CLINICAL PROTOCOL

AN 8-WEEK, RANDOMIZED, CONTROLLED, EXAMINER-BLIND, CLINICAL STUDY TO EVALUATE THE EFFICACY OF A CALCIUM SODIUM PHOSPHOSILICATE TOOTHPASTE FOR THE RELIEF OF DENTIN HYPERSENSITIVITY IN A POPULATION OF DENTIN HYPERSENSITIVITY SUFFERERS

Protocol Number:	300100
Product Name:	5.0 percent (%) weight/weight (w/w) calcium sodium phosphosilicate (CSPS) toothpaste
Health Canada Clinical Trial Application (CTA) Number:	Not applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	N/A
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Sponsor Information

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Document History

Document	Version	Summary of Changes
Original Protocol	1.0	N/A
Protocol	2.0	(1) Correction of administrative errors relating to DHEQ endpoints and analysis: **Section 1.1. Synopsis, Objectives and Endpoints** and **Section 3. Study Objectives and Endpoints: DHEQ-related endpoints**. Section 1 Impact on Everyday Life (Q1-3) corrected to Section 1 Impact on Everyday Life (Q7-9). **12.3.2. Secondary Endpoint Analyses, DHEQ-48:** Section 1 - Impact on Everyday Life: Q1, Q2 & Q3 (separate scores) corrected to Section 1 - Impact on Everyday Life: Q7, Q8 & Q9 (separate scores). (2) **Section 1.1. Synopsis, Investigational Products** (footnote), **Section 2.2 Benefit/Risk Assessment** (paragraph 4) and **Table 6-1 Acclimatization/ Investigational Toothpastes** (footnote). Source of Acclimatization (Colgate Cavity Protection) and Reference (Crest Cavity Protection) toothpastes amended from Canada to US market.

Amendments incorporate all revisions to date, including amendments made at the request of country health authority, institutional review board (IRB), etc.

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, and applicable medical device regulations.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

Summary Title:

Clinical study to evaluate the anti-sensitivity efficacy of a calcium sodium phosphosilicate toothpaste in a population of dentin hypersensitivity sufferers.

Background and Rationale for the Study:

Calcium sodium phosphosilicate (CSPS) is a particulate, bioactive material incorporated into oral healthcare products for the relief of dentin hypersensitivity (DH). CSPS acts to relieve DH by the physical occlusion of exposed dentin tubules and was first marketed in a fluoridated, daily use anti-sensitivity toothpaste by GlaxoSmithKline (now Haleon) in 2011.

Randomized controlled clinical trials (with 4-12 weeks treatment duration) support the longer-term anti-sensitivity efficacy of 5% w/w CSPS-containing toothpastes with twice daily use. The aim of the current 8-week study is to confirm the clinical DH efficacy of a 5% CSPS toothpaste. Changes to the formulation, compared to those previously investigated by the sponsor, include removal of the opacifier, addition of a blue pigment, introduction of a new flavor for improved in-use experience, and modification of the dental abrasive system for improved stain removal and enamel polishing benefits. None these changes are expected to impact the occlusion mode of action (MoA) of CSPS and the anti-sensitivity efficacy of a 5% CSPS toothpaste.

In addition to confirming the longer-term DH efficacy of the investigational 5% CSPS toothpaste, time to onset of DH relief will be investigated, with clinical assessments completed after 3-, 7-, 14- and 28-days twice-daily use. At each post-Baseline time point, the efficacy of the 5% CSPS toothpaste will be compared with that of a regular fluoride toothpaste with no known anti-sensitivity efficacy (negative control).

Objectives and Endpoints:

Objectives	Endpoints
Efficacy	
Primary	
To demonstrate the clinical efficacy of a 5% CSPS toothpaste in reducing DH to an evaporative (air) stimulus (as measured by Schiff sensitivity score), compared to a negative control toothpaste, after 8 weeks twice daily use.	Change from Baseline in Schiff sensitivity score at Day 56 (Week 8).
Secondary	
To demonstrate the clinical efficacy of a 5% CSPS toothpaste in reducing DH to a tactile stimulus (as measured by tactile threshold in grams [g]), compared to a negative control toothpaste, after 8 weeks twice daily use.	Change from Baseline in tactile threshold (g) at Day 56 (Week 8).

To investigate the clinical efficacy of a 5% w/w CSPS toothpaste in reducing DH to evaporative (air) and tactile stimuli (as measured by Schiff sensitivity score and tactile threshold (g), respectively), compared to a negative control toothpaste, after 3-, 7-, 14- and 28-days twice daily use.	Change from Baseline in Schiff sensitivity score at Days 3, 7, 14 & 28. Change from Baseline in tactile threshold (g) at Days 3, 7, 14 & 28.
To describe subject-perceived changes in oral health-related quality of life (OHrQoL), as measured by the Dentin Hypersensitivity Experience Questionnaire (DHEQ-48), after 4- and 8-weeks twice daily use of their assigned investigational toothpaste.	*At Day 28 (Week 4) & Day 56 (Week 8):* Change from Baseline in DHEQ-48 endpoints. **Section 1** • Impact on Everyday Life (Q7-9) **Section 2** • Total Score (Q1-34) • Individual Domain Scores - Restrictions (Q1-4) - Adaptation (Q5-16) - Social Impact (Q17-21) - Emotional Impact (Q22-29) - Identity (Q30-34) • Global Oral Health Score (Q35) • Effect on Life Overall Score (Q36-39)
Exploratory	
To investigate subject satisfaction with their assigned investigational toothpaste for the overall management of DH, as measured by a Numeric Rating Scale (NRS), after 8 weeks treatment.	*At Day 56 (Week 8):* Satisfaction NRS score
Safety	
To monitor the safety and oral tolerability of the investigational toothpastes over 8 weeks twice daily use.	Treatment emergent adverse events (TEAEs).

Study Design:

This will be a single center, 8-week, randomized, controlled, examiner-blind, 2-treatment arm, parallel design, stratified (by maximum Baseline Schiff sensitivity score of the two selected 'Test Teeth') clinical study to evaluate the anti-sensitivity efficacy of a 5% CSPS toothpaste in a DH population. The clinical efficacy of the 5% CSPS toothpaste (Test Toothpaste) will be compared with that of a Reference Toothpaste, a commercially available, regular fluoride toothpaste with no known anti-sensitivity properties (negative control).

At Screening (Visit 1), following provision of written informed consent, suitability to participate will be reviewed against the protocol inclusion/exclusion criteria. Eligible subjects will enter an acclimatization period (14-28 days) prior to Baseline assessments during which

they will brush twice daily (morning and evening) with the acclimatization toothpaste (a different commercially available, regular fluoride toothpaste from the Reference Toothpaste). At Baseline (Visit 2), eligibility to continue will be assessed. Subjects who demonstrate the required qualifying levels of DH at Screening (Visit 1) and Baseline (Visit 2) will be randomized to study treatment and instructed to brush with their assigned investigational toothpaste twice daily (morning and evening) for the duration of the 8-week treatment period.

DH will be assessed at Screening (Visit 1), Baseline (Visit 2), and after 3-, 7-, 14-, 28- and 56-days treatment (Visits 3-7) using two independent clinical measures: (i) tactile threshold (g) following a tactile stimulus and (ii) Schiff sensitivity score following an evaporative (air) stimulus.

Oral health-related quality of life (OHRQoL) will be monitored over the treatment period using the Dentin Hypersensitivity Experience Questionnaire (DHEQ-48), completed by study subjects at Baseline (Visit 2), and after 28- and 56-days treatment (Visits 6 and 7). At the final visit (Day 56), subjects will rate their level of satisfaction with their assigned investigational toothpaste for the overall management of their DH, using a Numeric Rating Scale (NRS).

Safety and oral tolerability of the investigational toothpastes will be monitored over the 8-week usage period by review of treatment emergent adverse events (TEAEs).

Investigational Products:

Description	Test Toothpaste	Reference Toothpaste (Negative Control)
Name	5.0 % w/w CSPS toothpaste	Regular fluoride toothpaste (Crest Cavity Protection*)
Master Formulation Code	CCI [redacted]	N/A
Fluoride Level	1040 parts per million (ppm) fluoride†	1100 ppm fluoride†
Route of Administration	Topical Oral Use	
Toothpaste Usage Instructions	Dose the toothbrush with a ribbon of toothpaste, across the full brush head.	
	Brush the entire dentition thoroughly for at least 1-timed minute, twice daily (morning & evening), making sure to brush the sensitive areas of the two 'Test teeth' carefully first.	Brush the entire dentition thoroughly for at least 1-timed minute, twice daily (morning & evening).
	Subjects who wish to rinse after brushing will be instructed to rinse with 10 milliliter (ml) water using graduated rinsing cup provided.	

* Commercially available daily use, regular fluoride toothpaste, US market.
† As sodium fluoride (NaF)

Type and Planned Number of Subjects:

Male and female subjects aged 18-65 years (inclusive), in good general and oral health, with a minimum of 20 natural teeth, a self-reported history of tooth sensitivity and clinically confirmed

DH will be enrolled. Qualifying subjects with at least two teeth with clinically confirmed DH, (tactile threshold ≤ 20g and Schiff sensitivity score ≥ 2 at both Screening and Baseline visits) will be randomized to treatment.

Sufficient subjects will be screened and entered into the acclimatization period to randomize approximately 234 subjects to investigational product (approximately 117 per treatment group) and so ensure approximately 210 evaluable subjects complete the entire study (approximately 105 per treatment group), allowing for approximately 10% dropouts.

Statistical Analysis Summary:

A modified Intent-To-Treat (mITT) population (all randomized subjects who receive at least one dose of investigational product and complete at least one-post Baseline DH efficacy assessment) will be used for the efficacy analyses. Significance testing will be conducted at the two-sided 5% significance level.

Schiff sensitivity score and tactile threshold (g) will be derived as the mean score/value of the two 'Test Teeth' (selected at Baseline). Change from Baseline will be derived for each individual tooth first before calculating mean change for the two 'Test Teeth'.

The primary endpoint, change from Baseline in Schiff sensitivity score at Day 56, will be analyzed using a Mixed Model with Repeated Measures (MMRM) with investigational product, visit and [investigational product x visit] interaction as fixed effects, and Baseline Schiff sensitivity score as covariate. Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied. The difference between the least square mean changes from Baseline for the Test Toothpaste compared to Reference Toothpaste (negative control) at Day 56 from the MMRM will be presented, along with the two-sided p-value and 95% confidence intervals (CIs).

Key secondary endpoint, change from Baseline in tactile threshold (g) at Day 56, will be analysed using the same MMRM as the primary endpoint but with Baseline tactile threshold (g) as covariate. In addition, the maximum Baseline Schiff sensitivity score of the two 'Test Teeth' (2 or 3) will be fitted as a fixed effect. The difference between the least square mean changes from Baseline for the Test Toothpaste compared to Reference Toothpaste (negative control) at Day 56 from the MMRM will be presented, along with the two-sided p-value and 95% CIs.

Other key secondary endpoints will be analyzed using the same MMRM models as described for Schiff sensitivity score and tactile threshold (g), respectively. Differences between the least square mean changes from Baseline in Schiff sensitivity score and tactile threshold (g) will be presented for the Test Toothpaste compared to Reference Toothpaste (negative control) at Days 28, 14, 7 and 3 from their respective MMRMs, along with two-sided p-values and 95% CIs.

Summary statistics (mean, median, standard error (SE), standard deviation (SD), minimum, maximum) will be presented for each Schiff sensitivity score and tactile threshold (g) outcome variable at each assessment time point. Raw means (± SE) of Schiff sensitivity score and tactile threshold (g) at each assessment timepoint will be plotted by treatment group.

1.2 Schedule of Activities

The Schedule of Activities (Table 1-1) provides an overview of the subject 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 subject.

Table 1-1 Schedule of Activities

Procedure/Assessment	Study Visits							
	Visit 1 **Screening**		Visit 2 **Day 0 Baseline**	Visit 3 **Day 3**	Visit 4 **Day 7**	Visit 5 **Day 14** (± 1 day)	Visit 6 **Day 28** (± 2 days)	Visit 7 **Day 56** (± 3 days)
Informed Consent	X	Acclimatization Period (14-28 days)						
Demographics	X							
Review Subject's Oral Care Products	X							
Review Medical History & Current/Prior Concomitant Medication/Treatment [1]	X							
Review Changes in Health & Medications/Treatments [1]			X	X	X	X	X	X
Return Acclimatization Toothpaste, Toothbrush & Diary [2]			X					
Return Investigational Toothpaste, Toothbrush & Diary [2]								X
Compliance Checks [2]			X	X	X	X	X	X
Subject-Completed DHEQ [3]			X				X	X
Oral Soft Tissue (OST) Examination	X		X	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 [4]	X		X					
Qualifying Clinical Assessment of Evaporative (Air) Sensitivity [5]	X		X					
Clinical Examiner Selects Two 'Test Teeth' (Qualifying Subjects Only) [6]			X					
Review Inclusion/Exclusion Criteria	X		X					
Confirm Subject Eligibility/Qualification	X		X					
Dispense Acclimatization Toothpaste, Toothbrush, Timer, Rinsing Cups & Diary	X							
Supervised Brushing with Acclimatization Toothpaste	X							

Procedure/Assessment	Study Visits							
	Visit 1 **Screening**		Visit 2 **Day 0 Baseline**	Visit 3 **Day 3**	Visit 4 **Day 7**	Visit 5 **Day 14** (± 1 day)	Visit 6 **Day 28** (± 2 days)	Visit 7 **Day 56** (± 3 days)
Stratification/Randomization			X					
Dispense Investigational Toothpaste, Toothbrush, Rinsing Cups & Diary			X					
Supervised Brushing with Investigational Toothpaste			X					
Clinical Assessment of Tactile Sensitivity: Two 'Test Teeth' only [4]				X	X	X	X	X
Clinical Assessment of Evaporative (Air) Sensitivity: Two 'Test Teeth' only [5]				X	X	X	X	X
Supervised Brushing with Investigational Toothpaste				X	X	X	X	
Satisfaction with Treatment: Subject-Completed NRS								X
Study Conclusion								X
Monitor Adverse Events (AEs) and Medical Device Incidents [7]	X		X	X	X	X	X	X

FOOTNOTES:

1. Female subjects of child-bearing potential should be asked to confirm pregnancy status at each visit.
2. Subjects will be required to bring their study supplies (minus timer & rinsing cups) to every visit.
   Perform visual check of returned study supplies, review diary & evaluate compliance:
   Visit 2: check compliance with use of acclimatization toothpaste; **Visits 3-7:** check compliance with use of investigational toothpaste.
   Visits 2-7: check compliance with Lifestyle Guidelines/Medication requirements.
3. DHEQ-48 must be completed prior to the OST examination and clinical assessments.
   Visit 2: Complete all questions; **Visits 6 & 7:** Complete Section 1, Q7-9 & Section 2, all questions.
4. **Tactile Threshold Assessment: Visits 1-2:** Maximum force 20g (Screening and Baseline); **Visits 3-7:** Maximum force 80g.
5. **Evaporative (air) sensitivity** 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.
6. 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 ≤ 20g **and** Schiff sensitivity score ≥ 2.
7. AEs, and therefore all serious adverse events (SAEs), and incidents will be recorded from immediately after signing the informed consent form (ICF) until 5 days after the last use of investigational toothpaste. Incidents will be recorded from first to last use of the medical device (the manual toothbrush used to apply the acclimatization and investigational toothpastes).

