CLINICAL PROTOCOL

A randomised, controlled, examiner blind, methodology development study to evaluate the effect of a stannous fluoride toothpaste on the oral microbiome

Protocol Number:	300101
Compound/Product Name:	Stannous Fluoride
United States (US) Investigational New Drug (IND) Number:	NA
European Clinical Trials Database (EudraCT) Number:	NA
Other Regulatory Agency Identified Number:	NA
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This document contains confidentiality statements that are not relevant for this publicly available version

Sponsor Information

Sponsor Name & Legal Registered Address	**Haleon (UK)** St Georges Avenue, Weybridge, Surrey, KT13 0DE, United Kingdom (UK)
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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
New Version	2.0	• One of the areas of the mouth (cheek) has been removed from the sample collection throughout the document. • Removed a reference in Section 3.2 and reference list. • Typos corrected throughout the document.

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 INTRODUCTION

1.1 Study Rationale

The sponsor currently demonstrated the effect of stannous fluoride (SnF_2) on the oral microbial ecosystem in a new, validated *in vitro* biofilm model system which uses a saliva-derived inoculum to generate complex oral bacterial biofilms. This model, combined with 16S sequencing and metagenomics analyses, has been successfully used to generate data for a deeper understanding on the mechanism of action of stannous on the microbiome, specifically its inhibition of biofilm regrowth by affecting bacteria metabolism.

Furthermore, in a recent Haleon malodour study (Haleon clinical study 300025, 2023) a toothpaste containing 0.454% SnF_2 showed statistically significant improvements in oral malodour in all endpoints compared to a standard fluoride toothpaste. Given the main aetiological factor of oral malodour is the volatile sulphur compounds (VSC) produced by oral bacteria, and data from this study have been generated in a population with clinical diagnosed gingivitis, it is rational to hypothesize that the efficacy of a formulation containing 0.454% SnF_2 is linked to its ability to modulate the oral microbiome.

Taking all this information together, the conduct of a methodology clinical development study using a toothpaste containing 0.454% SnF_2 will generate information on how it may modulate the overall oral bacteria composition and activity. The results will then feed into the design of future microbiome clinical studies.

Furthermore, this methodology study will include novel technologies such as 16S sequencing and meta-transcriptomics and/or metagenomics, which will give a clear characterization of the overall oral bacterial species (microbial profiling) and their essential interlink with function (functional profiling).

1.2 Background

The oral bacterial communities are highly complex with around 1000 species present and has been shown to be the second most complex in the body, after the colon. The relationship between these communities (or microbiome) and the host is dynamic, can be influenced by many aspects of modern lifestyle, such as diet, tobacco consumption and stress, and it constitutes an important link between health and disease.

To date, there is no clear definition of a healthy microbiome. It has been shown that the composition of microbiome shows great diversity between compartments in the body, and it is highly variable within and between people. However, despite this variation in the composition, the overall functions of the microbiome are relatively consistent and resilient to small perturbations. This helps prevent the shift from symbiotic state (equilibrium between the highly diverse microbial community) to dysbiosis (outgrowth and overactivity of any single or few species which might lead to exceed the pathological threshold; Wade 2013).

Given the complexity of the microbial community, it might be considered impossible to clearly assign a role for each microorganism within the community and link its presence or absence to a particular disease state. There is emerging evidence in the literature of potential bacterial groups which could be associated with health or disease, as shown in a recent study by Adams and colleagues who reported some examples of the association of their identified taxa with gum health and/or disease (Adams SE et al. 2017). However, nowadays it is accepted that the bacteria historically considered as oral 'pathogens' can be found in low numbers at healthy sites, and

oral disease occurs due to negative changes to the natural balance of the overall microbiota (dysbiosis) and not to a single species (Killian 2016).

The advent of high throughput sequencing technologies such as 16S sequencing (community profiling), metagenomics (genetic composition – functional profiling), meta-transcriptomic (genes transcribed – functional profiling) has improved the characterisation of the overall oral bacterial species, including those which are difficult to grow in laboratory conditions using with conventional microbiology methods (i.e., plating) (Eren AM, et al. 2014). Furthermore, they have helped to understand the essential interlink between the bacterial composition and the function in order to explore the contribution of individual species to the overall community function (Gumber HK, et al. 2022).

Antimicrobial ingredients like stannous, tend to impact the bacterial community inhibiting the biofilm regrowth by affecting bacteria metabolism. Using the above techniques, Haleon have generated data to show its mode of action *in vitro*; it is then natural progression to explore this effect on the microbiome in a clinical study.

The aim of this study is to evaluate the effect of a toothpaste containing stannous fluoride over time on the oral bacterial composition and activity and to explore its effect in comparison to a regular fluoride toothpaste. Any changes observed from this methodology development study will provide insights to generate hypotheses on the potential effect of a stannous containing toothpaste on the overall community shift towards a stronger association to health and limiting dysbiosis (overgrowth of potential pathogenic species).

1.3 Benefit/Risk Assessment

This study will use commercially available formulations. Complete information for these products may be found in the commercially available pack.

1.4 Mechanism of Action/Indication

Stannous fluoride (SnF_2) is a well-known chemotherapeutic agent, incorporated into dentifrices since the 1940s for its anti-caries, anti-dentin hypersensitivity and anti-plaque/anti-gingivitis benefits (Makin, 2013; Miller et al, 1994; Van Loveren, 2001; Van Loveren, 1990b).

The stannous ion (Sn [II]) is a broad-spectrum antimicrobial with bacteriostatic and bactericidal properties (Archila et al, 2004; Bellamy et al, 2012; He et al, 2012; Tinanoff, 1995). It has been shown to interfere with the development and maturation of the plaque biofilm, inhibiting bacterial adherence and colonization of the oral surfaces, and penetrating the cell wall to interfere with bacterial metabolism (Tinanoff, 1990; Wilson and Pratten, 1999). These effects have been shown to carry through to in vivo effects on a range of microbial activities, resulting in anti-plaque benefits (Bacca et al, 1997; Kasturi et al, 1995; White et al, 1995).

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To describe the overall oral bacterial composition following 6 weeks use of a 0.454% Stannous fluoride (SnF_2) toothpaste and regular fluoride toothpaste (control) using microbiome profiling	• Changes in relative abundances of bacterial groups at Week 6 compared to Baseline by treatment
Exploratory	
To compare the overall oral bacterial composition following 6 weeks use of the 0.454% SnF_2 toothpaste to a regular fluoride toothpaste (control) using microbiome profiling	• Differences in relative abundances of bacterial groups at week 6 compared to control
To describe and compare the oral bacterial composition following 6 weeks use of a 0.454% SnF_2 toothpaste and regular fluoride toothpaste (control) for different areas of the mouth (tongue, supragingival, subgingiva and saliva) using microbiome profiling	For each of the different areas of the mouth: • Changes in Relative abundances of bacterial groups at Week 6 compared to Baseline by treatment • Differences in the relative abundances of bacterial groups at week 6 compared to control
To describe and compare the overall oral bacterial functionality following 6 weeks use of a 0.454% SnF_2 toothpaste and regular fluoride toothpaste (control), overall and for different areas of the mouth (tongue, supragingival, subgingiva and saliva), using functional profiling	Overall and for each of the different areas of the mouth: • Changes in bacterial activity at Week 6 compared to Baseline by treatment • Differences in bacterial activity at week 6 compared to control

No formal success criterion has been defined for this methodology development study; however, any changes observed from this methodology development study will provide insights to generate hypotheses on the potential effect of a stannous containing toothpaste on the overall community shift towards a stronger association to health and limiting dysbiosis.

