CLINICAL PROTOCOL

A Randomized, Examiner Blind, Crossover, *in situ* Erosion Study To Investigate The Efficacy Of An Experimental Dentifrice In Remineralization Of Softened Enamel Compared To Placebo and Reference Dentifrices

Protocol Number:	300057
Compound/Product Name:	Sodium Fluoride and Potassium Nitrate
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This document contains confidentiality statements that are not relevant for this publicly available version

Sponsor Information

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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	Change to description of number of subjects required from "approximately 33 subjects" to "up to 33 subjects" randomized and a change from "to ensure approximately 30 subjects complete" to "to ensure at least 30 subjects complete".
Amendment 2	3.0	Clarification that a ±10 mins window for appliance re-insertion following lunch/dinner is acceptable.

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

Principal Investigator Protocol Agreement Page

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

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

Short Title:

An *In Situ* Erosion Study to Investigate the Efficacy of an Experimental Dentifrice to Remineralize Enamel.

Background and Rationale:

This study will investigate the ability of an experimental dentifrice containing 1150ppm fluoride to remineralize acid-softened dental enamel and help prevent further demineralization compared to a 0ppm fluoride placebo dentifrice and a marketed, fluoride-containing dentifrice (Reference Dentifrice). The study will utilize an established *in situ* model where partially demineralized enamel specimens will be placed in a dental palatal appliance, treated intra orally then allowed to remineralize *in situ* for 4 and 12 hours. Efficacy will be evaluated through laboratory measurement of the surface microhardness recovery (SMHR), relative erosion resistance (RER), acid resistance ratio (ARR) and the enamel fluoride uptake (EFU).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to enhance remineralization of enamel compared to a placebo dentifrice (0ppm fluoride) after 4 hours of intra-oral exposure.	%SMHR at 4 hrs.
Secondary	
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to inhibit demineralization of enamel compared to a placebo dentifrice (0ppm fluoride) after 4 hours of intra-oral exposure.	%RER at 4 hrs.
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to enhance remineralization of enamel compared to a marketed, reference dentifrice containing 1100ppm fluoride after 4 hours of intra-oral exposure.	%SMHR at 4 hrs.
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to enhance remineralization of enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed, reference dentifrice containing 1100ppm fluoride after 12 hours of intra-oral exposure.	%SMHR at 12 hrs.
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to inhibit demineralization of enamel compared to a reference dentifrice containing 1100ppm fluoride after 4 hours of intra-oral exposure.	%RER at 4 hrs.
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to inhibit demineralization of enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed, reference dentifrice containing 1100ppm fluoride after 12 hours of intra-oral exposure.	%RER 12 hrs.
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to promote fluoride uptake in enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed, reference dentifrice containing 1100ppm fluoride after 4 and 12 hours of intra-oral exposure.	EFU at 4 and 12 hrs.

To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to reduce future acid-induced demineralization in enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed, reference dentifrice containing 1100ppm fluoride after 4 and 12 hours of intra-oral exposure.	ARR at 4 and 12 hrs.
To investigate the efficacy of a marketed, reference dentifrice containing 1100ppm fluoride. to enhance remineralization, inhibit demineralization, to reduce future acid-induced demineralization and to promote fluoride uptake in enamel compared to a placebo dentifrice (0ppm fluoride) after 4 and 12 hours of intra-oral exposure.	%SMHR, %RER, EFU, ARR at 4 and 12 hrs.
Exploratory	
To calculate the proportion of subjects who evidence a RER ratio (%RER 0ppm fluoride placebo and 5% KNO_3 : %RER experimental dentifrice containing 1150 ppm fluoride) >=3 and >=2.5	%RER at 4 and 12 hrs.
Safety	
To assess the oral tolerability of an experimental dentifrice containing 1150ppm fluoride and 5% KNO_3.	Treatment emergent adverse events

Abbreviations: SMHR: Surface micro hardness recovery, RER: Relative erosion resistance, EFU: Enamel fluoride uptake, ARR: Acid resistance ratio, KNO_3: potassium nitrate.

Study Design:

This will be a randomized, controlled, single center, single- blind (to the dental examiner and specimen analysts), 3 period, 3 treatment, cross-over, *in situ* design. Previously demineralized bovine enamel specimens will be place intra orally using a palatal appliance and the remineralizing performance of the experimental, reference and placebo dentifrices evaluated at 4 and 12 hours post toothbrushing, based on surface micro hardness measurements of the bovine enamel specimens. This study will be carried out in healthy adults with a maxillary dental arch suitable for the retention of the palatal appliance. Subjects will be recruited from an existing panel of subjects pre-fitted with a palatal appliance.

In this study there will be 7 visits, 1 screening visit to assess subject eligibility, 3 treatment visits, where the study dentifrices will be dispensed and used under the supervision of a suitably trained study site personnel, and 3 follow up visits to perform an OST examination, assess for Adverse Events and allow the subject to return their palatal appliance. Sufficient subjects will be screened to randomize up to 33 subjects to study treatment to ensure at least 30 subjects complete the study. At screening (Visit 1), subjects will give their written informed consent to participate in the study. Demography, relevant medical history and current medications/treatments will be recorded, followed by oral soft tissue (OST) and oral hard tissue (OHT) examinations. Subjects will then have their stimulated and unstimulated salivary flow rates measured and subjects meeting the relevant study inclusion/exclusion criteria will try-in their palatal appliance and be considered eligible to enroll in the study. Enrolled subjects will then be dispensed the wash-out dentifrice, toothbrush and diary.

Prior to each treatment visit, there will be a washout period of a minimum of 3 days. During this period subjects will use their own dentifrice and toothbrush for at least one day, and a 0ppm fluoride washout dentifrice and study toothbrush (provided) for two days immediately prior to the next scheduled visit (including on the morning of the scheduled visit).

At treatment visits (Visits 2, 4 & 6), subjects will provide details of their concomitant medications and undergo an OST examination. Subject's diaries will be reviewed to ensure compliance with the use of the wash-out dentifrice. Subjects deemed suitable to continue in the study will be randomized to the order of treatments (Visit 2 only) and wear an oral palatal

appliance holding 8 bovine enamel specimens. Details of enamel specimen preparation will be specified in the Laboratory Procedures Document. The palatal appliances will be specifically made for each eligible subject, and each will carry two plastic holders containing a total of eight bovine enamel specimens (four in each holder). Once the appliance is fitted in the mouth, a five minute equilibration period will ensue following which each subject will brush their teeth with their assigned product, one product per treatment visit as described below.

Under supervision while the intraoral appliance is in place, the subjects will brush the buccal surfaces of their natural teeth using 1.5±0.1g of dentifrice and a soft toothbrush for 25 seconds to create a slurry. Subjects will be instructed not to expectorate the slurry and will then swish the slurry around their mouth for 95 seconds to permit direct contact of the dentifrice slurry with the enamel specimens. After expectorating the slurry, the subjects will gently rinse their mouths with 15 mL of tap water for 10 seconds before expectorating again. The toothbrush, however, will not come into contact with the enamel specimens or the appliance as this could cause abrasion of the enamel specimens.

Subjects will then remain at the study site for 4 hours post toothbrushing when their appliance will be removed (at 4hrs ±10 mins post toothbrushing) and 4 designated enamel specimens will be withdrawn from the appliance. Subjects will then be served an optional lunch which will be consumed within a 30 ±10 minute time period. The subjects will then brush and rinse their mouth with water, after which they will have their appliance reinserted and be allowed to leave the site. Subjects will be reminded to not eat or drink (except for water) while wearing their appliance.

Subjects will be given verbal and written home instructions/diary which will instruct them to remove their appliance at 8.5 hours following the toothbrushing. The time for removal will be detailed on the instruction/diary sheet. They will be allowed to eat a meal of their choice over a 30 ±10 minute timed period, brush their teeth and rinse their mouth with water and refit their appliance after the 30 ±10 minute timed period is up. After 13 ±0.5 hours following the initial brushing time, the subject will be instructed to remove their appliance, rinse it under running water and store moist in the supplied container in their refrigerator overnight. The time for this removal will also be given on their instruction/diary sheet. In addition, a member of the study team will give a reminder call to the subject prior to the completion of the 12 hour intraoral exposure. Subjects will then attend a follow-up visit (Visits 3, 5 and 7) the following day to return their appliance to the site and to receive an OST examination to evaluate any potential oral AEs. At Visit 6 only, the subjects will return their washout dentifrice and at the final post treatment visit (Visit 7) the subject will also receive an OHT exam and end of study documentation will be completed.

The enamel specimens will be evaluated both prior to and after intra-oral exposure. Surface microhardness (SMH) will be used to evaluate changes in the mineral content of enamel and is used to calculate surface micro hardness recovery (%SMHR), relative erosion resistance (%RER) and acid resistance ratio (ARR). The incorporation of fluoride into the enamel specimens will be assessed by enamel fluoride uptake (EFU) measurements. For each treatment and subject, these measurements will be performed on the same enamel specimen as described in the Laboratory Procedure Document, in the four enamel specimens removed at each time point. The erosive acid challenges, with a commercially available grapefruit juice, will be carried out *ex vivo* and therefore does not pose a risk to the subject's teeth.

AEs and medical device incidents will be monitored through out the study and recorded at every site visit following signing of informed consent.

Study Products:

Test Dentifrice	Placebo Control	Reference Dentifrice
Experimental Dentifrice containing 1150ppm fluoride and 5% KNO_3*	0ppm fluoride dentifrice containing 5% KNO_3	Crest Pro-Health Densify Daily Protection

* KNO_3 is commonly used in other marketed anti sensitive toothpaste.

All dentifrices will be applied in the same manner by brushing 1.5±0.1g of dentifrice on to the buccal surfaces of their natural teeth for 25 timed seconds and then swishing the resulting dentifrice slurry around the mouth, without further brushing, for a timed period of 95 seconds.

Subjects will use a 0ppm fluoride washout dentifrice twice daily for 2 days prior to each treatment visit in place of their usual oral hygiene practice.

Type and Planned Number of Subjects:

Study subjects of either sex and any gender, aged 18-65 years, who are in good general health and a maxillary dental arch suitable for the retention of the palatal appliance.

Sufficient subjects will be screened to randomize up to 33 subjects to study treatment to ensure at least 30 evaluable subjects complete all periods of the study.

Statistical Analysis:

The %SMHR, %RER and ARR at the subject visit level (to be used in the analysis) will be derived as the mean of the specimen means (across replicates within a specimen) within that visit.

The mean EFU across specimens relating to a specific timepoint (4 or 12 hours) will be derived to represent the visit level EFU at the timepoint to be used in the analysis.

A separate mixed model (including results across all 3 study products) will be used to analyze each parameter at each timepoint (4 or 12 hours) with fixed effects for treatment and study visit, as well as random effect for subject. Kenward Rogers degrees of freedom approach will be applied. The least square means for each study product will be presented along with the 3 pairwise differences of interest between least square means (including two-sided p-value and 95% confidence interval) to test for a difference between products.

