The Clinical Protocol 204930

CONFIDENTIAL

SUMMARY INFORMATION

Title:	Study to Investigate the Impact on Oral Health Related Quality of Life of Managing Dentine Hypersensitivity with a Daily Use Anti-Sensitivity Toothpaste
Protocol Number:	204930
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) UK Trading Limited St Georges Avenue, Weybridge, Surrey, KT13 0DE, United Kingdom (UK) Tel: PPD
Product Name:	Dentifrice containing 0.454% w/w stannous fluoride (1100ppm fluoride)
Development Phase:	N/A

Expert Advice Outside of Normal Working Hours:	Tel: PPD

PRIMARY CONTACT **Clinical Study Manager:**	PPD ~~BSC HONS~~ PPD **BSC, MSC**

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PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current 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:	Dr Robert Maclure
Investigator Qualifications:	BSc, BDS
Investigator Signature:	PPD
Date of Signature/ Agreement:	

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PROCESS FOR AMENDING THE PROTOCOL

Protocol modifications to ongoing studies which could potentially adversely affect the safety of subjects or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria are considered major/substantial amendments and must be made only after appropriate consultation between an appropriate representative of GSKCH and the investigator.

Details of amendments to the protocols should be recorded on the following page. Protocol modifications must be prepared by a representative of GSKCH. All changes must be justified in the Reason for Amendment section of the following Protocol Amendment Page. Approval of amendments will be made by the original protocol signatories or their appropriate designees.

All major/substantial protocol modifications must be reviewed and approved by the appropriate IEC in accordance with local requirements, before the revised edition can be implemented.

All non-substantial/ minor/ administrative amendments should be submitted to the IEC as per country specific requirements. In some countries pre-approval of a minor amendment is not required and will just be held on file by the sponsor and investigator.

PROTOCOL AMENDMENT PAGE

Details of all amendments should be recorded in the table below. Affected sections should be listed in the table; the actual amendment/ change should be made in the relevant section of the main protocol.
To highlight the change, the following features will be used:
To **add** text: Use of **CAPITAL LETTERS, BOLD AND UNDERLINE**
To **delete** text: Use of Strikethrough e.g. ~~strikethrough~~

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 1	Non-Substantial/Minor ☒	This is Protocol amendment 1 (Protocol version 4.0) as previous amendments (2.0 and 3.0) were made prior to Ethics submission. Change the orientation of the LMS scales from horizontal to vertical. This will allow all 4 scales of the LMS Form to fit on one page making it easier for subjects to complete the scales. Personnel changes	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	Page 2- Personnel changes 6.2.1- Clarification text added Replace Appendix 12.3 and 12.4	Signature:
Protocol Version No.: 4	Substantial/ Major ☐				Date:

		Clarification text added			
Amendment No.: 2	Non-Substantial/Minor ☒	Personnel changes- change to Study Manager	Informed Consent ☐ Yes ☒ No	Page 2- Personnel changes	Signature:
Protocol Version No.: 5	Substantial/ Major ☐	Due to recruitment issues at Intertek Widnes site, a second site is being initiated at Ellesmere Port to recruit the remaining subject numbers. Addition of 2nd site address Change of text from "single centre" to "multi-site" Clarify actions to be taken if subject is prescribed antibiotics during the course of the study	Safety Statement ☐ Yes ☒ No CRF ☒ Yes ☐ No	Page 3- Summary Information Page14- Brief Summary Page 14- Overall Design Page 20- Section 3.1 Study Design Page 29- 4.4 Withdrawal/ Stopping criteria	Date:

		Change of text regarding how LMS scales will be measured. Change text from "left to right" to "bottom to top" Clarification of additional statistical analysis that will be carried out to provide endpoint summaries by site		Page 39 Section 6.2.4.2 Labelled Magnitude Scales (LMS) Page 55 Section 9.3.2 Primary Analysis Page 55 Section 9.3.3 Exploratory Analysis	
Amendment No.: 3	Non-Substantial/Minor ☒	Personnel changes- change to Study Statistician and clinical supplies lead Due to moving from single site to a multisite study, the primary and exploratory analysis has been changed from paired t test to mixed effect ANOVA	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	Page 2- Personnel changes Page 55,56- Section 9.3.2 Primary Analysis Section 9.3.3 Exploratory Analysis	Signature:
Protocol Version No.: 6	Substantial/ Major ☐				Date:

		for accounting effects by site.			

SCHEDULE OF EVENTS

Procedure	Screening Visit 1		Baseline Visit 2 Week 0 (Day 0)	Visit 3 Week 4 (Day 28 ±3)	Visit 4 Week 8 (Day 56 ±3)	Visit 5 Week 12 (Day 84 ±3)	Visit 6 Week 16 (Day 112 ±3)	Visit 7 Week 20 (Day 140 ±3)	Visit 8 Week 24 (Day 168 ±3)
Informed Consent	X	Acclimatisation Period - Minimum 3 weeks – Maximum 6 weeks							
Demographics, Medical History	X								
Current/Concomitant Medications	X		X	X	X	X	X	X	X
Inclusion/Exclusion	X		X						
Subject Eligibility	X		X						
Subject Continuance			X	X	X	X	X	X	X
Oral Soft Tissue (OST) and Oral Hard Tissue (OHT) Assessment	X		X	X	X	X	X	X	X
Eligible Teeth Assessments (Dentition Exclusions, EAR, MGI, Tooth Mobility)	X								
Qualifying Evaporative Air Sensitivity (Y/N)	X								
Dispense Acclimatisation Toothpaste, Toothbrush, Diary and Timer	X								
Supervised Brushing with Acclimatisation Toothpaste	X								
Return Acclimatisation Toothpaste, Toothbrush and Diary			X						
DHEQ completion [1,5]			X	X	X	X	X	X	X
LMS[5] training			X						

Procedure	Screening Visit 1		Baseline Visit 2 Week 0 (Day 0)	Visit 3 Week 4 (Day 28 ±3)	Visit 4 Week 8 (Day 56 ±3)	Visit 5 Week 12 (Day 84 ±3)	Visit 6 Week 16 (Day 112 ±3)	Visit 7 Week 20 (Day 140 ±3)	Visit 8 Week 24 (Day 168 ±3)
Evaporative Air Assessment (Schiff Sensitivity Score, LMS[5]) *on all Eligible Teeth from Screening*		Acclimatisation Period - Minimum 3 weeks – Maximum 6 weeks	X						
Selection of 2 *'Test Teeth'*			X						
Evaporative Air Assessment (Schiff Sensitivity Score, LMS[5]) *on 2 'Test Teeth'*				X	X	X	X	X	X
Evaporative Air Assessment (Schiff Sensitivity Score) *on Remaining Eligible Teeth from Screening*				X	X	X	X	X	X
Dispense Study Product			X[2]	X	X	X[2]	X	X	
Supervised Brushing			X	X[3]	X[3]	X[3]	X[3]	X[3]	
Return Study Product and Diary				X	X	X	X	X	X
Compliance checks			X	X	X	X	X	X	X
Adverse Events	X[4]		X	X	X	X	X	X	X
Incidents			X	X	X	X	X	X	X
Study Conclusion									X

1. To be completed prior to OST examination and any clinical assessments
2. Dispense a new toothbrush at this visit also
3. Subject instructed to bring all supplies back to all subsequent visits
4. After first supervised brushing with acclimatisation product
5. To be completed by subjects

PROTOCOL SYNOPSIS FOR STUDY 204930

Brief Summary

This ~~single centre~~ **MULTI-SITE**, non-comparative design study will be used to monitor the impact of long term management of dentine hypersensitivity (DH) with daily use of a sensitivity toothpaste on the quality of life of a population of sensitivity sufferers. Changes in oral health related quality of life will be monitored using the Dentine Hypersensitivity Experience Questionnaire (DHEQ). The study will be conducted in subjects in good general health, with pre-existing self-reported and clinically diagnosed tooth sensitivity at screening.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To monitor the impact of long term management of DH over a 24 week period, with twice daily use of a sensitivity toothpaste, on the oral health related quality of life in sensitivity sufferers, as measured by the DHEQ.	Change from baseline in DHEQ endpoints over time.
Exploratory	
To evaluate changes in dentine hypersensitivity over the 24 week treatment period, including the number of sensitive teeth, as measured by Schiff Sensitivity Score to assess examiner performance on this measure.	Mean Schiff Sensitivity Score for all timepoints. Change from baseline in Schiff sensitivity score (two test teeth) for all timepoints. Change from baseline in Schiff sensitivity score (all qualifying teeth) for all timepoints.
To evaluate changes in dentine hypersensitivity over the 24 week treatment period, as measured by Labelled Magnitude Scales (LMS).	Mean LMS (of each of 4 VAS scales) and change from baseline (for the two test teeth) at each time point.

Study Design

Overall Design
A ~~single centre~~ **MULTI-SITE**, non-comparative design study will be used to monitor the impact of long term management of DH with daily use of a sensitivity toothpaste

on the quality of life of a population of sensitivity sufferers. Changes in oral health related quality of life will be monitored using the DHEQ. The study will be conducted in subjects in good general health, with pre-existing self-reported and clinically diagnosed tooth sensitivity at screening.
Visit 1 - Screening Visit
The following assessments will be conducted in the order written: • Written informed consent. • Review of the oral care products the subject is currently using to confirm they do not contain any ingredients intended for treating sensitive teeth. • Demographics, concomitant medications and medical history. • Oral examination including an oral soft tissue (OST) examination and oral hard tissue (OHT) assessments to determine eligible teeth. • Qualifying evaporative air sensitivity. • Inclusion/exclusion criteria review. • Confirmation of subject eligibility. • Dispensation of acclimatisation toothpaste, toothbrush, diary and timer. • Supervised brushing with acclimatisation toothpaste. • Adverse Events (AEs) will be documented from completion of the supervised brushing with acclimatisation toothpaste.
Visit 2 - Baseline Visit (Day 0)
The following assessments will be conducted in the order written: • Review of concomitant medications and AEs. • Return of acclimatisation toothpaste, toothbrush and diary. • Review of completed diary to determine usage compliance. • Inclusion/exclusion criteria review. • Confirmation of subject eligibility and continuance. • Completion of DHEQ Section 1 and Section 2. • LMS Training Exercise • OST and OHT examinations. • Evaporative air sensitivity assessment (Schiff Sensitivity Scale, LMS) on all eligible teeth from Visit 1. • Selection of two test teeth. • Dispensation of study toothpaste, toothbrush and diary. • Supervised brushing with study treatment. • AEs and Incidents from supervised brushing with study treatment
Visit 3 - Week 4 (Day 28 ± 3) **Visit 4 – Week 8 (Day 56 ± 3)** **Visit 5 – Week 12 (Day 84 ± 3)** **Visit 6 – Week 16 (Day 112 ± 3)** **Visit 7 – Week 20 (Day 140 ± 3)**

The following assessments will be conducted in the order written: • Review of concomitant medications, AEs and incidents. • Return of study toothpaste and diary. New toothbrush at Week 12. • Review of completed diary to determine usage compliance. • Inclusion/exclusion criteria review. • Confirmation of subject continuance. • Completion of DHEQ Section 1 (Q7-9) & Section 2. • OST and OHT examinations. • Evaporative air sensitivity assessment (Schiff Sensitivity Scale, LMS) on two test teeth. • Evaporative air sensitivity assessment (Schiff Sensitivity Scale) on remaining eligible teeth from Visit 1. • Dispensation of study toothpaste and diary (and toothbrush at Visit 5). • Supervised brushing with study treatment. • AEs and Incidents from supervised brushing with study treatment
Visit 8 – Week 24 (Day 168 ± 3)
The following assessments will be conducted in the order written: • Review of concomitant medications, AEs and incidents. • Return of study toothpaste, toothbrush and diary. • Review of completed diary to determine usage compliance. • Confirmation of subject continuance. • Completion of DHEQ Section 1 (Q7-9) & Section 2. • OST and OHT examination. • Evaporative air sensitivity assessment (Schiff Sensitivity Scale, LMS) on two selected test teeth. • Evaporative air sensitivity assessment (Schiff Sensitivity Scale) on remaining eligible teeth from Visit 1. • AEs and incidents will be recorded for 5 days after last treatment.

Type and Planned Number of Subjects

Sufficient subjects will be screened to ensure approximately 112 suitable subjects enter the acclimatisation phase. Approximately 75 eligible subjects will be allocated the study toothpaste in order to ensure that approximately 60 subjects complete the study.

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Diagnosis and Main Criteria for Inclusion

Subjects aged 18-55 years of age, with a minimum of 20 natural teeth and in good general health who suffer from tooth sensitivity. At Screening, subjects must have a minimum of two accessible non adjacent teeth (incisors, canines, or pre-molars) with signs of erosion or abrasion or facial/cervical gingival recession (EAR), with a modified gingival index (MGI) =0 adjacent to the test area and a clinical mobility of ≤1, and with signs of sensitivity measured by qualifying evaporative air assessment. At Baseline subjects must have a minimum of two, non-adjacent accessible teeth (incisors, canines or pre-molars), with signs of sensitivity, measured by an evaporative air assessment (Schiff Sensitivity Score ≥ 2).

Product Information

Treatment Group	Study Product
	Dentifrice containing 0.454% w/w stannous fluoride (1100ppm fluoride) Sensodyne Repair and Protect Daily Repair Toothpaste. German marketplace
MFC	Commercial Product [redacted]
Route of administration	Topical oral use
Dosing Instructions	Subjects will brush with a full brush head of toothpaste for 1 timed minute (in their usual manner), twice daily (morning and evening) from Visit 2-8

Statistical Methods

Mean values ~~and changes from baseline with 95% confidence intervals~~ will be plotted for all measures of DH (DHEQ, Schiff Sensitivity, and LMS (Intensity, Duration, Tolerability, Description) over time. Statistical ~~significance of changes from baseline at each timepoint~~ **EFFECT OVER TIME** will be assessed **USING MIXED EFFECT ANOVA WITH VISIT AND SITE AS FIXED EFFECT, SUBJECT AS RANDOM EFFECT**.

AEs, incidents and OST abnormalities will be listed by treatment.

1. INTRODUCTION

Dentinal hypersensitivity (DH) is described as 'pain derived from exposed dentine in response to chemical, thermal, tactile, or osmotic stimuli which can't be explained as arising from any other dental defect or pathology' [Addy, 1985, 2000]. The definition was later revised to replace the word 'pathology' with 'disease' to avoid confusion with pain originating from other dental conditions [Canadian Advisory Board, 2003]. DH originates from aetiologic factors such as gingival recession, erosion and/or abrasion, which result in loss of enamel or cementum and subsequent exposure of the underlying dentine with patent dentinal tubules [Orchardson, 1987]. Brännström's hydrodynamic theory of DH hypothesizes that the movement of fluid within the tubules when a stimulus is applied to the dentine, stimulates the nerve processes in the pulpal area of the dentine to transmit a pain impulse [Brannstrom, 1964; Hall, 2000].

