



## CLINICAL INVESTIGATION PLAN (CIP)

**A Medical Device study to measure the efficacy of a toothpaste containing calcium-silicate/phosphate on Dentinal Hypersensitivity compared to a control toothpaste containing fluoride.**

**Version 6 FINAL 4<sup>th</sup> October 2017**

**ORL-SEN-2530**

**NCT03244618**

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## **Approval of the Amended CIP**

I have thoroughly read and reviewed the study protocol. This study will be conducted in compliance with the protocol, the Declaration of Helsinki, principles of Good Clinical Practice (GCP) and any applicable regulatory requirement(s).

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## Glossary and Abbreviations

Abbreviation	Definition
AEs	Adverse Events
BNF	British National Formulary
CA	Competent Authority
CI	Colour index number
CIP	Clinical investigation plan
CRF	Case Record / Report Form
CRO	Clinical Research Organisation
CSSP	Calcium Silicate and Sodium Phosphate toothpaste
DH	Dental Health
DMC	Data Management Committee
EC	Ethics Committee
GCP	Good Clinical Practice
HAP	Hydroxyapatite
IEC	Investigational Ethics Committee
IFU	Instructions for Use
IRB	Investigational Review Board
ISO	International Standards Organisation
MDAEs	Adverse Effects related to the Medical Device
MedDev	Medical Device guideline
MHRA	Medicines and Healthcare products Regulatory Agency
MORE	Manufacturers online reporting environment
NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator
ppm	Parts per million
SMF	Study master file
SSRI	Serotonin specific reuptake inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
VAS	Visual Analog Score

## Contacts

[illegible]

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## **1. Introduction**

### **1.1 Background Information**

A novel technology toothpaste (Advanced Toothpaste Experimental) has been developed by Unilever which is based on the combination of calcium silicate and sodium phosphate salts. The technology augments the natural mineralisation processes of human saliva by providing additional calcium and phosphate, nucleating hydroxyapatite (HAP) formation and leading to overall remineralisation of tooth enamel mineral (HAP).

In-vitro studies to confirm the mode of action have indicated that the toothpaste can also help to block open dentine tubules and potentially protect dentine from acid challenges, which could contribute to possible anti-hypersensitivity benefits<sup>1</sup>. The results of an in-vitro study also indicate that the level of tubule occlusion increases over time. The technology has been formulated into a toothpaste containing calcium silicate, sodium phosphate salts (Monosodium Phosphate and Trisodium Phosphate).

The proposed study is being conducted to investigate the anti-hypersensitivity benefits of the toothpaste as supported by the results of the in-vitro study.

### **1.2 Anticipated Claims**

The clinical study is being conducted to support the following medical device claim:

- reduction of pain associated with dentinal hypersensitivity

## **2. Study Objectives**

### **2.1 Primary Objective(s)**

The primary objective of this superiority study is to measure the efficacy of a medical device toothpaste containing calcium-silicate/phosphate on reducing dentinal hypersensitivity compared to a negative control toothpaste.

The primary outcome measure is the thermoevaporative (Schiff air blast) stimuli after 4-weeks of product use (Day 28). Secondary endpoints are the tactile (Yeaple Probe) stimuli and the Visual Analogue Scale (VAS) after 4-weeks of product use. The tertiary efficacy endpoints are dentinal hypersensitivity as measured by all three measurements 12 hours after product use has ceased (Day 29).

### **2.2 Secondary Objective**

The secondary objective of the study is to assess the subjects' understanding of the instructions for use (IFU); as part of a usability assessment.

### **2.3 Tertiary Objective(s)**

The tertiary objectives of the study is to explore

- the relationship between gender and dentinal hypersensitivity
- if using a toothpaste containing calcium-silicate/phosphate and fluoride as instructed has an impact on the subjects' quality of life

### 3. Study Design

#### 3.1 Study Outline

This is a double blind parallel design, with respect to the clinical assessor and subject, study. A minimum of 280 (140 per group), male and female subjects will be recruited to ensure that a minimum of 200 subjects (100 per group) complete the study. Subjects will attend the test site on six (6) occasions.

Visit 1 – Enrollment

Visit 2 - Screening against the inclusion and exclusion criteria

Visit 3 – Baseline (4 weeks (+/-5days) after screening )

Visit 4 – After 14 days of product use (+/- 1 day)

Visit 5 – After 28 days of product use (+/- 1 day)

Visit 6 – After 29 days of product use (12 hours (+/-1 hour) from last brushing)

Subjects will be screened according to the inclusion and exclusion criteria. Suitable subjects will be given a standard fluoride toothpaste and a toothbrush to use for the following four to six weeks (Run-in Phase). On completion of the run in phase, the subjects will have a baseline sensitivity and soft tissue assessments conducted and randomised to product (visit 3). Subjects will be randomly assigned to the test groups according to a randomisation schedule as prepared by an independent Statistician.

Prior to leaving the test site at visit 3, the subjects will be asked to complete a quality of life questionnaire. In addition the subjects will be asked to brush their teeth as per the IFU and study staff will assess the subjects understanding of the IFU.

Subjects will be given sufficient supplies of their allocated toothpaste and a toothbrush to use for the following 2 weeks. Instructions for use (IFUs) will be given to the subjects along with a toothbrushing diary and an appointment to return to the test site 2 weeks (+/-1 day) later.

At the Day 14 visit, subjects will have the dentinal hypersensitivity and soft tissue assessments repeated. The Quality of Life questionnaire will be completed prior to the subjects leaving the study site.