2 INTRODUCTION

Dentin hypersensitivity (DH) is a common dental condition; prevalence is reported to range from 3% to 57% in the general population (Addy, 2002). It is typically associated with the enamel wear and/or gingival recession experienced in adulthood (both of which lead to exposure of the underlying dentin) (West, 2022) and has been described as a 'short, sharp pain arising from exposed dentin in response to stimuli typically thermal, evaporative, tactile, osmotic or chemical and which cannot be ascribed to any other form of dental defect or disease' (Addy, 1985; Canadian Advisory Board on Dentin Hypersensitivity, 2003). Clinically, the primary diagnosis of tooth hypersensitivity is made when a patient complains of brief, well-localized pain resulting from thermal (typically cold), tactile, or osmotic stimulation of exposed dentin in the absence of any other dental pathology (Addy, 2002).

The most widely accepted theory to explain DH is the hydrodynamic theory, first described in the literature by Gysi (Gysi, 1900) and expanded on later by Brännström (Brännström, 1963). The hydrodynamic theory proposes that an external stimulus, such as a temperature (cold or hot) or osmotic differential, or tactile pressure, applied to exposed dentin disrupts the movement of fluid within dentin tubules. This disruption is thought to stimulate mechanoreceptors associated with odontoblast processes and nerve fibers located near the cervical pulp-dentin complex, triggering the short, sharp pain characteristic of DH (Absi, 1987; Pashley, 1994). Other mechanisms for DH have been proposed, however only the hydrodynamic theory explains the paradoxical finding that the dentin-enamel junction is sensitive to external stimuli, even though the dentin itself appears not to be highly innervated (Dababneh, 1999). The theory is also consistent with the observation that treatment of hypersensitive dentin with agents that either occlude the exposed dentin tubules or reduce mechanoreceptor/nerve activity, results in a reduction in the discomfort or pain observed clinically (West, 2014).

Twice daily use of an anti-hypersensitivity toothpaste is generally recommended as the first line treatment for DH; treatment modalities are based on either dentin tubule occlusion or intra-dental nerve desensitization (Addy, 2002; Pereira, 2015). Calcium sodium phosphosilicate (CSPS) is a particulate, bioactive material incorporated into oral healthcare products for the relief of DH. It reacts in the oral environment (in the presence of saliva) to form deposits over the surface of exposed dentin and within dentin tubules; these deposits act as barriers to external stimuli, physically blocking or narrowing the openings of exposed tubules, thereby reducing dentin fluid movement and decreasing the ability of the stimulus to activate the intra-dental nerves and evoke a pain response (Layer, 2011; Parkinson, 2011).

2.1 Background and Rationale for Study

CSPS (tradename NovaMin®) was originally developed as a bone regenerative technology due to its ability to bond with bone tissue (Hench, 1971; Hench, 1973; Hench, 1980). It was first marketed in a fluoridated, daily use toothpaste (5% w/w CSPS) by GlaxoSmithKline (now Haleon) for the relief of DH in 2011 and continues to be sold globally (more than 60 countries), primarily as *Sensodyne Repair & Protect*. CSPS is included in the investigational toothpaste at 5% w/w to provide relief from the pain and discomfort of DH.

Randomized controlled trials (RCTs) with 4-12 weeks (typically 8 weeks) treatment duration (e.g., Acharya, 2013; Du, 2008; Gendreau, 2011; Hall, 2017[a]; Hall, 2017[b];Majji, 2016; Li, 2013; Pradeep, 2010; Pradeep, 2012; Salian, 2010; Sufi, 2016 [a]; Sufi, 2016 [b]; Young, 2016; Zang, 2016) and two 24-week clinical studies (Hall, 2017[b]; Mason, 2017) support the long-

term anti-sensitivity efficacy of 5% w/w CSPS-containing toothpastes, with twice daily use. The aim of the current 8-week study is to confirm the clinical efficacy of a 5% CSPS toothpaste. Changes to the formulation, compared to those previously investigated, include removal of the opacifier, addition of a blue pigment, introduction of a new flavor for improved in-use experience, and modification of the dental abrasive system for improved stain removal and enamel polishing benefits. None these changes are expected to impact the occlusion mode of action (MoA) of CSPS and the anti-sensitivity efficacy of a 5% CSPS toothpaste.

In addition to confirming the longer-term DH efficacy of the investigational 5% CSPS toothpaste, time to onset of DH relief will be investigated, with clinical assessments completed after 3-, 7-, 14- and 28-days twice-daily use. At all assessment time points (3-, 7-, 14-, 28- and 56-days), the efficacy of the 5% CSPS toothpaste will be compared with that of a regular fluoride toothpaste with no known anti-sensitivity efficacy (negative control).

2.2 Benefit/Risk Assessment

CSPS is included in the investigational toothpaste at 5.0 % w/w to provide relief from the pain and discomfort of DH. The formulation contains only ingredients with a history of safe use in oral healthcare products and is designed for daily use by DH sufferers. Complete safety information for this 5% CSPS toothpaste can be found in the single reference safety document for this product, which for this study is the Safety Statement.

Numerous clinical studies support the longer-term clinical efficacy and safety of 5% CSPS toothpastes in reducing the pain and discomfort associated with DH following exposure to a range of accepted stimuli (thermal and tactile (Holland, 1997)), see Section 2.1. In these studies, 5% w/w CSPS toothpastes were applied twice daily by toothbrushing for 4 to 24 weeks and were well tolerated.

Review of the sponsor's interventional clinical studies involving 5% CSPS toothpastes has not identified any significant safety issues. As per the sponsor's Global Data Sheet (GDS) for 5% CSPS toothpaste, which is continuously maintained by the ongoing post-marketing surveillance activities, the frequency of adverse reactions is rare or very rare. The sponsor considers the overall benefit-risk profile of 5% CSPS toothpaste to be favorable when used as directed in its intended target treatment population.

The Acclimatization and Reference Toothpastes will be daily use, regular fluoride toothpastes (two different products), sourced from the US market. The ingredients listed on both commercial packs have a history of safe use in oral healthcare products. The usage instructions given to study subjects will be consistent with the instructions on the commercial packs. No specific clinical benefits, risks or adverse effects are anticipated from their use in this study.

The manual toothbrush (Oral B Sensi-Soft toothbrush) to be used to apply the study toothpastes by toothbrushing is a medical device in Canada. Device usage instructions will be consistent with its commercial pack instructions. No specific clinical benefits, risks or adverse device effects are anticipated from its use in this clinical study.

Based on currently available data, the investigational and acclimatization toothpastes, and the manual toothbrush (medical device) used to apply them, are considered safe for use under the conditions of the proposed clinical study.

2.3 Mechanism of Action/Indication

Calcium sodium phosphosilicate (CSPS) is a particulate bioactive glass material incorporated

into daily use oral healthcare products at concentrations ranging from 5-15% w/w (typically 5%) for the relief of DH. Novamin® is the tradename of a specific composition and grade of inorganic, amorphous CSPS (Greenspan, 2010). The investigational product is an anhydrous toothpaste formulation containing 5% w/w CSPS.

Calcium sodium phosphosilicates have been shown to bind strongly to collagen. The organic matrix of dentin comprises primarily Type-I collagen, thus it was anticipated that CSPS materials, such as Novamin®, would bind to the surface of exposed dentin and patent dentin tubules (Layer, 2011).

When exposed to the aqueous environment of the mouth (saliva), CSPS particles begin to degrade at the dentin surface. As the CSPS particles release sodium ions, they develop a surface negative charge which facilitates binding to Type-I collagen fibers in the dentin. On contact with saliva, a rapid exchange of sodium and hydrogen ions takes place, causing a transient, localized increase in pH. This rise in pH, together with the release of calcium and phosphate ions, facilitates the precipitation of a calcium phosphate hydroxycarbonate apatite (HCA) layer over the dentin and within dentin tubules (Andersson, 1991; Burwell, 2010; Greenspan, 2010; Imperial College Study, 2013; LaTorre, 2010; Layer, 2011). The HCA layer is chemically and structurally similar to natural tooth mineral (Earl, 2011; Greenspan, 2010; La Torre, 2010; Ogino, 1980; Pantano, 1974) and acts to physically block dentin tubules through a process of remineralization (Litkowski, 1997). Dissolution of CSPS also generates soluble silica which has been shown accelerate the precipitation of calcium phosphate (hydroxyapatite) mineral by acting as a nucleation site for HCA formation (Damen, 1992; Sahai, 2005).

The longitudinal exposure of radicular or coronal primary dentin (due to enamel erosion, enamel abrasion and/or gum recession) results in the synthesis of tertiary or reparative dentin; the primary purpose of reparative dentin is to protect the pulp tissue where the tooth's normal protective tissues (enamel and gum) have been irreversibly lost (Linde, 1993). The reparative process can be initiated in response to the effect of external stimuli at the dentin surface, as experienced by DH sufferers (Cox, 1992; D'Souza, 1995; Magloire, 1992; Mjor, 2002). The occluding HCA layer formed over the dentin surface, and within the dentin tubules, with daily use of a 5% CSPS toothpaste functions in a similar way to the natural repair process. It too is reparative in nature, acting to protect the dentin and the underlying pulp tissue from external pain-inducing stimuli, where enamel and/or gingival tissue has been lost.

3 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Efficacy	
Primary	
To demonstrate the clinical efficacy of a 5% CSPS toothpaste in reducing DH to an evaporative (air) stimulus (as measured by Schiff sensitivity score), compared to a negative control toothpaste, after 8 weeks twice daily use.	Change from Baseline in Schiff sensitivity score at Day 56 (Week 8).
Secondary	

To demonstrate the clinical efficacy of a 5% CSPS toothpaste in reducing DH to a tactile stimulus (as measured by tactile threshold in grams [g]), compared to a negative control toothpaste, after 8 weeks twice daily use.	Change from Baseline in tactile threshold (g) at Day 56 (Week 8).
To investigate the clinical efficacy of a 5% w/w CSPS toothpaste in reducing DH to evaporative (air) and tactile stimuli (as measured by Schiff sensitivity score and tactile threshold (g), respectively), compared to a negative control toothpaste, after 3-, 7-, 14- and 28-days twice daily use.	Change from Baseline in Schiff sensitivity score at Days 3, 7, 14 & 28. Change from Baseline in tactile threshold (g) at Days 3, 7, 14 & 28.
To describe subject-perceived changes in oral health-related quality of life (OHrQoL), as measured by the Dentin Hypersensitivity Experience Questionnaire (DHEQ-48), after 4- and 8-weeks twice daily use of their assigned investigational toothpaste.	*At Day 28 (Week 4) & Day 56 (Week 8):* Change from Baseline in DHEQ-48 endpoints. **Section 1** • Impact on Everyday Life (Q7-9) **Section 2** • Total Score (Q1-34) • Individual Domain Scores - Restrictions (Q1-4) - Adaptation (Q5-16) - Social Impact (Q17-21) - Emotional Impact (Q22-29) - Identity (Q30-34) • Global Oral Health Score (Q35) • Effect on Life Overall Score (Q36-39)
Exploratory	
To investigate subject satisfaction with their assigned investigational toothpaste for the overall management of DH, as measured by a Numeric Rating Scale (NRS), after 8 weeks treatment.	*At Day 56 (Week 8):* Satisfaction NRS score
Safety	
To monitor the safety and oral tolerability of the investigational toothpastes over 8 weeks twice daily use.	Treatment emergent adverse events (TEAEs).

This study will be considered successful if the 5% CSPS toothpaste demonstrates statistically significant, superior anti-hypersensitivity efficacy, compared to the negative control toothpaste, as measured by Schiff sensitivity score at Day 56 (Week 8).

4 STUDY DESIGN

4.1 Overall Design

This will be a single center, 8-week, randomized, controlled, examiner-blind, 2-treatment arm, parallel group, stratified study in healthy subjects with DH. Subjects who meet the required study criteria at Screening and Baseline will be randomized to one of two study treatments: a 5% CSPS toothpaste (Test Toothpaste) or a regular fluoride toothpaste (Reference Toothpaste)

Two independent stimulus-based clinical measures will be employed to assess the efficacy of the investigational toothpastes.

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

DH will be assessed at Screening, Baseline, Day 3, Day 7, Day 14, Day 28 and Day 56. 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 dentition inclusion/exclusion criteria (Section 5.2 Inclusion Criteria 6 & 7; Section 5.3 Exclusion Criterion 26), specifically a tactile threshold ≤ 20g and a Schiff sensitivity score ≥ 2 at both Screening and Baseline visits.

Approximately 234 qualifying subjects will be stratified according to the maximum Baseline Schiff sensitivity score of their two 'Test Teeth' and randomized to treatment (approximately 117 subjects per treatment group). Randomized subjects will be instructed to brush twice daily (morning and evening) with their assigned investigational toothpaste for the next 56 days (8 weeks) and record each brushing in the diary provided. First use will be performed under supervision at the investigator site; to facilitate compliance throughout the treatment period, further supervised on-site brushings will be completed at Visits 3-6.

Changes in OHRQoL will be monitored over the treatment period using the validated Dentin Hypersensitivity Experience Questionnaire (DHEQ-48). The DHEQ-48 will be completed by study subjects at Baseline, and after 28- and 56-days treatment. At the final visit (Day 56), after all clinical procedures have been completed, subjects will rate their level of satisfaction with their assigned investigational toothpaste for the overall management of DH using a NRS.

To standardize oral hygiene practice in the study population prior to treatment and to help minimize the potential impact of 'placebo'/'no treatment' effects, eligible subjects will complete an acclimatization period (14-28 days duration) between the Screening and Baseline visits during which they will brush twice daily (morning and evening) with the regular fluoride toothpaste provided (a different commercially available product from the Reference Toothpaste). First use of acclimatization toothpaste will be performed under supervision at the investigator site.

Safety and oral tolerability of the investigational toothpastes will be monitored over the treatment period by review of TEAEs.

4.2 Scientific Rationale for Study Design

The randomized, controlled, examiner-blind, parallel group design selected for this DH study follows published guidance for the design and conduct of studies investigating the clinical efficacy of anti-sensitivity products (Holland, 1997). In line with these same recommendations, two independent, controllable DH stimuli (tactile and thermal) will be employed to assess the performance of the 5% CSPS toothpaste, with the least severe stimulus (tactile) applied first (Holland, 1997). To avoid inter-examiner variability, the same clinical examiner will administer a given stimulus (tactile and/or evaporative (air)) and assess its associated DH measure (tactile threshold (g) or Schiff sensitivity score) throughout the study.

DH will be clinically assessed at Screening and Baseline (pre-treatment) to determine suitability to participate and confirm subject qualification, and again after 3-, 7-, 14-, 28- and 56-days treatment to evaluate the efficacy of the Test Toothpaste with twice-daily use. At all post-Baseline time points, the anti-sensitivity efficacy of the Test Toothpaste will be compared with that of a Reference Toothpaste - a conventional, daily use fluoride toothpaste with no known anti-sensitivity efficacy (i.e., a non-desensitising toothpaste will act as negative control). Qualifying subjects will be randomized to one of the two investigational treatments using a 1:1 allocation ratio.