3 STUDY DESIGN

3.1 Overall Design

This will be a single-center, 6-week, randomized, controlled, analyst and examiner-blind, two-treatment, parallel group design, methodology development clinical study, investigating the efficacy of a toothpaste containing 0.454% SnF_2 in healthy adult volunteers with mild-moderate gingivitis.

At Screening (Visit 1), subjects will provide their written informed consent to participate in the study. Demographics, medical history and current medications will then be recorded, followed by an oral examination, which will include OHT and OST examinations, and gingival health will be assessed with MGI and BI assessments. Subjects will then use a disclosing solution, and supra-gingival plaque (TPI) assessments will be completed. Subjects will be considered eligible with a minimum of 20 natural teeth, at least 40 evaluable surfaces, with $10\% < BS < 30\%$ (BS=bleeding sites) and overall mean TPI ≥ 1.5

To standardize oral hygiene practice, eligible subjects will complete a lead-in period prior to Visit 2 during which they will brush with the toothbrush and regular fluoride toothpaste provided. Subjects will return to the study site for Baseline visit (Visit 2) having abstained from oral hygiene for the past 12-18 hours i.e., with overnight plaque accumulation. Following an OST examination, samples will be collected from 4 different areas of the mouth (saliva, tongue, supragingival plaque and subgingival surface).

Following sample collection, randomized subjects will receive their assigned study toothpaste and they will be instructed to brush twice daily (morning and evening) in their usual manner, for 1-timed minute, for the next 6 weeks and to record each brushing in the diary provided. They will complete the first brushing at the study site, under supervision.

Subjects will return to the study site after 6 weeks (Visit 3) of treatment, having abstained from oral hygiene for 12-18h before study visit. Wherever possible, remaining visit should be scheduled at approximately the same time of day as the subject's Baseline visit (Visit 2). At Visits 3, study product usage and the completed diary will be reviewed for compliance with study requirements, and changes in health/concomitant medications and AEs will be recorded. Following an OST and OHT examination, samples will be collected (as Visit 2). At Visit 3, subjects will return all study materials.

3.2 Scientific Rationale for Study Design

Several Haleon clinical studies (Haleon clinical studies 207014, Parkinson et al. 2014, Acherkouk et al. 2021, Parkinson et al. 2018b, Parkinson et al 2018a, Parkinson et al. 2020) have demonstrated the efficacy of stannous on gingivitis and plaque removal across different intervention periods (*short term* – up to 3 weeks; *long term* – up to 6 months). This is the first time Haleon is evaluating the impact of SnF_2 on the oral microbiome and a 6-week study period was selected as deemed sufficient for this methodology development study to see changes in 4 different areas of the mouth.

A parallel group design has been selected as the most appropriate to observe the anticipated differential changes in the microbial composition and activity from baseline and between the treatment groups, avoiding the potential for carryover effects had a crossover experimental design been employed.

According to the ICH-GCP guidelines, for a study to be classified as truly double blind neither the subject nor the investigator, study staff involved in the treatment or clinical evaluation of the subjects, monitors or data analysts should be aware of the treatment received. This includes anyone determining subject eligibility, evaluating endpoints, or assessing compliance with the protocol. Furthermore, the products under test should be identical (color, flavor, appearance and packaging). Given that this study will be using commercially available toothpastes, it is almost impossible to ensure identical appearance, taste and packaging, therefore the level of blindness for this study is described as 'analyst and examiner blind'.

Whilst the study products are not contra-indicated for pregnancy and breastfeeding, pregnant and/or lactating females will be excluded from this study due to the increased prevalence and severity of gingivitis and periodontal disease observed during pregnancy (Samant et al., 1976) and breastfeeding (Aghazadeh et al, 2019) which, together with the increased amounts of calculus and plaque observed during pregnancy, could impact study outcome (Samant et al., 1976).

To ensure study subjects demonstrate the required propensity for plaque formation, only subjects with a mean TPI $\geq$ 1.5 at Screening (Visit 1) will enter the lead-in period. Furthermore,

subjects with mild-moderate gingivitis will be included based on the new classification of subjects' gingival health (Chapple et al., 2018) therefore, only subjects with 10% < BS < 30% (BS derived from BI assessment) will enter the lead-in period.

Eligible subjects will complete a lead-in period prior to Visit 2, during which they will be provided with a standard flat trim toothbrush and regular fluoride toothpaste (both marketed products) to use in place of their own oral hygiene products. Use of these products will provide the study population with a standardized oral hygiene regimen prior to the Baseline visit and familiarize them with required usage regimen (1-minute timed brushing, twice daily) and completion of a diary after each brushing.

Eligible subjects will be asked to refrain from oral hygiene for 12-18 hours prior to Visits 2 and 3 (i) to standardize oral hygiene practice in the study population and (ii) ensure sufficient plaque growth to allow the collection of sufficient amounts of samples and reduce impact on study outcomes.

In most published studies, the effect of oral hygiene formulations has been reported for dental plaque organisms, however evaluating microbial populations in other areas of the mouth could give insights into their relation to oral diseases (Haraszthy VI, et al. 2019). For example, the main aetiological factor of oral malodour is the volatile sulphur compounds (VSC) produced by oral bacteria present on tongue surface (Takahashi 2015). Saliva has been used widely in microbiological studies to explore microbial diversity, examine person-to-person transmission of organisms within the mouth, and determine antimicrobial effects of formulations (Svanberg M & Rolla G. 1982). Therefore, in this study samples will be collected from different areas of the mouth (tongue, supragingival plaque, subgingival surface and saliva) in order to examine the effect of stannous on microorganisms present in different oral niches which could provide broader information across the overall oral cavity.

Microbial and functional profiling will be assessed using high throughput sequencing technologies:

- 16s rRNA gene amplicon sequencing is a methodology which allows the study of the bacterial community (microbial profiling) identifying bacteria present within a given sample down to the genus and/or species level.
- Metagenomics and meta-transcriptomics are methodologies which allow the study of the bacterial functions (functional profiling). Metagenomics generates data on the genetic composition, allowing the understanding of the functional potential of the various bacterial groups. Meta-transcriptomics generates information on the genes which are transcribed, giving deeper insight into the activity of the various bacterial groups.

Data generated with these techniques will help to generate hypotheses on the potential effect of a stannous containing toothpaste on the overall bacterial community and activity and to inform the design of future microbiome studies.

3.3 Justification for Dose

Study products are toothpastes, intended for topical oral use, and will be applied by toothbrushing using a manual toothbrush.

The usage regimen of twice daily brushing (morning and evening) will be the same for all subjects, based on widely recommended oral hygiene practice and typical consumer habit.

Study subjects will brush for 1-timed minute with their assigned study toothpaste on each brushing occasion in line with typical brushing times specified for similar efficacy studies.

After 6 weeks (43 ± 4 days) twice daily usage, each subject should complete between 78-94 brushings with their randomized product. Subjects will complete a supervised brushing with their assigned study toothpaste at the end of each study visit (while still at the study site) to enable staff to confirm correct usage and to encourage compliance with the required usage regimen for the duration of the study.

3.4 End of Study Definition

A subject will be 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 this study is defined as the date of the last scheduled procedure, as described in the Schedule of Activities (Table 7-1), for the last subject.

4 STUDY POPULATION

4.1 Type and Planned Number of Subjects

The study will be conducted in male and female subjects in good general health, aged 18-65 years inclusive, that meet all study criteria.

