# CLINICAL PROTOCOL

## A 12-Week, Randomised, Controlled, Examiner-blind, Clinical Study to Evaluate the Efficacy of a Stannous Fluoride Toothpaste with a Cetylpyridinium Chloride Mouthwash in Improving Gingival Health and Reducing Plaque Accumulation

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| **Protocol Number:** | 300211 |
| **Compound/Product Name:** | 0.454% weight/weight (w/w) Stannous Fluoride ($SnF_2$) toothpaste<br>0.07% w/w Cetylpyridinium chloride (CPC) mouthwash |
| **Phase:** | N/A |

## Sponsor Information

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|---|---|
| **Sponsor Name & Legal Registered Address** | **Haleon (UK)**<br>Building 5, First Floor,<br>The Heights,<br>Weybridge,<br>Surrey,<br>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 | • Clarification that the Satisfaction survey will be conducted as an Exit Satisfaction Survey<br>• 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)"<br>• Clarification of roles that will be blinded (in addition to the examiner) in section 7.3 |
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| | | |

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, 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.

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| 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 soft, sticky, colorless deposit of bacteria which collects on the teeth and along the gingival margin. 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). Gingivitis is an inflammatory response to the presence of dental plaque (Kinane and Hodge, 2001), which typically presents as redness, swelling (oedema), and/or bleeding of the gums at the gingival margin surrounding the tooth. Gingivitis is a reversible condition but, if left untreated, can progress to the irreversible phase of periodontitis, where inflammation extends to the underlying tissues, periodontal ligament, and alveolar bone. The resulting loss of these structures can eventually lead to tooth loss through destruction of the periodontal tissues supporting the tooth. Periodontitis is reported to affect 5 to 20% of the world's population (Petersen and Ogawa, 2012). The maintenance of good gingival health is therefore important in preventing gingivitis and the development of periodontal disease (Chapple et al., 2015).

Many people are unable to achieve adequate plaque control by toothbrushing alone. Antimicrobial agents (such as metal salts, 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).

Stannous Fluoride ($SnF_2$) is a well-known chemotherapeutic agent which has been incorporated into dentifrices since the 1940s for its oral health benefits (Makin, 2013, Miller et al., 1994, Van Loveren, 2001, Van Loveren, 1990). The stannous ion (Sn[II]) is a broad-spectrum antimicrobial agent which has been shown to reduce bacterial biomass/ virulence and inhibit bacterial metabolism (Archila et al., 2004, Bellamy et al., 2012, He et al., 2012, Tinanoff, 1995, Tinanoff, 1990). Sn [II] ions rapidly oxidize to "inactive" stannic ions (Sn [IV]) and hydrolyze to form insoluble tin compounds (for example, stannous hydroxide) in the presence of water (and saliva) and saliva-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 in a population with mild-moderate plaque-induced gingivitis at timepoints ranging from 4 to 24 weeks (Mallatt et al., 2007, Mankodi et al., 1997, Mankodi et al., 2005, Parkinson et al., 2018a, Parkinson et al., 2018b).

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 leads 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 high plaque reduction efficacy of 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

et al., 2015, Mankodi et al., 2005, Rawlinson et al., 2008, Stookey et al., 2005). Haleon also has conducted several sponsored clinical trials to evaluate the plaque regrowth inhibition efficacy of 0.05% or 0.1% CPC mouthwash. Study results demonstrated the high plaque reduction efficacy 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 adjuncts 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). Nevertheless, Haleon's latest market research findings indicate that using toothpaste alone is consumers' most common practice for their daily oral hygiene.

The design of this study is intended to reflect the real-world consumer behavior of those that use a therapeutic toothpaste and mouthwash. Therefore the primary objective is to determine if using a mouthwash containing an antimicrobial ingredient used after toothbrushing with a toothpaste with demonstrate the anti-gingivitis/anti-plaque efficacy provides better plaque and gum health control compared to those that only use a regular fluoride toothpaste, in a population with clinically diagnosed gingival inflammation. The absence of a placebo mouthwash used following toothbrushing with the negative control toothpaste as a treatment arm is a limitation of this type of study design.

This study aims to assess the ability of a marketed CPC mouthwash alongside a marketed $SnF_2$ toothpaste in improving gingival health and reducing plaque accumulation, compared to the use of a regular fluoride toothpaste alone in subjects with clinically measurable plaque-induced gingivitis. This study will also explore whether a CPC mouthwash used with a $SnF_2$ toothpaste could provide benefits in plaque accumulation reduction and gingival health improvement over the sole use of $SnF_2$ toothpaste. This study will thus include three treatment arms, using currently marketed products:

1. Toothpaste/mouthwash: a toothpaste containing 0.454% w/w $SnF_2$ followed by a mouthwash containing 0.07% w/w CPC
2. Reference product, negative control: a toothpaste containing 0.243% w/w sodium fluoride (NaF)
3. Reference product: a toothpaste containing 0.454% w/w $SnF_2$

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 recruitment strategy will include a diverse population, with balanced distribution of subjects based on the prevalence of gingivitis considering sex, age, race and ethnicity.