- Day 56 has been selected as the primary time point to confirm the anti-sensitivity efficacy of the investigational 5% CSPS toothpaste with twice daily use; 56-day (8-week) study duration is accepted as appropriate to evaluate the long-term efficacy of most anti-sensitivity products (Holland, 1997).
- Evaporative (air) is a thermal stimulus representative of the impact of chilled foods and drinks, or an intake of cold air, on sensitive teeth. ‘Cold’ is reported to be the most common stimuli for DH pain (Fischer, 1992; Flynn, 1985; Gillam, 2002). Thus, change from Baseline in Schiff sensitivity score at Day 56 has been selected as the primary endpoint, with study success defined as statistically significant, superior anti-hypersensitivity efficacy for the 5% CSPS toothpaste, compared to negative control, as measured by Schiff sensitivity score at Day 56 (Week 8).
- Earlier assessment time points (3-, 7-, 14- and 28-days) will also be included in the study design to investigate time to onset of DH relief.

On completion of the Baseline assessments, the clinical examiner will select two ‘Test Teeth’ from those that qualify at both Screening (Visit 1) and Baseline (Visit 2) for assessment of tactile and evaporative (air) sensitivity at all subsequent visits. Qualifying subjects will be stratified according to the maximum Schiff sensitivity score of their two selected ‘Test Teeth’ to ensure treatment groups are balanced for DH severity. Repeated stimulation of multiple sensitive teeth may alter the pain response as testing continues around the mouth; the anticipation of pain or discomfort with protracted testing, along with the discomfort of having to keep the mouth open for an extended period of time, may also affect subject perception of pain (Holland, 1997). Thus, the selection of two representative ‘Test Teeth’ to evaluate changes in DH with treatment is common practice in DH efficacy studies. To be representative of different areas of the mouth, with independent innervation, ‘Test Teeth’ should be non-adjacent and in different quadrants.

To help minimize exposure to environmental triggers for sensitivity prior to clinical DH assessment, subjects will be instructed to refrain from oral hygiene, chewing gum, eating and drinking for a period of time prior to their arrival at the investigator site.

Clinical trials evaluating pain-related endpoints 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 the DH condition also highlighted the existence of a 'no treatment' effect, characterized by an improvement in sensitivity simply as a result of study participation (Leight, 2008). To help minimize the potential impact of such effects, an acclimatization period (14-28 days duration) will precede the Baseline visit. During this period, study subjects will brush twice daily with the regular fluoride toothpaste and toothbrush provided (in place of their own oral hygiene products) and record each brushing occasion in a diary. The acclimatization period will also serve to standardize oral hygiene practice across the study population and familiarize participants with several important study procedures (e.g., toothpaste dosage, timed brushings, diary completion) prior to treatment.

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 subject or selected test tooth without the condition under investigation (i.e., DH) during the treatment period. To help minimize the potential for this to occur in the current study, randomized subjects will be required to demonstrate consistency in response to both DH stimuli at both the Screening and Baseline visits. Qualifying subjects will have a minimum of two eligible teeth with a tactile threshold ≤ 20g and a Schiff sensitivity score ≥ 2 at both Screening and Baseline. In line with published guidelines for the design and conduct of studies investigating the clinical efficacy of anti-sensitivity products, inconsistent responders will be excluded (Holland, 1997).

The etiology of DH requires tooth wear (loss of enamel) and/or gingival recession (with loss of cementum) to expose the underlying dentin (Addy, 1987). In the absence of an underlying condition or pathology, these processes are slow and progressive, leading to dentin 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 dentin and pulp of the tooth which act to reduce both dentin 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 18-65 years has been selected for this study to target individuals with tooth sensitivity due to DH.

Currently, there is no published evidence to indicate that gender, race or ethnicity impacts the pathophysiology of DH. Thus, the investigator site will make every effort to enroll subjects representative of the adult population who would benefit from use of an anti-sensitivity toothpaste. The study population will comprise male and female subjects and the protocol inclusion/exclusion criteria will not unnecessarily preclude any subject from participation. To further increase the diversity of enrolled subjects: (i) the investigator site will be encouraged to employ a range of advertising methods (e.g., posters in local community centers, retail outlets and healthcare facilities, local radio, social media) to maximize their ability to reach a diverse population within their geographic location; (ii) wherever possible, the investigator site will ensure accessibility to clinical areas for subjects with mobility issues; (iii) from Day 14 onwards, flexibility will be added to visit timings to facilitate subject attendance at site (Day 14 ± 1 day; Day 28 ± 2 days; Day 56 ± 3 days); (iv) study payment will appropriately compensate potential subjects for the anticipated costs of participation (e.g., travel to the investigator site for scheduled visits) to ensure financial considerations do not impede participation.

Female subjects 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 DH assessment (Aghazadeh, 2019; Samant, 1976).

Potential study subjects will be asked to bring their current oral hygiene products to Screening (Visit 1) where they will be checked for presence of known anti-sensitivity ingredients. Individuals already using anti-sensitivity product(s) as part of their normal oral hygiene routine will be excluded. If they are using such products and continuing to experience DH, they would be unlikely to respond to further use of anti-sensitivity toothpaste in this study and will be advised to seek help from their dental healthcare provider.

'Patient-reported outcomes' (PROs) can provide valuable information about the effect of a condition, and its treatment, on day-to-day life from the perspective of the person suffering with the condition. The inclusion of well-defined, reliable 'PROs' in clinical studies is increasingly encouraged to ensure the impact of treatment on quality of life and participant-reported symptoms is assessed alongside conventional clinical outcomes. Indeed, published guidelines for the design and conduct of studies investigating the clinical efficacy of anti-sensitivity products (Holland, 1997), recommend that treatment evaluations include subject-assessment of overall change to every day triggers for DH. Two 'PRO' measures will be included in this study: (i) the Dentine Hypersensitivity Experience Questionnaire (DHEQ) and (ii) a Treatment Satisfaction Numeric Rating Scale (NRS). Given study participants will not be patients, for the purposes of this study, these measures will be described as 'subject-reported outcomes'.

The DHEQ is a validated, condition-specific measure of OHRQoL used to investigate the impacts of tooth sensitivity on everyday life. It was developed by the sponsor in collaboration with Sheffield University through a robust theoretical framework, (Baker, 2014; Boiko, 2010; Robinson, 2014) and has shown reliability and validity in both a general population (Porritt, 2016) and in clinical studies (Boiko 2010; Gibson, 2015). It has been validated as both long- and short-form versions (DHEQ-48 and DHEQ-15), comprising 48 (Baker, 2014; Boiko, 2010) and 15 (Machuca, 2014) questions, respectively, and has been translated into multiple languages (e.g., Chinese, Turkish, Portuguese), confirming its global relevance (Başaran, 2018; Douglas-De-Oliveira; 2018; He, 2015[a]; He, 2015[b]).

- Study subjects will complete a DHEQ-48 (Appendix 15.2) at Baseline (Visit 1), and after 28- and 56-days treatment (Visits 6 and 7), prior to any clinical examinations or assessments.

To investigate satisfaction with their assigned investigational toothpaste for the overall management of DH, subjects will be asked to complete a NRS (an 11-point ordinal scale) at the end of the treatment period. They will record the numeric value (from 0 to 10) that best describes their level of satisfaction and describe why they gave the product that rating (free text).

Per International Conference on Harmonization (ICH) CGP guidance (ICH E6 (R2) Good Clinical Practice), for a study to be classified as double blind, the subjects, investigator(s) and staff involved in the treatment or clinical evaluation of subjects should be unaware of treatment received; this includes staff involved in the determination of subject eligibility, evaluation of endpoints (clinical examiners), or assessments of protocol compliance (e.g., monitors, data

analysts). In summary, neither the subject nor the researchers should know if the subject has been assigned to Test or Reference treatment. In addition, the products under test should have the same appearance, smell and taste (i.e., study arms should not be distinguishable from each other). Given this will not be possible for the investigational products evaluated in this study (an experimental toothpaste and commercially available regular fluoride toothpaste), the study is described as 'examiner blind'. However, given design of the study and the procedures in place at the investigator site to maintain the blind during study conduct, it is highly unlikely that the subjects, investigator, clinical examiner(s) or any member of the site staff involved in efficacy and safety assessments will be aware of treatment allocation.

- In this parallel-design study, study subjects will see and use only one of the two investigational toothpastes for the duration of the treatment period. They will be instructed not to discuss the appearance, usage or perceived performance of their assigned investigational toothpaste with the clinical examiner(s), with staff involved in clinical assessments or with other study subjects.
- Both investigational products are blue toothpastes. They will be provided to the investigator site overwrapped in white vinyl, to mask their identity, and to obscure any branding on the Reference Toothpaste, with a study label affixed.
- The investigational toothpastes will be supplied in cartons; each carton will contain 4 over-wrapped tubes of toothpaste; each carton and its 4 tubes will be labelled with the same unique randomization number. Subjects will be centrally randomized to treatment in order of qualification using an Interactive Response Technology (IRT); product codes will not be used.
- The clinical examiner(s) and site staff involved in efficacy and safety assessments will not be permitted in any area where the investigational toothpastes or diaries are stored, dispensed or in use.
- Site staff involved in the dispensing of investigational toothpastes, providing brushing and diary completion instruction, supervision of on-site brushings, treatment compliance checks and product accountability will not be involved in clinical efficacy and safety assessments and will work in a separate area from the clinical examiner(s) and site staff involved in efficacy and safety assessments.
- Subjects will be instructed not to remove their assigned investigational toothpaste or diary 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.

4.3 Justification for Dose

The investigational products are toothpastes; they are intended for topical oral use and will be applied by toothbrushing using a manual toothbrush.

In line with widely recommended oral hygiene practice and typical consumer habit, qualifying subjects will be instructed to brush twice daily (morning and evening) with their assigned investigational toothpaste, covering the toothbrush head with full ribbon of toothpaste (approximately 1.5g) on each brushing occasion.

- Subjects randomized to Test Toothpaste will be instructed to brush their entire dentition thoroughly for at least 1-timed minute, making sure to brush the sensitive areas of their two selected 'Test teeth' carefully first.
- Subjects randomized to Reference Toothpaste will be instructed to brush their entire dentition thoroughly for at least 1-timed minute.

Usage instructions are consistent with the proposed labelling for the Test Toothpaste and with the commercial pack instructions of the Reference Toothpaste. At least 1-minute brushing is aligned with the brushing times typically specified in similar DH efficacy studies (Docimo, 2009; Hall, 2017[a]; Parkinson, 2013; Young, 2016).

After 8 weeks (i.e., 56 ± 3 days) twice daily usage, each subject should complete between 106-118 brushings.

4.4 End of Study Definition

A subject will be considered to have completed the study if they have completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Activities (Table 1-1). The end of this study is defined as the date of the last scheduled procedure for the last subject, as described in the Schedule of Activities (Table 1-1).

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

The study will be conducted in male and female subjects in good general/oral health, with pre-existing self-reported 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 subjects will be screened and entered into the acclimatization phase to ensure approximately 234 subjects are randomized to investigational product (approximately 117 subjects per treatment group) and approximately 210 subjects complete the study (approximately 105 subjects per treatment group), allowing for approximately 10% dropouts. Subjects will be recruited primarily from the investigator site database.

For this study, an enrolled subject is defined as a subject 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.

The investigator site will make every effort to enroll subjects representative of the adult population who would benefit from use of an anti-sensitivity toothpaste; the rationale for study population selection is provided in the Scientific Rationale for Study Design (Section 4.2).

A clinical study can only fulfill its objectives if appropriate subjects are enrolled. The following eligibility criteria have been designed to select subjects for whom participation in the study is considered appropriate while not unnecessarily precluding any subject from study participation. All relevant medical and non-medical conditions should be taken into consideration when deciding whether or not a subject is suitable. Eligibility to participate will be reviewed and documented by the investigator (or medically qualified designee) before each subject is included in the study.

5.2 Inclusion Criteria

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

1. Subject provision of signed and dated informed consent before any study procedures are performed.
2. Subject is male or female.
3. Subject is 18 to 65 years of age, inclusive, at the time of signing the informed consent.
4. Subject is willing and able to comply with the study visit schedule, product usage instructions, lifestyle restrictions and other study procedures.
5. Subject is in good general, oral and mental health with, in the opinion of the investigator or medically qualified designee, 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)**

   Subject 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 accessible, non-adjacent teeth (incisors, canines, premolars), in different quadrants, which meet all of the following criteria:

   - Exposed dentin due to facial/cervical erosion, abrasion or gingival recession (EAR).
   - MGI = 0 directly adjacent to the exposed dentin (i.e., the test area only) (Lobene, 1986).
   - Clinical mobility = 0 (Laster, 1975).
   - Clinically confirmed DH to both tactile and evaporative (air) stimuli:
     - Qualifying tactile threshold ≤ 20g
     - Qualifying Schiff sensitivity score ≥ 2.

7. **BASELINE (Visit 2, Pre-Treatment)**

   Subject 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).

   - Qualifying tactile threshold ≤ 20g at Screening & Baseline
   - Qualifying 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 ≤ 20g and a Screening Schiff sensitivity score ≥ 2) will be*

assessed for tactile sensitivity at Baseline. Teeth with a Baseline tactile threshold ≤ 20g will then be assessed for Baseline evaporative (air) sensitivity.

5.3 Exclusion Criteria

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

1. Subject 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. Subject is an employee of the sponsor directly involved in the conduct of the study or a member of their immediate family.
3. Female subject who is pregnant or intending to become pregnant during the study (self-reported).
4. Female subject who is breastfeeding (self-reported).
5. Subject with known or suspected intolerance or hypersensitivity to the study products, any of their stated ingredients or closely related compounds (self-reported).
6. Subject with a recent history (within the last year) of alcohol or other substance abuse (self-reported).
7. Subject 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. Subject has participated in a tooth sensitivity study within 8 weeks of Screening (Visit 1).
9. Subject is currently using an oral care product indicated for DH relief or care of sensitive teeth or has used an anti-sensitivity product within 8 weeks of Screening (Visit 1)

   Subjects will be required to bring their current oral care products to Screening (Visit 1) for staff to verify the absence of known anti-sensitivity ingredients and sensitivity-related claims on the product packaging/label text.
10. Subject 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)**

    Subject has taken antibiotics in the 2 weeks prior to Screening (Visit 1).
12. **BASELINE (Visit 2, Pre-Treatment)**

    Subject has taken antibiotics in the 2 weeks prior to Baseline (Visit 2), i.e., during the acclimatization period.
13. Subject takes daily doses of a medication which, in the opinion of the investigator or medically qualified designee, is causing xerostomia.
14. Subject requires antibiotic prophylaxis for dental procedures.
15. Subject has had professional tooth de-sensitising treatment within 8 weeks of Screening (Visit 1).

16. Subject has had a tooth bleaching procedure within 8 weeks of Screening (Visit 1).
17. Subject has had dental prophylaxis within 4 weeks of Screening (Visit 1).
18. Subject has had treatment for periodontal disease (including surgery) within 12 months of Screening (Visit 1).
19. Subject has had scaling or root planning within 3 months of Screening (Visit 1).
20. Subject with gross periodontal disease.
21. Subject with a tongue or lip piercing.
22. Subject with evidence of gross intra-oral neglect or the need for extensive dental therapy.
23. Subject with a fixed or removable partial prosthesis which, in the opinion of the investigator or dentally qualified designee, could impact study outcomes.
24. Subject with multiple dental implants which, in the opinion of the investigator or dentally qualified designee, could impact study outcomes.
25. Subject with fixed or removable orthodontic braces/bands or a fixed orthodontic retainer.
26. **SPECIFIC DENTITION EXCLUSIONS FOR 'TEST TEETH':**
    a) Tooth with evidence of current/recent caries
    b) Tooth with (self-reported) treatment for decay within 12 months of Screening (Visit 1).
    c) Tooth with exposed dentin 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 dentin.
    g) Sensitive tooth not expected to benefit from use of an anti-sensitivity toothpaste, in the opinion of the investigator or dentally qualified designee.
27. Subject has previously been enrolled in this study.
28. Subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.

