

CLINICAL PROTOCOL

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

Protocol Number:	300107
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Document History

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Original protocol	1.0	Not applicable (N/A)
New Version	2.0	<ul style="list-style-type: none"> Clarified AE and medical device incident monitoring in study design synopsis and overall study design (section 4.1) Clarified statistical analyses Typographical administrative changes
Amendment 1		
Amendment 2		

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

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines and applicable portions of EU MDR 2017/745 and European Nation International Organisation for Standardisation (ISO) 14155:2011 and ISO 14155:2020.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	PPD
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1 PROTOCOL SUMMARY

1.1 Synopsis

Background and Rationale:

This clinical study will investigate the efficacy of a dentifrice containing 0.454% stannous fluoride (SnF₂), on gingivitis treatment and plaque reduction, compared to a regular fluoride dentifrice after 12 weeks twice daily brushing in a population of clinically diagnosed gingivitis without undergoing dental prophylaxis. Gingival health and plaque reduction will be evaluated using bleeding index (BI), number of bleeding sites (NBS), modified gingival index (MGI) and Turesky modification of the Quigley Hein Plaque Index (TPI).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the performance of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by NBS, after 12 weeks twice daily toothbrushing.	<i>At Week 12:</i> <ul style="list-style-type: none"> Change from Baseline in NBS
Secondary	
To evaluate the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by NBS, compared to a negative control after 12 weeks twice daily toothbrushing.	<i>At Week 12:</i> <ul style="list-style-type: none"> Change from Baseline in NBS
To evaluate the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by NBS, compared to a negative control, after 3 and 6 weeks twice daily toothbrushing.	<i>At Weeks 3 & 6:</i> <ul style="list-style-type: none"> Change from Baseline in NBS
To evaluate the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing plaque accumulation, as measured by the TPI (overall and interproximal), compared to a negative control, after 3, 6 and 12 weeks twice daily toothbrushing.	<i>At Weeks 3, 6 & 12:</i> <ul style="list-style-type: none"> Change from Baseline in Mean TPI (overall and interproximal)
To evaluate the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by BI, compared to a negative control, after 3, 6 and 12 weeks twice daily toothbrushing.	<i>At Weeks 3, 6 & 12:</i> <ul style="list-style-type: none"> Change from Baseline in BI
To evaluate the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by MGI, compared to	<i>At Weeks 3, 6 & 12:</i> <ul style="list-style-type: none"> Change from Baseline in MGI

a negative control, after 3, 6 and 12 weeks twice daily toothbrushing.	
Exploratory	
To explore the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by NBS, BI and MGI, compared to a negative control, after 3, 6 and 12 weeks twice daily toothbrushing, in the low and high baseline mean MGI subgroup: <ul style="list-style-type: none"> • Low: MGI ≤ 2 • High: MGI > 2 	<p><i>At Weeks 3, 6 & 12:</i></p> <p>Change from Baseline in</p> <ul style="list-style-type: none"> • NBS • Mean BI • Mean MGI <p>For each MGI subgroup</p>
To explore the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing plaque accumulation, as measured by TPI, compared to a negative control, after 3, 6 and 12 weeks twice daily toothbrushing, in the low and high baseline mean MGI subgroup: <ul style="list-style-type: none"> • Low: MGI ≤ 2 • High: MGI > 2 	<p><i>At Weeks 3, 6 & 12:</i></p> <p>Change from Baseline in</p> <ul style="list-style-type: none"> • Mean TPI (overall and interproximal) <p>For each MGI subgroup</p>
Safety	
To assess the oral tolerability of dentifrice containing 0.454% w/w SnF ₂ , over 12 weeks twice daily use.	Treatment-emergent adverse events over 12 weeks

Study Design:

This will be a single center, randomized, controlled, single blind (examiner blind), randomized, two-treatment arm, parallel 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.

Approximately 160 subjects (approximately 80 per group) will be randomized to ensure approximately 144 evaluable subjects (approximately 72 per group) complete the study.

This study will consist of 5 study visits: Screening, Baseline, Week 3, 6 and 12. Gingivitis will be assessed using MGI ([Lobene et al. 1986](#)) and BI ([Saxton and van der Ouderaa, 1989](#)) (The NBS is derived from the BI assessment). Plaque will be assessed using TPI ([Lobene et al. 1982](#)).

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) examination, oral hard tissue (OHT) examination, dentition exclusions, a gross gingival assessment and pocket depth assessment.

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Eligible subjects will be given a washout dentifrice and toothbrush to use in between Screening and Baseline Visits. They will also be issued with a study diary to record product usage.

Within 14±3 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] immediately before the visit).

