PROTOCOL

A Clinical Study Investigating the benefits of a hydroxylapatite /potassium nitrite and aluminium lactate cosmetic toothpaste to help the discomfort associated with Dentine Hypersensitivity compared to a benchmark marketed toothpaste

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SUMMARY INFORMATION

Title:	A Clinical Study Investigating the benefits of a hydroxylapatite /potassium nitrite and aluminium lactate cosmetic toothpaste to help the discomfort associated with DH compared to a benchmark marketed toothpaste
Short Title:	Effect of toothpaste on tooth plaque and sensitivity
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PROTOCOL SYNOPSIS

Brief Summary

This single centre, double blind, parallel, randomised controlled design study will investigate the benefits of a hydroxylapatite /potassium nitrite and aluminium lactate cosmetic toothpaste to help the discomfort associated with dentine hypersensitivity compared to a benchmark marketed toothpaste, Sensodyne Daily Care.

The study will be conducted in subjects in good general health, with pre-existing self-reported and clinically diagnosed tooth sensitivity at screening.

1. INTRODUCTION

It is important to maintain a healthy mouth with regards to both gingival inflammation (due to plaque accumulation) and pain from exposed dentine due to dentine hypersensitivity. These are both common oral conditions, 42% of adults have dentine hypersensitivity (DH), due to exposed dentine, and 40-50% of adults have gingivitis (Chapple et al 2014) due to plaque accumulation. There is some evidence that the aetiology of DH is due to plaque bacteria in the dentine tubules (Brittan et al 2016, Adriaens et a l1988). A number of cosmetic toothpastes on the market aim to prevent and or help these conditions.

Dentinal hypersensitivity (DH) is described by Addy et al 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). DH originates from aetiologic factors such as gingival recession, erosion and/or abrasion that result in loss of enamel or cementum and exposure of underlying dentine with patent dentinal tubules (Orchardson, 1987)], and possibly plaque accumulation (Adriaens et al 1988, Brittan et al 2016). Brännström's hydrodynamic theory of DH hypothesises movement of the fluid within the dentine tubules when an external stimulus is applied to the dentine, which in turn stimulates nerve processes in the pulpal area of the dentine and produces pain impulse transmission (Brannstrom, 1964)].

Currently there are two approaches to the management of DH.

- Nerve depolarisation
- Dentinal tubule occlusion.

Nerve depolarising agents, such as potassium nitrate, are believed to result in depolarisation of the afferent nerve membrane thereby blocking the pain response [Orchardson, 1975]. Agents which give a surface deposit to the and block the open tubules such as bioglasses, hydroxyapatites or silicas serve to physically seal or block the dentine tubules and thereby reduce the effect of external stimuli. Aluminum lactate is known to work as a tubule occluding agent (Nakajima et al 1990, Han et al 2013). The aluminum ions react with phosphate ions in saliva to become insoluble aluminum phosphate, which block the dentinal tubules.

Gingivitis is ubiquitous to all populations and is caused by inadequate control of dental plaque. This causal relationship was first demonstrated by Löe et al (1965)[1]. Gingivitis is caused by plaque accumulation on the teeth with gingivitis preceding periodontal disease in the majority of cases, when teeth lose bone and are eventually lost. Aluminum lactate is known to help plaque reduction and promote healthy gums (Rathe et al 2007, Mason et al 2017, Bellamy et al 2009) when brushed twice daily on the teeth. Plaque on the cervical margin of teeth could also be an aetiological cause of DH due to bacteria invading the dentine tubules ((Brittan et al 2016, Adriaens et al 1988) and causing irritation in the pulp.

The current study will investigate the ability of an experimental hydroxylapatite /potassium nitrite and aluminium lactate paste compared to a marketed benchmark product, Sensodyne Daily Care (potassium, fluoride, sodium lauryl sulphate) to promote a healthy mouth with regards to the reduction of sensitive teeth from dentine hypersensitivity and reduction of plaque.