# 2 STUDY OBJECTIVES AND ENDPOINTS

**Table 2-1 Study Objectives and Endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary** | |
| To evaluate the efficacy of toothpaste/mouthwash (a toothpaste containing 0.454% w/w $SnF_2$ with a mouthwash containing 0.07% w/w CPC) in reducing gingivitis, as measured by NBS (overall), compared to a negative control (containing 0.243% w/w NaF), after 12 weeks twice daily toothbrushing | *At Week 12, overall:*<br><br>Number (no.) of bleeding sites |
| **Secondary** | |
| To evaluate the efficacy of toothpaste/mouthwash (a toothpaste containing 0.454% w/w $SnF_2$ with a mouthwash containing 0.07% w/w CPC) in reducing gingivitis, as measured by NBS (interproximal), compared to a negative control (containing 0.243% w/w NaF), after 12 weeks twice daily toothbrushing | *At Week 12, interproximal:*<br><br>Number (no.) of bleeding sites |
| To evaluate the efficacy of toothpaste/mouthwash (a toothpaste containing 0.454% w/w $SnF_2$ with a mouthwash containing 0.07% w/w CPC) in reducing gingivitis, as measured by NBS (overall and interproximal), compared to a negative control (containing 0.243% w/w NaF), after 6 weeks twice daily toothbrushing | *At Week 6, overall and interproximal:*<br><br>Number (no.) of bleeding sites |
| To evaluate the efficacy of toothpaste/mouthwash (a toothpaste containing 0.454% w/w $SnF_2$ with a mouthwash containing 0.07% w/w CPC) in reducing gingivitis and plaque accumulation, as measured by bleeding index (BI), Modified Gingival Index (MGI) and Turesky Plaque Index (TPI), overall and interproximal, compared to a negative control (containing 0.243% w/w NaF), after 6 and 12 weeks twice daily toothbrushing | *At Weeks 6 & 12, overall and interproximal:*<br><br>Mean BI<br>Mean MGI<br>Mean TPI |
| To evaluate the efficacy of a reference toothpaste (containing 0.454% w/w $SnF_2$) in reducing gingivitis and plaque accumulation, as measured by NBS, BI, MGI and TPI, overall and interproximal, compared to a negative control toothpaste (containing 0.243% w/w NaF), after 6 and 12 weeks twice daily toothbrushing | *At Weeks 6 & 12, overall and interproximal:*<br><br>Number (no.) of bleeding sites<br>Mean BI<br>Mean MGI<br>Mean TPI |
| **Exploratory** | |

| | |
|---|---|
| To evaluate the efficacy of toothpaste/mouthwash (a toothpaste containing 0.454% w/w $SnF_2$ with a mouthwash containing 0.07% w/w CPC) in reducing gingivitis and plaque accumulation, as measured by NBS, BI, MGI and TPI, overall and interproximal, compared to a reference toothpaste (containing 0.454% w/w $SnF_2$), after 6 and 12 weeks twice daily toothbrushing | *At weeks 6 and 12, overall and interproximal:*<br><br>Number (no.) of bleeding sites<br>Mean BI<br>Mean MGI<br>Mean TPI |
| To investigate subject satisfaction with toothpaste/mouthwash (a toothpaste containing 0.454% w/w $SnF_2$ with a mouthwash containing 0.07% w/w CPC) for the overall liking, as measured by a Numeric Rating Scale (NRS), after 12 weeks treatment. | *At Week 12*<br><br>Satisfaction NRS score |
| **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 0.454% w/w $SnF_2$ with a mouthwash containing 0.07% w/w CPC) compared to the negative control toothpaste (containing 0.243% w/w NaF), and the difference is in favor of the toothpaste/mouthwash group.

# 3 STUDY DESIGN

This will be a single center, 12-week, randomized, controlled, examiner-blind, 3-treatment arm, parallel group, stratified (by sex (male/female)) study to evaluate the efficacy of using the toothpaste/mouthwash twice daily in reducing gingivitis and plaque accumulation in a population with clinically measurable levels of gingivitis.

The clinical efficacy of the commercially available toothpaste/mouthwash will be compared with that of a commercially available, regular fluoride toothpaste with no known anti-gingivitis nor anti-plaque efficacy properties (negative control).

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

Approximately 198 subjects (approximately 66 per group) will be randomized to ensure approximately 180 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 (Haleon study 212537, Haleon study 300107), 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.

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), 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 reviewed to determine treatment compliance. During the visit 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, 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 (the subject for the MGI repeat assessment and the subject for the TPI assessment can be different). Depending on subject visit scheduling, every effort will be made to complete one repeatability examination for each clinical measure during each clinical assessment day, that is, at least one MGI and one TPI repeat assessment on each assessment day. Repeatability examinations will be separated by a minimum of 10 minutes and,

where possible, separated by another subject. Due to the invasive nature of the EBI assessment, it is not feasible to conduct an accurate repeatability assessment for this index.

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, examiner-blind, 3-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 198 subjects to ensure approximately 180 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.
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 mean interproximal whole mouth 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 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 outcomes and/or subject safety.
5. A subject who is a pregnant female (self-reported) or intending to become pregnant over the duration of the study.
6. A female subject who is breastfeeding.

7. A subject with known or suspected intolerance or hypersensitivity to the 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 vaping) 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 (e.g., type 2 diabetes).
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 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 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.

**18. Medication exclusions:**

**At Baseline (Visit 2):**

a. A subject who has taken (in the previous 4 weeks), any antibiotics.
b. A subject who has taken (in the previous 4 weeks) 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 plaque formation or measures of gingivitis, in the period between Screening and the Baseline visit.

**19. 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.

**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

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

### 4.4.1 Meals and Dietary Restrictions

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

Subjects should not chew gum or consume any confectionery containing xylitol (e.g., mints).

**Before Clinical Efficacy Assessment Visits:** Baseline (Visit 2) to Last Study Visit

Subjects must abstain from all food and drink (except water) for at least 4hrs prior to their scheduled assessment visits and until all assessments are complete during visit days. Water is permitted until 1 hour prior to their scheduled study visits.

### 4.4.2 Alcohol, Caffeine and Tobacco

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

### 4.4.3 Dental Product/Treatment and Oral Hygiene Restrictions

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

- Subjects will not be permitted to use any oral care products (e.g., dentifrices, toothbrushes, mouthwash) other than those provided during the study.
- Subjects will not be permitted to use any dental floss, toothpicks, water floss, or inter-dental brushes (except for the removal of impacted food with nonantimicrobial products only).
- Subjects will be instructed to delay any non-emergency dental treatment until study completion (including dental prophylaxis). They will be required to inform site staff of any emergency treatment they receive during the study.

**Before Clinical Efficacy Assessment Visits:**

Subjects should refrain from oral hygiene procedures for 12 hours (+6 hours, -2 hours) before their visit, and attend the study site with overnight plaque growth.

### 4.4.4 Medication and Treatment Restriction

The following medication and treatment restrictions apply for the duration of the study:

- If current/ concomitant medications/ treatments or traditional herbal ingredients/ treatments are used during the study, their identity, as well as their dosage and frequency, start and stop dates must be reported to the Investigator and recorded in the CRF.