5.4 Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria. Each qualifying subject will be stratified by the maximum Baseline Schiff sensitivity score of their two selected 'Test Teeth'. The stratification factor will give rise to two strata.

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

5.5 Lifestyle Considerations

The investigator site may contact subjects 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 subject 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 1-1)). 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 (Visit 2):** the subject will be withdrawn from the study (Section 7.1). No clinical assessments will be performed. The subject may be replaced.
- **Days 3, 7, 14 and 28 (Visits 3-6):** the subject will continue in the study. No clinical assessments will be performed.
- **Day 56 (Visit 7)**: if the subject cannot be reappointed, they will be withdrawn from the study (Section 7.1). No clinical assessments will be performed. The subject will not be replaced.

5.5.1 Oral Hygiene Restrictions

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

- Subjects should not use any other oral care products (e.g., toothpastes, toothbrushes, oral rinses, tongue cleaners, whitening/bleaching products, inter-dental cleaning products) than those provided during the study.

  Note: *Use of dental floss is permitted to remove impacted food only.*

- Subjects should not use any other products intended for treating or caring for sensitive teeth (including herbal remedies) than those provided during the study.
- Subjects should not chew gum.

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

- Subjects will refrain from all oral hygiene procedures for at least 8 hours before a study visit.

5.5.2 Dietary and Alcohol Restrictions

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

- Subjects must not eat or drink for at least 2 hours before a clinical assessment visit.

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

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

5.5.3 Contraception

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) and there will be no pregnancy warnings on the labelling of any of the study products. Thus, study-specific contraceptive requirements are not deemed necessary for study subjects (female or male).

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography, screen failure reason (e.g., withdrawal of consent), eligibility criteria, any protocol deviations and any AEs, as applicable.

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

5.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified and experienced medical/dental personnel or Clinical Research Scientist (CRS) for this study is documented in the Study Contact List located in the investigator site file held at the investigator site.

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

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

5.8 Rater/Clinical Assessor Qualifications

The examiner(s) responsible for the clinical efficacy measures will be qualified dentist(s), trained in the clinical assessment of DH (tactile and/or evaporative (air) sensitivity).

Additional qualified dentists, not trained in the clinical assessment of DH, will be permitted to conduct the oral (OST and/or OHT) examinations, as required, at each study visit.

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per ICH guidelines and sponsor 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 subject according to the study protocol.

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

6.1 Study Product Supplies

Each subject will receive sufficient tubes of the acclimatization toothpaste and their assigned investigational toothpaste to cover usage during the acclimatization and treatment periods, respectively. The following study products (acclimatization and investigational toothpastes) will be supplied by the sponsor's Clinical Supplies department (Table 6-1).

Table 6-1 Acclimatization/Investigational Toothpastes

Description	Acclimatization Toothpaste	Test Toothpaste	Reference Toothpaste (Negative Control)
Product Name	Regular fluoride toothpaste (Colgate Cavity Protection*)	5.0 % w/w CSPS toothpaste	Regular fluoride toothpaste (Crest Cavity Protection*)
Fluoride Level	1000 ppm fluoride≠	1040 ppm fluoride†	1100 ppm fluoride†
Master Formulation Code	N/A	CCI	N/A
Dispensing Details	One carton containing 2 tubes of toothpaste at Screening (Visit 1)	One carton containing 4 over-wrapped tubes of toothpaste at Baseline (Visit 2)	
Route of Administration	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).		
	Brush the entire dentition thoroughly for at least 1-timed minute, twice daily (morning & evening).	Brush the entire dentition thoroughly for at least 1-timed minute, twice daily (morning & evening), making sure to brush the sensitive areas of the two 'Test teeth' carefully first.	Brush the entire dentition thoroughly for at least 1-timed minute, twice daily (morning & evening).
	Subjects who wish to rinse after brushing will be instructed to rinse with 10 ml water using graduated rinsing cup provided.		
Duration of Treatment	Approximately 8 weeks (56 ± 3 days)		
Return Requirements	All used/unused tubes to be returned to the sponsor.		

* Commercially available daily use, regular fluoride toothpaste, US market.
≠ As sodium monofluorophosphate
† As NaF

The toothpaste usage instructions are consistent with the proposed labelling for the Test Toothpaste, when marketed, and with the commercial pack instructions for the Reference and Acclimatization Toothpastes.

Sufficient supplies of the following sundry items (Table 6-2) will be supplied to complete the study by the sponsor's Clinical Supplies department (to be dispensed by site staff, as required).

Table 6-2 Sundry Items

Item	Pack Design	Dispensing Details	Return/Disposal Details	
			Used Samples	Unused Samples
Oral B Sensi-Soft toothbrushes (Canadian market) *Manual, flat trim, medium toothbrushes*	One toothbrush in its commercial pack	**Screening (Visit 1):** One toothbrush **Baseline (Visit 2):** One toothbrush	Destroy at site using site disposal procedures.	Return to sponsor
Countdown Timers	One timer in its commercial pack	**Screening (Visit 1):** One timer	Subject to keep or destroy at site using site disposal procedures.	
Graduated Rinsing Cups	N/A	**Screening (Visit 1):** 4 cups **Baseline (Visit 2):** 8 cups	Subject to keep or destroy at site using site disposal procedures.	
Opaque Carrier Bags	N/A	**Screening (Visit 1):** One bag **Baseline (Visit 2):** One bag		

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

6.1.1 Medical Devices

The medical device provided by the sponsor for use in this study is the manual toothbrush (Oral B Sensi-Soft toothbrush - Canadian market) to be used to apply the study products by twice daily toothbrushing. The device will be supplied to study subjects in its commercial pack; usage instructions will be consistent with the commercial pack instructions.

Device deficiencies, (including malfunction, use error and inadequate labelling) will be documented and reported by the investigator throughout the study and appropriately managed by the sponsor (see Section 10.10). The device does not include any medicinal, human or animal or biologically active materials.

6.1.2 Dosage Form and Packaging

The study products are toothpastes. They are intended for topical oral use and will be applied using a manual toothbrush.

The investigational toothpastes will be provided to the investigator site in laminate tubes, overwrapped in white vinyl (to mask their identity, and to obscure any branding, images and text on the commercial pack of the Reference Toothpaste) with a study label affixed. The acclimatization toothpaste will be supplied in its commercial pack, without overwrapping, with a study label affixed. The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the sponsor's Clinical Supplies department. Each study label will contain (but not be limited to) the protocol number and storage requirements.

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

Study products will be received at site by members of the investigator team responsible for product administration. These individuals will not be involved in any safety or efficacy assessments or any other aspect of the study that could be influenced by knowledge of the investigational toothpaste a subject has been assigned to.

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

6.1.3 Product Dispensing

Subjects will be assigned to investigational toothpaste in accordance with the randomization schedule generated by a sponsor-approved vendor, prior to the start of the study, using validated software.

The product dispensing area(s) will be separate from the clinical examination area(s). Investigational toothpastes will be dispensed to the subject, per protocol, in blinded fashion by trained study personnel. These staff members will not be involved in any safety or clinical efficacy assessments or any other aspect of the study that could be influenced by knowing which product a subject has been assigned to. An additional member of the dispensing staff will verify the dispensing procedure has been completed correctly for each subject.

A record of product dispensing to each subject will be maintained in the dispensing log; completion of the dispensing procedure will be recorded in the eCRF.

6.2 Administration

Only subjects enrolled in the study may receive study products and only authorized site staff may supply and administer study products. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the product label storage conditions with access limited to the authorized site staff only.

Subjects will self-administer the acclimatization toothpaste, and their assigned investigational toothpaste, according to the usage instructions provided by the dispensing staff at the investigator site and as described in their diary. Subjects will be instructed to record each brushing with study product in their diary.

To help ensure subjects fully understand the amount of toothpaste to use, the brushing instructions and how to complete the diary:

- **Screening (Visit 1):** Staff will demonstrate dispensing a full ribbon of toothpaste along the length of the toothbrush head to each enrolled subject and supervise their first timed brushing with the acclimatization toothpaste and diary completion at the end of the visit, after all clinical assessments have been completed.
- **Baseline (Visit 2):** Staff will supervise the dispensing of a full ribbon of toothpaste by each randomized subject and supervise the first timed brushing with their assigned investigational toothpaste and diary completion. Staff will show each subject randomized to Test Toothpaste the location of their 'Test Teeth' and confirm the subject can correctly locate the two 'Test Teeth' themselves, prior to starting their on-site brushing.
- **Visits 3-6:** Staff will supervise each subject brushing with their assigned investigational toothpaste and completing their diary at the end of the visit, after all clinical assessments have been completed. Staff will check that subjects randomized to Test Toothpaste can correctly identify their 'Test Teeth' prior to starting their on-site timed brushing. If a subject cannot correctly identify their two 'Test Teeth', they will be re-instructed in their location and a deviation will be recorded.

On-site administration of study products will be recorded in the dispensing log and the eCRF.

6.2.1 Medication/Dosing Errors

In this study, dosing errors may result from the administration or use of the wrong study product, by the wrong subject, at the wrong time, in the wrong way. Such dosing errors should be captured in the eCRF.

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

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

If a dosing error is accompanied by an AE, as determined by the investigator or medically qualified designee, the dosing error and any associated AEs are to be recorded in the eCRF.

6.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a study product at an amount higher than specified in the protocol. Overdose is not likely to occur in this study.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (or serious adverse event (SAE), as appropriate) per protocol following the AE and SAE reporting instructions.

6.3 Study Product Storage

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

The investigator or designee will ensure that all study products are stored in a secured area with controlled access under the required storage conditions, in accordance with applicable regulatory requirements and the product label.

Investigator site systems must be capable of measuring and documenting (e.g., via a log), as a minimum, daily minimum and maximum temperatures for all study product storage locations (including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of first product receipt throughout the study. For continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be in place. The operation of temperature-monitoring devices and temperature-controlled storage units (e.g., refrigerators) should be regularly inspected to ensure they are maintained in working order.

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

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

Site staff will instruct subjects on the proper storage requirements for all take-home study products, in accordance with the label requirements.

6.4 Study Product Accountability

Study products are supplied for use in this clinical study only and should not be used for any other purpose. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

Study products must be received by designated personnel at the investigator site, handled and stored safely and properly, and kept in a secured location to which only authorized staff have access. Upon receipt, each study product should be stored in accordance with the instructions specified on the product label.

Study products will be dispensed to enrolled/randomized subjects only, in accordance with the protocol, by authorized site staff. Subjects will return all used/unused tubes of acclimatization toothpaste to the investigator site at their Baseline visit (Visit 2). Subjects will bring all used/unused tubes of their assigned investigational toothpaste to each of their scheduled visits to the investigator site (per Schedule of Activities, Table 1-1) and return all used/unused study product to the investigator site at study conclusion. Returned study products should not be re-dispensed to any subject.

The investigator site must maintain adequate records (e.g., product accountability forms) documenting the receipt, use, loss, return or other disposition of all study product and supplies. Accountability records must be available for inspection by the study monitor during the study. Product accountability will be monitored during investigator site visits and on the completion of the study, as required by the study monitoring plan.

6.4.1 Destruction of Study Product Supplies

At the end of the study, the investigator or an appropriate designee and the sponsor's representative (study monitor) will inventory all used and unused study products and the study product accountability record for returned study products will be completed.

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 the sponsor's Clinical Supplies Department.

Unused sundry items will be returned to the sponsor; used items will be disposed of at the investigator site as described in Section 6.1 (Table 6.2). Documented approval for disposal of used sundry items must be received from the sponsor's Clinical Supplies Department prior to destruction.

Detailed instructions for the return of study products, and the destruction of sundry items, will be provided by the sponsor prior to the study close out visit.

6.5 Blinding and Allocation/Randomization

Qualifying subjects will be centrally randomized to one of two investigational 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. Investigational toothpaste will be dispensed according to the instruction received through the IRT at the Baseline visit (Visit 2). Returned study products should not be re-dispensed to any subject.

Only subjects who meet the study selection criteria will be randomized to treatment. Qualifying subjects 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 (the clinical examiner(s) will be blinded to treatment received). However, study subjects, investigator site staff involved in safety or efficacy assessments, study statistician(s), data management staff, other employees of the Sponsor (including the 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 subjects brushing with their allocated treatment while at the investigator site.

As described in Section 4.2, to maintain the blind throughout the study:

- Study subjects will see and use only one of the two investigational toothpastes for the duration of the treatment period. They will be instructed not to discuss the appearance, usage or perceived performance of their assigned investigational toothpaste with the clinical examiner(s), with staff involved in clinical assessments or with other study subjects.
- The investigational toothpastes will be provided to the investigator site overwrapped in white vinyl to mask their identity, and to obscure any branding on the Reference Toothpaste, with a study label affixed.
- The investigational toothpastes will be supplied in cartons; each carton will contain 4 over-wrapped tubes of toothpaste; each carton and its 4 tubes will be labelled with the

same unique randomization number. Subjects will be centrally randomized to treatment in order of qualification using an IRT; product codes will not be used.

- The clinical examiner(s) and site staff involved in efficacy and safety assessments will not be permitted in any area where the investigational toothpastes or diaries are stored, dispensed or in use.
- Site staff involved in the dispensing of investigational toothpastes, providing brushing and diary completion instruction, supervision of on-site brushings, treatment compliance checks and product accountability will not be involved in clinical efficacy and safety assessments and will work in a separate area from the clinical examiner(s) and site staff involved in efficacy and safety assessments.
- Subjects will be instructed not to remove their assigned investigational toothpaste or diary 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.

6.6 Breaking the Blind

At study initiation, the investigator site will be instructed on the method for breaking the blind; this will be an electronic process.

The electronic system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has sole responsibility for determining if the unblinding of the subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, they should make every effort to contact the sponsor prior to unblinding the subject's treatment assignment unless this would delay emergency treatment of the subject.

Once treatment assignment is unblinded, the sponsor must be notified within 24 hours of breaking the blind. The date and reason for breaking the blind must be recorded in source documentation and the eCRF, as applicable. The investigator site may also be required be required to inform the IRB if the blind is broken.

Any AE associated with breaking the blind must be recorded and reported per protocol.

6.7 Compliance

Diaries will be supplied to promote compliance and to capture details of study product use throughout the study period. Each subject will be provided with two diaries, one at Screening (Visit 1) and one at Baseline (Visit 2) to record each brushing with acclimatization toothpaste and investigational toothpaste, respectively. The diaries will also provide product usage instructions for the subject to refer to throughout their participation in the study.

- Subjects will be instructed to note any missed/additional brushings and the reasons for missed/additional brushings in the diary.
- Subjects will also be instructed to record additional information in the diary such as changes in health, oral problems, changes in medications/treatments, new medications/treatments and any issues with the toothpaste they are using.

Subjects will be instructed to bring their diary (completed to date) to each scheduled study visit. Completed diaries will be reviewed by investigator staff at the start of each study visit (to maintain the blind, staff performing diary reviews should not be involved in any safety or efficacy assessments). Any missed or additional brushings will be recorded in the eCRF as protocol deviations and subjects will be re-instructed in correct product usage requirements and diary completion, as needed.

