CLINICAL PROTOCOL

A 12-Week, Randomized, Controlled, Examiner-blind, Clinical Study to Evaluate the Efficacy of a Cetylpyridinium Chloride Mouthwash in Improving Gingival Health and Reducing Plaque Accumulation

Protocol Number:	300268
Compound/Product Name:	CCI Cetylpyridinium chloride (CPC) mouthwash
Phase:	N/A

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Key Study Design:

Design: Randomized, single center, parallel group
# of Treatment Arms: 2
Blinding: Single Blind (Examiner)
Treatment Duration: 12 weeks
Washout Period: 2-4 weeks
Population: Healthy adult volunteers aged 18 and over with generalized clinically measurable plaque-induced gingivitis.
Product Use: Twice daily brushing, mouth rinse after brushing (one group)
Product Assignment: Randomization

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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)
Original Protocol	2.0	Not applicable (N/A)
Amendment 1	3.0	• Section 4.2 (AT BASELINE (Visit 2)): updated the order number (a,b) to (d,e), which helps to differentiate the items in “AT SCREENING (Visit 1)” • Table 6-1, Updated the name of Comparator product from “Crest Cavity Protection” to “Crest Plus Cavity Protection”. • Table 6-1, Updated fluoride type and level for wash out product to 0.76% w/w sodium monofluorophosphate.

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.

A Study Operational Manual accompanies this protocol which describes further operational detail for the study execution.

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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 Harmonization Good Clinical Practice (ICH GCP) guidelines, and applicable medical device regulations.
- 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

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1 INTRODUCTION

1.1 Background & Study Rationale

Dental plaque is a structured, resilient biofilm composed of microbial communities that adhere to the tooth surface, it is primarily composed of bacteria, extracellular polysaccharides, proteins, and lipids. It is a causative agent of gingivitis and periodontitis (Silness and Loe, 1964, Kinane and Hodge, 2001, Theilade et al., 1966, Davies, 2008, Chapple et al., 2015, Marsh et al., 2004).

Gingivitis is an inflammatory condition of the gingival tissues, primarily caused by the accumulation of dental plaque at the gingival margin (Kinane and Hodge, 2001). It is characterized by symptoms such as redness, swelling, and bleeding of the gums. If left untreated, gingivitis can progress to periodontitis, a more severe form of periodontal disease that can lead to tooth loss and other systemic health issues (Loe, 1967). The pathogenesis of gingivitis involves a complex interplay between microbial factors and the host immune response. Plaque bacteria release toxins that trigger an inflammatory response, leading to the clinical manifestations of gingivitis (Page & Kornman, 1997). Gingivitis and dental plaque are prevalent oral health issues that significantly impact gingival health and overall oral hygiene. Despite the availability of various preventative and therapeutic strategies, gingivitis remains a common condition affecting a significant portion of the adult population worldwide. According to the global burden of disease study, severe periodontal diseases including gingivitis, affect approximately 11% of the global population, making it a major public health concern (Kassebaum et al., 2014).

Many people are unable to achieve adequate plaque control by toothbrushing alone. Antimicrobial agents (such as metal salts, Cetylpyridinium Chloride (CPC) and chlorhexidine) have been included in daily use dentifrice and mouthwash formulations for many years, with a view to delivering improved plaque control and gum health benefits (Chapple et al., 2015). They complement mechanical plaque removal by inhibiting the growth of bacteria (via bacteriostatic and/or bactericidal activity) in areas of the mouth less accessible to the toothbrush and by interfering with the re-colonization of plaque bacteria (Teles and Teles, 2009).

Antimicrobial mouthwashes play a crucial role in maintaining oral health by reducing the microbial load in the oral cavity and inhibiting plaque formation. Various formulations, including those containing chlorhexidine, essential oils, and cetylpyridinium chloride, have been shown to be effective in controlling plaque and gingivitis. Clinical studies have demonstrated that the regular use of antimicrobial mouthwashes can lead to significant improvements in oral hygiene and gingival health (Van Strydonck et al., 2012). These mouthwashes are particularly beneficial for individuals who may have difficulty achieving adequate plaque control through mechanical means alone, such as those with limited dexterity or orthodontic appliances.

CPC is a broad-spectrum antimicrobial agent. It is reported to have both bacteriostatic and bactericidal properties to improve gingival health by effectively removing and preventing plaque build-up (Scheie et al., 1989). CPC's surface-active properties lead to its prolonged effect in the oral cavity by binding to glycoproteins that cover the teeth and oral mucosa (Allen et al., 1998). Multiple clinical trials reported in scientific publications have shown significant reduction plaque score for 0.3% to 1% CPC mouthwash (Ashley et al., 1984, Ayad et al., 2011, Barnes et al., 2011, Gunsolley, 2006, He et al., 2011, Tadakamadla et al., 2020, Van Leeuwen

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et al., 2015, Mankodi et al., 2005, Rawlinson et al., 2008, Stookey et al., 2005). Haleon also has conducted several clinical trials to evaluate the effectiveness of 0.05% or 0.1% CPC mouthwashes at inhibiting the regrowth of dental plaque. Study results demonstrated the high reduction in plaque score from 0.05% CPC mouthwash, as well as the significant higher efficacy of the 0.1% CPC mouthwash (vs 0.05% CPC mouthwash) CCI .

The use of antimicrobial mouthwash as adjunct to mechanical oral hygiene routine is considered a means to enhance plaque removal (Fine, 1988) and recommended by dental professionals. The mouthwash format complements brushing and flossing as a means of enhancing plaque removal and allows the antimicrobial active ingredient to contact the area of the mouth where brushing access could be an issue, such as between teeth, and the back of the mouth, and areas that would not be easily accessible for consumers with reduced manual dexterity (Barnett, 2006, Milleman et al., 2022).