### 4.4.5 Contraception

The are no contraception requirements for subjects entered into this study. 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** | **Study Visits** | | | | |
|---|---|---|---|---|---|
| | Visit 1 **Screening** | | Visit 2 **Baseline**[1] Day 0 | 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 |
| Expanded Bleeding Index (EBI) Assessment[4] | | | X | X | X |
| Disclose Dental Plaque | | | X | X | X |
| Turesky Plaque Index (TPI) Assessment | | | X | X | X |
| Repeat TPI Assessment[5] | | | X | X | X |
| Dental Prophylaxis | | | X | | |

| Procedure/Assessment | Study Visits | | | | |
|---|---|---|---|---|---|
| | Visit 1 **Screening** | | Visit 2 **Baseline**[1] Day 0 | Visit 3 **Week 6**[1] Day 42 (± 4) | Visit 4 **Week 12**[1] Day 84 (± 4) |
| 2nd Clinician Check to Confirm TPI=0 (Additional Dental Cleaning Will Be Performed if Required) | | | X | | |
| Stratification/Randomization | | | X | | |
| Dispense Study Product(s), Toothbrush and Dosing Cups for Mouthwash[6], Timer | | | X | | |
| Dispense Additional Mouthwash and Dosing Cups[6] | | | | X[6] | |
| Supervised Study Product Use | | | X | X | |
| Subject Brings Study Product(s) and Toothbrush to Site for Compliance Checks | | | | X | X |
| Subject Returns Study Product to Site | | | | | X |
| Adverse Events (AEs) Review [7] | X | | X | X | X |
| End of Study Dental Prophylaxis (Optional) | | | | | X |
| Exit Satisfaction Survey: Subject-Completed NRS and Questionnaire[6] | | | | | X[6] |
| 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 one MGI repeatability assessments during each clinical assessment day; MGI repeatability assessment at Baseline visit will be conducted after the subject's eligibility has been confirmed.

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

5: Minimum one TPI repeatability assessments during each clinical assessment day; TPI repeatability assessment at Baseline visit will be conducted after the subject's eligibility has been confirmed.

6: Toothpaste/mouthwash treatment arm only

7: 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 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, Medical history (including smoking) and prior/concomitant medication/treatment
3. OST examination
4. OHT examination
5. Gross gingival health assessment
6. Pocket depth assessment
7. Review of inclusion/exclusion criteria
8. Subject eligibility
9. Dispense washout toothpaste and toothbrush.
10. Record Adverse events & incidents

### 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 Screening Assessments

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

- OST examination
- OHT examination
- Gross assessment of gingival health
- Pocket depth assessment

The oral examinations/assessments should be carried out as described in Section 6. All findings will be recorded in the CRF.

Findings from this examination performed at the Screening Visit will be used to determine subject eligibility.

### 5.2.5 Inclusion/Exclusion Criteria

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

### 5.2.6 Subject Eligibility

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

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

### 5.2.7 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.

### 5.2.8 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.

## 5.3 Visit 2 / Baseline (Day 0)

Subjects will visit the clinical study site 14 - 28 days after the Screening visit. The following procedures/ assessments will take place in the order listed below as much as possible and be recorded in the CRF:

1. Collect washout products returned by subjects to assess compliance.
2. Review of concomitant medication or non-drug treatments/procedures, adverse events, incidents and lifestyle restrictions
3. OST examination
4. MGI assessment
5. EBI assessment (including number of bleeding sites which is derived from EBI 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. Dental prophylaxis
13. 2$^{nd}$ clinician check to confirm TPI=0
14. Randomization
15. Dispense study products, toothbrush, dosing cups (toothpaste/mouthwash group only), and timer
16. Oral hygiene instructions
17. Supervised product usage at site
18. Record Adverse events & incidents

Changes in concomitant medication 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 non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF.

## 5.4 Visit 3 / Week 6 (Day 42 ± 4 days)

The following procedures/ assessments will take place in the order listed below and be recorded in the CRF:

1. Collect study products returned by subjects to assess compliance. Also ask subjects about product usage compliance and remind them to follow product usage instructions.
2. Review of concomitant medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions
3. Subject continuance
4. OST examination
5. MGI assessment
6. EBI assessment (including number of bleeding sites which is derived from EBI assessment)
7. Plaque disclosure
8. TPI assessment
9. MGI repeatability assessment (where applicable)
10. TPI repeatability assessment (where applicable)
11. Return study products to subject
12. Dispense additional mouthwash and dosing cups (Group toothpaste/mouthwash only)
13. Oral hygiene instruction
14. Supervised product usage at site
15. Record Adverse events & incidents

Changes in concomitant medication 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 non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF.

## 5.5 Visit 4 / Week 12 (Day 84 ± 4 days)

The following procedures/ assessments will take place in the order listed below and be recorded in the CRF:

1. Collect study products returned by subjects to assess compliance. Also ask subjects about product usage compliance.
2. Review of concomitant medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions
3. Subject continuance

4. OST examination
5. OHT examination
6. MGI assessment
7. EBI 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. Complete optional dental prophylaxis (as if deemed necessary by examiner)
13. Record adverse events & incidents
14. Exit Satisfaction survey (toothpaste/mouthwash treatment arm only)
15. Study conclusion

Changes in concomitant medication 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 non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

# 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 well-being of the subject. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments in a timely manner.

## 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 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.

### 6.1.1 Gross Assessment of Gingival Health

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).

### 6.1.2 Pocket Depth Measurement

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.

## 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.

If in the opinion of the examiner a subject is between defined grades/scores, a conservative approach should be used to provide the final score. The same approach should be applied throughout the study to ensure consistency in the grading of the scores at all timepoints.

### 6.2.1 MGI Assessment (Lobene et al., 1986)

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 6-1 Modified Gingival Index Scoring System**

| 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, 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.

### 6.2.2 EBI Assessment (Van der Weijden et al., 1994a, Van der Weijden et al., 1994b)

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 6-2 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.**

### 6.2.3 Plaque Disclosure

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.

### 6.2.4 TPI Assessment (Lobene et al., 1982)

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 6-3 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.

### 6.2.5 Repeatability Assessments

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 1 repeat assessment should be performed for each index on each clinical assessment day, that is, at least one MGI and one TPI repeat assessment on each assessment day. 'Repeat' subjects will be selected at random from those in attendance. Different subjects can 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.

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.

