CLINICAL PROTOCOL

A 4-Week Randomised, Controlled, Examiner-blind, Clinical Study Investigating the efficacy of an Experimental Toothpaste containing Stannous Fluoride in improving gingival health

Protocol Number:	300178
Compound/Product Name:	0.454% Stannous Fluoride 0.3% Zinc Chloride 1% Alumina
Phase:	Not applicable (N/A)

This document contains confidentiality statements that are not relevant for this publicly available version

Sponsor Information

Sponsor Name & Legal Registered Address	**Haleon (UK)** Building 5, First Floor, The Heights, Weybridge, Surrey, KT13 0NY.
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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	To align baseline visit as Day 1 throughout (it was referred to as Day 0 in places). To add comparison of pre-brushing at Day 1 and post-brushing at Week 4 to the exploratory analysis in section 8.3.1 Addition of prophy and snack consumption to sections 5.3 & 5.4 to align with rest of protocol.
Amendment 2	3.0	CCI [redacted] Change to protocol requirements on repeatability assessments (Sections 3, 6.2.7, 8.3.4 and Table 5.1 (Schedule)) from at least one subject per clinical assessment day to at least 3 subjects over the entire duration of each of visits 2&3. Correction to typo in document history where V2.0 was described as a new version rather than as Amendment 1.

New versions incorporate all revisions to date prior to submission to institutional review boards/ethics committees (IRBs/ECs), etc.

Amendments incorporate all revisions to date, including amendments made at the request of 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 Background & Study Rationale

Gingivitis is a reversible inflammation of the periodontal tissues surrounding the tooth in response to the presence of dental plaque (Kinane 2001). It is reported to have a high prevalence worldwide in large population surveys (Albandar 2002) and by the World Health Organization (Petersen and Ogawa 2012) but is also largely preventable. Left untreated, it is the main cause of tooth loss and considered one of the main threats to oral health (Murphy 2010). Gingivitis is in fact a pre-requisite for periodontitis (an irreversible severe inflammatory gum condition and major cause of tooth loss); while not all individuals with gingivitis go on to develop periodontitis, management of gingivitis is the primary measure employed in the prevention of this periodontal disease (Kinane, Attstr et al. 2005, Chapple, Van der Weijden et al. 2015). The prevalence of periodontitis has remained largely unchanged over the last 25 years and the evidence-base shows periodontitis has associations with certain non-communicable diseases.

It is also important to highlight that the worldwide economic impact of unmanaged oral health is large. The intangible cost (pain, difficulties with speech, low self-confidence, problems with expressing emotions such as smiling, etc.) of poor oral health on people's self-confidence and quality of life should also be considered (Peres, Thomson et al. 2020).

Recent reports highlighted that prevention, diagnosis and management of periodontitis is cost-effective and, preventing the progression of gingivitis to periodontitis, could save even many more costs associated with other health conditions that share risk factors with periodontitis (Murphy 2010).

Plaque-induced gingivitis is a reversible condition caused by the host's inflammatory immune response to the accumulation of dental plaque at the gingival margin and within the gingival sulcus (Chapple, Mealey et al. 2018). Thus, gingivitis can be managed and prevented by removal of plaque with regular effective oral hygiene (Brook 2003, Ower 2003). While mechanical plaque removal (i.e., toothbrushing) is fundamental to the successful control of dental plaque, additional benefits can be achieved by adjunctive use of chemical anti-plaque agents included in daily use dentifrices or mouth rinses (Chapple, Van der Weijden et al. 2015).

Anti-microbial agents have been incorporated into toothpastes for many years with a view to enhancing plaque control and associated periodontal benefits (Cummins and Creeth 1992). Their addition to toothpaste formulations complements mechanical plaque removal by helping to reduce/inhibit the growth of bacterial plaque in areas of the mouth less accessible to toothbrushing, and by helping to prevent/slow subsequent re-colonization of 'cleaned' surfaces by the plaque bacteria (Cummins and Creeth 1992, Teles and Teles 2009).

Stannous Fluoride (SnF_2) is a well-known chemotherapeutic agent which has been incorporated into dentifrices since the 1940s for its oral health benefits (Van Loveren 1990, Miller, Truong

et al. 1994, Van Loveren 2001, Makin 2013). The stannous ion (Sn[II]) is a broad-spectrum antimicrobial agent which has been shown to reduce bacterial biomass/ virulence and inhibit bacterial metabolism (Tinanoff 1990, Tinanoff 1995, Archila, Bartizek et al. 2004, Bellamy, Boulding et al. 2012, He, Barker et al. 2012). Sn [II] ions rapidly oxidize to "inactive" stannic ions (Sn [IV]) and hydrolyse to form insoluble tin compounds (for example, stannous hydroxide) in the presence of water derived ions (Makin 2013). To maximize the delivery of bioavailable Sn[II] ions to the oral cavity, SnF_2 dentifrices are often "stabilized" by the addition of complexing agents or developed as low water content/anhydrous formulations.
Numerous clinical studies reported in the scientific literature demonstrate the anti-gingivitis/ anti-plaque efficacy of 0.4-0.454% SnF_2 dentifrices, for example, (Mankodi, Petrone et al. 1997, Mankodi, Bartizek et al. 2005, Mallatt, Mankodi et al. 2007, Parkinson, Targett et al. 2014, Parkinson, Amini et al. 2018, Parkinson, Amini et al. 2018, Parkinson, Milleman et al. 2020, Acherkouk, Patel et al. 2021) in a population with mild to moderate plaque-induced gingivitis at timepoints ranging from 2 to 24 weeks.

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CCI. It provides cleaning and polishing action on the tooths surface with low abrasivity (Milleman, Milleman et al. 2016).

Zinc is known for its ability to reduce oral malodour, inhibiting the production of volatile sulfur compounds (VSCs). Zinc ion has also bacteriostatic properties, but it is not expected to impact the efficacy of stannous ions. Haleon have conducted 5 studies investigating the ability of zinc salts to reduce VSCs produced by oral bacteria. CCI

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CCI. Data from recent Haleon study 300025, have been generated in a population with clinical diagnosed gingivitis. Therefore, this formulation could offer reduction in breath odour (not investigated as part of this clinical study).

The aim of the current 4-week clinical study is to evaluate the ability of an experimental toothpaste, containing 0.454% SnF_2, 0.3% $ZnCl_2$ and 1% Alumina, to improve gingival health and plaque accumulation compared to a regular fluoride toothpaste (negative control) in subjects with plaque-induced mild to moderate gingivitis; CCI

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Although a diversity recruitment plan is not required for this study, the recruitment strategy will include a diverse population, with balanced distribution of subjects based on the prevalence of gingivitis considering sex, age, race and ethnicity.
Research has found that periodontal disease is more prevalent in males (56.4%) than females (38.4%); five out of ten adult males are affected by gum diseases, while 4 out of 10 females are affected. The difference has been found to be associated with females following better oral care regimens. Gingivitis prevalence is also positively associated with increasing age and typically, it affects more Asians, White East European and Black African than White British (based on UK ethnicity) (Peres, Thomson et al. 2020, Rathee and Jain 2023).

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate gingival health, as measured by the Bleeding Index (BI), of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control following 4 weeks twice daily use	Mean BI at Week 4.
Secondary	
To evaluate gingival health, as measured by the Number of Bleeding Sites (NBS) of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control following 4 weeks twice daily use	Mean NBS at Week 4
To evaluate gingival health, as measured by Modified Gingival Index (MGI) of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control following 4 weeks twice daily use	Mean MGI at Week 4.
To evaluate supragingival plaque levels, as measured by the Turesky Plaque Index (TPI), of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control for following 4 weeks twice daily use	• Mean overall TPI at Week 4. • Mean interproximal TPI at Week 4.

Exploratory	
[redacted]	
Safety	
To evaluate the safety and oral tolerability of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina following 4 weeks twice daily use	Treatment emergent adverse events (TEAEs) over 4 weeks

This study will be considered successful if there is a statistically significant difference in mean Bleeding Index (BI) after 4 weeks of twice daily brushing with the experimental toothpaste containing 0.454% SnF_2, 0.3% $ZnCl_2$ and 1% Alumina compared to the control toothpaste.

3 STUDY DESIGN

This will be a single-center, 4 weeks, randomized, controlled, examiner-blind, 2 treatment arms, stratified, parallel group design clinical study, investigating gingival health and supra-gingival plaque reduction on healthy subjects after using an experimental toothpaste containing 0.454% SnF_2, 0.3% $ZnCl_2$ and 1% Alumina; the antimicrobial effect of the toothpaste will be also evaluated as exploratory objective.

Study subjects will be healthy adult volunteers, aged 18-70 years (inclusive), with mild to moderate plaque-induced gingivitis and with ≥ 20 natural teeth that meet all study criteria at both the Screening and Baseline visits (including ≥ 40 evaluable surfaces for Modified Gingival Index (MGI) Bleeding Index (BI), Basic Periodontal Examination (BPE) and Turesky Plaque Index (TPI) (BI and TPI will be performed at Baseline (V2), as part of the inclusion criteria, and BPE at Screening (V1) as per exclusion criteria).

This design is typical of many studies conducted to evaluate the clinical efficacy of dentifrices for gingival health. A parallel group design has been selected as more appropriate for this investigation. Anticipated differential changes in clinical variables among treatment groups could lead to carryover effects and an altered oral health state should a crossover design be employed. The dosage regimen of twice daily use (morning and evening) will be the same for each treatment group and is based on consumer habit and common practice within oral care clinical trials.

Only study subjects with a pre-specified level of gingivitis will be randomized to study product. The baseline levels of measures of gingivitis and plaque are consistent with previous Haleon gingivitis studies with mean MGI 1.75-2.30 considered representative of generalised mild-moderate gingivitis. Furthermore, a minimum of 20 permanent gradable teeth is CCI CCI representative of a minimum of a "shortened dental arch" (Käyser 1989) equating to anywhere between 20-28 gradable teeth (excluding 3rd molars) per subject.

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Sufficient subjects will be screened to assess approximately 180 subjects so that at least 160 subjects are randomized (approximately 80 per group) to ensure approximately 144 (approximately 72 per group) evaluable subjects complete the entire study (allowing for 10% for drop-outs post-baseline).

The clinical efficacy of the experimental toothpaste will be compared with that of a regular fluoride toothpaste. A standard fluoride dentifrice has been chosen as the negative control dentifrice in this study, as this is likely to reflect a subject's typical oral care product use.

This study will consist of 3 study visits: Screening (Visit 1), Baseline (Visit 2) and Week 4 (Visit 3). Gingival health will be assessed using MGI and BI; plaque will be assessed by TPI, overall and interproximal. CCI [redacted] CCI [redacted]

At Screening visit (Visit 1), subjects will provide their written informed consent to participate in the study. Demographics, medical history, prior/current medications will be recorded, subject's current oral care product used, and inclusion and exclusion criteria will be checked followed by an oral examination consisting of oral soft tissue (OST), oral hard tissue (OHT) examination, MGI and BPE assessments (as per inclusion/exclusion criteria) to identify subjects likely to meet the qualifying levels of gingivitis at baseline.

Subjects that show signs of periodontitis as assessed by BPE, with a score of 4 or above in one or more sextants will be excluded from the study. In addition, subjects with BPE ≥ 3 will undergo a pocket depth assessment, and those with ≥ 5mm pocket depth in a single tooth will be excluded.

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Within approximately 3-5 weeks (21-35 days) of Screening (Visit 1), eligible subjects will return to the site for the Baseline visit (Visit 2), with overnight plaque (subjects will be instructed to abstain from oral hygiene for 12 hours [+3 hours; -2 hours] i.e., overnight immediately before the visit). At the Baseline visit, concomitant medication and inclusion/exclusion criteria will be checked and then subjects will undergo a full OST examination, CCI [redacted], MGI, BI and TPI assessments.
Subjects will be considered eligible with a minimum of 20 natural teeth, at least 40 evaluable surfaces, overall MGI ≥1.75 and ≤ 2.3 and overall TPI ≥ 1.5. Subjects with MGI and TPI score outside the study range will be discontinued from the study at this visit.

After CCI [redacted] all initial clinical assessments, eligible subjects will receive a standardise snack followed by a full mouth dental prophylaxis to remove sub and supra-gingival calculus, stain, plaque and debris from the teeth. Post-prophylaxis, the subject's teeth will be re-disclosed, and a second clinician will check all plaque and calculus has been

removed. Any residual plaque and/or calculus will be removed to bring the subject to zero plaque (TPI = 0) before entering the treatment period.