The aim of this 12-week clinical study is to evaluate the ability of an experimental mouthwash, containing CCI CPC as an adjunct to toothbrushing with a regular fluoride toothpaste, to improve gingival health and plaque accumulation compared to a regular fluoride toothpaste alone in subjects with plaque-induced mild to moderate gingivitis. The design of this study follows published studies, where the efficacy of mouthwash in reducing gingivitis and plaque accumulation was evaluated (Min, K., et al., 2024; Bosma, M.L., et al., 2024). The absence of a placebo mouthwash use following toothbrushing with the regular fluoride toothpaste in the Control Group is a limitation of this study design. As the study subjects may be unblinded due to the presence of mouthwash in the Test Group, this study will be an examiner blind only. To maintain the study as examiner blind, staff involved in the preparation and dispensing of study products will work in a separate area and the examiner cannot enter the dispensing area.

According to CDC website (About Periodontal (Gum) Disease | Oral Health | CDC), Periodontitis is a very common type of gum disease among U.S. adults: About 4 in 10 U.S. adults 30 years or older had a mild, moderate, or severe level of periodontitis in 2009–2014 (Eke et al., 2018). About 1 in 2 men and 1 in 3 women 30 years or older had some level of periodontitis (Eke et al., 2018). Based on analysis of data from National Health and Nutrition Examination Survey (NHANES) collected from 2009 to 2014, roughly 42% of dentate adults 30 years of age or older in the United States have mild to moderate or severe periodontitis. The prevalence of periodontitis increases with age; it is significantly more common in males than in females, and in non-Hispanic Blacks and Hispanics than non-Hispanic Whites (Eke et al., 2018), (NIH; Oral Health in America, 2021). Although a diversity recruitment plan is not required for this study, the recommended recruitment strategy will include a diverse population, with balanced distribution of subjects based on the prevalence of gingivitis considering sex, age, race and ethnicity.

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2 STUDY OBJECTIVES AND ENDPOINTS

Table 2-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate the efficacy of toothpaste/mouthwash (toothpaste containing 0.243% w/w NaF with a mouthwash containing CCI CPC) in reducing gingivitis, as measured by NBS (overall), compared to a regular toothpaste alone (containing 0.243% w/w NaF), after 12 weeks twice daily use	*At Week 12, overall:* Number (no.) of bleeding sites
Secondary	
To evaluate the efficacy of toothpaste/mouthwash (toothpaste containing 0.243% w/w NaF with a mouthwash containing CCI CPC) in reducing gingivitis, as measured by NBS (interproximal), compared to a regular toothpaste alone (containing 0.243% w/w NaF), after 12 weeks twice daily use	*At Week 12, interproximal:* Number (no.) of bleeding sites
To evaluate the efficacy of toothpaste/mouthwash (toothpaste containing 0.243% w/w NaF with a Mouthwash containing CCI CPC) in reducing gingivitis, as measured by NBS (overall and interproximal), compared to a regular toothpaste alone (containing 0.243% w/w NaF), after 6 weeks twice daily use	*At Week 6, overall and interproximal:* Number (no.) of bleeding sites
To evaluate the efficacy of toothpaste/mouthwash (toothpaste containing 0.243% w/w NaF with a Mouthwash containing CCI CPC) in reducing gingivitis, as measured by bleeding index (EBI), Modified Gingival Index (MGI) and Turesky Plaque Index (TPI), overall and interproximal, compared to a regular toothpaste alone (containing 0.243% w/w NaF), after 6 and 12 weeks twice daily use	*At Week 6 and 12, overall and interproximal:* Mean EBI Mean MGI Mean TPI

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CCI	
CCI	CCI
Safety	
To evaluate the safety and oral tolerability of the study products when used twice daily for 12 weeks	Treatment emergent adverse events (TEAEs) over 12 weeks

This study will be considered successful if there is a statistically significant difference in NBS (overall) after 12 weeks of twice daily use of the toothpaste/mouthwash (a toothpaste containing 0.243% w/w NaF with a Mouthwash containing CCI CPC) compared to a regular fluoride toothpaste (containing 0.243% w/w NaF), and the difference is in the favor of the toothpaste/mouthwash group.

3 STUDY DESIGN

This will be a single-center, 12-week, randomized, controlled, single blind (examiner only), 2-treatment arms, parallel group, stratified (by sex (male/female)) study, investigating gingival health and CCI on healthy subjects after twice daily using of an experimental mouthwash containing CCI CPC in combination with a commercially available regular toothpaste containing 0.243% w/w NaF compared to a commercially available regular toothpaste containing 0.243% w/w NaF with no known anti-gingivitis nor anti plaque efficacy properties as control group.

Study subjects will be healthy adult volunteers, aged 18 and over with generalized clinically measurable plaque-induced gingivitis.

Approximately 132 subjects (approximately 66 per group) will be randomized to ensure approximately 120 evaluable subjects (approximately 60 per group) complete the study (allow up to 10% dropout).

This study will consist of 4 study visits: Screening, Baseline, Week 6 and 12.

MGI, BI (NBS is derived from BI) and TPI will be used to assess gingival inflammation, bleeding and plaque accumulation. For MGI, instead of measuring 4 sites per eligible tooth (total up to 108 sites) as in previous studies CCI, six sites per tooth (total up to 168 sites) will be assessed in order to evaluate gingival inflammation both overall and interproximal. EBI (expanded BI) is an expanded version of the Angulated bleeding index (AngBI) on the marginal gingiva (Van der Weijden et al., 1994a, Van der Weijden et al., 1994b), which measures all 6 sites surrounding a tooth and emphasizes the interproximal area where most bleeding occurs.

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CCI

All evaluable teeth (in relation to the inclusion/ exclusion general dentition criteria) will be assessed.

At Screening visit (Visit 1), subjects will provide their written informed consent to participate in the study. Demographics, medical history, and current medications will be recorded, followed by an oral examination (oral soft tissue (OST), oral hard tissue (OHT) examination) and dentition exclusions, a gross gingival assessment and pocket depth assessment. Eligible subjects will be given a washout toothpaste and toothbrush to use in between the Screening and Baseline Visits.

