had scaling or root planning within 3 months of Screening (Visit 1).
20. Participant with gross periodontal disease.
21. Participant with a tongue or lip piercing.
22. Participant with evidence of gross intra-oral neglect or the need for extensive dental therapy.
23. Participant with a fixed or removable partial prosthesis which, in the opinion of the investigator or dentally qualified designee, could impact study outcomes.
24. Participant with multiple dental implants which, in the opinion of the investigator or dentally qualified designee, could impact study outcomes.
25. Participant has had orthodontic treatment (fixed or removable orthodontic braces/bands) within 6 months of Screening (Visit1)
26. Participant with a fixed or removable orthodontic retainer which, in the opinion of the investigator or dentally qualified designee, could impact study outcomes (e.g., Participant who is an intermittent user of a removable orthodontic retainer).

Note: Teeth involved in a fixed orthodontic retainer may be used as 'test teeth' if, in the opinion of the investigator or dentally qualified designee, their selection would not impact study outcomes.

27. SPECIFIC DENTITION EXCLUSIONS FOR 'TEST TEETH':

- a) Tooth with evidence of current/recent dental caries.
- b) Tooth having had (self-reported) treatment for dental caries within 12 months of Screening (Visit 1).
- c) Tooth with exposed dentine and deep, defective, or facial restorations.
- d) Tooth with a full crown or veneer.
- e) Tooth adjacent to a bridge abutment or crown which, in the opinion of the investigator or dentally qualified designee, could impact study outcomes.
- f) Sensitive tooth with contributing etiologies other than EAR to exposed dentine.

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- g) Sensitive tooth not expected to benefit from use of a sensitivity toothpaste, in the opinion of the investigator or dentally qualified designee.

28. **CCI**

29. Participant who, in the opinion of the investigator or medically qualified designee, should not participate in the study.

4.4 Lifestyle Considerations

The investigator site may contact participants to remind them of an approaching scheduled visit and any applicable lifestyle restrictions.

If, in the opinion of the investigator or medically qualified designee, a Participant has not complied with a lifestyle restriction (oral hygiene, dietary or alcohol-related) prior to a study visit, every effort will be made to re-appoint them within the permitted visit tolerances, as defined in the Schedule of Activities (Table 5-1). The reason for re-appointment will be documented in the electronic case report form (eCRF).

If re-appointment is not possible, the following visit specific actions should be taken.

- **Baseline, Day 1 (Visit 2):** the participant will be withdrawn from the study (Appendix 9.3). No clinical assessments will be performed. The Participant may be replaced.
- **Day 2, (Visit 3):** The participant will complete all procedures, examinations and clinical assessments scheduled for that visit and continue in the study.
- **Day 8 & 15 (Visits 4 & 5):** If re-appointment within the permitted visit windows is not possible, the participant will complete all procedures, examinations and clinical assessments scheduled for that visit and continue in the study.

4.4.1 Oral Hygiene Restrictions

For the Duration of the Study: From Screening (Visit 1) to the Participant's Last Visit

- Participants should not use any other oral care products (e.g., toothpastes, toothbrushes, oral rinses, whitening/bleaching products, inter-dental cleaning products, herbal remedies) than those provided by authorised study staff during the study.
Note: Use of dental floss is permitted to remove impacted food only.
- Participants should not chew gum.

Before a Clinical Assessment Visit: From Baseline (Visit 2) to the Participant's Last Visit

- To minimise exposure to environmental triggers for sensitivity prior to clinical assessments, Participants will be instructed to refrain from all oral hygiene procedures for at least 8 hours before a study visit.

4.4.2 Dietary Restrictions

Before a Clinical Assessment Visit: Baseline (Visit 2) to the Participant's Last Visit

- To minimise exposure to environmental triggers for sensitivity prior to clinical assessments, participants will be instructed to refrain from eating and drinking for at least 2 hours before a study visit.

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***Note:** Small sips of room-temperature water will be permitted to take medications or to relieve a dry mouth up to 1 hour before their appointment time*

4.4.3 Alcohol Restrictions

Before a Clinical Assessment Visit: Baseline (Visit 2) to the Participant's Last Visit

- Participants will abstain from excessive alcohol consumption for 24 hours before a clinical assessment visit and any alcohol consumption for 8 hours prior to a study visit.

4.5 Concomitant Medications/Treatments

Any medications and/or treatments (including vaccines, OTC or prescription medicines, dietary supplements, and herbal remedies) taken or received during the study, from the signing of the ICF, must be recorded in the eCRF with the indication, reason for use, unit dose, daily dose and start/stop dates of administration. Participants will be questioned about changes in their medications/treatments at the start of each study visit.

Medications and treatments taken or received in the 30 days prior to signing the consent/assent form will be documented as prior medication/treatment. New medications and treatments, started after signing the consent/assent form, will be documented as concomitant medications/treatments (including daily, regular or intermittent use medications/treatments).

For the Duration of the Study: Screening (Visit 1) to the Participant's Last Study Visit:

- Participants should delay any non-emergency, elective dental treatments until after study completion (including dental prophylaxis).
- Should an enrolled/randomised participant change the dosage regimen of a medication, details of the change will be recorded in the eCRF.
- Should a participant take a medication within 8 hours of their scheduled visit which, in the opinion of the investigator or their medically qualified designee, could impact their perception of DH (e.g., an analgesic), a deviation will be recorded and every effort will be made to reappoint them within the permitted visit window (as per Table 1-1) as specified in Section 4.4. The medication (and any associated AE) will be documented in the eCRF.

5 STUDY PROCEDURES

This section details the procedures and assessments to be completed at each scheduled study visit. The timing of each procedure and assessment is listed in the Schedule of Activities ([Table 5-1](#)). Adherence to the study design requirements, including all procedures and assessments is essential and required for successful study conduct.

Every effort should be made to ensure that protocol-required procedures and assessments 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 a particular procedure or assessment. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required procedure or assessment cannot be performed, the investigator (or designee) will document the reason as a protocol deviation and any corrective and preventative actions they have taken to

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Haleon

Clinical Protocol

Protocol Number: 300212



ensure that protocol requirements are adhered to as soon as possible. The sponsor must be informed of any missed procedures or assessments in a timely manner.

Oral examinations and assessments to determine Participant eligibility and to monitor the safety/performance of study products will be performed by appropriately trained clinical examiners, with relevant clinical experience. This will be the first clinical study to be conducted by Haleon with this DH examiner at this well-established investigator site.

5.1 Schedule of Activities

The [Schedule of Activities \(Table 5-1\)](#) provides an overview of the Participant visits, study procedures and assessments. The investigator may schedule additional (unplanned) visits to conduct additional evaluations or assessments required to protect the well-being of the participant.

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Haleon

Clinical Protocol

Protocol Number: 300212

HALEON**Table 5-1 Schedule of Activities**

Procedure/Assessment	Study Visits					
	Visit 1 Screening		Visit 2 Baseline Day 1	Visit 3 Day 2	Visit 4 Week 1 Day 8 (± 1 day)	Visit 5 Week 2 Day 15 (± 1 day)
Informed Consent	X	Acclimatisation Period (14 ± 2 Days)				
Demographics	X					
Review Participant's Current Oral Care Product(s)	X					
Review Medical History & Current/Prior Concomitant Medications/Treatments	X					
Review Changes in Health & Medications/Treatments ¹			X	X	X	X
Compliance Checks ¹			X	X	X	X
CCI [REDACTED]	X					
						X ⁶
						X ⁶
Oral Soft Tissue (OST) Examination	X		X	X	X	X
Oral Hard Tissue (OHT) Examination	X					X
Eligible Teeth Assessments (Dentition Exclusions, Erosion/Abrasion/ Recession [EAR], Modified Gingival Index [MGI], Tooth Mobility)	X					
Qualifying Clinical Assessment of Tactile Sensitivity ²	X		X			
Qualifying Clinical Assessment of Evaporative (Air) Sensitivity (Schiff sensitivity score) ³	X		X			

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Haleon

Clinical Protocol

Protocol Number: 300212

HALEON

Procedure/Assessment	Study Visits					
	Visit 1 Screening		Visit 2 Baseline Day 1	Visit 3 Day 2	Visit 4 Week 1 Day 8 (± 1 day)	Visit 5 Week 2 Day 15 (± 1 day)
CCI			X			
Clinical Examiner Selects Two ‘Test Teeth’ (Qualifying Participants Only) ⁵			X			
Review Inclusion/Exclusion Criteria	X		X			
Confirm Participant Eligibility/Qualification	X		X			
Dispense Acclimatisation Toothpaste, Toothbrush, Rinsing Cups & Timer	X					
Supervised Brushing with Acclimatisation Toothpaste	X					
Stratification/Randomisation			X			
Return Acclimatisation Toothpaste & Toothbrush			X			
Dispense Study Toothpaste, Toothbrush & Rinsing Cups			X			
Supervised Brushing with Allocated Study Toothpaste			X			
Clinical Assessment of Tactile Sensitivity: Two ‘Test Teeth’ Only ²				X	X	X
Clinical Assessment of Evaporative (Air) Sensitivity (Schiff sensitivity score): Two ‘Test Teeth’ Only ³				X	X	X
CCI				X	X	X
Return Study Toothpaste & Toothbrush						X
Study Conclusion						X
Monitor Adverse Events (AEs) ⁷	X		X	X	X	X