2. OBJECTIVES AND ENDPOINTS

Primary	Endpoint
To investigate the ability of an experimental hydroxylapatite /potassium nitrite and aluminium lactate paste compared to a benchmark control product (Sensodyne Daily Care) as elicited by a cold stimulus (Schiff sensitivity scale) after 6 days use	Analyses on post-treatment Schiff sensitivity score after 6- days use using pre-treatment baseline scores as covariate
Secondary	**Endpoint**
To investigate the ability of an experimental hydroxylapatite /potassium nitrite and aluminium lactate paste compared to a benchmark control product (Sensodyne Daily Care) as elicited by a tactile stimulus (Yeaple probe) after 6 days use.	Analyses on post-treatment tactile sensitivity score after 6 days use using pre-treatment baseline scores as covariate.
To investigate the ability of an experimental hydroxylapatite /potassium nitrite and aluminium lactate paste compared to a benchmark control product (Sensodyne Daily Care) as elicited by a cold stimulus (Schiff sensitivity scale) and a tactile stimulus (Yeaple probe) after a single use (60 second direct application)	Analyses on post-treatment Schiff sensitivity score after a single 60 second direct application using pre-treatment baseline scores as covariate. Analyses on post-treatment tactile sensitivity score after single 60 second application using pre-treatment baseline scores as covariate.
To investigate the ability of an experimental hydroxylapatite /potassium nitrite and aluminium lactate paste compared to a benchmark control product (Sensodyne Daily Care) as elicited by a cold stimulus (Schiff sensitivity scale) and a tactile stimulus (Yeaple probe) after and acclimatisation period of 1-2 weeks	Analyses on post-treatment Schiff sensitivity score after 2 weeks using pre-treatment baseline scores as covariate Analyses on post-treatment tactile sensitivity score after and acclimatisation period of 1-2 weeks using pre-treatment baseline scores as covariate
To investigate the ability of an experimental hydroxylapatite /potassium nitrite and aluminium lactate paste compared to a benchmark control product to provide relief from DH, as determined by VAS	Analyses on post-treatment VAS sensitivity score after 60 seconds, 6 days and 2 weeks each using pre-treatment baseline scores as covariate.
To investigate the ability of an experimental hydroxylapatite /potassium nitrite and aluminium lactate paste compared to a benchmark control product (Sensodyne Daily Care) to reduce plaque scores after 6 days and 2 weeks	Analyses on post-treatment plaque score after 6 days and 2 weeks use using pre-treatment baseline scores as covariate.

3. STUDY PLAN

3.1. Study Design

This will be a 2 week, randomised, examiner blind, two treatment arm, parallel design, stratified (by maximum baseline Schiff sensitivity score of the two selected test teeth), controlled study, in subjects with at least two sensitive teeth that meet all the criteria at the screening and baseline (pre-treatment) visits. DH will be assessed at baseline (pre-treatment), post-treatment, after 4 days and 2 weeks twice daily brushing.

Plaque scores from baseline will be compared between the 2 groups at 6 days and 2 weeks. A quality of life questionnaire will be completed.

The assessments to be performed at each study visit are outlined below:

Visit 1 Assessment 1- Screening Visit
The following procedures and assessments will be conducted: • Written informed consent. • Inclusion/exclusion criteria • 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, current/concomitant medications and medical history. • Oral examination including an oral soft tissue (OST) and oral hard tissue (OHT) examinations and assessments to determine eligible teeth • Qualifying sensitivity test to a cold stimulus to identify 2 teeth with sensitivity • Confirmation of subject eligibility. • Dispensation of acclimatisation toothpaste, toothbrush, for acclimatisation period
Visit 2 – Assessment 2 Baseline (Pre-treatment) (7-14 days after screening)
The following procedures and assessments will be conducted: • Review of current/concomitant medications, AEs. • Return of acclimatisation toothpaste, toothbrush. • Confirmation of subject eligibility and continuance. • OST examination. • Plaque scores (Appendix 2) • Tactile sensitivity assessment of eligible teeth. • Cold stimulus sensitivity assessment of eligible teeth which meet the tactile sensitivity entry criterion. • VAS (Appendix 3) • Selection of two test teeth. • Quality of life questionnaire (QoL) (Appendix 4) • Randomisation • Dispensation of study toothpaste with usage instructions
Visit 2 – Assessment 3 Post-treatment (immediately after pre-treatment)

The following procedures and assessments will be conducted:

- Review of current/concomitant medications, AEs.
- Confirmation of subject continuance.
- OST examination.
- Tactile sensitivity assessment of the two selected test teeth.
- Cold stimulus sensitivity assessment of the two selected test teeth.
- VAS

Visit 3 – Assessment 4 Day 6 (±1 day)

The following procedures and assessments will be conducted:

- Review of current/concomitant medications, AEs.
- Confirmation of subject continuance.
- OST examination.
- Plaque scores
- Tactile sensitivity assessment of the two selected test teeth.
- Cold stimulus sensitivity assessment of the two selected test teeth.
- VAS
- Quality of life questionnaire (QoL)

Visit 4 – Assessment 5 14 days (±1 day)

The following procedures and assessments will be conducted:

- Review of current/concomitant medications, AEs.
- Return of study supplies (toothpaste, toothbrush)
- Confirmation of subject continuance.
- OST examination.
- Plaque scores
- Tactile sensitivity assessment of the two selected test teeth.
- Cold stimulus sensitivity assessment of the two selected test teeth.
- VAS
- Quality of life questionnaire (QoL)
- Questionnaire on products (Appendix 5)
- Subjects will be reminded to report AEs for 5 days after last treatment.
- Study conclusion.