At the Baseline visit, subjects will undergo, in the following order, a full OST examination, gingival inflammation (MGI), gingival bleeding (BI), supra-gingival plaque (TPI). Subjects with bleeding sites % (derived from BI assessment) or TPI score outside the inclusion criteria range will be discontinued from the study at this visit. 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. The subjects will then be instructed to brush for at least one (timed) minute at site with their assigned study product (supervised brushing) after which they will be instructed to continue using their product twice daily (morning and evening until their next visit), at least one (timed) minute /each time.

After using the study dentifrice for 3, 6, and 12 weeks, subjects will return to the study site (Visits 3, 4, and 5, 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 dentifrice and the diary will be reviewed to determine treatment compliance. Subjects will have a full OST examination and then undergo, in the following order, MGI, BI, and TPI. At Visit 5, subjects will also have a full OHT examination, return all study supplies and have a dental prophylaxis if deemed appropriate by the investigator or examiner.

At Visits 2, 3, 4, and 5, 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 BI assessment, it is not feasible to conduct an accurate repeatability assessment for this index.

Safety and oral tolerability of the study dentifrices will be monitored over the 12-week usage period by review of TEAEs. Medical device incidents will be recorded (the medical device in this study is the manual toothbrush used to apply the study toothpastes) throughout the study.

Study Products:

	Washout Dentifrice	Test Dentifrice	Reference Dentifrice (negative control)
Product Name	Colgate Cavity Protection (0.76% w/w Sodium Monofluorophosphate and 0.1% w/w Sodium Fluoride)	Parodontax Complete Protection Dentifrice (0.454% SnF ₂)	Crest Cavity Protection (0.243% sodium fluoride)
Product Master Formulation Code (MFC)	N/A	CCI [REDACTED]	N/A
Dose/Application	Visit 1-2: Subjects will use the provided washout product. Subjects will brush their teeth according to their normal brushing habits twice daily (morning and evening).	Visit 2-5: Subjects will use their allocated study product. Subjects will brush for at least one (timed) minute twice daily (morning and evening).	
	Subjects will dose the toothbrush provided with a ribbon of paste to cover the brush head (a full brush head) on each brushing occasion. Each brushing occasion will be recorded by the subject in their diary to enable assessment of treatment compliance.		
Route of Administration	Oral topical		
Return Requirements	All used/unused samples to be returned		

Type and Planned Number of Subjects:

Approximately 160 subjects (approximately 80 per group) will be randomized to ensure approximately 144 evaluable subjects (approximately 72 per group) complete the study, allowing for approximately 10% dropouts.

Based on previous, similar Haleon studies evaluating plaque reduction and gingivitis treatment provided by daily-use of 0.45% w/w SnF₂ dentifrice, approximately 72 evaluable subjects per product group is considered sufficient for this study.

Statistical Analysis:

A modified Intent-To-Treat (mITT) population will be used for the efficacy analyses (all randomized subjects who complete at least one use of study product and have at least one post-baseline clinical efficacy assessment)

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CCI [REDACTED] Clinical Protocol Template v10.0

The primary endpoint is NBS (NBS is derived from the BI and it is the number of evaluable sites with a BI score of either 1 or 2) at Week 12. The primary comparison is change from Baseline at Week 12 for the test dentifrice.

A mixed model with repeated measures (MMRM) will be performed on the change from baseline with product (test or reference), time point and product by time point interaction as fixed effects, and baseline NBS as a covariate.

The key secondary comparison is change from Baseline at Week 12 for the test dentifrice versus the reference dentifrice (negative control) and will be analyzed using the same MMRM from the primary analysis

All p-values will be two-sided and assessed at the 5% significance level. Adjusted means for both treatments and treatment differences will be provided along with 95% confidence intervals (CIs), as appropriate.

1.2 Schedule of Activities

The Schedule of Activities table provides an overview of the subject visits and study procedures.

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

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening		Study Visits			
	Visit 1		Visit 2 Day 0 Baseline ¹	Visit 3 Day 21±3 (Week 3) ¹	Visit 4 Day 42±4 (Week 6) ¹	Visit 5 Day 84±4 (Week 12) ¹
Informed consent	X	Washout period 14 days±3 days				
Medical history	X					
Demographics	X					
Current/prior/concomitant medication review	X		X	X	X	X
OST Examination	X		X	X	X	X
OHT Examination	X					X
Gross gingival assessment ²	X					
Pocket Depth Assessment ²	X					
Review of Inclusion/exclusion Criteria	X		X			
Subject eligibility	X		X			
Subject continuance				X	X	X
Dispense toothbrush washout toothpaste, and washout diary ³	X					
Return Washout Toothpaste/Toothbrush			X			
Modified Gingival Index (MGI) assessment			X	X	X	X
MGI repeatability assessment ⁴			X	X	X	X
Bleeding Index (BI) assessment ⁵			X	X	X	X
Plaque disclosure and plaque index (TPI) assessments			X	X	X	X
TPI repeatability assessment ⁶			X	X	X	X
Randomization			X			
Dispense study products, timer, and study diary			X			
Oral hygiene instruction & supervised brushing with study dentifrice ⁷			X	X	X	
Review diary completion			X	X	X	X
Collect study products, assess compliance, and return to subject				X	X	
Return study products (end of study)						X
End of study dental prophylaxis (optional)						X

Adverse events review ⁸	X		X	X	X	X
Medical device incidents review			X	X	X	X
Study conclusion						X

Abbreviations: OST: Oral Soft Tissue, OHT: Oral Hard Tissue, MGI: Modified Gingivitis Index, BI: bleeding index; TPI: Turesky Plaque Index.