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Page 22 of 82

Haleon

Clinical Protocol

Protocol Number: 300212

HALEON**FOOTNOTES:**

1. Participants will be required to bring their study supplies (minus timer & rinsing cups) to every visit.
Perform visual check of returned study supplies & question Participant to evaluate compliance.
Visit 2: Check compliance with use acclimatisation toothpaste.
Visits 3-5: Check compliance with use of study toothpaste.
CCI
- Visits 2-5: Check compliance with Lifestyle Restrictions and medication requirements.
2. **Tactile Threshold Assessments:** Visits 1-2: Maximum force 20g (Screening and Baseline); Visits 3-5: Maximum force 80g.
3. **Evaporative (air) sensitivity** (Schiff sensitivity score) should be assessed after tactile sensitivity; ensure minimum 5-minute delay after the last tactile assessment before the first evaporative (air) assessment for tooth recovery.
Visit 1 (Screening): Assess evaporative (air) sensitivity for all teeth with a Screening tactile threshold $\leq 20g$.
Visit 2 (Baseline): Assess evaporative (air) sensitivity for all 'eligible teeth' identified at Screening with a Baseline tactile threshold of $\leq 20g$.
Visits 3, 4 & 5: Assess evaporative (air) sensitivity for the two 'Test Teeth' only.
'Eligible Teeth' = Teeth with no dentition exclusions which meet EAR, MGI & mobility criteria, with Screening tactile threshold $\leq 20g$ & Screening Schiff sensitivity score ≥ 2 .
4. **CCI**
5. Selected 'Test Teeth' should be in different quadrants, with the requisite qualifying levels of DH at both Screening (Visit 1) and Baseline (Visit 2), i.e., tactile threshold $\leq 20g$ and Schiff sensitivity score ≥ 2 .
6. **CCI**
7. AEs, and therefore all serious adverse events (SAEs) will be recorded from immediately after signing the informed consent form (ICF) until 5 days after the last use of study toothpaste.

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Page 23 of 82

5.2 SCREENING (Visit 1)

Screening procedures for each study participant will be completed 14 ($\pm$ 2) days prior to their Baseline visit (Visit 2). Where practically feasible, they should be completed in the order listed below. Data collected will be recorded in the electronic Case Report Form (eCRF).

5.2.1 Informed Consent

The investigator (or designee) must obtain informed consent from each participant 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 Participant and the investigator, or designee; the participant will be provided with one copy, the other will be kept at site.

The time of consent will be recorded on the ICF; AEs will be captured from this point. The date and time of consent will be recorded in the eCRF. Appropriate forms for documenting informed consent will be provided by the investigator or by the sponsor.

If, during a participant's participation in the study, any new information becomes available that may affect the participant's willingness to participate in the study, each ongoing Participant should receive a copy of this new information and be re-consented into the study. Each Participant should be provided with a copy of the signed and dated amended consent form.

5.2.2 Demographics

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

5.2.3 Review of Oral Care Products

Participants will be required to bring their current oral care products to the investigator site for staff to confirm the absence of antisensitivity ingredients and tooth sensitivity-related claims on the product packaging/label text. Participants who are currently using an oral care product indicated for DH relief or care of sensitive teeth, or who has used such a product within 8 weeks of Screening, will be excluded.

5.2.4 Medical History and Prior Medication/Treatment

The following will be recorded for all Participants:

- Details of relevant medical history and recent surgery (within the last year), including allergies and drug sensitivities.
- Prior medications and treatments (including vaccines, OTC or prescription medicines, dietary supplements and herbal remedies) taken in the 30 days prior to Screening.

Female Participants only:

- Female participants who report being pregnant or confirm plans to become pregnant during the study will be excluded.

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- Given the potential impact of pregnancy on study outcomes, female participants of child-bearing potential will be reminded to inform the investigator site immediately if pregnancy is known or suspected.

5.2.5 CCI

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5.2.6 Clinical Examinations and Dentine Hypersensitivity Assessments

The following clinical examinations and DH assessments will be completed as described in Section 6 (Study Assessments) of this protocol.

- Oral soft tissue (OST) examination.
- Oral hard tissue (OHT) examination.
- Clinical assessment of incisors, canines and pre-molars for dentition exclusions, EAR, MGI (adjacent to the test area only) and clinical mobility to identify eligible teeth for DH assessment.
- Clinical assessment of tactile sensitivity (tactile threshold (g); maximum force 20g).**
Assess all teeth with no dentition exclusions (Section 4.3 Exclusion Criterion 27) which meet EAR, MGI and tooth mobility requirements (Section 4.2 Inclusion Criteria 6c).
Ensure at least a 5-minute break between completing the tactile assessments and starting the evaporative (air) assessments.
- Clinical assessment of evaporative (air) sensitivity (Schiff sensitivity score).**
Assess each tooth with a Screening tactile threshold of $\leq 20g$.

Participants must have a minimum of two 'eligible teeth' to continue in the study (Section 4.2 Inclusion Criterion 6c). 'Eligible teeth' will have a Screening tactile threshold $\leq 20g$ and a Screening Schiff sensitivity score ≥ 2 .

Participants with fewer than two 'eligible teeth' will be discontinued.

To facilitate Participant flow, source documents can be used to record clinical data for later transcription into the eCRF (transcription must be completed promptly of recording the data for a given Participant).

5.2.7 Inclusion/Exclusion Criteria

Update information relating to inclusion/exclusion criteria in the eCRF.

5.2.8 Participant Eligibility

The investigator or medically qualified designee will review the medical history, prior

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medications/treatments, clinical examination/assessment data and the inclusion/exclusion criteria for each participant to determine their eligibility to participate in the study. If confirmed as eligible to participate, the Participant will be considered enrolled in the study.

5.2.9 Enrolled Participants and Screen Failures

For this study, an enrolled participant is defined as a Participant who has agreed to participate in the study following completion of the informed consent process and successfully met the study eligibility criteria to proceed beyond the screening visit.

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. To ensure transparent reporting of screen failure Participants, a minimal set of screen failure information will be recorded in the eCRF and will include demography, screen failure reason (e.g., withdrawal of consent), eligibility criteria, any protocol deviations and any AEs or incidents as applicable. Individuals who do not meet the criteria for participation in this study (screen failures) may not be re-screened.

5.2.10 Supervised Brushing with Acclimatisation Toothpaste

Enrolled participants will be provided with the acclimatisation toothpaste, a toothbrush, rinsing cups, a timer and written usage instructions to use during the acclimatisation period.

Designated dispensing staff will describe the toothpaste usage instructions to the participant, demonstrate covering the full brush head with a ribbon of toothpaste and how to use the timer. Staff will then supervise the Participant carrying out their first timed brushing with the acclimatisation toothpaste. Any deviation from the product usage instructions will be captured as a protocol deviation and the Participant will be re-instructed in the correct directions for use.

Dispensing of the acclimatisation toothpaste and completion of the supervised first brushing will be documented in the eCRF.

Spontaneously reported AEs and any AEs elicited by asking the participant to respond to non-leading questions (e.g., ‘how do you feel?’) on completion of the supervised brushing will be recorded in the eCRF.

Dispensing staff will remind participants (i) of the lifestyle considerations (Section 4.5) and concomitant medication/treatment (Section 4.6) requirements of the study, as detailed in the ICF; (ii) to note any changes in their health, medications or treatments between visits so they can inform staff at their next visit (or to report such changes to the investigator staff using the contact numbers provided, if preferred) and (iii) to bring their acclimatisation toothpaste and toothbrush to their next study visit.

5.3 BASELINE (Visit 2, Day 1)

The following procedures and assessments will be completed by the investigator, the clinical examiner, or suitably qualified, trained and experienced designees. Where practically feasible, the procedures and assessments should be completed in the order listed below. Data collected will be recorded in the eCRF.

5.3.1 Product Usage Compliance Checks

Designated dispensing staff will complete visual checks of the participant's returned acclimatisation toothpaste and toothbrush and question the Participant about compliance with the usage instructions. Any deviation from the required usage instructions (e.g., suspected over or under use. Participant-reported missed or additional brushings) will be captured as a protocol deviation and Participants will be re-instructed in the correct usage.

Do not return the acclimatisation toothpaste or toothbrush to the participant.

5.3.2 Changes in Medical History and Concomitant Medications/Treatments

Investigator staff will ask participants if there have been any changes in their health, concomitant medications and non-drug treatments. Changes will be recorded.

Spontaneously reported AEs and any AEs elicited during questioning about changes in health or by asking participants to respond to non-leading questions (e.g., 'how are you feeling?') will be recorded.

Female participants only:

- Female participants of child-bearing potential will be asked about pregnancy. Those who report being pregnant will be withdrawn from the study.
- Female participants of child-bearing potential will be reminded to inform the investigator site immediately if pregnancy is known or suspected.

5.3.3 Participant Adherence and Continuance

Investigator staff will question Participants about adherence to the lifestyle considerations (Section 4.4) and concomitant medication/treatment (Section 4.5) requirements of the protocol; any deviations from study requirements will be recorded in the eCRF. Participant continuance will be confirmed.

5.3.4 Clinical Examinations and Assessments

The following clinical examinations and DH assessments will be completed as described in Section 7 (Study Assessments) of this protocol.