Currently there are two approaches to the management of DH;

- nerve depolarisation (physiological action);
- dentinal tubule occlusion (physical action).

Nerve depolarising agents, such as potassium nitrate, generally require a period of use (for example, 14 to 28 days) before their benefit is established. The delivery of potassium ions to the dentine-pulp junction (odontoblastic layer) via dentinal tubules is believed to result in depolarisation of the afferent nerve membrane thereby blocking the pain response [Orchardson, 1975]. The second approach uses tubule occluding agents which physically block the exposed ends of the dentinal tubules, thus reducing dentinal fluid movement and pulpal irritation. Tubule occluding agents such as strontium salts, stannous salts, bioglasses or silicas serve to seal or block the dentine tubules, and thereby reduce the effect of external stimuli. Tubular occlusion can be favoured over nerve depolarisation primarily due to the more rapid onset of relief from DH which can be associated with the occlusion approach [Gillam, 2006].

Stannous fluoride has been incorporated into oral hygiene products indicated for the reduction of DH since the 1960s [Schiff, 2006a]. Its long-term efficacy has been reported in a number of published studies [Schiff, 2000a, 2000b, 2006b; Sharma, 2010, 2012; Chaknis, 2011; Du, 2011; Ni, 2011; Parkinson, 2013] with a few studies reporting short term efficacy also [He, 2011; Sharma, 2011].

With the growing acknowledgment of the value of the information gleaned directly from the subject, self-reported outcome measures have become increasingly important barometers of the benefit of clinical interventions. These are increasingly

used in dentistry to capture the psychosocial experiences of, for example, pain, discomfort and malfunctioning [Jokovic, 2002]. Broad, multidimensional quality of life measures such as the Oral Health Impact Profile (OHIP) are commonly used [Slade, 1994, 1997]. Use of the OHIP in a study among patients diagnosed with DH attending a group of general practices in Germany reported considerably more impaired oral health related quality of life (OHRQoL) than subjects in the general population indicating that DH is significantly associated with impaired OHRQoL [Bekes, 2009]. Research on OHRQoL commonly uses instruments like the OHIP that are generic for a number of oral health conditions. They cover a broad spectrum of limitations and dysfunctions and may not detect the nuances of a specific condition. The dentine hypersensitivity experience questionnaire (DHEQ) is a validated, condition specific measure of OHRQoL in relation to DH [Boiko, 2010; Baker, 2014; Robinson, 2015]. It has been shown to have good psychometric properties in both the general population and in a clinical sample of DH sufferers. In a pooled analysis of clinical studies conducted by GSK [GSKCH Study RH02026], the DHEQ has shown the significant impact that DH can have on the everyday life of the sufferer (for example, 70.4% of sufferers reported "Having sensations in my teeth takes a lot of the pleasure out of eating and drinking"). The data included in the pooled analysis were primarily generated from studies of 8 week duration. The current study will explore the impact of long term management of DH by daily use of a sensitivity toothpaste on the oral health related quality of life of a population of sensitivity sufferers, over six months, using the DHEQ. The long term clinical efficacy of the study product (a marketed, sensitivity toothpaste containing 0.454% w/w stannous fluoride) for the relief of DH has been previously demonstrated in two, 8 week randomised, controlled clinical studies [GSKCH Study RH01685; Parkinson, 2013].

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To monitor the impact of long term management of DH over a 24 week period, with twice daily use of a sensitivity toothpaste, on the oral health related quality of life in sensitivity sufferers, as measured by the DHEQ.	Change from baseline in DHEQ endpoints over time.
Exploratory	
To evaluate changes in dentine hypersensitivity over the 24 week treatment period, including the number of sensitive teeth, as measured by Schiff Sensitivity Score to assess examiner performance on this measure.	Mean Schiff Sensitivity Score for all timepoints. Change from baseline in Schiff sensitivity score (two test teeth) for all timepoints. Change from baseline in Schiff sensitivity score (all qualifying teeth) for all timepoints.
To evaluate changes in dentine hypersensitivity over the 24 week treatment period, as measured by Labelled Magnitude Scales (LMS).	At each time point the mean LMS (of each of 4 VAS scales) and change from baseline (for the two test teeth) and will be calculated.

3. STUDY PLAN

3.1. Study Design

Overall Design
This ~~single centre~~ **MULTI-SITE**, non-comparative design study will be used to monitor the impact of long term management of dentine hypersensitivity with daily use of a sensitivity toothpaste on the quality of life of a population of sensitivity sufferers. Changes in oral health related quality of life will be monitored using the Dentine Hypersensitivity Experience Questionnaire. The study will be conducted in subjects in good general health, with pre-existing self-reported and clinically diagnosed tooth sensitivity at screening.
Visit 1 - Screening Visit

The following assessments will be conducted in the order written:

- Written informed consent.
- Review of the oral care products the subject is currently using to confirm they do not contain any ingredients intended for treating sensitive teeth.
- Demographics, concomitant medications and medical history.
- Oral examination including an oral soft tissue (OST) examination and assessments to determine eligible teeth.
- Qualifying evaporative air sensitivity.
- Inclusion/exclusion criteria review.
- Confirmation of subject eligibility.
- Dispensation of acclimatisation toothpaste, toothbrush, diary, and timer.
- Supervised brushing with acclimatisation toothpaste.
- Adverse Events (AEs) and incidents will be documented from completion of the supervised brushing with acclimatisation toothpaste.

Visit 2 - Baseline Visit (Day 0)

The following assessments will be conducted in the order written:

- Review of concomitant medications and AEs.
- Return of acclimatisation toothpaste, toothbrush and diary.
- Review of completed diary to determine usage compliance.
- Inclusion/exclusion criteria review.
- Confirmation of subject eligibility and continuance.
- Completion of DHEQ Section 1 and Section 2.
- LMS Training Exercise
- OST examination.
- Evaporative air sensitivity assessment (Schiff Sensitivity Scale, LMS) on all eligible teeth from Visit 1.
- Selection of two test teeth.
- Dispensation of study toothpaste, toothbrush and diary.
- Supervised brushing with study treatment.
- Incidents from supervised brushing with study treatment

Visit 3 - Week 4 (Day 28 ± 3) **Visit 4 – Week 8 (Day 56 ± 3)** **Visit 5 – Week 12 (Day 84 ± 3)** **Visit 6 – Week 16 (Day 112 ± 3)** **Visit 7 – Week 20 (Day 140 ± 3)**
The following assessments will be conducted in the order written: • Review of concomitant medications, AEs and incidents. • Return of study toothpaste and diary. New toothbrush at Week 12. • Review of completed diary to determine usage compliance. • Confirmation of subject continuance. • Completion of DHEQ Section 1 (Q7-9) & Section 2. • OST examination. • Evaporative air sensitivity assessment (Schiff Sensitivity Scale, LMS) on two test teeth. • Evaporative air sensitivity assessment (Schiff Sensitivity Scale) on remaining eligible teeth from Visit 1. • Dispensation of study toothpaste and diary (and toothbrush at Visit 5). • Supervised brushing with study treatment. • Incidents from supervised brushing with study treatment
Visit 8 – Week 24 (Day 168 ± 3)
The following assessments will be conducted in the order written: • Review of concomitant medications, AEs and incidents. • Return of study toothpaste, toothbrush and diary. • Review of completed diary to determine usage compliance. • Confirmation of subject continuance. • Completion of DHEQ Section 1 (Q7-9) & Section 2. • OST examination. • Evaporative air sensitivity assessment (Schiff Sensitivity Scale, LMS) on two selected test teeth. • Evaporative air sensitivity assessment (Schiff Sensitivity Scale) on remaining eligible teeth from Visit 1. • AEs and incidents will be recorded for 5 days after last treatment.

3.2. Subject Restrictions

Lifestyle/ Dietary
For the duration of the study (Screening – Week 24): • Eligible subjects will be asked to stop using their regular oral care products from Screening for the duration of the study. Subjects will not be permitted to use any other oral care products (i.e., oral rinses, tongue cleaners, whitening/bleaching

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products) than those provided to them. Subjects will not be permitted to use any dental products, including home remedies, intended for treating sensitive teeth.
- Subjects will be permitted to use dental floss for the removal of impacted food only.
- Subjects will not be permitted to chew gum.

Prior to study visits: (Baseline-Week 24)
- In order to standardize oral hygiene practices, subjects will be asked to refrain from all oral hygiene procedures for **at least 8 hours**, and from eating and drinking for **at least 4 hours**, prior to their scheduled Baseline and Week 4 to Week 24 visits. Within four hours of the visit (but not within one hour of the visit), small sips of room-temperature water will be permitted to take medications and relieve thirst.
- Subjects will be requested to refrain from excessive alcohol consumption **for 24 hours** prior to the Baseline and all subsequent visits. If, in the opinion of the Investigator, the subject has consumed an excessive amount of alcohol prior to a visit, every effort will be made to reappoint them to the next day. If this is not possible, the subject should be treated as per section 4.4.

Medications and Treatments

For the duration of the study (screening – last visit):
- If concomitant medications and traditional herbal ingredients/treatments are used during the study, their identity, as well as their dosage and frequency, start and stop dates must be recorded in the CRF.
- Should a subject take an analgesic **within 8 hours** of a scheduled visit, every effort will be made to reappoint them to the next day. If this is not possible, the subject should be treated as per section 4.4.
- Subjects who enter the study will be requested to delay having any non-emergency, elective dental treatment until after study completion (including dental prophylaxis).

3.3. Type and Planned Number of Subjects

Approximately 200 subjects will be screened to ensure approximately 112 suitable subjects enter the acclimatisation phase. Approximately 75 eligible subjects will be allocated the study toothpaste in order to ensure that approximately 60 subjects complete the study.

Subjects will be recruited by the CRO, primarily from their volunteer database. Subjects may also be recruited via advertisements placed in the local press, by use of leaflets and posters or by word of mouth.

3.4. Study Design and Dose Justification

The current study will explore the impact of long term management of DH with daily use of a sensitivity toothpaste on the quality of life of a population of sensitivity sufferers, using the DHEQ. Changes in DH will also be monitored clinically over the 24 week treatment period.

A non-comparative, monadic study design has been selected as appropriate to achieve the aims of this research. The inclusion of a control or comparator treatment is not considered necessary to meet the objectives of the study (which is to monitor To monitor the impact of long term management of DH over a 24 week period, with twice daily use of a sensitivity toothpaste, on the oral health related quality of life in sensitivity sufferers, as measured by the DHEQ). All subjects will use the same sensitivity toothpaste (a clinically proven 0.454% w/w stannous fluoride formulation [GSKCH Study RH01685; Parkinson, 2013] for the duration of the 24 week study period.

The anti-sensitivity efficacy of toothpastes containing 0.454% w/w stannous fluoride has been established in a number of published studies [for example Schiff, 2000a, 2000b, 2006a; Pradeep, 2010; Sharma, 2010; Chaknis, 2011; Du, 2011; Ni, 2011; Parkinson, 2013]; and will not be investigated further here. The study toothpaste contains 0.454% stannous fluoride and will be provided in commercial tubes, overwrapped to mask its identity. The dosage regimen of twice daily brushing (morning and evening) will be the same for all subjects, and has been selected based on dental health care professionals (DHCP) recommended practice.

It is anticipated that DH symptoms will decrease over the 24 week study period with daily use of a clinically proven, sensitivity toothpaste. A validated, condition specific measure of oral health-related quality of life for DH (Dentine Hypersensitivity Experience Questionnaire (DHEQ) [Boiko, 2010; Baker, 2014] will be completed by the subjects at Baseline and 4, 8, 12, 16, 20 and 24 weeks to monitor the impact of a reduction in DH on everyday life. The DHEQ (48 item) has been shown to have good psychometric properties in both the general population, and in DH sufferers [Boiko, 2010; Baker, 2014].

An evaporative air stimulus will be administered using a dental air syringe. Response to this stimulus will be evaluated using

- Schiff Sensitivity Scale [Schiff, 1994]: This is an examiner assessment of the subject's response to an evaporative air stimulus. It is scored immediately following the stimulus and focuses on a combination of specific, observable, physical, behavioural and verbal responses from the subject as a result of the

stimulation of exposed dentine, rather than solely an oral request from the subject to discontinue stimulation and may facilitate discrimination.

- Labelled Magnitude Scales (LMS) [Heaton, 2013]: These are completed by the subject following the evaporative stimulus (on a tooth by tooth basis) and apply psychophysical procedures (magnitude estimation and cross-modality magnitude matching) to condition specific descriptive words relevant to the subject's response. The descriptive words are then aligned along a Visual Analogue Scale (VAS) at distances that reflect the psychological distances between words. These scales have been piloted and validated in a previously reported dentine hypersensitivity trial.

The selection of two 'test teeth' to evaluate changes in DH is common practice in sensitivity studies [Docimo, 2009]. The sensitivity of the remaining teeth that qualified following assessments of EAR, MGI and tooth mobility at Screening will also be assessed at Baseline and 4, 8, 12, 16, 20 and 24 weeks.

The dosage regimen of twice daily usage (morning and evening) for 1 timed minute will be the same for all subjects, and has been selected based on widely recommended oral hygiene practice, and typical consumer habit.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Safety Statement.

Deviations from inclusion and exclusion criteria are not allowed as they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. CONSENT
Demonstrates understanding of the study and willingness to participate as evidenced

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by voluntary written informed consent and has received a signed and dated copy of the informed consent form.

2. AGE
Aged 18-55 years.

3. GENERAL HEALTH
Good general and mental health with, in the opinion of the investigator or medically qualified designee: a) No clinically significant and relevant abnormalities of medical history or oral examination. b) Absence of any condition that would impact on the subject's safety or wellbeing or affect the individual's ability to understand and follow study procedures and requirements.

4. COMPLIANCE
Understands and is willing, able and likely to comply with all study procedures and restrictions.

5. DENTAL HEALTH
At Visit 1 (Screening): a) Self-reported history of dentinal hypersensitivity (DH) lasting more than six months but not more than 10 years. b) Minimum of 20 natural teeth. c) Minimum of 2 accessible non-adjacent teeth (incisors, canines, pre-molars), preferably in different quadrants, that meet all of the following criteria: – Signs of facial/cervical gingival recession and/or signs of erosion or abrasion (EAR). – Tooth with MGI score =0 adjacent to the test area (exposed dentine) only [Lobene, 1986] and a clinical mobility of ≤1 – Tooth with signs of sensitivity measured by qualifying evaporative air assessment (Y/N response) ***At Visit 2 (Baseline):*** d) Minimum of two, non-adjacent accessible teeth (incisors, canines, pre-molars), that meet all of the following criteria: – with signs of sensitivity, measured by a qualifying evaporative air assessment (Schiff Sensitivity Score ≥ 2) Note: All teeth which meet the EAR, GI and mobility inclusion criteria and none of the dentition exclusion criteria at Screening should be assessed by

evaporative air stimulus at Baseline. *Test Teeth* should not be adjacent to each other and preferably in different quadrants.