3.2. Subject Restrictions

Lifestyle/ Dietary

For the duration of the study (screening – last visit):

- Subjects will not be permitted to use any mouthwashes or whitening/bleaching products) other than those provided to them from Screening to completion of the study. Subjects will not be permitted to use any dental products, including home remedies, intended for treating sensitive teeth from Screening until completion of the study.

- In order to standardise oral hygiene practice prior to efficacy assessments, subjects will be asked to refrain from all oral hygiene procedures for **at least 1 hour** and from eating and drinking for **at least 1 hour**, prior to their scheduled Visit 2, and 4.
- Subjects will not be permitted to chew gum.

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 will 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.
- 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

Sufficient subjects, approximately 150, will be screened to ensure approximately 90 subjects will be randomised to ensure 80 subjects complete the study (approximately 40 per treatment group). Approximately equal number of male and female gender will be recruited to the study in each group scoring 2 or 3 on a Schiff test to a cold stimulus.

Healthy participants will be recruited from the University of Bristol, Bristol Dental Hospital and School and from the Clinical Trials Unit database of staff and students from around the University and hospital trust precinct who have expressed an interest in taking part in healthy participant trials. All potential participants will be informed that a new trial is going to take place. Our database also includes previous participants from the general public who have shown an interest in partaking in future dental research studies and have requested to be contacted. Participants may also be recruited via posters, advertisements in University news bulletins or by word of mouth.

3.4. Study Design and Dose Justification

A randomized, single-blind (examiner blind), parallel group design is a recognized approach for providing evidence for improving DH discomfort and plaque reduction.

In line with published recommendations [Holland, 1997], two independent stimulus-based efficacy measures will be employed (tactile and cold stimulus). To avoid inter-examiner variation, a single examiner will be responsible for the conduct of a given clinical measure of DH for the duration of the entire study for all study subjects.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

2. AGE
   Aged 18-65 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) Minimum of 20 natural teeth.
   b) 2 sensitive teeth as defined by Schiff scores 2/3 to cold stimuli

   At Visit 2, Baseline (Pre-treatment):
   Minimum of two, non-adjacent accessible teeth (incisors, canines, pre-molars), that meet all of the following criteria:
   Tooth with signs of sensitivity, measured by qualifying tactile stimulus (Yeaple ≤ 20g) and cold stimulus assessment (Schiff sensitivity score ≥ 2)

4.2. Exclusion Criteria

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

1. ALLERGY/ INTOLERANCE

   Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients

2. CLINICAL STUDY/ EXPERMENTAL PRODUCT

   a) Participation in another clinical study (including cosmetic studies) or receipt of an investigational drug within 15 days of the screening visit.
   b) Previous participation in this study.

3. SUBSTANCE ABUSE

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

4. PERSONNEL

   An employee of the sponsor or the study site or members of their immediate family.
   The site for this protocol is the Clinical trials Unit in the Bristol Dental School and Hospital. Employees of the Bristol Dental School and Hospital not associated with the Clinical Trials unit are eligible to participate.

5. 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

6. GENERAL DENTITION EXCLUSIONS
   a) Dental prophylaxis within 4 weeks of Screening.
   b) Tongue or lip piercing.
   c) Desensitizing treatment within 2 weeks of Screening (professional sensitivity treatments and non-dentifrice sensitivity treatments).
   d) Active periodontal disease
   e) Teeth bleaching within 8 weeks of Screening

7. SPECIFIC DENTITION EXCLUSIONS FOR *TEST TEETH*
   a) Tooth with exposed dentine but used as abutments for fixed or removable partial dentures, teeth with full crowns or veneers, orthodontic bands or cracked enamel.
   b) Tooth with evidence of caries

8. CONCOMITANT MEDICATION
   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.

9. 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 randomised. 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, behavioural or administrative reasons.

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

	Test Dentifrice	Control Dentifrice
Treatment Description	Hydroxylapatite /potassium nitrite and aluminium lactate (Calcium aluminium phosphate precipitate) (Sunstar Suisse S.A. Route de Pallatex 11, 1163 Etoy Switzerland)	Sensodyne Daily Care (GSK, 980 Great West Rd, London TW8 9GS)
Commercial product	Experimental	Benchmark Control
Route of administration	Topical oral use	
Home use instructions **Twice daily (morning/ evening)**	Subjects will be instructed to apply a full brush head of toothpaste to a dry toothbrush	Subjects will be instructed to apply a full brush head of toothpaste to a dry toothbrush.