Statistical testing of all endpoints in this study will be conducted at a two-sided significance level of 0.05. A sequential testing strategy will be applied to preserve the overall type-1 error control for the respective sequential comparisons between the Experimental dentifrice and Placebo Control at 12 hours for the %SMHR (primary endpoint) and %RER (secondary endpoint). There will be no further adjustments for multiplicity.

1.2 Schedule of Activities

The schedule of activities table provides an overview of the subject visits and study procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, to conduct evaluations or assessments required to protect the well-being of the subject.

Procedure/Assessment	Screening	Study Period 1			Study Period 2			Study Period 3		
	Visit 1		Visit 2 (Treatment)	Visit 3 (V2+1day)		Visit 4 (Treatment)	Visit 5 (V4+1day)		Visit 6 (Treatment)	Visit 7 (V6+1day)
Informed consent	X	Minimum 3 days including a 2 days washout using supplied non-fluoride dentifrice			Minimum 3 days including a 2 days washout using supplied non-fluoride dentifrice			Minimum 3 days including a 2 days washout using supplied non-fluoride dentifrice		
Demographics	X									
Medical history	X									
Current/prior/concomitant medication review	X		X	X		X	X		X	X
OST Examination[1]	X		X	X		X	X		X	X
OHT Examination	X									X
Assessment of stimulated and unstimulated saliva flow rate[2]	X									
Review of inclusion/exclusion criteria	X									
Try-in of palatal appliance	X									
Subject eligibility	X									
Dispense wash-out products and diary	X									
Diary review			X	X		X	X		X	X
Subject continuance			X	X		X	X		X	
Randomization to treatment sequence			X							
Place palatal appliance fitted with enamel specimens into subject's mouth[3]			X			X			X	
Supervised toothbrushing			X			X			X	
Intra oral phase 4 hours [3,4]			X			X			X	

Procedure/Assessment	Screening	Study Period 1		Study Period 2		Study Period 3	
	Visit 1	Visit 2 (Treatment)	Visit 3 (V2+1day)	Visit 4 (Treatment)	Visit 5 (V4+1day)	Visit 6 (Treatment)	Visit 7 (V6+1day)
Intra oral phase 12 hours [3,5]		X		X		X	
Adverse events review[6]	X	X	X	X	X	X	X
Medical device incidents review[1]		X	X	X	X	X	X
Return wash-out products						X	
Return palatal appliance			X		X		X
Study conclusion							X

Abbreviations: OST: Oral Soft Tissue, OHT: Oral Hard Tissue.

Footnotes:

1. At Visits 2, 4 & 6 OST examination will be performed prior to insertion of the appliance and at Visits 3, 5 & 7 when the subject returns their palatal appliance.
2. Re-evaluation of saliva flow may be required within the study should the subject begin a treatment of medications likely to induce xerostomia.
3. Laboratory analysis of enamel specimens performed prior to placing and after removing the specimens from the palatal appliance as described in the separate laboratory procedures document.
4. Four enamel specimens will be removed from the palatal appliance after wearing the appliance for 4 hours ± 10 min after toothbrushing. Subject will be offered lunch to be eaten over a 30 ±10 minute period and then be allowed to leave the site with instructions on how and when to eat dinner (30 ±10 minute period between hours 8.5 and 9), and remove (hour 13), store and return their appliance.
5. Subjects will remove their appliance after 12 hours ± 30 mins of wearing post toothbrushing (13 ±0.5 hours since brushing with product). Subjects will then rinse and store the appliance as instructed by the site staff. Subjects will return the appliance to the study site the following day. The study site staff will recover the 4 remaining enamel sections, then the appliance will be cleaned, disinfected and stored at site until the next treatment visit.
6. Adverse Events (AEs), Serious Adverse Events (SAEs) and medical device incidents collected from immediately after subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF). Medical device in this study is the supplied toothbrush.

2 INTRODUCTION

Dental erosion is the irreversible loss of tooth substance by chemical processes not involving bacteria. It is a cyclical process, influenced by demineralization and remineralization. Demineralization of the enamel surface can occur by the exposure to acids either from internal origin, such as gastric acids from refluxes, and or external from dietary sources; if of sufficient frequency and severity. The erosive challenges *in vivo* are brief and it's unlikely they are a major cause of surface loss when occurring on their own (Shellis et al., 2011), but this softening of the hard tissues surface makes it more susceptible to further physical wear from abrasion (tooth brushing) and attrition (grinding) resulting in tissue loss. The process of demineralization cycles with remineralization, which is the process of placing minerals back into the previously demineralized hard tissue by the ionic constituents of saliva, ideally to achieve mineral that is more resistant to subsequent demineralization (Cochrane et al., 2012).

It is well accepted that fluoride containing dentifrices should be part of an appropriate clinical management strategy for the prevention of caries (Brunelle and Carlos, 1990) (Stephen, 1993) (Bartizek et al., 2001) and to promote tooth remineralization and reduce demineralization (Featherstone et al., 1990) (Chow, 1990). Fluoride can be administered in many different forms, most commonly sodium fluoride (NaF), sodium monofluorophosphate (NaMFP) and stannous fluoride (SnF_2). However, besides the fluoride form and concentration, there are other aspects of a dentifrice that have an influence in the uptake of fluoride to enamel as has been shown in *in vitro* and *in situ* investigations (Barlow et al., 2009, Fowler et al., 2006, Fowler et al., 2009).

In vitro and *in situ* erosion models are the most commonly used methods to investigate the short-term performance of new dentifrice formulations indicated for dental erosion (Shellis et al., 2011). Currently, there is no validated clinical methodology or clinical index to monitor the progression of erosive tooth wear and enamel tissue loss (Shellis et al., 2011), and most of the devices used for detection of changes in mineral content can only be performed on specially prepared specimens (Attin, 2006). *In situ* dental erosion models involve the use of appliances or other devices in the human mouth that simulate the process (Zero, 1995) and they allow the effect of an erosive challenge to be evaluated under intra oral conditions but with some controlled experimental variables. *In situ* models are placed in between the continuum of *in vitro* models and clinical studies and can provide evidence of the potential effect of new therapies in inhibiting demineralization and promoting remineralization (Zero, 1995). However, the extrapolation of their result to clinically relevant evidence must be carefully considered.

In this study, an *in situ* dental erosion model will be used to investigate the efficacy of an experimental dentifrice in promoting the enamel remineralization of previously demineralized (eroded) bovine enamel. The experimental dentifrice will contain 1150ppm fluoride (as sodium fluoride [NaF]) and 5% w/w potassium nitrate [KNO_3], an ingredient with well-established efficacy at providing relief from dentinal hypersensitivity (Schiff et al., 1994, Gillam, 1996). This study will employ as a reference control a marketed, dentifrice indicated for erosion and containing 1100 ppm fluoride as stannous fluoride, and a placebo dentifrice which will be similar to the experimental dentifrice but will contain 0ppm fluoride.

2.1 Study Rationale

This *in situ* study has been designed to evaluate the efficacy of an experimental dentifrice to remineralize previously demineralized (eroded) enamel over a 12 hour period. Existing clinical data supports the ability of sodium fluoride to remineralize enamel over a 4 hour period in this *in situ* model (see Section 2.2), however the specific combination of ingredients (actives and

excipients) in the experimental dentifrice have not been tested previously. Additionally, the intended claims associated with the experimental dentifrice require a test period of 12 hours which is longer than previously evaluated.

Whilst the experimental dentifrice will make claims on the suitability of the formulation to help mitigate against dentinal hypersensitivity (DH), the anti-DH performance of 5% KNO_3 is already well established (see Section 2.2). DH assessments are therefore not required.

2.2 Background

This is a randomized, controlled, single-blind (to the dental examiner and specimen analysts), single-center, 3 treatment, 3 treatment period cross-over, *in situ* study in generally healthy subjects.

The experimental formulation tested in this study is based on the currently marketed Sensodyne Pronamel dentifrice and tested *in vitro* for superior performance. In order to support the marketing of the dentifrice, an *in situ* investigation comparing the experimental dentifrice with a 0ppm fluoride placebo dentifrice (primary objective) and with a relevant marketed dentifrice (secondary objectives) is needed to investigate the efficacy in enhancing remineralization and preventing further demineralization. Therefore, the aim of this study is to investigate the performance of an experimental dentifrice formulation in promoting enamel remineralization and inhibiting post-treatment enamel demineralization in an *in situ* erosion model, in comparison with a 0ppm fluoride placebo and with a marketed competitor dentifrice product.

When dental enamel contacts an acidic medium it can demineralize, resulting in dissolution of calcium and phosphate ions from the hydroxyapatite that constitutes the majority of the mineral phase of the enamel. In dental enamel erosion, the dissolution occurs predominantly from the surface of the enamel, resulting in a reduction in the hardness of the surface. This can be measured using the technique of surface microhardness (SMH) where a small diamond (Knoop) is used to produce an indent on the surface under a controlled load/duration. The length of the indent on the enamel surface can then be measured under a microscope and is directly related to the hardness of the enamel (the longer the indent, the softer the enamel). Thus, the extent of re/demineralization can be evaluated by measurement of the SMH.

In situ models employing SMH to measure the softness of dental enamel specimens can therefore be used to evaluate the effect of dentifrices on the re- and de-mineralization processes involved in dental erosion. The *in situ* model to be used in this study has been extensively used to investigate the performance of the currently marketed Sensodyne Pronamel in previously published studies (Barlow et al., 2009, Creeth et al., 2020, Creeth et al., 2018, Maggio et al., 2010, Nehme et al., 2016, Nehme et al., 2019) and other studies performed by GSK CH CCI CCI. The model consists of placing previously demineralized, sterilized bovine enamel specimens intra orally using a palatal appliance. The enamel specimens are exposed to the test treatments in the mouth during the treatment application, then the specimens are allowed to remineralize intra orally under the action of the subject's saliva. The specimens are then removed from the palatal appliance at time intervals post treatment and the extent of remineralization evaluated by comparison of the SMH pre and post oral exposure to yield the surface microhardness recovery [SMHR] (expressed as a percentage). The enamel specimens can then be further treated with acid *ex situ* and followed by additional SMH evaluations to calculate the resistance of the remineralized enamel to further acid softening (the acid resistance ratio [ARR]) and the combined impact of the treatment on remineralization and demineralization (the relative erosion resistance [RER]). Additionally, the enamel specimens can be chemically analyzed to measure the amount of fluoride incorporated into the enamel by the treatment (the enamel fluoride uptake [EFU]. Taken as a whole, these endpoints can be

utilized to evaluate the performance of a dentifrice to remineralize existing erosive lesions and help protect against future erosive challenges.

In this study, most of the design will be retained from previous studies (Creeth et al., 2020), but the time points will be modified and performance will be evaluated 4 and 12 hours post brushing rather than after 2 and 4 hours as used previously.

2.3 Benefit/Risk Assessment

Complete information for this experimental dentifrice may be found in the single reference safety document (SRSD), which for this study is the Safety Statement.