4.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. PREGNANCY
Women who are known to be pregnant or who are intending to become pregnant over the duration of the study.

2. BREAST-FEEDING
Women who are breast-feeding

3. ALLERGY/ INTOLERANCE
Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.

4. CLINICAL STUDY/ EXPERMENTAL PRODUCT
a) Participation in another clinical study (including cosmetic studies) or receipt of an investigational drug within 30 days of the screening visit. b) Previous participation in this study.

5. SUBSTANCE ABUSE
Recent history (within the last year) of alcohol or other substance abuse.

6. PERSONNEL
An employee of the sponsor or the study site or members of their immediate family.

7. DISEASE
a) Presence of chronic debilitating disease which, in the opinion of the investigator, could affect study outcomes. b) Any condition which, in the opinion of the investigator, causes xerostomia.

8. GENERAL DENTITION EXCLUSIONS
a) Dental prophylaxis within 4 weeks of Screening. b) Tongue or lip piercing or presence of dental implants. c) Desensitizing treatment within 8 weeks of Screening (professional sensitivity treatments and non-dentifrice sensitivity treatments). d) Gross periodontal disease, treatment of periodontal disease (including surgery)

within 12 months of Screening, scaling or root planning within 3 months of Screening.

e) Teeth bleaching within 8 weeks of Screening.

9. SPECIFIC DENTITION EXCLUSIONS FOR *TEST TEETH*

a) Tooth with evidence of current or recent caries, or reported treatment of decay within 12 months of Screening.

b) Tooth with exposed dentine but with deep, defective or facial restorations, teeth used as abutments for fixed or removable partial dentures, teeth with full crowns or veneers, orthodontic bands or cracked enamel. Sensitive teeth with contributing aetiologies other than erosion, abrasion or recession of exposed dentine.

c) Sensitive tooth not expected to respond to treatment with an over-the-counter dentifrice in the opinion of the investigator.

10. PRODUCT USE

Use of an oral care product indicated for the relief of dentine hypersensitivity within 8 weeks of screening (subjects will be required to bring their current oral care products to the site in order to verify the absence of known anti-sensitivity ingredients).

11. CONCOMITANT MEDICATION

a) Daily doses of medication/treatments which, in the opinion of the investigator, could interfere with the perception of pain. Examples of such medications include analgesics, anticonvulsants, antihistamines that cause marked or moderate sedation, sedatives, tranquilisers, anti-depressants, mood-altering and anti-inflammatory drugs.

b) Currently taking antibiotics or has taken antibiotics within 2 weeks of Baseline.

c) Daily dose of a medication which, in the opinion of the investigator, is causing xerostomia.

12. OTHER

Any subject who, in the judgment of the investigator, should not participate in the study.

4.3. Screening/ Baseline Failures

Screen failures are defined as subjects who consent to participate in the study but are never subsequently provided with study product at the Baseline visit. In order to

ensure transparent reporting of screen failure subjects, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events. Re-screening of subjects will not be allowed in this study.

4.4. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. Where applicable, if a subject withdraws or is withdrawn from the study, all human biological samples collected before they exited the study will be analysed and reported unless the subject requests otherwise. A subject may request for their human biological samples to be destroyed. In these cases, the investigator must document this in the site study records and the samples should not be used for any further research.

If the reason for removal of a subject from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the electronic case report form (CRF). If a subject is withdrawn from the study because of a product limiting AE, thorough efforts should be clearly made to document the outcome. Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilizes, is otherwise explained, or the subject is lost to follow-up.

Should a subject take an analgesic medication within 8 hours of a treatment visit, or should any other factor, in the opinion of the investigator, be thought to affect study outcomes (e.g. excessive alcohol consumption), the following actions must be taken

- Baseline visit: every attempt will be made to reschedule the subject, if they cannot be reappointed they will be withdrawn from the study. No clinical efficacy measures will be performed.
- Week 4, Week 8, Week 12, Week 16, Week 20 visit: every attempt will be made to reschedule the subject. If they cannot be reappointed they will continue in the study with all procedures other than clinical efficacy measures completed. The subject will not be withdrawn.
- Week 24 visit: every attempt will be made to reschedule the subject, if they cannot be reappointed they achieve study conclusion with all procedures other than clinical efficacy measures completed. The subject should not be replaced.

SHOULD A SUBJECT TAKE ANTIBIOTIC MEDICATION TWO WEEKS PRIOR TO A TREATMENT VISIT, THE FOLLOWING ACTIONS MUST BE TAKEN

- **BASELINE VISIT: EVERY ATTEMPT WILL BE MADE TO RESCHEDULE THE SUBJECT, IF THEY CANNOT BE REAPPOINTED THEY WILL BE WITHDRAWN FROM THE STUDY. NO CLINICAL EFFICACY MEASURES WILL BE PERFORMED.**

- **WEEK 4, WEEK 8, WEEK 12, WEEK 16, WEEK 20 VISIT: EVERY ATTEMPT WILL BE MADE TO RESCHEDULE THE SUBJECT WITHIN THE 3 DAY VISIT WINDOW. IF THEY CANNOT BE REAPPOINTED THEY WILL CONTINUE IN THE STUDY WITH ALL PROCEDURES OTHER THAN CLINICAL EFFICACY MEASURES COMPLETED. THE SUBJECT WILL NOT BE WITHDRAWN.**

- **WEEK 24 VISIT: EVERY ATTEMPT WILL BE MADE TO RESCHEDULE THE SUBJECT, IF THEY CANNOT BE REAPPOINTED WITHIN THE 3 DAY VISIT WINDOW THEY ACHIEVE STUDY CONCLUSION WITH ALL PROCEDURES OTHER THAN CLINICAL EFFICACY MEASURES COMPLETED. THE SUBJECT SHOULD NOT BE REPLACED.**

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, at least 2 telephone calls). The contact attempt should be documented in the subject's record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

4.5. Subject Replacement

Subjects who withdraw from the study post allocation of study product will not be replaced.

4.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study. The end of the study is defined as the date of the last subject's last visit.

5. PRODUCT INFORMATION

5.1. Study Product

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

Treatment Group	Study Product
	Dentifrice containing 0.454% w/w stannous fluoride (1100ppm fluoride) Sensodyne Repair and Protect Daily Repair Toothpaste. German marketplace
MFC	Commercial Product CCI [redacted]
Route of administration	Topical oral use
Dosing Instructions	Subjects will brush with a full brush head of toothpaste for 1 timed minute (in their usual manner), twice daily (morning and evening) from Visit 2-8

Other items to be supplied by the Clinical Supplies Department, GSKCH:

Name of Item	Purpose
Signal® Family Protection toothpaste containing 1450 ppm fluoride as sodium monofluorophosphate (SMFP), (UK market place product)	Acclimatisation product - to standardise oral hygiene practice prior to Visit 2
Aquafresh Clean Control (Everyday Clean) toothbrushes (UK market place product)	Toothpaste application by tooth brushing

® Signal is a registered trademark of Unilever plc.

Countdown timers	To ensure accurate brushing duration

The subject diary will be supplied by the clinical site.

5.2. Dose Schedule

For both the acclimatisation and study toothpaste, the subjects will apply a full brush head of the toothpaste and brush for one timed minute in their usual manner twice daily (morning and evening).

5.3. Dose Modification

No dose modification is permitted in this study.

5.4. Product Compliance

Diaries will be used throughout the study to a) allow the subject to familiarize themselves with their completion during the acclimatisation phase and b) promote compliance during the treatment phase. Subjects will not be excluded due to missed brushings but will be reminded to use the products supplied as per the instructions provided and to complete the diary after each product usage to encourage compliance.

Study site staff will review the diaries at the start of each visit for compliance and any reports of changes/new medications.

5.5. Precautions

No special precautions are necessary provided the study is carried out in accordance with this protocol.

5.6. Overdose

An overdose is a deliberate or inadvertent administration of a product at a dose higher than specified in the protocol.

Overdose is not likely to occur in this study. Limited quantities of the product will be supplied, and closely monitored by the site for each subject.

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

5.7. Rescue Therapy

No rescue therapy is required in this study.

5.8. Product Assignment

All eligible subjects at Visit 2 will be provided with the same study product.

5.8.1 Randomisation

There is no randomisation in this study. All subjects eligible at Visit 2 will be provided with the same study product.

5.8.2 Blinding

The subject is blinded to the identity of the study toothpaste (they will not be aware of the brand name of the toothpaste they are using). The packaging will be overwrapped as detailed below. Neither the study staff nor the sponsor are blinded.

5.9. Packaging and Labelling

The acclimatisation product (Signal Family Protection Toothpaste) will be sourced from the UK market and supplied in its commercial tube (no overwrapping) with a study label affixed. Each subject will receive a sufficient number of tubes to cover usage during the acclimatisation phase.

The study toothpaste will be sourced from the German market. The tubes will be overwrapped in white vinyl to obscure any branding on the commercial tube pack. Each subject will receive a carton containing sufficient number of tubes to cover usage during each 4 week visit. Each tube and carton will have a study label affixed. The contents of the label will be in accordance with all applicable regulatory requirements (including the device precautionary statement 'Exclusively For Clinical Investigation)' and will be the responsibility of the Clinical Supplies Department, GSKCH. Re-dispensing of product will occur at each treatment visit (Visit 3 – Visit 7). At Visit 2 and 5 a new toothbrush will be dispensed to each subject.

All sundry items will be supplied in their commercial packaging.

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

5.9.1. Accountability of Product

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

The investigator or designee will maintain a full record of study product accountability. A Product Dispensing Log must be kept current and will contain the following information:

- The identification of the subject to whom the study product was dispensed.
- The date(s) and quantity of the study product dispensed to the subject.
- The date(s) and quantity of the study product returned by the subject (if applicable).

The inventory must be available for inspection by the study monitor during the study. At the end of the study, study product supplies will be verified by the monitor. Study product supplies will then be either collected by the study monitor or returned by the investigator or designee to the GSKCH Clinical Supplies Department or designated vendor.

5.9.2. Storage of Product

Study product supplies must be stored in compliance with the label requirements in a secure place with limited or controlled access.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Schedule of Events section.

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

6.1. Visit 1 - Screening Visit

6.1.1 Telephone Screening

Prior to the screening visit, telephone screening of interested subjects will be conducted using a telephone script. This will be conducted by the site recruitment staff or designee.

6.1.2. Informed Consent

The investigator, or designee, must obtain written (signed and dated by the subject) informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent will be provided by the investigator or by GSKCH. The investigator, or designee, should sign and date the consent form to confirm that the consent process was completed correctly. The subject will be provided with a copy of their signed and dated consent form and any other written information which they should be instructed to retain.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Subjects should be provided with a copy of the signed and dated amended consent form. The date of consent will be recorded on the CRF.

6.1.3. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, gender, ethnicity and race.

6.1.4. Medical History and Concomitant Medication

Medical history will be assessed as related to the inclusion/exclusion criteria by the Investigator or medically qualified designee. Details of any relevant medical or surgical history (within the last year), including allergies or drug sensitivity, will be recorded on the CRF. Any concomitant therapy taken in the 30 days prior to the Screening Visit and throughout the study will also be recorded.

6.1.5. Oral Hard Tissue (OHT) Examination

The dentist will perform a visual examination of the oral hard tissue to confirm that the subject has a minimum of 20 natural teeth and to evaluate the dentition for exclusions.

6.1.6. Oral Soft Tissue (OST) Examination

Where possible, this procedure should be conducted by a single trained dental examiner. The examination will be accomplished by direct observation and palpation with retraction aids as appropriate. The examiner will include examination of the Labial Mucosa (including lips), Buccal Mucosa, Mucogingival folds, Gingival

Mucosa, Hard Palate, Soft Palate, Tonsilar Area, Pharyngeal Area, Tongue, Sublingual Area, Submandibular Area and Salivary Glands. The results of the examination will be recorded in the CRF as either normal or abnormal with details of any abnormalities. A brief description of any abnormality observed by the examiner or reported by the subject at the application site following the administration of the acclimatisation or treatment toothpastes will be recorded as an AE.

An OST examination will be conducted at every study visit prior to any clinical assessments. While it is preferable to use the same OST examiner throughout the study, to facilitate subject flow, OST examinations may be carried out by different examiners.

6.1.7. Eligible Tooth Assessment

Eligible tooth assessment will include an oral hard tissue examination (visual assessment only to evaluate dentition exclusions - see Exclusion Criteria 8 and 9); erosion, abrasion and/or gingival recession; modified gingival index; tooth mobility and qualifying evaporative air assessment. Assessments will be carried out by the Investigator or medically qualified designee against the inclusion/exclusion criteria and recorded in the CRF.

6.1.7.1. Erosion, Abrasion and Recession (EAR) assessment

The presence of cervical erosion, abrasion and/or gingival recession [Addy, 2000] will be determined on the facial surfaces of individual teeth. Teeth exhibiting EAR will be assessed to ensure they do not meet any of the general dentition exclusion criteria and the specific dentition exclusion criteria for test teeth (see Exclusion Criteria 8 and 9).

6.1.7.2. Modified Gingival Index (MGI)Assessment

The MGI is a non-invasive visual evaluation of gingival health [Lobene, 1986] scored on a scale of 0-4. MGI will be assessed for the facial gingiva adjacent to the test area (exposed dentine) only of teeth exhibiting facial cervical erosion, abrasion and/or recession at the Screening visit. MGI = 0 is required for eligible teeth.

Score	Description
0	Absence of inflammation
1	mild inflammation; slight change in color, little change in color; little change in texture of any portion of the marginal or papillary gingival unit.
2	mild inflammation; criteria as above but involving the entire marginal or papillar gingival unit.

3	moderate inflammation; glazing, redness, edema, and/or hypertrophy of the marginal or papillary gingival unit.
4	severe inflammation; marked redness, edema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

6.1.7.3. Tooth Mobility Assessment

The clinical mobility assessment will only be performed on teeth exhibiting facial cervical erosion, abrasion and/or recession and that have a MGI = 0. Clinical mobility will be classified in the following way (based on a modification to the Miller Index) [Laster, 1975] and the degree of mobility will be recorded. A clinical mobility of ≤1 is required for eligible teeth.

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

6.1.7.4. Qualifying Evaporative air Sensitivity

The screening dentist will assess sensitivity by a simple air blast on the facial surface of all teeth that meet the EAR, MGI and mobility criteria. This assessment is made by directing a one second application of air from a standard dental syringe perpendicular to the tooth surface approximately 1- 2 mm coronal to the free gingival margin and from a distance of approximately 1cm. Following the air blast, the dentist will ask the subject if they experienced sensitivity. In order to qualify, the subject should confirm they experienced sensitivity and a simple "yes/no" response will be recorded.

6.2. Visit 2 to Visit 8

6.2.1. Dentine Hyersensitivity Experience Questionnaire (DHEQ)

The DHEQ (Appendix 2) will be completed by the subjects at Visit 2 (Baseline) and Visits 3 - 8 (Week 24), prior to any clinical assessments (including OST assessment). Section 1 asks questions about "your sensitive teeth and the impact it has on your everyday life". Section 2 asks questions about "the ways in which the sensations in your teeth affect you in your daily life", and is grouped into domains as follows.