The test and control toothpaste tubes will be overwrapped to obscure any branding on the commercial tube pack. Each tube will have study label affixed. Each subject will receive a sufficient number of tubes to cover usage during the treatment phase.

The acclimatisation product 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.

All sundry items will be supplied in their commercial packaging for dispensing by study staff as required. Other items to be supplied to the participants:

Name of Item	Purpose
Signal Toothpaste (Unilever)	Acclimatisation product - to standardize oral hygiene practice prior to treatment phase. Subjects will apply a strip of dentifrice to cover the head of the toothbrush provided and brush teeth for one timed minute twice daily (morning and evening).
Toothbrush Gum Procare 518 (Sunstar)	Toothbrush to be supplied for use by participants with their allocated toothpaste. New toothbrush will be supplied for each phase of the study.

5.2. Dose Schedule

Subjects will brush with the study product twice on the day of baseline.

Subjects will be assigned to study product in accordance with the randomisation schedule generated by the statistician running the study, prior to the start of the study, using validated internal software.

At Visit 2, subjects will be given a new toothbrush and the study toothpaste (test or benchmark control toothpaste according to the randomisation schedule) and will brush their teeth under supervision for 1 minute and then enter visit 2 (post-treatment). The toothbrush and acclimatisation toothpaste will be collected in.

5.3 Randomisation and stratification

Subjects will be randomised to a product according to the table prepared by the Statistician.

5.3.1 Blinding

The study statistician and other employees of the Sponsor who may influence study outcomes are blinded to the product allocation of subjects. The examiner will be blinded to the treatment received. To ensure the examiner remains blinded throughout the study, the examiner is not permitted in the room whilst product is dispensed. In addition, subjects should be treated in a separate area. The dispensing staff will not be involved in any efficacy assessments during the study.

As the dosing instructions for the two products are slightly different the subjects will be given the dosing instructions on a separate sheet. Only the dispensing staff should have sight of the dosing instructions.

5.4. 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 will 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).

5.5. Storage of Product

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

6. STUDY ASSESSMENTS AND PROCEDURES

This section details the procedures, assessments and parameters that will occur at each of the planned study assessment visits. Also included in this section are actions being taken in light of the Covid-19 pandemic relating to participant and study staff safety.

Procedure/ Assessment	**Visit 1**		**Visit 2**		**Visit 3**	**Visit 4**
	Assessment 1 Screening		Assessment 2 **Day 0** Baseline (Pre-Treatment)	Assessment 3 **Day 0** Baseline (Post-Treatment)	Assessment 4 **Day 6 (±1 day)**	Assessment 5 **Week 2 (±1 day)**
Informed consent	X	**Acclimatisation Period (between 7-14 days)**				
Demographics + Medical History	X					
Current / Concomitant medication	X		X	X	X	X
Inclusion / Exclusion Criteria	X		X			
Subject Eligibility	X		X	X	X	X
Continuation Criteria			X	X	X	X
Oral Soft Tissue (OST) Examination	X		X	X	X	X
Oral Hard Tissue Examination including Eligible Teeth Assessments	X					
Plaque score (Turesky) (Appendix 2)			X		X	X
Qualifying Cold stimulus Sensitivity Assessment	X					
Dispense Acclimatisation Toothpaste, Toothbrush	X					
Return Acclimatisation Toothpaste, Toothbrush			X			
Tactile Sensitivity Assessment (Yeaple Probe)			X			
Cold stimulus Sensitivity Assessments (Schiff sensitivity score)			X			

Select two 'Sensitive Test Teeth'			X			
Stratification/Randomisation			X			
Dispense Study Supplies			X			
Tactile and Cold stimulus Assessments (Test Teeth only)				X	X	X
VAS assessment for mouth (Appendix 3)			X	X	X	X
Quality of life questionnaire (Appendix 4)			X		X	X
Questionnaire on products used (Appendix 5)						X
Return Study Supplies						X
Adverse Events	X		X	X	X	X
Study Conclusion						X

6.1. Screening

Prior to the screening visit, participants who have expressed an interest in taking part in a dental sensitivity study will be contacted from the Bristol Dental Clinical Trials Unit data base to see if they would like to take part.

6.2. Informed Consent

The investigator, or designee, will 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 member of the study team, will also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. 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.

6.3. Demographics

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

6.4. 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.

6.5. Oral Hard and Soft Tissue Examination.

6.5.1 Oral Soft Tissue Examination (OST)

An OST examination will be conducted at every study visit prior to any clinical assessments (Visits 1, 2, 3 and 4). 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.

