CLINICAL PROTOCOL

A REAL-WORLD EVIDENCE STUDY EVALUATING ORAL HEALTH RELATED QUALITY OF LIFE WITH USE OF A STANNOUS FLUORIDE ANTI-SENSITIVITY TOOTHPASTE FOR DENTIN HYPERSENSITIVITY MANAGEMENT

Protocol Number:	300058
Compound/Product Name:	0.454% Stannous Fluoride (SnF_2)
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This document contains confidentiality statements that are not relevant for this publicly available version

Sponsor Information

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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
New Version	2.0	• Removal of objectives, endpoints and statistical analyses relating to population sub-groups. • Re-structuring of objectives, endpoints and statistical analyses.
Amendment 1	3.0	• Clarified participants' compliance in section 6.7 • Clarified the question of the product name in OHQ section 15.3

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Principal Investigator Protocol Agreement Page

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

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

Short Title:

A real-world evidence study evaluating oral health related quality of life with use of a stannous fluoride anti-sensitivity toothpaste for dentin hypersensitivity management

Background and Rationale:

This study will evaluate the impact of long-term use of a desensitizing toothpaste containing 0.454% stannous fluoride (SnF_2) on oral health related quality of life (OHrQoL) in a population of self-reported dentin hypersensitivity (DH) sufferers. Data generated will provide real world information on the DH experience and DH management with a daily use anti-sensitivity treatment.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To describe changes in OHrQoL over 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF_2, as measured by the Dentin Hypersensitivity Experience Questionnaire (DHEQ-48: Total Score and Domain Scores), in a DH population.	Change from Baseline in DHEQ endpoints at Weeks 4, 8, 12, 16, 20 & 24. **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)
Secondary	
To describe changes in OHrQoL over 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF_2, as measured by the DHEQ-48 (other endpoints), in a DH population.	Change from Baseline in DHEQ endpoints at Weeks 4, 8, 12, 16, 20 & 24. **Section 1** • Impact on Everyday Life (Q1-3) **Section 2** • Global Oral Health Score (Q35) • Effect on Life Overall Score (Q36-39)
To summarize the individual DHEQ domain items of concern in a DH population before and after 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF_2.	*Baseline and Week 24*: • Percentage (%) of participants who 'agree' (score 5-7) with each item (statement) in the 5 DHEQ domains (DHEQ Section 2, Q1-34).

To describe changes in the intensity of self-reported DH pain over 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF_2, as measured by a Numeric Pain Rating Scale (NPRS), in a DH population.	Change from Baseline in NPRS score at Weeks 1, 2, 4, 8, 12, 16, 20 & 24.
To describe participant satisfaction with the DH treatment (anti-sensitivity toothpaste containing 0.454% SnF_2), as measured by a Satisfaction Numeric Rating Scale (NRS).	*Week 24*: Satisfaction NRS score
To describe the oral hygiene habits of a DH population using an oral hygiene questionnaire (OHQ).	*Baseline*: OHQ responses

Study Design:

This will be a decentralized, prospective, 24-week, monadic design, open label study in a DH population. The study will evaluate changes in OHrQoL in participants with self-reported DH symptoms over 24 weeks of use of a DH treatment (anti-sensitivity toothpaste). OHrQoL will be measured using a validated questionnaire, the Dentin Hypersensitivity Experience Questionnaire (DHEQ-48), completed by study participants at Baseline, and Weeks 4, 8, 12, 16, 20 and 24.

Participants will be recruited through social media and other digital platforms. Individuals who are interested in the study will be sent to a landing page after clicking on an advertisement or study link where they will complete an initial pre-screening questionnaire. If eligible to participate, they will be sent an email invitation to download the CCI application (app). After downloading and logging into the CCI app, they will be able to review the electronic Informed Consent (eIC), ask questions about the study, and communicate with the CCI virtual site team via the app chat, phone (using the study number listed in the eIC) or email. Individuals who decide to participate may then choose to sign the eIC (electronic signature). No study-specific data will be collected prior to signing the eIC. Individuals who do not actively access the study-specific app and provide consent will not be permitted to participate in the study.

Once the participant has signed the eIC, they will complete a detailed screening questionnaire to identify and exclude individuals whose tooth sensitivity could be caused by other factors/clinical pathology for which dental healthcare professional advice should be sought. In addition to the screening questionnaire, participants will be required to provide demographic information and complete Medical History and Concomitant Medications forms. Participants who qualify, based on their responses to the screening questionnaire and the protocol inclusion/exclusion criteria, will be enrolled and sent sufficient study treatment (desensitizing toothpaste containing 0.454% SnF_2) to complete the study. Participants will confirm receipt of study toothpaste in the CCI app (date of confirmation of receipt = Day 0) and will be instructed to start using it on the same day. They will use the study toothpaste for 24 weeks according to the instructions on the commercial pack and their normal oral healthcare habits.

Participants will complete a DHEQ-48 at Baseline (before first treatment use) and at 4-week intervals throughout the treatment period (Weeks 4, 8, 12, 16, 20 and 24). In addition to the

DHEQ-48, they will rate their DH-related pain using a Numeric Pain Rating Scale (NPRS) at Baseline, and after 1, 2, 4, 8, 12,16, 20 and 24 weeks of treatment.

Participants will describe their oral hygiene habits at Baseline by completion of an Oral Hygiene Questionnaire (OHQ). On completion of the 24-week study, they will rate their satisfaction with the DH treatment using a Numeric Rating Scale (NRS).

Self-reported adverse events (AEs) will be collected remotely via the CCI app.

Study Product:

Product Description	Anti-sensitivity toothpaste containing 0.454% SnF_2
Product Name	Sensodyne Repair and Protect (US market)
Master Formulation Code	CCI
Fluoride Content	1100 parts per million (ppm) fluoride as SnF_2

Type and Planned Number of Participants:

Sufficient numbers will be screened (estimated up to 50% screen failure rate) to enroll approximately 500 participants to ensure approximately 400 evaluable participants complete the entire study (estimated up to 20% drop out rate).

Statistical Analysis Summary:

DHEQ data will be analyzed using a modified Intent-To-Treat (mITT) population.

Change from Baseline in DHEQ Total Score and each individual Domain across all post-baseline timepoints will be analyzed using a MMRM with time point fitted as a fixed effect, Baseline DHEQ score as a covariate and participant fitted as a repeated measure with unstructured covariance matrix. Kenward-Rogers degrees of freedom will be applied. The estimate of the adjusted mean (SE) change from Baseline at each timepoint will be presented for each DHEQ endpoint along with 95% CIs.

1.2 Schedule of Activities

The Schedule of Activities (Table 1-1) provides an overview of the study procedures. CCI virtual study team may schedule other (unplanned) interactions, additional to those listed in the schedule of activities, to make assessments required to protect the well-being of study participants.

Table 1-1 Schedule of Activities

Procedure	Pre-Screening	Baseline Activities[1]	Day 0[3]	Week 1 Day 7 (±1 days)	Week 2 Day 14 (±2 days	Week 4 Day 28 (±7 days)	Week 8 Day 56 (±7 days)	Week 12 Day 84 (±7 days)	Week 16 Day 112 (±7 days)	Week 20 Day 140 (±7 days)	Week 24 Day 168 (±7 days)
Pre-Screening Questionnaire	X										
Confirm Initial Eligibility	X										
eMail invitation to download CCI app with Unique Participant ID	X										
e-Informed Consent (eIC)		X									
Screening Questionnaire		X									
Demographics		X									
Medical History		X									
Concomitant Medications		X		X	X	X	X	X	X	X	X
Check Inclusion/Exclusion Criteria		X									
Confirm Participant Eligibility[1]		X									
DHEQ-48 Completion		X				X	X	X	X	X	X
NPRS Completion		X		X	X	X	X	X	X	X	X
OHQ Completion		X									
Study Toothpaste Dispatched[2]		X									
Participant Confirms Receipt of Study Toothpaste in CCI App			X								
Subject Instructed to Start Using Study Toothpaste			X								
DH Treatment Satisfaction NRS Completion											X
Complete End of Study (EOS)/Open Ended Survey Questions											X
Self-reported AEs[4]		X	X	X	X	X	X	X	X	X	X
Study Conclusion											X

Footnotes:

1. Baseline activities must be completed by participant within 14 days of enrollment.
2. Study toothpaste will be dispatched to qualifying participants only after all 'Baseline' activities have been completed.
3. Participant will confirm receipt of study toothpaste in the CCI app (date of confirmation of receipt = Day 0) and will be instructed to start using it on the same day.
4. Self-reported changes in health and medical occurrences from immediately after participant provides e-consent signature until the last use of study toothpaste will be recorded as AEs; thus, serious AEs (SAEs) will also be collected from immediately after participant provides e-consent signature until last use of study toothpaste.

2 INTRODUCTION

2.1 Study Rationale

Clinical data supporting the efficacy of anti-sensitivity toothpastes are typically generated in randomized controlled trials (RCTs), conducted in well-defined populations (self-reported and clinically confirmed DH), with the investigational products used and evaluated according to a strict set of study procedures. Such studies do not necessarily fully reflect the general DH population behavior. Real-world evidence (RWE) studies offer an opportunity to gather information on marketed products from real-world heterogeneous populations that can complement clinical evidence, consumer insight data, and post-marketing surveillance. Real world data (RWD) can be generated in a number of different study designs ranging from observational (prospective/retrospective) to interventional studies, with or without randomization, and help to address the accepted limitations of randomized controlled studies which can make it difficult to generalize findings to larger, more inclusive populations (Sherman *et al*, 2016).