Information recorded in the diary relating to changes in health, medications and treatments will be reviewed by the investigator, or medically qualified designee, with the subject and transcribed into the eCRF, as appropriate (e.g., as an AE). Information related to product use or issues should also transcribed into the eCRF, as needed, taking care to maintain the blind.

Subjects will be instructed to bring all tubes of study product (used and unused) and their toothbrush to each scheduled study visit. Study staff will perform a visual check of product usage and toothbrush condition. Any suspected over or under use will be documented in the eCRF and the subject will be re-instructed in the correct usage requirements.

To confirm the subject understands the usage instructions provided at Screening (Visit 1) and Baseline (Visit 2), their first use of study product (acclimatization toothpaste and investigational toothpaste, respectively) will be supervised on-site. To facilitate compliance, further supervised brushings will be completed on-site at the end of Visits 3-6. Subjects deemed non-compliant with any aspect of the usage requirements or diary completion will be re-instructed in the correct procedure. Any deviation from protocol requirements will be recorded in the eCRF.

6.8 Concomitant Medication/Treatment

Any medications, treatments or vaccines (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) taken or received during the study, from the signing of informed consent, must be recorded in the eCRF with indication, reason for use, unit dose, daily dose and start/stop dates of administration. Subjects 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 informed consent will be documented as prior medication/treatment. Medications and treatments taken or received after signing the informed consent will be documented as concomitant medication/treatments.

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

- Subjects should delay any non-emergency, elective dental treatments until after study completion (including dental prophylaxis).
- Should an enrolled/randomized subject start a course of treatment which includes daily, regular or intermittent use of any medication, details of that treatment will be recorded in the eCRF. The investigator or their medically qualified designee will decide if the subject should continue in the study or be withdrawn.
- Should a subject take a medication which, in the opinion of the investigator or their medically qualified designee, could impact the subject's perception of pain (e.g., an analgesic) within 8 hours of a scheduled study visit, every effort will be made to reappoint them within permitted visit tolerances (see Schedule of Activities, Table 1-1). The reason for re-appointment will be documented in the eCRF. The medication and any associated AE should be recorded in the eCRF. If re-appointment is not possible, the following visit specific actions should be taken:

- **Screening (Visit 1):** The subject will be withdrawn from the study. No tooth sensitivity assessments will be performed. The subject may be replaced.
- **Baseline (Visit 2):** The subject will be withdrawn from the study. No tooth sensitivity assessments will be performed. The subject will not be replaced.
- **Visits 3-7:** The subject will continue in the study. Tooth sensitivity assessments will be performed.

Subjects should not participate in any other clinical study (including cosmetic studies) or be in receipt of another investigational product for the duration of this study.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at their own request or may be withdrawn from the study at any time at the discretion of the investigator or the sponsor for safety or behavioral reasons, or due to the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

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

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

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

7.2 Lost to Follow Up

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

A subject will be considered lost to follow up if they repeatedly fail to attend scheduled visits and cannot be contacted by the study staff. Before the subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with them (where possible three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or equivalent local methods). Each contact attempt should be documented. If contact is made, the investigator or designee should inquire about the reason for their withdrawal, request that the subject return all products provided and, if appropriate, request that the subject return for a final visit and follow-up any unresolved AEs. Final safety assessments may be carried out when the subject returns to the investigator site, at the investigator's discretion, which may include an oral examination.

Should the subject continue to be unreachable, they will be considered to have withdrawn from the study and lost to follow up. This will be documented in the eCRF. Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations provided subject safety was preserved.

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

8 STUDY PROCEDURES

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

8.1 Visit 1 / Screening

Screening procedures will be conducted by the investigator, the clinical examiner(s) or suitably qualified/experienced and trained designees, 14-28 days prior to the Baseline visit (Visit 2). Where practically feasible, they should be completed in the order listed below. Data collected will be recorded in the eCRF.

8.1.1.1 Informed Consent

The investigator or designee must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. The investigator or designee must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Subjects will be provided with an ingredients list for the products to be used in the study to enable them to confirm they are not aware of any allergy or hypersensitivity to any of the ingredients listed.

Two copies of the informed consent form (ICF) will be signed and dated by the subject. The investigator or designee will also sign and date each copy of the ICF, after the subject has signed it, to confirm that the consent process was completed correctly. The subject will retain one copy and the other will be kept at the investigator site.

The time of consent will also be captured 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 new information becomes available during the conduct of the study that might affect subject willingness to participate in the study, each ongoing subject should receive a verbal explanation and written summary of the new information and be re-consented into the study. Each subject will be provided with a copy of their signed/dated amended ICF. Date of re-consent will be recorded in the eCRF.

After signing the ICF, each subject will undergo a series of screening procedures and clinical assessments to confirm that they meet the protocol required inclusion criteria and none of the exclusion criteria.

8.1.2 Demographics

The following demographic information will be recorded in the eCRF: year of birth, gender, race and ethnicity.

8.1.3 Review of Oral Care Products

Subjects will be required to bring their current oral care products to Screening (Visit 1) for investigator staff to confirm the absence of known anti-sensitivity ingredients and sensitivity-related claims on the product packaging/label text. Subjects who are currently using anti-sensitivity oral care product(s) will be excluded.

Subjects will also be asked about the oral care products they have been using in the last 8 weeks; those who report using anti-sensitivity product(s) in the 8 weeks prior to Screening will be excluded.

8.1.4 Medical History and Prior Medications/Treatments

The following will be documented in the eCRF:

- Details of relevant medical history and recent surgery (within the last year), including allergies and drug sensitivities.
- Female subjects: pregnancy status (self-reported).
- Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the 30 days prior to Screening.

8.1.5 Clinical Examinations and Assessments

The following clinical examinations and DH assessments will be completed as described in Study Assessments (Section 9) and the findings recorded in the eCRF. To facilitate subject flow, source documents can be used to record clinical data for later transcription into the eCRF. Transcription into the eCRF must be completed within 5 days of recording the data for each subject.

- Oral soft tissue (OST) examination
- Oral hard tissue (OHT) examination
- Clinical assessment of incisors, canines and pre-molars for dentition exclusions, erosion abrasion and attrition (EAR), Modified Gingival Index (MGI), adjacent to the test area only, and clinical mobility to 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 5.3 Exclusion Criterion 26) which meet EAR, MGI and tooth mobility requirements (Section 5.2 Inclusion Criteria 6(c)).

  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) for each tooth with a Screening tactile threshold of ≤ 20g.

Subjects must have a minimum of two 'eligible teeth', in different quadrants, with a tactile threshold ≤ 20g and a Schiff sensitivity score ≥ 2 to continue in the study (Section 5.2 Inclusion Criterion 6c)**.**

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

8.1.6 Inclusion/Exclusion Criteria

Information relating to inclusion/exclusion criteria will be completed in the eCRF.

8.1.7 Subject Eligibility

The investigator or medically qualified designee will review the medical history, prior medications/treatments, clinical examination/assessment data and the inclusion/exclusion criteria for each subject to determine their eligibility to participate in the study. The eligibility decision will be documented in the eCRF.

If confirmed as eligible to participate, the subject will be considered enrolled in the study.

To prepare for study participation, enrolled subjects will be instructed in the Lifestyle Guidelines (Section 5.5) and Concomitant Medications/Treatments (Section 6.8) requirements of the study (as already detailed in the ICF and described during the consent process). Adherence to the requirements of the study protocol is essential for successful study conduct.

8.1.7.1 Supervised Brushing with Acclimatization Toothpaste

Enrolled subjects will be provided with the acclimatization toothpaste, a toothbrush, a timer, rinsing cups and a diary to use during the acclimatization period.

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

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

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

Dispensing staff will remind subjects to note any changes in their health, medications or treatments in the diary (or report such changes to the investigator staff between visits using the contact numbers provided or inform staff at their next visit, if preferred) and to bring their acclimatization toothpaste, toothbrush and completed diary to their next study visit.

8.2 Study Period

8.2.1 Visit 2 / Baseline (Day 0)

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

8.2.1.1 Compliance Checks

Dispensing staff will complete visual checks of the returned acclimatization toothpaste and toothbrush and review the completed diary to assess compliance.

Suspected over or under use and the number of missed or additional brushings will be recorded in the eCRF. Any deviation from the required usage instructions will be captured as a protocol deviation in the eCRF and subjects will be re-instructed in the correct usage.

Do not return the acclimatization toothpaste, toothbrush or completed diary to the subject.

8.2.1.2 Changes in Medical History and Concomitant Medications/Treatments

Investigator staff will ask subjects if there have been any changes in their health, concomitant medications and non-drug treatments; female subjects of child-bearing potential will self-report pregnancy status. All changes will be documented in the eCRF.

Spontaneously reported AEs and any AEs elicited during questioning about changes in health or by asking subjects to respond to non-leading questions (such as 'how do you feel?') will recorded in the eCRF. AEs and/or changes in medications/treatments identified during review of the diary will be recorded in the eCRF.

8.2.1.3 Subject Adherence and Continuance

Investigator staff will question subjects about adherence to the requirements of the protocol; any deviations from study requirements will be recorded in the eCRF. Subject continuance will be confirmed.

8.2.1.4 Subject-Reported Outcomes

Prior to commencing the clinical examination/assessments, each subject will independently (without supervision) complete a hard copy of the DHEQ-48 (source), Sections 1 and 2 (i.e., all questions in both sections), see Appendix 15.2. Subject responses will be transcribed in to the eCRF.

8.2.1.5 Clinical Examinations and Assessments

The following clinical examination and DH assessments will be completed as described in Study Assessments (Section 9). To facilitate subject flow, source documents can be used to record clinical data for later transcription into the eCRF.

- OST examination
- **Clinical assessment of tactile sensitivity (tactile threshold (g); maximum force 20g).** Assess each tooth with a Screening tactile threshold of ≤ 20g **and** a Screening Schiff sensitivity score ≥ 2.

  Ensure at least a 5-minute break between completing the tactile sensitivity assessments and starting the evaporative (air) sensitivity assessments.
- **Clinical assessment of evaporative (air) sensitivity (Schiff sensitivity score)**. Assess each tooth with a Baseline tactile threshold of ≤ 20g.

Subjects must have at least two 'qualifying teeth', in different quadrants, with a tactile threshold ≤ 20g and a Schiff sensitivity score ≥ 2 at both Screening and Baseline to continue in the study (Section 5.2 Inclusion Criterion 7).

Subjects with fewer than two 'qualifying teeth' will be discontinued.

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

8.2.1.6 Selection of 'Test Teeth'

The clinical examiner responsible for evaporative (air) assessments will select two 'Test Teeth' for assessment of both tactile and evaporative (air) sensitivity at all subsequent study visits.

'Test Teeth' should only be selected from teeth which met the EAR, MGI and tooth mobility requirements and had no dentition exclusions at Screening, with the required qualifying levels of DH at **both** Screening (Visit 1) **and** Baseline (Visit 2):

- Tactile threshold ≤ 20g at Screening and Baseline.
- Schiff sensitivity score ≥ 2 at Screening and Baseline.

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 two 'Test Teeth' will be recorded in the eCRF.

8.2.1.7 Subject Eligibility

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 each subject's suitability to continue in the study; the eligibility decision will be documented in the eCRF.

8.2.1.8 Stratification and Randomization

Each qualifying subject will be stratified to one of two strata as described in Section 6.5 and randomized to treatment. Subject stratum will be entered directly into the eCRF.

Each subject will be assigned a randomization number from their designated stratum in ascending numerical order, and as each subject is determined to be fully eligible. The randomized toothpaste code will be entered directly into the eCRF.

8.2.1.9 Supervised Brushing with Investigational Toothpaste

Randomized subjects will be provided with their allocated investigational toothpaste, a new toothbrush, additional rinsing cups and a new diary.

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

- Subjects randomized to the Test Toothpaste will be shown the location of their two 'Test Teeth' within the mouth (using a tooth diagram/model and a mirror, as needed).

  They will be then instructed to start their timer (pre-set for 1-minute) and brush their entire dentition thoroughly for at least 1-timed minute, **making sure to brush the sensitive areas of their two selected 'Test teeth' carefully first**.

- Subjects randomized to the Reference Toothpaste will be instructed to start their timer (pre-set for 1-minute) and brush their entire dentition thoroughly for at least 1-timed minute.

Dispensing staff will supervise each subject carrying out the first brushing with their allocated investigational toothpaste and recording the first use in their diary. Any deviation from the required product usage instructions will be captured as a protocol deviation in the eCRF and the subject will be re-instructed in the correct directions for use.

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

Spontaneously reported AEs and any AEs elicited by asking the subject to respond to non-leading questions (such as 'how do you feel?') on completion of the supervised brushing will be recorded in the eCRF.

Dispensing staff will remind subjects to note any changes in their health, medications or treatments in the diary (or report such changes to the investigator staff between visits using the contact numbers provided or inform staff at their next visit, if preferred) and to bring their investigational toothpaste, toothbrush and completed dairy to their next study visit.

Randomized subjects will be re-instructed in the Lifestyle Guidelines (Section 5.5) and Concomitant Medications/Treatments (Section 6.8) requirements of the study.

8.2.2 Visit 3 / Day 3

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

8.2.2.1 Compliance Checks

Dispensing staff will complete visual checks of the returned investigational toothpaste and toothbrush and review the partially completed diary to assess compliance.

Suspected over or under use and the number of missed or additional brushings will be recorded in the eCRF. Any deviation from the required usage instructions will be captured as protocol deviations in the eCRF and subjects will be re-instructed in the correct usage.

Return the investigational toothpaste, toothbrush and partially completed diary to the subject.

8.2.2.2 Changes in Medical History and Concomitant Medications/Treatments

Investigator staff will ask subjects if there have been any changes in their health, concomitant medications and non-drug treatments; female subjects of child-bearing potential will self-report pregnancy status. All changes will be documented in the eCRF.

Spontaneously reported AEs and any AEs elicited during questioning about changes in health or by asking subjects to respond to non-leading questions (such as 'how do you feel?') will recorded in the eCRF.

AEs and/or changes in medications/treatments identified during review of the diary will be recorded in the eCRF.

8.2.2.3 Subject Adherence and Continuance

Investigator staff will question subjects about adherence to the requirements of the protocol; any deviations from study requirements will be recorded in the eCRF. Subject continuance will be confirmed.

8.2.2.4 Clinical Examinations and Assessments

The following clinical examination and DH assessments will be completed as described in Study Assessments (Section 9). To facilitate subject flow, source documents can be used to record clinical data for later transcription into the eCRF.

- 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 sensitivity assessments and starting the evaporative (air) sensitivity assessments.
- **Clinical assessment of evaporative (air) sensitivity (Schiff sensitivity score).** Assess two 'Test Teeth' only.

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

8.2.2.5 Supervised Brushing with Investigational Toothpaste

Dispensing staff will visually check the condition of the subject's toothbrush. If it is damaged, a new toothbrush should be provided; supply of a replacement toothbrush will be documented in the eCRF.

Dispensing staff will re-describe the toothpaste usage instructions to each subject (reminding them to cover the full brush head with a ribbon of toothpaste and use the timer each time they brush) and then supervise each subject completing an on-site brushing with their allocated investigational toothpaste and recording this use in their diary. Dispensing staff will ask subjects randomized to the Test Toothpaste to indicate the location of their two 'Test Teeth' in the mouth (before they start brushing) and confirm the subject brushes these two teeth first, prior to brushing their entire dentition.