Within 14-28 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 [+6 hours; -2 hours] i.e., overnight immediately before the visit).

At the Baseline visit, subjects will undergo, in the following order, a full OST examination, assessments of gingival inflammation (MGI), CCI , gingival bleeding (EBI), and supra-gingival plaque (TPI). Subjects with % bleeding sites (derived from EBI assessment) and TPI score outside the study range will be discontinued from the study at this visit. Eligible subjects will then receive full mouth dental prophylaxis and be randomized to study product. The dental prophylaxis (followed by flossing) is to remove sub and supra-gingival calculus, stain, plaque and debris from the teeth. All subjects will enter the treatment period with no visible plaque (TPI=0).

Subjects will then undergo a supervised product use. Subjects will be instructed to use their product twice daily, per instruction, until their next visit.

After using the study product(s) for 6, and 12 weeks, subjects will return to the study site (Visits 3 and 4, respectively) with overnight plaque (subjects will be instructed to abstain from overnight toothbrushing for 12 hours [+6 hours; -2 hours] immediately before each assessment visit), at approximately the same time of day as the Baseline visit. The study product use will be inspected visually to determine treatment compliance. During visits 3 and 4, the investigator will ask subjects about product usage compliance and remind them to follow product usage instructions (visit 3 only). The investigator will also ask subjects if there are any changes in their health and medical occurrences since the last visit. Subjects will have a full OST examination and then undergo, in the following order, MGI, CCI CCI EBI, and TPI assessments. At Visit 4, subjects will also have a full OHT examination, return all study supplies if required and have a dental prophylaxis if deemed appropriate by the investigator or examiner.

At Visits 2, 3, and 4, repeatability data will be generated for MGI and TPI assessments from replicate examinations on the same subject. At least 3 repeatability examinations for each clinical measure will be obtained over the duration of each of visit 2, 3 and 4. This will give a total of at least 9 repeatability assessments for each endpoint collected across the 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. Due to the invasive nature of the EBI assessment, it is not feasible to conduct an accurate repeatability assessment for this index.

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Adverse events (AEs) and incidents will be recorded from informed consent and at the end of each study visit.

4 STUDY POPULATION

4.1 Type and Planned Number of Subjects

This will be a single center, 12-week, randomized, controlled, single blind (examiner only), 2-treatment arm, parallel group, stratified (by sex) study.

Study subjects will be over 18 years old, non-smokers, in good general health with clinically measurable levels of gingivitis that meet all study criteria at the Screening and Baseline visits.

Sufficient subjects will be screened to randomize approximately 132 subjects to ensure approximately 120 evaluable subjects (approximately 60 subjects per group) complete the entire study.

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

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

4.2 Inclusion Criteria

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

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is of either sex and any gender who, at the time of screening, is at least 18 years old, inclusive.
3. A subject who is willing and able to comply with scheduled visits, treatment plan and other study procedures.

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4. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, no clinically significant or relevant abnormalities in medical history or upon oral examination, or condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.
5. Subject oral health that meets all the following:

AT SCREENING (Visit 1):

a. Subject with at least 20 natural, permanent teeth.

b. 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.

c. A subject with plaque-induced gingivitis, in the opinion of the clinical examiner, as confirmed by a gross visual examination at the Screening Visit.

AT BASELINE (Visit 2; Prior to Dental Prophylaxis):

d. A subject with 10% - 30% bleeding sites.

e. A subject with 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. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or a Haleon employee directly involved in the conduct of the study or a member of their immediate family.
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, psychiatric condition or laboratory abnormality or any other clinical serious or unstable conditions (e.g., cardiovascular diseases, diabetes, liver disorders, and kidney disorders) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study

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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 is a pregnant female (self-reported) or intending to become pregnant over the duration of the study.
5. A female subject who is breastfeeding.
6. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
7. A subject unwilling or unable to comply with the Lifestyle Considerations described in this protocol.
8. A subject who is a current smoker or an ex-smoker (including vaping) who stopped within 6 months of Screening.
9. A subject who is using smokeless forms of tobacco (e.g., chewing tobacco, gutkha, pan containing tobacco, nicotine-based e-cigarettes).
10. A subject who is diagnosed with xerostomia or is taking any medication that in the view of the investigator is causing xerostomia.
11. A subject who has a medical condition which could have directly influenced gingival bleeding (e.g., type 2 diabetes).
12. A subject who has a bleeding disorder that could have affected study outcomes and/or subject safety.
13. A subject who has a recent history (within the last year) of alcohol or other substance abuse.
14. 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.
15. Presence of a tongue or lip piercing, or any other oral feature that could interfere with the usage of a toothbrush.
16. **Medication exclusions:**

    At screening (Visit 1):

    a. A subject using any antibiotic medication within 4 weeks prior to screening or at any time during the study.
    b. A subject currently taking an anti-inflammatory medication which, in the opinion of the Investigator, could affect gingival condition.
    c. A subject currently taking a systemic medication (e.g., anti-inflammatory, anticoagulant, immunosuppressants) or traditional/ herbal remedy or as a premedication requirement before an invasive examinations and prophylaxis (e.g., knee replacement, Mitral valve prolapse, etc), which, in the opinion of the Investigator, could affect plaque/ gingival condition (e.g., ibuprofen, aspirin, warfarin, cyclosporin, phenytoin, calcium channel blockers).
    d. 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 plaque formation or measures of gingivitis, within 4 weeks prior to screening.

17. Medication exclusions:

At Baseline (Visit 2):

a. A subject who has taken (in the previous 4 weeks), any antibiotics.
b. A subject who requires the need for antibiotic premedication prior to a dental prophylaxis or taking some blood thinning medication that prohibit the safe conduct of a dental cleaning. Note: Medical consultation may need to be obtained from subject's physician at the examiner's discretion.
c. A subject who has taken (in the previous 4 weeks) a systemic medication (e.g., anti-inflammatory, anti-coagulant, immunosuppressants) or traditional/ herbal remedy as a premedication requirement before an invasive examinations and prophylaxis (e.g., knee replacement, Mitral valve prolapse, etc), which, in the opinion of the Investigator, could affect plaque/ gingival condition (e.g., ibuprofen, aspirin, warfarin, cyclosporin, phenytoin, calcium channel blockers).
d. 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 plaque formation or measures of gingivitis, in the period between Screening and the Baseline visit.