- OST examination.
- Clinical assessment of tactile sensitivity (tactile threshold (g); maximum force 20g). Assess all 'eligible teeth' (Section 4.2 Inclusion Criterion 6c) identified at Screening, i.e., teeth with a Screening tactile threshold of $\leq 20g$ and a Screening Schiff sensitivity score ≥ 2 .
Ensure at least a 5-minute break between completing the tactile assessments and starting the evaporative (air) assessments.
- Clinical assessment of evaporative (air) sensitivity (Schiff sensitivity score **CCI**).
Assess each 'eligible tooth' with a Baseline tactile threshold of $\leq 20g$.

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Participants must have at least two ‘qualifying teeth’ with a tactile threshold $\leq 20\text{g}$ and a Schiff sensitivity score ≥ 2 at both Screening and Baseline to continue in the study (Section 4.2 Inclusion Criterion 7).

Participants with fewer than two ‘qualifying teeth’ will be discontinued.

Transcription of data from any source documents used into the eCRF must be completed within 5 days of recording the data for each Participant.

5.3.5 Selection of Test Teeth

The clinical examiner responsible will select two ‘test teeth’ for DH assessment at all subsequent study visits.

‘Test teeth’ should only be selected from ‘eligible teeth’ identified at Screening with qualifying levels of DH at both Screening (Visit 1) and Baseline (Visit 2).

- Tactile threshold $\leq 20\text{g}$ at Screening (Visit 1) and Baseline (Visit 2).
- Schiff sensitivity score ≥ 2 at Screening (Visit 1) and Baseline (Visit 2).

To be representative of different areas of the mouth with independent innervation, ‘test teeth’ should be non-adjacent and in different quadrants. The identity of the ‘test teeth’ will be recorded in the eCRF.

5.3.6 Participant Qualification

The investigator, or medically qualified designee, will review the inclusion/exclusion criteria and verify the presence of two ‘test teeth’ which meet all study criteria before confirming the Participant’s suitability to continue in the study; their decision will be documented in the eCRF.

5.3.7 Stratification and Randomisation

Each qualifying participant will be stratified to one of two strata and randomised to study toothpaste as described in Section 7.3. Participant stratum will be entered into the eCRF.

Qualifying Participants will be assigned a randomisation number from their designated stratum in ascending numerical order, as each Participant is determined to be fully eligible.

5.3.8 Supervised Brushing with Study Toothpaste

Randomised participants will be provided with their allocated study toothpaste, a new toothbrush, new rinsing cups and written usage instructions. Allocation of study toothpaste (number) will be recorded in the eCRF prior to supervised brushing of study product.

Designated dispensing staff will describe the toothpaste usage instructions to each Participant, reminding them to cover the full toothbrush head with a ribbon of toothpaste and to use the timer each time they brush.

- Participants randomised to the test toothpaste will be shown the location of their two

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‘test teeth’ within the mouth (using a tooth diagram and/or model and a mirror, as needed).

• CCI

Dispensing staff will supervise each participant carrying out their first timed brushing with their allocated study toothpaste. Any deviation from the product usage instructions will be recorded as a protocol deviation and the Participant will be re-instructed in the correct directions for use.

Dispensing and completion of the supervised first brushing with study toothpaste will be recorded in the eCRF.

Spontaneously reported AEs and any AEs elicited by asking the participant to respond to non-leading questions (e.g., ‘how do you feel?’) on completion of the supervised brushing will be recorded.

Randomised participants will be re-instructed in the lifestyle considerations (Section 4.4) and concomitant medication/treatment (Section 4.5) requirements and reminded to bring their allocated study toothpaste and toothbrush to their next study visit.

CCI

5.4 Day 2 (Visit 3) and Week 1 (Visit 4, Day 8 (± 1 day))

The following procedures and assessments will be completed by the investigator, the clinical examiner, or suitably qualified, trained and experienced designees. Where practically feasible, the procedures and assessments should be completed in the order listed below. Data collected will be recorded in the eCRF.

5.4.1 Product Usage Compliance Checks

Designated dispensing staff will complete visual checks of each Participant’s returned tubes of study toothpaste and toothbrush and question the participant about compliance with the product usage instructions.

CCI

Return the study toothpaste and toothbrush to the Participant.

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5.4.2 Changes in Medical History and Concomitant Medications/Treatments

Investigator staff will ask participants if there have been any changes in their health, concomitant medications and non-drug treatments. Changes will be recorded.

Spontaneously reported AEs and any AEs elicited during questioning about changes in health or by asking Participants to respond to non-leading questions (e.g., ‘how are you feeling?’) will be recorded.

Female Participants only:

- Female participants of child-bearing potential will be asked about pregnancy. Those who report being pregnant will be withdrawn from the study.
- Female participants of child-bearing potential will be reminded to inform the investigator site immediately if pregnancy is known or suspected.

5.4.3 Participant Adherence and Continuance

Investigator staff will question Participants about adherence to the lifestyle considerations (Section 4.4) and concomitant medication/treatment (Section 4.5) requirements of the protocol; any deviations from study requirements will be recorded. Participant continuance will be confirmed.

5.4.4 Clinical Examinations and Assessments

The following clinical examinations and DH assessments will be completed as described in Section 7 (Study Assessments) of this protocol.

- OST examination.
- Clinical assessment of tactile sensitivity (tactile threshold (g); maximum force 80g). Assess the two ‘test teeth’ only.
Ensure at least a 5-minute break between completing the tactile assessments and starting the evaporative (air) assessments.
- Clinical assessment of evaporative (air) sensitivity (Schiff sensitivity score **CCI**)
CCI
Assess the two ‘test teeth’ only.

CCI

Transcription of data from any source documents used into the eCRF must be completed within 5 days of recording the data for each participant.

5.5 Week 2 (Visit 5, Day 15 (± 1 day))

The following procedures and assessments will be completed by the investigator, the clinical examiner(s) or suitably qualified/experienced and trained designees. Where practically feasible, the procedures and assessments should be completed in the order listed below.

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5.5.1 Product Usage Compliance Checks

Designated dispensing staff will complete visual checks of each Participant's returned study toothpaste and toothbrush and question the participant about compliance with the usage instructions. Any deviation from the required usage instructions (e.g., suspected over or under use, Participant-reported missed or additional brushings) will be captured as a protocol deviation.

Do not return the study toothpaste or toothbrush to the participant.

5.5.2 Changes in Medical History and Concomitant Medications/ Treatments

Investigator staff will ask participants if there have been any changes in their health, concomitant medications and non-drug treatments. Changes will be recorded.

Spontaneously reported AEs and any AEs elicited during questioning about changes in health or by asking Participants to respond to non-leading questions (e.g., 'how are you feeling?') will be recorded.

Female Participants only:

- Female participants of child-bearing potential will be asked about pregnancy. Those who report being pregnant will complete the procedures, examinations and clinical assessments scheduled for Visit 5; the Participant will be followed-up to determine pregnancy outcome (see Appendix 9.2).

5.5.3 Participant Adherence and Continuance

Investigator staff will question participants about adherence to the lifestyle considerations (Section 4.4) and concomitant medication/treatment (Section 4.5) requirements of the protocol; any deviations from study requirements will be recorded. Participant continuance will be confirmed.

5.5.4 Clinical Examinations and Assessments

The following clinical examinations and DH assessments will be completed as described in Section 7 (Study Assessments) of this protocol.

- OST examination.
- OHT examination.
- Clinical assessment of tactile sensitivity (tactile threshold (g); maximum force 80g).**
Assess the two 'test teeth' only.
Ensure at least a 5-minute break between completing the tactile assessments and starting the evaporative (air) assessments.
- Clinical assessment of evaporative (air) sensitivity (Schiff sensitivity score** CCI
CCI
Assess the two 'test teeth' only.

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5.6 Study Conclusion

The Study Conclusion screen of the eCRF will be completed for all participants whether or not they complete all study procedures (i.e., even if they discontinue early). If a Participant is discontinued early, the primary reason for withdrawal should be recorded in the Study Conclusion data. For participants who attend all scheduled study visits, Study Conclusion will be completed at Visit 5.

Investigator staff will instruct each participant to inform the investigator site if they experience any change in health, medications or treatments (including pregnancy) in the 5 days following their last use of a study product.

If a participant has any clinically significant, study-related abnormalities or AEs at the end of the study, the sponsor should be notified. The Participant may be asked to return to the investigator site for a follow-up visit to ensure any issue is resolved or deemed not clinically significant.

5.7 Follow-Up Contact

The investigator site may contact a participant to follow up an AE post-study completion or withdrawal and, in some circumstances, may request they return to the investigator site for additional follow-up visits (i.e., final safety assessments). At the discretion of the investigator or medically qualified designee, additional oral examinations may be carried out at such visits.

6 STUDY ASSESSMENTS

6.1 Screening Assessments (Visit 1)

Screening examinations and DH assessments will be performed by appropriately trained and experienced clinical examiners at the times and in the order defined in Section 6 (Study Assessments) of the protocol.

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The eligibility of each tooth will be assessed against the protocol inclusion/exclusion criteria (Section 4.2 and Section 4.3) and recorded in the eCRF. If, in the opinion of the clinical examiner, the value/score for a particular tooth or area of gingiva lies between two values/descriptions, a conservative approach should be adopted, and the more conservative value/score recorded. The same approach should be applied throughout the study to ensure consistency of assessment at all timepoints.