Sufficient subjects will be screened to ensure approximately a total of 55 subjects 15andomizat to study product and approximately 50 evaluable subjects complete the entire study (approximately 25 subjects per product arm), allowing 10% dropouts. No formal sample size has been performed as per nature of this study (methodology development), however based on a previous *in situ* clinical study evaluating the mode of action of a stannous fluoride toothpaste using 16S sequencing and meta-transcriptomics in 13 subjects, this was considered a small sample size and one of the reasons for the high variability in amplicon and gene expression data (Gumber et al. 2022). Recruiting more participants would potentially reduce this risk and therefore N=50 is considered sufficient to provide reliable estimates of performance for the purposes of this methodology development study and to aid in the design of future clinical studies.

An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process 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.

4.2 Inclusion Criteria

An individual must meet all the following inclusion criteria to be eligible for enrollment into 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 male or female who, at the time of screening, is aged 18-65 years, inclusive.
3. Subject who is willing and able to comply with scheduled visits, sampling schedule, treatment plan and other study procedures.
4. Subject, in the opinion of the investigator or medically qualified designee, in good general and mental health.

AT SCREENING (Visit 1):

5. Subject with at least 20 natural, permanent teeth (excluding 3rd molars).
6. Subjects with at least 40 evaluable surfaces.

   An evaluable surface is defined as having 2/3rds of the natural tooth surface gradable for the selected clinical indices.

   The following should not be included in the evaluable surface count: third molars; fully crowned/extensively restored teeth; grossly carious teeth; orthodontically banded/bonded or abutment teeth; surfaces with calculus deposits which, in the opinion of the clinical examiner, would interfere with the baseline assessments of the selected clinical indices.
7. Overall mean TPI score ≥ 1.5
8. Subjects with 10% < BS < 30 %

4.3 Exclusion Criteria

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

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or otherwise supervised by the investigator, or a member of their immediate family; or a sponsor employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) in the 30 days prior to study entry and/or who is participating in other studies during study participation.
3. A 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. A subject with any medical/oral condition which, in the opinion of the investigator or medically qualified designee, could impact study outcomes (for example, oral dryness or could directly influence gingival bleeding).
5. A subject taking daily doses of medication/having daily treatments which, in the opinion of the investigator or medically qualified designee, could impact study outcomes (for example, is causing oral dryness).

6. A subject who is pregnant (self-reported; no pregnancy test required) or intending to become pregnant over the course of the study.
7. A subject who is breastfeeding.
8. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
9. A subject who is unwilling or unable to comply with the Lifestyle Considerations described in this protocol.
10. A subject who has difficulty complying with study procedures and examinations, such as excessive gagging during oral assessments.
11. A subject who has had routine dental prophylaxis within 12 weeks of Screening.
12. A subject who has undergone a tooth bleaching procedure (at-home or professional) within 8 weeks of Screening.
13. A subject with any of the following which, in the opinion of the investigator or medically qualified designee, could impact study outcomes or the oral health of the subjects if they were to participate in the study:
    a. severe gingivitis.
    b. signs of active periodontal disease or who is receiving or has received treatment for periodontal disease (including surgery) within 12 months of Screening.
    c. active caries.
    d. evidence of gross intra-oral neglect or the need for extensive dental therapy.
    e. restorations in a poor state of repair or metal fillings.
    f. any dental condition (e.g., malalignment, overcrowding)
    g. high levels of extrinsic dental stain or calculus deposits.
14. A subject with the following:
    a. a tongue or lip piercing.
    b. multiple dental implants which, in the opinion of the investigator or medically qualified designee, could impact study outcomes.
    c. fixed bridge(s) or removable partial dentures.
    d. has or has had fixed or removable orthodontic braces/bands or a fixed orthodontic retainer within 3 months of Screening.
15. A subject who is unwilling to forgo use of an orthodontic retainer for the duration of the study, provided there would be no impact on the outcome of any previous, completed orthodontic treatment or the subject's well-being.
16. Subject who is a current smoker or an ex-smoker who stopped within 6 months of Screening (Visit 1).
17. Subject who is a currently user of recreational drugs (e.g., cannabis) within 6 months of Screening.
18. Subject who currently uses smokeless forms of tobacco (e.g., chewing tobacco, nicotine-based e-cigarettes) within 6 months of Screening.

19. **VISIT 1 (Screening)**
    - A subject who has taken antibiotics within 4 weeks of Screening.
    - Subject who has used an anti-bacterial mouthwash (e.g., chlorhexidine) or another oral care product within 2 weeks of Screening that, in the opinion of the investigator or dentally qualified designee, could affect plaque formation or gingival health.
20. **VISIT 2 (Baseline)**
    - A subject who has taken antibiotics during the lead-in period (between Screening and Baseline).
21. Subject with a recent history (within the last year) of alcohol or other substance abuse.
22. A subject who has previously been enrolled in this study.
23. Subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.

4.4 Randomization Criteria

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

4.5 Lifestyle Considerations

If, in the opinion of the investigator or medically qualified designee, a subject has not complied with a study restriction (e.g., oral hygiene, dietary or alcohol-related) prior to a study visit or cannot attend a study visit, every effort will be made to reappoint them within the permitted visit tolerances (see Schedule of Activities, Table 7-1 and Section 6.2, Lost To Follow Up). The reason for re-appointment will be documented in the electronic case report form (eCRF).

If re-appointment is not possible (within the visit tolerance), the following visit specific actions should be taken:

- **Visit 2:** the subject will be withdrawn from the study. Subjects can be rescheduled in outside window visit where AEs will be recorded, and the OST examination completed; no samples will be collected. The subject may be replaced.
- **Visit 3:** the subject will be withdrawn from the study. Subjects can be rescheduled in outside window visit where AEs will be recorded, and the OST examination completed; no samples will be collected. The subject will not be replaced.

4.5.1 Dental Product/Treatment and Oral Hygiene Restrictions

From Screening (Visit 1) to the Subject's Last Study Visit:

- Subjects should not use any other oral care products (for example, toothpastes, toothbrushes, oral rinses, tongue cleaners, whitening/bleaching products) than those provided during the study.
- Subjects should not carry out any interproximal dental cleaning. Use of dental floss, toothpicks, waterpicks or inter-dental brushes is prohibited (except for the removal of impacted food with non-antimicrobial products only).
- Subjects should not chew gum or consume any confectionery containing xylitol (e.g. sugar-free mints, mint-flavour candies).

- Subjects should delay any non-emergency dental treatment until after study completion (including dental prophylaxis).
- Subjects should delay any tooth whitening treatments (professional and/or home use) until after study completion.

Before Visits 2 & 3:

- Subjects should refrain from oral hygiene procedures for 12-18 hours before their visit.

4.5.2 Meals and Dietary Restrictions

Before Visits 2 & 3:

- Subjects must not eat for at least 4 hours and before study visit.
- Subjects must not drink for at least 2 hours before study visit.
  Note: *Small sips of room-temperature water are permitted if required to take medications or to relieve a dry mouth up to 1 hour before their appointment time*
- Subjects should refrain from alcohol consumption for 24 hours before a clinical assessment visit.

4.5.3 Contraception

Given the toothpastes used in this study are commercially available toothpastes, and no drugs will be utilised in this clinical study, pregnancy testing and contraceptive requirements are not deemed necessary. However, if subject reports pregnancy at screening, she will not be included in the study.

4.6 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, a minimum set of information will be recorded for each screen fail subject including demography, reason for screen failure (e.g., withdrawal of consent), eligibility criteria, protocol deviations and AEs, as applicable.