18. Periodontal exclusions:

a. A subject who has more than three tooth sites with probing pocket depth ≥ 4 mm.
b. A subject who is receiving or has received treatment for periodontal disease (including surgery) within 12 months of Screening.
c. 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.

19. 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.

20. A subject who has previously been enrolled in this study.

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21. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.

4.4 Lifestyle Considerations

The site may contact subjects prior to study visits, as a reminder of the approaching scheduled visit and any applicable lifestyle restrictions as outlined below:

	Screening V1	Baseline V2	V3-V4
No gum chewing or consumption of confectionary containing xylitol (e.g., Mints)	entire study period		
Restricted Oral Care Products (*1)	entire study period		
Restricted Dental Treatments (*2)	entire study period		
All Concomitant medications and natural products reporting	entire study period		
Restricted Food and drink		4 hours prior to scheduled assessments	4 hours prior to scheduled assessments
Water	permitted 1 hour prior to scheduled study visits		
Alcohol	refrain 24 hours before all clinical assessments		
Oral Hygiene Procedures for Plaque Growth (*1)		refrain for 12(+6, -2) hours before visit	refrain for 12(+6, -2) hours before visit

(*1) dentifrices, toothbrushes, mouthwash, dental floss, toothpicks, water floss, or inter-dental brushes (except for the removal of impacted food with nonantimicrobial products only).
(*2) delay any non-emergency dental treatment until study completion (including dental prophylaxis).

4.4.1 Contraception

The study toothpastes are not contra-indicated for pregnancy or breastfeeding (their use would not be expected to cause harm to the mother, the fetus or a baby) and there will be no pregnancy warnings on the labelling of any of the study products. Thus, study-specific contraceptive requirements are not deemed necessary for the study subjects (female or male). Females of

childbearing potential should verbally confirm they are not currently pregnant or planning to become pregnant.

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 CRF, unless stated otherwise.

5.1 Schedule of Activities

Table 5-1 Schedule of Activities

Procedure/Assessment	Screening				
	Visit 1		Visit 2 **Baseline**[1] Day 1	Visit 3 **Week 6**[1] Day 42 (±4)	Visit 4 **Week 12**[1] Day 84 (±4)
Informed Consent	X	WASHOUT PERIOD (14 –28 Days)			
Medical History	X				
Demographics	X				
Current/Prior/Concomitant Medication Review	X		X	X	X
Oral soft tissue (OST) examination	X		X	X	X
Oral hard tissue (OHT) examination	X				X
Gross visual assessment of gingival health	X				
Pocket Depth Assessment[2]	X				
Inclusion/Exclusion Criteria	X		X		
Subject Eligibility	X		X		
Subject continuance				X	X
Dispense Washout Toothpaste and Toothbrush	X				
Return Washout Toothpaste and Toothbrush			X		
Modified Gingival Index (MGI) assessment			X	X	X
Repeat MGI assessment[3]			X	X	X
CCI			X		X

Procedure/Assessment	Screening Visit 1		Visit 2 **Baseline**[1] Day 1	Visit 3 **Week 6**[1] Day 42 (±4)	Visit 4 **Week 12**[1] Day 84 (±4)
Expanded Bleeding Index (EBI) assessment[5]			X	X	X
Disclose dental plaque			X	X	X
Turesky Plaque Index (TPI) assessment			X	X	X
Repeat TPI assessment[6]			X	X	X
Dental prophylaxis			X		
2nd clinician check to confirm TPI=0 (additional dental cleaning will be performed as required)			X		
Stratification/Randomization			X		
Dispense study product, toothbrush and dosing cups for Mouthwash[7], timer			X		
Dispense additional study supplies[7]				X	
Supervised study product use			X	X	
Subject returns study product(s) and toothbrush to site for compliance checks				X	X
Subjects returns study product to site					X
Adverse Events (AEs) Review[8]	X		X	X	X
End of study dental prophylaxis (optional)					X
Study Conclusion/Subject Exit from Study					X

Footnotes:

1: Subjects will abstain from overnight toothbrushing for a minimum of 12hrs (+6hr, -2hr) immediately prior to the assessment visits (Visits 2, 3 and 4)

2: In relation to the general dentition inclusion/ exclusion criteria

3: Minimum 3 MGI repeatability assessments will be obtained over the duration of each of visits 2, 3 and 4; MGI repeatability assessment at Baseline visit will be conducted on an eligible subject. If the repeat exam is performed on a subject that was deemed non-eligible, another repeatability exam will be performed until it is completed on a subject that was deemed eligible

4: CCI

5: NBS and bleeding sites % are derived from EBI assessment

6: Minimum 3 TPI repeatability assessments will be obtained over the duration of each of visits 2, 3 and 4; TPI repeatability assessment at Baseline visit will be conducted after the subject's eligibility has been confirmed.

7: Toothpaste/mouthwash treatment arm only

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8: Adverse Events (AEs), Serious Adverse Events (SAEs) and medical device incidents collected immediately after subject provides consent participate in the study by the completion of the Informed Consent Form (ICF).

5.2 Study Assessments

Efforts should be made to complete all required protocol tests and procedures. However, if circumstances beyond the investigator's control prevent an assessment, the investigator must prioritize the subject's safety. Any missed assessments should be documented as protocol deviations, including reasons and corrective actions taken. The Sponsor must be informed promptly of any missed assessments.

Screening, efficacy and safety assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in this protocol.

A single examiner will be responsible for the conduct of the clinical measures of gingivitis/ plaque accumulation for the duration of the study.