Subjects will be then stratified based on gender and baseline mean whole mouth MGI score (Low: ≤2.00/High >2.00), to ensure a balance of gingivitis across both treatment groups and will be then randomized to study products. Gender is a known modifier of the initiation and outcome of conditions related to gingival health (Alam, Mishra et al. 2012). Stratifying by MGI will facilitate evaluation of BI and MGI in low and high MGI subgroups.

The MGI and the BI are established clinical measures of gingival inflammation and gingival bleeding, respectively (i.e. gingival health); the TPI is an established clinical measure of supra-gingival plaque accumulation. To avoid inter-examiner variability, a single examiner will be responsible for the conduct of each of the clinical indices (MGI, BI, TPI).

Randomized subjects will then receive their assigned study product, a toothbrush, rinsing cups and instructions on product usage. Subjects will be instructed to brush twice daily (morning and evening) with their allocated study product, in their usual manner, for 1-timed minute for the next 4 weeks. They will complete the first brushing at the study site, under supervision.

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After using the study products for 4 weeks, subjects will return to the study site (Visit 3) with overnight plaque (subjects will be instructed to abstain from overnight toothbrushing for 12 hours [+3 hours; -2 hours] immediately before each assessment visit), at approximately the same time of day as the Baseline visit. Changes in health/concomitant medications will be recorded and compliance check will be performed by visual inspection of study products by study stuff to ensure adequate brushing. Subjects will then have a full OST examination followed by a CCI , MGI, BI and TPI assessments.

Subjects will be offered a standardised snack and then will be asked to brush their teeth on site, under supervision, with the assigned toothpaste. CCI CCI . Subjects will also have a full final OST/OHT examination.

At the end of V3 (Week 4), study closeout procedures (return of study product etc.) will take place and the subject may undergo an additional prophylaxis if it is deemed necessary by the examiner. Adverse events (AEs) will be recorded from informed consent and at the end of each study visit.

To assess examiner reproducibility across the treatment period, repeat MGI and TPI assessments will be performed on selected subjects at Visits 2-3. (Replicate BI examinations cannot be performed due to the inherent invasiveness of this measure). At least 3 subjects will be selected for repeatability examinations for each of the 2 clinical measures over the duration of each of visits 2 and 3. This will give a total of at least 6 subjects with repeatability examinations for each of the MGI and TPI assessments across the entire study. Repeatability examinations should be separated by a minimum of 10 minutes and, where possible, separated by another subject. MGI and TPI repeat assessments should be performed on different subjects.

All assessments will be carried out on the facial and lingual/palatal surfaces of each incisor, canine, pre-molar and molar, excluding third molars. To control inter-examiner variability, the same examiner will be used throughout the study for each clinical index.

Subjects will not be able to eat or drink, except for small sips of water used to alleviate thirst or to aid with medication, following supervised brushing at V2 and V3 CCI [redacted] CCI [redacted].

4 STUDY POPULATION

4.1 Type and Planned Number of Subjects

Subjects will be male or female, non-smokers, aged 18-70 years (inclusive), with a minimum of 20 natural teeth and generalized mild-moderate plaque-induced gingivitis. At Baseline (pre-prophylaxis), qualifying subjects will have a mean overall MGI ≥ 1.75 to ≤ 2.30 and an overall mean TPI ≥ 1.5.

Sufficient subjects will be screened to assess approximately 180 subjects so that at least 160 subjects are randomized (approximately 80 per group) to ensure approximately 144 (approximately 72 per group) evaluable subjects complete the entire study (allowing for 10% for drop-outs post-baseline).
An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process and has successfully met the eligibility criteria to proceed beyond the screening visit, as described in this protocol.

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 to be included into the study:

1. 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. Biological sex at birth was male or female.
3. Aged 18 to 70 years inclusive, at the signing of the informed consent.
4. Willing and able to comply with scheduled visits, treatment plan, saliva sample collection, study restrictions, **Lifestyle Considerations** and other study procedures.
5. In good general and mental health with, in the opinion of the investigator or medically qualified designee, no clinically significant or relevant abnormalities in medical history or upon oral examination, or condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.
6. Subject oral health that meets all the following:

AT SCREENING (Visit 1)

7. Subject with at least 20 natural, permanent teeth, (excluding 3rd molars).
8. Subject with at least 40 evaluable surfaces for MGI, BI, and TPI.

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, grossly carious, 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.

9. A healthy subject with mild to moderate plaque-induced gingivitis in the opinion of the clinical examiner
10. Overall MGI ≤ 1.75 to ≤ 2.30

AT BASELINE (V2):

11. Overall MGI ≥ 1.75 to ≤2.30
12. Overall TPI score ≥ 1.5

4.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will be excluded from the study:

1. An employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or a Haleon employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.
3. 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 who has any other clinical serious or unstable conditions (e.g., cardiovascular diseases, diabetes, liver disorders, and kidney disorders) which could have affected study out comes and/or subject safety.
5. A subject who is pregnant (self-reported) or intending to become pregnant over the duration of the study.
6. A subject who is breastfeeding.
7. A subject with known or suspected intolerance or hypersensitivity to any study materials (or closely related compounds) or any of their stated ingredients.
8. A subject unwilling or unable to comply with the **Lifestyle Considerations** described in this protocol.
9. A subject who is a current smoker or an ex-smoker (including vaper) who stopped within 6 months of Screening.
10. A subject who is using smokeless forms of tobacco (e.g., chewing tobacco, gutkha, pan containing tobacco, nicotine-based e-cigarettes).
11. A subject who is diagnosed xerostomia or is taking any medication that in the view of the investigator is causing xerostomia.
12. A subject who has a medical condition which could have directly influenced gingival bleeding.
13. A subject who has a bleeding disorder that could have affected study outcomes and/or subject safety.
14. A subject who has a recent history (within the last year) of alcohol or other substance abuse.

15. A subject who has a severe oral condition (e.g., acute necrotizing ulcerative gingivitis or oral or peri-oral ulceration including herpetic lesions) that could, in the opinion of the investigator, compromise study outcomes or the oral health of the subject/examiner if they participate in the study.
16. Presence of a tongue or lip piercing, or any other oral feature that could interfere with the usage of a toothbrush.
17. **Medication exclusions:**

    At screening (Visit 1):

    a. A subject using any antibiotic medication within 28 days prior to screening or at any time during the study.
    b. Subject who has used an anti-bacterial toothpaste/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 gingival health, plaque formation or oral bacteria.
    c. A subject currently taking an anti-inflammatory medication which, in the opinion of the Investigator, could affect gingival condition.
    d. A subject currently taking a systemic medication (e.g., anti-inflammatory, anticoagulant, immunosuppressants) or traditional/ herbal remedy which, in the opinion of the Investigator, could affect plaque/ gingival condition (e.g., ibuprofen, aspirin, warfarin, cyclosporin, phenytoin, calcium channel blockers, statins).

18. **Medication exclusions:**

    At Baseline (Visit 2):

    a. A subject who has taken any antibiotics during the washout period (between Screening and Baseline).
    b. A subject who has taken (in the previous 14 days) a systemic medication (e.g., anti-inflammatory, anti-coagulant, immunosuppressants) or traditional/ herbal remedy which, in the opinion of the Investigator, could affect plaque/ gingival condition (e.g., ibuprofen, aspirin, warfarin, cyclosporin, phenytoin, calcium channel blockers).
    c. A subject who has used an antibacterial dentifrice or mouthwash (e.g., chlorhexidine) or any oral care product that in the view of the investigator could interfere with gingival health, plaque formation and oral bacteria, in the period between Screening and the Baseline visit.

19. **Periodontal exclusions:**

    a. A subject who shows signs of periodontitis (at both Screening (V1) and Baseline visits (V2)).
    b. A subject with a BPE score of 4 or above in one or more sextants.

c. A subject with BPE score ≥ 3, if with probing pocket, a single tooth dept is ≥ 5mm.
d. A subject who is receiving or has received treatment for periodontal disease (including surgery) within 12 months of Screening.
e. A subject who has gingivitis, which in the opinion of the investigator, is not expected to respond to treatment with an over the counter (OTC) dentifrice.

20. Dental Exclusions:

a. A subject who has active caries that could, in the opinion of the investigator, compromise study outcomes or the oral health of the subject if they participate in the study.
b. A subject who has dentures (partial or full).
c. A subject who has an orthodontic appliance (bands, appliances, or fixed/ removable retainers).
d. A subject who received orthodontic therapy within 3 months of Screening.
e. A subject who has numerous restorations in a poor state of repair.
f. A subject who has any dental condition (e.g., overcrowding) that could, in the opinion of the investigator, compromise study outcomes or the oral health of the subject if they participate in the study.
g. A subject who has had dental prophylaxis within 12 weeks of Screening.
h. A subject who has had teeth bleaching within 12 weeks of Screening.
i. A subject who has high levels of extrinsic stain or calculus deposits, in the opinion of the investigator, that could have interfered with plaque assessments.

21. A subject who has previously been enrolled in this study.
22. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.

4.4 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 5-1**). The reason for re-appointment will be documented in the electronic case report form (eCRF).

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

- **Baseline (Visit 2):** if the subject cannot be reappointed (within the 3-5 weeks visit tolerance), they will be withdrawn from the study. No clinical efficacy assessments will be performed. The subject may be replaced.

- **Week 4 (Visit 3):** if the subject cannot be reappointed (within the visit tolerance), they will be withdrawn from the study. No clinical efficacy assessments will be performed. The subject will not be replaced.

4.4.1 Dietary, Tobacco and Alcohol restrictions

Before a Clinical Assessment Visit: Baseline (Visit 2) and Week 4 (Visit 3)

- Subjects must not eat or drink for at least 4 hours before a clinical assessment visit and until all clinical assessments are complete during visit day.

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*

Note: *A standardize snack will be offered after clinical assessments have been completed and before brushing on site*

- Subjects will not be permitted to smoke, vape or use tobacco (e.g., chewing tobacco, gutkha, pan containing tobacco, nicotine-based e-cigarettes) products during their scheduled visits to the study site.

- Subjects should refrain from alcohol consumption for 24 hours before the clinical assessment visits.

4.4.2 Oral Care Restrictions

From Screening (Visit 1) to the Subject's Last Study Visit (Visit 3):

- 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 confectionery containing xylitol (e.g., sugar-free mints).

- Subjects should delay any non-emergency dental treatment until after study completion (including dental prophylaxis).

From Baseline (Visit 2) to the Subject's Last Study Visit (Visit 3):

- Subjects should not use any other oral care products (e.g., toothpastes, toothbrushes, mouthrinses) than those provided during the study.

Before Clinical Efficacy Assessment Visits: Baseline (Visit 2) and Week 4 (Visit 3)

- Subjects should refrain from oral hygiene procedures for 12 hours (+3 hours, -2 hours) before their visit and attend the study site with overnight plaque growth.

5 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study visit. Each procedure is listed in **Table 5-1 Schedule of Activities**.

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

All information and data collected at each study visit will be documented in the eCRF, unless stated otherwise.

5.1 Schedule of Activities

Table 5-1 Schedule of Activities

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

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

Procedure/Assessment	Screening			
	Visit 1		Visit 2 Baseline Day 1	Visit 3 Week 4 Day 28 (± 2)
Informed Consent	X	Lead in period [approximately 3-5 weeks (21-35 days)]		
Demographics	X			
Medical History	X			
Current/Prior Medication Review	X			
Review subject's current oral care products	X			
Oral soft tissue (OST) examination	X		X	X
Oral hard tissue (OHT) examination	X			X
Inclusion/exclusion criteria	X		X	
Modified Gingival Index (MGI)	X[1]		X[1]	X
Basic Periodontal Examination (BPE)	X[1]			
BI (Bleeding index)			X	X

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Disclose dental plaque			X	X
Turesky Plaque Index (TPI) assessment			X	X
Subject eligibility	X		X	
Repeat MGI assessment[3]			X	X
Repeat TPI assessment[4]			X	X
Compliance Checks			X	X
Concomitant medications and treatments			X	X
Subject Continuance				X
Dental prophylaxis			X	
2nd clinician check to confirm TPI=0 (additional dental cleaning will be performed as required)			X	
Randomization			X	
Dispense study product, toothbrush, rinsing cups and oral hygiene instructions			X	
Supervised brushing with study product			X	X
CCI			X	X
Subject brings study product, toothbrush for brushing on site				X
Visual inspection of study product to check compliance				X
Adverse Events (AEs) Review[5]	X		X	X
Optional dental prophylaxis at the end of Visit 3				X
Study Conclusion/Subject Exit from Study				X

Footnotes:

1. In relation to the general dentition inclusion/ exclusion criteria
2. Subjects will abstain from overnight toothbrushing for a minimum of 12hrs (+3hr, -2hr) immediately prior to the assessment visits (Visits 2-3)
3. At least 3 subjects at each of visits 2&3 will be selected for repeat MGI assessments.
4. At least 3 subjects at each of visits 2&3 will be selected for repeat TPI assessments.
5. Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF).