- Restrictions (Section 2, Q1-4)
- Adaptation (Section 2, Q5-16)

- Social Impact (Section 2, Q17-21)
- Emotional Impact (Section 2, Q22-29)
- Identity (Section 2, Q30-34)

Visit	DHEQ questions to be answered by subjects	
Visit 2	Section 1: All questions, Q1-9	Section 2: All questions, Q1-39
Visit 3-8	Section 1: Q7-9	Section 2: All questions Q1-39

THE SITE WILL CHECK AND CROSS REFERENCE THE SUBJECT'S RESPONSE TO DHEQ SECTION 1 QUESTION 2, AT VISIT 2 (BASELINE), WITH THE INCLUSION CRITERIA 5(A) BEFORE THE SUBJECT LEAVES THE STUDY SITE, AND CLARIFY ANY DISCREPANCY WITH THE SUBJECT IF NECESSARY.

6.2.2 Labelled Magnitude Scales (LMS) Training Exercise

At Baseline (Visit 2), eligible subjects will be given instructions on how to use the LMS and asked to complete the LMS training exercise. The investigator or designee will determine whether or not the subject understands how to use the LMS. Investigator instructions for administrating and interpreting the LMS training exercise can be found in Appendix 3. Subject instructions for completing the LMS training exercise can also be found in Appendix 3. The data from this exercise are for training purposes only and will not be recorded in the CRF.

6.2.3. Oral Soft Tissue (OST) Examination

Complete as described in Section 6.1.6.

6.2.4. Evaporative Air Sensitivity Assessments

This assessment will be conducted by a single examiner for all subjects at each visit by directing a maximum one second application of air from a dental air syringe to the exposed dentine surface from a distance of approximately 1 cm. The examiner should take appropriate measures to isolate the test tooth surface in order to prevent stimulus exposure to adjacent tooth or surrounding soft tissue.

At Baseline, the examiner will assess the evaporative air sensitivity of all clinically eligible teeth identified at Screening (teeth that qualified on EAR, MGI and tooth mobility criteria, and had none of the dentition exclusions), using the Schiff

Sensitivity Scale and LMS (Appendix 4). Two test teeth will be selected according to specific eligibility criteria in an individual subject.

At Week 4, 8, 12, 16, 20 and 24 visits the examiner will first assess the evaporative air sensitivity of the two identified test teeth from the Baseline visit using the Schiff Sensitivity Scale and LMS. The examiner will then assess the evaporative air sensitivity of the remaining Eligible Teeth from Screening (teeth that qualified on EAR, MGI and tooth mobility criteria, and had none of the dentition exclusions), using the Schiff Sensitivity Scale.

6.2.4.1. Schiff Sensitivity Scale

This is an examiner based index [Schiff, 1994], scored immediately following administration of the evaporative air stimulus. This scale focuses on a combination of specific, observable, physical, behavioural and verbal responses from the subject as a result of the stimulation of exposed dentine, rather than solely an oral request from the subject to discontinue stimulation and may facilitate discrimination. The examiner will indicate the subject's response to the evaporative air stimulus, after the stimulation of each individual tooth, using the Schiff Sensitivity Scale as follows.

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

6.2.4.2. Labelled Magnitude Scales (LMS)

The LMS score should be completed after the Schiff Sensitivity score assessment to avoid examiner bias. The examiner should not use the subjects response to the LMS to guide their Schiff assessment score. These are completed by the subject immediately following the evaporative stimulus and apply psychophysical procedures (magnitude estimation and cross-modality magnitude matching) to condition specific descriptive words relevant to the subject's response [Gracely, 1978]. The descriptive words are then aligned along a VAS at distances that reflect the psychological distances between words. These scales have been piloted and validated in a previously reported dentine hypersensitivity trial [Heaton, 2013]. Subjects will use LMS (see Appendix 3 and 4) to rate the intensity, duration, tolerability and descriptive quality of their response to the evaporative air stimulus, after the

stimulation of each individual tooth, using 100 millimetre (mm) LMS. The study staff will measure the line segment marked-off in mm from ~~left to right~~ **BOTTOM TO TOP** along the line and record this measurement.

6.2.5. Study Conclusion

Subjects will be evaluated to determine if they completed all study procedures or if they were discontinued from the study early. If the subject discontinued at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page of the CRF by selecting one of the options below.

- Subject did not meet study criteria
- Adverse Event
- Lost to Follow Up
- Protocol Violation
- Withdrawal of Consent
- Other

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of an investigational or washout product, whether or not considered related to the investigational or washout 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 an investigational or washout product.

Events meeting AE definition include:
• Any abnormal laboratory test results (if applicable) or other safety assessments, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition(s) detected or diagnosed after study product administration

even though it may have been present prior to the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected 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).

Events NOT meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder/ condition being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition..
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- 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.

7.1.2. Serious Adverse Events

Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

A. Results in death

B. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

C. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient 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.
D. Results in disability/incapacity NOTE: 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 or prevent everyday life functions but do not constitute a substantial disruption.
E. Is a congenital anomaly/birth defect
F. Other Situations • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are 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 or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:
• The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. • The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual

signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

- AEs will be collected from the start of the investigational product and until 5 days following last administration of the study product.
- SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Note: An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality:

- The investigator is obligated to assess the relationship between study product and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes (source document) or CRF that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

- AEs will be recorded in the AE section of the CRF.
- Medical conditions recorded by the subject on a diary card or similar document that meet the definition of an AE must also be recorded in the AE section of the CRF, if not previously well-characterized by the investigator in the subject's medical history.
- AEs elicited by the investigator in a standard manner at the study visits should also be recorded in the AE section of the CRF. The investigator or designee must ask the subject the following question during each visit including any follow-up visits: ***"Have you felt unwell, experienced any symptoms or taken any medication (since your last visit) (today) (since your last dose) (since the last session)?"***
- The medically qualified investigator should review adverse events in a timely manner; this review should be documented in writing in the source document or in the CRF.
- After the study is completed at a given site, and the site has received their study data on Compact Discs (CDs), the electronic data collection tool will be removed from the internet to prevent the entry of new data or changes to existing data.

SAE Reporting to GSKCH:

A paper copy of the SAE form provided in the investigator study master file should

be completed as fully as possible.
It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (see section 8.3)
- Criterion for seriousness.

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

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken on study product
- Outcome if known

The SAE form, completed as fully as possible, and SAE fax cover sheet must be faxed or e-mailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax Serious Adverse Events to:
UK: PPD

The GSKCH Study Manager will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Phamacovigilance, the Medical Director responsible for the study and other GSKCH personnel as appropriate via email.

The initial report will be followed up with more information as relevant, or as requested by the GSKCH study manager.

7.5. Follow-up of Adverse Events and Serious Adverse Events

Follow-up of AEs and SAEs:

- After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.
- All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- Investigators are not obliged to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including the death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify GSKCH.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Regulatory and ethics reporting requirements for SAEs:

- The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.
- GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC and investigators.
- Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.
- An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the Investigator Brochure (or safety statement) and will notify the IRB or IEC, if appropriate according to local requirements.

7.6. Definition of and Procedure for Reporting Medical Device Incidents

Medical devices are being provided by GSKCH for use in this study; the medical device in this study is the study toothpaste. GSKCH medical device incidents,

including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator on the CRF throughout the study.

7.6.1. Definition of an Incident

Definition of an Incident:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have lead to the death of a patient or user or of other persons or to a serious deterioration in their state of health.

7.6.2. Reporting of Incidents and Malfunctions

Incident Reporting to GSKCH:

- **All incidents must be reported to GSKCH within 24 hours (or sooner if possible) of the investigator or designee becoming aware of the situation.**
- Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE or an SAE, the appropriate AE CRF page or SAE form will be completed and reported as per the AE and SAE reporting sections.
- The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSKCH. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
- The completed Incident Report Form should be faxed or emailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE pages should be sent together with this report form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will remain with the subject's records.
- The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax the Incident Report Forms to:

UK: PPD

- The GSKCH Study Manager will be responsible for forwarding the Incident Report Form to the Case Management Group, Global Clinical Safety and Pharmacovigilance, the Medical Director responsible for the study and other

GSKCH personnel as appropriate.

- The initial report will be followed up with more information as relevant, or as requested by the GSKCH study manager.

Reporting of Malfunctions to GSKCH:

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

- Notify GSKCH immediately.
- Schedule the subject to return to the site promptly to return the failed device.
- Record any incidents on the CRF and Incident Report Form following instructions given in the section above.
- Return the failed device to the sponsor as soon as possible, including documentation of the details of the failure.

7.6.3. Follow-up of Incidents

Follow-up of Incidents:

During the study:

- All incidents will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

After the study:

- Investigators are not obligated to actively seek reports of incidents in former subjects. However, if the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a GSKCH medical device provided for the study, the investigator will promptly notify GSKCH.

Regulatory and Ethics Reporting Requirements for Incidents:

- The investigator will promptly report all incidents occurring with any GSKCH medical device provided for use in the study within 24 hours. GSKCH has a legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in

clinical studies. Prompt notification of incidents by the investigator to GSKCH is essential in order to meet legal obligations and ethical responsibility towards the safety of subjects.

- The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IEC.

7.7. Collection of Pregnancy Information

7.7.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:

- Pregnancy information will be collected on all pregnancies reported following administration of any investigational product. Information on pregnancy identified during the screening phase and prior to investigational product administration does not need to be collected.

7.7.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:

- The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product . The investigator will record pregnancy information on the appropriate form and submit it to GSKCH within 2 weeks of learning of the subject becoming pregnant. The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to GSKCH. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.
- While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject completed the study and considered by the investigator as possibly related to the investigational product, must be promptly forwarded to GSK.
- While the investigator is not obliged to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous

reporting.

- For non-medicinal or licensed products with no pregnancy warning on the label, use the following text: "There is no requirement for the subject to be withdrawn from the study as a result of the pregnancy. However if they are withdrawn, this should be recorded in the appropriate section of the CRF."

8. DATA MANAGEMENT

For this study subject data will be entered into an electronic case report form, using a GSKCH validated data system.

8.1. Source Documents/ Data

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in the Source Document Designation Form. In some cases the CRF can be used as a source document.

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

8.2. Electronic Case Report Form

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

For each subject who has given informed consent/assent and has been screened, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with applicable GSKCH standards and data cleaning procedures to ensure the integrity of the data e.g. removing errors and inconsistencies in the data.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded in the CRF or as part of the query text.

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

Subject data will be entered into GSKCH defined CRFs and transmitted electronically to GSKCH in a validated (21 CFR Part 11 compliant) web-based electronic data capture system (InFormTM).

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

The CRFs (including queries, query responses and audit trails) will be retained by GSKCH. Site data archived compact discs (CD(s)) prepared by a third party will be sent to the investigator to maintain as the investigator copy following the decommissioning of the study.

8.3. Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance. Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

8.3.1. Data Queries

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

The study monitor at the study site will review the CRFs in accordance with the monitoring plan, and any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data

Management review. Monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction

8.4. Processing Patient Reported Outcomes

Patient reported outcome (PRO) data are collected directly from the subject PRO measures e.g. diary cards, questionnaires etc, and entered into the sponsor's clinical data management system (DMS) by the study site representative. In instances where the PRO data is entered into the DMS by GSKCH, the PROs will be anonymised, and forwarded to GSKCH for entry, as agreed and documented ahead of the study starting. PROs that are source will be retained by the investigator and certified copies will be sent to GSKCH.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded on all PRO's that will be forwarded to GSKCH.

In this study the DHEQ is a PRO. The DHEQ will be completed by the subjects as described in section 6.2.1. A member of the study site staff will enter the data into the CRF.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Sample Size Determination

The sample size is based on DHEQ total Score, restrictions, adaptation, social impact, emotional impact and identity, from a previous study [GSKCH Study RH01897].

A sample size of 60 subjects will have at least 90% power to detect significant changes to week 24 for each of the DHEQ variables, with a significance level (alpha) of 0.05 using a two-sided one-sample t-test. No adjustments for multiple testing have been used. Approximately 75 eligible subjects will be allocated the study toothpaste in order to ensure that approximately 60 subjects complete the study. Sixty subjects will provide reasonable precision on estimates of DHEQ response and clinical DH assessments.

9.2. General Considerations

9.2.1. Definition of Analysis Populations

The Safety population will consist of all subjects who received the study toothpaste.

The intention to treat (ITT) population will be defined as all subjects who received the study toothpaste and have at least one post- baseline DHEQ/clinical assessment.

The per-protocol (PP) population will be defined as all subjects who received the study toothpaste and have at least one post-baseline DHEQ/clinical efficacy assessment and have no protocol violations deemed to affect DHEQ/clinical efficacy assessments during the study. Further details will be provided in the statistical analysis plan (SAP).

Violations deemed to affect DHEQ/clinical efficacy assessments will be identified between the Biostatistician and Medical Director or designee pre analysis.

Analysis of the DHEQ and clinical efficacy measures (Schiff, LMS) will be performed on the ITT population. Analysis on the PP population will also be performed if there is more than 10% difference in the number of subjects between the ITT and PP populations.

9.2.2. Exclusion of Data from Analysis

Any of the following will be considered a protocol violation which may warrant exclusion of data or the subject from efficacy analysis:

- Violation of inclusion or exclusion criteria that are deemed to affect efficacy.
- Medical history which is deemed to affect efficacy.
- Use of prohibited treatment or medication before or during the study, which is felt to affect the assessment of efficacy.
- Treatment non-compliance
- Assessments outside the scheduled time windows
- Protocol deviations captured in CRF.
- Any other reason identified likely to affect efficacy

Protocol violations which warrant exclusion from efficacy analysis will be identified between the statistician and medical director or designee ahead of database lock.

9.2.3. Criteria for Evaluation

DHEQ measures captured in the study will be used evaluate changes in oral health related in quality of life over time. OST abnormalities, incidents and AEs reported in the study will be used for safety evaluations of the study treatments.

9.2.4. Criteria for Assessing Efficacy

There are no formal success criteria in this study however it is expected that statistically significant changes from baseline will be observed for the DHEQ measures, in particular the Total score.

9.2.5. Criteria for Assessing Tolerability

Safety will be assessed with respect to AEs, Incidents and OST abnormalities (oral tolerability).

9.2.6. Handling of Dropouts and Missing Data

No data will be imputed in the case of dropouts or missing data.

9.2.7. Other Issues

An interim analysis is not planned for this study.

9.3. Statistical Methods and Analytical Plan

More details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalisation of the protocol and prior to study unblinding.

Selected raw data will be listed as defined in the SAP.

9.3.1. Demographic and Baseline Characteristics

Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for demographic and baseline data.