Subjects will be given sufficient supplies of their allocated toothpaste and a toothbrush to use for the following 2 weeks. A fresh toothbrushing diary will be given to the subject along with an appointment to return to the test site 2 weeks later (Week 4 assessment). Subjects will be instructed to brush their teeth as per the IFU for the following 2 weeks.

At the Day 28 visit subjects will have the dentinal hypersensitivity and soft tissue assessments repeated. The Quality of Life questionnaire will be completed prior to the subjects leaving the study site. Prior to leaving the study site, the subjects will be asked to brush their teeth as per the IFU, if they were unable to brush before their test visit due to subject restrictions (see 3.2.4 Subject Restrictions). Subjects will be requested to brush their teeth at a specific time and return to the study site the following day.

At the Day 29 visit, subjects will have the dentinal hypersensitivity and soft tissue assessments repeated. On completion of the assessments, subjects will receive their remuneration for the participating in the study.

#### 3.2 Selection of Subjects

##### 3.2.1 Planned number of subjects

Screening:

A minimum of 280 subjects meeting the inclusion and exclusion criteria will be recruited.

Baseline:

A minimum of 240 subjects (120 per regimen/group) will be randomly allocated to product.

A minimum of 200 subjects (100 per regimen/group) are required to complete the study. The selection of suitable subjects will be made according to the inclusion and exclusion criteria described in the following sections.

Subjects will be recruited by the University's Clinical Trials Unit (Periodontology). The Clinical Trials Unit has a database of subjects suitable for sensitivity clinical studies.

Subjects will be screened for suitability against the inclusion and exclusion criteria shown in section 3.2.2 and 3.2.3. Inclusion and exclusion criteria are being adopted in the study to ensure that confounding issues e.g. taking of medication which may impact on dentinal hypersensitivity, are excluded.

### **3.2.2 Inclusion Criteria**

- Male and female subjects aged 18 years and older.
- Willing and physically able to carry out all study procedures.
- Willing and able to give written informed consent and complete a medical history form.
- Have at least one hypersensitive tooth in two quadrants, which are anterior to the molars and demonstrate cervical dentine, which have an air-blast hypersensitivity score of 2 or 3 on the Schiff sensitivity scale at Screening and Baseline and a tactile hypersensitivity score of 10-20 grams of force at baseline.
- Willing to comply with the oral hygiene and food and drink restrictions.

### **3.2.3 Exclusion Criteria**

- Subjects who have used anti sensitivity products in the 4 weeks prior to screening
- Subjects with an active oral ulcer (Aphthous ulcer), or have similar experience within past 1 month.
- Subjects who use a powered toothbrush at least 4 times a week to brush their teeth
- Subjects whose indicator teeth have abnormal oral pathology, for example:
  - Extensive restorations.
  - Observable caries.
  - Observable cracked enamel.
  - Leaking fillings or other restorations.
  - Cracked Tooth Syndrome
  - Suspected pulp pathology/abscess/pulpitis.
  - Atypical facial pain
  - Any tooth surface adjacent to those surfaces under investigation, which in the opinion of the investigator have any other condition(s) that provide confusing symptoms to those of cervical dentine hypersensitivity.
- Currently undergoing dental treatment, including orthodontic treatment.
- Subjects who have had vital bleaching within 4 weeks of the screening visit
- Known allergies to any toothpaste ingredients, including the flavour components.
- Obvious physical disability reducing tooth brushing ability.
- Receiving concomitant medication/therapy that might affect dentine hypersensitivity, e.g. regular use of analgesics, anti-histamines, NSAID and SSRI medication
- Severe gingivitis, periodontitis and/or marked tooth mobility.
- Gingival surgery in the previous six months.

- In the opinion of the investigator unable to comply fully with the trial requirements.
- Participation in other dental clinical trials in the previous 28 days
- Subjects who have participated in an dentinal hypersensitivity study within the previous 1 month.
- Diabetic (both Type 1 and Type 2)
- Medical condition(s) and/or regular use of any medication, which either could affect the scientific validity of the study or if the subject was to participate in the study could, affect their wellbeing.
- Smokers or e-cigarette use or those who have smoked/vaped in the previous 12 months
- Brushing  $\leq 10$  times a week during the Run-In period (self-reported)
- Using  $\leq 17g$  or  $\geq 53g$  of toothpaste in a two week period during the test phase
- The subject is an employee of Unilever or the site conducting the study.

#### 3.2.4 Subject Restrictions

- For the duration of the study, subjects will be instructed to refrain from undertaking routine dental treatment (specifically scale and polish) but subjects should not defer any necessary or emergency dental treatment. Subjects embarking on a course of medication during the study should inform the Study Coordinator so that a decision can be made as to whether they can continue.
- Before visits 2, 3, 4 and 5 subjects are required to refrain from all oral hygiene procedures and chewing gum for a minimum of 2 hours and eating and drinking for 4 hours prior to their hypersensitivity evaluation. Tap water may be sipped up to 30 minutes prior to the appointment. The restrictions on eating and drinking may further exclude pregnant women and women who are breast feeding/nursing.
- Before visit 6 subjects will be given specific instructions on when to brush their teeth. They must refrain from eating and drinking for 4 hours prior to their hypersensitivity evaluation. Tap water may be sipped up to 30 minutes prior to the appointment. The restrictions on eating and drinking may further exclude pregnant women and women who are breast feeding/nursing.
- Subjects will be asked to complete a toothbrushing diary during both the run-in and test phases of the study.
- Subjects will be asked to use the specific instructions for use (Appendix A) when they brush their teeth during the test phase of the study.