## 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 OST Examination

This procedure will be conducted by a qualified, experienced clinical examiner. The OST examination will be accomplished by direct observation and palpation with retraction aids, as appropriate. The examination will cover the oral labial mucosa (including lips), buccal mucosa, mucogingival folds, gingival mucosa, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands. 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 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.

### 6.3.2 OHT Examination

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

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

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

### 6.3.3 Pregnancy Testing

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. Subjects will be instructed to inform site staff if they find they are pregnant while participating in the study. In case of a positive confirmed pregnancy, the subject will be withdrawn from the study.

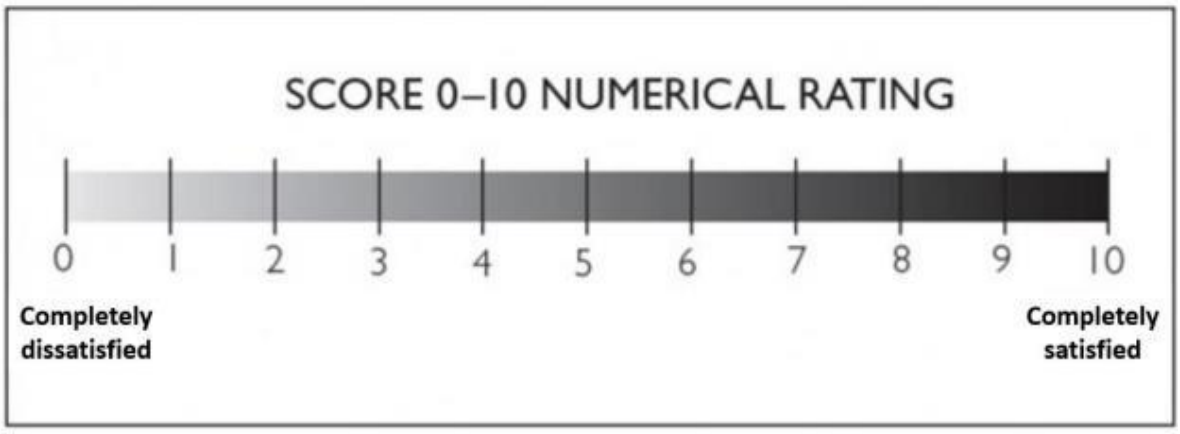
### 6.3.4 Exit Satisfaction Survey

At the end of the study (Visit 4), subjects in toothpaste/mouthwash treatment arm will be asked to rate their level of satisfaction with the toothpaste and the mouthwash using a Numeric Rating Scale (NRS).

The NRS is an 11-point ordinal scale used to assess the subject's satisfaction with the toothpaste and mouthwash. The scale ranges from 0 (completely dissatisfied) to 10 (completely satisfied), with higher scores indicative of greater satisfaction (van Berckel et al., 2017):

see example below.

Subjects will be asked to record the numeric value on the segmented scale that best describes their level of satisfaction after 12 weeks twice daily use and indicate why they select a particular score in answer to the question 'Please give more details on why you are satisfied or dissatisfied with the product' (free text response).




***Example NRS - Not to Scale***

In addition, subjects will be asked whether they would recommend this product to their family and friends who have gum problems. The responses will be either "yes" or "no" followed by free text describing why the choice is made.

An example of a satisfaction survey questionnaire is included in section 10.2.

To ensure the examiner remains blinded throughout the study, subjects will complete the exit satisfaction survey in a separate area.

# 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 Products (Toothpaste/Mouthwash) | Reference product (Negative control, toothpaste) | Reference product (Toothpaste) |
|---|---|---|---|
| **Product Name** | parodontax Complete Protection Toothpaste (0.454% w/w $SnF_2$) + parodontax Active Gum Health Mouthwash (0.07% w/w CPC) | Crest Cavity Protection (0.243% w/w sodium fluoride) | parodontax Complete Protection (0.454% w/w $SnF_2$) |
| **Pack Design** | Carton of 6 over-wrapped tubes (toothpaste) + 12 blinded bottles (mouthwash) | Carton of 6 over-wrapped tubes | Carton of 6 over-wrapped tubes |
| **Dispensing Details** | One carton (toothpaste) – baseline visit + 6 blinded bottles (mouthwash) – baseline visit | One carton – baseline visit | One carton – baseline visit |

| | | | |
|---|---|---|---|
| | 6 blinded bottles (mouthwash) – week 6 visit | | |
| **Product Master Formulation Code (MFC)** | Toothpaste CCI (US Commercial Product)<br><br>Mouthwash CCI (US Commercial Product) | US Commercial Product | CCI (US Commercial Product) |
| **Dose/Application** | Toothpaste:<br>Full ribbon of toothpaste on head of toothbrush provided<br><br>Mouthwash:<br>20 milliliters of mouthwash | Full ribbon of toothpaste on head of toothbrush provided | Full ribbon of toothpaste on head of toothbrush provided |
| **Route of Administration** | Oral, Topical | Oral, Topical | Oral, Topical |
| **Usage Instructions** | Subjects will brush their teeth for at least one (timed) minute twice a day (morning and evening).<br><br>After each brushing (morning and evening), subject will swish 20 milliliters of the mouthwash vigorously between teeth for 30 seconds. No further rinsing with water is permitted. | Subjects will brush their teeth for at least one (timed) minute twice a day (morning and evening) | Subjects will brush their teeth for at least one (timed) minute twice a day (morning and evening) |
| **Return Requirements** | All used/unused samples to be returned | All used/unused samples to be returned | All used/unused samples to be returned |

**Table 7-2 Washout/Acclimatization/Lead-in Product Supplies**

| | |
|---|---|
| | Washout toothpaste |
| **Product Name** | Colgate Cavity Protection |
| **Pack Design** | Labelled commercial tube |
| **Dispensing Details** | One tube – screening visit |
| **Product Master Formulation Code (MFC)** | N/A - commercial product |
| **Dose/Application** | Apply a full ribbon of toothpaste on the head of toothbrush provided |
| **Route of Administration** | Topical oral use |
| **Usage Instructions** | Subjects will brush their teeth according to their normal brushing habits twice a day (morning and evening). |
| **Return Requirements** | All used/unused samples to be returned |