The site may contact subjects prior to study visits, either as part of pre-screening activities or as a reminder of the approaching scheduled visit. Further details included in the ICF.

5.2 Visit 1/Screening

Screening procedures will be conducted by the Investigator (or suitably qualified designee), prior to randomization to study product. Where practically feasible, they should be completed in the order listed below.

1) Informed consent
2) Demographics
3) Medical history and prior/concomitant medication/treatment
4) Review of subject's current oral care product
5) OST examination
6) OHT examination
7) Inclusion/exclusion criteria (including MGI and BPE)
8) Subject eligibility
9) Record Adverse Events.

5.2.1 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, potential hazards of the study and their rights to refuse to enter the study or to withdraw from it at any time.

Informed consent must be obtained before any study specific activity is performed. Two copies of the informed consent form (ICF) will be signed and dated by the subject, and the subject will be provided with one copy and the other will be kept at site.

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.

5.2.2 Demographics

The following demographic information will be collected: year of birth, sex at birth, race and ethnicity.

5.2.3 Review of subject's current oral care product

Subjects will be encouraged to bring their current oral care products to the study site to enable staff to check the ingredient listings for compliance with Exclusion Criterion 19. Ingredient listings and on-pack claims will be reviewed to confirm that products do not contain any anti-bacterial ingredients (e.g. Stannous Fluoride, chlorhexidine, cetyl pyridinium chloride, zinc

salts) or make any antibacterial/ anti-gingivitis claims. Subjects using any oral care product that, in the opinion of the investigator, could interfere with plaque formation or measures of gingivitis will be excluded.

5.2.4 Medical History and Prior Medication/Treatment

Relevant medical and/or surgical history (in the last 1 year), including allergies or drug sensitivity and prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days, that began before obtaining informed consent will be recorded as the Medical History/Current Medical Conditions.

5.2.5 Oral examination/Assessments

The following procedures will be completed, and data recorded in the eCRF. The following screening procedures should be carried out by a qualified dental professional:

- OST examination
- OHT examination
- MGI and BPE assessments (as part of the eligibility criteria)

The oral examinations/assessments should be carried out as described in Section 6.

All findings will be recorded in the eCRF.

5.2.6 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria as per Section **4.2** and **4.3.**

5.2.7 Subject Eligibility

The investigator and/or medically qualified designee will review inclusion/exclusion criteria, medical history and prior medications and oral examinations to confirm subject eligibility to participate in the study.

5.2.8 Enrolled Subjects and Screen Failures

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

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized.

To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography, screen failure details (e.g., withdrawal of consent), eligibility criteria, any protocol deviations and any adverse events.

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

5.3 Visit 2/Day 1 (Baseline)

1) Review of concomitant medication or non-drug treatments/procedures, adverse events, and lifestyle restrictions.
2) OST examination
3) CCI [redacted]
4) MGI assessment
5) BI assessment (including number of bleeding sites which is derived from BI assessment)
6) Plaque disclosure
7) TPI assessment
8) Inclusion/exclusion criteria
9) Subject eligibility
10) MGI repeatability assessment (where applicable)
11) TPI repeatability assessment (where applicable)
12) Subject is offered snack to consume
13) Prophylaxis tooth cleaning followed by confirmation of zero plaque by second clinician
14) RandomizationDispense study product, toothbrush, rinsing cups and oral hygiene instructions
15) Supervised brushing at site
16) CCI [redacted]
17) AE recording (if applicable)

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

5.4 Visit 3/Day 28 (week 4)

1) Collection and visual inspection of study products returned by subjects to assess compliance
2) Review of concomitant medication or non-drug treatments/procedures, adverse events, and lifestyle restrictions.
3) Subject continuance confirmation
4) OST examination
5) CCI [redacted]
6) MGI assessment

7) BI assessment (including number of bleeding sites which is derived from BI assessment)
8) Plaque disclosure
9) TPI assessment
10) MGI repeatability assessment (where applicable)
11) TPI repeatability assessment (where applicable)
12) Subject is offered snack to consume
13) Supervised brushing at site
14) CCI [redacted]
15) Optional dental prophylaxis (if deemed necessary by examiner)
16) AE recording (if applicable)
17) Study conclusion

Changes in concomitant medication or non-drug treatments/procedures will be documented in the eCRF.

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

6 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 wellbeing 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.

6.1 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.
A single examiner will be responsible for the conduct of the clinical measures of gingivitis/ plaque accumulation CCI [redacted] for the duration of the study.
Eligible tooth assessments will be accomplished by oral examination and will evaluate dentition exclusions along with a gross gingival assessment in relation to the general dentition inclusion/exclusion criteria.

Assessments will be carried out by the investigator, or qualified designee, against the inclusion/ exclusion criteria. Ineligible subjects will not be re-screened.

Findings from these examinations will be used to determine subject eligibility.

6.2 Efficacy Assessments

The following efficacy 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.

6.2.1 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:

- CCI [redacted]
- CCI [redacted]
- Sample destruction at the clinical site

6.2.2 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.

6.2.3 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 millimetre (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

6.2.4 Basic Periodontal Examination (BPE)

The BPE is a simple, rapid and routinely used screening tool for periodontitis. The mouth is divided into sextants and the highest BPE score per sextant is recorded (on all teeth in that sextant, excluding wisdom teeth).

To perform BPE assessment, a BPE probe is used. This has a 'ball end' 0.5mm in diameter and a black band from 3.5mm to 5.5mm. Light probing force should be used (20-25 grams). The probe should be 'walked around' the teeth in each sextant. All sites should be examined to ensure that the highest score in the sextant is recorded before moving on to the next sextant.

The BPE scores are:

0	Probing depth <3.5mm, no bleeding on probing and no plaque retentive factors
1	Probing depth <3.5mm, bleeding on probing and no plaque retentive factors
2	Probing depth <3.5mm, and presence of plaque retentive factors

3	Probing depth ≥3.5mm but <5.5 mm
4	Probing depth ≥5.5mm
*	Presence of furcation involvement (can be added to any BPE score)

Both the number and the * should be recorded if a furcation is detected - e.g. the score for a sextant could be 3* (e.g. indicating probing depth 3.5-5.5 mm PLUS furcation involvement in the sextant).

6.2.5 Plaque Disclosure Procedure

Dental plaque forms as a colourless 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.

6.2.6 Turesky Modification of the Quigley Hein Index (TPI)

The TPI is a non-invasive assessment of supra-gingival plaque accumulation (Turesky 1970, Lobene 1986). 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 6.2.5, 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

6.2.7 Repeatability Assessments

Repeat MGI and TPI assessments will be performed by the clinical examiners at Visits 2 and 3. At least 3 subjects will be selected for repeat assessments over the duration of each of visit 2 and 3. Thus a total of at least 6 subjects repeat assessments for each endpoint will be collected during this study. 'Repeat' subjects will be selected at random from those in attendance on any given assessment day. Different subjects should be used for repeat MGI and TPI assessments.

There should be a delay of at least 10 minutes between the original and the repeat assessment for a given subject; ideally, repeat assessments should be separated by another subject. No other clinical procedure should be carried out on the selected subject between repeat assessments.

Scores from the first assessment must not be visible to the examiner/scribe when the repeat assessment is carried out.

6.3 Safety and Other Assessments

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

6.3.1 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.

6.3.2 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.

6.3.3 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.

6.4 Banked Bio specimens

Aliquots of saliva samples collected during the study will be stored at the study site Biobank for future additional analysis (i.e microbiome analysis). Unless prohibited by local regulations or ethics committee decision, subjects will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the specified research.

7 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and Haleon policy, study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

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

7.1 Investigational/Study Product Supplies

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

Table 7-1 Investigational/Study Product Supplies

	Test Product	Reference Product (Negative Control)
Product Name	Experimental toothpaste containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride,1% Alumina	Colgate Cavity Protection (UK Marketplace)
Pack Design	Carton of 2 over-wrapped tubes	
Dispensing Details	One carton – baseline visit	
Product Master Formulation Code (MFC)	CCI [redacted]	Commercial Product
Fluoride concentration	1100ppm	1450ppm
Dose/Application	Full ribbon of toothpaste on head of toothbrush provided	
Route of Administration	Oral	
Usage Instructions	Subjects will brush their teeth for one timed minute twice a day (morning and evening) Rinsing is not a study requirement. Subjects who wish to rinse after brushing will be provided with a measuring cup to rinse once with 10mL water.	
Return Requirements	All used/unused samples to be returned	

Table 7-2 Sundry Items

Item	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples

Aquafresh® Clean Control toothbrush (medium)	Haleon	Individual commercial pack	One at baseline for use with test/reference product	Destroy at site using site disposal procedures- following approval from Haleon Clinical Supplies	Return
Opaque Carrier bag	Haleon	Individual bags	One at Baseline visit	Subject to keep or destroyed at site using site disposal procedures following approval from Haleon Clinical Supplies	Return

7.2 Product Supplies, Product Storage, Accountability, Returns and Destruction

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

Guidance will be provided to the Investigator and site staff for the receipt, storage and management of products for the duration of the trial by Haleon Clinical Supplies during the Site Initiation Visit and with further instructions included with the shipping documentation.

The site should ensure that the room or area set aside for storage is able to maintain the correct temperature to meet the product label storage conditions, is sufficient to store all products and is secure and access controlled.

Any temperature excursions or discrepancies during transit or whilst study products are stored at site require the affected products to be quarantined and this must be communicated immediately to the Sponsor who will provide documentation to approve further usage.

Use of any of the affected product(s) prior to sponsor approval will be considered a protocol deviation.

Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorised site staff. Subjects will be informed on product usage, storage, return and what to do in the event of product loss when they are first dispensed after enrolment.

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.

Detailed instructions for the return of study product/study supplies will be provided by Haleon during the study in time for study close out. Investigational products can only be destroyed at site in agreement with and after approval from the Sponsor.

7.3 Blinding and Allocation/Randomization

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.
All subjects will be centrally randomized using an Interactive Response Technology (IRT).
Returned study products should not be re-dispensed to any subject.
The investigator's knowledge of the product allocation should not influence the decision to enroll a subject or affect the order in which subjects are enrolled.
This study is described as examiner-blind (the examiner will be blinded to the product received).
To ensure the examiner remains blinded throughout the study, staff involved in the preparation and dispensing of study products will work in a separate area.
Subjects will be instructed not to remove study products from the opaque bags provided/cartons outside of the dispensing room, while at the study site. Dispensing staff will not be involved in any efficacy/safety assessment procedures during the study.

Qualifying subjects will be stratified by their gender and Baseline Mean MGI resulting in the following stratum:

- Male, baseline Mean MGI ≤2.00 (low)
- Male, baseline Mean MGI >2.00 (high)
- Female, baseline Mean MGI ≤2.00 (low)
- Female, baseline Mean MGI >2.00 (high)

This study is described as examiner-blind (the clinical examiner(s) will be blinded to treatment received). However, study subjects, investigator site staff involved in safety or efficacy assessments, study statistician(s), data management staff, other employees of the Sponsor (including the clinical research scientist (CRS)) and vendors acting on behalf of the sponsor who may influence study outcomes will also be blinded to treatment allocation.

7.4 Breaking the Blind

In case of an emergency, the investigator or designee has the sole responsibility for determining if unblinding of a subject's product assignment is warranted. Subject safety must always be the

first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a subject's product assignment unless this could delay emergency treatment of the subject.