### 3.3 Randomisation Procedure

Subjects will be randomised to a product according to the tables prepared by the Statistician. Gender will be used as a stratification variable when randomising subjects to a test product.

### 3.4 Withdrawal of Subjects.

Subjects may discontinue from the clinical study at any time. In addition, the Principal Investigator (PI) or designee has the right to withdraw a subject for any reason that is in the best interests of the subject. Withdrawals due to non-attendance must be followed up to attempt to obtain the reason that the subject is 'lost to follow up'. Withdrawn subjects will not be replaced.

Subjects will be advised at the start of the study that they may withdraw from the study at any time, without giving a reason. Subjects will also be told they may be removed from the study by the Investigator without prior notice:

- If they do not follow the study protocol.
- If they fail to report to the study site when scheduled, unless suitable alternative arrangements can be made (subject to the discretion of the Investigator / Assessor).

A subject may be withdrawn from the study if, in the opinion of the PI and study staff a subject has not complied with the Instructions for Use given to them at the start of the study. Subjects may be withdrawn for non-compliance if

- a) According to their toothbrushing diary they have brushed less than 10 per week in the Run-In phase of the study
- b) Have used less than 17g or more than 53g of toothpaste between the Baseline and Week 2 assessments

All withdrawals will be documented. For withdrawals because of an adverse event or adverse effect, see Section 5. If a subject is withdrawn from the study due to an adverse event, follow up phone call and/or visits to the test site will continue until the adverse event or adverse effect has resolved.

If a subject is withdrawn from the study, no further data will be collected after the date of the withdrawal.

## 3.5 Endpoints

### 3.5.1 Assessment of Efficacy

At screening, indicator teeth will be selected by the use of the air blast method (Schiff cold air sensitivity).

Dentine hypersensitivity assessments will take place at the baseline visit and after 14, 28 and 29 days of product use. Dentinal hypersensitivity will be measured using tactile stimulation (Yeaple probe) and the air blast method (Schiff cold air sensitivity assessment). The interval time between sensitivity assessments methods will be 5 minutes (+/- 30 seconds). The score of subject's Visual Analogue Scale (VAS) values of the same teeth will also be recorded at baseline, and after 14, 28 and 29 days of product use.

#### Yeaple probe assessment:

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 cement-enamel 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, or until 20 grams (Baseline) or 60 grams (post product use) of force is reached. A force of 60 grams is considered the cut-off point at the post baseline assessments.

#### Air-blast (Schiff):

Air blast sensitivity will be assessed by directing a one-second blast of air onto the exposed buccal root surface of sensitive tooth, from a distance of one centimetre, using the air component of a dental air syringe. After shielding the adjacent proximal teeth from the air blast through the replacement of two fingers, the air blast will be applied with a pressure of 60 p.s.i. ( $\pm 5$  p.s.i) and a temperature of 19-21°C for one second.

Sensitivity will be recorded in accordance with the air sensitivity scale as described as follows:

- 0 = Tooth/Subject sensitivity does not respond to air stimulation;
- 1 = Tooth/subject responds to air stimulus, but does not request discontinuation of stimulus;
- 2 = Tooth/subject responds to air stimulus, and requests discontinuation or moves from stimulus;
- 3 = Tooth/subject responds to air stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus.

#### Visual Analogue Scale (VAS):

VAS values of the same teeth will 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).

#### Quality of Life Questionnaire

Subjects will be asked to complete a Quality of Life questionnaire at visits 2, 3, 4 and 5. The questionnaire is shown in Appendix B.

#### Label Comprehension and Ergonomics (Usability assessment)

Subjects' ability to understand the specific instructions for use (Appendix A) and the ergonomics of the medical device will be assessed at visit 3. The results of the assessment will be recorded on the CRF shown in Appendix B.

#### Soft Tissue Assessments

A visual assessment of the perioral area, lips, buccal mucosa, labial mucosa, sublingual mucosa, free and attached gingivae, tongue, hard and soft palate, Uvula, oropharynx will be made at each visit prior to any other clinical procedures being conducted.

### 3.5.2 Assessment of Safety

Adverse events (AEs) and Medical Device Adverse Effects / Incidents will be monitored throughout the study (section 5). Soft tissue assessments will be conducted at each visit and any change from enrollment will be recorded as an adverse event.

## 3.6 Concomitant medication

Any concomitant medication, including food supplements and prophylactic treatments or use of other oral medical devices will be recorded in the case report form (CRF). Subjects who are taking concomitant medications which may interact with the test products will be excluded by the Study Dentist. Examples of the concomitant medication are serotonin specific reuptake inhibitors (SSRI) and non-steroidal anti-inflammatory drugs (NSAID) medications. If a subject is taking medication the Study Dentist will consult the British National Formulary (BNF) or MIMS to check for any potential interactions.

## 3.7 Assessments at Each Visit

Following MHRA agreement and Ethics Committee approval, the Investigator will arrange recruitment and screening of potential subjects. There will be 6 visits to the clinical study center. All assessments to be conducted at each study visit are presented in Table 1.