**Table 7-3 Sundry Items**

Sundry Items to be supplied:

| **Item** | **Supplied By** | **Pack Design** | **Dispensing Details** | **Return/Disposal Details** | |
|---|---|---|---|---|---|
| | | | | **Used Samples** | **Unused Samples** |
| Sensodyne Sensitive Care soft-bristled Toothbrushes (US marketplace) | Haleon | Commercial pack (2 brushes/pack) | 1 brush at screening visit<br>1 brush at baseline visit | Destroy at site using site disposal procedures | Return not required |
| Countdown Timer | Haleon | Individual commercial pack – 1 per subject | Baseline visit | Subject to keep or destroy at site using site | Return not required |

| | | | | | |
|---|---|---|---|---|---|
| | | | | disposal procedures | |
| Opaque Bags | Haleon | Commercial Pack | Screening Visit, baseline visit & week 6 visit (toothpaste/mouthwash group) | Subject to keep or destroy at site using site disposal procedure | Return not required |
| Dosing cups for mouthwash home use (toothpaste/mouthwash group) | Haleon | Commercial Pack | 6 cups at Baseline visit<br>6 cups at week 6 visit | Subject to keep or destroy at site using site disposal procedure | Return not required |
| Acclean Disclosing Solution | Haleon | Commercial Pack | Baseline, week 6 and 12 | Destroy at site using site disposal procedure | Return not required |

## 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 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.

## 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).

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, dispensing of study products and in sharing the Exit Satisfaction Survey Questionnaire 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.

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

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

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

## 7.4 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.

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 so that approximately 198 subjects are randomized (approximately 66 per group) to ensure approximately 180 (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 0.454% w/w $SnF_2$ with a mouthwash containing 0.07% w/w CPC) compared to the negative control (a toothpaste containing 0.243% w/w sodium fluoride) for mean NBS (overall) at Week 12 (primary objective). CCI

CCI

The dropout rate and SD estimates are based on the review of the sponsor clinical study evaluating 0.454% $SnF_2$ toothpastes (Haleon study 205045). As the estimate was based on only one study, the sample size was inflated from the initial calculation to account for this.

## 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 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.

The Per-Protocol (PP) population will comprise all subjects in the mITT population who have at least one non-missing efficacy 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

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior to study unblinding/analysis (as appropriate). This section is a detailed summary of the planned statistical analyses of the primary and key secondary endpoints and a brief summary of how other collected data will be analyzed.

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. A sequential testing strategy will be used to adjust for the comparisons between the Toothpaste/Mouthwash combination and the Negative Control groups in overall NBS and interproximal NBS at each assessment time point.

At each time point, the interproximal NBS will only be assessed for confirmatory evidence if the overall NBS achieves a statistically significant greater reduction for the Toothpaste/Mouthwash combination group compared to the Negative Control group. This strategy will begin at Week 12, then move to Week 6, only moving to the earlier time point for confirmatory evidence if the Week 12 time point achieves statistically significant greater reductions for the group Toothpaste/Mouthwash compared to the Negative Control for both overall NBS and interproximal NBS. There will be no further adjustments for multiplicity for the other secondary endpoints.

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.

The observed margin (OM) option in SAS will be used when estimating least square means/ performing MMRM analysis.

### 8.3.1 Primary Endpoint Analysis(es)

The primary endpoint of this study is NBS at Week 12; the primary hypothesis test will be the comparison between the Toothpaste/Mouthwash (a toothpaste containing 0.454% w/w SnF2

with a mouthwash containing 0.07% w/w CPC) group and the negative control (a toothpaste containing 0.243% w/w NaF) group in the mITT population.

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, 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.

### 8.3.2 Secondary Endpoint Analysis(es)

The secondary endpoints comparing the Toothpaste/Mouthwash (a toothpaste containing 0.454% w/w $SnF_2$ with a mouthwash containing 0.07% w/w CPC) and the negative control (a toothpaste containing 0.243% w/w sodium fluoride) will be analyzed using the same MMRM model described above for the primary endpoint (mITT population), but with Baseline overall NBS replaced with the Baseline of the respective endpoint as follows:

Baseline interproximal NBS for interproximal NBS at Week 12

Baseline interproximal NBS for interproximal NBS at Week 6

Baseline Mean overall BI for Mean overall BI at Week 12

Baseline Mean interproximal BI for Mean interproximal BI at Week 12

Baseline Mean overall BI for Mean overall BI at Week 6

Baseline Mean interproximal BI for Mean interproximal BI at Week 6

Baseline Mean overall MGI for Mean overall MGI at Week 12

Baseline Mean interproximal MGI for Mean interproximal MGI at Week 12

Baseline Mean overall MGI for Mean overall MGI at Week 6

Baseline Mean interproximal MGI for Mean interproximal MGI at Week 6

Baseline Mean overall TPI for Mean overall TPI at Week 12

Baseline Mean interproximal TPI for Mean interproximal TPI at Week 12

Baseline Mean overall TPI for Mean overall TPI at Week 6

Baseline Mean interproximal TPI for Mean interproximal TPI at Week 6

For the secondary endpoint of overall NBS at Week 6, Baseline overall NBS will remain in the model.

The secondary endpoints comparing the $SnF_2$ Toothpaste alone (a toothpaste containing 0.454% w/w SnF2) to the negative control (a toothpaste containing 0.243% w/w sodium fluoride) will be analysed using the same MMRM model described above.

### 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(es)**

**Toothpaste/Mouthwash Compared to Reference Toothpaste**

The exploratory endpoints comparing the Toothpaste/Mouthwash (a toothpaste containing 0.454% w/w $SnF_2$ with a mouthwash containing 0.07% w/w CPC) to the $SnF_2$ Toothpaste (toothpaste containing 0.454% w/w SnF2) will be analysed using the same MMRM model described above for the primary and secondary endpoints.

**Exit Satisfaction Survey Questionnaire (toothpaste/mouthwash treatment arm )**

A summary of the number and percentage of subjects reporting at each level of the NRS and the cumulative number of subjects reporting at each level or higher at Week 12 will be presented, and the numeric (integer) NRS score at Week 12 will be summarized descriptively, by the test product toothpaste and the test product mouthwash.

Subject free text comments will be listed after each NRS rating.

In addition to each NRS, subjects will be asked whether they would recommend the products to their family and friends who have gum problems at the end of the study. Responses ("yes" or "no") will be summarised by the number and percentage of subjects in the test product toothpaste and the test product mouthwash treatment respectively.