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

8 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

8.1 Sample Size Determination

Sufficient subjects will be screened to assess approximately 180 subjects so that at least 160 subjects are randomized (approximately 80 per group) to ensure approximately 144 (approximately 72 per group) evaluable subjects complete the entire study (allowing for 10% for drop-outs post-baseline).
The study will be sufficiently powered to demonstrate statistically significant differences between Test Product compared to the Reference Product (negative control) for mean BI at Week 4 (primary objective). A sample size of 72 evaluable subjects per treatment group will provide at least 90% power to detect a mean difference of 0.07 units (SD = 0.128) in mean BI score after 4 weeks of treatment, using a 2-tailed 2-sample t-test with a 5% significance level. The sample size calculation was performed using PASS software version 23.0.1.

The assumed treatment efficacy estimates come from a review of sponsor clinical studies (CCI and 212537, sponsor data held on file and available on request) where the mean difference (SD) between the test and reference product reported a mean difference in BI of 0.07 between groups with standard deviation ranging from 0.04 to 0.128 at 12 weeks. The higher SD of 0.128 was used to calculate the sample size for this study.

8.2 Populations for Analysis

8.2.1 Definitions of Analysis Populations

The Safety population will comprise all randomized subjects who receive at least one dose of investigational product. Summaries and analyses of this population will be based on the investigational product the subject received.

The primary population for the assessment of efficacy will be a modified intention-to-treat (mITT) population. The mITT population will comprise all randomized subjects who receive at least one dose of investigational product and complete at least one-post Baseline BI assessment. This population will be based on the investigational product the subject was randomized to. All subjects who receive a randomization number will be considered randomized.

The Per-Protocol (PP) population will comprise all subjects in the mITT population who have at least one non-missing BI assessment considered to be unaffected by protocol deviations.

The repeatability population for MGI is defined as all subjects who have at least one repeat MGI clinical assessment at any visit.

The repeatability population for TPI is defined as all subjects who have at least one repeat TPI clinical assessment at any visit.

8.2.2 Exclusions of Data from Analysis

Exclusion of any data from the analyses will be agreed during a Blinded Data Review (BDR) Meeting prior to database lock. Any reasons for exclusion of a subject from an analysis population or data from an analysis will be listed, if applicable.
A PP analysis will be performed for the primary endpoint if ⩾ 10% subjects in the mITT population are excluded from the PP population. Efficacy data determined to have been potentially impacted by a protocol deviation will be excluded from the PP analysis. The decisions as to whether or not a protocol deviation impacts efficacy data and whether to perform a PP analysis will be made during BDR, prior to database lock.

8.3 Statistical Analyses

This is a summary of the planned statistical analyses; the detail of the proposed statistical analyses will be documented in the Statistical Analysis Plan (SAP), to be written following finalization of the protocol and prior to study unblinding.
The mITT population will be used for all efficacy analyses.
All p-values presented will be two-sided and assessed at the 5% significance level. No adjustments will be made for multiple comparisons in this study.
Summary statistics (mean, median, SE, SD, minimum, maximum) will be presented for the primary and secondary endpoints at each assessment time point for both the observed value and change from baseline.

Raw means (± SE) of primary and secondary endpoints will be plotted by treatment group at each assessment timepoint.

8.3.1 Primary Endpoint Analysis(es)

The primary endpoint of this study Mean BI at Week 4; the primary hypothesis test will be the comparison between the Test product and the Reference product (negative control) in the mITT population as follows:
Mean BI will be calculated by taking the average over all tooth sites assessed for a subject.
Mean BI at Week 4 will be analysed using an ANCOVA Model with treatment group as fixed effects and Baseline Mean BI and Baseline Mean MGI as a covariate. Gender will also be included as stratification factor. The MGI stratificationfactor is not included in the model as the actual value is included as a covariate. The adjusted mean treatment difference will be presented, along with the two-sided p-value and 95% CIs. The observed margin (OM) option in SAS will be used when estimating least square means.
The assumptions of normality and homogeneity of variance in the model will be investigated. In case of violation of these assumptions, a data transformation, or a suitable non-parametric test (adjusted for the randomization stratification) will be performed; the results will be provided to support the ANCOVA results.

8.3.2 Secondary Endpoint Analysis(es)

The secondary endpoints will be analysed using the same ANCOVA model described above for the primary endpoint, but with Baseline Mean BI replaced with the Baseline of the respective endpoint (Baseline Mean overall TPI for Mean overall TPI at Week 4; Baseline Mean interproximal TPI for Mean interproximal TPI at Week 4; Baseline NBS for NBS at Week 4. For Mean MGI at Week 4, no additional term will be added as Baseline Mean MGI is already included in the model as a covariate).

8.3.3 Safety Analysis(es)

Safety analyses will be performed on the Safety population, according to investigational product received. AEs will be regarded as ‘treatment emergent’ if they occur on or after the first use of investigational product at Baseline. In the event of a missing start date, an AE will be assumed to be ‘treatment emergent’ unless the end date is prior to starting treatment. In case of misallocation, compared to the randomization schedule, TEAEs will be associated with the most recent study investigational received.

Each AE will be categorized as oral or non-oral by the investigator or medically qualified designee. All will be reviewed by the CRS and coded using the MedDRA prior to database lock and unblinding.
A listing of all AEs will be presented for all subjects in the Safety population with the following AE summaries (number of distinct AEs and frequency/proportion of subjects affected) presented by treatment group and overall:

• TEAEs

• TEAEs by System Organ Class (SOC) and Preferred Term (PT)

• TEAEs by Oral/Non-Oral and PT

• Treatment emergent treatment related AEs by Oral/Non-Oral and PT

• Treatment emergent treatment related serious AEs by SOC and PT

Separate listings will be presented for:

• Deaths, SAEs and any AEs leading to product or study discontinuation.

• OST findings (with a summary of abnormalities by visit)

8.3.4 Other Analysis(es)

Exploratory Analysis

CCI

- Day 1 post-brushing compared to Day 1 pre-brushing
- Week 4 post-brushing compared to Week 4 pre-brushing
- Week 4 pre-brushing compared to Day 1 pre-brushing
- Week 4 post-brushing compared to Day 1 pre-brushing

Note: post-brushing is 3 hours post-brushing on site

CCI

Between treatment difference will be analysed using a Mixed Model with Repeated Measures (MMRM) with investigational product, visit and [investigational product x visit] as fixed effects and Baseline CCI as a covariate. Gender and Baseline MGI will also be included as stratification covariates. Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied (Kenward and Roger 1997). The difference between the least square mean changes from Baseline for the Test Product compared to Reference Product (negative control) at Week 4 from the MMRM will be presented, along with the two-sided p-value and 95% CIs.
The assumptions of normality and homogeneity of variance in the MMRM will be investigated. Similarly, the assumptions for the paired t-test will be investigated. In case of violation of these assumptions, a suitable non-parametric test will be performed to support the results.

Repeatability of Examiner

The repeatability of the examiner in conducting the MGI and TPI assessments will also be performed for at least 3 subjects (for each index) over the duration of each of visit 2 and 3. The repeat assessments will be compared to the original assessments. The repeat assessments will not to be used in any efficacy analysis.

The first and second assessments of each index will be analyzed with a Fleiss-Cohen weighted kappa coefficient (κ), along with the 95% CI, to assess the intra-examiner reliability. Reliability will be deemed: Excellent if $\kappa > 0.75$, Fair to good if $0.4 \leq \kappa \leq 0.75$ and Poor if $\kappa < 0.4$.

This analysis will be conducted on each respective index repeatability population (MGI population and TPI population).

8.3.5 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized by treatment group for the Safety and mITT populations (and for the PP population, if a PP analysis is performed) using descriptive statistics.
Categorical variables (such as sex, race, ethnicity and Baseline Mean MGI stratification value) 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.

8.3.6 Use of Other Therapies

8.3.6.1 Prior and Concomitant Medications

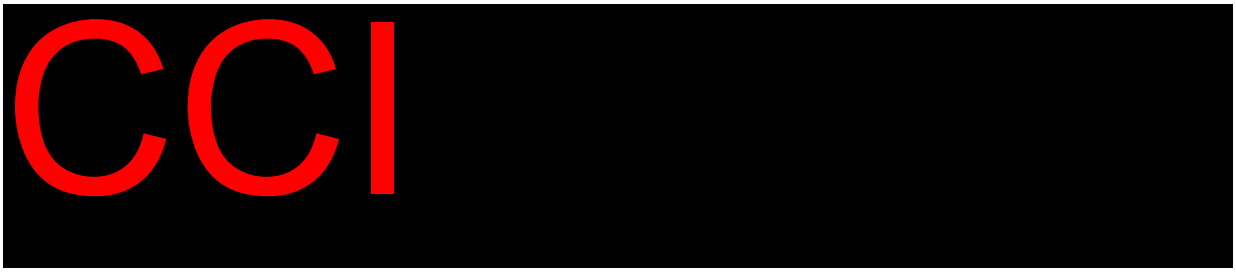
Prior medications/non-drug therapies and concomitant medications/significant non-drug therapies taken during the study will be listed for the Safety population.

8.3.7 Handling of Dropouts and Missing Data

Primary and Secondary Analysis:

Subjects who withdraw from the study early will be included in the statistical analysis up to the point of when they withdraw. There will be no imputation for missing data (i.e. analyses will be conducted on an observed case basis).

Exploratory Analysis:



9 APPENDICES

9.1 Adverse Event (AE) and Serious AE (SAE)

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an adverse event (AE) or serious AE (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.

All AEs will be reported on the AE page of the eCRF by the investigator or site staff from the completion (signature) of the ICF and until 5 days following last administration of the study product (or last procedure).

In addition to that, a SAE form should be completed (if required). 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.

The SAE form, completed as fully as possible, must be scanned and e-mailed to the Case Management Group mailbox **(see Table 9-1),** with a copy to the appropriate Haleon 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.

Table 9-1 Case Management Group mailbox

EMEA: Europe, Middle East, Commonwealth of Independent State (CIS), Africa	PPD

9.2 Definition of an 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).

9.3 Definition of a SAE

A 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**
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
- **Results in persistent or significant disability/incapacity**
- **Results in congenital anomaly/birth defect**
- **Other serious (important) medical events**

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

9.4 Pregnancy

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.

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the Case Management Group mailbox **(see Table 9-1),** with copy to the appropriate Study Manager, within 24 hours. 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 **(see Table 9-1),** 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.

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

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

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the 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

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 SAE or 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.

The investigator will submit any updated SAE data to Haleon within 24 hours.

9.7 DISCONTINUATION OF STUDY PRODUCT AND SUBJECT DISCONTINUATION/WITHDRAWAL

If a subject is discontinued early from the study product (Section **9.7.1**) or discontinued or prematurely withdraws from the study (Section **9.7.2**), the reason(s) for intervention discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the eCRF. If a subject is discontinued early from the study product, the subject should stay in the study and complete the remaining assessments unless they need to be withdrawn (see Section **9.7.2**).

9.7.1 Discontinuation of Study Product

A subject may be discontinued from the study product at any time whilst still in the study at the discretion of the investigator related to safety, subject consent or a potential worsening of the risk / benefit assessment from the subject of remaining on the intervention for the following reasons:

- Adverse Event
- Lack of efficacy from the intervention
- Subject request
- Subject to be withdrawn from the study (see Section **9.7.2**)

9.7.2 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
- Withdrawal of informed consent
- Subject lost to follow-up
- Unblinding of the subject
- Pregnancy

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.

9.7.3 Lost to Follow up

If a subject fails to return to the site for a required study visit, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls or emails or local equivalent methods) 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 and withdrawn from the study if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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).

9.8 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 source documents which contain the source of data recorded in the CRF should be specified. The CRF 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.

9.8.1 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 Biostatistics and Data Management (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.

9.8.2 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 (WHODrug dictionary).

9.8.3 Data Queries

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

9.9 Regulatory and Ethical Considerations

9.9.1 Institutional Review Board/ Ethics Committee

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

9.9.2 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.

9.9.3 Subject Information

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.

9.10 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.

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 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.

9.11 Disclosure and Publication Policy

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

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

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with sponsor policy and as per the country specific requirements for disclosure.