Few published RWE studies focus on DH and most formed part of larger, observational dental practice-based studies investigating the range of methods used for diagnosing and treating DH (Cunha-Cruz *et al*, 2010; Heft *et al*, 2018; KopyckaKedzierawski *et al*, 2017a; Kopycka-Kedzierawski *et al*, 2017b; Litaker *et al*, 2019). The effectiveness of a variety of treatments used to manage DH in clinical practice has been investigated in a 'real-world' setting (Heft *et al*, 2018). Patients self-assessed the effectiveness of their dentist-selected method for DH management (e.g., dental treatment, anti-sensitivity product use, oral hygiene advice, dietary advice) using Visual Analogue Scales (VAS), Labelled Magnitude Scales (LMS), and patient satisfaction questionnaire. Patients who experienced a reduction in DH pain also reported a positive satisfaction rating for their treatment strategy. The RWD generated in such studies can be used to improve clinical practice for the management of DH (Heft *et al*, 2018). The sponsor of this study recently completed a RWE study evaluating the impact of a commercially available anti-sensitivity toothpaste containing 5% potassium nitrate (KNO_3) on OHrQoL in a self-reported DH population (Haleon clinical study 216953). RWD supported the effectiveness of a 5% KNO_3 toothpaste in improving OHrQoL in this population.

The aim of this study is to evaluate the impact of a commercially available desensitizing toothpaste containing 0.454% SnF_2 on OHrQoL in a DH population in a real-world setting.

Stannous fluoride has been incorporated into oral hygiene products indicated for the treatment of DH since the 1990s (Schiff, 2006), with longitudinal data generated in RCTs supporting its clinical efficacy (Ni, 2010; Parkinson, 2011; Makin, 2013; Parkinson *et al*, 2013; Parkinson *et al*, 2015. It is therefore relevant to explore its effectiveness in a real-world setting and obtain data reflective of DH sufferers in their own environment.

2.2 Background

Dentin hypersensitivity (DH) has been defined as 'pain derived from exposed dentin in response to chemical, thermal, tactile, or osmotic stimuli which can't be explained as arising from any other dental defect or disease' (Addy *et al*, 1985; Canadian Advisory Board on Dentin Hypersensitivity, 2003). The hydrodynamic theory of DH hypothesizes that a stimulus external to the tooth (for example, a temperature/osmotic differential, pressure) causes movement of the fluid resident within exposed dentinal tubules (Brännström, 1963). This movement may

stimulate nerve processes in the dental pulp (Addy, 2002; Hall *et al*, 2000), resulting in the characteristic short, sharp pain of DH.

Currently there are two approaches for the management of DH: nerve desensitization and the occlusion of exposed dentin tubules. The dentin occlusion approach uses tubule occluding agents which physically block the exposed end of the dentinal tubules, thus reducing dentinal fluid movement and pulpal irritation. Dentin tubule occluding agents, such as strontium salts, stannous salts, bioglasses, arginine/calcium carbonate complex, or silicas serve to physically block or narrow the exposed ends of dentin tubules, reducing dentinal fluid movement, thereby decreasing the effect of external stimuli. Numerous clinical studies demonstrate the DH efficacy of SnF_2-containing formulations [e.g., short term (typically 1-14 days treatment): (He *et al*., 2014a, He *et al*., 2011a, He *et al*., 2011b, He *et al*., 2011c, He *et al*., 2011d, Cepeda-Bravo *et al*., 2014, Creeth *et al*., 2017a, Creeth *et al*., 2017b, Goyal *et al*., 2017, Parkinson *et al*., 2016, Seong *et al*., 2017, Sharma *et al*., 2011, Creeth *et al*., 2021); longer term (typically 4-12 weeks treatment): (Chaknis *et al*., 2011, Day *et al*., 2010, Du *et al*., 2011, Gallob *et al*., 2017, Hazen *et al*., 1968, He *et al*., 2014b, Ni *et al*., 2011, Ni *et al*., 2010, Parkinson *et al*., 2013, Parkinson *et al*., 2015a, Schiff *et al*., 2006, Schiff *et al*., 2005, Sharma *et al*., 2010, Vinaya *et al*., 2010, Hines *et al*., 2019, Amini *et al*., 2019, He *et al*., 2019, Mason *et al*., 2019, Haleon Clinical Study 209723, 2020, Creeth and Burnett, 2021, Kim *et al*., 2021).

Recently, greater consideration has been given to the psychosocial impacts of DH on everyday life (Gibson *et al*, 2015). One qualitative study showed that DH can be triggered by several stimuli and present multiple responses, not always described as pain, affecting everyday activities such as eating, drinking, tooth brushing, talking, and social interactions (Gibson *et al*, 2015).

Oral health-related quality of life (OHrQoL) questionnaires are increasingly used in dentistry to capture the impact of clinical interventions on OHrQoL; they typically cover a number of oral health conditions and so may not detect the nuances of a specific condition (Bekes *et al*, 2009). The Dentin Hypersensitivity Experience Questionnaire (DHEQ) is a validated, condition specific measure of OHrQoL in relation to DH (Baker *et al*, 2014, Boiko *et al*, 2010). It was developed by the sponsor in collaboration with Sheffield University through a robust theoretical framework, specific to DH (Boiko *et al*, 2010), and has shown reliability and validity in both a general population (Porritt *et al*, 2016) and in clinical studies (Boiko 2010, Gibson *et al*, 2015). The conception, development, validation, and initial usage of the DHEQ has been published (Robinson, 2014). The measure has been validated as both long- (DHEQ-48) and short- (DHEQ-15) form versions, comprising 48 (Baker *et al*, 2014; Boiko *et al*, 2010) and 15 (Machuca *et al*, 2014) questions respectively, and has been translated into multiple languages (e.g., Chinese, Turkish, Portuguese) confirming its global relevance (Başaran and Celik, 2018, Douglas-De-Oliveira *et al*, 2018, He and Wang, 2015a, He and Wang, 2015b).

Data generated in clinical efficacy studies provide robust and positive support for the use of the sponsor's desensitizing toothpastes for the relief and management of DH, as measured by clinical indices and the DHEQ. However, these results were generated under the highly controlled conditions of a RCT in response to controlled but contrived DH stimuli. These studies may not necessarily fully reflect the experience of the general DH population when challenged with real world stimuli for DH.

Based on these assumptions, this RWE study will include participants from the general population who suffer with DH (self-reported symptoms) and will evaluate the impact of daily use of an anti-sensitivity toothpaste containing 0.454% SnF_2 on DH-related OHrQoL. Data

generated will provide real world information on the impact of daily use of a desensitizing treatment for DH management.

2.3 Benefit/Risk Assessment

The study product is a commercially available anti-sensitivity toothpaste containing 0.454% SnF_2, marketed in the United States (US), and will be supplied to study participants in its commercial pack. Safety information is printed on the commercial pack.

2.4 Mechanism of Action/Indication

Stannous fluoride is an occlusion agent that reacts in the oral environment to form deposits on the surface of exposed dentin and within exposed dentin tubules (Miller, 1994). These deposits act as a barrier to external stimuli by physically blocking or narrowing the openings of the exposed tubules, thereby reducing dentinal fluid movement, and decreasing the ability of the stimulus to activate intra-dental nerves and evoke a pain response (Miller, 1994, Addy, 2002; Parkinson and Willson, 2011, Burnett *et al* 2013).

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To describe changes in OHrQoL over 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF_2, as measured by the Dentin Hypersensitivity Experience Questionnaire (DHEQ-48: Total Score and Domain Scores), in a DH population.	Change from Baseline in DHEQ endpoints at Weeks 4, 8, 12, 16, 20 & 24. **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)
Secondary	
To describe changes in OHrQoL over 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF_2, as measured by the DHEQ-48 (other endpoints), in a DH population.	Change from Baseline in DHEQ endpoints at Weeks 4, 8, 12, 16, 20 & 24. **Section 1** • Impact on Everyday Life (Q1-3) **Section 2** • Global Oral Health Score (Q35) • Effect on Life Overall Score (Q36-39)

To summarize the individual DHEQ domain items of concern in a DH population before and after 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF_2.	*Baseline and Week 24*: • Percentage (%) of participants who 'agree' (score 5-7) with each item (statement) in the 5 DHEQ domains (DHEQ Section 2, Q1-34).
To describe changes in the intensity of self-reported DH pain over 24 weeks use of an anti-sensitivity toothpaste containing 0.454% SnF_2, as measured by a Numeric Pain Rating Scale (NPRS), in a DH population.	Change from Baseline in NPRS score at Weeks 1, 2, 4, 8, 12, 16, 20 & 24.
To describe participant satisfaction with the DH treatment (anti-sensitivity toothpaste containing 0.454% SnF_2), as measured by a Satisfaction Numeric Rating Scale (NRS).	*Week 24*: Satisfaction NRS score
To describe the oral hygiene habits of a DH population using an oral hygiene questionnaire (OHQ).	*Baseline*: OHQ responses

This study will be considered successful if a trend of improvement in OHrQoL is observed over the 24-week treatment period; however, it is expected that statistically significant improvements from Baseline will be observed in DHEQ endpoints, particularly DHEQ Total Score.