6.5.2. Oral Hard Tissue (OHT) Visual Examination

A suitable qualified individual will perform an examination of the oral hard tissue at Visit 1 to confirm that the subject has a minimum of 20 natural teeth and to evaluate dentition exclusions. The examination will be performed by direct observation.

6.6 Questionnaires

6.6.1 Quality of Life questionnaire (QoL)

A quality of life questionnaire relating to oral health will be completed by the participant at Visits 2 (pre-treatment), 3 and 4. (see Appendix 1)

6.6.2 Questionnaire on Product used

At Visit 4, the participant will be asked to complete a short questionnaire about the toothpaste they used during the study. (see Appendix 2)

6.7 Tooth Sensitivity Assessments

6.7.1 Qualifying Tooth Sensitivity Assessment (Visit 1)

At Visit 1, the screening dentist will assess tooth sensitivity by a simple cold stimulus on the facial surface of all teeth that meet the study entrance criteria. This cold stimulus assessment is made by directing a one second application of either a cold air blast from a dental air syringe at a distance of approximately 1 cm, or a drop of 0 degree water to the tooth surface approximately 1- 2 mm coronal to the free gingival margin. 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. Response to this stimulus will be evaluated using the Schiff Sensitivity Scale and scored on a scale 0-3 (see Appendix 3). The examiner will decide the method of cold stimulus to be applied as appropriate in accordance with COVID related guidance. If the air blast is classed as an aerosol generating procedure (AGP) with use of enhanced PPE, the application of a drop of cold water may be employed as an alternative stimulus. The type of cold stimulus used will be noted.

To qualify at screening, a Schiff score of 2 or 3 needs to be confirmed on teeth that will be designated as the test teeth for the study. Up to 4 sensitive teeth can be identified in order to obtain 2 test teeth in different quadrants of the mouth excluding adjacent central incisors for ongoing sensitivity assessment.

6.7.2 Cold Stimulus Sensitivity Assessment (Visit 2-4)

This assessment will be conducted by a single examiner for all subjects at each visit by directing a one second application of a cold stimulus to the exposed dentine surface. 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. Response to this stimulus will be evaluated using the Schiff Sensitivity Scale and by the participant using a Visual Analogue Scale (VAS scale) (see section 6.7.3).

At Visit 2 pre-treatment, the examiner will assess the cold stimulus sensitivity of all test teeth identified at Screening, that qualified for the tactile assessment using the Schiff Sensitivity Scale. Two teeth will then be identified in different quadrants to be the “Test Teeth” for the next visits or the participant will be disqualified.

Cold stimulus sensitivity assessment will be performed 5 minutes post Tactile sensitivity assessments.

6.7.3 Visual Analogue (VAS) Scale

VAS values for the test teeth will be also be recorded to give the outcome variable per subject at the same time of Schiff assessment. The VAS values will be assigned a numerical value in the conventional order from 0 (no pain) to 100 (extremely pain). VAS values will be recorded by the participant by marking a point across a 100mm line on a scale provided.

6.7.4. Tactile Sensitivity Assessment (Yeaple probe)

Tactile assessments will be performed by a single trained examiner at Visit 2 (pre and post treatment), 3 and 4. The identified test teeth from the screening visit will be assessed at each timepoint.

The Yeaple score will be recorded in terms of quantified reproducible force (grams). After presenting the force to 10 grams, the probe tip will be passed over the exposed dentin on the buccal surface of the selected teeth, apical to the cementenamel junction. Subsequent passes will be made, each time with the applied force increased by 10 grams, until the subject indicates that he/she is experiencing discomfort by providing a "yes" response. The force setting which elicited the “yes” response will be repeated. If a second "yes" is not obtained, the force setting will be increased by 10 g and continue until a force is found which elicits two consecutive "yes" responses. The gram setting, which elicits the two consecutive “yes” responses, will be recorded as the threshold.

At Visit 2 pre-treatment the upper test limit is 20g. If no pain response is found, the threshold will be recorded as >20 g and the tooth will be disqualified from further tactile testing.

At Visit 2 post-treatment, Visit 3 and Visit 4, the upper force setting and cut-off point will be 80g. If no sensitivity is found, the threshold will be recorded as >80g

The cold stimulus (with Schiff Sensitivity Score) should follow the tactile assessment, with a minimum of five minutes in between each assessment type to allow recovery time.

6.7.4.1 Calibration of the Yeaple Probe

See Appendix 4.

6.8 Plaque Score

A plaque score will be obtained for the mouth by disclosing the plaque with a food colouring. The plaque scoring index used will be the Turesky (1970) - Modified Quigley Hein Index. There will be 2 scores per tooth of Plaque Index (on the buccal and on the lingual/palatal surface) of all scorable teeth and scored on the following scale:

0 = no plaque;

1 = separate flecks or discontinuous band of plaque at the gingival (cervical) margin;

2 = thin (up to 1 mm), continuous band of plaque at the gingival margin;

3 = band of plaque wider than 1 mm, but less than one-third of surface;

4 = plaque covering one-third or more, but less than two-thirds of surface;

5 = plaque covering two-thirds or more of surface.