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

4.7 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 investigational staff seeking advice on medical/ dental questions or problems in the event that the established communication pathways between the investigational site and the 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 investigational site, and contact details in the event that the investigational site cannot

be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5 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.

5.1 Investigational/Study Product Supplies

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

Table 5-1 Study Product Supplies

Product Description	Test Toothpaste	Reference Toothpaste (Control)
Product Name	Sensodyne Repair and Protect (US market)	Colgate Cavity Protection (Regular fluoride toothpaste, US market)
Fluoride content	1100 ppm fluoride as SnF_2	1100 ppm fluoride as SMFP
Pack Design	One carton containing 3 overwrapped tubes of toothpaste	
Dispensing Details	Day 1 (Visit 2): One carton	
Product Master Formulation Code	CCI [redacted]	Commercial product (N/A)
Route of Administration	Topical Oral Use	
Dose/Application	Dose the toothbrush with a strip of toothpaste (ribbon of toothpaste across the full brush head) on each brushing occasion	
Usage Instructions	Subjects will brush their teeth for one timed minute twice a day (morning and evening) in their usual manner. Minimize swallowing and spit out.	
Return Requirements	Used and unused samples to be returned to sponsor	

Table 5-2 Lead-In Product Supplies

Product Description	**Lead-In Toothpaste**
Product Name	Colgate Cavity Protection (Regular fluoride toothpaste, US market)
Fluoride Content	1100 ppm fluoride as SMFP
MFC	Commercial product (N/A)
Pack Design	One overwrapped tube of toothpaste
Dispensing Details	Screening (Visit 1): One tube
Product Application	Dose the toothbrush with a strip of toothpaste (a ribbon of toothpaste across the full brush head) on each brushing occasion
Route of Administration	Topical Oral Use
Usage Instructions	Subjects will brush their teeth for one timed minute twice a day (morning and evening) in their usual manner. Minimize swallowing and spit out.
Return Requirements	All used/unused samples to be returned to sponsor

Table 5-3 Sundry Items

Sundry Items to be supplied:

Items	**Supplied By**	**Pack Design**	**Dispensing Details**	**Return/Disposal Details**	
				Used Samples	**Unused Samples**
Aquafresh® Flex toothbrush (UK market)	Sponsor or designated vendor	Commercial pack	**Visit 1** One toothbrush **Day 1 (Visit 2)** One toothbrush	Dispose at site	Return to sponsor
Countdown timer		Commercial pack (1 timer)	**Visit 1** One timer	Subject to keep or dispose at site	
Opaque plastic bags		N/A	**Visit 1** One bag **Day 1 (Visit 2)** One bag		
Dosing cups for on-site use (plaque disclosing procedure)		N/A	**Provide to site** Sufficient for clinical study needs	Dispose at site	
Plaque Disclosing Solution		Commercial pack	**Provide to site** Sufficient for clinical study needs. To be used as described in Section 9.1.3.1 Plaque Disclosure	Dispose at site	

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

5.1.1 Dosage Form and Packaging

All toothpastes will be provided to the clinical study site overwrapped in white vinyl (to mask their identity and obscure any branding) 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 Global Clinical Supplies Department. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

Care should be taken with the supplied products and their labels to ensure 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 over-wrapping or study label.

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

5.1.2 Preparation and Dispensing

Subjects will be assigned to products in accordance with the randomization schedule generated by an approved Haleon vendor, prior to the start of the study, using validated software.

The product dispensing area will be separate from the clinical examination area. Study toothpastes will be dispensed per protocol in blinded fashion to the subject, by trained study personnel. These staff members will not be involved in any safety or clinical efficacy assessments or any other aspect of the study that could be influenced by knowing which product a subject has been assigned to. An additional member of the study staff will verify the dispensing procedure has been completed accurately for each subject.

A record of product dispensing to each subject will be maintained in the dispensing log; completion of the dispensing procedure will be recorded in the eCRF.

5.2 Administration

Subjects will self-administer the lead-in toothpaste (from Visit 1 to Visit 2) and their assigned study toothpaste (from Visit 2 to Visit 3) according to the usage instructions provided by study personnel at the study site and record each brushing in their diary.

To help ensure subjects fully understand the amount of toothpaste to use, the brushing instructions and how to complete the diary:

- **Screening (Visit 1):** Staff will demonstrate dispensing a full ribbon of toothpaste along the length of the toothbrush head to each qualifying subject and supervise their first brushing with the lead-in toothpaste/diary completion at the end of the visit, after all clinical assessments have been completed.
- **Baseline (Visit 2):** Staff will check the dispensing of a full ribbon of toothpaste by each randomized subject and supervise the first brushing with their assigned study toothpaste/diary completion.

On-site administration of study products will be recorded in the dispensing log and the eCRF.

5.2.1 Product Dosing Errors

In this study, dosing errors may result from the administration or consumption of the wrong product, by the wrong subject, in the wrong way. Such dosing errors should be captured in the eCRF. Dosing errors are reportable irrespective of the presence of an associated AE, including:

- Dosing errors involving subject exposure to any of the study products.
- Potential dosing errors or uses outside of what was foreseen in the protocol that do or do not involve the participating subject.

If a dosing error is accompanied by an AE, as determined by the investigator or medically qualified designee, the dosing error and any associated Aes are to be captured in the eCRF AE form.

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

5.2.2 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.

5.3 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 area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and the product label.

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.

5.4 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 the 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 investigative 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 return used and unused tubes of the lead-in toothpaste to the study site at their Baseline visit (Visit 2). Subjects will bring the used and unused tubes of their assigned study toothpaste to each of their scheduled visits to the study site, per the Schedule of Activities (Table 7-1); all study products will be returned at study conclusion. Study product return will be documented using the study product accountability form/record.

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.

5.4.1 Destruction of Study Product Supplies

At the end of the study, the Principal Investigator or an appropriate designee, and a representative of Haleon (study monitor) will inventory all used and unused study products and sundry items. The investigational/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 Haleon Clinical Supplies Department 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 Haleon during the study in time for study close out visit.

5.5 Blinding and Allocation/Randomization

All subjects will be centrally randomized to one of the two study toothpastes using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided to the study site. 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 analyst and examiner-blind (analyst and clinical examiners will be blinded to product received). Subjects, site staff, study statistician(s), data management staff, other employees of the Sponsor (including the CRS) and vendors acting on behalf of the sponsor, who may influence study outcomes will also be blinded to product allocation. The monitors and the sponsor's Clinical Study Manager may not be fully blinded as they will observe subjects brushing with their allocated study product while at the study site. As a matter of study conduct, including emergency unblinding events, only the investigator may learn the contents of one or

more of the product codes used to allocate study product, not the clinical examiners. Given the application of IRT within this study, any such knowledge will not affect the decision to enroll a subject or influence the order in which subjects are enrolled.

To ensure the analyst and clinical examiners remain blinded throughout the study:

- Site staff involved in the dispensing of study products and supervision of on-site brushing will work in a separate area and will not be involved in any safety or product efficacy assessments.
- Analyst and clinical examiners will not be permitted in any area where study product or diaries are stored, dispensed, or in use.
- Subjects will be instructed not to remove their study product or diary from its opaque carrier bag outside of the dispensing room, while at the study site.

Subjects will be instructed not to discuss which study product they have been assigned or usage instructions with the clinical examiners.

5.6 Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind in case of emergency. 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 the eCRF, 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.