4 STUDY DESIGN

4.1 Overall Design

This will be a decentralized, prospective, 24-week, monadic design, open label, study in a DH population. The study will evaluate changes in OHrQoL in participants with self-reported DH symptoms over 24 weeks of use of a DH treatment (anti-sensitivity toothpaste). OHrQoL will be measured using a validated questionnaire, the Dentin Hypersensitivity Experience Questionnaire (DHEQ-48), completed by study participants at Baseline, and Weeks 4, 8, 12, 16, 20.

Participants will be recruited through social media and other digital platforms. Individuals who are interested in the study will be sent to a landing page after clicking on an advertisement or study link where they will complete an initial pre-screening questionnaire. If eligible to participate, they will be sent an email containing their unique participant ID and an invitation to download the CCI app. After downloading and logging into the CCI app, they will be able to review the electronic Informed Consent (eIC), ask questions about the study, and communicate with the CCI virtual site team via the app chat, phone (using the study number listed in the eIC), or email. Individuals who decide to participate may then choose to sign the eIC (electronic signature). No study-specific data will be collected prior to signing the eIC. Individuals who do not actively access the study-specific app and provide consent will not be permitted to participate in the study.

Once the participant has signed the eIC, they will complete a detailed screening questionnaire to identify and exclude individuals whose tooth sensitivity could be caused by other

factors/clinical pathology for which dental healthcare professional advice should be sought. In addition to the screening questionnaire, participants will be required to provide demographic information (year of birth, age, gender, geographic area, ethnicity and race) and complete Medical History and Concomitant Medications forms. Participants who qualify, based on their responses to the screening questionnaire and the protocol inclusion/exclusion criteria, will be enrolled and sent sufficient study treatment (desensitizing toothpaste containing 0.454% SnF_2) to complete the study. Participants will confirm receipt of study toothpaste in the CCI app (date of confirmation of receipt = Day 0) and will be instructed to start using it on the same day. They will use the study toothpaste for 24 weeks according to the instructions on the commercial pack and their normal oral healthcare habits.

Participants will complete a DHEQ-48 at Baseline (prior to first treatment use) and at 4-week intervals throughout the treatment period (Weeks 4, 8, 12, 16, 20 and 24). In addition to the DHEQ-48, they will rate their DH-related pain using a Numeric Pain Rating Scale (NPRS) at Baseline, and after 1, 2, 4, 8, 12,16, 20 and 24 weeks of treatment.

Participants will describe their oral hygiene habits at Baseline by completion of an Oral Hygiene Questionnaire (OHQ). On completion of the 24-week study, they will rate their satisfaction with the DH treatment using a Numeric Rating Scale (NRS) and complete a number of End of Study (EOS)/open ended 'survey' questions.

Self-reported adverse events (AEs) will be collected remotely via the CCI app.

4.2 Scientific Rationale for Study Design

Numerous clinical studies demonstrate the DH efficacy of SnF_2-containing formulations (e.g., short term studies (typically 1-14 days treatment): He *et al*., 2014a, He *et al*., 2011a, He *et al*., 2011b, He *et al*., 2011c, He *et al*., 2011d, Cepeda-Bravo *et al*., 2014, Creeth *et al*., 2017a, Creeth *et al*., 2017b, Goyal *et al*., 2017, Parkinson *et al*., 2016, Seong *et al*., 2017, Sharma *et al*., 2011, Creeth *et al*., 2021; longer term studies (typically 4-12 weeks treatment): Chaknis *et al*., 2011, Day *et al*., 2010, Du *et al*., 2011, Gallob *et al*., 2017, Hazen *et al*., 1968, He *et al*., 2014b, Ni *et al*., 2011, Ni *et al*., 2010, Parkinson *et al*., 2013, Parkinson *et al*., 2015a, Schiff et al., 2006, Schiff *et al*., 2005, Sharma *et al*., 2010, Vinaya *et al*., 2010, Hines *et al*., 2019, Amini *et al*., 2019, He *et al*., 2019, Mason *et al*., 2019, GSKCH Clinical Study 209723, 2020, Creeth and Burnett, 2021, Kim *et al*., 2021). Such RCTs include a well-defined DH population and follow defined study procedures and may not, therefore, fully reflect the experience and behaviors of the general DH population. RWE studies may more accurately represent population responses to an intervention when the product is used as part of everyday life, thereby making the results more easily generalized. They offer opportunities to gather information on marketed products to bolster existing clinical evidence and gain additional insights in the target population.

The few DH-related RWE studies published to date were conducted as part of larger, observational dental practice-based studies investigating methods available for diagnosing and treating DH (Cunha-Cruz *et al*, 2010; Heft *et al*, 2018; KopyckaKedzierawski *et al*, 2017a; Kopycka-Kedzierawski *et al*, 2017b; Litaker *et al*, 2019). The sponsor has completed a RWE study evaluating the impact of anti-sensitivity toothpaste on OHrQoL in a DH population (Haleon clinical study 216953). RWD generated in this study supports the effectiveness of a marketed 5% KNO_3 toothpaste in improving OHrQoL in a DH population.

A monadic design has been selected for this current study. Accepting the limitations of this design, the rationale for its selection is described in the publication for a similar extended use clinical study which also evaluated participant reported OHrQoL outcomes in a DH population

(Mason *et al*, 2019): a negative-controlled study would require DH sufferers to use a regular fluoride toothpaste with no desensitizing properties for nearly 6 months, with associated ethical implications; additionally, a positive control study design would require far higher participant numbers to achieve its scientific objectives (e.g., equivalence/non-inferiority).

A commercially available toothpaste will be used in this open label study; participants will use the product according to the label instructions on commercial pack, as fits the nature of the RWE study.

Typically, to participate in a clinical efficacy study, participants are required to have clinically confirmed DH (determined by clinical examination), with each qualifying test tooth identified against protocol-defined inclusion/exclusion criteria. In this RWE study, participants will be identified as DH sufferers from the general population using a screening questionnaire (Porritt *et al*, 2016) to identify and exclude individuals whose sensitivity could be caused by other factors/clinical pathology.

The age range over which an individual can experience DH is wide (early teens to 70s) (Fischer *et al*, 1992), with peak incidence known to occur between the ages of 20-40 years (Flynn *et al*, 1985). The fall in prevalence observed in later decades reflects age-related changes in the dentine and pulp of the tooth which act to reduce both dentine permeability and the tooth's response to external triggers of DH (Seltzer and Bender, 1975; Dababneh *et al*, 1999; West, 2006; Pashley, 2008). The dental pain experienced by much 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.

Eligible participants will complete the Dentin Hypersensitivity Experience Questionnaire (DHEQ) - a validated, condition-specific measure of impacts on the everyday life for DH sufferers (Baker *et al*, 2014) (Boiko *et al*, 2010) - at Baseline and at 4-weekly intervals over 24-week period. The choice of the time points (Baseline, Weeks 4, 8, 12, 16, 20 and 24) reflects the designs of a published sponsor study (Mason *et al*, 2019) and a recently completed RWE study (Haleon clinical study 216953). Mason *et al* reported statistically significant, ongoing improvements in OHrQoL (compared to Baseline): DHEQ Total Score was statistically significant from Week 8; domains scores and Effect on Life Overall followed a similar pattern. They concluded that long-term use of an anti-sensitivity toothpaste had a beneficial impact on the OHrQoL of DH sufferers (Mason *et al*, 2019).

In addition, participants will be asked to self-report the intensity of their DH pain at Baseline, and Weeks 1, 2, 4, 8, 12, 16, 20 & 24 using a Numeric Pain Rating Scale (NPRS).The proportion of participants who experience > 30% reduction in NPRS score in this study will be determined; a reduction of > 30% has been described as clinically important in pain-related clinical efficacy studies (Hawker *et al*, 2011). At the end of the study (Week 24), participants will be asked to rate their satisfaction with the DH treatment (Heft *et al*, 2018; van Berckel *et al*, 2017).

4.3 Justification for Dose

Directions for use of the study toothpaste will be as stated on its' commercial tube.

4.4 End of Study Definition

The end of the study is defined for each participant as 168 days (± 7days) from the date of confirmation of receipt of study toothpaste (Day 0), participant death, early withdrawal from the study, participant lost to follow-up, or overall study termination.

5 STUDY POPULATION

5.1 Type and Planned Number of Participants

Sufficient numbers will be screened (estimated up to 50% screen failure rate) to enroll approximately 500 participants to ensure 400 evaluable participants complete the entire study (estimated up to 20% drop out rate).

An enrolled participant is one who has agreed to participate in the RWE study following completion of the eIC process and has successfully met the eligibility criteria to proceed beyond the screening procedures, as applicable for the protocol design.

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select individuals for whom participation in the study is considered appropriate. Relevant medical and non-medical conditions should be taken into consideration when deciding whether a potential participant is suitable.

Eligibility to participate in this RWE study should be reviewed and documented by an appropriate member of the CCI study team before a participant is included in the study.

5.2 Inclusion Criteria

An individual must meet the following inclusion criteria to be eligible for enrollment into the study:

1. Participant who has provided consent indicating they have been informed of all pertinent aspects of the study.
2. All genders who, at the time of screening, are aged between 18 and 65 years (inclusive).
3. Participant who is willing to complete all activities as described in the Schedule of Activities (Table 1-1).
4. Participant who is able to independently complete all activities on their smart devices as described in the Schedule of Activities (Table 1-1).
5. Participant who has tooth sensitivity (self-reported symptoms).