Evaluable surfaces for clinical assessments will be identified by oral examination against the oral inclusion/exclusion criteria described in Sections 4.2 and 4.3 of this protocol. Ineligible subjects will not be re-screened.

Assessments will be carried out by the investigator, or qualified designee, against the inclusion/ exclusion criteria.

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

If in the opinion of the examiner during scoring procedure a subject is between defined grades/scores, a conservative approach should be used to provide the final score which is the score assigned to a more severe condition (e.g., if in doubt between scoring 4 or 5 for TPI, the conservative approach would be scoring 5). The same approach should be applied throughout the study to ensure consistency in the grading of the scores at all timepoints.

Table 5-2 Order of Procedures

Visit 1 (Screening)	Visit 2 (Baseline- Day 1)	Visit 3 (Week 6)	Visit 4 (Week 12)
1. Informed consent 2. Demographics, Medical history (including smoking) and prior/con-med/treatment 3. OST 4. OHT 5. Gross gingival health assessment 6. Pocket depth 7. Inclusion/exclusion 8. Subject eligibility 9. Dispense washout toothpaste and toothbrush. 10. Record AEs & incidents	1. Collect washout products returned by subjects to assess compliance. 2. Review con-med, or non-drug treatments/procedures, AEs, incidents and lifestyle restrictions 3. Subject continuance 4. OST 5. MGI 6. MGI repeatability 7. CCI 8. EBI 9. Plaque disclosure/TPI 10. Inclusion/exclusion* 11. Subject eligibility	1. Collect study products, assess compliance. 2. Review con-med, or non-drug treatments/procedures, AEs, incidents and lifestyle restrictions 3. Subject continuance 4. OST 5. MGI 6. MGI repeatability* 7. EBI 8. Plaque disclosure / TPI 9. TPI repeatability* 10. Return study products to subject	1. Collect study products, assess compliance. 2. Review con-med, or non-drug treatments/procedures, AEs, incidents and lifestyle restrictions 3. Subject continuance 4. OST 5. OHT 6. MGI 7. MGI repeatability* 8. CCI 9. EBI 10. Plaque disclosure / TPI 11. TPI repeatability **

	12. TPI repeatability 13. Dental prophylaxis 14. 2nd clinician check to confirm TPI=0 15. Randomization 16. Dispense study products 17. Oral hygiene instructions 18. Supervised product usage at site 19. Record AEs & incidents	11. Dispense additional mouthwash and dosing cups (Group toothpaste/mouthwash only) 12. Oral hygiene instruction 13. Supervised product usage at site 14. Record AEs & incidents	12. Optional dental prophylaxis 13. Record AEs & incidents 14. Study conclusion

*In situations that plaque is collected but subject is not deemed eligible, plaque samples should be disposed.
**Where is applicable
Changes in con-med or non-drug treatments/procedures will be documented in the CRF.

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

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 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.

5.2.4 Inclusion/Exclusion Criteria

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

5.2.5 Subject Eligibility

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

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

5.2.6 Enrolled Subjects and Screen Failure

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 or incidents as applicable.

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

5.2.7 Dispense Washout Products

Eligible subjects will be provided with the washout toothpaste and toothbrushes to use during the washout period (14 -28 days). Subjects will be instructed to use only their supplied oral care products (washout products) according to their normal habit until their next appointment. Completion of all procedures will be documented in the CRF.

5.2.8 Gross Assessment of Gingival Health (completed at Screening visit 1)

Visual assessment of gingival health will be performed to record the presence/absence of plaque-induced gingivitis as per the inclusion criteria during Screening visit (Visit 1).

5.2.9 Pocket Depth Measurement (completed at Screening visit 1)

Pocket depth assessment will be performed during Screening visit. Michigan “O” probe with Williams Markings will be used as a "sensing" instrument to determine pocket depth. The probe tip will be inserted gently into the gingival sulcus or pocket and the total extent of the sulcus or pocket will be assessed.

5.2.10 CCI



5.2.11 MGI Assessment (Lobene et al., 1986) (Efficacy assessment completed at Visit 2 ,3 & 4)

The MGI assessment is a non-invasive evaluation which focuses on the visual symptoms of gingivitis (for example, redness, texture, edema). The MGI will be assessed on the buccal and lingual marginal gingiva and interdental papillae of all scorable teeth (second permanent molar to second permanent molar in each arch) by an appropriately qualified examiner. Three scores will be recorded buccally/labially (papilla and margin) and three scores lingually/palatally (papilla and margin). The scoring of the MGI will be performed under dental office conditions using a standard dental light for illuminating the oral cavity.

The MGI scoring system will be as follows:

Table 5-3 Modified Gingival Index Scoring System

Score	Description
0	Absence of inflammation
1	Mild inflammation; slight change in color, little change in color; 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, edema, and/ or hypertrophy of the marginal or papillary gingival unit
4	Severe inflammation; marked redness, edema and/ or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

The MGI will be assessed by the same examiner on all evaluable teeth from Baseline onwards as indicated in the Schedule of Activities.

5.2.12 EBI Assessment (Van der Weijden et al., 1994a, Van der Weijden et al., 1994b) (Efficacy assessment completed at Visit 2, 3 & 4)

Gingival bleeding will be assessed according to the EBI, by inserting a periodontal probe into the gingival crevice and sweeping from distal to mesial around the tooth at an approximate angle of 60°, while in contact with the sulcular epithelium. Each of six gingival areas (distobuccal, midbuccal, mesiobuccal, distolingual, midlingual, and mesiolingual) around each tooth will be assessed. All scorable teeth in one quadrant should be probed first (approximately 30 seconds) before recording the number of gingival units which bleed.

The EBI scoring system will be as follows:

Table 5-4 Bleeding Index scoring system

Score	Description

0	No bleeding after 30 seconds
1	Bleeding observed within 30 seconds of probing
2	Bleeding observed immediately on probing

The EBI will be assessed by the same examiner on all evaluable teeth from Baseline onwards as indicated in the Schedule of Activities.