The total score recorded for all teeth is calculated, then divided by the number of tooth surfaces assessed, giving the Turesky plaque score.

Plaque scores will be recorded at Visit 2 (pre-treatment), visit 3 and 4, and will be prior to Tactile sensitivity assessments.

6.9 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

6.10 Safety measures related to Covid-19

In response to the current coronavirus pandemic, a number of measures have put in place to protect the participants and the study staff from risk of Covid-19 infection. The study will operate to current Public Health England and the Chief Dental Officer England guidelines relating to the use of PPE, social distancing and patient flow through the surgery, disinfection and Covid-19 symptom checks. Before any study activities, all study staff will be trained in the new guidelines and any subsequent updates.

For the participants, prior to their initial appointment (Visit 1, screening), they will be sent a letter from the study team by either email or post to outline the social distancing and safety measures employed at the study site. The letter will provide details as to what the participant can expect when they attend the study site and what processes they will need to follow from when they arrive to when they leave the study site. By

sending the information in advance, the participants will have time to ask any questions they may have about what they will be required to do in advance of the appointment.

The study staff will also contact participants approximately 24-48 hours prior to each of their scheduled appointments (Visits 1-4 inclusive) to assess the participants current Covid status. This screening will be performed by telephone using a checklist and the responses will be charted, following the answers will be risk assessed prior to confirmation of the appointment. This is to ensure the risk of transmission of Covid-19 is minimised for both the participants and study team.

7. Safety Monitoring

7.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a participant, whether or not related to the study procedures. Adverse events include any occurrence that is new in onset, an exacerbation of a pre-existing condition and clinically significant laboratory values.

An incident is 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.

7.1.1 Exceptions

The following medical occurrences will not be reported as AEs;

- Pre-treatment Adverse Events; Any medical occurrence that occurs after informed consent, but before any study assessment is considered as medical history and only recorded as an AE if it worsens during the study.
- Pre-existing medical condition; Events that occur with comparable frequency and severity to the participant's baseline condition are reported as medical history, not AEs.

7.1.2 Study Specific Expected Adverse Event

There are no AEs known to be associated with the use of the 3D intra-oral camera and/or procedures in this study.

7.2 Reporting of Adverse Events

The handling and reporting of AEs has been formally delegated by the University of Bristol, as Sponsor, to UH Bristol.

All SAEs will be reported to the UH Bristol contact (0117 3420233) by investigational staff within 24 hours of their knowledge of the event. The initial SAE report may be incomplete but will provide the minimal information which is the study number, participant number, start date and SAE term.

8. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

8.1 Sample Size Determination

With 40 participants per group, the detectable difference in the trial formulation is 0.406 Schiff units which is 0.626 times the estimated within-groups standard deviation of 0.6478.

8.2. General Considerations

Schiff sensitivity scores will be characterised at scoring assessments 1, 2, 3, 4 and 5 by the average of the scores for the two designated study teeth. Tactile sensitivity scores will be characterised at scoring assessments 2, 3, 4 and 5 by the average of the scores for the two designated study teeth

Schiff and tactile sensitivity scores will be characterised at each of assessments 3 to 5, by the average of the scores for the two designated study teeth. Plaque will be characterised at each scoring assessment (1, 2, 4 and 5) by the average of the scores for all teeth scored. Means and standard deviations will then be calculated for Schiff and tactile sensitivity scores, QoL score and plaque score for each visit at which they are scored, for each treatment group.

The primary analysis of efficacy is analysis of covariance to compare the groups allocated to the two pastes, with the corresponding baseline (assessment 2) value as covariate. This is performed for each outcome measure at each response time point. In each analysis, adjusted mean treatment differences will be reported with 95% confidence intervals, as well as p-values. In the event of substantial departure from Gaussian distributional form, non-parametric analyses will be considered.

Means and standard deviations will also be reported for changes from baseline in each treatment group.

At each follow-up time point, the analysis will also determine how many (2, 1 or 0) of the designated teeth remain sensitive (Schiff score 3 or 2), calculating the corresponding proportions in each group, then the relative risk for the test paste relative to the control paste, all with 95% confidence intervals.

8.3 Definition of Analysis Populations

All assessments of safety will be based on the safety population, defined as all subjects who are randomised and receive at least one dose of study treatment during the study. Safety population summaries will be presented by treatment received.