Whilst the exact formulation of the experimental dentifrice under investigation has not been previously clinically tested, similar products containing sodium fluoride have been evaluated in clinical studies (see Background Section 2.2). These studies demonstrated the anti-erosion efficacy and safety of similar formulations containing sodium fluoride. The active ingredients and formulation excipients contained in the study dentifrices have a history of safe use in oral care products and are currently used in marketed daily use dentifrices.

2.4 Mechanism of Action/Indication

The test dentifrice formulation being investigated contains 0.254% w/w NaF, equivalent to 1150 ppm fluoride and 5% w/w KNO_3. The efficacy of the experimental dentifrice in enhancing enamel remineralization is being investigated in an *in situ* intraoral model with bovine enamel specimens in healthy subjects.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to enhance remineralization of enamel compared to a placebo dentifrice (0ppm fluoride) after 4 hours of intra-oral exposure.	%SMHR at 4 hrs.
Secondary	
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to inhibit demineralization of enamel compared to a placebo dentifrice (0ppm fluoride) after 4 hours of intra-oral exposure.	%RER at 4 hrs.
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to enhance remineralization of enamel compared to a marketed, reference dentifrice containing 1100ppm fluoride after 4 hours of intra-oral exposure.	%SMHR at 4 hrs.
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to enhance remineralization of enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed, reference dentifrice containing 1100ppm fluoride after 12 hours of intra-oral exposure.	%SMHR at 12 hrs.
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to inhibit demineralization of enamel compared to a reference dentifrice containing 1100ppm fluoride after 4 hours of intra-oral exposure.	%RER at 4 hrs.

To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to inhibit demineralization of enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed, reference dentifrice containing 1100ppm fluoride after 12 hours of intra-oral exposure.	%RER 12 hrs.
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to promote fluoride uptake in enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed, reference dentifrice containing 1100ppm fluoride after 4 and 12 hours of intra-oral exposure.	EFU at 4 and 12 hrs.
To investigate the efficacy of an experimental dentifrice containing 1150 ppm fluoride and 5% KNO_3 to reduce future acid-induced demineralization in enamel compared to a placebo dentifrice (0ppm fluoride) and a marketed, reference dentifrice containing 1100ppm fluoride after 4 and 12 hours of intra-oral exposure.	ARR at 4 and 12 hrs.
To investigate the efficacy of a marketed, reference dentifrice containing 1100ppm fluoride. to enhance remineralization, inhibit demineralization, to reduce future acid-induced demineralization and to promote fluoride uptake in enamel compared to a placebo dentifrice (0ppm fluoride) after 4 and 12 hours of intra-oral exposure.	%SMHR, %RER, EFU, ARR at 4 and 12 hrs.
Exploratory	
To calculate the proportion of subjects who evidence a RER ratio (%RER 0ppm fluoride placebo and 5% KNO_3 : %RER experimental dentifrice containing 1150 ppm fluoride) >=3 and >=2.5	%RER at 4 and 12 hrs.
Safety	
To assess the oral tolerability of an experimental dentifrice containing 1150ppm fluoride and 5% KNO_3.	Treatment emergent adverse events

Abbreviations: SMHR: Surface micro hardness recovery, RER: Relative erosion resistance, EFU: Enamel fluoride uptake, ARR: Acid resistance ratio, KNO_3: potassium nitrate.

This study will be considered successful if the experimental dentifrice containing 1150ppm fluoride and 5% KNO_3 demonstrates a statistically significant enhancement of remineralization, as measured by %SMHR in comparison with the placebo dentifrice after 4 hours intraoral phase.

4 STUDY DESIGN

4.1 Overall Design

This will be a randomized, controlled, single center, single- blind (to the dental examiner and specimen analysts), 3 period, 3 treatment, cross-over, *in situ* design which consists of placing previously demineralized bovine enamel specimens intra orally using a palatal appliance and evaluating the remineralizing performance of the experimental, reference and placebo dentifrices 4 and 12 hours post toothbrushing, based on surface micro hardness measurements of the bovine enamel specimens. This study will be carried out in healthy adults with a maxillary dental arch suitable for the retention of the palatal appliance. Subjects will be recruited from an existing panel (IRB #CCI [redacted]) of subjects pre-fitted with a palatal appliance.

In this study there will be 7 visits, 1 screening visit to assess subject eligibility, 3 treatment visits to assess product efficacy, where the study dentifrices will be dispensed and used under the supervision of a suitably trained study site personnel, and 3 follow up visits to perform an OST examination, assess for Adverse Events and allow the subject to return their palatal

appliance. Sufficient subjects will be screened to randomize up to 33 subjects to study treatment to ensure at least 30 subjects complete the study. At screening (Visit 1), subjects will give their written informed consent to participate in the study. Demography, relevant medical history and current medications/treatments will be recorded, followed by oral soft tissue (OST) and oral hard tissue (OHT) examinations. Subjects will then have their stimulated and unstimulated salivary flow rates measured and subjects meeting the relevant study criteria will try-in their palatal appliance and be considered eligible to enroll in the study. Enrolled subjects will then be dispensed the wash-out dentifrice, toothbrush and diary.

Prior to each treatment visit, there will be a washout period of a minimum of 3 days. During this period subjects will use their own dentifrice and toothbrush for at least one day, and a 0ppm fluoride washout dentifrice and study toothbrush (provided) for two days immediately prior to the next scheduled visit (including on the morning of the scheduled visit).

At treatment visits (Visits 2, 4 & 6), subjects will provide details of their concomitant medications and undergo an OST examination. Subject's diaries will be reviewed to ensure compliance with the use of the wash-out dentifrice. Subjects deemed suitable to continue in the study will be randomized to the order of treatments (Visit 2 only) and wear an oral palatal appliance holding 8 bovine enamel specimens. Details of enamel specimen preparation will be specified in the Laboratory Procedures Document. The palatal appliances (Fig 4-1) will be specifically made for each eligible subject, and each will carry two plastic holders containing a total of eight bovine enamel specimens (four in each holder). Once the appliance is fitted in the mouth, a five minute equilibration period will ensue following which each subject will brush their teeth with their assigned product, one product per treatment visit as described below.

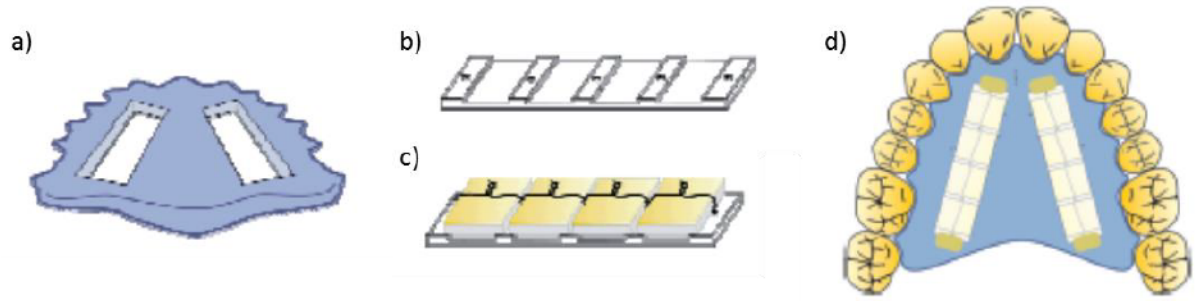

Figure 4-1 **Schematic diagram of a) intraoral appliance, b) enamel specimens' holder, c) enamel specimens placed in the holder and d) palatal appliance with enamel specimens in the mouth.**

Under supervision while the intraoral appliance is in place, the subjects will brush the buccal surfaces of their natural teeth using 1.5±0.1g of dentifrice and a soft toothbrush for 25 seconds to create a slurry. Subjects will be instructed not to expectorate the slurry and will then swish the slurry around their mouth for 95 seconds to permit direct contact of the dentifrice slurry with the enamel specimens. After expectorating the slurry, the subjects will gently rinse their mouths with 15 mL of tap water for 10 seconds before expectorating again. The toothbrush, however, will not come into contact with the enamel specimens or the appliance as this could cause abrasion of the enamel specimens.

Subjects will then remain at the study site for 4 hours post toothbrushing when their appliance will be removed (at 4hrs ±10 mins post toothbrushing) and 4 designated enamel specimens will be withdrawn from the appliance. Subjects will then be served an optional lunch which will be consumed within a 30 ±10 minute time period. The subjects will then brush and rinse their

mouth with water, after which they will have their appliance reinserted and be allowed to leave the site.

Subjects will be given verbal and written home instructions/diary which will instruct them to remove their appliance at 8.5 hours following the toothbrushing. The time for removal will be detailed on the instruction/diary sheet. They will be advised to eat a meal of their choice over a 30 ±10 minute timed period, brush their teeth and rinse their mouth with water and refit their appliance after the 30 ±10 minute timed period is up. After 13 ±0.5 hours following the initial brushing time, the subject will be instructed to remove their appliance, rinse it under running water and store moist in the supplied container in their refrigerator overnight. The time for this removal will also be given on their instruction/diary sheet. In addition, a member of the study team will give a reminder call to the subject prior to the completion of the 12 hour intraoral exposure. Subjects will then attend a follow-up visit (Visits 3, 5 and 7) the following day to return their appliance to the site and to receive an OST examination to evaluate any potential oral AEs caused by the previous day's procedures. At Visit 6 only the subjects will return their washout dentifrice and at the final post treatment visit (Visit 7) the subject will also receive an OHT exam and end of study documentation will be completed.

The enamel specimens will be evaluated both prior to and after intra-oral exposure. Surface microhardness (SMH) will be used to evaluate changes in the mineral content of enamel and is used to calculate surface micro hardness recovery (%SMHR), relative erosion resistance (%RER) and acid resistance ratio (ARR). The incorporation of fluoride into the enamel specimens will be assessed by enamel fluoride uptake (EFU) measurements. For each treatment and subject, these measurements will be performed on the same enamel specimen as described in the Laboratory Procedure Document, in the four enamel specimens removed at each time point. The erosive acid challenges, with a commercially available grapefruit juice, will be carried out *ex vivo* and therefore does not pose a risk to the subject's teeth. The overall study design sequence of events is detailed in Fig 4-2, with a pictorial of when the appliance is worn/removed shown in Fig 4-3.