6.1.1 Erosion, Abrasion and Recession (EAR)

The facial surfaces of all incisor, canine and pre-molar teeth (Figure 6-1) that do not present any of the general dentition exclusion criteria, or specific dentition exclusion criteria for 'eligible teeth', will be examined for signs of facial/cervical erosion and abrasion (i.e., tooth wear) and recession (Addy, 2000).

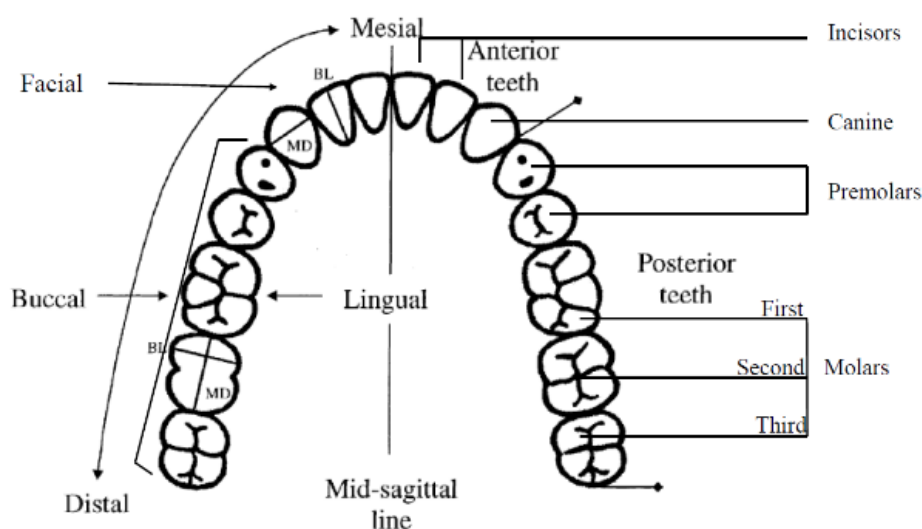


Figure 6-1 Dental Nomenclature (Adapted from Dempsey, 2001)

6.1.2 Modified Gingival Index (MGI)

The MGI is a non-invasive visual assessment of gingival health (Lobene, 1986). MGI will be assessed for incisor, canine and pre-molar teeth (Figure 6-1) exhibiting none of the dentition exclusions and presenting with facial/cervical EAR and recession. MGI should be scored for the facial gingiva directly adjacent to the area of exposed dentine (i.e., the test area only).

Eligible teeth must have a MGI of zero (0) directly adjacent to the area of exposed dentine.

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

2	Mild inflammation; criteria as above but involving the entire marginal or papillary gingival unit.
3	Moderate inflammation; glazing, redness, 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.

6.1.3 Clinical Mobility

Clinical mobility will be assessed for incisor, canine and pre-molar teeth (Figure 6-1) exhibiting none of the dentition exclusions, with facial/cervical EAR and a MGI = 0 adjacent to the test area only, using a modification of the Miller Index (Laster, 1975).

Eligible teeth must have clinical mobility = 0.

Score	Description
0	No movement or mobility of the crown of the tooth < 0.2 millimetre (mm) in a horizontal direction
1	Mobility of the crown of the tooth 0.2 – 1 mm in a horizontal direction
2	Mobility of the crown of the tooth exceeding 1 mm in a horizontal direction
3	Mobility of the crown of the tooth in a vertical direction as well.

6.1.4 Screening Tactile Sensitivity Assessment

The tactile sensitivity of incisor, canine and pre-molar teeth (Figure 6-1) exhibiting none of the dentition exclusions, and meeting the EAR, MGI and clinical mobility criteria, will be assessed using a constant pressure probe (Yeaple probe (Polson, 1980)). The probe tip will be placed perpendicular to the facial surface of the tooth and drawn slowly across the exposed dentine to ensure application of the stimulus across the potentially ‘sensitive’ area.

After each application of the tactile stimulus, the participant will be asked to indicate whether they experienced any pain or discomfort. The examiner will tell the participant to only respond ‘yes’ if they feel pain or discomfort when the probe is applied to their tooth. ‘Yes’ and ‘no’ are the only acceptable answers. The participant may respond ‘yes’ if they feel pressure. The examiner will remind them, if needed, that they will feel pressure each time the probe is in contact with the tooth but they should only respond ‘yes’ if they feel pain or discomfort.

The gram setting which elicits two consecutive ‘yes’ responses will be recorded as the tactile threshold (g) for that tooth. At Screening, the upper force setting will be 20g.

- **To be deemed ‘eligible’ for Baseline DH assessment, the tooth must have a Screening tactile threshold $\leq$ 20g.**

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- **If no sensitivity is found at the upper force setting, Screening tactile threshold will be recorded as > 20g and the tooth will be disqualified from further testing.**

If a participant fails to give a definite answer, the examiner will re-prompt them to provide a response ('yes' or 'no'). If their uncertainty continues, this should be recorded in the source document. If the Participant continues to be unsure, or the examiner is unsure of the reliability of their response, the examiner may opt to re-probe at the same force setting (indicated to the scribe by a non-verbal signal, e.g., a hand gesture) or move to the next force setting (10g increase). If the examiner considers the participant's 'yes' response may be between gram settings, a conservative approach should always be adopted, and the lower (more 'severe') tactile threshold (g) recorded.

The examiner will generally make the force setting adjustments (this can also be done by an assistant or the scribe); the scribe will record the micro-amperage setting and participant's responses in the source document.

Calibration of the Yeaple Probe:

The Yeaple probe will be calibrated by an appropriately trained member of the investigator staff (typically the clinical examiner, their assistant or scribe) before use on each day participants are assessed. The microamp settings may vary from day to day (partly due to battery power consumption), but the difference should not be significant. Thus, previous probe settings can be used as a guide. Calibration should start at the lowest microamp setting and then increase.

Either calibration method described below is acceptable.

- **Method 1 ('Water Cup'):** The Yeaple probe is fixed to a clamp attached to a ring stand so that the probe tip is vertical. A small paper cup attached with cotton thread is balanced over the end of the Yeaple probe, without the probe tripping. The probe dial is set to the microamp setting and water is fed into the paper cup using a dropper until the probe trips. The gram setting is recorded, and the Yeaple probe reset to the next microamp value. The procedure is repeated until data has been collected to more than 80g.
- **Method 2:** The Yeaple probe is fixed to a clamp attached to a ring stand so that the top is perpendicular to the pan of an ohaus dial-o-gram[®] balance or equivalent. The probe tip is positioned to just touch the pan when the balance is set at zero grams. The probe dial is set to the microamp setting and the gram setting is increased on the balance until the probe trips. The gram setting is recorded, and the Yeaple probe reset to the next microamp value.

The data are plotted, and the points connected with line segments in order to interpolate the micro-amp values equivalent to 10, 20, 30, 40, 50, 60, 70 and 80 g. This calibration should be repeated three times and the average of the three used for that day's settings.

The settings will be recorded on the Yeaple probe calibration record (along with the probe's serial number) which will serve as the force setting guide for that day's examinations.

6.1.5 Screening Evaporative (Air) Sensitivity Assessment

Evaporative (air) sensitivity will be assessed on the facial surfaces of incisor, canine and pre-

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molar teeth (Figure 6-1) which exhibit none of the dentition exclusions, meet the EAR, MGI, clinical mobility inclusion criteria and have a Screening tactile threshold ≤ 20 g. Evaporative (air) assessments will start a minimum of 5 minutes after the tactile assessments have completed (tooth recovery time).

The assessment will be made by directing a 1-second application of air from a standard dental syringe held perpendicular to the tooth surface, approximately 1-2 mm coronal to the gingival margin, and from a distance of approximately 1 cm. The clinical examiner will take appropriate measures to isolate the tooth surface to prevent stimulation of adjacent teeth or surrounding soft tissue.

Participant response to the stimulus will be evaluated using the Schiff sensitivity scale (Schiff, 1994). This is an examiner-based index, scored immediately following application of the evaporative (air) stimulus. The scale focuses on a combination of specific, observable, physical, behavioural and verbal responses from the participant, which may facilitate discrimination.

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

- To be deemed ‘eligible’ for Baseline DH assessments, a tooth must have a Screening tactile threshold ≤ 20 g and a Screening Schiff sensitivity score ≥ 2 .
- Teeth with a Screening Schiff sensitivity score < 2 will be disqualified from further testing.

6.2 Dentine Hypersensitivity Assessments (Visits 2-5)

The following DH assessments will be performed by an appropriately trained clinical examiner at the times and in the order defined in Section 6 (Study Assessments) of the protocol. If, in the opinion of the clinical examiner, the value/score for a particular tooth is between two values/descriptions, a conservative approach should be adopted, and the more conservative value/score recorded. The same approach should be applied throughout the study to ensure consistency of assessment at all timepoints.

6.2.1 Tactile Sensitivity Assessment (Visits 2-5)

Tactile sensitivity will be assessed at Baseline (Day 1), Day 2, Week 1 (Day 8) and Week 2 (Day 15). The tactile stimulus will be administered, and participant response recorded, as described in Section 7.1.4. The gram setting which elicits the two consecutive ‘yes’ responses will be recorded as the tactile threshold (g).