**Repeatability of Examiner**

The repeatability of the examiner in conducting the MGI and TPI assessments will also be performed for a random sample of subjects. 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)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 Study Product Compliance and 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

MMRM analyses account for missing data using 'a missing at random' assumption, i.e., there is a systematic relationship between the propensity for missing values and the observed data, but not the missing data.

Under such assumptions, MMRM is shown to provide unbiased estimates of the treatment effect whilst analysis of only complete cases using analysis of covariance (ANCOVA) is biased (Ashbeck, 2016; Baron, 2008).

Such complete case analysis requires a 'missing completely at random' assumption to remain unbiased and this is unlikely to hold, i.e., the fact that the data are missing is independent of the observed and unobserved data.

Using an MMRM, it will therefore be assumed that a subject with missing data at one post-Baseline assessment visit would have obtained a similar efficacy result at that visit compared to a subject using the same investigational product with similar non-missing results at other timepoints (Baseline and the other post-Baseline assessment visits).

# 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 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 **(see Table 9-1),** with a copy to the appropriate Haleon Study Manager, with the study number and 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**

| | |
|---|---|
| United States | 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 nonserious); 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 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.

### 9.7.1 Definition of an Incident

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

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

### 9.7.2 Reporting of Incidents and Malfunctions

All incidents must be reported to Haleon **immediately and under no circumstance should this exceed 24 hours** of the investigator or designee becoming aware of the situation in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The completed Incident Report Form should be scanned and emailed to the relevant Case Management Group mailbox **(see Table 9-1)**, with copy to the appropriate Study Manager, with the study number and subject number in the subject line of the email. If there is an SAE, the completed SAE form should be sent together with this report form.

## 9.8 DISCONTINUATION OF STUDY PRODUCT AND SUBJECT DISCONTINUATION/WITHDRAWAL

If a subject is discontinued early from the study product (Section **9.8.1**) or discontinued or prematurely withdraws from the study (Section **9.8.2**), the reason(s) for intervention discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the CRF. 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 **9.8.2**).

### 9.8.1 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 **9.8.2**)

### 9.8.2 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.

### 9.8.3 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).

## 9.9 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.

The source documents which contain the source of data recorded in the CRF should be specified. The CRF and/or diary can be used as a source document at the discretion of data management.

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

### 9.9.1 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.

### 9.9.2 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.

### 9.9.3 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 Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

The study monitor will perform ongoing review the of the CRFs in accordance with the monitoring plan, to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of

participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

### 9.9.4 Processing Subject Reported Outcomes

Subject reported outcomes (NRS) will be recorded in questionnaires for later transcription into the eCRF.

Source documents recording subject-reported outcomes will be reviewed by the investigator staff and the study monitor to ensure the data, and any potential AEs or concomitant medications reported in these documents, are accurately transcribed into the eCRF.

Subjects from group toothpaste/mouthwash will complete paper copies of the Treatment Satisfaction NRS (source). To facilitate subject flow, paper forms (source) may also be used to record clinical data for later transcription into the eCRF. Transcription of NRS responses and clinical data into the eCRF must be completed within 5 days of the data being recorded. The eCRF and the subject-completed diary can be used as a source document at the discretion of Data Management.

Subject reported outcomes classed as source data will be retained by the investigator; true/certified copies may be sent to the sponsor or a third-party vendor, as required. To protect subject privacy, no PI (including subject name, initials or birth date) is to be recorded in any subject reported outcome source document that will be forwarded to the sponsor or a third party vendor.

## 9.10 Regulatory and Ethical Considerations

### 9.10.1 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.

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

### 9.10.3 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.

## 9.11 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.

## 9.12 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 APPENDICIES

## 10.1 ABBREVIATIONS

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

**Table 10-1 Abbreviations**

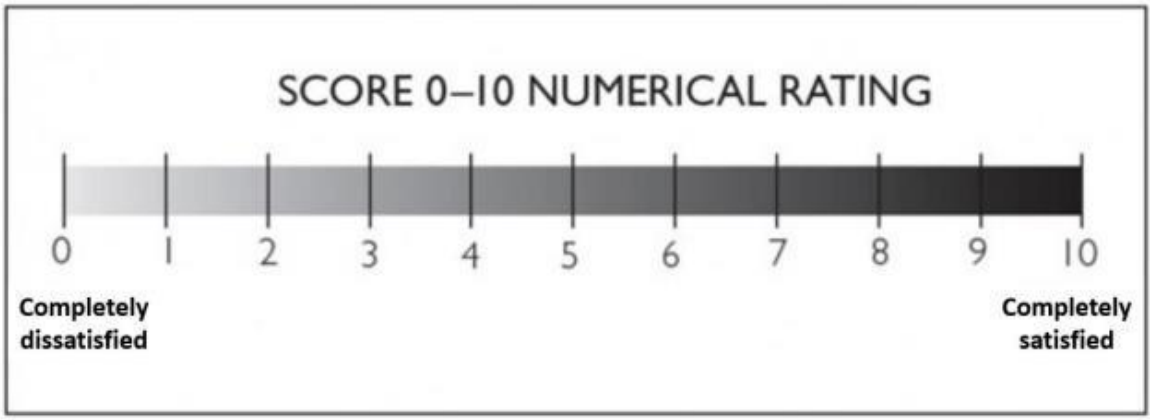
| Abbreviation | Term |
|---|---|
| AE | Adverse event |
| ANCOVA | Analysis of covariance |
| BDM | Biostatistics and Data Management |
| BDR | Blinded data review |
| BI | Bleeding index |
| CI | confidence interval |
| CRF | case report form |
| CRS | Clinical Research Scientist |
| CSR | Clinical study report |
| Da | Dalton |
| DMS | Data management system |
| EBI | Expanded bleeding index |
| EC | ethics committee |
| ECG | echocardiogram |
| 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 |

| Abbreviation | Term |
|---|---|
| IB | investigator's brochure |
| 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 |
| MedDRA | medical Dictionary for Regulatory Activities |
| MFC | Manufacturing formulation code |
| MGI | Modified gingival index |
| mITT | Modified Intent-to-Treat |
| mm | Millimeter |
| N/A | Not applicable |
| NaF | Sodium Fluoride |
| NBS | number of bleeding sites |
| No. | Number |
| NRS | Numeric Rating Scale |
| OH | Oral health |
| OHT | Oral hard tissue |
| OST | Oral soft tissue |
| PI | Principal investigator |
| PI | Personal information |
| PP | Per protocol |
| PRO | Patient reported outcome |
| RAP | Reporting and analysis plan |
| REC | Research ethics committee |
| SAE | serious adverse event |
| SD | Standard deviation |
| SE | Standard error |

| Abbreviation | Term |
|---|---|
| Stannous Fluoride | $SnF_2$ |
| 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 |