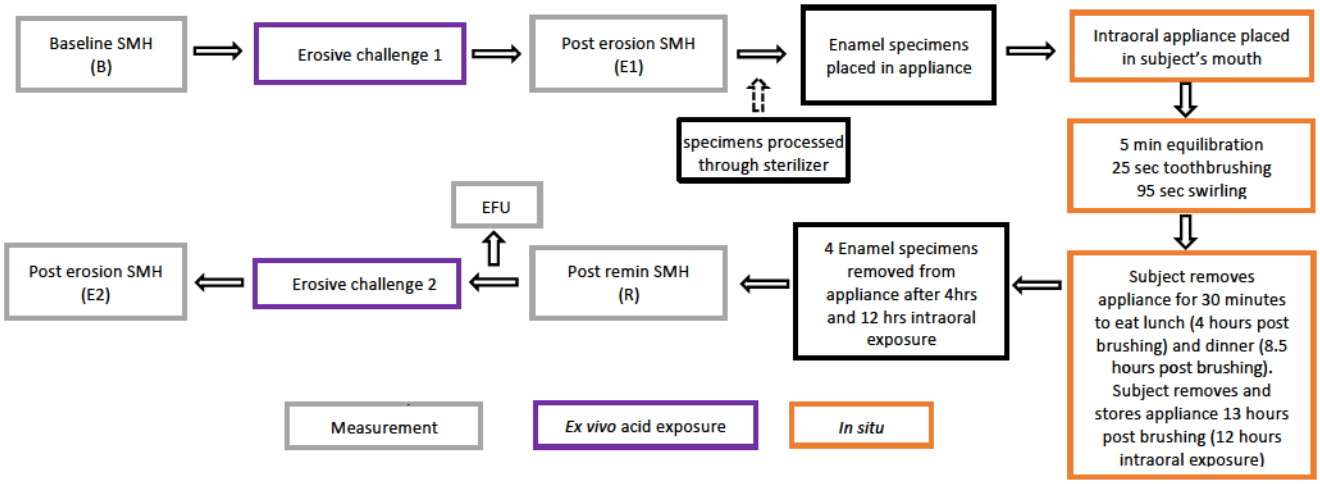

Figure 4-2 Schematic diagram showing flow of procedures.

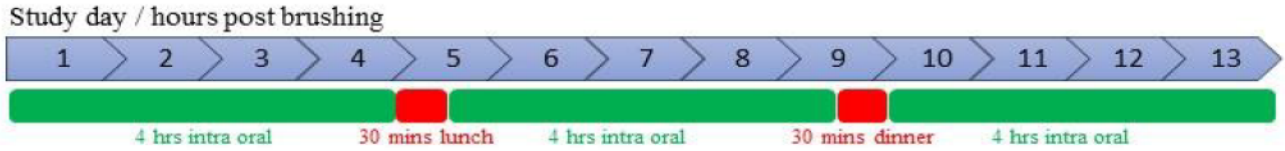

Figure 4-3 Schematic diagram showing insertion and removal of palatal device over the 13 hour study day.

AEs and medical device incidents will be monitored for and recorded at every site visit following signing of informed consent.

4.2 Scientific Rationale for Study Design

The processes of remineralization and demineralization associated with dental enamel erosion cannot currently be evaluated *in vivo* since the techniques required to assess these are destructive to enamel. An *in situ* design utilizing enamel specimens is therefore appropriate.

The appliances and the positioning of the enamel specimens will be unique for each individual subject, and so the most appropriate method to evaluate the performance of the three dentifrices in this study is a within subject comparison, and therefore a cross over design will be used for this study.

The ability for fluoride to reharden/remineralize acid-softened enamel has been observed as early as 1 h after dentifrice use in *in situ* experimental conditions similar to those used here and seen to progressively increase after 2 and 4 h (Nehme et al., 2019). Evaluation of the effect of the experimental dentifrice after 4 and 12 hours intra oral remineralization is therefore expected to be sufficient time for measurable benefits to be observed. Time intervals of longer than 12 hours may not be informative given the recommendations provided by the American Dental Association for effective toothbrushing (ADA, 2022) include brushing teeth twice daily.

The SMH technique used here to evaluate the mineralisation state has been widely used in many previous studies where it has proven to be sufficiently sensitive to detect changes in the mineral content of dental enamel (Barlow et al., 2009, Creeth et al., 2015, Zero et al., 2006, Lippert and Lynch, 2014, Nehme et al., 2019). The technique can therefore be considered appropriate for the evaluation of the endpoints in this study.

Bovine enamel is used in this study as a model for Human enamel. Bovine enamel has previously been demonstrated to be a suitable substitute for erosion studies (White et al., 2010). The advantages of Bovine over Human enamel are that larger specimens of Bovine enamel may be obtained (owing to larger tooth size), greater availability of Bovine enamel and most importantly that Bovine enamel is substantially fluoride-free compared to Human enamel that has been subjected to fluoridated water supply / dental products.

A 2-day washout period where the subjects do not use any oral health product containing fluoride, is required prior to each treatment visit to ensure no residual fluoride resides in the mouth that could compromise the ability to accurately assess the efficacy of the test products. Based on experience from previous studies, two days are sufficient to minimize any carry-over effect. Subjects will use their own dentifrice for at least 1 day between study periods to ensure sufficient exposure to fluoride to provide an anti-caries benefit.

According to the International Conference on Harmonisation (ICH) guidelines (ICH, Nov 2016), for a study to be classified as truly double-blind, not only does the examiner (and any appropriate member of staff who may be involved in the dispensing of products, analysis of data etc.) need to be blind to the treatment a subject receives, but the products under test must be identical in every way (color, flavor, rheology, appearance, packaging). Given the experimental dentifrices and the reference dentifrice will differ in appearance and flavor, the level of blindness for this study is described as 'examiner blind' only. The study will be blinded with respect to the dental examiner and enamel specimen analysts to ensure there is no bias in the assessments.

For the primary objective of this study, a 0ppm fluoride placebo dentifrice will be used as comparator to establish if the fluoride present in the experimental dentifrice can provide enhancement of remineralization and prevention of demineralization in this *in situ* model. Additionally, a relevant commercially available fluoride-containing dentifrice will be used as a Reference (secondary objectives) to investigate the superior performance of the experimental dentifrice in enhancing remineralization and preventing demineralization.

Whilst the individual products being tested in this study are not contra-indicated for pregnancy and use of them would not be expected to cause harm either to the mother or foetus, pregnant females will be excluded from this study due to the increased prevalence and severity of gingivitis and periodontal disease along with increased amounts of calculus and plaque observed with pregnancy. The severity of these conditions is known to vary during the course of pregnancy (Samant et al., 1976), and thus pregnancy would be a confounding factor of the objectives in this study. Pregnant females and those intending to become pregnant are thus excluded in this study. Pregnancy will be evaluated through self-reported pregnancy status by subjects.

4.3 Justification for Dose

Subjects will use their assigned dentifrices for 2 minutes, in agreement with recommendations provided by the American Dental Association for effective toothbrushing (ADA, 2022) and to align with previous similar clinical studies performed by the sponsor (Barlow et al., 2009, Creeth et al., 2020).

On each brushing occasion, the toothbrush will be dosed with 1.5±0.1g of dentifrice. This dose is in line with the proposed product labelling for the experimental dentifrice and the current product labelling for the marketed reference dentifrice. Whilst the product label will not contain details of a mass of dentifrice to be used, for this study design it is imperative that a standardized dose is utilized to avoid between subject/period differences. 1.5g is considered to be consistent with the product label which details a full-brush head of dentifrice to be used.

No dose modification is permitted in this study. Any variation from the product usage instructions should be communicated to study site personnel and recorded as a deviation.

4.4 End of Study Definition

A subject is considered to have completed the study if they have completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Activities.

The End of Study is defined as the date of the last laboratory testing related to primary and secondary endpoints, to be achieved no later than 2 months after the date of the last subject last visit.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Volunteers of either sex and any gender, aged 18 – 65 years will be recruited who comply with the inclusion and exclusion criteria. Subjects will be initially recruited from the study site's database, although additional subjects from outside of the database may be recruited if required.

Sufficient subjects will be screened to randomize up to 33 subjects to ensure at least 30 evaluable subjects complete the entire study.

An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process directly or via their legally authorized representative and successfully met eligibility criteria to proceed beyond the screening visit as applicable for the protocol design.

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this protocol.

Subject eligibility to participate in the clinical study should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

5.2 Inclusion Criteria

An individual must meet all the following inclusion criteria to be eligible for enrollment into, and continuance in the study:

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is of either sex and any gender who, at the time of screening, is between the ages of 18-65 years, inclusive.
3. Subject is willing and able to comply with scheduled visits, and other study procedures and restrictions.
4. Subject is in good general and mental health with, in the opinion of the investigator or medically qualified designee, no clinically significant or relevant abnormalities in medical history or upon oral examination, or condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.
5. Subject with generally good oral health that fulfil all of the following:
    a. Having an unstimulated salivary flow rate of at least 0.2 mL/minute and a stimulated salivary flow rate of at least 0.8 mL/minute.
    b. Having a maxillary dental arch suitable for the retention of the palatal appliance.
    c. Having no lesions of the oral cavity that could interfere with the study evaluations.

5.3 Exclusion Criteria

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

1. Subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a Haleon employee

directly involved in the conduct of the study or a member of their immediate family (employees of the study site and associated academic institutes who are not directly involved in the conduct of the study are eligible to be considered as subjects.)

2. Subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.
3. Subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
4. Subject who is pregnant (self-reported) or intending to become pregnant over the duration of the study or who is breastfeeding.
5. Subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
6. A subject who, in the opinion of the investigator or medically qualified designee, can't comply with study requirements or who should not participate in the study for other reasons.
7. Subject unwilling or unable to comply with the Lifestyle Considerations described in this protocol.
8. Subject taking medication that may interfere significantly with the saliva flow in the judgment of the investigator. Should new medications that may interfere with the saliva flow be added, a second salivary flow test will be performed.
9. Subject with any condition that would impact on their safety or wellbeing or affect their ability to understand and follow study procedures and requirements.
10. Subject with any sign of grossly carious lesions (active), moderate or severe periodontal conditions, or severe tooth wear. Subject presenting at screening with minor caries may continue in the study if their carious lesions are repaired prior to the first treatment visit of the study.
11. Subject who wears an oral piercing or oral appliance or orthodontia (besides subjects wearing permanent lower retainers, which are eligible).
12. Subject who has previously been enrolled in this study.

5.4 Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

5.5 Lifestyle Considerations

The clinical site may contact subjects to remind them of lifestyle restrictions and approaching scheduled visits.

5.5.1 Oral Hygiene Restrictions

During the entire study:

- Subjects will be asked to stop using their own dentifrice two days before Visit 2, 4 and 6, when they will use the provided 0ppm fluoride washout dentifrice and toothbrush to brush their teeth (including in the morning of the scheduled Visit).
- Subjects will not be permitted to use any fluoride-containing products (including dentifrices and mouthwashes) for 2 days prior to Visit 2, 4 and 6.
- Subjects will be requested not to have any elective dental procedures including teeth professionally cleaned other than those performed within the study (excluding emergency dental treatment).

Visit 2, 4 and 6:

- Subjects should refrain from talking for the first hour after brushing on each treatment visit.
- Subjects should not leave the study site during the first 4.5 hours of each treatment visit until after the enamel specimens have been removed and the appliance has been re-inserted post lunch.
- Subjects should refrain from sleeping while wearing their palatal appliance.