9.3.2. Primary Analysis

The following DHEQ endpoints will be analysed:

- Section 1, questions 7, 8 and 9 as separate questions
- Total Score (34 item total from Section 2 questions 1 to 34)
- Domains:
  1. Restrictions (4 item total from Section 2 questions 1 to 4)
  2. Adaptation (12 item total from Section 2 questions 5 to 16)
  3. Social Impact (5 item total from Section 2 questions 17 to 21)
  4. Emotional Impact (8 item total from Section 2 questions 22 to 29)
  5. Identity (5 item total from Section 2 questions 30 to 34)
- Global Oral Health Rating (response to Section 2 question 35)

- Effect on Life Overall (4 item total from Section 2 questions 36 to 39)

ABOVE DHEQ ENDPOINTS WILL BE ANALYSED USING MIXED EFFECT ANOVA WITH VISIT AND SITE AS FIXED EFFECT, SUBJECT AS RANDOM EFFECT. ADJUSTED MEANS WILL BE COMPUTED FOR EACH VISIT. USING THIS MODEL THE POST BASELINE VISITS WILL BE COMPARED TO THE BASELINE VISIT AND DIFFERENCE OF THEIR EFFECT WILL BE COMPUTED ALONG WITH P-VALUES AND 95% CONFIDENCE INTERVALS.

THE VISIT BY SITE INTERACTION WILL BE INVESTIGATED BY INCLUDEING THE VISIT BY SITE INTERACTION TERM.

IF THE VISIT BY SITE INTERACTION TERM IS NOT SIGNIFICANT AT THE 10% LEVEL OF SIGNIFICANCE THEN THIS TERM WILL BE REMOVED FROM THE MODEL.

IF THE VISIT BY SITE INTERACTION TERM IS SIGNIFICANT AT 10% LEVEL OF SIGNIFICANCE THEN THE INTERACTION WILL BE INCLUDED IN THE MODEL AND ALL MODEL ESTIMATES (ADJUSTED MEANS, 95% CI'S ANF P-VALUES) FOR WITHIN AND BETWEEN VISITS WILL BE REPORTED SEPARATELY FOR EACH SITE BASED ON THE RESULTS FROM VISIT BY SITE INTERACTION.

Each of the DHEQ endpoints will be summarised by time point (Baseline, Week 4, 8, 12, 16, 20 and 24) ~~together with changes from baseline~~.

Standard summary measures ~~together with the changes from baseline,~~ 95% CIs and p-values ~~of changes from baseline~~ will be presented. A plot of means of raw scores over time (mean ± standard errors) will also be presented for all measures. **PRESENTATIONS OF ENDPOINT SUMMARIES WILL ALSO BE PERFORMED BY SITE. ~~NO INFERENCES WITHIN SITE WILL BE PROVIDED.~~**

~~P-values will be provided to test for non-zero changes from baseline in all measures.~~ Due to the exploratory nature of the study no correction ~~of~~ **FOR** multiple testing will be performed.

THE ASSUMPTION OF NORMALITY AND HOMOGENEITY OF VARIANCE IN THE ANCOVA MODEL WILL BE INVESTIGATED. VIOLATION OF THESE ASSUMPTIONS MAY BE OVERCOME USING SUITABLE TRANSFORMATION OR PERFORMING A NON-PARAMETRIC TEST (E.G., THE WILCOXON SIGNED-RANK TEST).

9.3.3. Exploratory Analyses

The following exploratory analyses will be conducted.

At each time point the mean Schiff Sensitivity Score (for the two test teeth and all qualifying teeth) and mean LMS scores [each of 4 scales (description, tolerability, description, intensity] as well as the change from baseline will be calculated.

THE MEAN SCHIFF SENSITIVITY (TWO TEST TEETH), MEAN SCHIFF SENSITIVITY (ALL QUALIFYING TEETH) AND MEAN LMS SCORE WILL BE ANALYSED USING THE SAME MODEL MENTIONED AT PRIMARY ANALYSIS AND SIMILAR STATISTICS WILL BE PROVIDED.

THE VISIT BY SITE INTERACTION WILL ALSO BE INVESTIGATED AS PER THE PROCEDURE MENTIONED AT PRIMARY ANALYSIS.

Standard summary measures together with the ~~changes from baseline,~~ 95% CIs and p-values ~~of changes from baseline~~ will be presented. A plot of means of raw scores over time (mean ± standard errors) will also be presented for all ~~measures~~ **VARIABLES**.

~~Due to the exploratory nature of the study no correction of FOR multiple testing will be performed.~~

The percentage of teeth that are sensitive (Schiff sensitivity score >0 of all qualifying teeth from screening (termed 'the qualifying teeth') will be summarised for each timepoint and also plotted over time.

PRESENTATIONS OF ENDPOINT SUMMARIES WILL ALSO BE PERFORMED BY SITE. ~~NO INFERENCES WITHIN SITE WILL BE PROVIDED.~~

THE ASSUMPTION OF NORMALITY AND HOMOGENEITY OF VARIANCE IN THE ANCOVA MODEL WILL BE INVESTIGATED. VIOLATION OF THESE ASSUMPTIONS MAY BE OVERCOME USING SUITABLE TRANSFORMATION OR PERFORMING A NON-PARAMETRIC TEST (E.G., THE WILCOXON SIGNED-RANK TEST).

9.3.4. Safety Analyses

AEs, incidents and OST abnormalities will be listed by treatment and reviewed.

9.3.5. Other Analyses

No further analyses are planned.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IEC for the trial protocol (including amendments), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), investigator brochure/ safety statement (including any updates) and any other written information to be provided to subjects. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also when subsequent amendments to the protocol are made.
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, GSK or designee (i.e. third party vendor) monitors will contact the site prior to the start of

the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

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

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

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

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

10.4. Quality Assurance

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

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

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

10.5. Conditions for Terminating the Study

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

Both GSKCH and the Investigator reserve the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies (if applicable), this can occur at one or more or at all sites.

If the trial is prematurely terminated or suspended for any reason, the investigator site should promptly inform the trial subjects and should assure appropriate therapy/ follow-up for the subjects. Where required by the applicable regulatory requirements, GSKCH should inform the regulatory authority(ies).

In addition:

- If the investigator terminates or suspends a trial without prior agreement of GSKCH, the investigator site should promptly inform the sponsor and the IEC, and should provide the sponsor and the IEC a detailed written explanation of the termination or suspension.
- If the GSKCH terminates or suspends a trial, the investigator should promptly inform the IEC and provide the IEC a detailed written explanation of the termination or suspension.
- If the IEC terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the GSKCH and provide GSKCH with a detailed written explanation of the termination or suspension.

10.6. Records Retention

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

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

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

there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

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

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements (GSKCH recommends that documents be kept for 10 years). The investigator is also required to keep subject identification codes on file for at least 15 years after completion or discontinuation of the study. 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, GSK standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSKCH and the investigator. The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, posting of Information on Publicly Available Clinical Trials Registers and Publication

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

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

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

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

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12. APPENDICES

12.1. Appendix 1 - Abbreviations

Abbreviations

AE	Adverse Event
CD	Compact Disc
CRF	Case Report Form
DH	Dentine Hypersensitivity
DHEQ	Dentine Hypersensitivity Experience Questionnaire
EAR	Erosion, Abrasion, Recession
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GSKCH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ITT	Intention to Treat
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PII	Personally Identifiable Information
LMS	Labelled Magnitude Scales
PP	Per Protocol
ppm	Parts per million
PRO	Patient Reported Outcome
SAE	Serious Adverse Event

12.2. Appendix 2 – DHEQ

Example

Dentine Hypersensitivity Experience Questionnaire

SECTION ONE

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

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

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

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

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

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

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

- [1] ☐ Top front
- [2] ☐ Top back
- [3] ☐ Bottom front
- [4] ☐ Bottom back
- [5] ☐ None

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

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

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

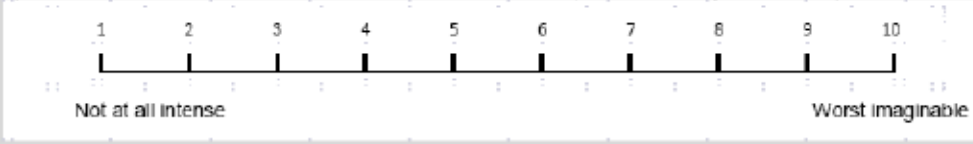
- ☐ Several times a day (7)
- ☐ Once a day (6)
- ☐ Several times a week (5)
- ☐ Once a week (4)
- ☐ Several times a month (3)
- ☐ Once a month (2)
- ☐ Less than once a month (1)
- ☐ Never (0)

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

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

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

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



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

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

Dentine Hypersensitivity Experience Questionnaire

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?	☐	☐	☐	☐	☐

~~12.3. Appendix 3 Instructions for LMS Training Exercise~~

~~Subjects will be given instructions for using the LMS and asked to complete the LMS training exercise form. The investigator or designee should read the instructions aloud while the subject reads along. Subjects will be permitted to ask questions. However, most questions should be answered by rereading the appropriate section of the instructions. The investigator, or designee, will then determine whether the subject understands how to use the LMS based on the line scale training exercise answers and the criteria below.~~

~~Interpretation of the Line Scale Training Exercise~~

~~The objective of this exercise is NOT to determine whether the subject can get the exact answers, but to determine whether they understand the concept. Therefore, the following general criteria are suggested:~~

- ~~Are markings only on the verbal descriptors? If so, provide feedback that they are to use the entire scale, including areas between the descriptors.~~
- ~~Are subjects marking on the same place on all the scales for one stimulus (particularly if the LMS measures are all presented on one page?) If so, make sure subjects understand what each scale is meant to measure (intensity, duration, ability to tolerate, and description) and that stimuli will likely produce different marks on each scale.~~
- ~~The stimuli are presented generally in increasing intensity. Are subjects indicating an increasing intensity across stimuli?~~
- ~~Are subjects marking their ratings with an "X" on the scale? If not (subjects are circling descriptors, making unclear marks, etc.), provide feedback on the use of the correct mark.~~

~~If subjects appear unable to complete each of the LMS scales (intensity, duration, tolerability and description) with the appropriate response (s), the investigator/ designee should talk them through the grading of the first two LMS scenarios, if required. If the marks are generally correctly ordered, but far from their true positions, the investigator/ designee should try to get the subject to verbalize why they placed the marks as they did. However, the investigator/ designee should be careful not to pressure the subject to change their responses. One approach would be for the investigator/ designee to start with an item that the subject did well, ask about that and then continue by asking about an item where they did less well.~~

~~If subjects are not able to provide proper responses to the stimuli questions across all four figure scales, it is unlikely they will provide appropriate responses on the clinical response LMS scales. These subjects should be disqualified.~~

~~**Subject Instructions for LMS Training Exercise (Example)**~~

~~"The purpose of this exercise is to introduce you to the scales you will be using. There are no right or wrong answers.~~

~~Please read each item carefully. Then try to remember or imagine what each sensation feels like. If you haven't had exactly the experience described, try to think of something similar.~~

~~The scales you will be using each have words that can be used to describe different feelings or sensations people have in their mouths. As you think about each sensation, you should think about the word that best describes what that sensation feels like. Then, if appropriate, you can "fine tune" your rating by marking the line between that word and the next word up or down the scale.~~

~~FOR EACH ITEM PLEASE INDICATE HOW YOU WOULD RATE THE FEELING DESCRIBED BY PLACING AN "X" ON THE LINE. YOU MAY MARK ANYWHERE ALONG THE LINE.~~

~~**Please turn to the next page for the first example in this exercise.**~~

Let's start with this example.

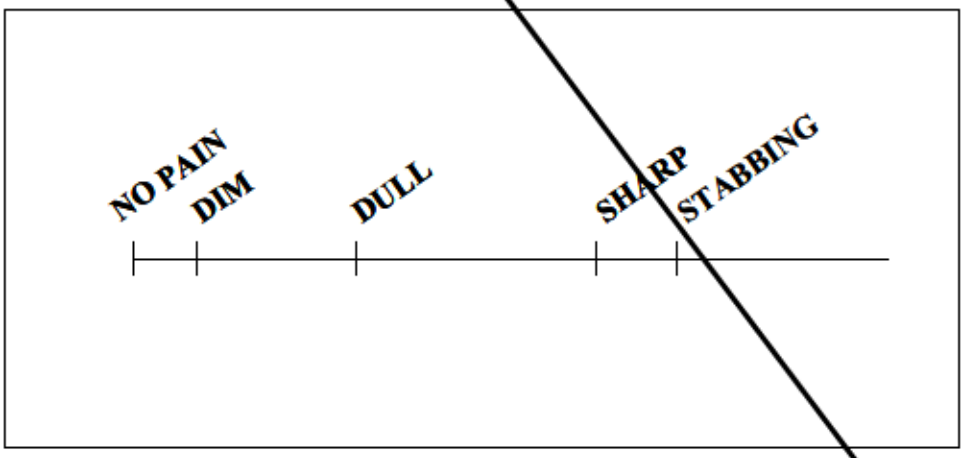
The touch of a pill on your tongue.

Have you ever experienced this feeling or sensation before?

(Please circle one): Yes / No

First please rate the **INTENSITY** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

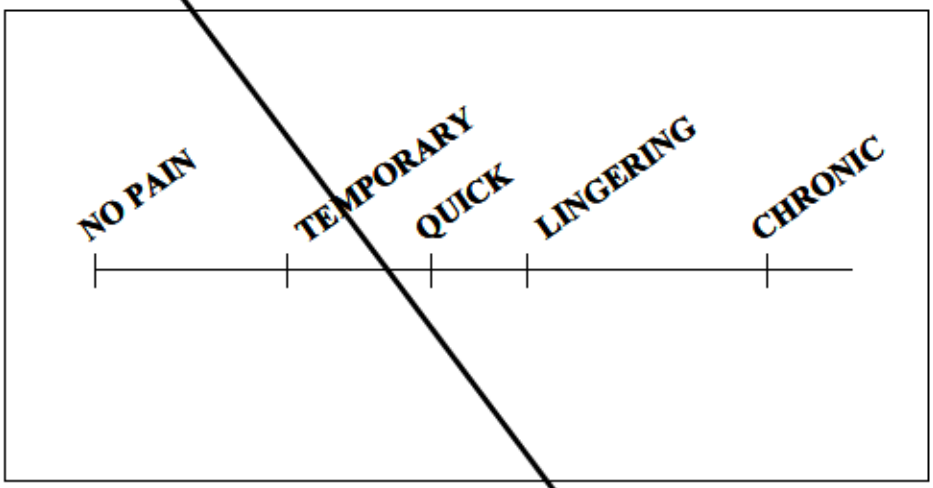


NOT TO SCALE

Please turn to the next page.