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- **Baseline (Day 1):** Assess the tactile sensitivity of each ‘eligible tooth’ identified at Screening (i.e., all teeth which exhibit none of the dentition exclusions and meet the EAR, MGI and clinical mobility criteria, with a Screening tactile threshold of $\leq 20g$ and a Screening Schiff sensitivity score ≥ 2).
The upper force setting will be 20g; if no sensitivity is found at the upper setting, record the tactile threshold as $> 20g$.
- **Day 2, Week 1 (Day 8) and Week 2 (Day 15):** Assess the tactile sensitivity of the ‘test teeth’ only (i.e., the two teeth selected by the clinical examiner at Baseline, as described in Section 5.3.5).
The upper force setting will be 80g; if no sensitivity is found at the upper setting, record the tactile threshold as $> 80g$.

6.2.2 Evaporative (Air) Sensitivity Assessment (Visits 2-5)

Evaporative (air) sensitivity will be assessed at Baseline (Day 1), Day 2, Week 1 (Day 8) and Week 2 (Day 15). The evaporative (air) stimulus will be administered, and participant response recorded, as described in Section 6.1.5. Evaporative (air) assessments will start a minimum of 5 minutes after the tactile assessments have completed (tooth recovery time).

- **Baseline (Day 1):** Assess the evaporative (air) sensitivity of each ‘eligible tooth’ identified at Screening with a Baseline tactile threshold of $\leq 20g$.
- **Day 2, Week 1 (Day 8) and Week 2 (Day 15):** Assess evaporative (air) sensitivity for the two ‘test teeth’ only.

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Page 37 of 82

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Page 38 of 82

Haleon
Clinical Protocol
Protocol Number: 300212

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Page 39 of 82

6.3 Safety Assessments

The following safety assessments will be performed by appropriately trained and experienced clinical examiners at the times and in the order defined in Section 6 (Study Assessments) of the protocol.

6.3.1 Oral Soft Tissue (OST) Examination

The OST examination will be accomplished by direct visual observation and palpation, using retraction aids if needed, and will include examination of the labial mucosa (including lips), buccal mucosa, mucogingival folds, gingival mucosa, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands.

The findings of the OST examination will be recorded as either 'normal' or 'abnormal'; details of any abnormalities will be described in the eCRF. Any observation that changes from 'normal' to 'abnormal' or worsens from the OST examination completed at Screening will be recorded as an AE.

6.3.2 Oral Hard Tissue (OHT) Examination

The OHT examination will be accomplished by direct visual observation, using retraction aids if needed, and will identify enamel irregularities, tooth fractures, grossly carious lesions/gross decay, defective/faulty restorations (both direct and indirect restorations, including fixed/removable prostheses), non-carious tooth surface loss (abrasion, attrition, abfraction and erosion), any other hard tissue irregularities (e.g., hypo- and hyper-mineralisation, decalcification) and significant tooth staining.

Findings will be recorded as 'absent' or 'present'; conditions noted as 'present' will be described in the eCRF. Any observation that changes from 'absent' to 'present' or worsens from the OHT examination completed at Screening will be recorded as an AE.

The location of any implants, fixed or removable dentures, fixed or removable orthodontic braces/bands, fixed or removable orthodontic retainers, full crowns or veneers will be recorded, along with evidence of gross intra-oral neglect or the need for extensive dental therapy.

The OHT examination will also be used to assess the participant's dentition against the general and specific dentition exclusions described in Section 4.3 (Exclusion Criteria 22-26 & 27 a-g).

7 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 authorisation 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 Study Product Supplies

Each participant will receive sufficient tubes of the acclimatisation toothpaste and their allocated study toothpaste to cover usage during the acclimatisation and investigational periods, respectively. The following study products (acclimatisation and study toothpastes) will be supplied by the sponsor's Clinical Supplies department ([Table 7-1](#)). Toothpaste usage instructions are consistent with the commercial pack instructions.

Table 7-1 Study Products

	Acclimatisation Toothpaste	Test Toothpaste	Negative Control Toothpaste
Product Name	Regular fluoride toothpaste (Aquafresh Fresh & Minty*)	0.454 % w/w SnF ₂ toothpaste (Sensodyne Rapid Relief*)	Regular fluoride toothpaste (Colgate Cavity Protection*)
Fluoride Level	1450 parts per million (ppm) fluoride [†]	1100 ppm fluoride [‡]	1000 ppm fluoride [#]
Master Formulation Code	CCI	CCI	N/A
Dispensing Details	1 tube of toothpaste at Screening (Visit 1)	1 tube of toothpaste at Baseline (Visit 2)	1 tube of toothpaste at Baseline (Visit 2)
Route of Administration	Topical Oral Use	Topical Oral Use	Topical Oral Use
Toothpaste Usage Instructions	Dose the toothbrush with a ribbon of toothpaste, across the full brush head. Start the timer (pre-set for 1-minute).		
			
	Participants who wish to rinse after brushing will be instructed to rinse with 10 millilitres (ml) water using graduated rinsing cups provided.		
Duration of Product Usage	Acclimatisation Toothpaste: Approximately 2 weeks (14 ± 2 days) Study Toothpaste: Approximately 2 weeks (14 ± 1 days)		
Return Requirements	All used/unused tubes to be returned to the sponsor.		

* Commercially available daily use toothpaste, United Kingdom (UK) market.

* Commercially available daily use toothpaste, United States (US) market.

[†] As sodium fluoride [‡] As SnF₂ [#] As sodium monofluorophosphate

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The brushing instructions for each study product (acclimatisation and study toothpastes) are aligned with the directions for use on their respective commercial packs. Sufficient supplies of the following sundry items ([Table 7-2](#)) will be supplied to complete the study by the sponsor's Clinical Supplies department (to be dispensed by site staff, as required).

Table 7-2 Sundry Items

Item	Pack Design	Dispensing Details	Return/Disposal Details	
			Used Samples	Unused Samples
Oral B Sensi-Soft (US market) <i>Manual, flat trim, soft toothbrush</i>	One toothbrush in its commercial pack	Screening (Visit 1): One toothbrush Baseline (Visit 2): One toothbrush	Destroy at site using site disposal procedures.	Return
Countdown Timer	One timer in its commercial pack	Screening (Visit 1): One timer	Participant to keep or destroyed at site using site disposal procedures.	Return
Graduated Rinsing Cups	N/A	Screening (Visit 1): 2 cups Baseline (Visit 2): 2 cups	Participant to keep or destroyed at site using site disposal procedures	Return
Opaque Carrier Bags	N/A	Screening (Visit 1): One bag Baseline (Visit 2): One bag	Participant to keep or destroyed at site using site disposal procedures	Return

Detailed instructions for the return of study products and sundry supplies for accountability checks and subsequent destruction will be provided by the sponsor at study initiation and prior to study close out.

7.2 Study Product Storage, Accountability, Returns and Destruction

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

Guidance on the receipt, storage and management of study products and supplies will be provided to the investigator and investigator staff by Haleon Clinical Supplies at Site Initiation, with further instructions included in the shipping documentation.

The investigator should ensure that areas used for study product storage are secure and access controlled, able to maintain the temperature requirements specified by the product label storage conditions, and sufficient in size to accommodate all study products.

Any temperature excursions or discrepancies that occur during transit or whilst study products are stored at the investigator site will require the affected products to be quarantined. Any

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temperature excursions or discrepancies 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 receipt of sponsor approval will be considered a protocol deviation.

Study products (acclimatisation toothpaste and study toothpastes) are to be dispensed to participants in accordance with the protocol, by designated investigator staff. Enrolled/randomised Participants will be instructed on correct product usage, storage and return and what to do in the event of product loss when the products are first dispensed.

All study products will be accounted for using the study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

All study product (used and unused) for this clinical study will be returned to the sponsor or designated vendor for destruction using the return instructions provided by Haleon Clinical Supplies department. If the investigator site has the capability to destroy study products, they can only be destroyed at site with the agreement of, and after written approval from the sponsor.

7.3 Randomisation and Blinding

Qualifying participants will be centrally randomised to one of two study toothpastes using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided to the investigator site. Study toothpastes will be dispensed according to the instruction received through the IRT at Baseline (Visit 2). Returned study toothpastes should not be re-dispensed to any Participant.

Only participants who meet the study selection criteria will be randomised to study toothpaste. Qualifying participants will be stratified by the maximum Baseline Schiff sensitivity score of their two selected 'test teeth'; this stratification factor will give rise to two strata.

- **Stratum 1:** Maximum Schiff sensitivity score = 2.
- **Stratum 2:** Maximum Schiff sensitivity score = 3.

This study is described as examiner-blind (i.e., the clinical examiner will be blinded to the study toothpaste each Participant receives). However, study participants, investigator staff involved in the clinical (DH) or safety assessments, study statistician(s), data management staff, other employees of the sponsor (including the sponsor's Clinical Research Scientist (CRS)) and vendors acting on behalf of the sponsor who may influence study outcomes, will also be blinded to treatment allocation. Monitors and the sponsor's Clinical Study Manager (CSM) cannot be fully blinded as they may observe participants brushing with their allocated treatment while at the investigator site.