5.5.2 Meals and Dietary Restrictions

Visit 2, 4 and 6:

- Subjects must abstain from all food and drink (except water) at least 30 minutes prior to Visits 2, 4 and 6.
- Subjects will not be permitted to drink for the first two hours of the intraoral test period (after treatment administration) but may drink water after this under the supervision of the study personnel. They may drink water at home, as desired. The palatal appliance must be removed before drinking water and re-inserted immediately after.
- Subjects will not be permitted to eat while wearing their intraoral appliance. They can only eat in the 30 ±10 minute periods designated for lunch and dinner when the appliance is removed from the mouth.
- Subjects will be allowed a 30 ±10 minute lunch time to consume a meal after the completion of the 4 hour intraoral phase (with their appliance removed). Prior to leaving the site subjects will brush their teeth and rinse their mouth with water and have their appliance refitted and the site staff will provide oral and written instructions/diary for the remainder of the day.
- At home the subjects will be advised to eat a meal of their choice over a 30 ±10 minute period with their palatal appliance removed between hours 8.5 and 9 following treatment brushing. Subjects will then brush their teeth and rinse their mouth with water and refit their appliance at the end of the allotted 30 ±10 minute period.

5.5.3 Alcohol and Tobacco

During Visit 2, 4 and 6:

- Subjects will not be permitted to smoke, use chewing tobacco or vape, drink alcohol or chew gum during the treatment days from insertion of their appliance until it is removed after 12 hours of intraoral exposure.

5.5.4 Medication and Treatment Restrictions

- The details of current and concomitant medications will be collected, and subjects will be allowed to participate if these medications are judged to be non-interfering by the investigator as per inclusion and exclusion criteria.

- Subjects must use only the dentifrice and toothbrush provided between study visits. Subjects should not use any other oral hygiene product other than those supplied.
- Should a subject begin a course of medication that could induce xerostomia, salivary flow for that subject will be re-assessed to ensure compliance to inclusion criteria 5a.

5.5.5 Contraception

There are no contraception requirements for subjects participating in this study. At each visit, female subjects of child-bearing potential should verbally confirm they are not currently pregnant or planning to become pregnant.

5.6 Screen Failures

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

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

5.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical/dental personnel for the study is documented in the Study Contact List located in the investigator study master file held at the study site.

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

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

5.8 Clinical Assessor Rater/Clinical Assessor Qualifications

Clinical examiner(s) involved in the screening, and safety assessments will be appropriately qualified dental professionals, registered to practice in the US. Laboratory personnel involved in analysis and preparation of the enamel blocks will be appropriately experienced and trained.

Oral examinations to determine subject eligibility and to monitor the safety/performance of study products will be performed by appropriately trained clinical examiner(s), with prior relevant clinical experience.

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and Haleon policy, study intervention is defined as any investigational

intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

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

6.1 Investigational/Study Product Supplies

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

Table 6-1 Investigational/Study Product Supplies

	Test Dentifrice	Placebo Control Dentifrice	Reference Dentifrice
Product Description	Experimental Dentifrice containing 1150ppm fluoride and 5% KNO_3	0ppm fluoride placebo dentifrice containing 5% KNO_3	Crest Pro-Health Densify Daily Protection [1100ppm fluoride as SnF_2]
Product Master Formulation Code (MFC)	CCI [redacted]	CCI [redacted]	Commercial product – US Marketplace
Pack Design	Supplied in plain white toothpaste tubes		Supplied in overwrapped commercial tubes
Dispensing Details	Study staff to weigh 1.5±0.1g of dentifrice onto the supplied brush.		
Dose/ Product Application	Subjects will use 1.5±0.1g of the allocated product and brush the buccal surfaces of their natural teeth for 25 timed seconds and then swish the resulting dentifrice slurry around the mouth, without further brushing, for a timed period of 95 seconds. After expectorating the slurry, the subjects will gently rinse their mouths with 15 mL of tap water for 10 seconds before expectorating again. Application will be under supervision of the study staff.		
Route of Administration	Oral topical		
Return Requirements	Used and unused study product to be returned to the sponsor		

Table 6-2 Washout Product Supplies

	Washout Dentifrice
Product Name	0ppm fluoride, 5% potassium nitrate Washout Dentifrice
Pack Design	Supplied in standard white toothpaste tubes.
Dispensing Details	One tube at screening
Product Master Formulation Code (MFC)	CCI [redacted]
Dose/Application	Full ribbon of dentifrice on head of toothbrush provided
Route of Administration	Oral topical
Usage Instructions	Subjects will brush their teeth according to their normal brushing habits twice a day (morning and evening)
Return Requirements	Used and unused washout dentifrice to be returned to the sponsor

Table 6-3 Sundry Items

Sundry Items to be supplied:

Item	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
Oral-B Sensi Soft Manual Toothbrush (extra soft) [USA Marketplace]	Haleon	Individual toothbrush	2 at each treatment visit. 1 provided at screening	Destroy at site using site disposal procedures	Return
Countdown Timers	Haleon	Individual supplied in commercial pack	Timers remain at the study site, they are not dispensed	Destroy at site using site disposal procedures	Return
Dosing cups	Haleon	Commercial pack	1 at each treatment visit	Destroy at site using site disposal procedures	Return

All other sundry items such as saliva sampling collection equipment and unflavored gum will be supplied by the study site. Grapefruit juice (commercially available) for the *ex vivo* acid challenge will also be sourced by the study site.

Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction which will be provided by the sponsor during the study in time for study close out visit.

Other materials required for the study eg Bovine enamel blocks and manufacture of the palatal appliances are detailed in the laboratory procedures document or CCI SOPs.

6.1.1 Medical Devices

The toothbrushes to be used in this study are medical devices.

All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 10.10) and appropriately managed by the sponsor.

6.1.2 Dosage Form and Packaging

The study products are dentifrices, intended for topical oral use, and will be applied by toothbrushing using a manual toothbrush.

The experimental, washout and placebo control dentifrices will be manufactured and filled into plain white tubes by the sponsor; the reference dentifrice will be supplied in its commercial pack. All study dentifrices will be either overwrapped in white vinyl [the commercial Reference Product] or provided in a plain white tube [placebo control and Test Dentifrice] (to mask their identity and obscure the branding of the marketed product) with a study label affixed. The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the sponsor's Clinical Supplies Group. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

Each subject will be provided with a standardized dose of their assigned study dentifrice weighed by the study site.

Sundry items will be supplied in their commercial packaging for dispensing by study staff as specified in Table 6.2 and Table 6.3 respectively.

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

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

6.1.3 Preparation and Dispensing

Subjects will be assigned to study treatment in accordance with the randomization schedule generated by the study sponsor, prior to the start of the study, using validated software.

The product dispensing area will be separate from the clinical examination area. Study dentifrices will be dispensed to the subject, by trained site personnel. These staff members will not be involved in any safety/product performance assessments or any other aspect of the study that could be influenced by the knowledge of product a subject has been assigned to. An additional member of the site staff will verify the dispensing procedure has been completed accurately for each subject.

6.2 Administration

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

Subjects will be instructed to administer their assigned product per the usage instructions provided to the subject under supervision by a member of the study site who will not be involved in any safety/product performance assessments or any other aspect of the study that could be influenced by the knowledge of product a subject has been assigned to.

On-site administration of study products will also be recorded in the CRF.

Instructions on usage of the study products are detailed in Table 6-1.

Subjects should ensure they comply with the oral hygiene restrictions (Section 5.5.1), particularly to ensure that the 0ppm fluoride washout dentifrice is used for 2 days prior to a treatment visit, and that no other dentifrice/mouthrinse is used in this period. Details of the subject's oral hygiene will be documented in the provided subject diary which will be checked by site staff at each visit to monitor compliance.

6.2.1 Product Usage Errors

In this study, product usage errors may result, in this study, from the administration or consumption of:

- the wrong product,
- by the wrong subject,
- at the wrong time,
- or at the wrong dosage.

Such errors occurring to a study subject are to be captured in the CRF. In the event of a product usage error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours.**

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

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

If a study product usage error is accompanied by an AE, as determined by the investigator, the usage error and, any associated adverse event(s) are to be captured in the CRF AE form.

6.2.2 Overdose

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

Overdose is not likely to occur in this study.

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

6.3 Investigational/Study Product Storage

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

The investigator, or designee, will ensure that all study products are stored in a secured, environmentally monitored (manual or automated) area with controlled access (authorized site staff only) in accordance with the labeled storage conditions and Clinical Study Supplies Checklist, and in accordance with applicable regulatory requirements.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of first product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

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

Site staff will instruct subjects on the proper storage requirements for all take-home products.

6.4 Investigational/Study Product Accountability

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

All study products must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only authorized site staff have

access. Upon receipt, all study products should be stored according to the instructions specified on the product labels. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff.

The study site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

Subjects will complete diaries to detail their usage of the washout dentifrice which will be used to monitor usage compliance.

The accountability records must be available for inspection by the study monitor during the study. Monitoring of product accountability will be performed by the monitor during site visits and at the completion of the study.

6.4.1 Destruction of Investigational/Study Product Supplies

At the end of the study, the Principal Investigator or an appropriate designee, and a representative of the sponsor (study monitor) will inventory all used and unused study products and sundry items. The study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study will be returned for destruction to the sponsor's Clinical Supplies Group or designated vendor using the return instructions provided. Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction will be provided by the sponsor during the study in time for study close out visit.

6.5 Blinding and Allocation/Randomization

All subjects will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided. Study products will be dispensed according to the instruction received through the IRT at the appropriate study visits. Returned study products should not be re-dispensed to any subject.

This study is described as single-blind (the dental examiner(s) and laboratory specimen analysts performing the study assessments will be blinded to the product received).

Employees of the Sponsor who may influence study outcomes and the dental examiner(s) and laboratory-based specimen analyst(s) will be blinded to the product allocation of subjects. To ensure the examiner and specimen analyst(s) remain blinded throughout the study, they are not permitted in the room while product is dispensed. All commercial study products will be overwrapped to conceal any labelling. In addition, subjects will receive treatment in a separate area from where clinical assessments are performed. The dispensing staff will not be involved in any clinical assessments or laboratory analysis during the study. Study site staff that perform study consent can also dispense the study product but cannot perform any clinical assessments. Laboratory personnel that carry out the specimen analysis will also be blinded to product allocation and not be involved in any clinical assessment. Additionally, subjects should be kept separate from the area where the study dentifrices are dispensed onto the toothbrushes to prevent them observing the dentifrice tubes.

All study site staff will be blinded except for those staff members directly dealing with dispensing study products. Site staff, study statistician(s), data management staff and other

employees of the sponsor and vendors acting on behalf of the sponsor, who may influence study outcomes will be blinded to the product allocation.

6.6 Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be an electronic process.

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

If a subject's product assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Any AE associated with breaking the blind must be recorded and reported as specified in this protocol. The study site may also be required be required to inform the Institutional Review Board (IRB) if the blind is broken.

6.7 Compliance

Study products will be administered under the supervision of investigator site personnel. The date and time of each dose/application/administration will be recorded in the source documents or directly in the CRF.

A diary will be supplied to promote compliance and to capture details of use of the washout dentifrice during the 2 days prior to treatment visits. Subjects may also record additional information such as AEs or medications used. Any additional details relevant to efficacy or safety should be reviewed by the investigator (or suitably qualified designee) with the subjects and transcribed to the CRF as appropriate.