10 ABBREVIATIONS

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

Table 10-1 Abbreviations

Abbreviation	Term
AE	Adverse Event
ACNOVA	Analysis Of Covariance
BPE	Basic Periodontal Examination
BDM	Biostatistics and Data Management
BDR	Blinded Data Review
BI	Bleeding Index
CFU	Colony Forming Unit
CRF	Case Report Form
CRS	Clinical Research Scientist
DMS	Data Management System
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent To Treat
MedDRA	medical Dictionary for Regulatory Activities
MFC	Manufacturing Formulation Code
MGI	Modified Gingival Index

Abbreviation	Term
mITT	Modified Intent-To-Treat
mm	Millimetre
MMRM	Mixed Model with Repeated Measures
N/A	Not Applicable
NBS	Number of Bleeding Sites
OH	Oral Health
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PI	Principal Investigator
PI	Personal Information
PP	Per Protocol
SAE	Serious Adverse Event
SD SE	Standard Deviation
SE	Standard Error
SnF_2	Stannous Fluoride
SS	Safety Statement
TEAE	Treatment Emergent Adverse Event
TPI	Turesky Modification of The Quigley Hein Plaque Index
VSCs	Volatile Sulphur Compounds
w/w	Weight For Weight
$ZnCl_2$	Zinc Chloride

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STATISTICAL ANALYSIS PLAN

A 4-Week Randomised, Controlled, Examiner-blind, Clinical Study Investigating the efficacy of an Experimental Toothpaste containing Stannous Fluoride in improving gingival health

Protocol Number: 300178

Phase: N/A

This document contains confidentiality statements that are not relevant for this publicly available version

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	04-Dec-2024	Not applicable (N/A)

Table of contents

List of Tables

Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
BPE	Basic Periodontal Examination
BDM	Biostatistics and Data Management
BDRM	Blinded Data Review Meeting
BI	Bleeding Index
CFU	Colony Forming Unit
CRF	Case Report Form
CRS	Clinical Research Scientist
DMS	Data Management System
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent To Treat
MedDRA	medical Dictionary for Regulatory Activities
MFC	Manufacturing Formulation Code
MGI	Modified Gingival Index
mITT	Modified Intent-To-Treat
Ml	Milliliter
mm	Millimeter
MMRM	Mixed Model with Repeated Measures
N/A	Not Applicable
NBS	Number of Bleeding Sites
OH	Oral Health
OHT	Oral Hard Tissue
OST	Oral Soft Tissue
PI	Principal Investigator
PI	Personal Information
PP	Per Protocol

Abbreviation	Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SnF_2	Stannous Fluoride
SS	Safety Statement
TEAE	Treatment Emergent Adverse Event
TPI	Turesky Modification of The Quigley Hein Plaque Index
w/w	Weight For Weight
$ZnCl_2$	Zinc Chloride
CI	Confidence Interval
CS	Compound Symmetry
LS	Least Square
WHODD	World Health Organization Drug Dictionary

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 300178 (Version 3.0, dated 14-Nov-2024).

1 Summary of Key Protocol Information

The purpose of this trial is to evaluate the ability of an experimental toothpaste containing 0.454% Stannous Fluoride (SnF_2), 0.3% Zinc Chloride ($ZnCl_2$) and 1% Alumina, to improve gingival health and plaque accumulation compared to a regular fluoride toothpaste (negative control) after 4 weeks twice daily brushing in subjects with plaque-induced mild to moderate gingivitis. Gingival health and plaque reduction will be evaluated using the Bleeding Index (BI), number of bleeding sites (NBS), Modified Gingival Index (MGI) and Turesky modification of the Quigley Hein Plaque Index (TPI).

CCI

The study will follow a randomized, controlled, single blind (examiner blind), two-treatment arm, parallel study. Study subjects will be healthy adult volunteers, aged 18-70 years (inclusive), with mild to moderate plaque-induced gingivitis and with ≥ 20 natural teeth that meet all study criteria at both the Screening and Baseline visits.

Sufficient subjects will be screened to assess approximately 180 subjects so that at least 160 subjects will be randomized (approximately n=80 per group) to ensure approximately 144 (approximately 72 per group) evaluable subjects complete the entire study (allowing for 10% for drop-outs post-baseline).

1.1 Study Design

This will be a single center, 4 weeks, randomized, controlled, examiner-blind, 2 treatment arms, stratified, parallel group design clinical study, investigating gingival health and supragingival plaque reduction on healthy subjects after using an experimental toothpaste containing 0.454% SnF_2, 0.3% $ZnCl_2$ and 1% Alumina. CCI

CCI

Study subjects will be healthy adult volunteers, aged 18-70 years (inclusive), with mild to moderate plaque-induced gingivitis and with ≥ 20 natural teeth that meet all study criteria at both the Screening and Baseline visits (including ≥ 40 evaluable surfaces for MGI, BI, Basic Periodontal Examination (BPE) and TPI. BI and TPI will be performed at Baseline (Visit 2), as part of the inclusion criteria, and BPE at Screening (Visit 1) as per exclusion criteria. All evaluable teeth (in relation to the inclusion/exclusion general dentition criteria) will be assessed.

Sufficient subjects will be screened to assess approximately 180 subjects so that at least 160 subjects are randomized (approximately n=80 per group) to ensure approximately 144

(approximately 72 per group) evaluable subjects complete the entire study (allowing for 10% drop-outs post-baseline).

This study will consist of 3 study visits: Screening (Visit 1), Baseline (Visit 2) and Week 4 (Visit 3). Gingival health will be assessed using MGI and BI. Plaque will be assessed by TPI, overall and interproximal. CCI [redacted] CCI [redacted]

At the Screening visit (Visit 1), subjects will provide their written informed consent to participate in the study. Demographics, medical history, prior/current medications will be recorded, subject's current oral care product used, and inclusion and exclusion criteria will be checked followed by an oral examination consisting of oral soft tissue (OST), oral hard tissue (OHT) examination, MGI and BPE assessments (as per inclusion/exclusion criteria) to identify subjects likely to meet the qualifying levels of gingivitis at baseline.

Subjects that show signs of periodontitis as assessed by BPE, with a score of 4 or above in one or more sextants will be excluded from the study. In addition, subjects with BPE ≥ 3 will undergo a pocket depth assessment, and those with ≥ 5mm pocket depth in a single tooth will be excluded.

Within approximately 3-5 weeks (21-35 days) of Screening (Visit 1), eligible subjects will return to the site for the Baseline visit (Visit 2), with overnight plaque (subjects will be instructed to abstain from oral hygiene for 12 hours [+3 hours; -2 hours] i.e., overnight immediately before the visit). At the Baseline visit, concomitant medication and inclusion/exclusion criteria will be checked and then subjects will undergo a full OST examination, CCI [redacted], MGI, BI and TPI assessments.

Subjects will be considered eligible with a minimum of 20 natural teeth, at least 40 evaluable surfaces, overall MGI ≥1.75 and ≤ 2.3 and overall TPI ≥ 1.5. Subjects with MGI or TPI score outside the study range will be discontinued from the study at this visit.

After saliva sample collection and all initial clinical assessments, eligible subjects will receive a standardised snack followed by a full mouth dental prophylaxis to remove sub and supragingival calculus, stain, plaque and debris from the teeth. Post-prophylaxis, the subject's teeth will be re-disclosed, and a second clinician will check all plaque and calculus has been removed. Any residual plaque and/or calculus will be removed to bring the subject to zero plaque (TPI = 0) before entering the treatment period.

Subjects will be then stratified based on gender and baseline mean whole mouth MGI score (Low: ≤2.00/High >2.00), to ensure a balance of gingivitis across both treatment groups and will be then randomized to study products. Gender is a known modifier of the initiation and outcome of conditions related to gingival health. Stratifying by MGI will facilitate evaluation of BI and MGI in low and high MGI subgroups.

The MGI and the BI are established clinical measures of gingival inflammation and gingival bleeding, respectively (i.e. gingival health); the TPI is an established clinical measure of

supragingival plaque accumulation. To avoid inter-examiner variability, a single examiner will be responsible for the conduct of each of the clinical indices (MGI, BI, TPI).

Randomized subjects will then receive their assigned study product, a toothbrush, rinsing cups and instructions on product usage. Subjects will be instructed to brush twice daily (morning and evening) with their allocated study product, in their usual manner, for 1-timed minute for the next 4 weeks. They will complete the first brushing at the study site, under supervision. CCI

CCI

After using the study products for 4 weeks, subjects will return to the study site (Visit 3) with overnight plaque (subjects will be instructed to abstain from overnight tooth brushing for 12 hours [+3 hours; -2 hours] immediately before the assessment visit), at approximately the same time of day as the Baseline visit. Changes in health/concomitant medications will be recorded and compliance check will be performed by visual inspection of study products by study stuff to ensure adequate brushing. Subjects will then have a full OST examination followed by a saliva sample collection, MGI, BI and TPI assessments.

To assess examiner reproducibility across the treatment period, repeat MGI and TPI assessments will be performed on selected subjects at Visits 2-3. (Replicate BI examinations cannot be performed due to the inherent invasiveness of this measure). At least 3 subjects will be selected for repeatability examinations for each of the 2 clinical measures over the duration of each of visits 2 and 3. This will give a total of at least 6 subjects with repeatability examinations for each of the MGI and TPI assessments across the entire study. Repeatability examinations should be separated by a minimum of 10 minutes and, where possible, separated by another subject. MGI and TPI repeat assessments should be performed on different subjects.

All assessments will be carried out on the facial and lingual/palatal surfaces of each incisor, canine, pre-molar and molar, excluding third molars. To control inter-examiner variability, the same examiner will be used throughout the study for each clinical index.

Subjects will not be able to eat or drink, except for small sips of water used to alleviate thirst or to aid with medication, following supervised brushing at Visit 2 and Visit 3 CCI

CCI

Table 1-1 presents the schedule of activities.

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening Visit 1		Visit 2 Baseline Day 1	Visit 3 Week 4 Day 28 (± 2)
Informed Consent	X	Lead in period [approximately 3-5 weeks (21-35 days)]		
Demographics	X			
Medical History	X			
Current/Prior Medication Review	X			
Review subject's current oral care products	X			
Oral soft tissue (OST) examination	X		X	X
Oral hard tissue (OHT) examination	X			X
Inclusion/exclusion criteria	X		X	
Modified Gingival Index (MGI)	X[1]		X[1]	X
Basic Periodontal Examination (BPE)	X[1]			
BI (Bleeding index)			X	X
CCI			X	X
Disclose dental plaque			X	X
Turesky Plaque Index (TPI) assessment			X	X
Subject eligibility	X		X	
Repeat MGI assessment[3]			X	X
Repeat TPI assessment[4]			X	X
Compliance Checks			X	X
Concomitant medications and treatments			X	X
Subject Continuance				X
Dental prophylaxis			X	
2nd clinician check to confirm TPI=0 (additional dental cleaning will be performed as required)			X	
Randomization			X	
Dispense study product, toothbrush, rinsing cups and oral hygiene instructions			X	
Supervised brushing with study product			X	X
CCI			X	X

Procedure/Assessment	Screening Visit 1		Visit 2 Baseline Day 1	Visit 3 Week 4 Day 28 (± 2)
Subject brings study product, toothbrush for brushing on site				X
Visual inspection of study product to check compliance				X
Adverse Events (AEs) Review[5]	X		X	X
Optional dental prophylaxis at the end of Visit 3				X
Study Conclusion/Subject Exit from Study				X

Footnotes:

1. In relation to the general dentition inclusion/exclusion criteria.
2. Subjects will abstain from overnight tooth brushing for a minimum of 12hrs (+3hr, -2hr) immediately prior to the assessment visits (Visits 2-3).
3. At least 3 subjects at each of visits 2&3 will be selected for repeat MGI assessments.
4. At least 3 subjects at each of visits 2&3 will be selected for repeat TPI assessments.
5. Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF).

The site may contact subjects prior to study visits, either as part of pre-screening activities or as a reminder of the approaching scheduled visit. Further details included in the ICF.

1.2 Study Objectives

Study objectives and endpoints are defined in Table 1-2.

Table 1-2 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To evaluate gingival health, as measured by the Bleeding Index (BI), of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control following 4 weeks twice daily use	Mean BI at Week 4.
Secondary Objectives	**Secondary Endpoints**
To evaluate gingival health, as measured by the Number of Bleeding Sites (NBS) of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control following 4 weeks twice daily use	Mean NBS at Week 4.
To evaluate gingival health, as measured by Modified Gingival Index (MGI) of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control following 4 weeks twice daily use	Mean MGI at Week 4.
To evaluate supragingival plaque levels, as measured by the Turesky Plaque Index (TPI), of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina compared to a negative control for following 4 weeks twice daily use	• Mean overall TPI at Week 4. • Mean interproximal TPI at Week 4.
Exploratory Objectives	**Exploratory Endpoints**
CCI	
Safety	

Objectives	Endpoints
To evaluate the safety and oral tolerability of an experimental dentifrice containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride and 1% Alumina following 4 weeks twice daily use	Treatment emergent adverse events (TEAEs) over 4 weeks.