The primary population for efficacy assessment will be the intent-to-treat (ITT) population, defined as all subjects who are randomized, receive the study treatment at least once and provide at least one post-baseline (post treatment) assessment of efficacy. All ITT population summaries and analyses will be presented by treatment randomized.

The per protocol (PP) population is defined as all subjects in the ITT population who have at least one assessment of efficacy considered unaffected by protocol violations.

PP analysis will be performed only on those data considered unaffected by protocol violations.

Efficacy analysis on the PP population will be performed on the clinical sensitivity measures (tactile threshold and Schiff sensitivity score) only if there is more than 10% difference in the number of subjects between PP and ITT populations. A decision on whether a PP analysis will be performed will be made prior to study unblinding.

8.4. Exclusion of Data from Analysis

Any of the following will be considered a protocol violation which will warrant exclusion of the subjects or some of their data from the 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
- 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 clinical director or designee ahead of database lock and breaking the study blind.

8.5 Criteria for Assessing Efficacy

The success criterion for this study is to observe a statistically significant greater reduction in cold stimulus sensitivity (Schiff Sensitivity Scale) for subjects using the experimental paste compared to the control paste, after 6 (±1 day) days use.

8.6 Criteria for Assessing Tolerability

The assessment for safety will be based on OST abnormalities, incidents and AEs reported following dosing with study treatment.

8.7 Handling of Dropouts and Missing Data

Subjects who withdraw from the study early will be included in the study analysis up to the point of withdrawal. Subjects who withdraw later will not be replaced. No data will be imputed in the case of dropouts or missing data.

8.8 Other Issues

An interim analysis is not planned for this study.

8.9 Safety Analyses

For the assessment of safety/tolerability and AEs will be listed. AEs will be summarised by treatment group. AEs will be regarded as treatment emergent if they occur on or after the first treatment application at the baseline visit.

9. Monitoring

The University of Bristol has a policy for monitoring 10% of studies. Monitoring of studies is conducted in accordance with UH Bristol monitoring policy in relation to the service level agreement with the University of Bristol. The monitor will maintain the confidentiality of the study documents.

10. Data Handling and Record Keeping

There will be at least one Case Report Form (CRF) for each participant entered into the study. It is the responsibility of the CI to ensure the completeness and accuracy of the CRF and to authorise only trained members of staff to complete the CRF.

The CRF will be completed legibly, using a black ballpoint pen. Erroneous values and/or text will not be obliterated. Instead, the error will be crossed out with a single line, the correct value/text added, and the correction signed or initialled and dated.

There will be study specific records to record the identification of any data to be recorded directly on the CRFs or other written or electronic record of data, and to be considered to be source data.

All site staff will ensure that the participant's anonymity will be maintained. On all documents participants will be identified only by an identification code and not by their names. The Chief Investigator (CI) or designee will keep a separate confidential enrolment log that matches identifying codes with the participant's names and addresses. The CI or designee will maintain these documents at the site.

It is the responsibility of the CI or designee to maintain adequate clinical study records. Copies of all study material will be archived for a period of at least 15 years after the end of the study (or more as legally required). All documents will be archived in a secure place and treated as confidential material.

11. Quality Standards

It is the responsibility of the CI to ensure that the study is conducted in accordance with the principles of Good Clinical Practice, the 2008 version of the Declaration of Helsinki and according to applicable local laws and regulations concerning studies conducted on human participants which are outside of the definition of a medicinal product or medical device.

Quality assurance audits may be performed by the sponsor or any ethics committee or regulatory authority during the course of the study or at study completion.

12. Ethics and Informed Consent

The CI or designee will submit a copy of the protocol, participant information sheet and consent form to an NHS Research Ethics Committee (REC) who will provide written approval before study specific procedures commence. The REC will also approve any other information that is given to participants such as advertisements and may require other documents such as study product documentation.

The CI or designee will obtain informed consent from each participant participating in the study, after explanation of the aims, methods, benefits and potential hazards of the study. The consent will be obtained before any study-specific procedures are performed. It will be made completely and unambiguously clear to each participant that they are free to refuse to participate in the study, or that they can withdraw their consent at any time and for any reason, without incurring any penalty or withholding of treatment. The participant will be given their own copy of the information sheet and signed consent form. The original signed informed consent will be kept on file by the CI or designee.

Any modification to the agreed protocol will be agreed by both the Sponsor and the CI and approved in writing by the REC. Written approval will be obtained from the REC before any amendment is implemented, unless immediate change is required to eliminate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor(s), telephone number(s)). Major/substantial amendments to the protocol that affect the scope of the study at the participant level should be reflected in the consent form and active participants re-consented.

13. Sponsorship, Finance and Insurance

The sponsor of the study is the University of Bristol. The study will be funded by Sunstar.