The number of bleeding sites for each subject at each visit is calculated as the number of evaluable tooth sites with a BI score of either 1 or 2.

Bleeding sites % = the number of bleeding sites / total sites examined

Repeatability exercise will not be performed for EBI.

5.2.13 Plaque Disclosure (Efficacy assessment completed at Visit 2, 3 & 4)

Dental plaque is colorless and so is usually disclosed ('stained') prior to assessment. The disclosing solution will be used according to the manufacturer's instructions.

- At the request of the subject, the clinician may apply a thin layer of petroleum jelly to the subject's lips, as a barrier to help minimize staining by 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 clinical assessments in this region.
- The subject will rinse their mouth with 10 mL tap water for 10 seconds to remove any food debris and expectorate.
- The clinician will then apply the plaque disclosing solution as per the label instructions. Care will be taken not to dislodge the plaque during this process. The subject will then rinse with 10 mL tap water for 10 seconds and expectorate to remove excess solution.

Plaque may be redisclosed between the TPI and repeat assessments at the discretion of the clinical examiner.

5.2.14 TPI Assessment (Lobene et al., 1982) (Efficacy Assessment completed at Visit 2, 3 & 4)

TPI will be used to assess plaque on all gradable teeth meeting the inclusion/ exclusion criteria and will be performed by an appropriately qualified examiner. Only natural teeth can be assessed. This means no crowns, bridges, and teeth with fillings (surface that has 50% of the surface gradable or no more than 50% of the surface filled) which, in the examiner's judgment, would prevent an accurate grading should be assessed. Third molars should not be assessed.

The plaque will first be disclosed using a plaque disclosing dye solution, in agreement with the manufacturer's instructions. The TPI will be assessed on the facial and lingual surfaces of each scorable tooth (second molar to second molar). Three scores should be recorded buccally/ labially (distal, body, mesial sites) and three scores lingually / palatally (distal, body, mesial sites).

Disclosed plaque will be scored as follows:

Table 5-5 Turesky Plaque Index Scoring System

Score	Description
0	No plaque
1	Separate flecks of plaque at the cervical margin
2	Thin continuous band of plaque (up to 1 mm) at the cervical margin
3	Band of plaque wider than 1 mm but covering < 1/3 of the tooth surface
4	Plaque covering ≥ 1/3 but < 2/3 of the tooth surface
5	Plaque covering ≥ 2/3 of the tooth surface

The TPI will be assessed by the same examiner on all evaluable teeth from Baseline onwards as indicated in the Schedule of Activities.

5.2.15 Repeatability Assessments (completed at Visit 2, 3 & 4)

The clinical examiner selected for this study will have demonstrated their ability to replicate their own scores (intra-examiner repeatability/reliability) on a tooth site-by-tooth site basis in previous studies and/or calibration exercises. Repeat MGI and TPI assessments will be performed by the clinical examiner at Visits 2 - 4. At least 3 repeat assessments should be performed for each index over the duration of visits 2, 3 and 4. Thus a total of at least 9 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.

At Baseline visit, MGI and TPI repeatability will be only assessed on subjects with confirmed study eligibility. For MGI, if the repeat exam is performed on a subject that was deemed non-eligible, another repeatability exam will be performed until it is completed on a subject that was deemed eligible.

There should be a delay of at least 10 minutes between original and repeat assessments for a given subject and ideally separated by another subject. No other procedure on the subject should be carried out between the first and the repeat assessment. Where possible, the clinical examiner should assess a different subject in the intervening period.

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

5.2.16 OST Examination (Safety Assessment completed at all Study Visits)

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

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condition observed by the clinical examiner or reported by the subject after the screening examination will be recorded as an AE.

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

5.2.17 OHT Examination (Safety Assessment completed at Screening Visit (V1) & Last study Visit (V4)

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

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

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

6 INVESTIGATIONAL/STUDY PRODUCTS

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

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

6.1 Investigational/Study Product Supplies

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

Table 6-1 Investigational/Study Product Supplies

	Product Name	MFC #	Route of Administration and Dosage	Usage Instructions
Test Products (Toothpaste/Mouthwash)	Crest Cavity Plus Protection (0.243% w/w sodium fluoride) + Experimental Mouthwash (CCI CPC)	Toothpaste: US Commercial Product + Mouthwash CCI	Toothpaste: Full ribbon of toothpaste on head of toothbrush provided Mouthwash: 20 milliliters of mouthwash	Brush teeth for at least one minute twice daily (morning and evening). After each brushing, Swish 20 ml of mouthwash for 30 seconds without rinsing with water after use of mouthwash.
Reference product (control group, toothpaste)	Crest Cavity Plus Protection (0.243% w/w sodium fluoride)	US Commercial Product	Full ribbon of toothpaste on head of toothbrush provided	Brush teeth for at least one minute twice daily (morning and evening)
Washout/Acclimatization	Colgate Cavity Protection (0.76% w/w sodium monofluorophosphate)	US Commercial Product		
Toothbrush	Sensodyne Sensitive Care soft-bristled Toothbrushes (US marketplace)	Commercial Product	Topical oral use	As above for Test, Reference and washout

6.2 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.

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Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized 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. Returned study products should not be re-dispensed to any subject.

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.

6.3 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).

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 only (the examiner(s) will be blinded to the product received). Study subjects may be unblinded due to the presence of mouthwash in the Test Group. 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. The examiner cannot enter the dispensing 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.

Eligible subjects will be stratified according to their sex (male or female) to ensure a balance of sex across both treatment groups and then randomized to study product. This will give rise to two strata:

- Stratum 1: Sex = Male
- Stratum 2: Sex = Female

Site staff will be instructed to not enter any information into the clinical database that could potentially unblind study personnel.

6.4 Breaking the Blind

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

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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.