Table 1. Time and Event Schedule

Task	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Enrolment	Screening	Baseline (4 weeks (+/- 5days after screening)	After 14 days of product use (+/- 1 day)	After 28 days of product use (+/- 1 day)	After 29 days of product use
Informed Consent Collection	x					
Medical History Check	x	x	x	x	x	x
Oral Soft Tissue Check	x	x	x	x	x	x
Inclusion / Exclusion Criteria Checked	x	x	x	x	x	x
Adverse Event Check		x	x	x	x	x
Schiff assessment		x	x	x	x	x
VAS Assessment		x	x	x	x	x
Quality of Life Questionnaire		x	x	x	x	
Run-In product and toothbrush Dispensed		x				
Toothbrushing Diary given		x	x	x	x	x
Run-In Product Returned			x			
Toothbrushing diary checked			x	x	x	x
Tactile sensitivity assessment			x	x	x	x
Randomisation to Test Product			x			
Dispensing of test product and toothbrush			x	x	x	
Use of test product at test site			x		x	

Label Comprehension Questionnaire			x			
Return of test product						x
Subject close out	x*	x*				
Remuneration	x*	x*				x

*\*For those subjects who are not suitable to participate in the study*

#### Visit 1: Enrolment

- Registration on arrival at test site, informed consent and medical history completion and oral soft tissue checks.
- Suitable subjects will be given an appointment for visit 2 and reminded that they must refrain from all oral hygiene procedures and chewing gum for between 2 and 4 hours, and eating and drinking for 4 hours prior to their following visits. Tap water may be sipped up to 30 minutes prior to the appointments.

#### Visit 2: Screening Sensitivity assessments

- After arriving at the test site, the subjects' compliance with the oral hygiene and dietary restrictions will be assessed.
- Subjects who have complied with the oral hygiene and dietary requirements will sit in the waiting room for 15 minutes to allow for acclimatisation
- Details of any adverse events and changes to medical history will be recorded
- A soft tissue pathology assessment will be conducted
- Anterior and premolar teeth will be assessed sequentially using Schiff Air-blast technique. At least one sensitive tooth in two quadrants will be selected
- Subjects meeting the inclusion criteria for sensitivity will be accepted into the study
- Subjects meeting the entry criteria will be asked to complete a Quality of Life questionnaire.
- Subjects will be provided with a fluoridated toothpaste, toothbrush and a toothbrushing diary for a wash-out period of 4 weeks duration.

#### Visit 3: Baseline measurements (Day 1) (4 weeks (+/- 5days) after screening)

- After arriving at the test site, the compliance with the oral hygiene and dietary restrictions will be assessed.
- Subjects who meet the inclusion and exclusion criteria will sit in the waiting room for 15 minutes to allow for acclimatisation
- Details of any adverse events and changes to medical history will be recorded
- A soft tissue pathology assessment will be conducted
- Hypersensitivity assessments using tactile stimulation, the air-blast technique and VAS will be conducted accordingly.
- Subjects will be randomly assigned to product
- Instructions on how to use the products will be given in the form of written instructions for use.
- Subjects will be asked to brush their teeth according to the IFU
- Study staff will record how well the subject understood the IFU (Appendix B)
- Details of the test teeth will be recorded on the instruction sheet so that the subjects know which teeth to massage with test product immediately prior to going to bed
- Quality of Life questionnaire completed
- Subjects given a toothbrushing diary to complete at home.
- An appointment for the next test visit will be given and the oral hygiene and dietary restrictions will be reinforced

#### Visit 4: After 14 days of product use (+/- 1 day)

- After arriving at the test site, the compliance with the oral hygiene and dietary restrictions will be assessed. This will include the checking of the toothbrushing diary.
- Subjects who have complied will sit in the waiting room for 15 minutes to allow for acclimatisation
- Details of any adverse events and changes to medical history will be recorded
- A soft tissue pathology assessment will be conducted

- Hypersensitivity assessments using tactile stimulation, the air-blast technique and VAS will be conducted accordingly
- Quality of Life questionnaire completed
- Subjects given a new toothbrushing diary to complete at home.
- An appointment for the next test visit will be given and the oral hygiene and dietary restrictions will be reinforced
- Additional test products provided

**Visit 5: After 28 days of product use (+/- 1 day)**

- After arriving at the test site, the compliance with the oral hygiene and dietary restrictions will be assessed. This will include the checking of the toothbrush diary
- Subjects who have complied will sit in the waiting room for 15 minutes to allow for acclimatisation
- Details of any adverse events and changes to medical history will be recorded
- A soft tissue pathology assessment will be conducted
- Quality of Life questionnaire completed
- Hypersensitivity assessments using tactile stimulation, the air-blast technique and VAS will be conducted accordingly
- Subjects will be asked to brush their teeth as per the IFU, if they were unable to brush before their test visit due to subject restrictions (see 3.2.4 Subject Restrictions)
- Subjects given a new toothbrushing diary to complete at home.
- An appointment for the next test visit will be given and the oral hygiene and dietary restrictions will be reinforced

**Visit 6: After 29 days of product use and 12 hours (+/- 1 hour) after last brushing**

- After arriving at the test site, the compliance with the oral hygiene and dietary restrictions will be assessed. This will include the checking of the toothbrush diary
- Subjects who have complied will sit in the waiting room for 15 minutes to allow for acclimatisation
- Details of any adverse events and changes to medical history will be recorded
- A soft tissue pathology assessment will be conducted
- Hypersensitivity assessments using tactile stimulation, the air-blast technique and VAS will be conducted accordingly
- Subjects will return all test products
- Study close-out: remuneration

## 4. Study Products

### 4.1 Details of Study Products

The table below details the toothpastes which will be used in the study.