Any deviation from the required product usage instructions will be captured as a protocol deviation in the eCRF and the subject will be re-instructed in the correct directions for use. Completion of each supervised on-site brushing will be documented in the eCRF.

Spontaneously reported AEs and any AEs elicited by asking the subject to respond to non-leading questions (such as 'how do you feel?') on completion of the supervised brushing will be recorded in the eCRF.

Dispensing staff will remind subjects to note any changes in their health, medications or treatments in the diary (or report such changes to the investigator staff between visits using the contact numbers provided or inform staff at their next visit, if preferred) and to bring their investigational toothpaste, toothbrush and completed diary to their next study visit.

Randomized subjects will also be re-instructed in the Lifestyle Guidelines (Section 5.5) and Concomitant Medications/Treatments (Section 6.8) requirements of the study.

8.2.3 Visit 4 / Day 7

Repeat procedures, clinical examination, DH assessments and supervised brushing as described for Visit 3 / Day 3.

8.2.4 Visit 5 / Day 14 (± 1 day)

Repeat procedures, clinical examination, DH assessments and supervised brushing as described for Visit 3 / Day 3.

8.2.5 Visit 6 / Day 28 (± 2 days)

Repeat procedures, clinical examination, DH assessments and supervised brushing as described for Visit 3 / Day 3.

In addition, prior to commencing the clinical examination/assessments, each subject will independently (without supervision) complete a hard copy of the DHEQ-48 (source), Section 1 Questions 7-9 and Section 2 all questions (Appendix 15.2). Subject responses will be later transcribed into the eCRF.

8.2.6 Visit 7 / Day 56 (± 3 days)

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

8.2.6.1 Compliance Checks

Dispensing staff will complete visual checks of the returned investigational toothpaste and toothbrush and review the completed diary to assess compliance. Suspected over or under use and the number of missed or additional brushings will be recorded in the eCRF. Any deviation from the required usage instructions will be captured as protocol deviations in the eCRF.

Do not return the investigational toothpaste, toothbrush or completed diary to the subject.

8.2.6.2 Changes in Medical History and Concomitant Medications/Treatments

Investigator staff will ask subjects if there have been any changes in their health, concomitant medications and non-drug treatments; female subjects of child-bearing potential will self-report pregnancy status. All changes will be documented in the eCRF.

Spontaneously reported AEs and any AEs elicited during questioning about changes in health or by asking subjects to respond to non-leading questions (such as ‘how do you feel?’) will recorded in the eCRF.

AEs and/or changes in medications/treatments identified during review of the diary will be recorded in the eCRF.

8.2.6.3 Subject Adherence and Continuance

Investigator staff will question subjects about adherence to the requirements of the protocol; any deviations from study requirements will be recorded in the eCRF.

8.2.6.4 Subject-Reported Outcomes

Prior to commencing the clinical examinations and assessments, each subject will independently (without supervision) complete a hard copy of the DHEQ-48 (source), Section 1 Questions 7-9 only, and Section 2 all questions (see Appendix 15.2). Subject responses will be later transcribed into the eCRF.

8.2.6.5 Clinical Examinations and Assessments

The following clinical examinations and DH assessments will be completed as described in Study Assessments (Section 9). To facilitate subject flow, source documents can be used to record clinical data for later transcription into the eCRF.

- 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 sensitivity assessments and starting the evaporative (air) sensitivity assessments.
- **Clinical assessment of evaporative (air) sensitivity (Schiff sensitivity score).** Assess two 'Test Teeth' only.

After the clinical examinations/assessments have been completed, subjects will complete a Satisfaction with Treatment NRS and describe (free text) why they gave their rating (Section 9.3.4).

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

8.3 Study Conclusion

The Study Conclusion page of the eCRF will be completed for all subjects whether or not they complete all study procedures (i.e., even if they are discontinued early at any point during the study). If the subject is discontinued early, the primary reason for withdrawal should be recorded on the Study Conclusion page. For subjects who attend all scheduled study visits, the Study Conclusion page of the eCRF will be completed at Visit 7.

Investigator staff will instruct each subject to inform the site if they experience any change in health, medications or treatments in the 5 days following their last use of study product.

If a subject has any clinically significant, study-related abnormalities or AEs at the end of the study, the sponsor's medical monitor (or designated representative) should be notified. The subject 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.

8.4 Follow-Up Contact

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

9 STUDY ASSESSMENTS

Every effort should be made to ensure study-required examinations and assessments are completed as described and scheduled in this protocol. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that make it unfeasible to complete an examination or assessment. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required

examination or assessment cannot be performed, the investigator or designee will document the reason for the missed procedure as a protocol deviation and any corrective and preventative actions they have taken to ensure the required procedures are adhered to as soon as possible. The sponsor should be informed of any missed examinations or assessments in a timely manner.

9.1 Screening Examinations/Assessments

Screening examinations and assessments will be performed by appropriately trained and experienced clinical examiners/staff at the times and in the order defined in the Study Procedures section of this protocol (Section 8).

The eligibility of each tooth will be assessed against the protocol inclusion/exclusion criteria (Sections 5.2 and 5.3) and recorded in the eCRF. If, in the opinion of the clinical examiner, the value/score for a particular tooth/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.

9.1.1 Erosion, Abrasion and Recession (EAR)

The facial surfaces of all incisor, canine and pre-molar teeth (Figure 9-1) 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 EAR (Addy, 2000).

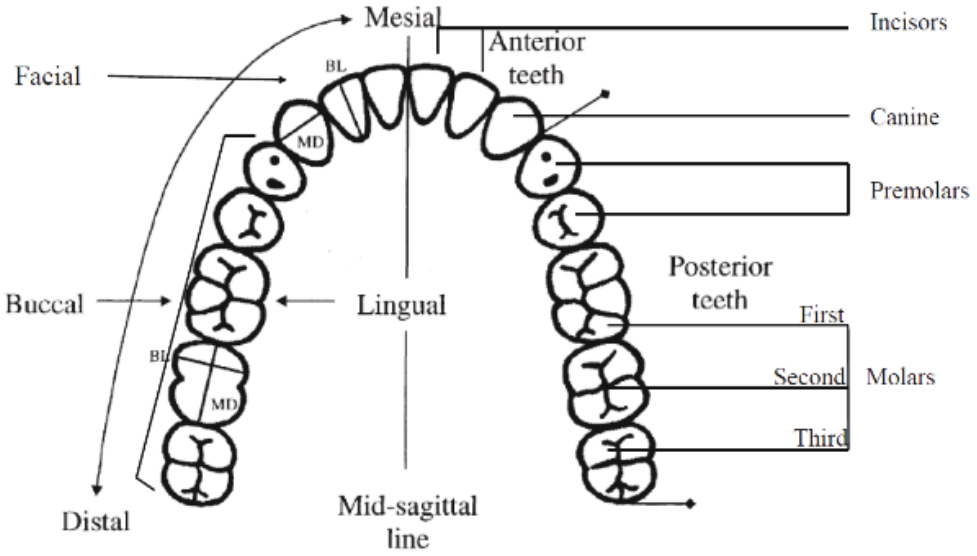


Figure 9-1 Dental Nomenclature (Dempsey, 2001)

9.1.2 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 9-1) exhibiting none of the dentition exclusions and presenting with facial/cervical EAR. MGI should be scored for the facial gingiva directly adjacent to the area of exposed dentin (i.e., the test area only).

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

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

9.1.3 Clinical Mobility

Clinical mobility will be assessed for incisor, canine and pre-molar teeth (Figure 9-1) 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 will have clinical mobility = 0.

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

9.1.4 Screening Qualifying Tactile Sensitivity

The tactile sensitivity of incisor, canine and pre-molar teeth (Figure 9-1) 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 dentin to ensure application of the stimulus across the potentially ‘sensitive’ area.

After each application of the tactile stimulus, the subject will be asked to indicate whether they experienced any pain or discomfort. The examiner will tell the subject 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 subject 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, a tooth must have a Screening tactile threshold ≤ 20g.**
- **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 subject 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 subject 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 subject'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 subject'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 subjects 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 80g. 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.

9.1.5 Screening Qualifying Evaporative (Air) Sensitivity

Evaporative (air) sensitivity will be assessed on the facial surfaces of incisor, canine and pre-molar teeth (Figure 9-1) which exhibit none of the dentition exclusions, meet the EAR, MGI, clinical mobility criteria and have a Screening tactile threshold ≤ 20g.

Evaporative (air) assessment 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 dental examiner will take appropriate measures to isolate the tooth surface to prevent stimulation of adjacent teeth or surrounding soft tissue.

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

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

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

9.2 Efficacy Assessments

The following efficacy assessments will be performed by appropriately trained and experienced clinical examiners/staff, at the times and in the order defined in the Study Procedures section of this protocol (Section 8).

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.

9.2.1 Dentine Hypersensitivity Experience Questionnaire (DHEQ-48)

The DHEQ-48 is a condition-specific measure of OHrQoL in relation to DH (Boiko, 2010) that has been previously validated in longitudinal studies and shown to be responsive to treatment (Baker, 2014). The DHEQ total score can be broken down into 5 separate 'domain' scores to provide a more granular understanding of the specific areas of improvement subjects experience in their OHrQOL.

- **Restrictions:** Derived from participant responses to Section 2, Q1-4 (‘*the ways in which any sensations in your teeth affect you in your daily life*’).
- **Adaptation:** Derived from participant responses to Section 2, Q5-16 (‘*the ways in which the sensations in your teeth have forced you to change things in your daily life*’; ‘*things you do in your daily life to avoid experiencing the sensations in your teeth*’).
- **Social Impact:** Derived from participant responses to Section 2, Q17-21 (‘*the way the sensations affect you when you are with other people or in certain situations*’).
- **Emotional Impact:** Derived from participant responses to Section 2, Q22-29 (‘*the way the sensations in your teeth make you feel*’).
- **Identity:** Derived from participant responses to Section 2, Q30-34 (‘*what the sensations in your teeth mean for you*’).

The DHEQ also provides specific information on how much the sensations in the participant’s teeth affect their life overall:

- **Global Oral Health:** Derived from participant response to Section 2, Q35 (‘*rate the health of your mouth, teeth and gums*’).
- **Effect on Life Overall:** Derived from participant responses to Section 2, Q36-39 (impact of DH on overall quality of life).

Subjects will independently (unsupervised) complete a hard copy of the DHEQ-48 (Appendix 15.2) at Baseline (Visit 2), Day 28 (Visit 6) and Day 56 (Visit 7), prior to any clinical examinations and assessments.

- **Baseline:** Complete Section 1 and Section 2 (i.e., all questions in both sections).
- **Day 28 & Day 56:** Complete Section 1 Questions 7-9 only, and Section 2 all questions.

9.2.2 Tactile Sensitivity Assessment

Tactile sensitivity will be assessed at Baseline (Visit 2), Day 3 (Visit 3), Day 7 (Visit 4), Day 14 (Visit 5), Day 28 (Visit 6) and Day 56 (Visit 7). The tactile stimulus will be administered, and subject response recorded, as described in Section 9.1.4. The gram setting which elicits the two consecutive ‘yes’ responses will be recorded as the tactile threshold (g).

- **Baseline:** Assess the tactile sensitivity of all teeth which exhibit none of the dentition exclusions and meet the EAR, MGI and clinical mobility criteria, with a Screening tactile threshold of ≤ 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 tactile threshold as > 20g.
- **Days 3, 7, 14, 28 & 56:** Assess the tactile sensitivity of the **two ‘Test Teeth’ only** (i.e., the two teeth selected by the clinical examiner at Baseline, as described in Section 8.2.1.6.

  The upper force setting will be 80g; if no sensitivity is found at the upper setting, record the tactile threshold as > 80g.

9.2.3 Evaporative (Air) Sensitivity Assessment

Evaporative (air) sensitivity will be assessed at Baseline (Visit 2), Day 3 (Visit 3), Day 7 (Visit 4), Day 14 (Visit 5), Day 28 (Visit 6) and Day 56 (Visit 7). The evaporative (air) stimulus will be administered, and subject response recorded, as described in Section 9.1.5.

Evaporative (air) assessments will start a minimum of 5 minutes after the tactile assessments have completed (tooth recovery time).

- **Baseline:** Assess evaporative (air) sensitivity for teeth with a Screening tactile threshold of ≤ 20g and a Screening Schiff sensitivity score ≥ 2.
- **Days 3, 7, 14, 28 & 56:** Assess the evaporative (air) sensitivity of the **two 'Test Teeth' only** (i.e., the two teeth selected by the clinical examiner at Baseline, as described in Section 8.2.1.6.

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

9.3 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol (Section 8).

9.3.1 Oral Soft Tissue (OST) Examination

The OST examination will be accomplished by direct visual observation and palpation, using retraction aids as appropriate, 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 results of the examination will be recorded in the eCRF as either 'normal' or 'abnormal'; details of any abnormalities will be documented 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.

9.3.2 Oral Hard Tissue (OHT) Examination

The OHT examination will be accomplished by direct visual observation, using retraction aids as appropriate, 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-mineralization, decalcification) and significant tooth staining. Observations will be listed 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 presence of any implants, fixed or removable dentures, fixed or removable orthodontic braces/bands, fixed 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 subject's dentition against the general and specific dentition exclusions described in Section 5.3 (Exclusion Criteria 22, 23, 24, 25, 26a-g).

9.3.3 Pregnancy

None of the study toothpastes are contra-indicated for pregnancy or breastfeeding (their use would not be expected to cause harm to the mother, the fetus or a baby). The commercial products (the Acclimatization and Reference Toothpastes) do not carry pregnancy warnings on the labelling (e.g., instructions to speak to a doctor before use if pregnant); the Test Toothpaste will not carry a pregnancy warning when marketed in Canada. Thus, pregnancy testing of female subjects is not required prior to their enrolment.

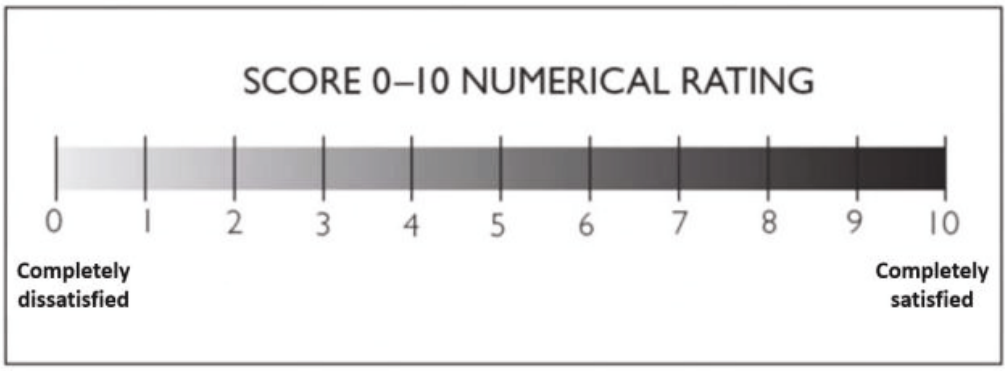
Female subjects will provide verbal confirmation of pregnancy status at Screening (Visit 1) and at each subsequent study visit; this will be recorded in the eCRF. They will be instructed to inform the investigator staff immediately should they find out they are pregnant at any point during the study.

Female subjects who are pregnant or intending to become pregnant during the study (self-reported) will be excluded (the rationale for exclusion is provided in Section 4.2).