Still thinking about **the touch of a pill on your tongue,** please rate the **DURATION** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

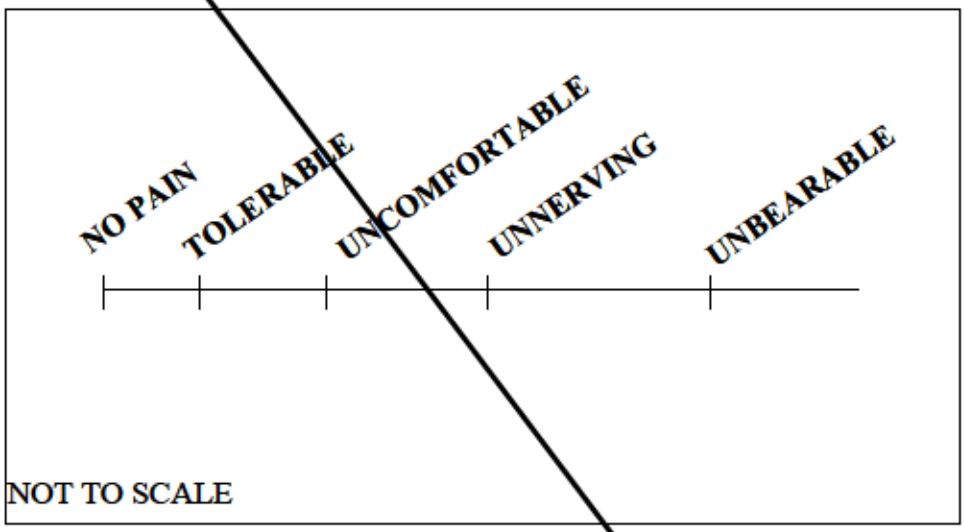


NOT TO SCALE

Please turn to the next page

Still thinking about **the touch of a pill on your tongue,** please rate how much you are able to **TOLERATE** with this feeling or sensation.

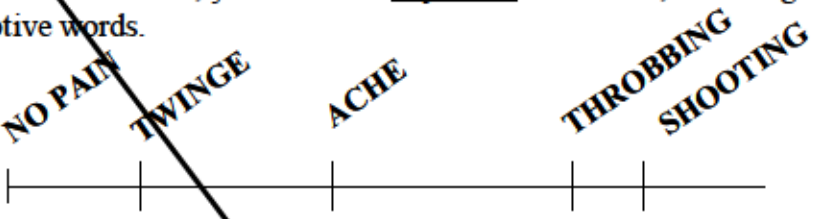
Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark <u>anywhere</u> on the line, including between the descriptive words.



Please turn to the next page.

Finally, thinking about the **the touch of a pill on your tongue**, please give a rating that **DESCRIBES** the kind of feeling or sensation this is.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.



NOT TO SCALE

Please turn to the next page.

Let's try this example.

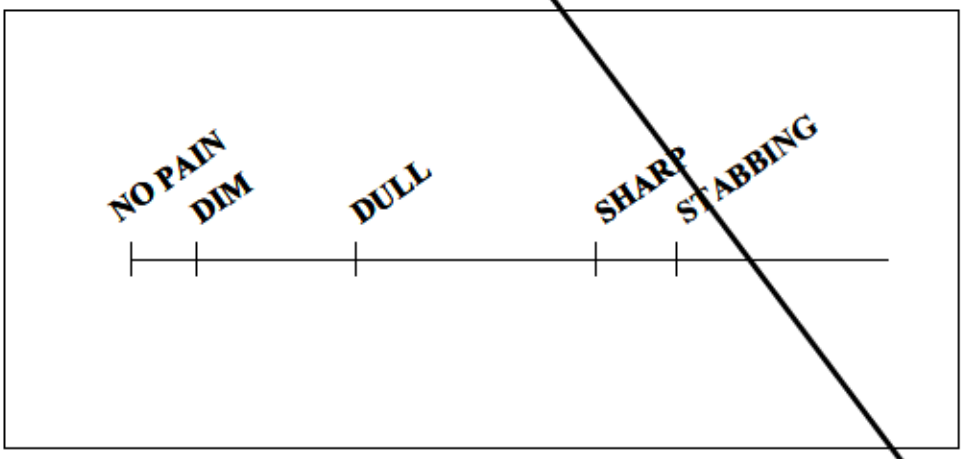
The pain from biting your tongue.

Have you ever experienced this feeling or sensation before?

(Please circle one): Yes / No

First please rate the **INTENSITY** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

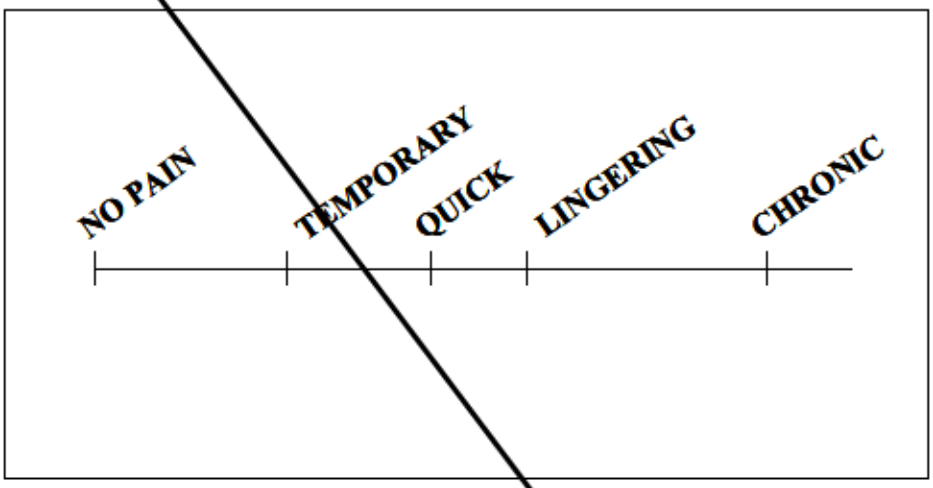


NOT TO SCALE

Please turn to the next page.

Still thinking about **the pain from biting your tongue**, please rate the **DURATION** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

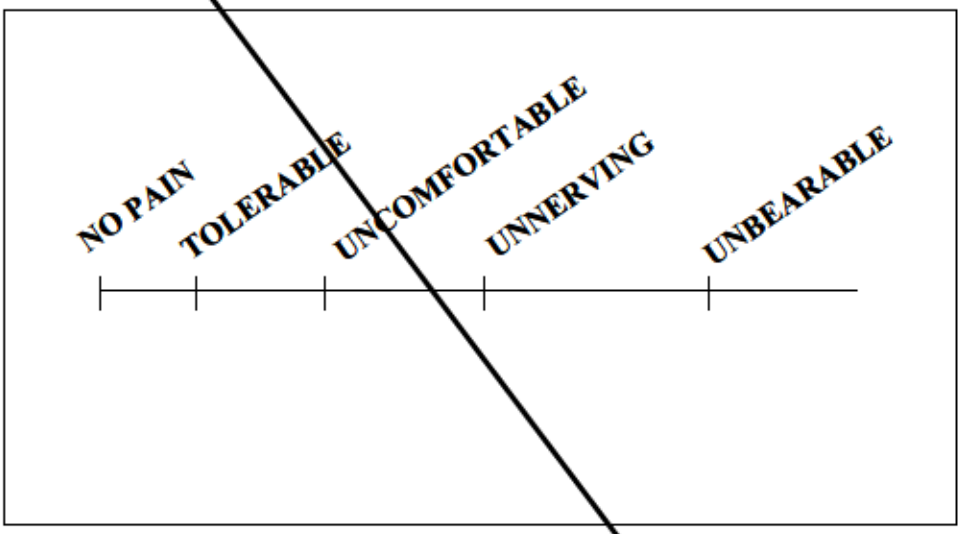


NOT TO SCALE

Please turn to the next page

Still thinking about **the pain from biting your tongue,** please rate how much you are able to **TOLERATE** with this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark <u>anywhere</u> on the line, including between the descriptive words.

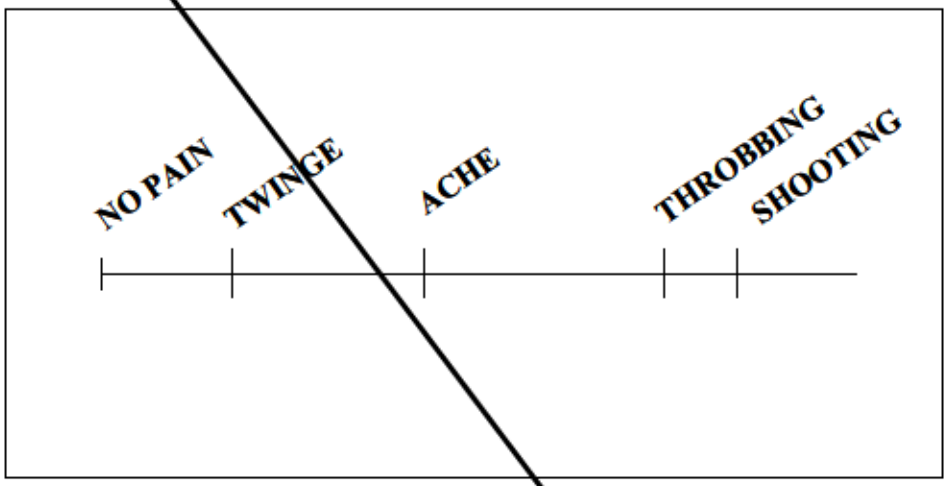


NOT TO SCALE

Please turn to the next page.

Finally, thinking about the **the pain from biting your tongue**, please give a rating that **DESCRIBES** the kind of feeling or sensation this is.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.



NOT TO SCALE

Please turn to the next page.

Let's try one last example.

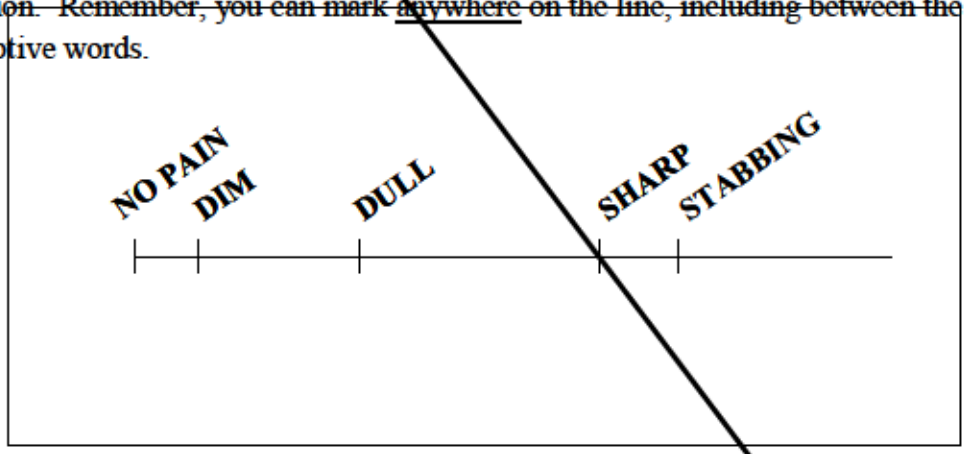
The pain of a persistent toothache.

Have you ever experienced this feeling or sensation before?

(Please circle one) Yes / No

First please rate the **INTENSITY** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. ~~Remember, you can mark anywhere on the line, including between the~~ descriptive words.

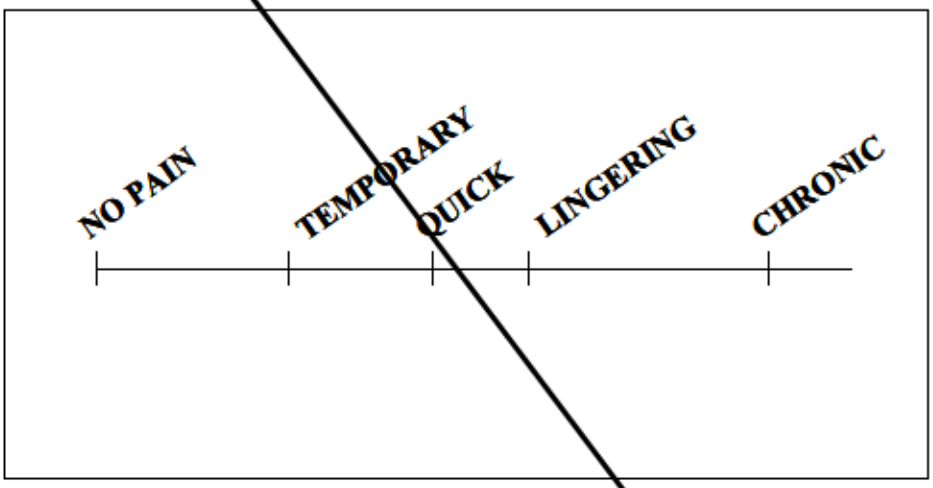


NOT TO SCALE

Please turn to the next page.

Still thinking about **the pain of a persistent toothache,** please rate the **DURATION** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark <u>anywhere</u> on the line, including between the descriptive words.

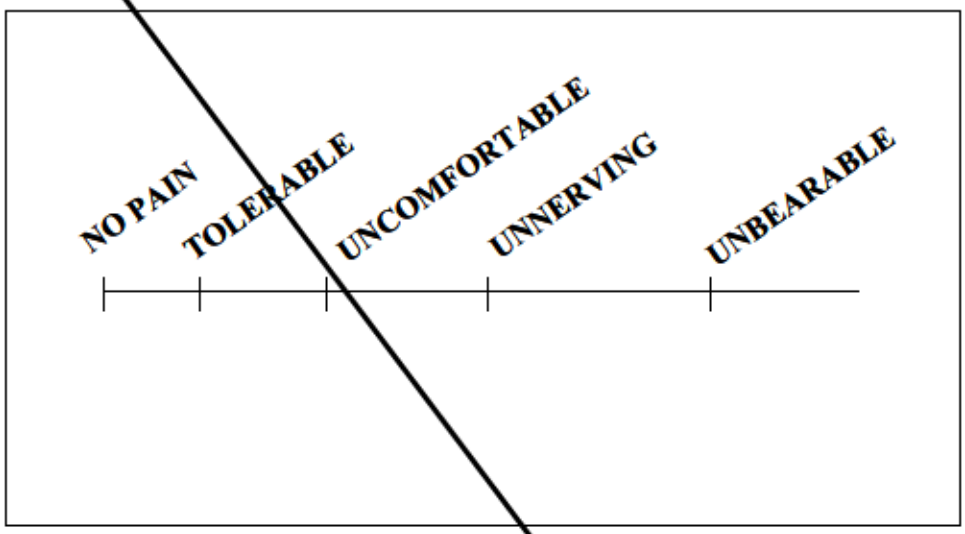


NOT TO SCALE

Please turn to the next page.

Still thinking about **the pain of a persistent toothache,** please rate how much you are able to **TOLERATE** with this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark <u>anywhere</u> on the line, including between the descriptive words.