5.7 Compliance

To facilitate compliance with product usage, subjects will be provided with a diary at Screening (Visit 1) and at Baseline (Visit 2) to record each brushing with the lead-in toothpaste and their assigned study product, respectively.

- The diaries will provide detailed usage instructions for the subject to refer to throughout their participation in the study.
- Subjects will be instructed to note any missed/additional brushings, the reasons for any missed/additional brushings, any issues with the toothpaste used, oral problems, illnesses and any new medications/treatments in their diaries.
- Completed diaries will be reviewed by study staff at the start of each study visit. Any missed or additional brushings will be captured in the eCRF as protocol deviations. Subjects will be re-instructed in correct product usage requirements/diary completion, as needed.

Information recorded in the diary relating to changes in health and medications/ treatments will be reviewed by the investigator, or medically qualified designee, with the subject and transcribed into the eCRF, as appropriate (e.g., as an AE). Information related to product use should also transcribed into the eCRF, as appropriate, taking care to maintain the blind.

Subjects will be instructed to bring all tubes of toothpaste provided (used and unused) to each study visit. Study staff will perform a visual check of product usage. Any suspected over or under use will be documented in the eCRF and the subject will be re-instructed in the correct usage requirements.

Supervised brushings will be carried out at the study site at the end of Visit 1 and 2 to facilitate compliance with usage instructions. If any deviations from per protocol product usage are observed, the subject will be re-instructed of correct product usage.

5.8 Concomitant Medication/Treatment(s)

Any medications, treatments or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken or received during the study, from signing the informed consent, must be recorded in the eCRF 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 or received within 30 days of signing the informed consent form will be documented as a prior medication/treatment. Medications/treatments taken or received after signing the informed consent form will be documented as concomitant medication/treatments.

For the Duration of the Study: Screening (Visit 1) to Subject's Last Study Visit

- Subjects should delay any non-emergency, elective dental treatments until after study completion (including dental prophylaxis).
- Should a randomized subject start a course of treatment which includes daily, regular or intermittent use of any medication, details of that medication/treatment will be recorded in the eCRF. The investigator, or their medically qualified designee, will decide if the subject can continue on the study or should be withdrawn.
- Should a subject take a medication which, in the opinion of the investigator or their medically qualified designee, could impact the study outcome within 8 hours of a scheduled study visit, the medication should be recorded in the eCRF and every effort will be made to reappoint them within permitted visit tolerances (see Schedule of Activities, Table 7-1). The reason for re-appointment will be documented in the eCRF.

If re-appointment is not possible, the following visit specific actions should be taken:

- **Screening (Visit 1):** the subject will be withdrawn from the study. No assessments will be performed. The subject may be replaced.
- **Baseline (Visit 2):** the subject will be withdrawn from the study. Subjects can be rescheduled in outside window visit where Aes will be recorded, and the OST examination completed; no samples will be collected. The subject may be replaced.
- **Weeks 6 (Visits 3):** the subject will be withdrawn from the study. Subjects can be rescheduled in outside window visit where Aes will be recorded, and the OST examination completed; no samples will be collected. The subject will not be replaced.

6 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

6.1 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her 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
- Inability of the subject to comply with the protocol-required schedule of study visits, procedures or lifestyle considerations
- 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 eCRF.

6.2 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 that they had been dispensed 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 the following:

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.

7 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 (Table 7-1).

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

Table 7-1 Schedule of Activities

Procedure/ Assessment	Visit 1 Screening		Visit 2 Day 1 Baseline	Visit 3 Week 6 Day 43 (±4 days)
Informed Consent	X	Lead-In (7 Days ± 2 Days)		
Demographics, Medical History, Prior/Current Medications/Treatments	X			
Inclusion/Exclusion Criteria	X			
Oral Examinations to Determine Eligibility Against Inclusion/Exclusion Criteria and to Identify Scorable surfaces	X			
Modified Gingival Index (MGI)	X			
Bleeding Index (BI)	X			
Disclose dental plaque	X			
Turesky Modified Quigley & Hein Plaque Index (TPI)	X			
Oral Soft Tissue (OST) Examination	X		X	X
Oral Hard Tissue (OHT) Examination	X			X
Dispense Lead-In Toothbrush, Regular Fluoride Toothpaste, Diary, Timer	X			
On-Site Supervised Brushing with Lead-In Toothbrush and Regular Fluoride Toothpaste; Complete Diary	X			
Subject Returns with Lead-In Toothbrush, Regular Fluoride Toothpaste, Completed Diary			X	
Compliance Checks			X	X
Concomitant Medications/Treatments			X	X
Subject Continuance[1]			X	
Sample collection			X	X
Randomization[2]			X	
Dispense Toothbrush, Study Toothpaste, Diary			X	
On-Site Brushing with Toothbrush and assigned study Toothpaste; Complete Diary[2]			X	
Subject Returns with Toothbrush, Study Toothpaste, Completed Diary				X
Adverse Events (AEs)[3]	X		X	X
Study Conclusion				X

Footnotes:

1. Subjects will be required to bring their study supplies to every visit.

Staff will perform a visual check of the returned study supplies/review the completed diary.

- Visits 2: compliance with lead-in toothpaste usage.
- Visits 3: compliance with assigned study toothpaste usage.

Check compliance with Lifestyle Considerations/Medication Requirements.

2. Randomization and on-site brushings to be carried out after sample collection.
3. AEs, and therefore all Serious Adverse Events (SAEs), will be collected from immediately after each subject consents to participate in the study (by the completion of the Informed Consent Form [ICF]) until 5 days after last use of study product.

7.1 Visit 1/Screening

The following procedures and assessments will be completed by the investigator, or a suitably qualified/experienced designee, and the clinical examiners, prior to randomization to study product. Where practically feasible, they should be completed in the order listed below. Data collected will be recorded in the eCRF.

7.1.1 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. Two copies of the informed consent form (ICF) will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

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 at which all Adverse Events will be captured from. The date and time of consent will be captured in the eCRF.

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 eCRF.

A list of Ingredients in the toothpastes to be used during the study will be provided to each subject during the consent process to enable them to confirm whether they have a known allergy or hypersensitivity to any of the ingredients listed.

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.

7.1.2 Demographics

The following demographic information will be recorded in the eCRF: year of birth, sex (male or female), race and ethnicity.

7.1.3 Medical History and Prior Medication/Treatment

The following will be documented in the eCRF.

- Details of relevant medical history and recent surgery (within the last year), including allergies and drug sensitivities.
- Female subjects: pregnancy and breast-feeding status (self-reported).
- Medications/treatments, including prescription and non-prescription drugs, dietary supplements, taken currently and in the last 30 days.

7.1.4 Clinical Examinations and Assessments

The following clinical examinations will be completed as described in Study Assessments and the findings recorded in the eCRF. To facilitate subject flow, source documents may be used for later transcription into the eCRF (transcription from source documents must be completed within 5 days of recording the data for each subject).

- OST examination
- OHT examination
- MGI assessment
- BI assessment
- Plaque disclosure
- TPI assessment

7.1.5 Inclusion/Exclusion Criteria

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

7.1.6 Subject Eligibility

The investigator and/or medically qualified designee will review inclusion/exclusion criteria, medical history, prior medications to confirm subject eligibility to participate in the clinical trial. This will be documented in the eCRF.

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

7.1.7 Supervised Brushing with Lead-in Toothpaste

Enrolled subjects will be provided with the lead-in toothpaste, a toothbrush, a timer and a diary to use during the lead-in period.