This study will be considered successful if there is a statistically significant difference in mean BI after 4 weeks of twice daily brushing with the experimental toothpaste containing 0.454% SnF_2, 0.3% $ZnCl_2$ and 1% Alumina compared to the control toothpaste.

1.3 Treatments

Table 1-3 presents the study products.

Table 1-3 Investigational/Study Product Supplies

	Test Product	**Reference Product (Negative Control)**
Product Name	Experimental toothpaste containing 0.454% Stannous Fluoride, 0.3% Zinc Chloride,1% Alumina	Colgate Cavity Protection (UK Marketplace)
Pack Design	Carton of 2 over-wrapped tubes	
Dispensing Details	One carton – baseline visit	
Product Master Formulation Code (MFC)	CCI [redacted]	Commercial Product
Fluoride concentration	1100ppm	1450ppm
Dose/Application	Full ribbon of toothpaste on head of toothbrush provided	
Route of Administration	Oral	
Usage Instructions	Subjects will brush their teeth for one timed minute twice a day (morning and evening) Rinsing is not a study requirement. Subjects who wish to rinse after brushing will be provided with a measuring cup to rinse once with 10mL water.	
Return Requirements	All used/unused samples to be returned	

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.

1.4 Sample Size Calculation

Sufficient subjects will be screened to assess approximately 180 subjects so that at least 160 subjects are randomized (approximately 80 per group) to ensure approximately 144 (approximately 72 per group) evaluable subjects complete the entire study (allowing for 10% drop-outs post-baseline).

The study will be sufficiently powered to demonstrate statistically significant differences between Test Product compared to the Reference Product (negative control) for mean BI at Week 4 (primary objective). A sample size of 72 evaluable subjects per treatment group will provide at least 90% power to detect a mean difference of 0.07 units (SD = 0.128) in mean BI score after 4 weeks of treatment, using a 2-tailed 2-sample t-test with a 5% significance level. The sample size calculation was performed using PASS software version 23.0.1.

The assumed treatment efficacy estimates come from a review of sponsor clinical studies CCI and 212537, sponsor data held on file and available on request) where the mean difference (SD) between the test and reference product reported a mean difference in BI of 0.07 between groups with standard deviation ranging from 0.04 to 0.128 at 12 weeks. The higher SD of 0.128 was used to calculate the sample size for this study.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned.

2.2 Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities including any external data reconciliation have been completed and database has been locked.
3. All criteria for unblinding the randomization codes have been met and the randomization codes have been distributed.

3 Considerations for Data Analyses and Data Handling Conventions

3.1 Baseline Definition

For all endpoints, the baseline value will be the Day 1 (Visit 2) pre-brushing assessment with a non-missing value.

Unless otherwise stated, if baseline data is missing no derivation will be performed and the baseline value will be set to missing.

3.2 Subgroups/Stratifications

Subjects who satisfy the study selection criteria will be stratified by their gender and Baseline Mean MGI resulting in the following strata:

- Male, baseline Mean MGI ≤2.00 (low)
- Male, baseline Mean MGI >2.00 (high)
- Female, baseline Mean MGI ≤2.00 (low)
- Female, baseline Mean MGI >2.00 (high)

3.3 Centers Pools

Since this is a single center study, pooling of centers is not applicable.

3.4 Timepoints and Visit Windows

The timepoints and visits for this study are defined in Table 1-1 "Schedule of Activities". Any deviation from the study schedule may be reviewed on a case-by-case basis at the Blind Data Review Meeting (BDRM) to determine whether the data should be excluded from the Per Protocol (PP) population.

4 Data Analysis

Data analysis will be performed by CCI [redacted] with oversight from Haleon. The statistical analysis software used will be SAS version 9.4 or higher.

Prior to database closure a BDRM will be conducted in which various aspects of the trial will be discussed and agreed.

Except as described below, all listings will be produced for all randomized subjects.

4.1 Populations for Analysis

4.1.1 Subject Disposition

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. An enrolled subject is a subject who has signed informed consent and is eligible to proceed beyond the screening visit.

The number of subjects screened, enrolled, and randomized will be presented in Table 14.1.1.

The number and percentage of screen failure subjects (subjects not randomized) with reasons why subjects are not randomized will be displayed. Percentages for screen failure subjects will be based on the total number of subjects screened.

The number and percentage of randomized subjects who complete and discontinue the study, broken down by reason for discontinuation, will be presented by study product and overall, in Table 14.1.1. The percentages will be based on the number of subjects randomized.

Table 14.1.1 will also present the number and percentage of randomized subjects in each of the defined analysis populations (as defined in Section 4.1.3) by study product and overall. Percentages will be based on the number of subjects randomized.

Subject disposition including demographic data (age, sex, race and ethnicity), screening date, study product start date/time, subject status (completer, Yes/No), study completion or withdrawal date, duration (in days) in the study (defined as [(date of completion or withdrawal – study product start date) + 1], and the primary reason for withdrawal and further details for withdrawal will be listed (Listing 16.2.1.1) by study product.

Subject disposition information will be listed for non-randomized subjects (Listing 16.2.1.2), including demographic information (age, sex, race and ethnicity), enrolled (Yes/No), screening date, reason for screen failure and any further details of reason for screen failure.

4.1.2 Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to unblinding and closure of the database to ensure all important deviations are captured and categorized. Subjects with important protocol deviations liable to influence the efficacy outcomes will be excluded from the PP population. Subjects may also be identified as having important protocol deviations not leading to exclusion from the PP population.

Important deviations of the protocol procedures may include, but will not necessarily be limited to the following:

- Consent procedures
- Inclusion or exclusion criteria
- Concomitant medication/therapy
- Laboratory Assessments
- Study procedures
- Randomization procedures
- Study drug dosing/study product administration/study product compliance
- Visit schedule/interval
- Other

The specific details of the important protocol deviations will be listed in the Protocol Deviation Management Plan, and the assessment process will be specified in the Blind Data Review Plan. Subjects with important protocol deviations will be identified at the BDRM.

The number and percentage of subjects with at least one important protocol deviation, subjects with important protocol deviations not leading to exclusion from PP population with reasons for deviations and subjects with important protocol deviations leading to exclusion from the PP population with reasons for deviations will be presented by study product and overall, for all randomized subjects (Table 14.1.2) and listed in Listing 16.2.2.1.

All protocol deviations collected on the protocol deviation case report form (CRF) will be listed in Listing 16.2.2.2. The listing will present date of deviation, type of deviation and deviation description.

4.1.3 Analysis Populations

Five analysis populations are defined.

Population	Definition / Criteria	Analyses Evaluated
Safety	Comprise of all randomized subjects who receive at least one dose of investigational product. Summaries and analyses of this population will be based on the investigational product the subject received.	• Demographics • Safety
Modified Intent-To-Treat (mITT)	Comprise of all randomized subjects who receive at least one dose of investigational product and complete at least one-post Baseline BI assessment. This population will be based on the investigational product the subject was randomized to. All subjects who receive a randomization number will be considered randomized.	• Demographics • Compliance • Efficacy
Per-Protocol (PP)	Comprise of all subjects in the mITT population who have at least one non-missing BI assessment considered to be unaffected by protocol deviations. Protocol deviations that may exclude subjects from the PP population are defined in Section 4.1.2 (Protocol Deviations).	• Efficacy
MGI Repeatability	Comprise of all subjects who have at least one repeat MGI clinical assessment at any visit.	• Repeatability for MGI
TPI Repeatability	Comprise of all subjects who have at least one repeat TPI clinical assessment at any visit.	• Repeatability for TPI

NOTE:

Please refer to Appendix 1: List of Data Displays, which details the population to be used for each display being generated.

The number of subjects included in each of the analysis populations will be presented (Table 14.1.1). Subjects excluded from any of the analysis populations will be listed in Listing 16.2.3.1, with the reason for exclusion.

The primary population for assessment of efficacy will be the mITT population. A PP analysis will be performed on the primary endpoint only if more than 10% of mITT subjects are excluded from the PP population. A decision on whether a PP analysis will be performed will be made prior to study unblinding (release of the randomization codes).

Any repeat clinical data collected for the repeatability assessment will only be used to assess repeatability. The main assessment of efficacy will be based on the initial assessment.

4.2 Subject Demographics and Other Baseline Characteristics

4.2.1 Demographic Characteristics

Descriptive statistics [number of subjects (n), mean, standard deviation (SD), median, minimum and maximum for continuous variables, and frequency count (n) and percentage (%) of subjects for categorical variables] will be presented for demographic characteristics by study product and overall. These variables include age (years), sex, race, ethnicity and baseline MGI subgroup, and will be presented for the Safety population (Table 14.1.3.1) and the mITT population (Table 14.1.3.2) and if applicable, for the PP population (Table 14.1.3.3).

Demographic information will be listed for all randomized subjects in Listing 16.2.4.1.

4.2.2 General Medical History

Medical and surgical history (in the last year) including allergies or drug sensitivity will be listed in Listing 16.2.4.2, with start date and end date or ongoing at the start of study product.

4.3 Treatments (Study Product, Rescue Medication, other Concomitant Therapies, Compliance)

Randomization details will be listed, including the randomization number, stratification group, the planned study product, the actual study product the subject was randomized to and the randomization date (Listing 16.1.7.1).

The study product kit allocations will be listed (Listing 16.1.7.2), including kit number and study product information.

4.3.1 Study Product Compliance and Exposure

Compliance data will be summarized for the mITT population.

A table (Table 14.2.1) with frequency count (n) and percentage (%) of subjects with each compliance response (Yes/No) will be presented by study product and Time period ‘Baseline to Week 4’.

Study product compliance (compliance response [Yes/No]) will be listed in Listing 16.2.5.1 for all randomized subjects by study product.

Supervised study product application (subject number, visit, and time of the supervised procedure) will be listed (Listing 16.2.5.2) for all randomized subjects.

4.3.2 Prior and Concomitant Medication

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days and prior to signing the informed consent form, will be documented in the CRF. The prior and concomitant medications will be coded using a validated medication dictionary, World Health Organization Drug Dictionary (WHODD).

Prior medications and prior non-drug therapies will be listed by subject, with drug name, WHODD drug synonym, reason for medication, route, dose, frequency, start date, start day relative to the study product start date, and end date and end day relative to the study product start date (Listing 16.2.4.3) for all randomized subjects. Prior medications are defined as those which stopped before the study product start date.

Concomitant medications and concomitant non-drug therapies taken during treatment will be listed similarly (Listing 16.2.4.4) for all randomized subjects with either ongoing or end date displayed. Concomitant medications are defined as medications that started or stopped on or after the study product start date or are ongoing.

Unknown dates will not be imputed. However, if the start or stop date is unknown, then it will be assumed to be concomitant medication unless the partial start date or stop date indicates differently.

4.4 Analysis of Efficacy

The primary population for assessment of efficacy will be the mITT population. No repeat assessment data is to be used in any efficacy analyses.

Descriptive summary statistics will be presented for the observed values and change from baseline at each time point for primary and secondary endpoints.

All p-values presented will be two-sided and assessed at the 5% significance level. No adjustments will be made for multiple comparisons in this study.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary endpoint for the study is the Mean BI at Week 4. The BI score for each subject at each visit will be calculated as the average index value over all evaluable tooth sites scored as follows:

- BI Score = Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites.

The BI score has a range of 0 to 2.

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).

The BI scoring system is described in Table 4-1.

Table 4-1 Bleeding Index Scoring System

Score	Description
0	Absence of bleeding on probing
1	Bleeding observed within 30 seconds of probing
2	Bleeding observed immediately on probing
9	Missing tooth or not qualified tooth

Descriptive statistics (n, mean, SD, standard error [SE], median, minimum, and maximum) will be presented for the BI score at each time point (observed value and change from baseline) in Table 14.2.2.1.1 for all subjects in the mITT population by study product.

Raw means (± SE) of the BI score at each time point will be presented graphically by study product in Figure 14.2.2.1.3 for all subjects in the mITT population.

Individual data for the BI assessment at each individual tooth site will be listed for each subject by study product group and visit in Listing 16.2.6.1.1, and individual data for the derived BI score will be listed for each subject in Listing 16.2.6.1.2, by study product group and visit for all randomized subjects.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in mean BI score at 4 weeks between the Test product and Reference product.
- H_1: There is a difference in mean BI score at 4 weeks between the Test product and Reference product.