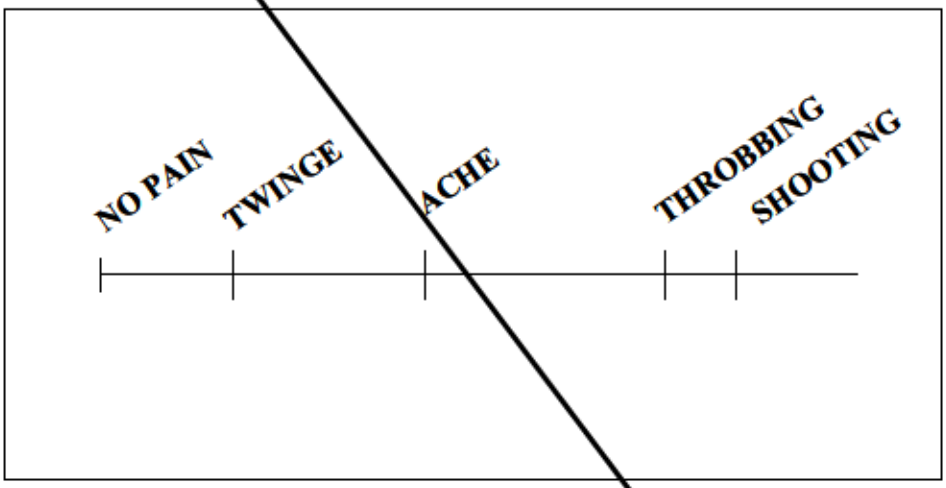


NOT TO SCALE

Please turn to the next page.

Finally, thinking about **the pain of a persistent toothache**, please give a rating that **DESCRIBES** the kind of feeling or sensation this is.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.



NOT TO SCALE

You have finished the practice exercise, and you are now ready to take part in the main part of the study.

If you have any questions about this exercise, please let a member of the study staff know.

If you feel that you understand how to use these scales, please see a member of the study staff, who will start you on the main part of the study.

Thank you for your time!

12.3. APPENDIX 3-SUBJECT INSTRUCTIONS FOR LMS TRAINING EXERCISE

Subjects will be given instructions for using the LMS and asked to complete the LMS training exercise form. The investigator or designee should read the instructions aloud while the subject reads along. Subjects will be permitted to ask questions. However, most questions should be answered by rereading the appropriate section of the instructions. The investigator, or designee, will then determine whether the subject understands how to use the LMS based on the line scale training exercise answers and the criteria below.

Interpretation of the Line Scale Training Exercise

The objective of this exercise is NOT to determine whether the subject can get the exact answers, but to determine whether they understand the concept. Therefore, the following general criteria are suggested:

- Are markings only on the verbal descriptors? If so, provide feedback that they are to use the entire scale, including areas between the descriptors.
- Are subjects marking on the same place on all the scales for one stimulus (particularly if the LMS measures are all presented on one page?) If so, make sure subjects understand what each scale is meant to measure (intensity, duration, ability to tolerate, and description) and that stimuli will likely produce different marks on each scale.
- The stimuli are presented generally in increasing intensity. Are subjects indicating an increasing intensity across stimuli?
- Are subjects marking their ratings with an "X" on the scale? If not (subjects are circling descriptors, making unclear marks, etc.), provide feedback on the use of the correct mark.

If subjects appear unable to complete each of the LMS scales (intensity, duration, tolerability and description) with the appropriate response (s), the investigator/ designee should talk them through the grading of the first two LMS scenarios, if required. If the marks are generally correctly ordered, but far from their true positions, the investigator/ designee should try to get the subject to verbalize why they placed the marks as they did. However, the investigator/ designee should be careful not to pressure the subject to change their responses. One approach would be for the investigator/ designee to start with an item that the subject did well, ask about that and then continue by asking about an item where they did less well.

If subjects are not able to provide proper responses to the stimuli questions across all four figure scales, it is unlikely they will provide appropriate responses on the clinical response LMS scales. These subjects should be disqualified.

Subject Instructions for LMS Training Exercise (Example)

The purpose of this exercise is to introduce you to the scales you will be using. There are no right or wrong answers.

Please read each item carefully. Then try to remember or imagine what each sensation feels like. If you haven't had exactly the experience described, try to think of something similar.

The scales you will be using each have words that can be used to describe different feelings or sensations people have in their mouths. As you think about each sensation, you should think about the word that best describes what that sensation feels like. Then, if appropriate, you can "fine tune" your rating by marking the line between that word and the next word up or down the scale.

FOR EACH ITEM PLEASE INDICATE HOW YOU WOULD RATE THE FEELING DESCRIBED BY PLACING AN "X" ON THE LINE. YOU MAY MARK ANYWHERE ALONG THE LINE.

Please turn to the next page for the first example in this exercise.

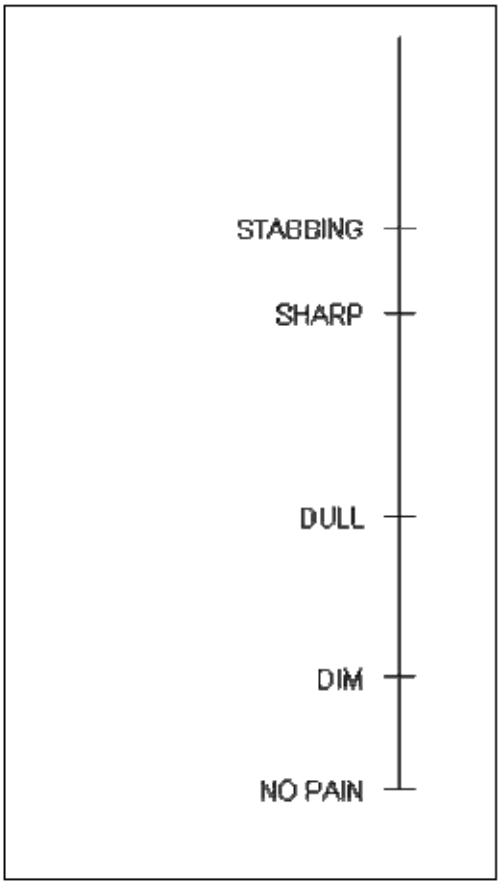
Let's start with this example.

The touch of a pill on your tongue.

Have you ever experienced this feeling or sensation before?
(Please circle one): Yes / No

First please rate the **INTENSITY** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

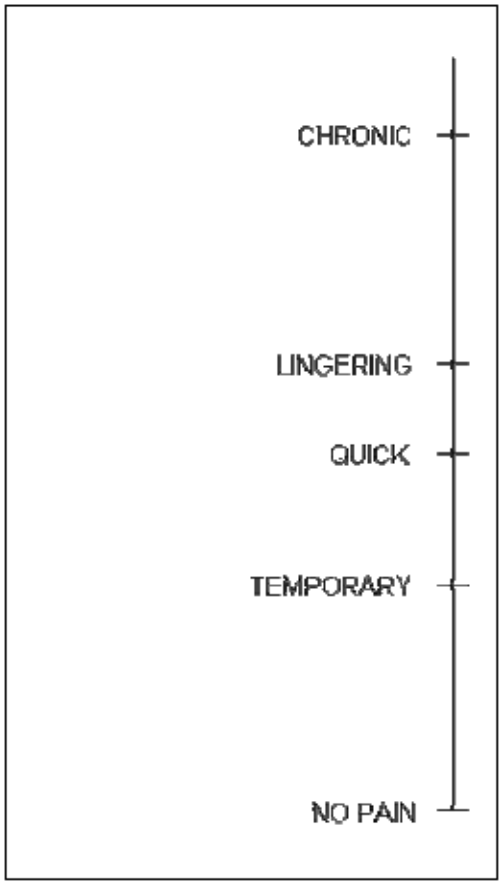


NOT TO SCALE

Please turn to the next page.

Still thinking about **the touch of a pill on your tongue,** please rate the **DURATION** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

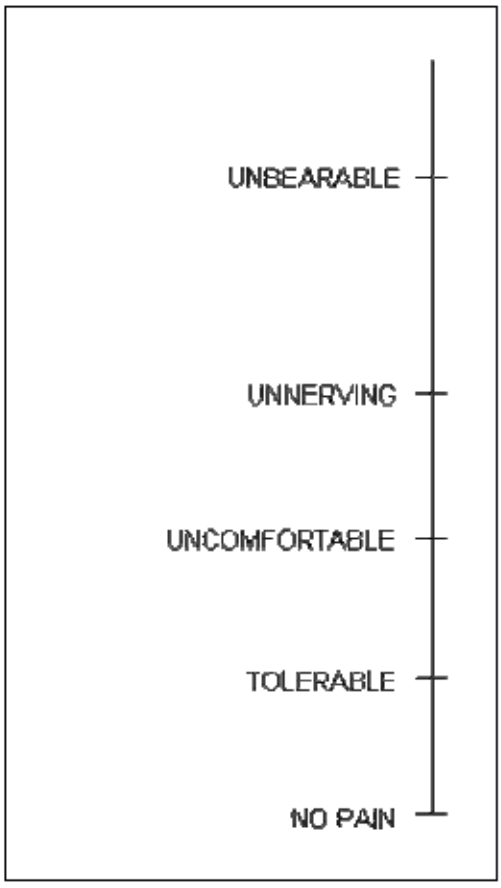


NOT TO SCALE

Please turn to the next page.

Still thinking about **the touch of a pill on your tongue,** please rate how much you are able to **TOLERATE** this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

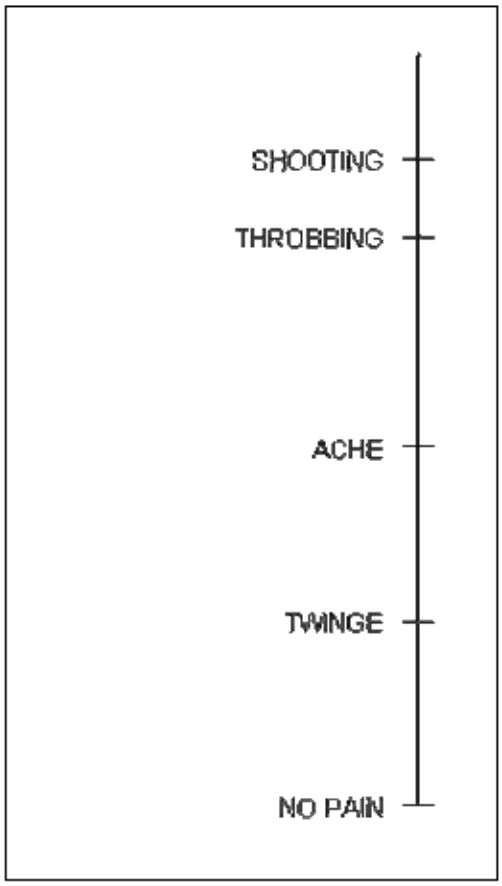


NOT TO SCALE

Please turn to the next page.

Finally, thinking about **the touch of a pill on your tongue**, please give a rating that **DESCRIBES** the kind of feeling or sensation this is.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.



NOT TO SCALE

Please turn to the next page

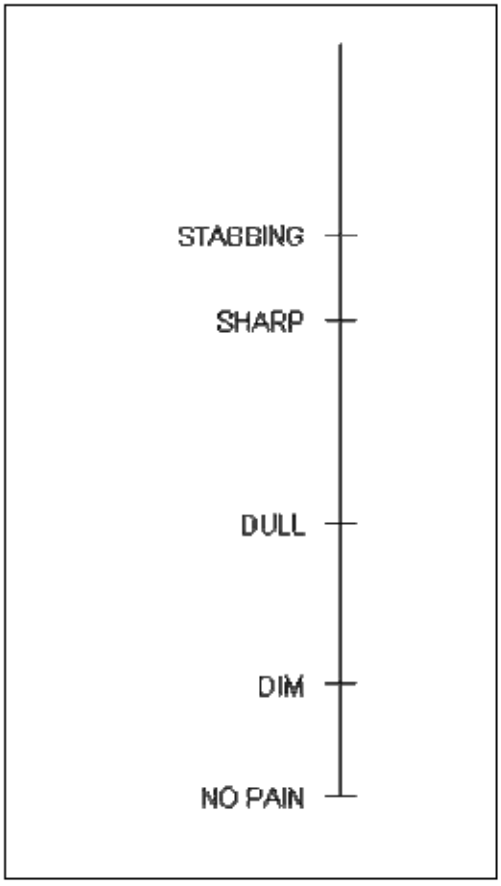
Let's try this example.

The pain from biting your tongue.

Have you ever experienced this feeling or sensation before?
(Please circle one): Yes / No

First please rate the **INTENSITY** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

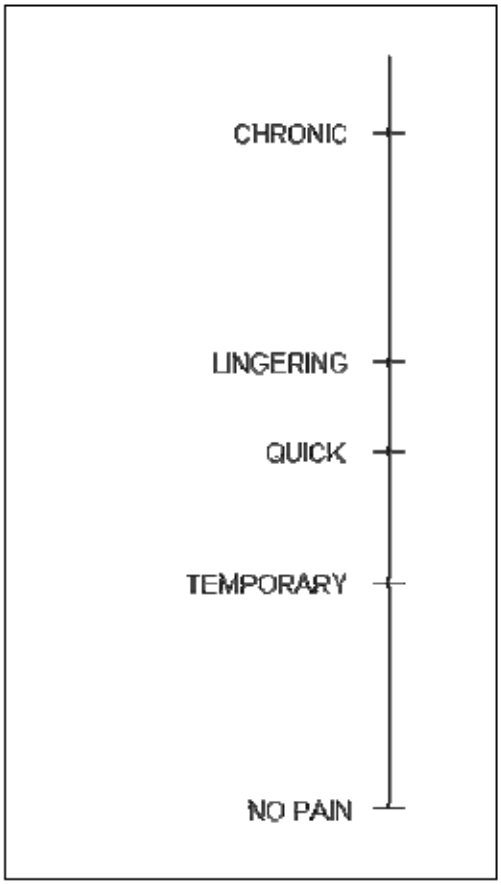


NOT TO SCALE

Please turn to the next page.

Still thinking about **the pain from biting your tongue,** please rate the **DURATION** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

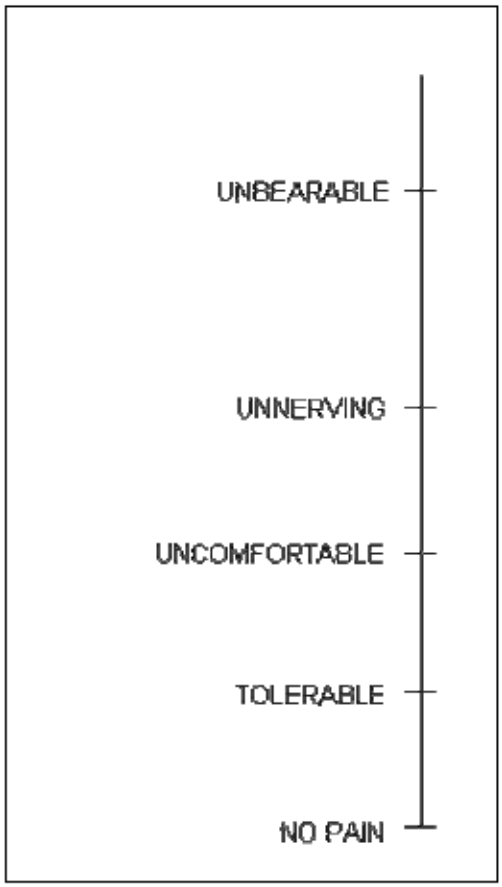


NOT TO SCALE

Please turn to the next page.