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will not be eligible for enrollment into the study:

1. Participant whose sensitivity could be caused by other factors or clinical pathology than DH, as self-reported on the screening questionnaire, which include:
    - Participant who has been/is on multiple prescription medications to treat severe acid reflux on a regular basis or has had surgery for acid reflux.
    - Participant with full or partial denture(s).
    - Participant who has undergone treatment for periodontal or gum disease within 6 months of screening or is currently undergoing treatment for periodontal or gum disease.
    - Participant who has been informed by a Dental Health Care Professional (DHCP) that they have active periodontitis.
    - Participant who has been informed by a DHCP that they have active caries.

- Participant with any chronic and/or severe painful health condition(s) which lead to regular use of pain relief medications (more than 3 days a week).

2. Participant with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.

5.4 Randomization Criteria

There will be no randomization in this study.

5.5 Lifestyle Considerations

This RWE study will not include any lifestyle considerations or restrictions.

5.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study (i.e., do not meet the protocol inclusion/exclusion criteria). To ensure transparent reporting of screen failures, a minimum set of screen failure information will be collected including demography, reason for screen failure (e.g., withdrawal of consent), eligibility criteria, protocol deviations, and AEs, as appropriate.

Individuals who do not meet the criteria for participation in this study (screen failure) or cannot complete Screening/Baseline activities due to a technical issue with the CCI app will not be re-screened.

5.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical/dental personnel for the study will be documented in the Study Contact List held by CCI.

The contact number should only be used by CCI staff seeking advice on medical/ dental questions or problems in the event that the established communication pathways are not available. The contact number is not intended for direct use by study participants.

To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, participants will be provided with contact information in the CCI app or will be able to use the chat function in the CCI app.

5.8 Rater/Clinical Assessor Qualifications

N/A

6 STUDY PRODUCT

6.1 Study Product Supply

The following study product will be supplied by the sponsor's Clinical Supplies Department.

Table 6-1 Study Product Supply

Product Description	Anti-sensitivity toothpaste containing 0.454% SnF_2
Product Name	Sensodyne Repair and Protect (US market)

Fluoride Content	1100 ppm fluoride as SnF_2
Pack Design	Carton containing 12 tubes of toothpaste
Dispensing Details	One carton dispatched to participant (on completion of all 'Baseline' activities)
Master Formulation Code	CCI [redacted]
Route of Administration	Topical Oral Use
Dose/Application	As per directions printed on commercial pack
Usage Instructions	As per directions printed on commercial pack
Return Requirements	Participants may keep their used and unused product at the end of the study or dispose of it, after first defacing or removing the study label. Participants will report how many unused tubes of study product remain at the end of the 24-week treatment period, and confirm the above instructions for disposal have been followed, in the CCI [redacted] app. These questions will be included in the EOS questions.

6.1.1 Dosage Form and Packaging

The study product will be supplied by the sponsor in its commercial pack to CCI [redacted] preferred vendor.

Study labels will be applied to the toothpaste tubes and to the outer carton. The content of the labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the sponsor's Global Clinical Supplies group. Each study label will contain, but not be limited to, the protocol number and directions for use (i.e., to follow usage instructions on the commercial pack). In addition, the outer carton label will contain product storage requirements. Study labels should not obscure the usage instructions and safety information on the commercial pack.

It is important that product labels remain intact and legible for the duration of the study. Participants will be instructed to not remove or deface any part of the study label until the end of the study.

Study product is supplied for use in this study only and should not be used for any other purpose or by anyone other than enrolled participant.

6.1.2 Preparation and Dispatch

The study product will be packaged and dispatched to study participants by CCI [redacted] preferred vendor according to CCI [redacted] instructions and the vendor's standard procedures. Product shipment will be tracked.

Only enrolled participants who have completed all Baseline activities will receive study product. Each eligible participant will receive 12 tubes of study product, sufficient to cover usage for the duration of the study. Participants will confirm receipt of study toothpaste in the CCI app (date of confirmation of receipt = Day 0) and will be instructed to start using it on the same day.

6.2 Administration

The app will advise participants to follow the instructions on the commercial pack. Participants will be asked to confirm their first use of the product through the CCI app.

6.2.1 Medication/Dosing Errors

N/A

6.2.2 Overdose

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

6.3 Study Product Storage

CCI, or their preferred vendor, must confirm appropriate temperature conditions have been maintained during transit for all study product received. Any discrepancies should be reported to the sponsor and resolved before use, according to the supplied shipping documentation.

CCI or their preferred vendor, will ensure that all study product is stored in a secured area, with controlled access, under the storage conditions specified on the commercial pack, and in accordance with applicable regulatory requirements.

Vendor systems must be capable of measuring and documenting (e.g., via a log), at a minimum, the daily minimum and maximum temperatures for all vendor site storage locations. This should be captured throughout the study from the time of first product receipt. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The temperature-monitoring system should be inspected regularly to ensure it is operating as expected and maintained in good working order.

The vendor will report any excursions from the permitted storage conditions to CCI upon discovery for communication to sponsor as soon as possible. The vendor site should actively pursue options for returning the product to the required storage conditions as soon as possible. Excursions from the storage requirements, including any actions taken, must be documented as a protocol deviation, and reported to the sponsor.

Once an excursion is identified, the affected product should be quarantined and not used until the sponsor provides written permission to use. Use of any of the affected product prior to sponsor approval will be considered a protocol deviation.

The sponsor's Clinical Supplies Department will provide CCI with written guidance for study product storage and actions to be taken in case of excursion prior to shipping the product to CCI preferred vendor. CCI will record product storage procedures in the electronic Trial Master File (eTMF).

6.4 Study Product Accountability

Product is supplied for use in this study only and should not be used for any other purpose.

CCI preferred vendor must maintain adequate records documenting the receipt, shipment, loss, or other disposition of all product supplies. The preferred vendor is responsible for product accountability/reconciliation and record maintenance for all study product stored at the vendor site.

6.4.1 Destruction of Study Product Supplies

At the end of the study, an appropriate designee of CCI preferred vendor (with guidance from the sponsor's Clinical Supplies Specialist) will inventory all unused study product remaining at the vendor site and complete the required product accountability documentation. Non-dispatched/unused study product retained at the vendor site will be returned to the sponsor's Clinical Supplies Department, or designated vendor, for destruction using the return instructions provided. The sponsor will provide CCI with detailed instructions for the return of study product, accountability checks and subsequent destruction, as applicable, prior to study close out.

On completion of the study, participants may keep any used/unused study product, or may choose to dispose study product after defacing or removing the study label.

6.5 Blinding and Allocation/Randomization

This is an open label, monadic study; blinding and randomization are not required.

6.6 Breaking the Blind

N/A

6.7 Compliance

Participants will be asked to follow the commercial pack usage instructions. To facilitate compliance, the CCI app will send study participants weekly notifications/reminders related to product usage (e.g., use the toothpaste every day, follow the usage instructions on the commercial pack), and participants will complete a questionnaire in the app to capture their product usage information. CCI virtual study team may also make additional contact with specific participants if low compliance or risk of drop out is detected.

Participants will be asked to confirm the date of last use of the study product and how many unused tubes of study product remain at the end of the study using the CCI app in the EOS/open ended 'survey' questions.

6.8 Concomitant Medications/Treatments

Participants will be asked to self-report changes to their existing medications/treatments and any new medications/treatments from time of e-consent to last use of study product through the CCI app. Reason for use, unit dose, daily dose, start and stop dates will be recorded, as appropriate.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Participant Discontinuation/Withdrawal

Participants may withdraw from the study at any time at their own request. Their right to withdraw and information about how to withdraw will be included in the eIC. Should a participant withdraw or be discontinued from the study, all further scheduled communication with that participant will be discontinued (e-mails, text messages, and/or notifications). The reason(s) for withdrawal or discontinuation will be recorded in the CCI portal.

If the participant withdraws from the study and withdraws consent for disclosure of future information, no additional data will be collected. The sponsor may retain and continue to use data collected before the withdrawal of consent.

7.2 Lost to Follow-Up

A participant will be considered lost to follow-up if CCI is repeatedly unable to contact them after continued non-response to repeated reminders to login and complete study activities (generated by the CCI app) up to 24 weeks (+7days) from the date of confirmation of receipt of study toothpaste (Day 0).

Before a participant is deemed lost to follow-up, CCI will make every effort to regain contact (3 communication attempts). Contact attempts made outside of the CCI app will be documented.

Should a participant continue to be unreachable, they will be considered to have withdrawn from the study and lost to follow-up.

8 STUDY PROCEDURES

This section describes the procedures to be completed at each planned study timepoint; the order in which procedures should be completed is listed in the Schedule of Activities (Table 1-1).

'Start' and 'expiration' windows will be set for each study-required activity, per timing tolerances specified in the Schedule of Activities (Table 1-1). Access to the CCI app will not be interrupted but outside of these tolerances the participant will not be able to start entering responses or submit late responses for a missed 'visit'. Participants are required to complete at least one post-Baseline DHEQ to be included in the modified Intent-To-Treat (mITT) population.

CCI will provide the app used to conduct all study activities, to provide participants with information and training, and to collect study data. Self-reported adverse events (AEs) will be collected via the CCI app.