7 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

7.1 Sample Size Determination

Sufficient subjects will be screened so that approximately 132 subjects are randomized (approximately 66 per group) to ensure approximately 120 (approximately 60 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 group Toothpaste/Mouthwash (a toothpaste containing 0.143% w/w sodium fluoride with a mouthwash containing CCI CPC) compared to the control group (a toothpaste containing 0.243% w/w sodium fluoride) for mean NBS (overall) at Week 12 (primary objective). CCI CCI CCI The sample size calculation was performed using PASS software version 23.0.1.

The dropout rate and SD estimates are based on the review of the sponsor clinical study evaluating CCI SnF_2 toothpaste mouthwash CCI. As the estimate was based on only one study, the sample size was inflated from the initial calculation to account for this.

7.2 Populations for Analysis

7.2.1 Definitions of Analysis Populations

Population	Definition
Safety	All randomized subjects who receive at least one dose of investigational product.
Modified Intent-to-Treat (mITT)	Used for efficacy assessments; comprise all randomized subjects who receive at least one dose of investigational product and complete at least one-post Baseline efficacy 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.
Per-Protocol (PP)	All subjects in the mITT population who have at least one non-missing efficacy assessment considered to be unaffected by protocol deviations
Repeatability Populations	MGI - all subjects who have at least one repeat MGI clinical assessment at any visit. TPI - all subjects who have at least one repeat TPI clinical assessment at any visit.

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7.2.2 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.

7.3 Statistical Analyses

The statistical analysis plan (SAP) will detail the analysis of the primary and key secondary endpoints and summarize the analysis of other data. The mITT population will be used for efficacy analyses, with all p-values two-sided at a 5% significance level. A sequential testing strategy will adjust comparisons between the Toothpaste/Mouthwash combination and Control Group for overall and interproximal NBS at each time point, starting at Week 12. Summary statistics will be presented for primary and secondary endpoints at each time point. The observed margin (OM) option in SAS will be used for estimating least square means and performing MMRM analysis.

7.3.1 Primary Endpoint Analysis(es)

The NBS (overall) for each subject at each visit is calculated as the number of evaluable tooth sites with a BI score of either 1 or 2.

NBS (overall) at Week 12 will be analysed using a Mixed Model with Repeated Measures (MMRM) with investigational product, visit and [investigational product x visit] interaction as fixed effects, and Baseline NBS as a covariate. Subject will be included as a repeated measure with unstructured covariance matrix. Kenward Rogers degrees of freedom approach will be applied (Kenward & Rogers, 1997). The least squares differences at Week 12 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. In case of violation of these assumptions, a suitable non-parametric test (adjusted for the randomization stratification) will be performed, and the results will be provided to support the MMRM results.

7.3.2 Secondary Endpoint Analysis(es)

The secondary endpoints comparing the Toothpaste/Mouthwash (a toothpaste containing 0.243% w/w NaF with a mouthwash containing CCI CPC) and the control group (a toothpaste containing 0.243% w/w NaF) will be analyzed using the same MMRM model described above for the primary endpoint (mITT population), but with Baseline of the interproximal and overall NBS, EBI, MGI, and TPI at week 6, and 12. Additional details of these endpoints will be documented in the SAP. For the secondary endpoints of overall NBS at week 6, Baseline overall NBS will remain in the model.

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7.3.3 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. AEs 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 summaries by treatment group and overall, including 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, and treatment emergent treatment-related serious AEs by SOC and PT. Separate listings will be provided for deaths, serious AEs (SAEs), and any AEs leading to product or study discontinuation, as well as OST findings with a summary of abnormalities by visit.

7.3.4 Other Analysis(es)

CCI



Repeatability of Examiner

Additional details of the repeatability analysis will be documented in the SAP.

7.3.5 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) 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.

7.3.6 Study Product Compliance and Use of Other Therapies

7.3.6.1 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.

7.3.7 Handling of Dropouts and Missing Data

MMRM analyses assume data is missing at random, meaning there's a systematic relationship between missing values and observed data. This method provides unbiased treatment effect estimates, unlike ANCOVA, which is biased unless data is missing completely at random. MMRM assumes that a subject with missing data at one post-Baseline visit would have similar efficacy results to a subject with similar non-missing results at other timepoints.

8 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 CRF 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. 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: PPD 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.

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8.1 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).

8.2 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.

8.3 Pregnancy

For this study, the products being tested are not contra-indicated for pregnancy or intended to be contra-indicated for pregnancy and use of them would not be expected to cause harm either to the mother or fetus. **A pregnancy test is therefore not required**. However, subjects of child-bearing potential will be asked to provide verbal confirmation of pregnancy status at screening (Visit 1) and at each subsequent study visit.

Pregnancy data will be gathered for all pregnancies reported during a female subject's participation in the study, from informed consent until 5 days after the last study product administration. Investigators must record this information on the appropriate form and email it to the Case Management Group mailbox: PPD and the Study Manager within 24 hours, retaining the original forms in the study master file.

Subjects will be monitored for pregnancy outcomes, with follow-up information on the mother and infant sent to the Case Management Group within 6 to 8 weeks post-delivery. Any pregnancy terminations must also be reported.

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While pregnancy itself is not classified as an adverse event (AE), abnormal outcomes (e.g., spontaneous abortion, stillbirth) are considered serious adverse events (SAEs) and must be documented. Female subjects who become pregnant during the study will be withdrawn.

8.4 Evaluating Adverse Events

8.4.1 Assessment of Intensity

The investigator or medically qualified designee will categorize each adverse event (AE) as follows:

- Mild: Easily tolerated, causing minimal discomfort and not affecting daily activities.
- Moderate: Discomfort that interferes with normal activities.
- Severe: Prevents normal daily activities.

Note: "Severe" refers to the intensity of an event and should not be confused with a serious adverse event (SAE). Both serious and non-serious AEs can be rated as severe. For instance, a severe headache may significantly disrupt daily function but is only classified as serious if it meets specific SAE criteria.