9.3.4 Satisfaction with Treatment

At the end of the study (Visit 7), subjects will be asked to rate their level of satisfaction with their allocated investigational toothpaste using a Numeric Rating Scale (NRS).

The NRS is an 11-point ordinal scale used to assess the subject's satisfaction with the product's overall management of their DH. The scale ranges from 0 (completely dissatisfied) to 10 (completely satisfied), with higher scores indicative of greater satisfaction (van Berckel, 2017): see example below. Subjects will be asked to record the numeric value on the segmented scale that best describes their level of satisfaction after 8 weeks twice daily use and indicate why they selected a particular score in answer to the question 'Please give more details on why you are satisfied or dissatisfied with the product' (free text response).



Example NRS - Not to Scale

10 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 subject to discontinue use of study product or study participation.

10.1 Definition of an Adverse Event (AE)

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

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

Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry or urinalysis) or other safety assessments (e.g., 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.
- '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 fulfill the definition of an AE.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- 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.

10.2 Definition of a Serious Adverse Event (SAE)

A serious adverse event (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., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred, or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to

prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Note: Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements.

10.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs, and therefore all SAEs, will be collected from immediately after a subject 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 subject in a diary or similar document that meet the definition of an AE must be discussed with the subjects 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 subject 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.

10.4 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 following up AEs that are serious, considered related to study product, a study procedure or study participation, or that caused the subject 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 subjects.

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

AEs spontaneously reported by study subjects and those elicited by asking subjects 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 subject'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 subject identifiers, except for the subject number, will be redacted on the copies of the medical records prior to submission to the sponsor.

The investigator or 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 the 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').

10.4.1 Reporting an AE

AEs will be reported by the investigator, their medically qualified designee or site 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).

10.4.2 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 subject identifiers
- Subject 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 PPD with the appropriate sponsor Study Manager in copy, with the study number and subject number in the subject line of the email **immediately after site 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.

10.5 Evaluating AEs

10.5.1 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 subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities
- **Severe:** An event that prevents normal everyday activities.

Note: An AE 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 subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed in Section 10.2. 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 10.2), **not** when it is rated as 'severe'.

10.5.2 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, subject 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.

10.6 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 subject and provide further information on the subject'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 subject 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, subject 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 subject 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 PPD 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.

10.7 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE provided (Section 10.1) and recorded in the AE section of the eCRF.

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

10.8 Regulatory Reporting Requirements for SAEs

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

The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, the IRB 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 Safety Statement) in the investigator site file and notify the IRB, if appropriate, according to local requirements.

10.9 Pregnancy

10.9.1 Time Period for Collecting Pregnancy Information

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

10.9.2 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 PPD with the appropriate sponsor Study Manager in copy. Original completed pregnancy information forms will be retained in the investigator site file.

The female subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant/neonate (including concomitant medications taken by the mother during pregnancy) will be forwarded by the investigator or their medically qualified designee to the sponsor's Case Management Group mailbox PPD with the appropriate sponsor Study Manager in copy. Generally, follow-up will be for no longer than 6 to 8 weeks following the estimated delivery date. Termination of pregnancy will be reported.

While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

Any female subject who becomes pregnant while participating will be withdrawn.

10.10 Medical Device Incidents

A medical device is being provided by the sponsor for use in this study; the medical device in this study is the manual toothbrush (Oral B Sensi-Soft - Canadian market) used to apply the study toothpastes.

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

10.10.1 Definition of an Incident

A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in their state of health.

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

It is sufficient that an **incident** associated with a device happened and the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents:

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

10.10.2 Reporting of Incidents and Malfunctions

All incidents must be reported to the sponsor **immediately** the investigator or their medically qualified designee becomes aware of the situation, **and under no circumstance should this exceed 24 hours** of the investigator or designee becoming aware of the situation.

Any medical device incident occurring during the study will be documented in the subject's medical records, if in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE (non-serious and serious), the AE section of the eCRF/SAE form will be completed and reported as per the AE/SAE reporting sections above.

The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.

The completed Incident Report Form should be scanned and emailed to the sponsor's Case Management Group mailbox PPD with the appropriate sponsor Study Manager in copy, with the study number and subject number in the subject line of the email **immediately** after site staff learn of the event **and under no circumstances should this exceed 24 hours** after site staff learn of the event. If there is an SAE, the completed SAE form should be sent together with the Incident Report Form. The copy of the SAE report sent with this Incident Report Form does not replace the procedure for reporting an SAE. The original completed Incident Report Form will be retained in the investigator site file.

The initial medical device incident report will be followed up with more information as relevant, or as requested by the sponsor's study manager.

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

- Notify the sponsor immediately (as described above).
- Schedule the subject to return to site promptly to return the failed device.
- Record any incidents in the eCRF and on the Incident Report Form (as described above).
- For any incident/malfunction occurring with a medical device (including those that are part of combination products) supplied by the sponsor, return the failed device to the sponsor as soon as possible, including documentation of the details of the failure.
- For any incident/malfunction occurring with a medical device (including those that are part of combination products) supplied by the investigator site, report the incident to the device manufacturer and follow the manufacturer instructions for the return of the failed device (whilst keeping the sponsor informed).

10.10.3 Follow-up of Medical Device Incidents

Medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all subjects, including those who discontinue study product or are withdrawn from the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed Incident Report form, with all changes signed and dated by the investigator.

10.10.4 Regulatory Reporting Requirements for Medical Device Incidents

To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during all periods of the study in which the medical device is used.

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator will comply with applicable local regulatory requirements relating to the reporting of incidents to the IRB.

11 DATA MANAGEMENT

As used in this protocol, the term CRF refers to either a paper form or an electronic data record or both, depending on the data collection method. For this study, subject data will be entered into an electronic CRF (eCRF), using a validated system. Data relating to SAEs, pregnancy and incidents will also be collected on paper forms.

Subjects will complete paper copies of the DHEQ-48 (source) and the Treatment Satisfaction NRS (source); to facilitate subject flow, paper forms (source) may also be used to record clinical data for later transcription into the eCRF. Transcription of DHEQ/NRS responses and clinical data into the eCRF must be completed within 5 days of the data being recorded. The eCRF and

the subject-completed diary can be used as a source document at the discretion of data management.

The source documents that contain source data recorded in the eCRF should be specified.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Each subject will be assigned and identified by a unique Screening Subject Number. Any reference made to an individual subject within the study must be done using their unique Screening Subject Number.

11.1 Case Report Form

A CRF is a printed, optical or electronic document designed to record protocol-required information to be reported to the sponsor on each study subject.

For each subject who gives 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) to support the information entered in the CRF.

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

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

All CRF pages should be completed during a subject 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.

11.2 Data Handling

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

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

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

11.2.1 Data Queries

Programmed edit checks will be generated automatically as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for investigator 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 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 errors to be addressed in parallel with Data Management review. The study monitor will also run reports and listings on the CRFs to raise manual queries, as needed, for investigator site clarification or correction.

11.3 Processing Subject Reported Outcomes

Subject reported outcomes will be recorded in paper-based diaries and in questionnaires (DHEQ-48 and NRS) for later transcription into the eCRF.

Source documents recording subject-reported outcomes will be reviewed by the investigator staff and the study monitor to ensure the data, and any potential AEs or concomitant medications reported in these documents, are accurately transcribed into the eCRF.

Subject reported outcomes classed as source data will be retained by the investigator; true/certified copies may be sent to the sponsor or a third-party vendor, as required. To protect subject privacy, no PI (including subject name, initials or birth date) is to be recorded in any subject reported outcome source document that will be forwarded to the sponsor or a third-party vendor.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

Sufficient subjects will be screened and entered into the acclimatization period to randomize approximately 234 subjects to investigational product (approximately 117 subjects per treatment group) to ensure approximately 210 complete the study (approximately 105 subjects per treatment group), allowing for approximately 10% dropouts.

The study will be sufficiently powered to demonstrate statistical superiority of the Test Toothpaste compared to the Reference Toothpaste (negative control*)* for the change from Baseline in the Schiff sensitivity score after 56 days, i.e., 8 weeks, (primary objective) and 3 days (key secondary objective, earliest time point) treatment. It is anticipated that the treatment effect will increase over time. A sample size of 105 evaluable subjects per treatment group will provide 90% power to detect a mean difference of 0.25 units (SD = 0.55) in change from Baseline in Schiff sensitivity score after 3 days treatment, using a 2-tailed 2-sample t-test with a 5% significance level. The sample size calculation was performed using PASS software version 23.0.1.

The dropout rate and SD estimates are based on the results of DH efficacy studies of similar design and duration (Clinical Studies CCI and CCI sponsor data held on file, available on request).

12.2 Populations for Analysis

12.2.1 Definitions of Analysis Populations

The Safety population will comprise all randomized subjects who receive at least one dose of investigational product. Summaries and analyses of this population will be based on the investigational product the subject received.

The primary population for the assessment of efficacy will be a modified intention-to-treat (mITT) population. The mITT population will comprise all randomized subjects who receive at least one dose of investigational product and complete at least one-post Baseline DH efficacy assessment. This population will be based on the investigational product the subject was randomized to. All subjects who receive a randomization number will be considered randomized.

The Per-Protocol (PP) population will comprise all subjects in the mITT population who have at least one DH efficacy assessment considered to be unaffected by protocol deviations.

12.2.2 Exclusions of Data from Analysis

Exclusion of data from any of the planned analyses will be agreed during Blinded Data Review (BDR), prior to database lock. The reason(s) for exclusion of a subject 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 endpoint if ≥ 10% subjects in the mITT population are excluded from the PP population. Efficacy data determined to have been potentially impacted by a protocol deviation will be excluded from the PP analysis. The decisions as to whether or not a protocol deviation impacts efficacy data and whether to perform a PP analysis will be made during BDR, prior to database lock.

12.3 Statistical Analyses

This is a summary of the planned statistical analyses; the detail of the proposed statistical analyses will be documented in the Statistical Analysis Plan (SAP), to be written following finalization of the protocol and prior to study unblinding.

The mITT population will be used for all efficacy analyses.

All p-values presented will be two-sided and assessed at the 5% significance level. A sequential testing strategy will be used to adjust for multiplicity for the comparisons between the Test and Reference Toothpastes in change from Baseline in Schiff sensitivity score and tactile threshold (g) at each assessment time point.

At each timepoint, change from Baseline in tactile threshold (g) will only be assessed for confirmatory evidence if the change from Baseline in Schiff sensitivity score achieves a statistically significant greater reduction for the Test Toothpaste compared to Reference Toothpaste (negative control). This strategy will begin at Day 56, then move to successively earlier timepoints (i.e., Day 56 →Day 28 → Day 14 → Day 7 → Day 3), only moving the next earlier timepoint for confirmatory evidence if all later timepoints achieve statistically significant greater reductions for the Test Toothpaste compared to Reference Toothpaste (negative control) for both Schiff sensitivity score and tactile threshold (g). There will be no further adjustments for multiplicity for the other secondary endpoints (DHEQ-48).

Summary statistics (mean, median, SE, SD, minimum, maximum) will be presented for each Schiff sensitivity score and tactile threshold (g) outcome variable at each assessment time point. Raw means (± SE) of Schiff sensitivity score and tactile threshold (g) at each assessment timepoint will be plotted by treatment group.

The results from each MMRM will be tabulated, presenting the following information, in addition to the results specified for the primary and secondary analyses below: least square mean change from Baseline for each investigational product at Days 3, 7, 14, 28 and 56 (based on the observed stratification margins for those MMRM with a term for randomized strata) and used to test for any change from Baseline, with two-sided p-values and 95% CIs.

12.3.1 Primary Endpoint Analysis

The primary endpoint of this study is the change from Baseline in Schiff sensitivity score at Day 56 (Week 8); the primary hypothesis test will be the comparison between the Test Toothpaste and the Reference Toothpaste (negative control) in the mITT population.

Schiff sensitivity score will be derived as the mean score for the two 'Test Teeth' (selected at Baseline). Change from Baseline will be derived for each individual tooth first before calculating mean change for the two 'Test Teeth' where change from Baseline in Schiff sensitivity score at Day X is defined as [(Schiff sensitivity score at Day X) minus (Baseline Schiff sensitivity score)].

Change from Baseline in Schiff sensitivity score at Day 56 will be analysed using a MMRM with investigational product, visit and [investigational product x visit] interaction as fixed effects, and Baseline Schiff sensitivity score as a covariate. Subject will be included as a repeated measure with unstructured covariance matrix. Kenward-Rogers degrees of freedom approach will be applied (Kenward, 1997). The difference between the least square mean changes from Baseline for the Test Toothpaste compared to Reference Toothpaste (negative control) at Day 56 from the MMRM will be presented, along with the two-sided p-value and 95% CIs.

The assumptions of normality and homogeneity of variance in the MMRM will be investigated. In case of violation of these assumptions, a suitable non-parametric test (adjusted for the randomization stratification) will be performed to assess the change from Baseline comparison (Test Toothpaste vs. Reference Toothpaste at Day 56); the results will be provided to support the MMRM results.

12.3.2 Secondary Endpoint Analyses

Tactile Threshold at Day 56

Tactile threshold (g) will be derived as the mean value for the two 'Test Teeth' (selected at Baseline). Change from Baseline will be derived for each individual tooth first before calculating mean change for the two 'Test Teeth' where change from Baseline in tactile threshold (g) at Day X is defined as [(tactile threshold at Day X) minus (Baseline tactile threshold)].

Key secondary endpoint, change from Baseline in tactile threshold (g) at Day 56, will be analysed using the same MMRM as the primary endpoint 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' (2 or 3) will be fitted as a fixed effect. The difference between the least square mean changes from Baseline for the Test Toothpaste compared to Reference Toothpaste (negative control) at Day 56 from the MMRM will be

presented, along with the two-sided p-value and 95% CIs.

Tactile Threshold/Schiff Sensitivity Score at Day 28, Day 14, Day 7 and Day 3

The other key secondary endpoints:

- Change from Baseline in Schiff sensitivity score at Day 28
- Change from Baseline in tactile threshold (g) at Day 28
- Change from Baseline in Schiff sensitivity score at Day 14
- Change from Baseline in tactile threshold (g) at Day 14
- Change from Baseline in Schiff sensitivity score at Day 7
- Change from Baseline in tactile threshold (g) at Day 7
- Change from Baseline in Schiff sensitivity score at Day 3
- Change from Baseline in tactile threshold (g) at Day 3

will be analyzed using the same MMRM models described above for Schiff sensitivity score and tactile threshold (g), respectively. Differences between the least square mean changes from Baseline in Schiff sensitivity score and tactile threshold (g) will be presented for the Test Toothpaste compared to Reference Toothpaste (negative control) at Days 28, 14, 7 and 3 from their respective MMRMs, along with two-sided p-values and 95% CIs.

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 (adjusted for the randomization stratification value) will be performed to assess change from Baseline comparisons (Test Toothpaste vs. Reference Toothpaste at Days 56, 28, 14, 7 and 3, as appropriate); the results will be provided to support the MMRM results.

DHEQ-48

Change from Baseline will be calculated at Day 28 and Day 56 for all DHEQ endpoints.