The number of any missed or additional applications of the washout dentifrice will be captured as protocol deviations and transcribed from the diary into the CRF. Subjects will be re-instructed in the correct usage requirements and diary completion as needed.

6.8 Concomitant Medication/Treatment(s)

Any medications, treatments or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken during the study, from signing the informed consent, must be recorded in the CRF with indication, reason for use, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about medications/treatments at each site visit.

Medication/treatments taken 28 days prior to signing the informed consent form and until first study product application will be documented as a prior medication/treatment. Medications/treatments taken after first study product application will be documented as concomitant medication/treatments.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

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

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

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

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

7.2 Lost to Follow up

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

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all products provided and, if appropriate, request that the subject return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs).

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion, which could include an oral examination.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow up.

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

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

8 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study visit. The timing of each procedure is listed in the Schedule of Activities section.

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

8.1 Visit 1/Screening

Screening procedures will be conducted by the Investigator, or suitably qualified designee.

Subjects will be screened a minimum of 3 days prior to randomization to confirm that they meet the subject selection criteria for the study and to ensure 2 days of fluoride-free dentifrice use.

The following procedures will be completed in the following order (wherever possible), and the findings recorded in the CRF:

1. Informed Consent.
2. Demographics.
3. Review of medical history (including smoking/tobacco use status) and prior/concomitant medication/treatment.
4. OST and OHT examinations.
5. Measurement of stimulated and unstimulated salivary flow rate.
6. Review of the inclusion/exclusion criteria.
7. Try-in palatal appliance.
8. Subject eligibility.
9. Dispense washout product toothbrush and washout diary. Instruct subjects in diary completion.
10. AEs recorded.

8.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. An ingredients listing for the study dentifrices will be provided to each subject during the consent process to enable them to confirm they are not aware of any allergy or hypersensitivity to any of the ingredients listed. The informed consent (ICF) will be signed and dated by the subject. A copy of the signed consent will be made and distributed to the subject prior to their leaving their study visit.

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a signed and dated consent will be provided by either the investigator or by Haleon.

The investigator, or designee, should sign and date each copy of the ICF to confirm that the consent process was completed correctly after the subject has signed.

The time the subject signed the informed consent form will be captured as this is the point from which all Adverse Events will be captured. The date and time of consent will be captured in the CRF.

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. Each subject should be provided with a copy of the signed and dated amended consent form. The date of re-consent will be recorded on the CRF.

After signing the ICF, subjects will undergo the screening assessments to confirm that they meet all the inclusion criteria and none of the exclusion criteria. If the subject is confirmed eligible by the investigator (or designee) to participate in the study the subject is considered enrolled in the study.

8.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, gender and race. Ethnicity and race of subjects will be recorded in accordance with FDA Guidance (US FDA, 2005).

8.1.3 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history (in the last year), including allergies or drug sensitivity, will be documented in the CRF.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 28 days and prior to signing the informed consent form, will be documented in the CRF.

8.1.4 Oral Examinations

The clinical examiner(s) will perform the following examinations/assessments.

- OST examination.
- OHT examination.

Oral examinations/assessments should only be performed by suitably qualified examiner(s) as described in Section 5.8.

To facilitate subject flow, clinical assessments may be recorded on a paper source document and any abnormalities later transcribed into the CRF.

8.1.5 Salivary Flow Rate Measurements

Measurement of the subject's stimulated and unstimulated salivary flow will be made per Section 9.1.1 and the findings documented in the CRF.

8.1.6 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be documented in the CRF.

8.1.7 Try-in of Palatal Appliance

Palatal appliances will be fitted and checked for comfort at the Screening visit. Subjects will be asked to wear their appliances for up to 15 minutes to determine comfort, fit and wearability. Appliances will be adjusted as needed. The subject may repeat the appliance try-in portion of the screening visit after adjustment.

8.1.8 Subject Eligibility

The investigator and/or medically qualified designee will review the inclusion/exclusion criteria, medical history, prior and current medications/treatments and the findings of the oral

examinations to confirm subject eligibility to participate in the clinical trial. This will be documented in the CRF.

Eligible subjects will be appointed to attend the study site for baseline assessments (Visit 2) a minimum of 3 days after their screening visit and will be instructed to use only their supplied 0ppm fluoride dentifrice [washout product] and supplied toothbrush (according to their normal habit) for the 2 days prior to their next appointment.

To prepare for study participation, subjects will be instructed in the Lifestyle Guidelines and any Concomitant Medication/Treatment(s) requirements of the protocol.

8.1.9 Dispense Wash-out Products and Diary Cards

Subjects will be dispensed with the washout toothbrush and the 0ppm fluoride washout dentifrice to use during the washout period. Subjects will be instructed to brush their teeth with the 0ppm fluoride washout dentifrice twice a day during the 2 days prior to Visit 2, 4 and 6 (including the morning of the treatment visit) and record it in the diary provided.

8.1.10 Adverse Events and Incidents

Adverse Events and Incidents will be recorded in the CRF as described in Section 10. Any AEs will be recorded in the CRF.

8.2 Study Period

There will be an interval of at least 3 days between study periods (i.e., administration of subsequent doses of investigational product will not occur until at least 3 days after the previous dose of investigational product). Prior to each treatment visit (Visits 2, 4 & 6), there will be a washout period of a minimum of 3 days. During this period subjects will use their own dentifrice and toothbrush for at least one day, and a 0ppm fluoride washout dentifrice and study toothbrush (provided) for two days immediately prior to the treatment visit (including in the morning of the scheduled visit).

All procedures will be conducted by the Investigator, or suitably qualified designee. To facilitate subject flow, clinical and instrumental assessments may be recorded on a paper source document and later transcribed into the CRF.

8.2.1 Visit 2/Study Period 1

Subjects will undergo, in the following order (wherever possible) and the findings recorded in the CRF.

1. Changes in concomitant medication or non-drug treatments/procedures will be documented.
2. Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF.
3. Subject undergoes an OST examination.
4. Review of subject diary to assess for compliance.
5. Subject continuance assessed.
6. Subjects randomized to treatment periods.
7. Subject has appliance containing enamel blocks fitted.
8. Subject undergoes supervised product application.

9. 4 hours after dentifrice application subject has 4 enamel blocks removed and a 30 ±10 minute lunch period will be given where the subject does not wear the palatal appliance. After the 30 minute lunch period, subject will brush their teeth and rinse their mouth with water and replace their appliance.
10. AEs and incidents recorded.
11. Subject is allowed to leave site after the 4.5 hour time point. Subject will receive oral and written instructions for dinner (at 8.5 hour time point to 9 hour ±10 mins time point) and will then brush their teeth and rinse their mouth with water prior to refitting their appliance and instructions/diary for the end of the treatment day (13 hour).
12. Subject removes, rinses and stores appliance in the container provided 13 ±0.5 hours after dentifrice application and brings it to the site on the following day.

Randomized subjects will be appointed to attend the study site the next day and reminded of the Lifestyle Guidelines and to bring their completed diary with them to the next visit.

8.2.2 Visit 3 / Study Period 1 – Follow up

Subjects will undergo, in the following order (wherever possible) and the findings recorded in the CRF.

1. Subject returns palatal appliance.
2. Changes in concomitant medication or non-drug treatments/procedures will be documented.
3. Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF.
4. Subject undergoes an OST examination.
5. Review of subject diary to assess for compliance.
6. Subject continuance assessed.
7. AEs and incidents recorded.

Randomized subjects will be appointed to attend the study site for their next visit and reminded of the Lifestyle Guidelines, the washout requirements and to bring their completed diary with them to the next visit.

8.2.3 Visits 4 & 5 – Study Period 2

Procedures will be the same as for Visits 2&3 with the exception that randomization will not be performed.

8.2.4 Visits 6 & 7 – Study Period 3

Procedures will be the same as for Visits 4&5 with the exception that at Visit 6 subjects will return their washout paste and brush and at Visit 7 an OHT examination will additionally be performed at the same time as the OST examination. The subject concludes the study at the end of Visit 7 procedures.

8.3 Study Procedures

8.3.1 Diary Review

The diary should be completed by the subjects detailing their oral hygiene from screening till the end of the study. Additionally, the removal and storage of the appliance by the subjects on test days should be detailed together with any changes in concomitant medication used by the subjects.

The diary should be reviewed at every visit by the investigator, or suitably qualified designee, and the subject. Any subject comment captured in the diary which is considered an adverse event will be assessed and reported as defined in the Adverse Event and Serious Adverse Events section of this protocol.

Any additional comments relating to medications/treatments provided in the diary will be reviewed by the investigator or medically qualified designee with the subject and entered into the CRF as appropriate.

Additional and missed washout product applications will be considered deviations from the protocol and will be recorded on the Deviations Log and as a deviation in the CRF.

8.3.2 Pre-Treatment Oral Soft Tissue assessment

The clinical examiner(s) will perform the following examinations/assessments.

- OST examination [Pre-treatment at Visits 2, 4 & 6 and post-treatment at Visits 3, 5 & &7].
- OHT examination [at Visits 1 (pre-treatment) and 7 (post treatment)].

Oral examinations/assessments should only be performed by suitably qualified examiner(s) as described in Section 5.8.

8.3.3 Place palatal appliance in subject's mouth.

A suitably trained study site designee will place the palatal appliance (containing 8 enamel specimens) in the subjects' mouth followed by an equilibration period of at least 5 minutes before treatment. Details of specimen preparation is provided in the Laboratory Procedures document. Assembly of the appliance is provided in the CCI Clinical SOP.

8.3.4 Supervised treatment

Study products will be used following the instructions (see Table 6-1) and under the supervision of study site personnel.

8.3.5 Palatal appliances intra oral phase – 4 hours

After completing the brushing procedures, subjects will wear their palatal appliance for 4 hours ± 10 min. After this period, the study site designee will remove the appliance and four pre-designated enamel specimens will be removed for analysis (Section 9.4). The subject will be offered a lunch to be consumed over a 30 ±10 minute period. Following this the subject will brush their teeth with water and the appliance will be reinserted. The subject will be instructed on when and how to remove their appliance for dinner and after 12 hours of intra-oral exposure (13 hour timepoint following brushing with investigational dentifrice) and how to wash / store it at home and scheduled to return to the site the following day. The subject will be allowed to leave the site for the rest of the day.

8.3.6 Palatal appliances intra oral phase – 12 hours

After 12 hours ± 30 mins intra-oral exposure, subjects will remove their appliance and gently rinse it under running tap water. The appliance will then be stored moist in the supplied container in their refrigerator overnight. The appliance will then be returned to the clinical site the following day.

8.3.7 Study Conclusion

The Study Conclusion page of the CRF will be completed for all subjects whether they completed all study procedures or if they were discontinued from the study early. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page.