Staff will describe the toothpaste usage instructions to the subject and demonstrate covering the full brush head with a ribbon of toothpaste. Staff will then supervise the subject carrying out first their first brushing with the lead-in toothpaste and recording the first use in their diary.

Any deviation from the product usage instructions will be captured as a protocol deviation in the eCRF and the subject will be reminded of the correct directions for use. Dispensing of the lead-in toothpaste and completion of the supervised first brushing will also be documented in the eCRF.

Spontaneously reported AEs, and any AEs elicited by asking subjects to respond to a non-

leading question, such as 'How do you feel?', on completion of the supervised brushing with the lead-in toothpaste will be recorded in the eCRF.

Staff will remind subjects to bring their lead-in products to their next study visit and to note any changes in health, medications or treatments in their diary (or report such changes to study staff between visits using the contact numbers provided or inform the staff at their next visit, if preferred.

7.2 Study Period

7.2.1 Visit 2/Day 1

The following procedures and assessments will be completed by the investigator, or a suitably qualified/experienced designee, and the clinical examiners. They should be completed in the order listed below. All data collected should be recorded in the eCRF.

7.2.1.1 Changes in Medical History and Concomitant Medications/Treatments

Staff will ask subjects if there have been any changes in their health, concomitant medications and non-drug treatments/procedures since their last visit. All changes will be documented in the eCRF.

Spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question, such as 'How do you feel?', will be assessed and AEs recorded in the eCRF.

7.2.1.2 Compliance check

Staff will complete visual checks of returned study toothpaste and review completed diary. Record any suspected over or under use and the number of any missed or additional brushings in the eCRF.

Any deviations from the required product usage instructions will be captured as protocol deviations in the eCRF and subjects will be re-instructed in the correct usage.

Note: *Staff will retain the lead-in toothpaste, completed lead-in diary. Staff will dispense Study period diary and new toothbrush to subjects*.

7.2.1.3 Subject Adherence and Continuance

Confirm subject adherence to the requirements of the protocol and document continuance in the eCRF. Record any deviations from study requirements in the eCRF.

7.2.1.4 Clinical Examinations and Sample collection

The following clinical safety examinations and sample collection will be carried out as described in Study Assessments. They must be completed in the order specified below and the findings recorded in the eCRF.

To facilitate subject flow, source documents can be used for later transcription into the eCRF (transcription from source documents must be completed within 5 days of recording the data for each subject).

- OST examination
- Sample collection in 4 areas of the mouth (supragingival plaque, tongue, saliva and subgingival surface) using swab and saliva collection kits

Note: Samples will be collected, frozen and processed for sequencing as describe in Section 9.2.3.

7.2.1.5 Randomization

Eligible subjects will be assigned a randomisation number in ascending numerical order, as each subject is determined to be fully eligible.

7.2.1.6 Supervised Brushing with Study Toothpaste

Randomised subjects will be provided with their allocated study toothpaste, a new toothbrush and a new diary.

Study staff will describe the toothpaste usage instructions to the subject, then supervise their first brushing with study toothpaste and recording of the first use in their diary. Any deviation from the product usage instructions will be captured as a protocol deviation in the eCRF and the subject will be reminded of the correct directions for use.

Dispensing of study toothpaste and completion of the supervised first brushing will be documented in the eCRF.

Spontaneously reported AEs, and any AEs elicited by asking subjects to respond to a non-leading question, such as 'How do you feel?', on completion of the supervised brushing will be recorded in the eCRF.

Randomized subjects will be re-instructed in the Lifestyle Considerations and Concomitant Medications/Treatments requirements of the study. Staff will remind them to bring their study products to their next study visit and to note any changes in health, medications or treatments in their diary. Alternatively, they can report such changes to study staff between visits using the contact numbers provided in the ICF or inform the staff at their next visit, if preferred.

7.2.2 Visit 3/Day 43 ± 4

The following procedures and assessments will be completed by the investigator, or a suitably qualified/experienced designee, and the clinical examiners. They should be completed in the order listed below. All data collected should be recorded in the eCRF.

7.2.2.1 Changes in Medical History and Concomitant Medications/Treatments

Staff will ask subjects if there have been any changes in their health, concomitant medications and non-drug treatments/procedures since their last visit. All changes will be documented in the eCRF.

Spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question, such as 'How do you feel?', will be assessed and AEs recorded in the eCRF.

7.2.2.2 Compliance check

Staff will complete visual checks of returned study toothpaste and review completed diary. Record any suspected over or under use and the number of any missed or additional brushings in the eCRF.

Any deviations from the required product usage instructions will be captured as protocol deviations in the eCRF and subjects will be re-instructed in the correct usage.

Note: *Staff will retain the study toothpaste, toothbrush and completed 'Week 6' diary.*

7.2.2.3 Clinical Examinations and Sample collection

The following clinical safety examinations and sample collection will be carried out as described in Study Assessments. They must be completed in the order specified below and the findings recorded in the eCRF.

To facilitate subject flow, source documents can be used for later transcription into the eCRF (transcription from source documents must be completed within 5 days of recording the data for each subject).

- OST examination
- OHT examination
- Sample collection in 4 areas of the mouth (supragingival plaque, tongue, saliva and subgingival surface) using swab and saliva collection kits

Note: Samples will be collected, frozen and processed for sequencing as describe in Section 9.2.3.

7.3 Study Conclusion

The Study Conclusion page of the eCRF 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.

7.4 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). At the discretion of the investigator, or medically qualified designee, additional oral examinations may be carried out at such visits.

8 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.

8.1 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.

8.1.1 Modified Gingival Index (MGI)

The MGI is a non-invasive visual assessment of gingival inflammation (Lobene, 1986). MGI will be assessed for all evaluable surfaces of the facial and lingual/palatal gingiva, four sites per tooth (facial gingiva: papilla and margin; lingual/palatal gingiva: papilla and margin) and scored as follows.

Score	Description
0	Absence of inflammation
1	Mild inflammation; slight change in colour, little change in colour; little change in texture of any portion of the marginal or papillary gingival unit.
2	Mild inflammation; criteria as above but involving the entire marginal or papillar gingival unit.
3	Moderate inflammation; glazing, redness, oedema, and/or hypertrophy of the marginal or papillary gingival unit.
4	Severe inflammation; marked redness, oedema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

8.1.2 Bleeding Index (BI)

The BI is an invasive assessment of gingival bleeding (Saxton and van der Ouderaa, 1989). BI will be assessed for all evaluable surfaces of the facial and lingual/palatal gingiva, six sites per tooth (mesiobuccal, buccal and distobuccal; mesiolingual/palatal, lingual/palatal and distolingual/palatal) and scored as follows.

Score	Description
0	Absence of bleeding on probing
1	Bleeding observed within 30 seconds of probing
2	Bleeding observed immediately on probing

Sites with a score of 1 or 2 will be classified as 'bleeding' sites.

To perform the bleeding assessment, a round-end probe (e.g., CPITN* probe) is inserted approximately 1 millimeter (mm) into the gingival sulcus (at approximately 60 degrees) and moved around the tooth from the distal interproximal area to the mesial interproximal area, gently stretching the gingival epithelium. Contact with the tooth surface should be avoided. Presence/absence of gingival bleeding is assessed for 30 secs after probing.

Assessments should be performed one quadrant at a time, with BI scores recorded for the most recently probed quadrant before moving on to the next.