Footnotes:

- 1: Subjects will abstain from overnight toothbrushing for a minimum of 12hrs (+6hr, -2hr) immediately prior to the assessment visits (Visits 2, 3, 4 and 5)
- 2: In relation to the general dentition inclusion/ exclusion criteria
- 3: No instruction or supervised brushing at screening visit
- 4: 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.
- 5: NBS and bleeding sites% are derived from BI assessment
- 6: 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.
- 7: At Baseline visit, site will confirm that 2nd toothbrush has not been used before the supervised brushing
- 8: Adverse Events (AEs), Serious Adverse Events (SAEs) and medical device incidents collected immediately after subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF).

2 INTRODUCTION

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](#), [Theilade et al 1966](#), [Kinane and Hodge 2001](#), [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. The effect of toothbrushing can be augmented by the use of dentifrice ([Davies, 2008](#)) and antimicrobial ingredients. Antimicrobial agents (such as metal salts, cetylpyridinium chloride and chlorhexidine) have been included in daily use dentifrice and mouth rinse 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-colonisation of plaque bacteria ([Teles and Teles, 2009](#)).

SnF₂ 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, 1990a](#); [Van Loveren, 2001](#)). 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, 1990](#); [Tinanoff, 1995](#)). Sn [II] ions rapidly oxidize to “inactive” stannic ions (Sn [IV]) and hydrolyse to form insoluble tin compounds (for example, stannous hydroxide) in the presence of water (and saliva) and saliva-derived ions ([Makin, 2013](#)). To maximise the delivery of bioavailable Sn[II] ions to the oral cavity, SnF₂ 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% SnF₂ dentifrices, for example, ([Mallatt et al, 2007](#); [Mankodi et al, 1997](#); [Mankodi et al, 2005](#); [Parkinson et al, 2014](#); [Parkinson et al, 2015](#); [Parkinson et al, 2018a](#); [Parkinson et al, 2018b](#)) in a population with mild-moderate plaque-induced gingivitis at timepoints ranging from 4 to 24 weeks.

This 12-week randomized controlled clinical study is to assess the efficacy of plaque reduction and gingivitis treatment following twice daily use of a 0.454% SnF₂ dentifrice (parodontax Complete Protection dentifrice, non-aqueous formula) in comparison with a standard fluoride dentifrice in a population of subjects with clinically measurable levels of gingivitis without pre-treatment dental prophylaxis.

2.1 Study Rationale

Daily dentifrices containing 0.454% w/w SnF₂ (0.15% w/v F ion) have been incorporated into dentifrices since the 1940s and marketed by several oral health companies, these products are

under the FDA OTC monograph. The US FDA recognizes its anti-plaque and gingivitis efficacy. ([Oral Health Care Drug Products for Over-the-Counter Human Use., \(1991\)](#))

Haleon has executed a number of clinical efficacy studies on twice daily use of 0.454% w/w SnF₂ dentifrice formulations. All studies were executed as randomized controlled clinical trials in well-defined populations of healthy volunteers with gingivitis and all of these studies had a dental prophylaxis once subjects have been enrolled into the clinical study. These studies demonstrated the efficacy of SnF₂ in reducing gingival inflammation and plaque accumulation in subjects with mild to moderate gingivitis following prophylaxis procedure. ([Parkinson et al., 2014](#), [Parkinson et al., 2015](#), [Parkinson et al., 2018a](#), [Parkinson et al., 2018b](#), [Haleon Study 207014, 2018](#), [Acherkouk et al., 2021](#)).

In all of these studies subjects received a dental prophylaxis once enrolled into the clinical study following ADA/FDA guidance with for reducing the incidence of gingivitis ([FDA., 2005](#)). Subjects receive a dental prophylaxis to restore gingival health and the endpoint provide an assessment the reappearance of gingivitis after a set period of time. ([FDA., 2005](#))

Subjects who already have measurable gingivitis before treatment may experience a significant reduction in the gingivitis and bleeding scores over time with twice daily use and compared to a control product. This reduction indicates that the test product reduces the severity of gingivitis. ([FDA., 2005](#)). Therefore, this plaque reduction and gingivitis treatment study (with no prophylaxis before commencing treatment) will generate evidence to support the effect of SnF₂ on existing plaque and gingivitis and will provide additional evidence into the effects of using SnF₂ parodontax over a 12-week period.