Following the final visit, participants will receive up to £200 in acknowledgement for time commitment and any out of pocket expenses from their participation in the study. If for any reason the participants do not complete the study, the sum received will be pro rata (Visit 1, £50; Visit 2 part 1, £25 if eligible to continue, Visit 2 part 2 £25; Visit 3, £50; Visit 4, £50). If participants fail the screening criteria for the study they will receive £10 for their time and to cover any out-of-pocket expenses.

The University has Clinical Research/ Public Liability Insurance to cover the liability of the University to research participants. In the event that something goes wrong and a participant is harmed during the research study there are no special compensation arrangements. If a participant is harmed and this is due to someone's negligence then they may have grounds for a legal action for compensation against Bristol University or the NHS Trust or one of the other parties to the research, but they may have to pay their own legal costs.

14. Registration, Reporting and Publication Policy

Statistical analysis will be performed for the study and a final study report will be prepared. Except for compelling legal reasons, neither the sponsor nor the site staff will communicate to third parties any result of the clinical study before the report has been released by the sponsor by mutual agreement.
As registration of the clinical study is strongly recommended by the ethics committee, the registration of the clinical study with ISRCTN will be completed by the research team as delegated by the Sponsor.

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16. APPENDICES

APPENDIX 1: Quality of Life Questionnaire

Thinking about yourself over the last month, to what extent would you agree or disagree with the following statements

(please tick one answer per question)

	Strongly Disagree	Disagree	Disagree a little	Neither agree or disagree	Agree a little	Agree	Strongly agree
Having sensations in my teeth takes a lot of the pleasure out of eating and drinking							
It takes a long time to finish some foods and drinks because of (painful) sensations in my teeth							
There have been times when I have had problems eating ice cream because of these sensations							
I have to change the way I eat or drink certain things							
I have to be careful how I breathe on a cold day							
When eating some foods I have made sure they don't touch certain teeth							
Because of the sensations I take longer than others to finish a meal							
I have to be careful what I eat when I am with others because of the sensations in my teeth							
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							
I've been anxious that something I eat or drink might cause sensations in my teeth.							
The sensations in my teeth have been irritating							
The sensations in my teeth have been annoying							
Having these sensations in my teeth makes me feel old							

	Strongly Disagree	Disagree	Disagree a little	Neither agree or disagree	Agree a little	Agree	Strongly agree
Having these sensations in my teeth makes me feel damaged.							
Having these sensations in my teeth makes me feel as though I am unhealthy							
My sensitive teeth make me anxious in social situations that involve eating							
I have stopped eating food that cause my teeth to feel sensitive							
I have stopped eating or drinking certain things because of these sensations							
I worry that eventually with age all my teeth will get more sensitive							
The anticipation of sensitivity pain affects what I eat/drink in my daily life							
I wish to go back to a time when I didn't have sensitive teeth							
Having these sensations makes me feel like I can't enjoy life as much Thinking of these sensations is a source of stress or anxiety							

On this scale, where would you rate your sensitivity? (before/after)

APPENDIX 2: Product Use Questionnaire

Thinking about the toothpaste you have used over the last month, to what extent would you agree or disagree with the following statements

(please tick one answer per question)

	Strongly Disagree	Disagree	Disagree a little	Neither agree or disagree	Agree a little	Agree	Strongly agree
I like the flavour of the toothpaste							
I like the freshness it leaves after use							
I like the freshness during use							
The level of foam is appropriate							
My teeth feel smooth after use							

What do you like about this product?

_____

_____

What do you dislike about this product?

_____

_____

APPENDIX 3

Schiff Sensitivity Scale

This is an examiner based index [Schiff, 1994], scored immediately following administration of the a cold 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 cold stimulus, after the stimulation of each individual tooth, using the Schiff Sensitivity Scale as follows.

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

APPENDIX 4

Calibration of the Yeaple Probe

The microamp settings will vary from day to day (partly due to battery power consumption), but the difference should not be significant. Thus, previous probe settings will serve as a guide. Calibration should start at the lowest microamp setting and then increase.

The yeaple probe is fixed to a clamp attached to a ring stand so that the top is perpendicular to the pan of an ohaus dial-o-gram® balance or equivalent. The probe tip is positioned to just touch the pan when the balance is set at zero grams. The probe dial is set to the microamp setting and the gram setting is increased on the balance until the probe trips. The gram setting is recorded and the yeaple probe reset to the next microamp value.

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

The settings will be recorded on the Yeaple probe calibration record. This form will also be dated and initialled by whoever performs the calibration. For convenience a separate form should be used for each probe (record the unit's serial number on the form). This record will serve as the guide for the force setting for that day's examinations.