Mean BI at Week 4 will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and Baseline Mean BI and Baseline Mean MGI as covariates. Gender will also be included as a stratification factor. The MGI stratification factor is not included in the model as the actual value is included as a covariate. The adjusted mean treatment difference will be presented in Table 14.2.2.2.1 for the mITT population, along with the two-sided p-value and 95% CIs. The observed margin (OM) option in SAS will be used when estimating least square means. The % adjusted mean difference will also be presented.

The assumptions of normality and homogeneity of variance in the model will be investigated. In case of violation of these assumptions, a data transformation, or a suitable non-parametric test (van Elteren test adjusting for gender and baseline MGI stratification) will be performed; the results will be provided to support the ANCOVA results.

4.4.1.3 Supportive Analyses

If there is a difference of 10% or more in the overall number of subjects between the PP and mITT populations, a summary of the primary efficacy variable will be presented for all subjects in the PP population (Table 14.2.2.1.2), mean and SE will be presented graphically over time (Figure 14.2.2.1.4) and the same ANCOVA model applied to the primary analysis will be performed on the PP population (Table 14.2.2.2.2).

4.4.2 Secondary Efficacy Endpoints

All secondary endpoint analyses will be performed on the mITT population.

For all the secondary efficacy variables described in subsections below, the comparison of interest will be the test product versus reference product. Secondary efficacy variables will be analyzed using the same ANCOVA model described above for the primary endpoint, but with Baseline Mean BI replaced with the Baseline of the respective endpoint (Baseline Mean overall TPI for Mean overall TPI at Week 4; Baseline Mean interproximal TPI for Mean interproximal TPI at Week 4; Baseline NBS for NBS at Week 4. For Mean MGI at Week 4, no additional term will be added as Baseline Mean MGI is already included in the model as a covariate). Adjusted mean product differences will be provided, along with 95% CIs. The % adjusted mean difference will also be presented.

The assumption of residual normality and variance homogeneity in the ANCOVA analysis used to analyze secondary endpoints will be investigated through residual plots. If violated, data transformation or a nonparametric method (van Elteren test adjusting for gender and baseline MGI stratification) will be used and the results will be provided to support the ANCOVA results.

4.4.2.1 Number of Bleeding Sites (NBS) at Week 4

The NBS for each subject at each visit is calculated as the number of evaluable tooth sites with a BI score of 1 or 2. The BI scoring system is described in Section 4.4.1.1.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of NBS at each time point will be provided by study product group for the mITT population (Table 14.2.3.1.1).

The raw mean and SE of the NBS will be presented graphically over time for each study product group in Figure 14.2.3.1.2 for the mITT population.

Individual data for the NBS will be listed for each subject by study product group and visit in Listing 16.2.6.2 for all randomized subjects.

4.4.2.1.1 Statistical Hypothesis, Model and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the NBS at 4 weeks between the Test product and Reference product.
- H_1: There is a difference in the NBS at 4 weeks between the Test product and Reference product.

NBS will be analyzed as described for the primary analysis (Section 4.4.1.2), using the Baseline NBS value as covariate. The adjusted means and SEs of the two product groups together with the product difference, SE, 95% CI of the difference and p-value will be provided in Table 14.2.3.2.1 for the mITT population. The % adjusted mean difference will also be presented.

4.4.2.2 Mean Modified Gingival Index (MGI) at Week 4

The MGI score for each subject at each visit will be calculated as the average index value over all evaluable tooth sites scored as follows:

- MGI Score = Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites.

The MGI score has a range of 0 to 4.

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.

The MGI scoring system is described in Table 4-2.

Table 4-2 Modified Gingival Index

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 papillary 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
9	Missing tooth or not qualified tooth

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) will be presented for the Mean MGI score at each time point (observed value and change from baseline) by study product group for the mITT population (Table 14.2.4.1.1).

Raw means (± SE) of the Mean MGI score at each time point will be presented graphically by study product group in Figure 14.2.4.1.2 for the mITT population.

Individual data for the MGI assessment at each individual tooth site will be listed for each subject by study product group in Listing 16.2.6.3.1, and individual data for the derived MGI score will be listed for each subject in Listing 16.2.6.3.2, by study product group for all randomized subjects.

4.4.2.2.1 Statistical Hypothesis, Model and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- H_0: There is no difference in the mean MGI score at 4 weeks between the Test product and Reference product.
- H_1: There is a difference in the mean MGI score at 4 weeks between the Test product and Reference product.

Mean MGI at Week 4 will be analyzed as described for the primary analysis (Section 4.4.1.2), using the Baseline MGI value as covariate. The adjusted means and SEs of the two product groups together with the product difference, SE, 95% CI of the difference and p-value will be provided in Table 14.2.4.2.1 for the mITT population. The % adjusted mean difference will also be presented.

4.4.2.3 Mean Turesky Plaque Index (TPI) [Overall and Interproximal] at Week 4

The Overall TPI score for each subject at each visit will be calculated as the average index value over all evaluable tooth sites scored as follows:

- Overall TPI Score = Sum of index values over all evaluable tooth sites/Number of evaluable tooth sites.

The Interproximal TPI score for each subject at each visit will be calculated as the average index value over all interproximal tooth sites (distal and mesial) scored as follows:

- Interproximal TPI Score = Sum of index values over all evaluable interproximal tooth sites (distal and mesial) /Number of evaluable interproximal tooth sites (distal and mesial).

The evaluable tooth sites are those scored as 0, 1, 2, 3, 4 or 5.

The Overall TPI score and Interproximal TPI score have a range of 0 to 5.

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 TPI scoring system is described in Table 4-3.

Table 4-3 Turesky Plaque Index

Score	Description
0	No plaque
1	Separate flecks of plaque at the cervical margin of the tooth
2	Thin continuous band of plaque (1 millimitre (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
9	Missing tooth or not qualified tooth

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) will be presented for the Mean Overall TPI score and Mean Interproximal TPI score at each time point (observed value and change from baseline) by study product group for the mITT population in Table 14.2.5.1.1 and Table 14.2.6.1.1, respectively.

Raw means (± SE) of the Mean Overall TPI score and Mean Interproximal TPI score at each time point will be presented graphically by study product group in Figure 14.2.5.1.2 and Figure 14.2.6.1.2 respectively, for the mITT population.

Individual data for the TPI assessment at each evaluable tooth site will be listed for each subject by study product group in Listing 16.2.6.4.1, and individual data for the derived TPI score (overall and interproximal, respectively), will be listed for each subject in Listing 16.2.6.4.2, by study product group for all randomized subjects.

4.4.2.3.1 Statistical Hypothesis, Model and Method of Analysis

The following null and alternative hypotheses will be evaluated:

- **Overall TPI:**

- H_0: There is no difference in the mean Overall TPI score at 4 weeks between the Test product and Reference product.
- H_1: There is a difference in the mean Overall TPI score at 4 weeks between the Test product and Reference product.

- **Interproximal TPI:**

- H_0: There is no difference in the mean Interproximal TPI score at 4 weeks between the Test product and Reference product.
- H_1: There is a difference in the mean Interproximal TPI score at 4 weeks between the Test product and Reference product.

Mean Overall and Interproximal TPI will be analyzed as described for the primary analysis (Section 4.4.1.2), using the Baseline mean Overall/Interproximal TPI value as covariate, respectively. The adjusted means and SEs of the two product groups together with the product difference, SE, 95% CI of the difference and p-value will be provided in Table 14.2.5.2.1 and

Table 14.2.6.2.1 for the mITT population, respectively for Overall TPI and Interproximal TPI. The % adjusted mean difference will also be presented.

4.4.3 Exploratory Efficacy Variables

4.4.3.1 CCI

CCI

- Day 1 post-brushing compared to Day 1 pre-brushing
- Week 4 post-brushing compared to Week 4 pre-brushing
- Week 4 pre-brushing compared to Day 1 pre-brushing
- Week 4 post-brushing compared to Day 1 pre-brushing

Note: post-brushing is 3 hours post-brushing on site.

CCI

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) of CCI CCI values at both the visits pre-brushing & post-brushing will be provided by study product group for the mITT population in Table 14.2.7.1.1.

Descriptive statistics (n, mean, SD, SE, median, minimum, maximum) CCI CCI values at all the comparison of interest timepoints will be provided by study product group for the mITT population in Table 14.2.7.1.2.

Individual data CCI will be listed for each subject by visit with pre-brushing & post-brushing timepoint in Listing 16.2.6.5.

4.4.3.1.1 Statistical Hypothesis, Model and Method of Analysis

For comparisons within each treatment group, the following null and alternative hypotheses will be evaluated:

- CCI

- CCI

For comparisons to negative control, the following null and alternative hypotheses will be evaluated:

- CCI

CCI

For within treatment differences, the above time points will be analyzed using a paired t-test in Table 14.2.7.2.1.

CCI

CCI . Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied (Kenward and Roger 1997). The difference between the least square mean changes from timepoint x to timepoint y (where x represents the later timepoint and y represents the earlier timepoint in each comparison) for the Test Product compared to Reference Product (Negative Control) from the MMRM will be presented, along with the two-sided p-value and 95% CIs in table 14.2.7.2.2. The % adjusted mean difference will also be presented.

The assumptions of normality and homogeneity of variance in the MMRM will be investigated. Similarly, the assumptions for the paired t-test will be investigated. In case of violation of these assumptions, a van Elteren test adjusting for gender and baseline MGI stratification (between products comparisons) and Wilcoxon Signed Rank Test (within product comparisons with baseline) will be performed to support the parametric results.

4.4.4 Handling of Missing Values/Censoring/Discontinuations

Primary and Secondary Analysis:

Subjects who withdraw from the study early will be included in the statistical analysis up to the point at which they withdraw. There will be no imputation for missing data (i.e. analyses will be conducted on an observed case basis).

Exploratory Analysis:

CCI

4.5 Analysis of Safety

The safety profile of the study products will be assessed with respect to adverse events (AEs), and OST/OHT abnormalities in this oral health study.

4.5.1 Adverse Events and Serious Adverse Events

All AEs will be reviewed by the Clinical Research Scientist or designee prior to database lock and unblinding, and will be coded to a system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be classified as oral and non-oral on the AE page of eCRF.

Treatment emergent adverse events (TEAEs) are defined as new AEs that occur on or after the first study product use (if this date is missing, a suitable alternative will be used e.g. date of randomization). AEs with an onset date/time prior to the first study product use at the baseline visit will be considered as non-treatment emergent.

The following summary tables and listings will be presented by study product group.

- Table of TEAEs overall summary (Table 14.3.1.1)
- Table of TEAEs by SOC and PT (Table 14.3.1.2)
- Table of TEAEs by Oral/Non-Oral and PT (Table 14.3.1.3)
- Table of treatment related TEAEs by SOC and PT (Table 14.3.1.4)
- Table of treatment related TEAEs by Oral/Non-Oral and PT (Table 14.3.1.5)
- Listing of all AEs (Listing 16.2.7.1 for all randomized subjects; Listing 16.2.7.2 for non-randomized subjects)
- Listing of deaths (Listing 14.3.2.1)
- Listing of non-fatal SAEs (Listing 14.3.2.2)
- Listing of TEAEs leading to study or product withdrawal (Listing 14.3.2.3)
- Listing of TEAEs classified as Oral (Listing 14.3.2.4)

In the event that there is nothing to report, a null table or listing will be produced.

4.5.2 Other Safety Variables

Other safety variables are listed below:

- OST examination
- OHT examination

4.5.2.1 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. Any abnormal findings from the OST examination will be recorded in the eCRF with details of the abnormalities.

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

OST will be summarized (number of subjects and percentages with abnormalities) by visit and study product in Table 14.3.4.1 for all subjects in the Safety Population. Abnormal findings from the OST examination will be listed (Listing 16.2.8.1) for all randomized subjects.

4.5.2.2 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. Any conditions noted as 'Present' from the OHT examination will be described in the eCRF with details of the 'Present' condition.

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

Any conditions noted as 'Present' from the OHT examination will be listed (Listing 16.2.8.2) for all randomized subjects.

4.6 Analysis of Other Variables

4.6.1 Repeatability of the Examiner

Repeat MGI and TPI assessments will be performed by the clinical examiners at Visits 2 and 3. At least 3 subjects will be selected for repeat assessments over the duration of each of visits 2 and 3. Thus a total of at least 6 subjects repeat assessments for each endpoint will be collected during this study. 'Repeat' subjects will be selected at random from those in attendance on any given assessment day. Different subjects should be used for repeat MGI and TPI assessments.