Product	Description
Run-In	A toothpaste containing 1450 ppm F as Sodium Monofluorophosphate
Advanced Toothpaste Experimental	A toothpaste containing calcium silicate, sodium phosphate and Sodium Monofluorophosphate (1450 ppm F)
Negative Control	A toothpaste containing 1450 ppm F as Sodium Monofluorophosphate

Subjects will be given a commercial CCI toothbrush to use at home. A new toothbrush will be dispensed at the start of the run-In phase and at the start of the test phase.



Full details of the formulations and biocompatibility are given the Investigator's Brochure<sup>(2)</sup>.

## 4.1 Presentation and Administration

The toothbrushes will be supplied in their commercial packaging.

All toothpastes have been manufactured according to ISO 13485 [REDACTED] PPD [REDACTED] who are a ISO 13485 certified company. The toothpastes are packed into plain white laminate tubes. The tubes will be labelled according to ISO 15223. An example of the label is shown below:

**DENTAL STUDY TOOTHPASTE FOR PARTICIPANT USE ONLY**  
 Study: ORL-SEN-2530  
 Product code: XXX  
**Clinical Trials Unit (Periodontology)**  
**School of Oral and Dental Science**  
 Bristol Dental School & Hospital, Lower Maudlin Street, Bristol BS1 2LY  
 Investigator: Professor Nicola West  
 Exclusively for Clinical Investigation  
 Store in a dry, cool place  
 ⓘ **Read the leaflet/instructions for use**  
 ⓘ **WARNINGS**  
 For medical enquiries, please [REDACTED] PPD [REDACTED] at all times quoting the study number  
 Volume of product: 75ml  
**KEEP OUT OF THE REACH AND SIGHT OF CHILDREN** - Product contains fluoride  
 ⓘ **8139**  
 ⓘ **Do not use after date: 2018/11**

Subjects will be instructed to brush as normal using their allocated toothpaste twice a day, morning and evening for two minutes. Immediately prior to going to bed subjects will be instructed to apply a small amount of toothpaste to a clean, dry fingertip and gently massage the toothpaste over the two test teeth, one tooth at a time for 30 seconds. The IFU which will be given to the subjects is shown in Appendix A. Details of the product use should be recorded on the Toothbrushing Diary (Appendix B).

When the subjects brush at the test site, the date and time the subjects brushed will be recorded on the CRF.

## 4.2 Storage

The test products will be stored securely in a dry, cool place at the study site until dispensed.

## 4.3 Accountability

Each individual toothpaste tube will be numbered with a four digit number, starting at 0001. Dispensing logs will be kept. The individual number of each tube dispensed to the subject will be recorded on the dispensing log. Subjects will be asked to initial and date the log when product is dispensed. Subjects will be asked to return all used and unused tubes of toothpaste. Study staff will record the number of used and unused tubes returned by the subject at each visit, weight them and check that the individual numbers of the tubes the subject has returned, matches those that which were dispensed.

Subjects will be asked to complete a usage diary (Toothbrushing Diary) to record how often they have used the toothpaste in between test visits.

## 4.4 Breaking the Code in an Emergency

The codes for the products will be maintained in the study file in a sealed envelope and only broken in case of a serious adverse event where knowing the identity of the product used would facilitate treatment. If breaking code happens during the study, the Clinical Research Organisation (CRO) will record details: who initiate this requirement, time informed the sponsor, when the code was broken, how many staffs and subjects involved etc.

## 4.5 Instructions for Use

Each subject will be given verbal and written instructions for use. The written instructions for use are shown in Appendix A.

## 5. Safety Monitoring

Before undertaking the study a Risk Assessment has been conducted according to ISO 14971. The output of the Risk Assessment are stored in the Study Master File (SMF).

### 5.1 Adverse Event and Medical Device Adverse Effects

An adverse event (AE) is any untoward medical occurrence in a subject whether or not related to study product or 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 Medical Device Adverse Effect (MDAE) is any untoward medical occurrence in a subject which is related to the study product. Medical Device Adverse Effects also include any adverse events resulting from insufficient or inadequate instructions for use (IFUs) and any event resulting from use error or from intentional misuse of the medical device.

No significant adverse effects or medical device adverse effects are expected during the study. AEs and MDAEs will be monitored and recorded throughout the study. Once the AEs and MDAEs have been reviewed, depending on the outcome, the Sponsor may consider a separate safety study.

#### 5.1.1 Exceptions

The following medical occurrences will not be reported as AEs in any study sponsored by Unilever;

- Pre-treatment Adverse Events; Any medical occurrence that occurs after informed consent, but before first administration of study product or first study procedure 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 subject's baseline condition are reported as medical history, not AEs.
- Pregnancy; This is not an AE however the PI must report any pregnancies to Unilever for advice regarding the appropriate course of action.
- Overdose; If the amount of study product that is taken or applied is higher than that stated in this protocol, this is not an AE. However any clinical sequelae (signs or symptoms) of the overdose must be reported as an AE. A MDAE must be recorded if the subject is assigned to the investigational product.

### 5.2 Serious Adverse Event

A serious adverse event (SAE) is an AE that results in any of the following outcomes: death; a life-threatening event; in-patient hospitalisation; prolongation of existing hospitalisation; a persistent or significant disability/incapacity; a congenital anomaly or birth defect. Any other important medical event may be considered a SAE when the event may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or convulsions that do not result in in-patient hospitalisation. Just as a stable pre-existing condition is not an AE, hospitalisation for elective treatment (e.g. cosmetic or dental procedure) of a pre-existing condition that did not worsen from baseline is not an SAE.