To maintain the blind throughout the study:

- Study participants will see and use only one of the two study toothpastes during the study. They will be instructed not to discuss the appearance, usage, or perceived performance of their allocated study toothpaste with the clinical examiner, with staff involved in clinical assessments or with other study participants.
- The study toothpastes will be provided to the investigator site overwrapped in white vinyl to mask their identity and to obscure any branding on the commercial packs, with

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a study label affixed.

- The study toothpastes will be supplied in individual packs. The tube will be labelled with the same unique container number. Each participant will be assigned to the container number associated with the tube containing only their randomised study toothpaste using the IRT; product codes will not be used.
- The clinical examiner and investigator staff involved in clinical (DH) or safety assessments will not be permitted in any area where study toothpastes are stored, dispensed or in use.
- Investigator staff involved in the dispensing of study toothpastes, providing brushing instruction, supervision of on-site brushings, usage compliance checks and product accountability will not be involved in the clinical (DH) or safety assessments and will work in a separate area from the clinical examiner and investigator staff involved in the clinical (DH) and safety assessments.
- Participants will be instructed not to remove their allocated study toothpaste from the opaque carrier bag provided outside of the dispensing/supervised brushing room, while at the investigator site.
- Where certain staff will be unblinded to carry out their responsibilities (e.g., staff involved in SAE reporting, monitors), the investigator and sponsor are required to put adequate procedures in place to prevent inappropriate dissemination of treatment identification.

7.4 Breaking the Blind

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study toothpaste assignment is warranted. Participant 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 participant's study toothpaste assignment unless this could delay emergency treatment of the participant.

If a participant's study toothpaste 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

Sufficient participants will be screened and entered into the acclimatisation phase to ensure approximately 80 participants are randomised to study toothpaste (approximately 40 participants per group) and approximately 70 participants complete the study (approximately 35 participants per study toothpaste group, allowing for up to 10% dropouts).

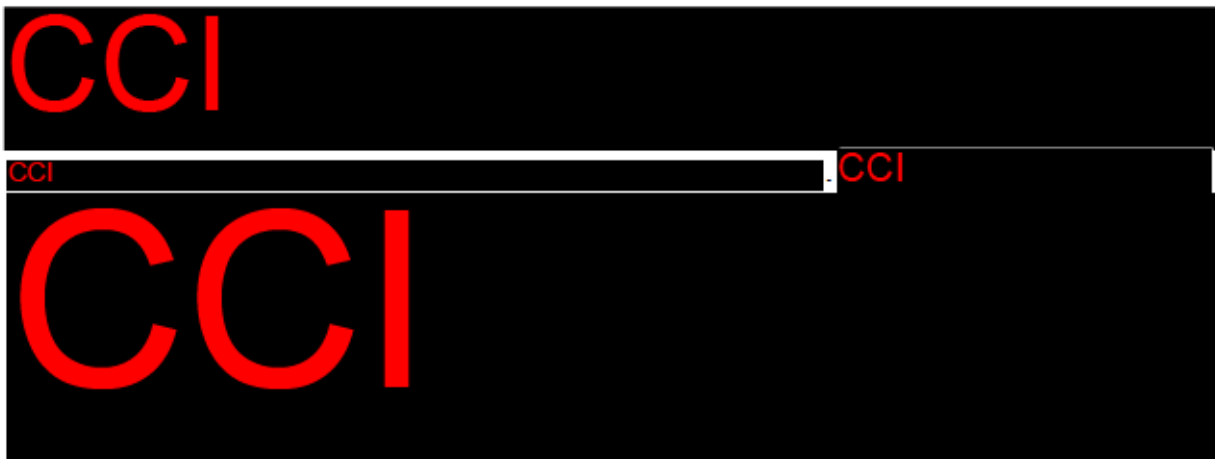
The aim of this study is to characterise the short-term DH protection profiles of a 0.454% SnF₂ toothpaste (test toothpaste) and a regular fluoride toothpaste (negative control) in order to familiarise a new DH examiner with Haleon DH protocol procedures, thus no formal sample

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size estimation has been performed, the formal power of this study is not the main driver for the selected sample size. That said, the power characteristics for the primary endpoints at Week 2 are described below.



8.2 Populations for Analysis

8.2.1 Definitions of Analysis Populations

The Screened population will include all the participants who provide the informed consent.

The Randomised population will include all the participants who are randomised in the study.

The Safety population will include all randomised participants who complete at least one use of study toothpaste. This population will be based on the study toothpaste the participant received. All summaries and assessments of safety will be based on this analysis population.

The modified Intent-To-Treat (mITT) population will include all randomised participants who complete at least one use of study toothpaste and have at least one post Baseline efficacy assessment. This population will be based on the study toothpaste the participant was randomised to. All assessments of efficacy will be primarily based on this analysis population.

The per protocol (PP) population will include all participants in the mITT population who have at least one efficacy assessment considered to be unaffected by protocol deviations.

8.2.2 Exclusions of Data from Analysis

Exclusion of data from any of the planned analyses will be agreed during Blinded Data Review (BDR) Meeting prior to database lock. The reasons for exclusion of a participant from an analysis population or specific data from an analysis will be documented and, if applicable, listed in the Clinical Study Report (CSR).

A PP analysis will be performed for the primary and secondary efficacy endpoints if there is more than 10% difference in the number of participants between the PP and mITT populations. The decision to perform a PP analysis should be made prior to study unblinding (release of the randomisation codes).

8.3 Statistical Analyses

The detail of the proposed statistical analysis will be documented in the Statistical Analysis Plan (SAP) to be written following protocol approval and prior to study unblinding. A summary of the planned statistical analyses (primary and key secondary endpoints) and a brief summary of how other collected data will be analysed is provided below.

The mITT population will be used for all efficacy analyses.

Schiff sensitivity score, tactile threshold (g) **CCI** for each visit will be derived as the average score or value of the 2 'test teeth' (identified at Baseline). Change from Baseline will be derived for the individual teeth first before calculating the average change for the 2 'test teeth'.

Descriptive summary statistics (mean, median, standard error (SE), SD, minimum, maximum) will be presented for the actual and change from Baseline for Schiff sensitivity score and tactile threshold (g) outcome variables at each assessment time point by study toothpaste group, or

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Raw and Change from Baseline means ($\pm$ SE) of the Schiff sensitivity score and tactile threshold (g) at each assessment timepoint will be plotted by study toothpaste group. Significance testing will be conducted at the two-sided 5% significance level.

8.3.1 Primary Endpoint Analyses

The primary hypotheses supporting the primary objectives will be the comparison of changes from baseline of (i) Schiff sensitivity score and (ii) tactile threshold (g) at Week 2, within the test toothpaste group. To account for multiplicity, the following sequence of testing will be used:

1. Schiff sensitivity score change from baseline to Week 2
2. Tactile threshold change from baseline to Week 2

P-values will be considered statistically significant up to the point of the first p-value in the sequence to be > 0.05 . That is to say, if the p-value of the testing in the first sequence > 0.05 and the following test in the sequence will be declared as insignificant. 95% confidence intervals will be provided for all point estimates within the sequence of tests regardless of statistical significance.

Change from Baseline in Schiff sensitivity score will be analysed using a Mixed Model with Repeated Measures (MMRM), with study products (test toothpaste, negative control), visit, and study products -by- visit interaction as fixed effects, and Baseline Schiff sensitivity score as a covariate. Participant will be included as a repeated measure with unstructured covariance matrix. Kenward-Rogers degrees of freedom will be applied (Kenward, 1997).

For the hypotheses listed above for Schiff sensitivity score, the LS means estimates for the Changes from Baseline from this model for the test toothpaste group at Week 2 will be the source for the two-sided p-values and 95% confidence intervals (CIs). Descriptive statistics for the Schiff sensitivity score at each assessment time point and the Change from Baseline in Schiff sensitivity score at Day 2, Week 1 and Week 2 will be provided for the test toothpaste

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arm and the negative control arm, or number of brushings (2 or 3) the participant has completed with allocated study toothpaste prior to attending this visit if applicable.

Change from Baseline in tactile threshold (g) will be analysed using the same MMRM but with Baseline tactile threshold (g) as a covariate, rather than Baseline Schiff sensitivity score. In addition, the maximum Baseline Schiff sensitivity score of the two 'test teeth' (score = 2 or 3) will be fitted as a fixed effect.

For the hypotheses listed above for Tactile threshold, the LS means estimates for the Changes from Baseline from this model for the test toothpaste group at Week 2 will be the source for the two-sided p-values and 95% confidence intervals (CIs). Descriptive statistics for the Tactile threshold at each assessment time point and the Change from Baseline in Tactile threshold at Day 2, Week 1 and Week 2 will be provided for the test toothpaste arm and the negative control arm.

The assumptions of normality and homogeneity of variance in each MMRM will be investigated. In case of violation of these assumptions, a suitable non-parametric test will be performed to assess change from Baseline to each visit within the test toothpaste group and the results will be provided to support the MMRM results; non-parametric results will be considered confirmatory under the observation of strong violations of the assumptions.

8.3.2 Secondary Endpoint Analyses

Change from Baseline in Schiff Sensitivity Score and Tactile Threshold (g) at Day 2 and Week 1, Within Test Toothpaste and Negative Control:

These secondary endpoints will be analysed using the same MMRM models described in Section 8.3.1 for Change from Baseline in Schiff sensitivity score and tactile threshold (g) at Week 2.