*CPITN = Community Periodontal Index of Treatment Needs

8.1.3 Turesky Modification of the Quigley Hein Index (TPI)

The TPI is a non-invasive assessment of supra-gingival plaque accumulation (Lobene et al. 1982, Turesky et al. 1970). TPI will be assessed for all evaluable surfaces of the facial and lingual surfaces of the teeth (7-7 in each arch). Each tooth surface is divided into 3 areas; three scores are recorded facially (mesiofacial, facial, distofacial) and three scores lingually (mesiolingual, lingual and distolingual), generating six scores per tooth.

The plaque is first disclosed, as described in Section 9.1.3.1, then each evaluable site is scored as follows:

Score	Description
0	No plaque
1	Slight flecks of plaque at the cervical margin of the tooth
2	Thin, continuous band of plaque (1millimetre (mm) or smaller) at the cervical margin of the tooth
3	Band of plaque wider than 1mm but covering less than 1/3 of the area
4	Plaque covering at least 1/3 but less than 2/3 of the area
5	Plaque covering 2/3 or more of the crown of the tooth

8.1.3.1 Plaque Disclosure Procedure

Dental plaque forms as a colorless deposit on the teeth and so requires 'staining' with disclosing solution prior to TPI assessment. The disclosing solution supplied by the sponsor will be used according to the manufacturer's instructions.

- At the request of the subject, to minimize staining of the lips, the clinical assessor may apply a thin layer of petroleum jelly to the subject's lips as a barrier, prior to applying the disclosing solution.

  Care should be taken to ensure no petroleum jelly comes into contact with the labial surfaces of the anterior teeth as this could impact TPI assessment for these surfaces.
- Subject rinses with 10 mL tap water for 10 seconds and expectorates to remove any food debris from the mouth.
- Disclosing solution will be dispensed into a dispensing cup (~2.5 ml) and subject rinses for 10 seconds to distribute this solution around their mouth. Care should be taken not to dislodge the plaque during this process.

Subject rinses with another 10 mL tap water for 10 seconds and expectorates to remove excess solution from the mouth.

8.2 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.

8.2.1 Oral Soft Tissue (OST) Examination

The OST examination will be accomplished by direct observation and palpation, using retraction aids as appropriate. It will include examination of the 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. The results of the examination will be recorded in the eCRF as either 'normal' or 'abnormal'; the details of any abnormalities will be described in the eCRF.

Any OST observation that changes from 'normal' to 'abnormal', or worsens, from Screening will be recorded as an AE in the eCRF.

8.2.2 Oral Hard Tissue (OHT) Examination

The OHT examination will be accomplished by direct observation, using retraction aids as appropriate. It will identify enamel irregularities, tooth fractures, grossly carious lesions/gross decay, defective/faulty restorations, direct & indirect restorations including fixed/removal prostheses, non-carious tooth surface loss (abrasion, attrition, abfraction and erosion), any other hard tissue irregularities (e.g., hypo/hypermineralisation, decalcification) and significant tooth staining. Conditions will be listed as 'absent' or 'present'; those noted as 'present' will be described in the eCRF. Any OHT observation that changes from 'absent' to 'present', or worsens, from Screening will be recorded as an AE in the eCRF.

The presence of implants, fixed or removable dentures, fixed or removable orthodontic braces/bands, fixed orthodontic retainers, full crowns or veneers will be recorded, along with evidence of gross intra-oral neglect or the need for extensive dental therapy.

8.2.3 Sampling and Laboratory Procedures

All sampling and laboratory procedures will be provided in separate work instruction documents. They will be prepared by PI or designee and reviewed by Haleon and they will be approved by PI or designee and CRS or designee, and stored in eDMS prior to Screening Visit.

The work instruction documents will cover, but not limited, the following elements:

- Sample collection, preservation processing and freezing at the clinical site
- DNA/RNA extraction, library preparation and sequencing
- Sample destruction

8.2.4 Pregnancy Testing

For Haleon studies in which no drug is utilized or studies of single-use marketed products that are classified as a non-medicinal product in the market where the testing is occurring and there is no pregnancy warning on labelling, a pregnancy test will not be required.

Female subjects will provide verbal confirmation of pregnancy status at Screening (Visit 1) and will be asked to inform study staff immediately should this change at any point during the study. Female subjects who are pregnant or intending to become pregnant during the study (self-reported) will be excluded.

9 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.

9.1 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 Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (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.

9.2 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.

9.3 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 eCRF 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 eCRF.

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.

9.4 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 eCRF 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 eCRF 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 eCRF 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 were 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 eCRF 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.

9.4.1 Reporting of an Adverse Event

All AEs will be reported on the AE page of the eCRF 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 eCRF. Where the same data are collected, the AE eCRF 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 eCRF as well as on the form for collection of SAE information.

9.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE eCRF 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.

9.5 Evaluating Adverse Events

9.5.1 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.

9.5.2 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 eCRF page and the SAE form (subject to the classification of the AE). The investigator will also document in the medical notes that he/she has 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 Product Information (marketed products), 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 eCRF, 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.

9.6 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 eCRF 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.

9.7 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 eCRF page.

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

9.8 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.

9.9 Pregnancy

9.9.1 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.

9.9.2 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.

9.10 Medical Device Incidents

The medical device in this study is the toothbrush (Class 1 Medical Device) supplied to all subjects for use at site and throughout the treatment period. Medical devices are being provided by Haleon for use in this study.

9.10.1 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.

9.11 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 eCRF 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 eCRF 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).

9.12 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.

9.13 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.

10 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 which contain the source of data recorded in the CRF should be specified. The CRF and/or 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.

10.1 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 Third Party BDM 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.

10.2 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.

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

10.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the eCRF 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 Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

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.

10.2.2 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. Reconciliation will be performed between the samples collected and the external data to ensure subject and time point referenced in the CRF and/or protocol.

11 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

11.1 Sample Size Determination

Sufficient subjects will be screened to ensure approximately a total of 55 subjects are randomized to study product and 50 evaluable subjects complete the entire study (approximately 25 subjects per product arm). No formal sample size has been performed as per nature of this study (methodology development), however based on a previous *in situ* clinical study evaluating the mode of action of a stannous fluoride toothpaste using 16S sequencing and meta-transcriptomics in 13 subjects, this was considered a small sample size and one of the reasons for lower precision in making inference regarding amplicon and gene expression data (Gumber et al. 2022). Recruiting more participants would potentially reduce this risk and therefore N=50 is considered sufficient to provide reliable estimates of performance for the purposes of this study and to aid in the design of future clinical studies.

11.2 Populations for Analysis

11.2.1 Definitions of Analysis Populations

The Safety population will include all randomized subjects who complete at least one use of study product. This population will be based on the study product the subject received. All safety assessments will be based on this analysis population.

An evaluable microbiome result will be 1) sufficient DNA/RNA extracted from the samples, and 2) after sequencing, at least 5000 16S rRNA amplicon reads per sample for 16S analysis, and 30 million shotgun reads per sample for the metagenomic/meta-transcriptomics analyses (Section 9.2.3).

The Microbiome population will include all randomized subjects who complete at least one use of study product and with an evaluable microbiome result (at least one area at both baseline and Week 6). This population will be based on the study product to which the subject was randomized.

The Per Protocol (PP) population is defined as all subjects in the microbiome population who are considered unaffected by protocol deviations.

Other 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.

11.3 Statistical Analyses

Additional details of the proposed statistical analyses will be documented in the statistical analysis plan (SAP) and the microbiome analysis plan, which will be written following

finalization of the protocol and prior to study unblinding/analysis (as appropriate). This section is a summary of the planned bioinformatics data analyses for microbial and functional profiling.

In both microbiome and functional profiling analyses the baseline samples will be evaluated to confirm homogeneity of the population.