### 5.3 Severity and Relatedness of Adverse Events

An AE will be recorded only once, with the most extreme severity. Severities are defined as:

<b>Mild</b>	Awareness of symptoms which require minimal or no treatment and do not interfere with daily activity
<b>Moderate</b>	Discomfort or low level of interference which is enough to interfere with but not prevent daily activity
<b>Severe</b>	Interrupted or unable to perform usual daily activity and usually requires treatment.

The likelihood that the AE was related to the study product or study procedure is defined as;

<b>Not Related</b>	The AE is clearly due to an alternative cause, even if this cannot be definitely identified. Alternative causes include disease or environmental factors.
<b>Unlikely</b>	A connection between the AE and the study product or procedure is unlikely. <ul style="list-style-type: none"> <li>• The AE has a relationship in time to the study product or procedure</li> <li>• An alternative cause (e.g. disease or environmental factors) is the most likely explanation, even if this cannot be identified.</li> </ul>
<b>Possibly</b>	A connection between the AE and the study product or procedure cannot be ruled out with certainty. <ul style="list-style-type: none"> <li>• The AE has a relationship in time to the study product or procedure</li> <li>• An alternative cause (e.g. disease or environmental factors) seems likely or possible or there is significant uncertainty about the cause of the AE.</li> </ul>
<b>Probably</b>	There is a high degree of certainty that the AE is related to the study product or procedure. <ul style="list-style-type: none"> <li>• The AE has a relationship in time to the study product or procedure</li> <li>• A possible alternative cause may be present.</li> <li>• AE disappears or decreases on withdrawal or reduction of study product or procedure (if performed).</li> </ul>
<b>Definitely</b>	The AE is clearly related to the study product or procedure. <ul style="list-style-type: none"> <li>• There is a strong relationship in time</li> <li>• An alternative cause is unlikely</li> <li>• AE disappears or decreases on withdrawal or reduction of study product or procedure (if performed)</li> </ul>

### 5.4 Reporting of Adverse Events

All minor adverse events (AEs) will be recorded in the Case Report Form (CRF) and submitted to Unilever the within 7 days of being reported to the study staff. The site staff must maintain source documents to fully record all AEs.

Additionally Serious Adverse Events (SAEs) and AEs that may affect the safety or continued participation of subjects on the study must be reported immediately. An SAE must be reported to Unilever with 24 hours of the site staff becoming aware of the event. The contact details for reporting any expedited AE are given in the Contacts section of this protocol.

All adverse events will be reported to the Competent Authority (CA) in accordance with the requirements of MedDev guideline 2.7/3 rev 3, via the Manufacturers Online Reporting Environment (MORE) or directly to the CA. The EU reporting form must be used for all device SAEs.

## 5.5 Follow-up of Adverse Events

If an AE is ongoing at the end of the study, follow-up will be performed until the AE has resolved, unless the PI and the Unilever contact named in the protocol agree that no further follow up is necessary. Follow-up may take the form of subject visits, a referral to another specialist, site telephone calls to the subject or letters from the treating physician. For expedited AEs, if applicable, the PI will submit follow up reports on additional expedited report forms.

The PI or designee must comply with the specific reporting requirement(s) of the ethics committee, reporting as a minimum any Serious Unexpected Suspected Adverse Reaction (SUSAR) which is an unexpected SAE that may be related to study product or procedure.

## 5.6 Pregnancy Testing

There is no known risk to the foetus associated with the use of the study products and/or procedures in this study. It is not required to take any additional contraceptive precautions or perform any pregnancy testing prior to inclusion of females of child bearing potential into this study.

## 5.7 Residual Risks

We do not anticipate any residual effects for the subjects on completion of the study.

## 6. Statistical Considerations

### 6.1 Sample Size Calculation

It is anticipated that 200 subjects will complete the study with 100 subjects per group. The primary outcome measure is the thermoevaporative (Schiff air blast) stimuli after 4-weeks of product use (Day 28). Based on published studies which have evaluated other efficacious anti-sensitivity technologies using this stimuli the standard deviation is not expected to exceed 1.0. Using this estimate a sample size of 200 subjects would give 80% power to detect a difference of 0.4 between the treatment groups.

### 6.2 Definition of Analysis Population

Data will be analysed using intention to treat (ITT) and per protocol. For the ITT analysis, all available data from subjects allocated to product will be analysed. For the per protocol analysis, data from randomised subjects will be included if there were no major protocol violations and have at least one post baseline efficacy assessment. Any outlier exclusion of the raw data will be documented by the statistician at Blind Data Review and discussed with clinical lead. The clinical lead will then confirm if there was a major protocol deviation and if the data can be used in the per protocol analysis.

A Blind Data Review analysis will be conducted prior to finalising the Analysis Population.

### 6.3 Statistical Methods

Dentinal hypersensitivity will be measured using tactile (Yeaple Probe) and thermoevaporative (Schiff air blast) stimuli at baseline and after 14, 28 and 29 days of product use. The subject's perception of pain will also be assessed at these time points using the visual analogue scale (VAS). Details of how each measurement is taken is included in the CIP.

The primary outcome measure is the response to thermoevaporative (air blast) stimuli as measured by Schiff score. The successful outcome will be measured by a statistically significant reduction in dentinal sensitivity as measured by the thermoevaporative (Schiff air blast) stimuli after 28 days of product use.