Change from Baseline in Schiff Sensitivity Score and Tactile Threshold (g) at Day 2, Week 1 and Week 2, Test Toothpaste versus (vs.) Negative Control:

These secondary endpoints will be analysed using the same respective MMRM models described in Section 8.3.1 for the change from Baseline in Schiff sensitivity score and tactile threshold (g) described above.

The LS mean difference between the test toothpaste compared to the negative control at Day 2, Week 1 and Week 2 will be presented along with two-sided p-value and 95% CIs.

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8.3.4 Safety Analyses

Safety analyses will be performed on the Safety population, according to study toothpaste received. AEs will be regarded as 'treatment emergent' if they occur on or after the first use of study toothpaste at Baseline (Visit 2). In the event of a missing start date, an AE will be assumed to be 'treatment emergent' unless the end date is prior to starting treatment. In case of misallocation, compared to the randomisation schedule, TEAEs will be associated with the most recent study toothpaste received.

Each AE will be categorized as oral or non-oral by the investigator, or medically qualified designee. All AEs will be reviewed by the CRS and the sponsor's Consumer Safety Scientist (CSS) prior to database lock and unblinding and coded using the MedDRA.

A listing of all AEs will be presented for all Participants in the Safety population with the following AEs summaries (number of distinct AEs and frequency/proportion of participants affected) will be presented by study toothpaste group and overall:

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

Separate listings will be presented for:

- Deaths, SAEs and any AEs leading to product or study discontinuation.
- OST findings (with a summary of abnormalities by visit)
- OHT findings (with a summary of changes by visit)
- Exposure to study toothpaste

8.3.5 Other Analyses

Not applicable.

8.3.6 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized by study toothpaste group for the Safety and mITT populations, and for the PP population if a PP analysis is performed.

Categorical variables (such as sex, race and Baseline Schiff sensitivity score stratification value) will be summarized by the number and percentage of participants with each relevant characteristic in each study toothpaste group. Continuous variables such as (age) will be summarized by mean, SD, median, minimum and maximum values in each study toothpaste group.

8.3.7 Study Product Compliance and Use of Other Therapies

8.3.7.1 Study Product Compliance

Compliance with product use (number of brushings) will be listed and summarised for the mITT population at each visit, and cumulatively for the overall treatment period (for most participants this will be Day 14) by product group.

Number of expected brushings = $2 \times$ Number of days between Visit X and Visit (X+1)

Number of actual brushings = (Number of expected brushings) – (Number of missed brushings) + (Number of additional brushings)

% Compliance at 'Visit X' = $\frac{\text{(Number of actual brushings prior to Visit X)}}{\text{(Number of expected brushings prior to Visit X)}} \times 100$

8.3.7.2 Prior and Concomitant Medications

Prior medications/non-drug therapies and concomitant medications/significant non-drug therapies taken during the study will be listed for the Safety population.

8.3.8 Handling of Dropouts and Missing Data

MMRM analyses account for missing data using 'a missing at random' assumption, i.e., there is a systematic relationship between the propensity for missing values and the observed data, but not the missing data. Under such assumptions, MMRM is shown to provide unbiased estimates of the treatment effect, whilst the analysis of only complete cases using ANCOVA are biased (Baron, 2008; Ashbeck, 2016). Such complete case analysis requires a 'missing completely at random' assumption to remain unbiased and this is unlikely to hold, i.e., the fact that the data are missing is independent of the observed and unobserved data.

Using an MMRM, it will therefore be assumed that a participant with missing data at one post-Baseline visit would have obtained a similar efficacy result at that visit compared to a Participant using the same study toothpaste with similar non-missing results at other timepoints (Baseline and the other post-Baseline visits).

For the participants who discontinued early from their study toothpaste, the Treatment Policy will be used for the data analysis. That is to say, the data will be collected and used for analysis if participants with early study toothpaste discontinuation but still stay in the study. The data

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will be imputed based on MMRM mentioned above for the Participants whose data can't be collected after early study toothpaste discontinuation.

8.3.9 Interim Analysis

No interim analysis is planned for this study.

9 APPENDICES

9.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator and their medically 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 study product, a study procedure or study participation, or that caused the participant to discontinue use of a study product or study participation.

9.1.1 Definition of an Adverse Event (AE)

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

Note: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study product including an acclimatisation product (or medical device).

Events Meeting the AE Definition:

- Any abnormal laboratory test results (haematology, clinical chemistry or urinalysis) or other safety assessments (e.g., electrocardiogram, 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).
Note: Any OST observation that changes from 'normal' to 'abnormal', or worsens, from the OST examination completed at Screening should be recorded as an AE' irrespective of clinical significance.
- 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.

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- ‘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 an AE if they fulfil 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 participant’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 participant’s condition.
- A medical or surgical procedure (e.g., endoscopy, appendectomy) is not an 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

An SAE is a particular category of AE 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., hospitalisation 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 participant 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 hospitalisation or prolongation of existing hospitalisation**
 - In general, hospitalisation signifies that the participant 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether ‘hospitalisation’ occurred, or was necessary, the AE should be considered serious.
 - Hospitalisation 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, diarrhoea, 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 hospitalisation but may jeopardize the participant 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 hospitalisation, 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 from immediately after a participant provides consent to participate in the study by the completion (signature) of the ICF until 5 days following the last administration of study product (or the last study procedure).

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

Details recorded by the participant that meet the definition of an AE must be discussed with the participants and transcribed into the AE section of the eCRF.

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 updated SAE data to the sponsor within 24 hours of it being available.

The investigator and their medically qualified designees are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the investigator or their medically qualified designee learns of an SAE, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to study product or study participation, they must promptly notify the sponsor.

9.1.4 Reporting Procedures

The investigator and their medically qualified designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for

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following up AEs that are serious, considered related to study product, a study procedure or study participation, or that caused the participant to discontinue use of study product or study participation.

The investigator and their medically qualified designees are to report all AEs directly observed at study visits and all AEs spontaneously reported by study participants.

Study participants will be questioned about AEs. Care will be taken not to introduce bias when questioning a Participant about any changes in their health. Open-ended and non-leading verbal questioning should be used.

AEs spontaneously reported by study participants and those elicited by asking participants to respond to non-leading questions (such as ‘how do you feel?’) will be assessed, recorded in the eCRF and reported, as appropriate.

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 their medically qualified designee to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator or study staff will then record all relevant information relating to the event in the AE section of the eCRF. In addition, all details relating to an SAE will be recorded on the paper SAE form provided.

It is **not** acceptable for the investigator or their medically qualified designee to send photocopies of a participant’s medical records to the sponsor in lieu of completion of the AE section of the eCRF/paper SAE form. There may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all Participant identifiers, except for the participant number, will be redacted on the copies of the medical records prior to submission to the sponsor.

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

9.1.5 Reporting an AE

AEs will be reported by the investigator, their medically qualified designee or investigator staff in the AE section of the eCRF. The paper form used for collection of SAE information is not the same as the AE section of the eCRF. AEs/SAEs should be reported using concise medical terminology. Where the same data are collected, the AE section of the eCRF and the SAE form must be completed in a consistent manner (e.g., the same AE term should be used for both).

9.1.6 Reporting an SAE

In addition to recording the details of each SAE in the AE section of the eCRF, an SAE form should be completed, as fully as possible. Hard copies of the ‘paper’ SAE form will be provided in the investigator site file. Original, completed SAE forms will be retained in the investigator site file.

It is essential to record the following information for each SAE:

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

The following are desirable and are of particular relevance for investigator and sponsor assessment of the SAE report:

- Date of onset of SAE
- Date SAE stopped, if relevant
- Study product start date
- Study product end date, if relevant
- Action taken in relation to study product
- Outcome, if known

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

The initial report will be followed up with more information as relevant, or as requested by the sponsor's Study Manager. The sponsor's Study Manager will be responsible for forwarding the SAE form to other sponsor personnel as appropriate.

9.1.7 Evaluating AEs

Assessment of Intensity

The investigator or their 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 participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently discomfoting to interfere with normal everyday activities
- **Severe:** An event that prevents normal everyday activities.

Note: An AE assessed as 'severe' should not be confused with an SAE. 'Severe' is a category utilized for rating the intensity of an event. Both non-serious AEs and SAEs can be assessed as severe, e.g., a headache may be severe (significantly interferes with the participant's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed

in [Section 9.1.2](#). An event is defined as ‘serious’ when it meets at least one of the pre-defined outcomes described in the definition of an SAE ([Section 9.1.2](#)), **not** when it is rated as ‘severe’.

Assessment of Causality

For each AE (non-serious and serious), the investigator or their medically qualified designee **must** provide an assessment of causality in the AE section of the eCRF and on the SAE form (as appropriate, participant to classification of the AE). Causality is one of the criteria used to determine regulatory reporting requirements.

A ‘reasonable possibility’ of a relationship conveys 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 in the AE/SAE report.

The investigator or their medically qualified designee will use clinical judgment to determine causality and will also consult the Investigator Brochure (IB), Safety Statement and/or Product Information, as appropriate, when making their assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors and the temporal relationship of the event to study product use will be considered and investigated.