8.1 Screening

8.1.1 Informed Consent

Participants will be recruited through social media and other digital platforms. Individuals who are interested in the study will be sent to a landing page after clicking on an advertisement or study link where they will complete an initial pre-screening questionnaire. If eligible to participate, they will be sent an email containing their unique participant ID and an invitation

to download the CCI app. After downloading and logging into the CCI app, they will be able to review the electronic Informed Consent (eIC), ask questions about the study, and communicate with the CCI site team, including the investigator, via the app chat, phone (using the study number listed in the eIC), or email. Individuals who decide to participate may then choose to sign the eIC (electronic signature). No study-specific data will be collected prior to signing the eIC. Individuals who do not actively access the study-specific app and provide consent will not be permitted to participate in the study.

The eIC will be IRB-approved prior to first use; any amendments to the approved eIC will be re-approved by the IRB prior to distribution or use. Before any study-specific data are collected, each participant must:

- Be informed of all aspects of the study (risks and benefits).
- Be given time to ask questions about the study and consider their decision to participate.
- Voluntarily agree to participate in the study.
- Electronically sign and date the IRB-approved eIC.

Each individual's decision to participate in the study is entirely voluntary. It will be clearly stated in the eIC that their consent to participate can be withdrawn at any time.

The participant will be able to save a signed copy of their eIC. A limited number of virtual study team members will have access to the online portal where the signed eICs are stored to enable them to perform their assigned study-related tasks (e.g., checks that consent signatures have been properly completed by each enrolled participant).

If, during participation in the study, new information becomes available that could affect participant willingness to continue, each continuing participant will receive the new information and be re-consented into the study.

8.1.2 Screening Questionnaire

Once the participant has signed the eIC, they will complete a detailed screening questionnaire in the CCI app to identify and exclude individuals whose tooth sensitivity could be caused by other factors/clinical pathology for which DHCP advice should be sought.

8.1.3 Demographics

The following demographic information will be recorded in the CCI app: year of birth, age, gender, US state of residency, ethnicity and race.

8.1.4 Medical History and Prior Medications/Treatments

Participants will self-report details of relevant medical and surgical history, including allergies and drug sensitivities, by completion of a Medical History form in the CCI app.

Participants will list any current medications/treatments using the Concomitant Medications form in the CCI app. Reason for use, unit dose, daily dose, start and stop dates will be recorded (where known and as appropriate).

Note: Once the participant has completed the Medical History and Concomitant Medication forms, the 'Change in Health' and 'Change in Medication' forms will become available.

8.1.5 Inclusion/Exclusion Criteria

Information relating to study inclusion and exclusion criteria will be documented in the CCI app. Individuals who meet the study criteria will be eligible to participate and enrolled into the study.

8.2 Study Period

8.2.1 Week 0 (Baseline)

Participants must complete the following Baseline activities within 14 days of enrollment to be able to continue in the study.

- Complete DHEQ-48
- Complete NPRS
- Complete OHQ
- Record any changes in their health/medical occurrences; record any changes to their existing medications/treatments and any new medications/ treatments (including reason for use, unit dose, daily dose, start and stop dates, where known and as appropriate).

Study toothpaste will only be shipped to those participants who complete all 'Baseline' activities. Participants will confirm receipt of their study toothpaste in the CCI app (date of confirmation of receipt = Day 0) and will be instructed to start using it on the same day.

8.2.2 Weeks 1 and 2

- Complete NPRS
- Record any changes in health/medical occurrences; record any changes to existing medications/treatments and any new medications/ treatments (including reason for use, unit dose, daily dose, start and stop dates, where known and as appropriate).

8.2.3 Weeks 4, 8, 12, 16 and 20

- Complete DHEQ-48
- Complete NPRS
- Record any changes in health/medical occurrences; record any changes to existing medications/treatments and any new medications/ treatments (including reason for use, unit dose, daily dose, start and stop dates, where known and as appropriate).

8.2.4 Week 24

- Complete DHEQ-48
- Complete NPRS
- Complete Treatment Satisfaction NRS
- Record any changes in health/medical occurrences; record any changes to existing medications/treatments and any new medications/ treatments (including reason for use, unit dose, daily dose, start and stop dates, where known and as appropriate).
- Complete EOS and 'open-ended survey' questions.

8.3 Study Conclusion

The Study Conclusion section of the [redacted] app will be completed for all participants by [redacted] virtual site team. If a participant is discontinued early, at any point during the study, the primary reason for withdrawal (if known) should be recorded on the Study Conclusion page.

AEs ongoing at the end of the study will be marked 'unresolved'. [redacted] medically qualified person (investigator or designee) will ask the participant to seek appropriate medical advice and/or care, as needed. The sponsor will be notified of any ongoing AEs at the end of the study.

8.4 SAE Follow-up

[redacted] will follow-up SAEs until resolution. Follow-up of ongoing SAEs will continue post-study completion and/or after withdrawal or discontinuation. [redacted] will attempt to contact participants with an ongoing SAE at least three times; should the participant continue to be unreachable the SAE will be marked as 'unresolved'.

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required procedures are completed as described in the protocol.

9.1 Screening Assessments

Eligibility will be determined against the protocol inclusion/exclusion criteria, based on participant responses to the initial and main screening questionnaire and participant-reported health and medication/treatment information.

9.2 Quality of Life (QoL) Assessment

9.2.1 Dentin Hypersensitivity Experience Questionnaire (DHEQ-48)

The DHEQ-48 is a condition-specific measure of OHrQoL in relation to DH (Boiko *et al*, 2010) that has been previously validated in longitudinal studies and shown to be responsive to treatment (Baker *et al*, 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 the participants 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:

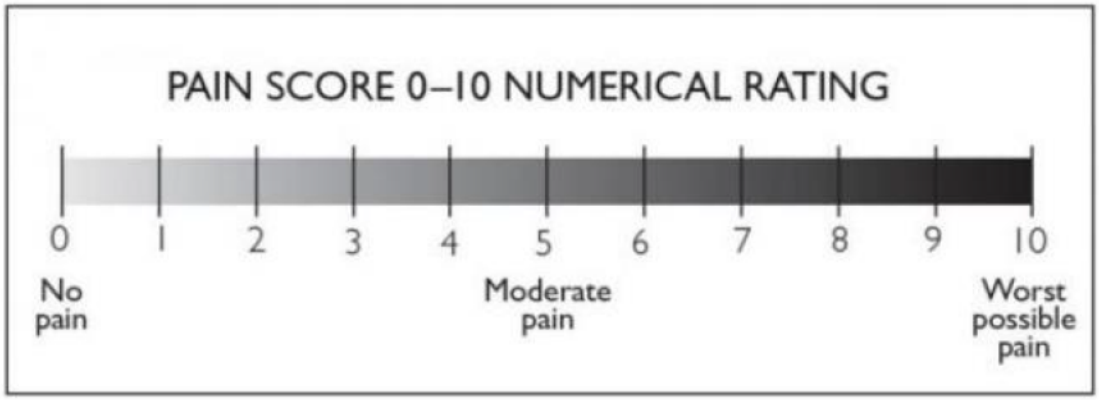
- **Global Oral Health:** Derived from participant response to Section 2, Q35 (‘*rate the health of your mouth, teeth and gums*’).
- **Effect on Life Overall:** Derived from participant responses to Section 2, Q36-39 (impact of DH on overall QoL).

9.3 Safety and Other Assessments

Changes in health and medical occurrences self-reported from immediately after the participant provides e-consent signature until the last use of the study toothpaste will be recorded as AEs; thus, SAEs will also be collected from immediately after the participant provides e-consent signature until last use of the study toothpaste.

9.3.1 DH Pain Assessment

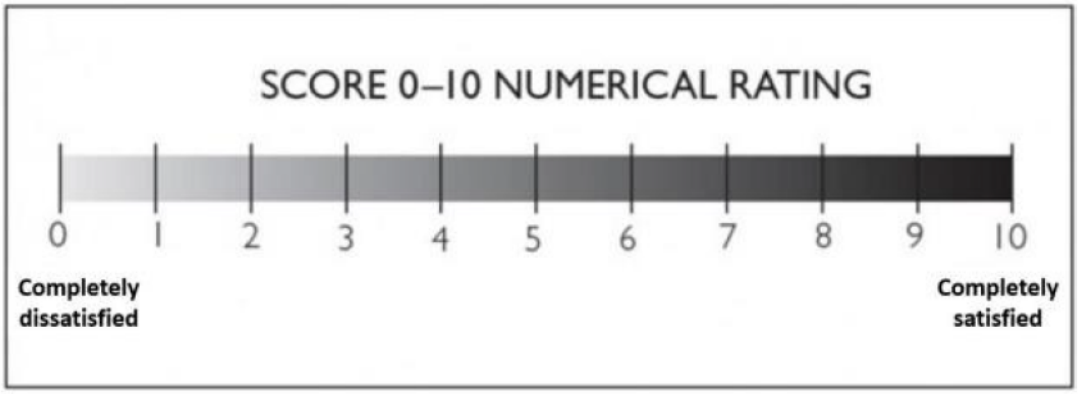
Participants will be asked to self-report the intensity of their DH pain at Baseline, 1, 2, 4, 8, 12, 16, 20 & 24 weeks using a Numeric Pain Rating Scale (NPRS). The 11-item NPRS is a segmented numeric version of a Visual Analogue Scale (VAS) from which the respondent selects the score (0–10) that best reflects the intensity of their pain (Hawker *et al*, 2011; Rocha *et al*, 2020). Similar to a VAS, the NPRS is anchored by terms describing pain severity extremes. It ranges from '0' representing one pain extreme (e.g., ‘no pain’) to '10' representing the other pain extreme (e.g., ‘worst possible pain’). Higher scores are indicative of greater pain intensity.