If a subject has any clinically significant, study-related abnormalities or AEs at the end of the study, the Haleon medical monitor (or designated representative) should be notified and, the subject may be asked to remain at the clinical site or be asked to return for a follow-up visit to ensure any issue is resolved or deemed not clinically significant.

8.3.8 Follow-up Visit / Phone Call

The study site may contact a subject to follow up an AE post-study completion/withdrawal and, in some circumstances, request they return to the site for additional follow-up visits (final safety assessments). If needed, additional clinical examinations may be carried out at such visits.

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to complete an assessment. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments in a timely manner. The outcome of all examinations and assessments should be recorded in the CRF.

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the Study Procedures section of this protocol.

9.1.1 Salivary flow

At the screening visit, both unstimulated and stimulated saliva will be collected for evaluation of flow rates as part of the inclusion criteria. Saliva samples collected will be destroyed immediately after they are weighed.

Unstimulated salivary flow

For the unstimulated saliva collection, subjects will sit quietly for five minutes before beginning the treatment period. During the five-minute test period, they will be instructed to allow their saliva to pool, emptying into a collection tube whenever they feel they need to swallow. The collection tube will be weighed, pre/post collection and unstimulated saliva flow rate calculated

(1g = 1ml). Unstimulated saliva flow rate must be ≥ 0.2 ml/min for the subject to be eligible for enrollment in the study.

Stimulated salivary flow

For the stimulated saliva collection, subjects will chew on a piece of unflavored gum base for one timed minute. After one minute, subjects will be instructed to swallow any pooled saliva. They will then chew the gum base for two timed minutes during which time they will empty any pooled saliva into a collection tube whenever they feel they need to swallow. The collection tube will be weighed, pre/post collection and unstimulated saliva flow rate calculated (1g = 1ml). Stimulated saliva flow rate must be ≥ 0.8 ml/min for the subject to be eligible for enrollment in the study.

9.2 Efficacy Assessments

In this study there are no clinical efficacy assessments performed. All efficacy assessments will be performed *ex vivo* on the enamel specimens removed at the times defined in the Study Procedures section of this protocol. Enamel specimen preparation and analysis are described in the Laboratory Procedures Document.

9.3 Safety and Other Assessments

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

9.3.1 Oral Soft Tissue (OST) Examination

This procedure will be conducted by a qualified, experienced clinical examiner. The OST examination will be accomplished by direct observation and palpation with retraction aids, as appropriate. The examination will cover the oral labial mucosa (including lips), buccal mucosa, mucogingival folds, gingival mucosa, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands. Abnormal findings from the examination will be recorded in the CRF, with details of any abnormalities. The results of the OST examination performed at screening will be used to determine subject eligibility. Any new OST abnormality or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject after the screening examination will be recorded as an AE.

Where possible, this procedure should be conducted by a single clinical examiner.

9.3.2 Oral Hard Tissue (OHT) Examination

This procedure should be conducted by a qualified, experienced clinical examiner. The OHT examination will be accomplished by direct observation, using retraction aids as appropriate and will identify any grossly carious lesions, signs of erosive wear, enamel irregularities, tooth fracture, gross generalized dental caries decay, decalcification and faulty restorations. The presence of any implants, fixed or removable dentures, fixed or removable orthodontic braces/bands, fixed orthodontic retainers, full crowns or veneers will be recorded. Observations will be listed as either absent or present, and conditions noted as present will be described in the CRF. Any change observed by the clinical examiner or reported by the subject after the screening examination will be recorded as an AE.

The results of the OHT examination performed at Screening will be used to determine subject eligibility.

Where possible, this procedure should be conducted by a single clinical examiner.

9.3.3 Pregnancy Testing

Pregnancy testing of subjects of child-bearing potential is not required for this study (see Section 4.2 for details). Subjects of child-bearing potential will be asked to provide verbal confirmation of pregnancy status at screening (Visit 1) and to inform site staff if they find they are pregnant while participating in the study. In case of a positive confirmed pregnancy, the subject will be withdrawn from the study.

9.4 Laboratory Tests

All laboratory procedures will be detailed in a separate Laboratory Procedures Document which will cover:-

Preparation

- Preparation of enamel specimens.
- *In vitro* erosive challenge.

Efficacy measurements

- Surface microhardness (SMH).
- Enamel fluoride uptake (EFU).

Enamel Specimen Storage

- All enamel specimen samples will be securely stored in a refrigerator at the clinical site to prevent the specimens from degradation and microbial colonization.

Specimen Retention

- Laboratory specimens will be retained by the study site for at least six months following database lock. Before destruction, a clinical study site designee will contact the sponsor in writing requesting permission to destroy the specimens. The sponsor will provide approval in writing for sample destruction. If destruction is not approved, then Sponsor will provide an alternate time period for destruction of specimens or provide instructions for transfer of the specimens to an alternative location for further laboratory analysis. Specimens will be ultimately destroyed *via* autoclaving.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study product or the study, or that caused the subject to discontinue the study product or study.

10.1 Definition of an Adverse Event (AE)

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

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

Events <u>Meeting</u> the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE if they fulfill the definition of an AE.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g. appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2 Definition of a Serious Adverse Event (SAE)

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

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

- **Results in death**
- **Is life- threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption
- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

10.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs, and therefore all SAEs will be collected immediately after a subject provides consent to participate in the study by the completion (signature) of the ICF and until 5 days following last administration of the study product (or last procedure).

Medical occurrences that began before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF not the AE section.

Details recorded by the subject on a diary or similar document that meet the definition of an AE must also be discussed with the subjects and transcribed in the AE section of the CRF.

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

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time

after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study product or study participation, the investigator must promptly notify the sponsor.

10.4 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up on AEs that are serious, considered related to the study product(s), participation in the study, or a study procedure, or that caused the subject to discontinue the study product or study.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to non-leading such as “How do you feel” will be assessed and any AE’s recorded in the CRF and reported appropriately.

The investigator (or medically qualified designee) is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for a SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE occurs, it is the responsibility of the investigator (or medically qualified designee) to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE in the CRF and all details relating to an SAE in the paper SAE Form provided.

It is **not** acceptable for the investigator (or medically qualified designee) to send photocopies of the subject’s medical records to Haleon in lieu of completion of the AE CRF page/SAE form.

There may be instances when copies of medical records for certain cases are requested by Haleon. In this instance, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records prior to submission to Haleon .

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

AEs elicited by the investigator (or medically qualified designee) in a standard manner at the study visits should also be recorded in the AE section of the CRF and/or using the SAE form (subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used. AEs will be categorized as oral or non-oral by the examiner prior to database lock.

10.4.1 Reporting of an Adverse Event

All AEs will be reported on the AE page of the CRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the AE CRF page and the SAE form must be completed in a consistent manner. For example, the same AE term should be used on both. AEs should be reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE CRF page, an SAE form should be completed, as fully as possible. Hard copies of the 'paper' SAE form will be provided in the investigator study master file. Original SAE forms will be retained in the investigator study master file.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (or study procedure, if appropriate)
- Criterion for seriousness.

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

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

The SAE form, completed as fully as possible, must be scanned and e-mailed to the Case Management Group mailbox PPD , with copy to the appropriate Study Manager, with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. The investigator will submit any updated SAE data to the sponsor, **immediately and under no circumstance should this exceed 24 hours** of it being available.

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

The Study Manager will be responsible for forwarding the SAE form to other Haleon personnel as appropriate.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both non-serious AEs and SAEs can

be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.5.2 Assessment of Causality

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

For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE CRF page and the SAE form (subject to the classification of the AE). The investigator will also document in the medical notes that they have reviewed the AE and assessed causality, where applicable.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The investigator will use clinical judgment to determine the relationship and will also consult the Safety Statement, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to Haleon. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to** Haleon**.** The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.6 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.

All AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

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

New or updated information will be recorded on the AE CRF page and on the SAE form (subject to the classification of the AE).

The investigator will submit any updated SAE data to Haleon within 24 hours of receipt of the information.

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the investigator will promptly notify Haleon by emailing the information to the Case Management Group mailbox at Haleon PPD, with copy to the appropriate Study Manager.

The investigator will submit any updated SAE data to Haleon within the designated reporting time frames.

10.7 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined.

10.8 Regulatory Reporting Requirements for SAEs

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

Haleon will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Both the investigator and the sponsor will comply with all local medical device reporting requirements

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure in the investigator study master file, and will notify the IRB/IEC, if appropriate according to local requirements.

10.9 Pregnancy

10.9.1 Time Period for Collecting Pregnancy Information

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

10.9.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the Case Management Group mailbox PPD, with copy to the appropriate Study Manager. Original pregnancy information forms will be retained in the investigator study master file.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the investigator to the Case Management Group mailbox at Haleon PPD, with copy to the appropriate Study Manager. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

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

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

10.10 Medical Device Incidents

The definitions and procedures detailed are in accordance with ISO 14155.

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

Medical devices are being provided by Haleon for use in this study; the medical device in this study is the supplied toothbrush.

10.10.1 Definition of an Incident

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

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

It is sufficient that:

An **incident** associated with a device happened and

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include any of the following:
- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents:

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

10.11 Reporting of Incidents and Malfunctions

All incidents must be reported to Haleon **immediately and under no circumstance should this exceed 24 hours** of the investigator or designee becoming aware of the situation.

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

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

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

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

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

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

10.12 Follow-up of Medical Device Incidents

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

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

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

10.13 Regulatory Reporting Requirements for Medical Device Incidents

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

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

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

11 DATA MANAGEMENT

As used in this protocol, the term CRF is understood to refer to either a paper form or an electronic data record or both, depending on the data collection method.

For this study, subject data will be entered into an electronic CRF (eCRF), using a validated system. Data relating to SAEs, pregnancy and incidents will also be collected on paper forms.

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

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

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

11.1 Case Report Form

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

For each subject who has given informed consent/assent the CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Management of clinical data will be performed in accordance with the Third Party Biostatistics and Data Management Vendor applicable standards and data cleaning procedures with oversight by Haleon to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

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

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

Haleon will obtain and retain all CRFs and associated study data as applicable at the completion of the study.

11.2 Data Handling

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

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

11.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction.

The study monitor will perform ongoing review the of the CRFs in accordance with the monitoring plan, to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

11.3 Processing Patient Reported Outcomes

Paper based patient reported outcome (PRO) data may be recorded to the study diaries and entered into the data management system (DMS).

All PRO source data should be reviewed by the study staff and the study monitor to ensure accurate transcription of data and that any potential AEs or concomitant medications reported on these documents are discussed with the subject and transcribed accurately to the CRF and/or DMS. PROs that are classed as source data will be retained by the investigator and true/certified copies may be sent to a designated vendor or Haleon as required.

To protect the privacy of subjects, no Personal Information (PI) (including the subject's name or initials or birth date) is to be recorded on any PRO that will be forwarded to Haleon or Third-Party Vendor.

11.4 External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by Haleon to identify the subject and time point referenced in the CRF and/or protocol.

An agreed quality control process will be performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to Haleon.

Reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

A sufficient number of healthy subjects will be screened to ensure that up to 33 subjects will be randomized to participate in the study to ensure at least 30 evaluable subjects complete the study. With a sample size of 30 subjects completing the study, there will be 97% power to detect a difference in means of 7.5% in %SMHR at 12 hours, assuming a standard deviation (SD) of differences of 9.94% using a paired t-test with a 0.05 two-sided significance level.

These differences and variability were observed when comparing a similar test product to a similar Placebo Control and Reference Dentifrice at 4 hours in GSKCH study 208166. In the absence of any historical studies with results at 12 hours, the result at 12 hours will be assumed to be similar to 4 hours for the purpose of sample size calculation.

A recent network meta-analysis (Haleon study 300033) across 14 studies using the same design involving 22 different grouped type of study products suggests a SD of differences as high as 12.16% at 4 hours. Even with such a higher SD, there would still be 90% (80%) power to detect a difference in means of 7.5% (6.5%) in %SMHR at 12 hours.

Previous Haleon study 208166 and network meta-analysis 300033 suggest respective SD of differences for %RER between 17.5% and 20.3%. Such estimates of variability would give 90% (80%) power to detect respective difference in means of 10.7% and 12.4% (9.3% and 10.7%).

12.2 Populations for Analysis

12.2.1 Definitions of Analysis Populations

The following analysis populations will be defined:

- The Screened population will include all subjects who are screened.
- The Intent-to-Treat (ITT) population will include all subjects who are randomized. Study product group will be assigned to each visit for analyses based on the study product sequence the subject was randomized to.
- The Safety population will include all randomized subjects who receive at least 1 dose of study product. Study product group will be assigned for analyses based on the last known study product the subject actually received prior to the safety event.
- The Per-Protocol (PP) population will include all subjects from the ITT population who have at least one visit with non-missing erosion parameters unaffected by protocol deviations. Study product group will be assigned to each visit for analyses based on the study product the subject received.

12.2.2 Exclusions of Data from Analysis

Exclusions of any data from the analyses will be determined during a Blinded Data Review (BDR) meeting prior to database lock and unblinding.

If it is not possible to derive the erosion parameter at the visit level due to missing data from specimens not collected and/or data deemed to be non-evaluable by the laboratory, the data will be treated as missing in the Intent-To-Treat (ITT) analyses.

If there are a sufficient number of protocol deviations (PD) identified which may impact the reliability of a visit level erosion parameters in the ITT analysis, a Per-Protocol (PP) analysis will be performed excluding the result in question. The PP analysis will be performed if the number of subjects in the ITT population excluded from the PP population is greater than 10%. Each PD will be assessed as part of the BDR, but possible PDs (list not exhaustive) which may impact the reliability of erosion parameters are non-compliance with the use of study product at the visit, lifestyle considerations or instructions for removal and return of palatal appliance.

The PDs will be assigned to study products based on the visit(s) affected. The number and percentage of ITT population subjects with the following PD events will be presented by study product (and overall):

- PD
- Important PD
- Important PD leading to exclusion of data from the PP analysis

12.3 Statistical Analyses

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

Statistical testing of all endpoints in this study will be conducted at a two-sided significance level of 0.05. A sequential testing strategy will be applied to preserve the overall type-1 error control for the respective sequential comparisons between the Experimental dentifrice and Placebo Control at 4 hours for the %SMHR (primary endpoint) and %RER (secondary endpoint). There will be no further adjustments for multiplicity.

All analyses of erosion parameters will be primarily based on the ITT population. If there is more than a 10% difference in the overall number of subjects included in the PP and ITT analyses, the PP analyses will also be performed as supportive analyses.

12.3.1 Primary Analysis

The primary endpoint will be the %SMHR at 4 hours and the comparison between the Experimental dentifrice and Placebo Control.

The null and alternative hypotheses are:

- •H0: there is no difference between the products.
- •H1: there is a difference between the products.

For each replicate within each specimen (collected after 4 hours *in situ* remineralization) within a particular study visit, the %SMHR (at the replicate level) will be derived as [(E1-R)/(E1-B)] * 100

where:

B = indentation length (µm) of sound enamel at baseline

E1 = indentation length (µm) after first erosive challenge

R = indentation length (µm) after 4 hours *in situ* remineralization

The %SMHR at the subject visit level (to be used in the analysis) will be derived as the mean of the specimen means (across evaluable replicate %SMHR within a specimen) within that visit. Missing data or data deemed as non-evaluable by the laboratory will not be used in these derivations.

A mixed model (including results across all 3 study products) will be used to analyze the %SMHR at 4 hours with fixed effects for treatment and study visit, as well as random effect for subject. Kenward Rogers degrees of freedom approach will be applied. The least square means for each study product will be presented along with the differences between least square means (Experimental dentifrice - Placebo Control; including two-sided p-value and 95% confidence interval) to test for a difference between products.

The assumption of residual normality and variance homogeneity will be investigated from the mixed model through residual plots. If violated, a non-parametric method (Wilcoxon Signed Rank Test) will be performed for each pairwise comparison of interest as supportive analyses.

12.3.2 Secondary Analyses

The results from the mixed model applied from the primary analysis for %SMHR at 4 hours will also be used to test and present the pairwise differences in %SMHR at 12 hours between the Experimental dentifrice versus the Reference dentifrice and the Reference dentifrice versus the Placebo Control.

The R in the derivation of each secondary endpoint represents the indentation length (µm) after the 4 or 12 hours *in situ* remineralization as appropriate.

The %RER and ARR at the subject visit level (to be used in the analysis) will be derived from within specimen replicate results in similar fashion to the %SMHR.

The %RER (at the replicate level) will be derived as [(E1−E2)/(E1−B)] * 100

where E2 = Indentation length (µm) after second erosive challenge.

The ARR will be derived as 1 − [(E2−R)/(E1−B)].

The EFU result will be received from the laboratory per specimen, pooled across multiple microdrill enamel biopsies within each specimen. The mean across specimens relating to a specific timepoint (4 or 12 hours) will be derived. The natural log of this mean will be used to represent the subject visit level EFU at the timepoint to be used in the analysis.

The same mixed model as applied for the primary analysis for %SMHR at 4 hours will be applied for the %SMHR at 12 hours and the %RER, ARR and EFU at 4 and 12 hours. The same 3 pairwise comparisons of interest will be presented. For EFU the back-transformed values will be presented to represent the least square geometric means and geometric mean ratio (and 95% CIs). The residuals from each model will be examined and similar to the primary analysis, supporting non-parametric results be presented if required.

Summary statistics including the counts (missing and non-missing), mean, SD, standard error (SE), median, minimum, and maximum will be presented by study product for each parameter (including B, E1, R, E2) for each time-point (4 and 12 hours).

12.3.3 Exploratory Analysis

The proportion of subjects who evidence a RER ratio (Placebo Control : Experimental dentifrice) >=3 and >=2.5 will be presented along with asymptotic 95% confidence intervals for both 4 and 12 hour time points. Assignments will be made in certain scenarios of RER values at the time point as follows:

- Experimental dentifrice RER ≥ 0 and Placebo Control < 0 = Subject evidenced RER ratio
- Placebo Control ≥ 0 = Subject did not evidence RER ratio

12.3.4 Safety Analyses

AEs will be regarded as treatment emergent if they occur on or after the first use of study product in the study. In this crossover trial, events will be assigned to the study product being received at the onset of the event. Treatment-emergent adverse events (TEAEs) with an onset date/time between visits will be assigned to the study product received in the previous period. TEAEs with an onset after last use of any study product will be assigned to the last study product used.

The number of distinct events and the number and percentage of subjects having at least one event will be presented by study product and overall for the following:

- AEs (overall only)
- SAEs (overall only)
- TEAEs
- Serious TEAEs
- Oral TEAEs
- Product Related TEAEs
- Device related AEs
- Device Incidents

All AEs and device incidents will be listed providing all relevant details collected in the CRF.

12.3.5 Exclusion of Data from Analysis

Exclusion of any data from the analyses will be determined during a Blind Data Review (BDR) Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

12.3.6 Demographic and Baseline Characteristics

Demographic data (age, sex, race, ethnicity) will be summarized descriptively.

Medical history will be listed providing all relevant details collected in the CRF.

12.3.7 Study Product Compliance and Use of Other Therapies

12.3.7.1 Study Drug/Product Compliance

Non-compliance with study product will be captured as a PD and summarized.

12.3.7.2 Prior and Concomitant Medications

All prior and concomitant medications will be listed providing all relevant details collected in the CRF.

12.3.8 Handling of Dropouts and Missing Data

If it is not possible to derive the erosion parameter at the visit level due to missing data from specimens not collected and/or data deemed to be non-evaluable by the laboratory, the data will be treated as missing in the Intent-To-Treat (ITT) analyses. Due to the *in situ* nature and design

of the study, the likelihood of missing data having a 'missing not at random' mechanism is very unlikely and is not relevant to the study objectives. As such this method to handle missing data is deemed adequate.

The mixed model analysis methods will ensure that subjects with some missing or excluded results for one or more of the study products will still contribute to the results but with much lower weighting compared to subjects with complete data. However, the inclusion of such data in the analysis for data 'missing at random' is unbiased and adds slightly improved precision to study results. If the number of subjects with complete data is very low in either the ITT and/or PP analyses, it may be decided at the BDR meeting to also include 'complete case' analyses as necessary supporting evidence.

12.3.9 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

In accordance with applicable regulations including GCP, and Haleon procedures, Haleon or designee (i.e. third-party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Haleon requirements.

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

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

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

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

13.2 Quality Assurance

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

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

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

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

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

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

13.3.2 Ethical Conduct of the Study

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

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

13.3.3 Subject Information and Consent

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

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

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

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

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

The investigator must ensure that each study subject, is fully informed about the nature and objectives of the study and possible risks associated with participation.

13.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

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

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

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

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

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

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

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

13.5 Provision of Study Results to Investigators

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

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

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

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

13.6 Records Retention

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

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

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

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

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

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator as per the signed contractual agreement, from the issue of the final Clinical Study Report (CSR) or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, Haleon standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between Haleon and the investigator. The Investigator must be able to inform the Sponsor at any time as to the location of the study records.

13.7 Conditions for Terminating the Study

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

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

If the IRB/EC terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the Haleon and provide Haleon with a detailed written explanation of the termination or suspension.

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

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15 APPENDICIES

15.1 Abbreviations

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

Table 15-1 Abbreviations

Abbreviation	Term
AE	Adverse event
ARR	Acid resistance ratio
BDR	Blinded data review
CI	Confidence interval
CRF	Case report form
eCRF	Electronic case report form
EFU	Enamel fluoride uptake
GCP	Good clinical practice
ICH	International Conference on Harmonisation
IRB	Institutional review board
N/A	Not applicable
CCI	CCI
OHT	Oral hard tissue
OST	Oral soft tissue
PI	Personal information
RER	Relative erosion resistance
SAE	Serious adverse event
SOP	Standard operating procedure
SMHR	Surface microhardness recovery
SS	Safety statement
TEAE	Treatment emergent adverse event
US	United States

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