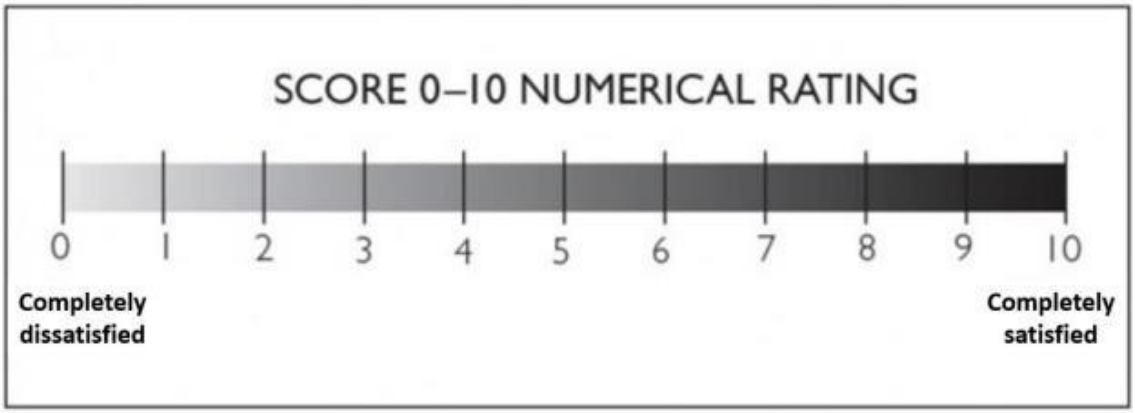
## 10.2 Satisfaction Survey Questionnaire (Example)

1: Please use the following NRS to rate your satisfaction with the **toothpaste** after 12 weeks of twice daily use




Please give more details on why you are satisfied or dissatisfied with the **toothpaste** (free text response).

2: Please use the following NRS to rate your satisfaction with the **mouthwash** after 12 weeks of twice daily use




Please give more details on why you are satisfied or dissatisfied with the **mouthwash** (free text response)

3: Will you recommend the products (**toothpaste and mouthwash**) to your family and friends who have gum problems? (yes or no)

Please give more details on why you will recommend or not recommend the products (**toothpaste and mouthwash**) to your family and friends who have gum problems (free text response)

# 11 REFERENCES

About Periodontal (Gum) Disease | Oral Health | CDC: https://www.cdc.gov/oral-health/about/gum-periodontal-disease.html

[Allen DR, Davies R, Bradshaw B, et al. (1998)] Efficacy of a mouthrinse containing 0.05% cetylpyridinium chloride for the control of plaque and gingivitis: a 6-month clinical study in adults. Compend Contin Educ Dent; 19(2 Suppl): 20-6.

[Archila L, Bartizek RD, Winston JL, et al. (2004)] The comparative efficacy of stabilized stannous fluoride/sodium hexametaphosphate dentifrice and sodium fluoride/triclosan/copolymer dentifrice for the control of gingivitis: a 6-month randomized clinical study. J Periodontol; 75(12): 1592-9.

[Ashley FP, Skinner A, Jackson PY, et al. (1984)] Effect of a 0.1% cetylpyridinium chloride mouthrinse on the accumulation and biochemical composition of dental plaque in young adults. Caries Res; 18(5): 465-71.

[Ayad F, Prado R, Mateo LR, et al. (2011)] A comparative investigation to evaluate the clinical efficacy of an alcohol-free CPC-containing mouthwash as compared to a control mouthwash in controlling dental plaque and gingivitis: a six-month clinical study on adults in San Jose, Costa Rica. J Clin Dent; 22(6): 204-12.

[Barnes VM, Arvanitidou E, Szewczyk G, et al. (2011)] Evaluation of the antiplaque efficacy of two cetylpyridinium chloride-containing mouthwashes. J Clin Dent; 22(6): 200-3.

[Barnett ML (2006)] The rationale for the daily use of an antimicrobial mouthrinse. J Am Dent Assoc; 137 Suppl: 16S-21S.

[Bellamy PG, Boulding A, Farmer S, et al. (2012)] Randomized digital plaque imaging trial evaluating plaque inhibition efficacy of a novel stabilized stannous fluoride dentifrice compared with an amine fluoride/stannous fluoride dentifrice. J Clin Dent; 23(3): 71-5.

[Chapple IL, Van der Weijden F, Doerfer C, et al. (2015)] Primary prevention of periodontitis: managing gingivitis. J Clin Periodontol; 42 Suppl 16: S71-6.

[Eke PI, Thornton-Evans GO, Wei L, et al. (2018)] Periodontitis in US Adults: National Health and Nutrition Examination Survey 2009-2014. J Am Dent Assoc; 149(7): 576-88 e6.

[Fine DH (1988)] Mouthrinses as adjuncts for plaque and gingivitis management. A status report for the American Journal of Dentistry. Am J Dent; 1(6): 259-63.

[Gunsolley JC (2006)] A meta-analysis of six-month studies of antiplaque and antigingivitis agents. J Am Dent Assoc; 137(12): 1649-57.

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[Haleon study 205045] A clinical study investigating the Gingivitis Efficacy of a Stannous Fluoride Dentifrice

[Haleon study 212537] A Randomized, Examiner Blind, Clinical Study Investigating the Efficacy of a Stannous Fluoride Dentifrice in Improving Gingival Health after 3 Weeks Use

[Haleon study 300107] A Randomized, Controlled, Examiner-Blind Clinical Study Investigating the Effects of a Dentifrice Containing 0.454% w/w Stannous Fluoride on Gingivitis Treatment and Plaque Reduction When Used Twice Daily for 12 Weeks

[He S, Wei Y, Fan X, et al. (2011)] A clinical study to assess the 12-hour antimicrobial effects of cetylpyridinium chloride mouthwashes on supragingival plaque bacteria. J Clin Dent; 22(6): 195-9.