At each assessment time point, participants will be asked to record the numeric value on the segmented scale that best describes their pain intensity in the last 24 hours.

9.3.2 Participant Satisfaction with Treatment

Participants will be asked to rate their satisfaction with the DH treatment using a Numeric Rating Scale (NRS). The NRS is an 11-point ordinal scale used to assess satisfaction with the overall management of the condition for which the individual sought help from treatment. It ranges from 0 (completely dissatisfied) to 10 (completely satisfied), with higher scores indicative of greater satisfaction (van Berckel *et al*, 2017).



Participants will be asked to record the numeric value on the segmented scale that best describes their satisfaction with the DH treatment after 24 weeks of use and indicate why they selected a particular score (e.g., 'Please give more details on why you are satisfied or dissatisfied with the product').

9.3.3 Other

On completion of the study (Week 24), participants will be asked to complete a number of EOS/'open-ended survey' questions.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

CCI is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE, and for following up AEs that are serious (SAEs), considered related to either the study product or study participation, or that caused the participant to discontinue use of the study product or study participation.

10.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a study participant, temporally associated with the use of a study product, whether or not considered related to the study product.

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.

Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator/CCI medically qualified person (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product usage 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.

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/CCI [redacted] medically qualified person to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g., appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2 Definition of a Serious Adverse Event (SAE)

A serious adverse event (SAE) is a particular category of an adverse event where the adverse outcome is serious. If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in 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 & SAE Information

Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected from time of e-consent signature until the last use of the study toothpaste.

Medical occurrences that began before e-consent will be participant-recorded on the Medical History form in the CCI app and considered as Medical History; once the Medical History form is completed, the 'Change in Health' form will become available

Information recorded by the participant on the CCI app that potentially meets the definition of an AE will be discussed with the participant by CCI medically qualified person (investigator or designee) to facilitate evaluation and enable correct classification.

SAEs will be recorded by the investigator or designee and reported to the sponsor (or designee) immediately, and under no circumstances should this exceed 24 hours. The investigator or designee will submit any updated SAE data to the sponsor within 24 hours of it being available.

CCI is not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, should CCI learn of an SAE (including a death), at any time after a participant has been discharged from the study, and considers the event to be reasonably related to the study product or study participation, they must promptly notify the sponsor by emailing the information to the sponsor's Safety Reporting email box PPD. CCI will submit updated SAE data to the sponsor within the designated reporting time frames.

10.4 Reporting Procedures

Participants will self-report changes in their health and medical occurrences using the 'Change in Health Form' or 'Change in Medication Form' available within the CCI app.

CCI is responsible for detecting, documenting, and reporting events that meet the definition of an AE and remains responsible for follow up of AEs considered related to the study product, participation in the study, or a study procedure, or that caused the participant to discontinue the study product or study, and SAEs.

Should a participant report a change in health status through the CCI app or by email/phone communication, CCI medically qualified person (investigator or designee) will review the information and assess if it meets the definition of an AE/SAE. If classified as an SAE, the investigator or designee will enter available information into the SAE form and forward the completed SAE form to the sponsor's Case Management Group (CMG), Global Safety (Haleon CMG) within 24 hours of the participant reporting the event.

If additional details are required to determine if the AE meets SAE criteria, the virtual site team will contact the participant to ask for more information. If it is not possible to re-contact the participant within 24 hours, the investigator or designee will complete the SAE form with the available information and send to Haleon CMG within the 24-hour time frame. The virtual site team will make every effort to contact the participant (at least 3 communication attempts) to collect further details and will share additional information with Haleon CMG as available.

When an AE occurs, it is the responsibility of CCI medically qualified person (the investigator or designee) to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event to ensure all relevant information regarding an AE is recorded in the CCI app, and all details relating to an SAE on the paper SAE form provided.

It is **not** acceptable for CCI to send copies of the participant's medical records to the sponsor in lieu of completion of the required AE/SAE documentation. There may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all participant identifiers, except for the participant number, will be redacted prior to submission to the sponsor.

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

10.4.1 Reporting of an Adverse Event

AEs will be reported using the CCI platform; SAEs will be reported using a paper SAE form. Where the same data are collected, the AE report and SAE form must be completed in a consistent manner (e.g., the same AE term should be used). Concise medical terminology should be used for both AE and SAE reporting.

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE in the CCI platform, an SAE form should be completed, as fully as possible with the information available. The sponsor will provide CCI with an electronic copy of the SAE form for the eTMF prior to study start.

Should an SAE occur, this form will be completed electronically (or printed out and completed as a hard copy, if needed).

It is essential to enter the following information on the SAE form:

- Protocol and participant identifiers
- Participant demography
- Description of events with diagnosis, if available
- Investigator (or medically qualified designee) opinion of relationship to study product (or study procedure, as appropriate)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator (or medically qualified designee) and sponsor assessment of the SAE report:

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

The SAE form, completed as fully as possible, will be emailed to the sponsor's CMG mailbox PPD, with copy to the appropriate sponsor Clinical Study Manager (CSM) **immediately after** the investigator or designee learn of the event, **under no circumstances should this exceed 24 hours**. Hard copy SAE forms (or portions of the SAE form that cannot be completed electronically) should be scanned and e-mailed.

The initial SAE report will be followed up with more information, as relevant, or as requested by the sponsor's CSM. CCI will submit any updated SAE data to the sponsor, **immediately** it becomes available; **under no circumstances should this exceed 24 hours of it being available**. Study number and participant number must be included in the title of all SAE-related emails.

Original, completed SAE forms will be retained by CCI

The sponsor's CSM will be responsible for forwarding the SAE form to other sponsor personnel as appropriate.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

- **Mild:** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities
- **Severe:** An event that prevents normal everyday activities.

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

10.5.2 Assessment of Causality

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

CCI medically qualified person (investigator or designee) **must** assign causality to each AE (serious and non-serious) in the AE report and on the SAE form (participant to the classification of the AE). Assignment of 'reasonable possibility' indicates there are facts (evidence) and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The facts (evidence) and/or arguments that suggest a causal relationship should be provided.

CCI medically qualified person (investigator or designee) will use their clinical judgment to assign the relationship, having also consulted the Product Information. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated, as needed.

There may be situations when CCI medically qualified person (investigator or designee) has minimal information to include in the initial SAE report. **However, it is very important include an assessment of causality in the initial SAE form transmitted to the sponsor.** CCI medically qualified person may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.6 Follow-up of AEs and SAEs

CCI is required to proactively follow up each AE/SAE and provide further information on the participant's condition, as appropriate. While the study is in field, all AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up. CCI medically qualified person (investigator or designee) will submit any updated AE/SAE data to the sponsor within the designated reporting time frames.

AEs ongoing at the end of a participant's participation in the study will be marked 'unresolved'; no further follow-up is required. CCI medically qualified person (investigator or designee) will ask the participant to seek appropriate medical advice and/or care, as needed. The sponsor will be notified of ongoing AEs at the end of the study.

Post-study completion, withdrawal, or discontinuation, CCI will contact any participant with an ongoing SAE to follow up that SAE to resolution. CCI must make every effort to contact the participant (3 communication attempts). Should the participant continue to be unreachable, the SAE will also be marked 'unresolved'.

CCI is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by the sponsor to elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

10.7 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier (Section 10.1) and recorded in the CCI app. When a participant withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined in Section 10.4.2.

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 investigation.

AEs/SAEs will be reported to local and regional health authorities by the sponsor, when appropriate, in accordance with applicable local and regional regulations. The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority (local, regional or national) and the IRB. Prompt notification of SAEs by CCI to the sponsor is essential so that legal obligations and ethical responsibilities for participant safety can be met. Safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy.

10.9 Pregnancy

Pregnancy information will be collected on pregnancies self-reported while a female participant is participating in the study (self-reported from time of e-consent signature until last use of study toothpaste).

10.9.1 Action to be Taken if Pregnancy Occurs

The sponsor will provide CCI with an electronic copy of the pregnancy reporting form for the eTMF prior to study start. Should pregnancy be self-reported by a female participant during the study, the form will be completed electronically (or printed out and completed as hard copy, if needed).

The completed pregnancy reporting form will be e-mailed to the sponsor's CMG mailbox PPD, with copy to the sponsor's CSM. Hard copy pregnancy reporting forms (or portions of the pregnancy reporting form that cannot be completed electronically) should be scanned and e-mailed.

Original, completed pregnancy reporting forms will be retained by CCI

The participant will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant/neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by CCI to the sponsor's CMG mailbox PPD, with copy to the sponsor's CSM. Generally, follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. Termination of the pregnancy will be reported.

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

11 DATA MANAGEMENT

As used in this protocol, the term case report form (CRF) is understood to refer to an electronic data record. For this study, this is the CCI app (portal), a validated system. Participant data will be primarily entered into the CCI app/portal (additional data relating to SAEs and pregnancy will be recorded outside of the app and platform). CCI is responsible for verifying that data entries are accurate, correct, and approved electronically.