There should be a delay of at least 10 minutes between the original and the repeat assessment for a given subject; ideally, repeat assessments should be separated by another subject. No other clinical procedure should be carried out on the selected subject between repeat assessments.

Scores from the first assessment must not be visible to the examiner/scribe when the repeat assessment is carried out.

The repeat MGI and TPI assessments will be compared to the respective original assessments (excluding any tooth surfaces assessed as missing or not qualified). The repeat assessments will not be used in any efficacy analysis.

The first and second assessments of each index will be analyzed with a Fleiss-Cohen weighted kappa coefficient (κ), along with the 95% CI, to assess the intra-examiner reliability. Reliability will be deemed:

- Excellent if $\kappa > 0.75$

- Fair to good if $0.4 \leq \kappa \leq 0.75$
- Poor if $\kappa < 0.4$

This analysis will be conducted on each respective index repeatability population (MGI population and TPI population).

4.6.1.1 MGI Repeatability

The first and repeat values of the MGI for each tooth site will be combined and cross-tabulated for the MGI Repeatability population (Table 14.2.8.1). Only subjects with both first and repeat MGI assessments available for a given tooth site at the same visit will be presented and analyzed.

4.6.1.2 TPI Repeatability

The first and repeat values of the TPI for each tooth site will be combined and cross-tabulated for the TPI Repeatability population (Table 14.2.9.1). Only subjects with both first and repeat TPI assessments available for a given tooth site at the same visit will be presented and analyzed.

5 Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 5-1 below.

Table 5-1 Changes to the Protocol Defined Statistical Analysis Plan

Protocol	Statistical Analysis Plan	
Statistical Analysis Section	**Statistical Analysis Plan**	**Rationale for Changes**
Section 6.3.1 of the Protocol states that 'The results of the examination will be recorded in the eCRF as either 'normal' or 'abnormal'.	Section 4.5.2.1 of the SAP has revised the Protocol text to state that 'Any abnormal findings from the OST examination will be recorded in the eCRF with details of the abnormalities.'	This study uses a redesigned standard eCRF, where only abnormal results will be captured in the eCRF for OST examination.
Section 6.3.2 of the Protocol states that 'Conditions will be listed as 'absent' or 'present'; those noted as 'present' will be described in the eCRF'.	Section 4.5.2.2 of the SAP has revised the Protocol text to state that 'Any conditions noted as 'Present' from the OHT examination will be described in the eCRF along with the details of the 'Present' condition.'	This study uses a redesigned standard eCRF, where only 'Present' conditions will be captured in the eCRF for OHT examination.

Appendix 1: List of Data Displays

CSR Section	TLF	Number	Title	Population	Template	Topline
14.1 Demographic Data Summary Tables and Figures						
	Table	14.1.1	Subject Disposition	All Screened Subjects	14.1.1	Yes
	Table	14.1.2	Incidence of Important Protocol Deviations	All Randomized Subjects	14.1.2	
	Table	14.1.3.1	Demographic and Baseline Characteristics	Safety Population	14.1.3.1	
	Table	14.1.3.2	Demographic and Baseline Characteristics	mITT Population	14.1.3.1	Yes
	Table	14.1.3.3	Demographic and Baseline Characteristics	PP Population	14.1.3.1	
14.2 Efficacy Data Summary Tables and Figures						
	Table	14.2.1	Summary of Brushing Compliance	mITT Population	14.2.1	
	Table	14.2.2.1.1	Summary of Bleeding Index (BI)	mITT Population	14.2.2.1.1	Yes
	Table	14.2.2.1.2	Summary of Bleeding Index (BI)	PP Population	14.2.2.1.1	
	Figure	14.2.2.1.3	Bleeding Index (BI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3	
	Figure	14.2.2.1.4	Bleeding Index (BI) (± SE) Plot Over Time by Study Product	PP Population	14.2.2.1.3	
	Table	14.2.2.2.1	Statistical Analysis of Bleeding Index (BI)	mITT Population	14.2.2.2.1	Yes
	Table	14.2.2.2.2	Statistical Analysis of Bleeding Index (BI)	PP Population	14.2.2.2.1	
	Table	14.2.3.1.1	Summary of Number of Bleeding Sites	mITT population	14.2.2.1.1	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Figure	14.2.3.1.2	Number of Bleeding Sites (± SE) Plot over Time by Study Product	mITT Population	14.2.2.1.3	
	Table	14.2.3.2.1	Statistical Analysis of Number of Bleeding Sites	mITT Population	14.2.2.2.1	
	Table	14.2.4.1.1	Summary of Modified Gingival Index (MGI)	mITT Population	14.2.2.1.1	Yes
	Figure	14.2.4.1.2	Modified Gingival Index (MGI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3	
	Table	14.2.4.2.1	Statistical Analysis of Modified Gingival Index (MGI)	mITT Population	14.2.2.2.1	Yes
	Table	14.2.5.1.1	Summary of Overall Turesky Plaque Index (TPI)	mITT Population	14.2.2.1.1	
	Figure	14.2.5.1.2	Overall Turesky Plaque Index (MGI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3	
	Table	14.2.5.2.1	Statistical Analysis of Overall Turesky Plaque Index (TPI)	mITT Population	14.2.2.2.1	Yes
	Table	14.2.6.1.1	Summary of Interproximal Turesky Plaque Index (TPI)	mITT Population	14.2.2.1.1	
	Figure	14.2.6.1.2	Interproximal Turesky Plaque Index (TPI) (± SE) Plot Over Time by Study Product	mITT Population	14.2.2.1.3	
	Table	14.2.6.2.1	Statistical Analysis of Interproximal Turesky Plaque Index (TPI)	mITT Population	14.2.2.2.1	
	CCI					

CSR Section	TLF	Number	Title	Population	Template	Topline
	CCI					
	Table	14.2.8.1	Intra-Examiner Repeatability Analysis of Modified Gingival Index (MGI)	MGI Repeatability	14.2.8.1	
	Table	14.2.9.1	Intra-Examiner Repeatability Analysis of Turesky Plaque Index (TPI)	TPI Repeatability	14.2.9.1	
14.3 Safety Data Summary Tables and Figures						
14.3.1 Displays of Adverse Events						
	Table	14.3.1.1	Treatment Emergent Adverse Events Overall Summary	Safety Population	14.3.1.1	Yes
	Table	14.3.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	14.3.1.2	
	Table	14.3.1.3	Treatment Emergent Adverse Events by Oral/Non-Oral and Preferred Term	Safety Population	14.3.1.3	
	Table	14.3.1.4	Treatment Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	14.3.1.2	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Table	14.3.1.5	Treatment Related Serious Treatment Emergent Adverse Events by Oral/Non-Oral and Preferred Term	Safety Population	14.3.1.3	
14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events						
	Listing	14.3.2.1	Deaths	All Randomized Subjects	16.2.7.1	
	Listing	14.3.2.2	Non-Fatal Serious Adverse Events	All Randomized Subjects	16.2.7.1	
	Listing	14.3.2.3	Treatment Emergent Adverse Events Leading to Study or Product Discontinuation	All Randomized Subjects	16.2.7.1	
	Listing	14.3.2.4	Treatment Emergent Adverse Events Classified as Oral	All Randomized Subjects	16.2.7.1	
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events						
	NA					
14.3.4 Other Observations Related to Safety and Abnormal Laboratory Values						
	Table	14.3.4.1	Summary of Oral Soft Tissue Examination Abnormalities	Safety Population	14.3.4.1	
APPENDIX						
16.1.6 Listing of Subjects Receiving Test Drug(s)/Investigational Product(s) from Specific Batches, where more than one batch was used						
	NA					
16.1.7 Randomization Scheme and Codes (Subject identification and treatment assigned)						

CSR Section	TLF	Number	Title	Population	Template	Topline
	Listing	16.1.7.1	Randomization Information	All Randomized Subjects	16.1.7.1	
	Listing	16.1.7.2	Kit List Allocation	All Randomized Subjects	16.1.7.2	
16.1.9 Documentation of Statistical Methods						
	Raw output	16.1.9.1.1	Statistical Analysis of Bleeding Index (BI) (Reference: Table 14.2.2.2.1)	mITT Population	SAS Output	Yes
	Raw output	16.1.9.1.2	Statistical Analysis of Bleeding Index (BI) (Reference: Table 14.2.2.2.2)	PP Population	SAS Output	
	Raw output	16.1.9.2	Statistical Analysis of Number of Bleeding Sites (Reference: Table 14.2.3.2.1)	mITT Population	SAS Output	
	Raw output	16.1.9.3	Statistical Analysis of Modified Gingival Index (MGI) (Reference: Table 14.2.4.2.1)	mITT Population	SAS Output	Yes
	Raw output	16.1.9.4	Statistical Analysis of Overall Turesky Plaque Index (TPI) (Reference: Table 14.2.5.2.1)	mITT Population	SAS Output	Yes
	Raw output	16.1.9.5	Statistical Analysis of Interproximal Turesky Plaque Index (TPI) (Reference: Table 14.2.6.2.1)	mITT Population	SAS Output	
	CCI					

CSR Section	TLF	Number	Title	Population	Template	Topline
	CCI					
16.2 Subject Data Listings						
16.2.1 Discontinued Subjects						
	Listing	16.2.1.1	Subject Disposition	All Randomized Subjects	16.2.1.1	
	Listing	16.2.1.2	Subject Disposition	Non-Randomized Subjects	16.2.1.2	
16.2.2 Protocol Deviations						
	Listing	16.2.2.1	Important Protocol Deviations	All Randomized Subjects	16.2.2.1	
	Listing	16.2.2.2	All Protocol Deviations	All Randomized Subjects	16.2.2.2	
16.2.3 Patients Excluded from the Efficacy Analysis						
	Listing	16.2.3.1	Exclusions from Analysis Populations	All Randomized Subjects	16.2.3.1	
16.2.4 Demographic Data						
	Listing	16.2.4.1	Demographic and Baseline Characteristics	All Randomized Subjects	16.2.4.1	
	Listing	16.2.4.2	Medical History and Current Medical Conditions	All Randomized Subjects	16.2.4.2	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Listing	16.2.4.3	Prior Medications	All Randomized Subjects	16.2.4.3	
	Listing	16.2.4.4	Concomitant Medications and Concomitant Non-Drug Therapies	All Randomized Subjects	16.2.4.4	
16.2.5 Compliance and/or Drug Concentration Data (if available)						
	Listing	16.2.5.1	Brushing Compliance	All Randomized Subjects	16.2.5.1	
	Listing	16.2.5.2	Supervised Brushing	All Randomized Subjects	16.2.5.2	
16.2.6 Individual Efficacy Response Data						
	Listing	16.2.6.1.1	Bleeding Index (BI) Individual Scores	All Randomized Subjects	16.2.6.1.1	
	Listing	16.2.6.1.2	Bleeding Index (BI) Derived Scores	All Randomized Subjects	16.2.6.1.2	
	Listing	16.2.6.2	Number of Bleeding Sites	All Randomized Subjects	16.2.6.2	
	Listing	16.2.6.3.1	Modified Gingival Index (MGI) Individual Scores	All Randomized Subjects	16.2.6.3.1	
	Listing	16.2.6.3.2	Modified Gingival Index (MGI) Derived Scores	All Randomized Subjects	16.2.6.3.2	
	Listing	16.2.6.4.1	Turesky Plaque Index (TPI) Individual Scores	All Randomized Subjects	16.2.6.4.1	

CSR Section	TLF	Number	Title	Population	Template	Topline
	Listing	16.2.6.4.2	Turesky Plaque Index (TPI) Derived Scores	All Randomized Subjects	16.2.6.4.2	
	CCI					
16.2.7 Adverse Event Listings						
	Listing	16.2.7.1	All Adverse Events	All Randomized Subjects	16.2.7.1	Yes
	Listing	16.2.7.2	All Adverse Events	Non-Randomized Subjects	16.2.7.1	
16.2.8 Other Listings and Listing of Laboratory Measurements, when required by regulatory authorities (if applicable)						
	Listing	16.2.8.1	Oral Soft Tissue Examination Abnormalities	All Randomized Subjects	16.2.8.1	
	Listing	16.2.8.2	Oral Hard Tissue Examination Findings	All Randomized Subjects	16.2.8.2	
16.4 Individual Subject Data Listings						
	NA					