[He T, Barker ML, Goyal CR, et al. (2012)] Anti-gingivitis effects of a novel 0.454% stabilized stannous fluoride dentifrice relative to a positive control. Am J Dent; 25(3): 136-40.

[Kinane DF, Hodge PJ (2001)] Periodontal disease in children and adolescents: introduction and classification. Periodontol 2000; 26: 7-15.

[Lobene RR, Soparkar PM, Newman MB (1982)] Use of dental floss. Effect on plaque and gingivitis. Clin Prev Dent; 4(1): 5-8.

[Lobene RR, Weatherford T, Ross NM, et al. (1986)] A modified gingival index for use in clinical trials. Clin Prev Dent; 8(1): 3-6.

[Makin SA (2013)] Stannous fluoride dentifrices. Am J Dent; 26 Spec No A: 3A-9A.

[Mallatt M, Mankodi S, Bauroth K, et al. (2007)] A controlled 6-month clinical trial to study the effects of a stannous fluoride dentifrice on gingivitis. J Clin Periodontol; 34(9): 762-7.

[Mankodi S, Bartizek RD, Winston JL, et al. (2005)] Anti-gingivitis efficacy of a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice. J Clin Periodontol; 32(1): 75-80.

[Mankodi S, Petrone DM, Battista G, et al. (1997)] Clinical efficacy of an optimized stannous fluoride dentifrice, Part 2: A 6-month plaque/gingivitis clinical study, northeast USA. Compend Contin Educ Dent; 18 Spec No: 10-5.

[Milleman K, Milleman J, Bosma ML, et al. (2022)] Role of mannual dexterity on mechanical and chemotherapeutic oral hygiene regimens. American Dental Hygenists Assciation; 96(3) 35-45.

[Miller S, Truong T, Heu R, et al. (1994)] Recent advances in stannous fluoride technology: antibacterial efficacy and mechanism of action towards hypersensitivity. Int Dent J; 44(1 Suppl 1): 83-98.

NIH: Oral Health in America: https://www.nidcr.nih.gov/sites/default/files/2021-12/Oral-Health-in-America-Advances-and-Challenges.pdf

[Parkinson C, Amini P, Wu J, et al. (2018a)] A 24-week randomized clinical study investigating the anti-gingivitis efficacy of a 0.454% w%#47;w stannous fluoride dentifrice. Am J Dent; 31(1): 17-23.

[Parkinson CR, Amini P, Jose A, et al. (2018b)] A 12-week randomized clinical study investigating the anti-gingivitis efficacy of a 0.454% w/w stannous fluoride dentifrice. Am J Dent; 31(2): 81-5.

[Petersen PE, Ogawa H (2012)] The global burden of periodontal disease: towards integration with chronic disease prevention and control. Periodontol 2000; 60(1): 15-39.

[Rawlinson A, Pollington S, Walsh TF, et al. (2008)] Efficacy of two alcohol-free cetylpyridinium chloride mouthwashes - a randomized double-blind crossover study. J Clin Periodontol; 35(3): 230-5.

[Scheie AA, Fejerskov O, Assev S, et al. (1989)] Ultrastructural changes in Streptococcus sobrinus induced by xylitol, NaF and ZnCl2. Caries Res; 23(5): 320-7.

[Silness J, Loe H (1964)] Periodontal Disease in Pregnancy. Ii. Correlation between Oral Hygiene and Periodontal Condtion. Acta Odontol Scand; 22: 121-35.

[Stookey GK, Beiswanger B, Mau M, et al. (2005)] A 6-month clinical study assessing the safety and efficacy of two cetylpyridinium chloride mouthrinses. Am J Dent; 18 Spec No: 24a-8a.

[Tadakamadla SK, Bharathwaj VV, Duraiswamy P, et al. (2020)] Clinical efficacy of a new cetylpyridinium chloride-hyaluronic acid-based mouthrinse compared to chlorhexidine and placebo mouthrinses-A 21-day randomized clinical trial. Int J Dent Hyg; 18(1): 116-23.

[Teles RP, Teles FR (2009)] Antimicrobial agents used in the control of periodontal biofilms: effective adjuncts to mechanical plaque control? Braz Oral Res; 23 Suppl 1: 39-48.

[Theilade E, Wright WH, Jensen SB, et al. (1966)] Experimental gingivitis in man. II. A longitudinal clinical and bacteriological investigation. J Periodontal Res; 1: 1-13.

[Tinanoff N (1990)] Review of the antimicrobial action of stannous fluoride. J Clin Dent; 2(1): 22-7.

[Tinanoff N (1995)] Progress regarding the use of stannous fluoride in clinical dentistry. J Clin Dent; 6 Spec No: 37-40.

[van Berckel MM, Bosma NH, Hageman MG, et al. (2017)] The Correlation Between a Numerical Rating Scale of Patient Satisfaction With Current Management of an Upper Extremity Disorder and a General Measure of Satisfaction With the Medical Visit. Hand (N Y); 12(2): 202-6.

[Van der Weijden GA, Timmerman MF, Nijboer A, et al. (1994a)] Comparison of different approaches to assess bleeding on probing as indicators of gingivitis. J Clin Periodontol; 21(9): 589-94.

[Van der Weijden GA, Timmerman MF, Saxton CA, et al. (1994b)] Intra-/inter-examiner reproducibility study of gingival bleeding. J Periodontal Res; 29(4): 236-41.

[Van Leeuwen MP, Rosema NA, Versteeg PA, et al. (2015)] Long-term efficacy of a 0.07% cetylpyridinium chloride mouth rinse in relation to plaque and gingivitis: a 6-month randomized, vehicle-controlled clinical trial. Int J Dent Hyg; 13(2): 93-103.

[Van Loveren C (1990)] The antimicrobial action of fluoride and its role in caries inhibition. J Dent Res; 69 Spec No: 676-81; discussion 82-3.

[Van Loveren C (2001)] Antimicrobial activity of fluoride and its in vivo importance: identification of research questions. Caries Res; 35 Suppl 1: 65-70.

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