The secondary outcome measures are tactile (Yeaple Probe) stimuli and the Visual Analogue Scale (VAS). The successful outcome will be measured by a statistically significant reduction in dentinal sensitivity as measured by the tactile (Yeaple Probe) stimuli and the Visual Analogue Scale (VAS) after 28 days of product use.

The tertiary measure of success is the statistically significant reduction in dentinal sensitivity as measured by all three measurements 12 hours after product use.

For each of the tactile stimulation, Schiff and VAS scores, the following analyses will be performed. Each subject will be characterised at each visit by the average of the relevant scores for the two indicator teeth. The usual summary statistics will be reported for the data at each assessment time. Changes from baseline to each assessment time will be calculated and summarised similarly.

The main analysis of efficacy will compare the mean Schiff scores after 4 weeks product use between active and control groups. It is anticipated that conformity to Gaussian distributional form will be adequate to support parametric analyses. A mean difference will be reported, with 95% confidence interval and p-value.

In this trial, because teeth are selected to be essentially similarly sensitive at baseline, it is anticipated that the correlation between response and baseline scores will be weak, consequently there is no strong indication for baseline covariate adjustment. Analysis of covariance using baseline score as covariate will be examined as a supportive analysis. Furthermore, in the event of substantial departure from Gaussian distributional form, scale transformation and/or equivalent non-parametric analyses will be developed, as supportive analyses.

For the DH-related quality of life questionnaire data subject will be characterised by an average score, scaled from -1 to +1, at each visit. These scores will be analysed similarly. In all these analyses, estimated treatment effects will be reported with 95% confidence intervals, as well as p-values.

The air blast response (Schiff score) will also be dichotomised, and analysed as in Newcombe (2003, 2013) to assess the percentage reduction in number of sensitive teeth, with a 95% confidence interval.

The dental health (DH)-related quality of life questionnaire data will be examined at baseline to determine correlations between items. It is anticipated that correlations will be positive, substantial and reasonably consistent. If this is the case, each subject will be characterised by an average score, scaled from -1 to +1, at each visit. These scores will be analysed similarly to the clinical scoring variables.

Appropriate exploratory statistical analysis techniques will be used to analyse the Quality of Life and Label Comprehension (usability) Questionnaire.

Exploratory objectives – differences in sensitivity by gender will be evaluated.

## **6.4 Data Management Committee**

A data management committee (DMC) will not be convened for this study as each subject is involved in the study for a short duration (approximately 8 weeks)

## **7. Monitoring**

The PI agrees that the site will permit, if required, study-related monitoring, audits, Investigational Review Board (IRB)/ Investigational Ethics Committee (IEC) review, and regulatory inspection(s), providing direct access to source data/documents.

Unilever personnel and their designees will monitor the study. The monitor has the responsibility to familiarise the PI and the entire centre staff involved in the study with all study procedures. The monitor can visit the clinical study centre on a regular basis such as before the first subject has been enrolled, during the course of the study, and at study completion. The monitor must maintain the confidentiality of the study documents.

A monitoring plan will be prepared prior to the first subject first visit.

## ***8. Data Handling and Record Keeping***

There will be at least eight CRFs for each subject randomised into the study. It is the responsibility of the PI to ensure the completeness and accuracy of the CRF and to authorise only trained members of staff to complete the CRF.

The CRFs are as follows

- Demographics
- Inclusion/Exclusion criteria assessment
- Soft tissue pathology CRF
- Tactile stimulation
- Schiff Assessment
- VAS assessment
- Quality of Life Questionnaire
- Label Comprehension questionnaire

The CRF must be completed legibly, using a black ballpoint pen. Erroneous values and/or text must not be obliterated. Instead, the error must be crossed out with a single line, the correct value/text added, and the correction signed or initialled and dated. At the end of the study, the original CRFs will be sent to Unilever and copies held at the study site.

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 must ensure that the subject's anonymity will be maintained. On all documents that are to be submitted to Unilever or external laboratory, subjects must be identified only by an identification code and not by their names. The PI or designee must keep a separate confidential enrolment log that matches identifying codes with the subject's names and addresses. The PI or designee must maintain these documents at the site.

It is the responsibility of the PI or designee to maintain adequate clinical study records. Copies of all clinical study material must be archived for a period of at least 15 years after the end of the study (or more as legally required) or until informed by Unilever that the documents can be destroyed. All documents must be archived in a secure place and treated as confidential material.

## ***9. Quality Standards***

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

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

## ***10. Ethics and Informed Consent***

The PI or designee must submit a copy of the protocol, subject information sheet and consent form to an Independent Ethics Committee or Institutional Review Board who must provide written approval before study specific procedures commence. The IEC/IRB must also approve any other information that is given to subjects such as advertisements and may require other documents such as study product documentation.



Any modification to the agreed protocol must be agreed by both Unilever and the PI and approved in writing by the IEC/IRB. Written approval must be obtained from the IEC/IRB before any amendment is implemented, unless immediate change is required to eliminate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor(s), telephone number(s)).

The PI or designee must obtain informed consent from each subject participating in the study, after explanation of the aims, methods, benefits and potential hazards of the study. The consent must be obtained before any study-specific procedures are performed. It must be made completely and unambiguously clear to each subject 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 subject must be given their own copy of the information sheet and signed consent form. The original signed informed consent must be kept on file by the PI or designee.

## **11. Finance and Insurance**

CCI

CCI

CCI

CCI

## **12. Reporting and Publication Policy**

CCI

CCI

The study will be registered on [clinicaltrials.gov](https://clinicaltrials.gov) by the Sponsor.