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

11.1 Case Report Form

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

For each participant who has given e-consent in the CCI app, the eCRF must be completed and reviewed for completion and accuracy. CCI must maintain accurate documentation (source data) as appropriate to support the information entered in the eCRF. Study data will be collected in the CCI app and CCI Electronic Data Capture (EDC) Platform.

Management of study data will be performed in accordance with CCI applicable standards and procedures with sponsor oversight to ensure the integrity of the data.

To protect the privacy of participants, no personal information (including the name(s) or initial(s) or full date of birth) is to be recorded in the eCRF or as part of the query text. Identifiable data are isolated to a special team at CCI and these data will not be transferred/available to the Sponsor.

All required eCRF screens in CCI app (portal) should be completed at the appropriate time point when the eCRF has been designated as the source. Data sourced elsewhere should be entered into the eCRF within the timeframe agreed between CCI and the sponsor.

The sponsor will obtain and retain all 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.

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

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and concomitant medications terms using an internal validated medication dictionary.

11.2.1 Data Queries

The CCI data management team will perform programmed logical checks to ensure consistent and complete data entry. The CCI data management team will perform logical manual checks, and queries will be entered on a Data Issues Log for decentralized site staff to address. The Clinical Dictionary Development and Management Group will raise queries on the safety data (AEs, concomitant medications), as needed, to code the terms appropriately.

11.3 Processing Patient Reported Outcomes

Electronic Patient Reported Outcome (ePRO) data will be collected using electronic devices and available electronically to the sponsor or CCI.

To protect the privacy of participants, no personal information (including the name(s) or initial(s) or full date of birth) is to be recorded in the eCRF or as part of the query text. Identifiable data are isolated to a special team at CCI and these data will not be transferred/available to the Sponsor.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

Sufficient participants will be screened (to allow for up to 50% screen failure rate) to ensure approximately 500 participants are enrolled and approximately 400 complete (to allow for up to 20% drop-out rate).

A sample size of 400 participants would ensure at least 90% power to achieve a statistically significant (two-sided 5% significance level) reduction in Baseline in DHEQ Total Score when using a one-sample t-test, assuming a true population effect size (mean reduction/standard deviation [SD]) of 0.2. The planned primary analyses (defined in Section 12.3.2) in this study will use a Mixed Model with Repeated Measures (MMRM) with time point as a fixed effect, Baseline DHEQ score as a covariate and participant as a repeated measure.

As well as providing adequate power to demonstrate statistically significant reductions from Baseline at each timepoint (4, 8, 12, 16, 20 & 24 weeks), 400 participants will ensure adequate precision of the corresponding 95% confidence intervals (CIs) for the mean reduction, and robust RWE relating to the magnitude of benefit from product use, at each timepoint. In a previous study (Haleon study 216953) assessing the same DHEQ-48 endpoints over 24 weeks in a RWE setting for an anti-sensitivity toothpaste containing 5% KNO_3, the SD of the change from Baseline in DHEQ Total Score was shown to increase from around 30 units at Week 4 to 50 units at Week 24. An SD of 30 units and 50 units across 400 participants would equate to precision of the 95% CIs for the mean reduction within +/- 3 and 5 units, respectively.

12.2 Populations for Analysis

12.2.1 Analysis Populations

The Screened population will include participants who electronically sign the eIC and enter the screening process for assessment of inclusion and exclusion criteria.

The Enrolled population will include all participants who meet the inclusion/exclusion criteria as identified by their responses to the screening questionnaire.

The Safety population will include all participants who complete at least one use of study product. Safety population will be used for the analysis of AEs.

The modified Intent-To-Treat (mITT) population will include all participants in the Safety population who have at least one post-baseline derived DHEQ Total Score. Efficacy data will be analyzed using the mITT population only.

12.2.2 Exclusion of Data from Analyses

Exclusion of any data from the analyses will be determined during a data review meeting prior to database lock and pre-defined in the SAP. Any reasons for exclusion from an analysis population will be listed, if applicable.

12.3 Statistical Analyses

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

Descriptive summaries of continuous endpoints will include counts (missing and non-missing), mean, SD, standard error (SE), median, minimum, and maximum. Descriptive summaries of categorical endpoints will include counts (missing and non-missing) and percentage (%) out of the participants with non-missing data.

Residual analyses will be conducted for each MMRM applied. If there are any obvious departures from normality and/or independence assumptions, these will be reported; alternative analyses will be described in the SAP.

12.3.1 Primary Analyses

Change from Baseline will be calculated at each post-Baseline time point (4, 8, 12, 16, 20 & 24 weeks) for the primary DHEQ endpoints:

- **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),

Change from Baseline in each DHEQ endpoint listed above will be analyzed using a MMRM with time point fitted as a fixed effect, the respective Baseline DHEQ score as a covariate and participant fitted as a repeated measure with unstructured covariance matrix. Kenward-Rogers degrees of freedom will be applied. The estimates of the adjusted mean (standard error [SE]) change from Baseline will be presented along with 95% CIs.

12.3.2 Secondary Analyses

DHEQ, Secondary Endpoints

Change from Baseline will be calculated at each post-Baseline time point (4, 8, 12, 16, 20 & 24 weeks) for the secondary DHEQ endpoints:

- **Section 1**
  - Change from Baseline in Impact on Everyday Life: Q1, Q2 & Q3 (separate scores)
- **Section 2**
  - Change from Baseline in DHEQ Global Oral Health (Q35)
  - Change from Baseline in DHEQ Effect on Life Overall (sum of Q36-Q39)

Each DHEQ endpoint listed above will be analyzed using a MMRM with time point fitted as a fixed effect, the respective Baseline score as a covariate and participant fitted 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 at each post-Baseline timepoint will be presented along with 95% CIs.

For each DHEQ endpoint listed above (Sections 12.3.1 and 12.3.2), and each individual DHEQ question, the score at each timepoint (including Baseline) and the corresponding change from Baseline (at each post-Baseline timepoint) will be summarized descriptively. Plots of mean score (SE) for each DHEQ endpoint listed above (Sections 12.3.1 and 12.3.2), and the individual DHEQ questions, over time will also be provided. These will also be presented by age and gender sub-groups with further details to be provided in SAP.

The number and percentage (%) of participants who 'agree' (score 5-7) with the 34 items (statements) in 5 domains of the DHEQ (Section 2, Q1-Q34) will be summarized at Baseline and Week 24. The percentage for each item will be summarized and presented in descending order.

Numeric Pain Rating Scale (NPRS)

Change from Baseline will be calculated at each post-Baseline time point (1, 2, 4, 8, 12, 16, 20 & 24 weeks) for the NPRS score. Change in NPRS score will be analyzed using identical methods to each of the DHEQ endpoints detailed above. Mean profile plots, descriptive summaries (including change from Baseline) and MMRMs will be presented.

An additional summary of the number of participants who achieve a reduction from Baseline in NPRS of > 30% will be presented at each post-Baseline time point (1, 2, 4, 8, 12, 16, 20 & 24 weeks).

Satisfaction Numeric Rating Scale (NRS)

Cross-tabulations of the number of participants reporting at each level of the NRS and the cumulative number of participants reporting at each level or higher at Week 24 will be presented. The NRS score at Week 24 will be summarized descriptively.

12.3.3 Safety Analyses

AEs will be coded using MedDRA and categorized as either oral or non-oral by CCI prior to database lock. The number of AEs/SAEs and the number of participants with AEs/SAEs will be listed and tabulated overall and by System Organ Class (SOC) and Preferred Term (PT). This will be repeated including only Oral AEs/SAEs.

12.3.4 Demographic and Baseline Characteristics

Demographics, Baseline characteristics (including DH diagnosis (self-diagnosed or diagnosed by dentist); use of anti-sensitivity toothpaste (current user, intermittent user or non-user); and frequency of DH symptoms (compiled from responses from the Screening Questionnaire and the OHQ), and oral hygiene habits (compiled from responses to the OHQ) will be summarized using descriptive statistics for the mITT population.

12.3.5 Study Product Compliance and Use of Other Therapies

12.3.5.1 Study Product Compliance

Compliance with study product usage and with the study schedule will be tabulated and summarized for the Safety population. Summaries will include a simple yes/no frequency (and percent) count at each timepoint:

- Summary of completion to study schedule and assessments (yes/no)
- Summary of product usage according to product instructions (yes/no)
- Summary of number of toothpaste tubes remaining at the end of the study (e.g., '2 or less tubes', '3 to 6 tubes' and 'more than 6 tubes')

12.3.5.2 Prior and Concomitant Medications

Prior and concomitant medications taken during the study will be listed for the Safety population.

12.3.6 Handling of Dropouts and Missing Data

Missing data due to dropouts/withdrawals will be assessed on an ongoing basis during the study. Any further sensitivity analyses needed due to missing data will be reviewed at the time of data review.

For the DHEQ data, for any timepoint if response is missing, it will be excluded from the primary analysis; the data available for each participant (even though some time points may be missing) will still be included in the analysis.

The MMRM approach will include all participants in the mITT population in the analysis. Any missing data from such participants will be treated as 'missing at random', i.e., their missing data at a particular time point will be assumed to behave in similar fashion to a participant with non-missing data at that time point who has similar data at other time points. This approach ensures an unbiased approach to handling missing data under the 'missing at random' assumption.

12.3.7 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

In accordance with applicable regulations including GCP and sponsor procedures, prior to the start of the study, the CCI virtual site team will be trained on the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor requirements.

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.