8.4.2 Assessment of Causality

Investigators must assess causality for all adverse events (AEs), both serious and non-serious, documenting their findings in the eCRF and medical notes. A "reasonable possibility" indicates evidence suggesting a causal relationship. Clinical judgment, along with the Safety Statement, guides this assessment, considering alternative causes like underlying diseases and concomitant therapies.

For each AE/SAE, the investigator must document their review and causality assessment.

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.

8.5 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.

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

8.6 Medical Device Incidents

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

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

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

8.6.1 Definition and Reporting of Incidents and Malfunctions

A medical device incident includes any malfunction, deterioration in performance, or inadequacy in labeling/instructions that could potentially lead to death or serious health deterioration. Not all incidents result in such outcomes; sometimes, fortunate circumstances or healthcare intervention may prevent them.

All incidents must be reported to Haleon within 24 hours of awareness by the investigator or designee. This ensures compliance with legal obligations to notify regulatory authorities about safety information related to medical devices in clinical studies. The completed Incident Report Form should be scanned and emailed to the relevant Case Management Group mailbox: PPD with a copy sent to the Study Manager, including the study and subject numbers in the email subject line. If there is a serious adverse event (SAE), the SAE form should accompany the report.

8.7 Discontinuation of study product and subject discontinuation/withdrawal

If a subject discontinues the study product or withdraws from the study, document the reasons and date in the CRF. The subject should complete remaining assessments unless withdrawal is necessary.

8.7.1 Discontinuation of Study Product

A subject may be discontinued from the study for:

- Adverse Event
- Lack of efficacy
- Subject request
- Investigator discretion for safety or risk/benefit concerns

8.7.2 Subject Withdrawal

A subject may withdraw at any time or be withdrawn by the investigator or sponsor for:

- Safety or behavioral reasons
- Inability to comply with study visits/procedures

- Protocol violation impacting safety
- Withdrawal of consent
- Lost to follow-up
- Unblinding
- Pregnancy

If a subject withdraws and withdraws consent for future information disclosure, no further evaluations should be performed, and no additional data collected. The sponsor may retain data collected before consent withdrawal.

8.7.3 Lost to Follow up

If a subject misses a required visit, the investigator or designee must attempt to contact the subject (3 calls or emails) and reschedule the visit. If repeated failures to return occur, and the subject cannot be contacted, they will be considered lost to follow-up and withdrawn. If contact is made, inquire about the reason for withdrawal, request the return of all dispensed products, and arrange a final visit to address any unresolved adverse events.

9 DATA MANAGEMENT

The Data Management Plan (DMP) document outlines the data management process for a clinical study. Key points include:

- **Data Management**: The term CRF refers to either a paper form or an electronic data record. Source documents containing data recorded in the CRF should be specified. Each subject will be assigned a unique Screening Subject Number.
- **Case Report Form (CRF)**: A CRF is a document designed to record protocol-required information for each trial subject. It must be completed and signed by the Principal Investigator to certify data accuracy.
- **Data Handling**: Documentation of data management activities should allow retrospective assessment of data quality. Changes to data will be performed in the Electronic Data Capture (EDC) System, which includes an audit trail.
- **Data Queries**: Programmed edit checks will be generated automatically as data are entered into the system. The study monitor will review CRFs to confirm data accuracy and compliance with the protocol.

10 REGULATORY AND ETHICAL CONSIDERATIONS

The investigator must obtain prospective approval for the study protocol, amendments, informed consent documents, and other relevant documents from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Amendments may be initiated prior to IRB/EC approval only if necessary to eliminate immediate hazards to subjects.

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10.1 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, ISO 14155:2011, and applicable local regulatory requirements and laws.

10.2 Subject Information

Subject personal data will be protected, and identifiable data will not be included in reports or disclosures, except where required by law. Data will be de-identified using numerical codes. The study site will maintain a confidential list linking numerical codes to actual identities.

10.3 Records Retention

After study closure, the investigator must maintain all site study records in a safe and secure location. Records may be maintained in formats other than hard copy, but caution is advised. The investigator must notify Haleon of any changes in archival arrangements.

10.4 Disclosure and Publication Policy

Study information may be posted on clinical trial registers before subject enrollment. Anonymized subject-level data will be made available to external researchers for scientific analyses. Public disclosure of results and manuscript development will follow sponsor policy and country-specific requirements.

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11 APPENDICIES

11.1 Abbreviations

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

Table 11-1 Abbreviations

Abbreviation	Term
AE	Adverse event
ANCOVA	Analysis of covariance
BDM	Biostatistics and Data Management
BDR	Blinded data review
BI	Bleeding index
CI	confidence interval
CCI	CCI
CRF	case report form
CRS	Clinical Research Scientist
CSR	Clinical study report
DMS	Data management system
EBI	Expanded bleeding index
EC	ethics committee
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSFV	First subject first visit
GCP	Good Clinical Practice
GI	gingival index
hrs	hours
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	institutional review board
ITT	Intent to treat
IoMT	Internet of Medical Things
LLC	limited liability company

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Abbreviation	Term
MedDRA	medical Dictionary for Regulatory Activities
MFC	Manufacturing formulation code
MGI	Modified gingival index
mITT	Modified Intent-to-Treat
ml	Milliliter
mm	Millimeter
N/A	Not applicable
NaF	Sodium Fluoride
NBS	number of bleeding sites
No.	Number
OH	Oral health
OHT	Oral hard tissue
OST	Oral soft tissue
PI	Principal investigator
PI	Personal information
PP	Per protocol
RAP	Reporting and analysis plan
REC	Research ethics committee
SAE	serious adverse event
SD	Standard deviation
SE	Standard error
SnF_2	Stannous Fluoride
SOP	standard operating procedure
SRSD	Single reference study document
SS	Safety statement
SUSAR	Suspected unexpected serious adverse reaction
TPI	Turesky modification of the Quigley Hein Plaque Index
UK	United Kingdom
w/w	Weight for weight

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11.2 References

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