### **13. References**

1. The investigation of a novel toothpaste for in-vitro dentine tubule occlusion via simulated brushing. Unilever Oral Care R&D Report REP 0030 Version 1 24<sup>th</sup> October 2014 Pages 1 to 14
2. Investigator's Brochure: A Medical Device study to measure the efficacy of a toothpaste containing calcium-silicate/phosphate and fluoride on Dentinal Hypersensitivity compared to a control toothpaste containing fluoride. Version 1 FINAL 30<sup>th</sup> November 2016



## Appendix A – Instructions for use

### INSTRUCTIONS FOR USE

Please read usage instructions carefully before use.

#### What is hypersensitivity?

Tooth sensitivity (dentine hypersensitivity) is normally caused by dentine becoming exposed. Dentine is the layer underneath tooth enamel. There are many reasons why the dentine becomes exposed, but the most common reasons are if the enamel is worn away through brushing too hard or if the gums recede. Dentine is substance that is full of tubes which connect the surface of the tooth with its inner core. This inner core contains nerves and blood vessels. The tubes are filled with a fluid. When the fluid flow within dentine is changed, the fluid movement causes the nerve endings to react, triggering a short, sharp pain. Some food and drinks, particularly if they are hot or cold, can cause changes in the fluid flow in these tubes. A similar effect can be experienced when eating chocolate or something very salty or drinking strong alcohol. The pain you feel is not harmful and usually only lasts for a short time.



-02-2017

#### Usage instructions

Use twice a day: in the morning and evening.

Brush for at least 2 minutes using your normal routine

Minimise swallowing and spit out

After brushing at night:

- 1) Apply a pea-sized amount of toothpaste onto the tip of a clean, dry finger.
- 2) Massage the toothpaste gently onto the sensitive tooth surface for 30 seconds of the teeth indicated in the picture below
- 3) Do not spit out.

Please massage the toothpaste onto the surfaces of the teeth indicated.



Before you use the toothpaste for the first time you will need to remove and dispose of the aluminium seal.

To protect the toothpaste from moisture, close the cap after each use.

Store in a dry and cool place.



#### Warnings

Contains: Sodium Monofluorophosphate (1450 ppm fluoride) and Limonene

For oral use only

For subject use only

**Keep out of the reach and sight of children**

Do not brush your teeth more than 3 times a day

For medical enquiries please call **PPD** at all times quoting the study number ORL-SEN-2530.

In case of questions, please call **PPD** at all times quoting the study number ORL-SEN-2530.

## Appendix B – Label Comprehension and Ergonomics

### Assessment of Label Comprehension and Ergonomics

**Subject Number:**  **Date of Assessment:**   
(DDMMYYYY)

**Product Code:**

Please ask the subject to imagine it is evening and to brush their teeth following the instructions. Please assess the subject undertaking the following tasks. Do not speak to or guide the subject if they are having a problem. Please do not ask the subject any of the questions detailed below. If you answer 'No' to any question, with the exception of the questions on rinsing, please give more details on the reverse of the questionnaire. Please give as much detail as possible to each negative response.

		No	Yes
1	Can the subject remove the outer cap from the tube of toothpaste?		
2	Can the subject remove the foil seal from the nozzle of the toothpaste?		
3	Can the subject squeeze a ribbon of toothpaste onto the toothbrush?		
4	Did the subject brush their teeth for the recommended time?		
5	Did the subject rinse their teeth after brushing?		
6	Did the subject apply the toothpaste using the finger?		
7	Did the subject massage the toothpaste on the correct teeth?		
8	Did the subject massage the toothpaste for the correct time period?		
9	Did the subject rinse after applying the toothpaste?		

Please ask the subject any of the questions detailed below. If you answer 'No' to any question, with the exception of the questions on rinsing, please give more details on the reverse of the questionnaire. Please give as much detail as possible to each negative response. The images are shown on page 3.

		No	Yes
10	Show the subject image 1. Do they understand what it means?		
11a	Show the subject image 2. Can the subject tell you what population should use the toothpaste?		
11b	Show the subject image 2. Does the subject understand the warnings?		
12	Show the subject image 3. Do they understand what it means?		
13	Show the subject image 4. Do they understand what it means?		
14	Show the subject image 5. Do they understand what it means?		

If you have completed all the questions and the comments section, please thank the subject for their time. Please make sure they have their allocated toothpaste, a toothbrush, a toothbrushing diary and instruction sheet and appointment for their next visit prior to leaving.

Questionnaire completed by: \_\_\_\_\_

<b>Subject Number:</b>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<b>Date of Assessment:</b>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
				(DDMMYYYY)								

Comments:

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IMAGE 1:



**Read the leaflet/instructions for use**

IMAGE 2:



**Warnings**

Contains: Sodium Monofluorophosphate (1450 ppm fluoride) and Limonene

For oral use only

For subject use only

**Keep out of the reach and sight of children**

IMAGE 3


 8139

IMAGE 4

 Do not use after date: 2018/11

IMAGE 5



**02-2017**

Please record below when you brush your teeth.

[illegible]

Please record below when you brush your teeth.

[illegible]

## Appendix D – Quality of Life Questionnaire

Subject Number:    Date of Assessment:          
(DDMMYYYY)

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							
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							

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	Strongly Disagree	Disagree	Disagree a little	Neither agree or disagree	Agree a little	Agree	Strongly agree
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?



	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?

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What do you dislike about this product?

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