Where applicable, the investigator or their medically qualified designee must document in the medical notes they have reviewed the AE/SAE and provided an assessment of causality.

There may be situations, when an SAE has occurred, where the investigator or their medically qualified designee has minimal information to include in the initial SAE report. **However, it is very important that the investigator or their medically qualified designee always makes an assessment of causality for every event prior to initial transmission of the SAE data to the sponsor.** The investigator may change their opinion of causality, in light of follow-up information, and send an SAE follow-up report with an updated causality assessment.

9.1.8 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator or their medically qualified designee is required to proactively follow up with each Participant and provide further information on the participant’s condition, as available.

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

The investigator or their medically qualified designee is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated (or as requested by the sponsor) to elucidate as fully as possible the nature and/or causality of the AE/SAE. These may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

New or updated information will be recorded in the AE section of the eCRF and on the SAE form (as appropriate, participant to classification of the AE). The investigator or their medically qualified designee will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

The investigator and their medically qualified designees are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the investigator or their medically qualified designee learns of an SAE, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to study product or study participation, they must promptly notify the sponsor by emailing the information to the sponsor's Case Management Group mailbox **CCI**, with the appropriate sponsor Study Manager in copy.

The investigator or their medically qualified designee will submit any updated SAE data to the sponsor within the designated reporting time frames.

9.1.9 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 provided (Section 10.1) and recorded in the AE section of the eCRF.

When a participant withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined in this protocol.

9.1.10 Regulatory Reporting Requirements for SAEs

The sponsor has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of participants are met.

The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, the REC and the investigator.

The investigator and the sponsor will comply with 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 the investigator, as appropriate.

If the investigator receives an investigator safety report describing a SAE or other specific safety information (e.g., a summary or listing of SAEs) from the sponsor, they will review it, file it with other safety information (e.g., the IB) in the investigator site file and notify the REC, if appropriate, according to local requirements.

9.2 PREGNANCY

9.2.1 Time Period for Collecting Pregnancy Information

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

9.2.2 Action to be Taken if Pregnancy Occurs

The investigator or their medically qualified designee will record pregnancy information on the appropriate form scan and e-mail it to the Case Management Group mailbox

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CCI [REDACTED], with the appropriate sponsor Study Manager in copy. Original completed pregnancy information forms will be retained in the investigator site file.

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

9.3 DISCONTINUATION OF STUDY PRODUCT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant is discontinued early from their allocated study toothpaste (Section 9.3.1) or discontinued or prematurely withdraws from the study (Section 9.3.2), the reason(s) for study toothpaste discontinuation or Participant withdrawal and the associated date must be documented in the relevant section(s) of the eCRF. If a Participant is discontinued early from their study toothpaste, the Participant should stay in the study, revert to use of their own oral hygiene products and complete the remaining study visits (with their associated procedures, examinations and assessments), unless they need to be withdrawn or choose to withdraw from the study (see Section 9.3.2).

9.3.1 Discontinuation of Study Product

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

- Adverse Event
- Lack of efficacy from the intervention
- Participant request
- Participant to be withdrawn from the study (see Section 9.3.2)

9.3.2 Participant Discontinuation/Withdrawal

A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioural reasons, or the inability of the Participant to comply with the protocol-required schedule of study visits or procedures. The following circumstances require discontinuation of study toothpaste and/or premature Participant withdrawal:

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

If the participant 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.

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9.3.3 Lost to Follow Up

If a participant fails to return to the site for a required study visit, the investigator or designee must make every effort to regain contact with the Participant (where possible, 3 telephone calls or emails or local equivalent methods) and reschedule the missed visit as soon as possible and counsel the Participant on the importance of maintaining the assigned visit schedule and ascertain whether the Participant wishes to and/or should continue in the study.

A participant will be considered lost to follow up and withdrawn from the study if they repeatedly fail to return for scheduled visits and cannot be contacted by the study site.

If contact is made with the participant, the investigator or designee should inquire about the reason for withdrawal, request that the Participant return all products they had received and, if appropriate, request that the Participant return for a final visit and follow-up with the Participant regarding any unresolved AEs.

9.4 DATA MANAGEMENT

As used in this protocol, the term CRF is understood to refer to either a paper form or an electronic data record or both, depending on the data collection method. For this study, Participant data will be entered into an electronic CRF (eCRF) using a validated system.

Data relating to SAEs and pregnancy will be collected on paper forms. To facilitate Participant flow, paper forms (source) may also be used to record clinical data for later transcription into the eCRF.

Source documents which contain the source of data recorded in the eCRF should be specified. The eCRF can be used as a source document at the discretion of the Sponsor's Data Management group.

Each participant will be assigned and identified by a unique Screening Participant Number. Any reference made to an individual Participant within the study must be done using this number.

9.4.1 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 Participant.

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

Management of clinical data will be performed in accordance with Third Party Biostatistics and Data Management (BDM) Vendor applicable standards and data cleaning procedures, with oversight by the sponsor to ensure data integrity (e.g., to remove errors and inconsistencies in the data).

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

All CRF pages should be completed during a participant assessment when the CRF is the designated source. Data recorded elsewhere should be transcribed from the source document into the CRF within 5 days of the data being recorded.

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

9.4.2 Data Handling

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

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

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

9.4.3 Data Queries

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

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

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



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9.6 STUDY GOVERNANCE CONSIDERATIONS

9.6.1 Quality Control

In accordance with applicable regulations (including the ICH guideline for Good Clinical Practice (GCP)) and sponsor procedures, the sponsor or designee (i.e., third-party vendor) monitors will contact the investigator site prior to the start of the study to review the protocol, study requirements and investigator site responsibilities to satisfy regulatory, ethical and sponsor requirements with the investigator staff.

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

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

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

The extent and nature of monitoring will be described in a written monitoring plan held on file by the sponsor. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

9.6.2 Quality Assurance

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

In the event of an assessment, audit or inspection, the investigator must agree to grant advisors, auditors and inspectors direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

The investigator will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator will promptly supply copies of the inspection findings to the sponsor or its agent. Before response

submission to the regulatory authority, the investigator will provide the sponsor or its agents with opportunity to review and comment on responses to any such findings.

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

9.6.3 Regulatory and Ethical Considerations

9.6.3.1 Research Ethics Committee (REC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documentation, Investigator Brochure and/or Safety Statement (including any updates) and other relevant documents, e.g. recruitment advertisements, if applicable, from the REC. All correspondence with the REC should be retained in the investigator file. Copies of REC approvals should be forwarded to Haleon prior to the initiation of the study, and when subsequent amendments to the protocol are made.

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

9.6.3.2 Regulatory and Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, applicable local legal and regulatory requirements, and 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 (Council for International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the ICH guideline for Good Clinical Practice (GCP).

9.6.3.3 Participant Information

All parties will ensure protection of participant personal data and will not include Participant 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, participant 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 Participants.

The investigator site will maintain a confidential list of participants who participated in the study, linking each Participant's numerical code to their actual identity. In case of data transfer, Haleon will maintain high standards of confidentiality and protection of participants' personal data consistent with applicable privacy laws.

9.7 Records Retention

Following closure of the study, the investigator must maintain all investigator site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

Records (investigator site file) must be maintained in such a way to allow easy and timely retrieval when needed (e.g., for sponsor audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems and relevant investigator site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible, are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generation of a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

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

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

9.8 Disclosure and Publication Policy

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

The sponsor will provide the investigator with a full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

Haleon intends to make anonymized participant-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.

9.9 Conditions for Terminating the Study

Premature termination of this study may occur because a change in REC opinion, study product safety problems, or at the discretion of the sponsor.

If the study is prematurely terminated, the sponsor will promptly notify the investigator. After notification, the investigator must promptly contact all participating participants and should assure appropriate therapy/follow-up for the Participants. As directed by the sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible. The investigator should promptly inform the REC and provide the REC a detailed written explanation for the termination or suspension.

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

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

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Page 64 of 82

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Page 65 of 82

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Page 66 of 82



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Page 68 of 82

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Page 69 of 82



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Page 71 of 82

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Page 74 of 82



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Page 76 of 82

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Page 77 of 82

10 ABBREVIATIONS**Table 11-1 Abbreviations**

Abbreviation	Term
AE	Adverse Event
BDR	Blinded Data Review
CI	Confidence Interval
CRF	Case Report Form
CRS	Clinical Research Scientist
CSM	Clinical Study Manager
CSR	Clinical Study Report
DH	Dentine Hypersensitivity
EAR	Erosion/Abrasion/Recession
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
g	Gram
GCP	Good Clinical Practice
CCI	
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRT	Interactive Response Technology
CCI	
LPLV	Last Participant Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Modified Gingival Index
mITT	Modified Intention-to-Treat
ml	Millilitre
mm	Millimetre
MMRM	Mixed Model with Repeated Measures
MoA	Mode of Action
N/A	Not Applicable
CCI	
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
OTC	Over the Counter
PI	Personal Information
PP	Per Protocol
ppm	Parts per Million
PRO	Patient-Reported Outcome
PT	Preferred Term
QC	Quality Control

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Page 78 of 82

Haleon
Clinical Protocol
Protocol Number: 300212



Abbreviation	Term
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SnF ₂	Stannous Fluoride
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
UK	United Kingdom
US	United States

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