Still thinking about **the pain from biting your tongue,** please rate how much you are able to **TOLERATE** this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

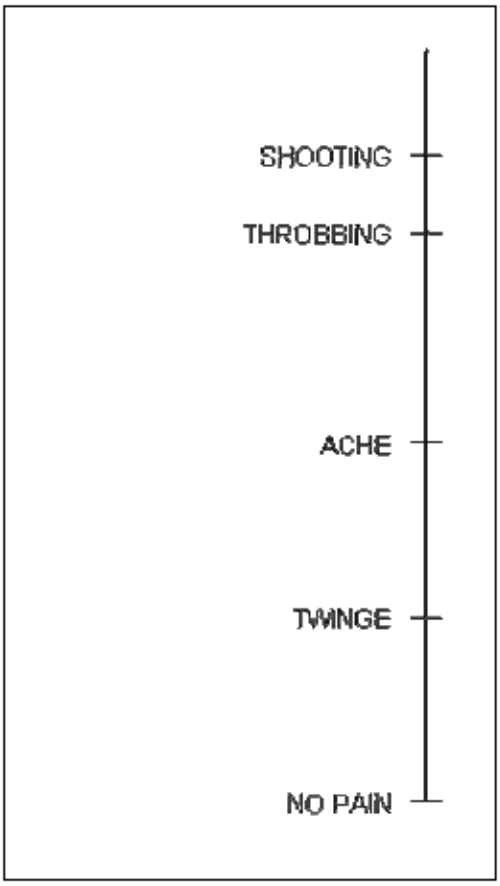


NOT TO SCALE

Please turn to the next page.

Finally, thinking about **the pain from biting your tongue**, please give a rating that **DESCRIBES** the kind of feeling or sensation this is.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.



NOT TO SCALE

Please turn to the next page.

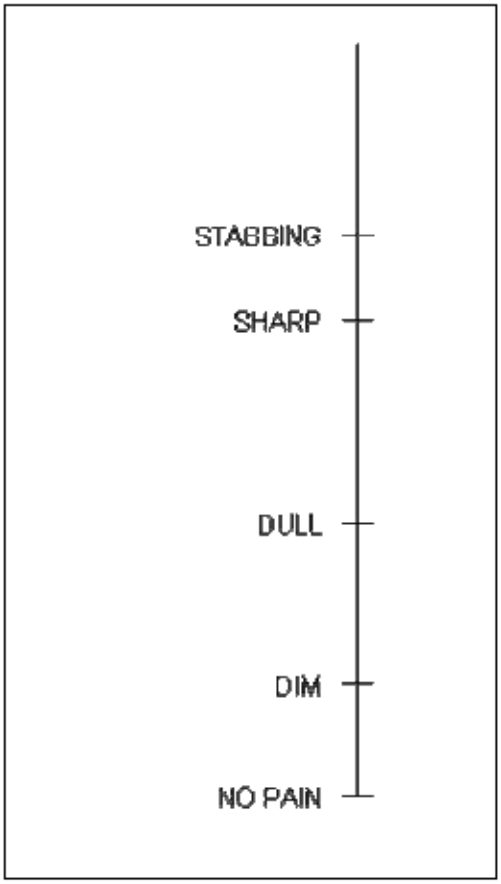
Let's try one last example.

The pain from persistent toothache.

Have you ever experienced this feeling or sensation before?
(Please circle one): Yes / No

First please rate the **INTENSITY** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

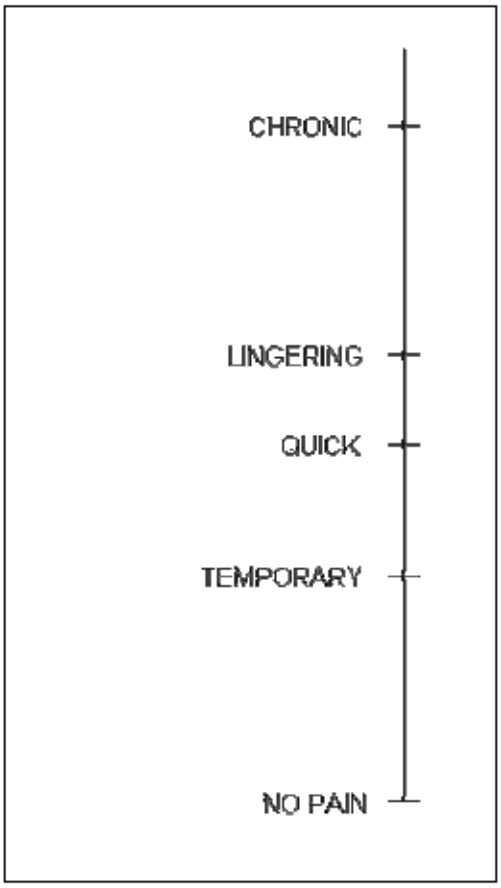


NOT TO SCALE

Please turn to the next page.

Still thinking about **the pain of a persistent toothache**, please rate the **DURATION** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

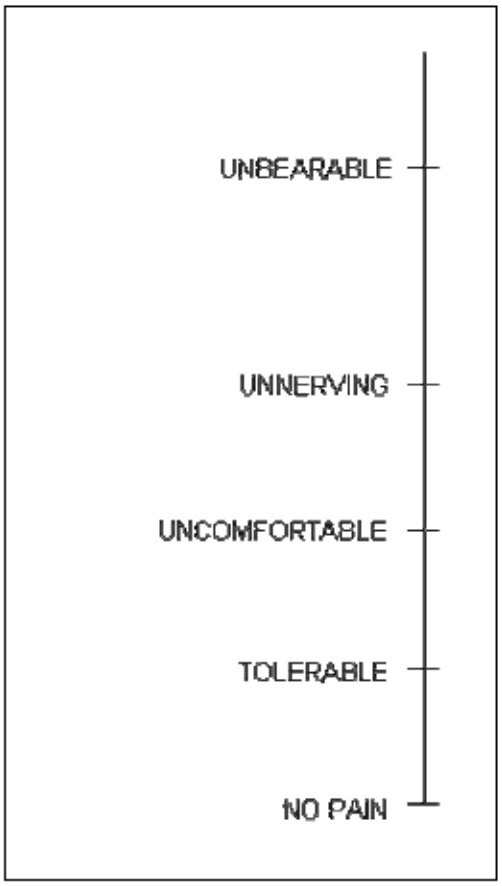


NOT TO SCALE

Please turn to the next page.

Still thinking about **the pain of a persistent toothache,** please rate how much you are able to **TOLERATE** this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

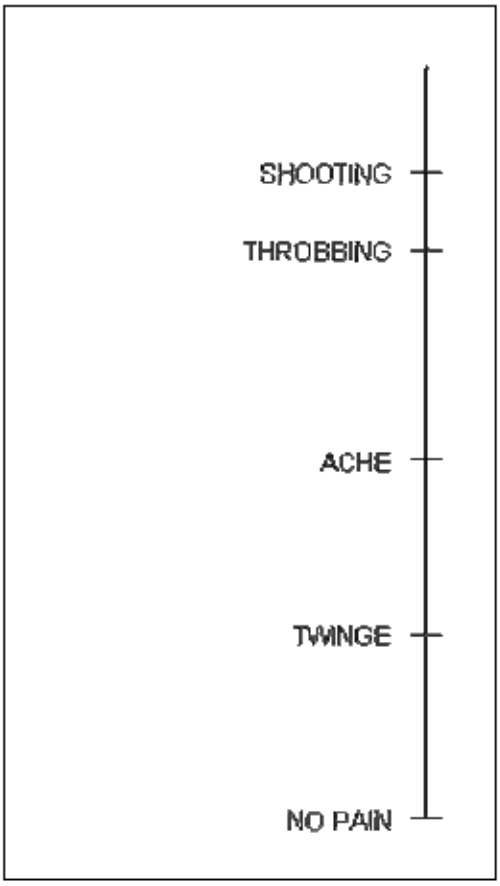


NOT TO SCALE

Please turn to the next page

Finally, thinking about **the pain of a persistent toothache**, please give a rating that **DESCRIBES** the kind of feeling or sensation this is.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.



NOT TO SCALE

You have finished the practice exercise, and you are now ready to take part in the main part of the study.

If you have any questions about this exercise, please let a member of the study staff know.

If you feel that you understand how to use these scales, please see a member of the study staff, who will start you on the main part of the study.

Thank you for your time!

GlaxoSmithKline

RH01897

Visit____

Site No 0 1 | Screening No S | Visit Date ___ ___ 2 0 (Day / Month / Year)

EVAPORATIVE (AIR) SENSITIVITY ASSESSMENT (LMS)

Please rate **INTENSITY** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

Tooth Number ___

For site use only: ___ mm ___ Initials

___of___ P___

GlaxoSmithKline

RH01897

Visit___

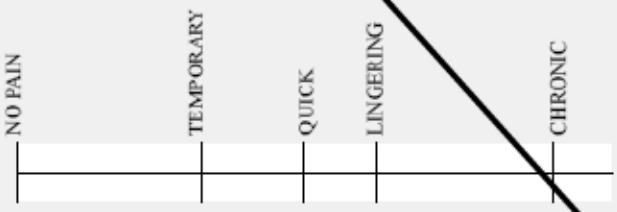
Site No 0 1 | Screening No S | Visit Date ___ (Day) ___ (Month) 2 0 (Year)

EVAPORATIVE (AIR) SENSITIVITY ASSESSMENT (LMS)

Please rate **DURATION** of this feeling or sensation.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

Tooth Number ___



For site use only: ___ mm ___ Initials

___of___ P ___

GlaxoSmithKline

RH01897

Visit___

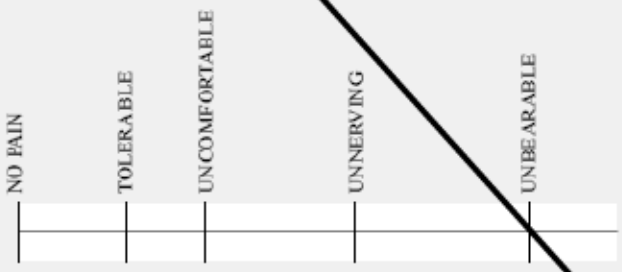
Site No 0 1	Screening No S	Visit Date ___ ___ 2 0 ___ (Day / Month / Year)

EVAPORATIVE (AIR) SENSITIVITY ASSESSMENT (LMS)

Please rate how much you are able to **TOLERATE** with this feeling or sensation.

Mark the scale below with an "**X**" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

Tooth Number ___



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GlaxoSmithKline

RH01897

Visit___

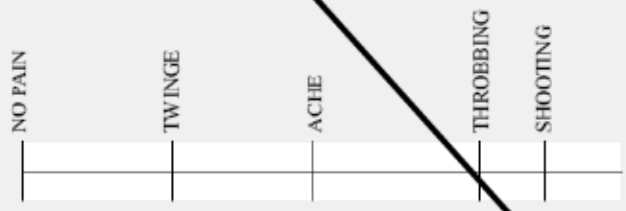
Site No	Screening No	Visit Date
0 1	S	Day / Month / 2 0 Year

EVAPORATIVE (AIR) SENSITIVITY ASSESSMENT (LMS)

Please give a rating that **DESCRIBES** the kind of feeling this is.

Mark the scale below with an "X" to indicate the best description of that feeling or sensation. Remember, you can mark anywhere on the line, including between the descriptive words.

Tooth Number [ ]



For site use only: [ ] mm [ ] Initials

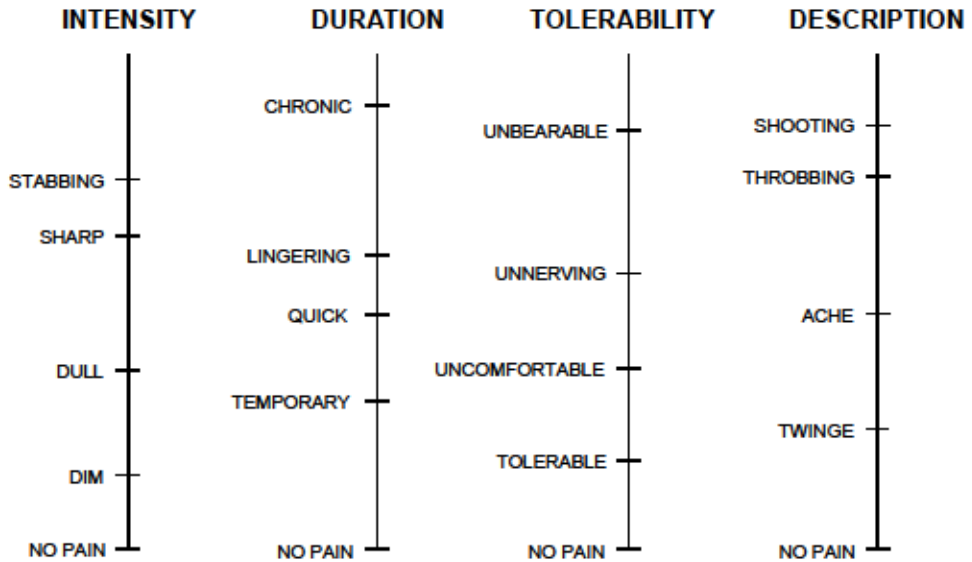
___of___ P ___

12.4. APPENDIX 4 - LMS SUBJECT ASSESSMENT FORM (EXAMPLE)

Screening No. S ___ ___ ___ ___ **Protocol: 204930**

Tooth No: | | | **Labelled Magnitude Scales** **Visit No:** ____ **Date** __ __/ __ __/ __ __

Please rate the **INTENSITY/DURATION/TOLERABILITY/DESCRIPTION** of this feeling or sensation.
Mark the scales below with an **"X"** to indicate the best description of that feeling or sensation.
Remember, you can mark anywhere on the line, including between the descriptive words.



Score: _____ mm _____ mm _____ mm _____ mm

Final v1.0 16 Oct 15

Scorer initials (site staff): _____

NOT TO SCALE

SIGNATURE PAGE

Clinical Protocol 204930

Date	Signed By
08-Sep-2016 17:03:11	PPD
Justification	Approved

Date	Signed By
09-Sep-2016 05:32:57	PPD
Justification	Biostatistics Approval

Date	Signed By
09-Sep-2016 15:29:05	PPD
Justification	Approved

Date	Signed By
12-Sep-2016 05:12:42	PPD
Justification	Clinical Operations Approval

Date	Signed By
Justification	

Date	Signed By
Justification	