- **Section** 1
  - Impact on Everyday Life: Q7, Q8 & Q9 (separate scores)
- **Section 2**
  - DHEQ Total Score (sum of Q1-34)
  - DHEQ Restrictions Domain score (sum of Q1-4)
  - DHEQ Adaptation Domain score (sum of Q5-16)
  - DHEQ Social Impact Domain score (sum of Q17-21)
  - DHEQ Emotional Impact Domain score (sum of Q22-29)
  - DHEQ Identity Domain score (sum of Q30-34)
  - DHEQ Global Oral Health (Q35)
  - DHEQ Effect on Life Overall (sum of Q36-Q39)

Change from Baseline will be calculated at the subject-level first then mean change from Baseline will be calculated for each DHEQ endpoint across all subjects.

Change from Baseline for each DHEQ endpoint listed above will be analyzed using a MMRM with time point and maximum Baseline Schiff sensitivity score of the two 'Test Teeth' (2 or 3) as fixed effects, and the respective Baseline DHEQ score as a covariate. Subject will be included

as a repeated measure with unstructured covariance matrix. Kenward-Rogers degrees of freedom will be applied. The estimates of the adjusted mean (SE) change from Baseline will be presented along with 95% Cis for each treatment group.

For each DHEQ endpoint listed above, and each individual DHEQ question, the value at each timepoint (Baseline, Day 28 and Day 56) and the corresponding change from Baseline will be summarized descriptively for each treatment group. Raw means (± SE) for each DHEQ endpoint, and the individual DHEQ questions, at each assessment timepoint will be plotted by treatment group.

12.3.3 Other Analyses

Satisfaction with Treatment NRS

A summary of the number of subjects reporting at each level of the NRS and the cumulative number of subjects reporting at each level or higher at Day 56 (Week 8) will be presented, and the NRS score at Day 56 (Week 8) will be summarized descriptively, by treatment group.

Subject free text comments will be listed by treatment group.

12.3.4 Safety Analyses

Safety analyses will be performed on the Safety population, according to investigational product received. AEs will be regarded as 'treatment emergent' if they occur on or after the first use of investigational product 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 randomization schedule, TEAEs will be associated with the most recent study investigational received.

Each AE will be categorized as oral or non-oral by the investigator or medically qualified designee. All will be reviewed by the CRS and coded using the MedDRA prior to database lock and unblinding.

A listing of all AEs will be presented for all subjects in the Safety population with the following AE summaries (number of distinct AEs and frequency/proportion of subjects affected) presented by treatment 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 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 product (Section 12.3.6.1.)

Medical device incidents will be listed; if there are no incidents, a null listing will be produced. While no specific risks or anticipated adverse device effects are expected from use of the medical device (manual toothbrush) provided, any medical device incidents reported during the conduct of this study will be assessed to evaluate the safety of the device.

12.3.5 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized by treatment group for the Safety and mITT populations (and for the PP population, if a PP analysis is performed) using descriptive statistics.

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

12.3.6 Study Product Compliance and Use of Other Therapies

12.3.6.1 Study Product Compliance

Compliance with investigational product use (number of brushings) will be listed and summarized for the mITT population at each visit, and cumulatively for the entire treatment period (for most subjects this will be 8 weeks) by treatment group.

Number of expected brushings = 2 × Number of days between Visit 2 and Visit X

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

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

12.3.6.2 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.

12.3.7 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 analysis of only complete cases using analysis of covariance (ANCOVA) is biased (Ashbeck, 2016; Baron, 2008). 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 subject with missing data at one post-Baseline assessment visit would have obtained a similar efficacy result at that visit compared to a subject using the same investigational product with similar non-missing results at other timepoints (Baseline and the other post-Baseline assessment visits).

12.3.8 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

In accordance with applicable regulations (including GCP) and 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 site responsibilities to satisfy regulatory, ethical and sponsor requirements with the study 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 site activity to verify that:

- Data are authentic, accurate, and complete.
- The safety and rights of subjects 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.

13.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance assessment and/or audit of the 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.

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board (IRB)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, the ICF, the IB and/or safety statement (including any updates), and other relevant documents (e.g., recruitment advertisements, diaries), as applicable, from the IRB. All correspondence with the IRB should be retained in the investigator site file. Copies of IRB approvals should be forwarded to the sponsor prior to the initiation of the study, and subsequently for any protocol amendments.

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

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and applicable local regulatory requirements and laws, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), Guidelines for GCP (ICH Topic E6 (R2) Guideline for Good Clinical Practice, Nov 2016), and the Declaration of Helsinki (World Medical Association, 64th General Assembly, Fortaleza 2013). In addition, the study will be conducted in accordance with applicable medical device regulations.

13.3.3 Subject Information and Consent

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

When study data are compiled for transfer to the sponsor and other authorized parties, subject names, addresses and other identifiable data will be replaced by numerical codes based on a numbering system provided by the sponsor in order to de-identify study subjects. Use of subject initials should be avoided.

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

Informed consent documents must be in compliance with ICH GCP, local regulatory requirements (including applicable local medical device regulations) and legal requirements (including applicable privacy laws). All documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study, and possible risks associated with participation. Informed consent documents should be comprehensive, concise, clear, relevant and understandable to a layperson.

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

13.3.4 Subject Recruitment

Advertising materials approved by the IRB and the investigator's database may be used to recruit study subjects. Use of an IRB approved pre-screening questionnaire to assess general suitability (basic subject characteristics) for the study is permitted. This generic questionnaire may be used as a phone script and/or to review internal databases to identify potential subjects.

The sponsor will have an opportunity to review and approve the content of any recruitment materials before such materials are submitted for IRB review and used to identify potential study subjects.

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

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

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

In addition, the investigator will inform the sponsor immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13.4 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable sponsor processes.

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

13.5 Provision of Study Results to Investigators

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

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

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge. The procedures and timing for public disclosure of

the results summary and for the development of a manuscript for publication will be in accordance with country specific regulatory requirements for disclosure and sponsor policy.

13.6 Records Retention

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

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.

The investigator must assure the subject's anonymity will be maintained. In CRFs or other documents submitted to the sponsor, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to the sponsor (e.g., subject signed consent forms) should be maintained by the investigator in strict confidence.

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 the sponsor of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the investigator site.

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, a change in IRB opinion, study product safety problems, or at the discretion of the sponsor. In addition, the sponsor retains the right to discontinue development of the investigational product at any time.

If a study is prematurely terminated, the sponsor will promptly notify the investigator. After notification, the investigator must promptly contact all participating subjects and should assure appropriate therapy/follow-up for the subjects. As directed by the sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible. Where required by the applicable regulatory requirements, the sponsor should inform the regulatory authority(ies)

and the investigator should promptly inform the IRB and provide the IRB a detailed written explanation for the termination or suspension.

If the IRB 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 site closure activities with the investigator and site staff, as appropriate, in accordance with applicable regulations, including GCP and sponsor Standard Operating Procedures.

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15 APPENDICIES

15.1 Abbreviations

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

Table 15-1 Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
BDR	Blinded Data Review
CI	Confidence Interval
CRF	Case Report Form
CRS	Clinical Research Scientist
CSPS	Calcium Sodium Phosphosilicate
CSR	Clinical Study Report
CTA	Clinical Trial Application
DCT	Data Collection Tool
DH	Dentin Hypersensitivity
DHEQ	Dentin Hypersensitivity Experience Questionnaire
EAR	Erosion/Abrasion/Recession
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
g	Gram
GCP	Good Clinical Practice
HCA	Hydroxycarbonate Apatite
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Modified Gingival Index
mITT	Modified Intention-To-Treat
mm	Millimeter
MMRM	Mixed Model with Repeated Measures
MoA	Mode of Action
N/A	Not Applicable
NaF	Sodium Fluoride

Abbreviation	Term
NRS	Numeric Rating Scale
OHrQoL	Oral Health-Related Quality of Life
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PI	Personal Information
PP	Per Protocol
ppm	Parts Per Million
PRO	Patient-Reported Outcome
PT	Preferred Term
Q	Question
QC	Quality Control
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedure
SRSD	Single Reference Study Document
SS	Safety Statement
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
UK	United Kingdom
US	United States
w/w	Weight/Weight

15.2 Dentin Hypersensitivity Experience Questionnaire (Example DHEQ-48)

SECTION ONE

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

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

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

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

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

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

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

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

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

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

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

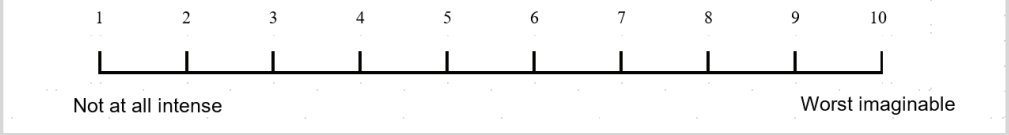
- ☐ Several times a day (7)
- ☐ Once a day (6)
- ☐ Several times a week (5)
- ☐ Once a week (4)
- ☐ Several times a month (3)
- ☐ Once a month (2)
- ☐ Less than once a month (1)
- ☐ Never (0)

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

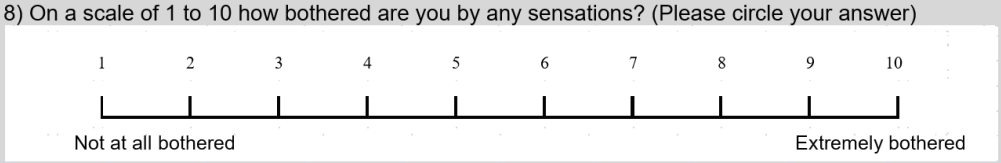
- ☐ A few seconds (5)
- ☐ About a minute (4)
- ☐ Several minutes (3)
- ☐ About half an hour (2)
- ☐ Longer than half an hour (Please specify) (1)
- ☐ Don't have them (0)

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

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



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



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

SECTION TWO

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

	Strongly agree (7)	Agree (6)	Agree a little (5)	Neither agree nor disagree (4)	Disagree a little (3)	Disagree (2)	Strongly disagree (1)
1) Having sensations in my teeth takes a lot of the pleasure out of eating and drinking.	☐	☐	☐	☐	☐	☐	☐
2) There have been times when I can't finish my meal because of the sensations.	☐	☐	☐	☐	☐	☐	☐
3) It takes a long time to finish some foods and drinks because of sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
4) There have been times when I have had problems eating ice cream because of these sensations.	☐	☐	☐	☐	☐	☐	☐

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

	Strongly agree (7)	Agree (6)	Agree a little (5)	Neither agree nor disagree (4)	Disagree a little (3)	Disagree (2)	Strongly disagree (1)
5) I have to change the way I eat or drink certain things.	☐	☐	☐	☐	☐	☐	☐
6) I have to be careful how I breathe on a cold day.	☐	☐	☐	☐	☐	☐	☐
7) I have to leave some cold foods or drinks to warm up before I can have them.	☐	☐	☐	☐	☐	☐	☐
8) I have to cool some foods or drinks down before I can have them.	☐	☐	☐	☐	☐	☐	☐
9) I have to cut up some fruits before being able to eat them.	☐	☐	☐	☐	☐	☐	☐
10) I have to wear a scarf over my mouth on cold days.	☐	☐	☐	☐	☐	☐	☐

The following questions are **about the things you do in your daily life to avoid experiencing the sensations in your teeth**. Thinking about yourself ***over the last month*** to what extent would you agree or disagree with the following statements (Please tick only one response for each question).

	Strongly agree (7)	Agree (6)	Agree a little (5)	Neither agree nor disagree (4)	Disagree a little (3)	Disagree (2)	Strongly disagree (1)
11) I have avoided very cold drinks or foods.	☐	☐	☐	☐	☐	☐	☐
12) I have avoided very hot drinks or foods.	☐	☐	☐	☐	☐	☐	☐
13) When eating some foods I have made sure they don't touch certain teeth.	☐	☐	☐	☐	☐	☐	☐
14) I have changed the way I brush my teeth.	☐	☐	☐	☐	☐	☐	☐
15) When eating some foods I have made sure I bite in small pieces.	☐	☐	☐	☐	☐	☐	☐
16) There are other foods I have avoided.	☐	☐	☐	☐	☐	☐	☐

The following questions are about **the way the sensations affect you when you are with other people or in certain situations**. Thinking about yourself ***over the last month*** to what extent would you agree or disagree with the following statements (Please tick only one response for each question).

	Strongly agree (7)	Agree (6)	Agree a little (5)	Neither agree nor disagree (4)	Disagree a little (3)	Disagree (2)	Strongly disagree (1)
17) Because of the sensations I take longer than others to finish a meal.	☐	☐	☐	☐	☐	☐	☐
18) I have to be careful what I eat when I am with others because of the sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
19) I hide the way I am eating when I am with others because of the sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
20) I am unable to fully take part in conversations because of the sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
21) Going to the dentist is hard for me because I know it is going to be painful as a result of sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐

The following questions are about ***the way the sensations in your teeth make you feel***. Thinking about yourself ***over the last month*** to what extent would you agree or disagree with the following statements (Please tick only one response for each question).

	Strongly agree (7)	Agree (6)	Agree a little (5)	Neither agree nor disagree (4)	Disagree a little (3)	Disagree (2)	Strongly disagree (1)
22) I've been frustrated because I can't find anything that deals with the sensations I have in my teeth.	☐	☐	☐	☐	☐	☐	☐
23) I've been anxious that something I eat or drink might cause sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
24) The sensations in my teeth have been irritating.	☐	☐	☐	☐	☐	☐	☐
25) I have been annoyed with myself because I did something that I knew caused these sensations.	☐	☐	☐	☐	☐	☐	☐
26) I felt guilty because I might have contributed to the sensations I am having with my teeth.	☐	☐	☐	☐	☐	☐	☐
27) The sensations in my teeth have been annoying.	☐	☐	☐	☐	☐	☐	☐
28) The sensations in my teeth have been embarrassing.	☐	☐	☐	☐	☐	☐	☐
29) I have been anxious because of the sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐

The following questions are **about what the sensations in your teeth mean for you.** Thinking about yourself ***over the last month*** to what extent would you agree or disagree with the following statements (please tick only one response for each question).

	Strongly agree (7)	Agree (6)	Agree a little (5)	Neither agree nor disagree (4)	Disagree a little (3)	Disagree (2)	Strongly disagree (1)
30) I find it difficult to accept that I am a person who has these sensations in my teeth.	☐	☐	☐	☐	☐	☐	☐
31) Having these sensations in my teeth makes me feel different from others.	☐	☐	☐	☐	☐	☐	☐
32) Having these sensations in my teeth makes me feel old.	☐	☐	☐	☐	☐	☐	☐
33) Having these sensations in my teeth makes me feel damaged.	☐	☐	☐	☐	☐	☐	☐
34) Having these sensations in my teeth makes me feels as though I am unhealthy.	☐	☐	☐	☐	☐	☐	☐

The last five questions ask about **how much the sensations in your teeth affect your life overall**.

	Excellent (1)	Very good (2)	Good (3)	Fair (4)	Poor (5)	Very poor (6)
35) Overall how would you rate the health of your mouth, teeth and gums?	☐	☐	☐	☐	☐	☐

	Very Much (4)	Quite a bit (3)	Somewhat (2)	A little (1)	Not at all (0)
36) Overall how much do the sensations in your teeth bother you?	☐	☐	☐	☐	☐
37) Overall, how much do the things you do to manage the sensations bother you?	☐	☐	☐	☐	☐
38) Overall, how much do the sensations in your teeth affect your quality of life?	☐	☐	☐	☐	☐
39) Overall, how much do the things you do to manage the sensations in your teeth affect your quality of life?	☐	☐	☐	☐	☐

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