11.3.1 Microbiome Profiling (16S rRNA gene amplicon analysis)

Each endpoint comparisons shown as primary and exploratory endpoints (overall and by different areas of the mouth) for microbiome profiling in Section 3 will include the following 4 types of analyses:

1. Taxonomy assignment
    a. Sequence quality filtering, pair merging and denoising
    b. Assign reads to species level taxonomy based on sequence alignment against HOMD Refseq database
    c. Interactive bar chart displaying taxonomy profiles for each sample
2. Alpha diversity comparison (diversity within samples)
    a. Rarefaction plots for individual samples or sample groups
        i. Observed species
        ii. Shannon index
        iii. Simpson index
    b. Boxplot representation of alpha-diversity for each endpoint comparison
        i. Observed species
        ii. Shannon index
        iii. Simpson index
    c. Group significance of Alpha-diversity indices

        Non-parametric Kruskal Wallis H test will be performed to determine whether any of the 3 alpha-diversity indices measured has significant difference between the groups or time points (within treatment) being compared.
3. Beta diversity comparison (diversity between samples)
    a. Beta diversity will be measured for each endpoint groups with two difference indices:
        i. Bray-Curtis dissimilarity
        ii. Aitchison distance (Euclidean distance calculated by center-log ratio transformed count data)
    b. Both Bray-Curtis and Aitchison indices will be displayed with two types of ordination plots:
        i. NMDS: Non-metric multi-dimensional scaling
        ii. PCoA: Principal Coordinate Analysis
    c. Group significance of beta-diversity indices

PERMANOVA (permutational multivariate analysis of variance) will be performed to determine whether the beta diversity between the groups or time points (within treatment) is significantly different.

4. Differential abundance analysis
    a. ANCOM-BC2 (Analysis of Compositions of Microbiomes with Bias Correction, version 2) will be used to identify species that are differentially abundant between compared groups. Species that are differentially abundant between groups will have p-values <0.05 after adjusted false discovery rate (FDR)
    b. Different abundant species will also be identified by a rank-based approach: LEfSe (Linear Discriminant Analysis Effect Size), which uses rank-based Kruskal-Wallis (KW) sum-rank test to detect features with significant differential (relative) abundance with respect to the class of interest.

11.3.2 Functional Profiling

The metagenomic/meta-transcriptomics analyses as shown in exploratory endpoints (overall and by different areas of the mouth) in Section 3 will be performed with the CCI Hub pipeline, that includes:

1. Characterization of functional potential of the microbiome community using CCI Pathways, Enzyme Commission (EC), Pfam, CAZy and Go Terms.
2. Strain-level taxonomic classification with phylogenetic inference of novel organisms meaning that if a novel strain is identified, the pipeline will call its nearest neighbor and inform users how to interpret the strain-level statistics.
3. Multi-kingdom ID & characterization with one single pipeline: Bacteria, Viruses, Phages, Fungi, Protists, Bacterial MAG's, AMR genes & Virulence Factors.
4. Precision Filters for confidence – advanced machine learning filters for differentiating signal from noise, meaning that the results are less impacted by false positives.
5. Sample-type agnostic analysis.

11.3.3 Safety Analyses

AEs will be regarded as 'treatment emergent' if they occur on or after the first study product use at Visit 2; each AE will be categorized as oral or non-oral by the investigator, or medically qualified designee. AEs will be reviewed by the sponsor's CRS prior to database lock and unblinding and coded using the MedDRA.

A listing of all AEs will be presented for all subjects in the Safety population, with the following AEs summaries (number of distinct AEs and frequency/proportion of subjects affected) presented by treatment group and overall:

- Treatment emergent AEs (overall oral/non oral, serious, treatment related)
- Treatment emergent AEs by System Organ Class (SOC) and Preferred Term (PT)

11.3.4 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized by treatment group for the Safety and microbiome populations, and for the PP population if a PP analysis is performed.

Categorical variables (such as sex, race and ethnicity) will be summarized by the number and percentage of subjects with each relevant characteristic in each treatment group. Continuous variables such as (age) will be summarized by mean, SD, median, minimum and maximum values in each treatment group.

11.3.5 Study Product Compliance and Use of Other Therapies.

11.3.5.1 Study Product Compliance

Compliance with product use (number of brushings) will be listed for the microbiome population at each visit, and cumulatively for the overall treatment period (for most subjects this will be 6 weeks) by treatment group.

Number of expected brushings at Visit 3 = 2 × Number of days between Visit 3 and V2

Number of actual brushings at Visit 3 = (Number of expected brushings) – (Number of missed brushings) + (Number of additional brushings) between Visit 3 and V2

% Compliance at 'Visit 3' = $\frac{\text{(Number of actual brushings between Visit 3 \& V2)}}{\text{(Number of expected brushings between V 3 \& V 2)}}$ x100

11.3.5.2 Prior and Concomitant Medications

Prior medications, concomitant medications and significant non-drug therapies taken during the study will be listed for the Safety population.

11.3.6 Handling of Dropouts and Missing Data

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

11.3.7 Interim Analysis

No interim analysis is planned for this study.

12 STUDY GOVERNANCE CONSIDERATIONS

12.1 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 eCRF 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.

12.2 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.

12.3 Regulatory and Ethical Considerations

12.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent, 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.

12.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations

of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

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

12.3.3 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.

12.3.4 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.

12.3.5 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.

12.4 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.

12.5 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.

12.6 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 notify Haleon of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

12.7 Microbial and Functional Profiling Data Retention

Raw 16S rRNA sequence reads and data will be stored and made accessible to Haleon through the CCI [redacted] storage service. CCI [redacted] has multiple back-up storage and redundancy strategies and data will be kept up to 6 months after the completion of the study. Data analyses are also provided in a bioinformatic report that is downloadable.

For the data uploaded to and stored in CCI [redacted] the data is stored on the hub securely for 6 months after completion of study without cost. Raw sequences data will also be stored on the CCI [redacted] server securely up to 6 months after the completion of study.

Raw sequence reads and functional profiling results of the meta-transcriptomic analyses, if applicable, will be stored and made accessible to Haleon through the CCI [redacted] up to 6 months after the completion of the study.

12.8 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.

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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14 APPENDICIES

14.1 ABBREVIATIONS

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

Table 14-1 Abbreviations

AE	adverse event
BDR	blinded data review
BI	Bleeding index
BS	Bleeding sites
CPITN	Community Periodontal Index of Treatment Needs
CRF	case report form
EC	ethics committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
CCI	CCI
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
IB	investigator's brochure
ICH	International Conference on Harmonisation
ICF	Informed consent form
IEC	Independent Ethics Committee
IRB	institutional review board
IRT	Interactive Response Technology
MedDRA	medical Dictionary for Regulatory Activities
MFC	Master Formulation Code
MGI	Modified gingival index
OST	Oral soft tissue
OHT	Oral health tissue
PERMANOVA	Permutational multivariate analysis of variance
PI	principal investigator
PP	Per protocol
PI	Personal information
Ppm	Part per million
PT	Preferred Term
QC	quality control
rRNA	Ribosomal ribonucleic acid

SAE	Serious adverse events
SAP	Statistical and analysis plan
SD	Standard deviation
SMFP	sodium monofluorophosphate
SnF_2	Stannous fluoride
SOC	System Organ Class
SOP	standard operating procedure
TPI	Turesky Modified Quigley & Hein Plaque Index
UK	United Kingdom
US	United States
VSC	Volatile sulphur compounds
$ZnCl_2$	Zinc chloride

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