During the study, the data will be monitored to verify that:

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

The extent and nature of monitoring will be described in the Data Management Plan.

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 CCI study-related records, and 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, CCI must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

CCI will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, CCI will cooperate with the sponsor or its agents to prepare the study site for the inspection and will allow the sponsor or its agents, whenever feasible, to be present during the inspection. CCI will promptly provide copies of the inspection findings to the sponsor or its agents. Before response submission to the regulatory authority, CCI will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board (IRB)

It is the responsibility of CCI to have prospective approval of the study protocol, protocol amendments, informed consent documents, the safety statement (including any updates) and other relevant documents (e.g., recruitment advertisements), if applicable, from the IRB. All correspondence with the IRB should be retained in CCI master study file. Copies of IRB approvals should be forwarded to the sponsor prior to the initiation of the study, and also when subsequent amendments to the protocol are made.

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

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

13.3.3 Participant Information and Consent

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

When study data are compiled for transfer to the sponsor and other authorized parties, participant names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by the sponsor to de-identify study participants (Note: the use of initials should be avoided).

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

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB before use, and available for inspection.

CCI must ensure that each study participant is fully informed about the nature and objectives of the study and possible risks associated with participation.

13.3.4 Participant Recruitment

Advertisements approved by the IRB may be used as part of the recruitment procedures. Use of an IRB-approved, generic, prescreening questionnaire to assess basic participant characteristics to determine general eligibility for this study is allowed.

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

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 participant 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 CCI is aware of any new information

that might influence the evaluation of the benefits and risks of the study product, the sponsor should be informed immediately.

In addition, CCI will inform the sponsor immediately of any urgent safety measures taken by CCI to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that CCI 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 participants begins in accordance with applicable sponsor processes.

The sponsor intends to make anonymized participant-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. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding

13.5 Provision of Study Results to the Investigator

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the Clinical Study Report (CSR). CCI 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 CCI with the full summary of the study results. CCI is encouraged to share the summary results with the study participants, as appropriate.

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

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

13.6 Records Retention

Following closure of the study, CCI must assure that the participant's anonymity will be maintained. eCRFs or other documents submitted to the sponsor should not identify participants by their names or initials but by an identification code. CCI should keep a separate log of participant codes, names and addresses. Documents not for submission to the sponsor should be maintained by CCI in strict confidence.

CCI must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location.

CCI study records (eTMF) must be maintained to allow easy and timely retrieval, when needed (e.g., for a sponsor audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant study 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.

CCI must ensure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if

required. Furthermore, CCI must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Records and documents, including signed eIC, pertaining to the conduct of this study must be retained by CCI 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 site for the 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 CCI. CCI 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 CCI is no longer associated with the site.

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, a change in opinion of the IRB, a study product safety problem, or at the discretion of the sponsor.

If a study is prematurely terminated, the sponsor will promptly notify CCI. After notification, CCI must promptly contact all participating participants and should ensure appropriate therapy/follow-up for the participants. As directed by the sponsor, all study materials must be collected and all eCRF's completed to the greatest extent possible. Where required by the applicable regulatory requirements, the sponsor should inform the regulatory authority(ies) and CCI should promptly inform the IRB and provide the IRB with a detailed written explanation of the reason(s) for termination or suspension.

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

Upon completion or premature discontinuation of the study, the sponsor's monitor(s) will conduct study closure activities with CCI, as appropriate, in accordance with applicable regulations including GCP, and the sponsor's 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
app	Application
CI	Confidence Interval
CMG	Case Management Group
CRF	Case Report Form
CSM	Clinical Study Manager
CSR	Clinical Study Report
DH	Dentin Hypersensitivity
DHCP	Dental Health Care Professional
DHEQ	Dentin Hypersensitivity Experience Questionnaire
EC	Ethics Committee
ECG	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eIC	Electronic Informed Consent
EOS	End of Study
ePRO	Electronic Patient Reported Outcome
eTMF	Electronic Trial Master File
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IRB	Institutional Review Board
KNO_3	Potassium Nitrate
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-To-Treat
MMRM	Mixed Model with Repeated Measures
N/A	Not Applicable
NPRS	Numeric Pain Rating Scale
NRS	Numeric Rating Scale
OHrQoL	Oral Health Related Quality of Life
OHQ	Oral Hygiene Questionnaire

PII	Personal Identifiable Information
PPM	Parts Per million
Q	Question
QOL	Quality of Life
RCT	Randomized Controlled Trial
RWD	Real World Data
RWE	Real World Evidence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SnF_2	Stannous Fluoride
SUSAR	Suspected Unexpected Serious Adverse Event
US	United States
VAS	Visual Analogue Scale
Vs.	Versus

15.2 Screening Questionnaire

We are going to call what you feel in your teeth 'sensations'.

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

Itchy	Aching	Shooting
Piercing	Tingling	Sharp
Dull	Flashing	Shivery
Lingering	Twinging	Flickering
Stabbing	Shattering	Freezing
Fleeting	Quivering	Pricking
Pain	Discomfort	Twinges
Sensitivity	None of the Above	

If answer is 'none of the above', participant should not proceed further

2. How long have you been experiencing these sensations or sensitivity in your teeth? (*Tick only one response*)

Less than six months	Proceed
More than six months but less than a year	Proceed
More than a year but less than five years	Proceed
More than five years but less than 20 years	Proceed
More than 20 years	Proceed
None of the above	Exclude

3. Which teeth have been/are affected? (Tick all that apply)

Top front teeth	Proceed
Top back teeth	Proceed
Bottom front teeth	Proceed
Bottom back teeth	Proceed
None of the above	Exclude

4. Which of the following cause you to have these sensations or sensitivity in your teeth? (*Tick all that apply*)

Cold fluids	Acidy fruits (e.g., oranges)	Having teeth cleaned at the dentist
Hot foods	Sweet things	Tooth whitening products
Hard foods	Sticky foods	Metals touching my teeth
Cold air	Ice cream	Flossing certain teeth
Salty foods	Cold foods	Tooth brushing
Hot fluids	None	

If answer is 'none', participant should not proceed further

5. How often do you experience these sensations or sensitivity in your teeth? (*Tick only one response*)

Several times a day	Proceed
Once a day	Proceed
Several times a week	Proceed
Once a week	Proceed
Several times a month	Proceed
Once a month	Proceed
Less than once a month	Proceed
Never	Exclude

6. If you have any of these sensations or sensitivity in your teeth, on average how long do they last? (*Tick only one response*)

A few seconds	Proceed
About a minute	Proceed
Several minutes	Proceed
About half an hour	Proceed
Longer than half an hour (Please specify)	Proceed
Don't have them	Exclude

7. Do you have severe acid reflux? (*Severe is defined as taking more than one medication daily to treat your reflux or considering surgery to correct*)

Yes	Exclude
No	Proceed

8. Can you tell me if you have:
(*Tick all that apply*)

All your own teeth	Proceed
Mainly natural teeth and a few crowns / bridges / implants	Proceed
Fixed or removable orthodontic braces/bands or a fixed orthodontic retainer	Proceed
Partial dentures	Exclude
Full dentures	Exclude
Recent treatment for periodontal disease or gum disease (including surgery) within 6 months	Exclude
Active tooth decay	Exclude
Loose teeth as a result of severe gum disease (active periodontitis)	Exclude
Any chronic and/or severe painful health conditions which lead to regular use pain medications (more than 3 days a week)	Exclude

15.3 Oral Hygiene Questionnaire (OHQ)

1. How frequently do you normally brush your teeth?

   3 or more times a day, twice a day, once a day, less often

2. Have you had a professional or self-applied tooth whitening treatment in the last 2 weeks?

   Y or No

   If a self-applied whitening treatment was used, please specify (free text)

3. Have you had a professional tooth cleaning in the last 2 weeks?

   Y or No

4. Have you ever been diagnosed with sensitive teeth by a dentist?

   Y or No

5. When was the last time you visited a dentist/hygienist?

Within the last 6 months
Within the last year
Within 2 years
Between 2-3 years ago
More than 3 years ago

6. Do you use a toothpaste designed specifically for sensitive teeth?

   Yes (current users)

   No (non-users)

   Sometimes (intermittent users)

   Unknown

7. What brand of toothpaste do you most frequently use? (Select from drop down list)

   If other, specify (free text)

8. What is the product name of the brand selected in the previous question that you most frequently use? (Select from drop down list)

   If other product name/variant, specify (free text)

9. Which toothpaste are you using right now? If you currently use more than one toothpaste, please list them all (brand and product name). How long have you been using it/them for?

   _____ (free text)

10. What type of toothbrush do you use? (Select from drop down list)

11. Can you tell me if you have any of the following:
    (*Tick all that apply*)

Cracked tooth or teeth
Chipped tooth or teeth
Cold sores
Grinding teeth
Gum swelling or inflammation
Receding gums
Painful/tender gums when brushing
Ulcers in the mouth
Stained/yellow teeth
Seeing blood when you spit when you brush your teeth
Bad breath
None of these

15.4 Dentin Hypersensitivity Experience Questionnaire (DHEQ-48)

SECTION ONE

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

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

1 2 3 4 5 6 7 8 9 10

Not at all intense — Worst imaginable

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

1 2 3 4 5 6 7 8 9 10

Not at all bothered — Extremely bothered

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

1 2 3 4 5 6 7 8 9 10

Can easily tolerate — Can't tolerate at all

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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