2.2 Benefit/Risk Assessment

Study products are commercially available daily use toothpastes which contain only ingredients with a history of safe use in oral healthcare products. Summary safety information for the acclimatization and study products will be provided on the product labels.

2.3 Mechanism of Action/Indication

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, 1990](#), [Tinanoff, 1995](#), [Haraszthy et al., 2019](#)).

It has been shown to interfere with the development and maturation of the plaque biofilm, inhibiting bacterial adherence and colonization of the oral surfaces, and penetrating the cell wall to interfere with bacterial metabolism. ([Tinanoff, 1990](#); [Wilson and Pratten, 1999](#))

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the performance of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by NBS, after 12 weeks twice daily toothbrushing.	<i>At Week 12:</i> <ul style="list-style-type: none"> Change from Baseline in NBS
Secondary	
To evaluate the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by NBS, compared to a negative control after 12 weeks twice daily toothbrushing.	<i>At Week 12:</i> <ul style="list-style-type: none"> Change from Baseline in NBS
To evaluate the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by NBS, compared to a negative control, after 3 and 6 weeks twice daily toothbrushing.	<i>At Weeks 3 & 6:</i> <ul style="list-style-type: none"> Change from Baseline in NBS
To evaluate the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing plaque accumulation, as measured by the TPI (overall and interproximal), compared to a negative control, after 3, 6 and 12 weeks twice daily toothbrushing.	<i>At Weeks 3, 6 & 12:</i> <ul style="list-style-type: none"> Change from Baseline in Mean TPI (overall and interproximal)
To evaluate the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by BI, compared to a negative control, after 3, 6 and 12 weeks twice daily toothbrushing.	<i>At Weeks 3, 6 & 12:</i> <ul style="list-style-type: none"> Change from Baseline in BI
To evaluate the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by MGI, compared to a negative control, after 3, 6 and 12 weeks twice daily toothbrushing.	<i>At Weeks 3, 6 & 12:</i> <ul style="list-style-type: none"> Change from Baseline in MGI
Exploratory	
To explore the efficacy of a dentifrice containing 0.454% w/w SnF ₂ in reducing gingivitis, as measured by NBS, BI and MGI, compared to a negative control, after 3, 6 and 12 weeks twice daily toothbrushing,	<i>At Weeks 3, 6 & 12:</i> Change from Baseline in <ul style="list-style-type: none"> NBS Mean BI

<p>in the low and high baseline mean MGI subgroup:</p> <ul style="list-style-type: none"> • Low: $MGI \leq 2$ • High: $MGI > 2$ 	<ul style="list-style-type: none"> • Mean MGI <p>For each MGI subgroup</p>
<p>To explore the efficacy of a dentifrice containing 0.454% w/w SnF₂ in reducing plaque accumulation, as measured by TPI, compared to a negative control, after 3, 6 and 12 weeks twice daily toothbrushing,</p> <p>in the low and high baseline mean MGI subgroup:</p> <ul style="list-style-type: none"> • Low: $MGI \leq 2$ • High: $MGI > 2$ 	<p><i>At Weeks 3, 6 & 12:</i></p> <p>Change from Baseline in</p> <ul style="list-style-type: none"> • Mean TPI (overall and interproximal) <p>For each MGI subgroup</p>
Safety	
<p>To assess the oral tolerability of dentifrice containing 0.454% w/w SnF₂, over 12 weeks twice daily use.</p>	<p>Treatment-emergent adverse events over 12 weeks</p>

This study will be considered successful if there is a statistically significant difference in NBS after 12 weeks of twice daily brushing with the SnF₂ dentifrice compared to its baseline and the difference is in favor of the SnF₂ dentifrice.

4 STUDY DESIGN

4.1 Overall Design

This will be a single center, controlled, single blind (examiner blind), randomized, two-treatment arm, parallel 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.

Approximately 160 subjects (approximately n= 80 per group) will be randomized to ensure approximately 144 evaluable subjects (approximately 72 per group) complete the study.

As per synopsis, this study will consist of 5 study visits: Screening, Baseline, Week 3, 6 and 12. Gingivitis will be assessed using MGI ([Lobene et al, 1986](#)) and BI ([Saxton and van der Ouderaa, 1989](#)) (The NBS will be derived from the BI assessment). Plaque will be assessed using TPI ([Lobene et al, 1982](#)).

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

At Screening visit (Visit 1; in relation to subject screening), 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) examination, oral hard tissue (OHT) examination, dentition exclusions, a gross gingival assessment and pocket depth assessment. Eligible subjects will be given a washout dentifrice

and toothbrush to use in between Screening and Baseline Visits. They will also be issued with a study diary to record product usage.

Within 14±3 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] immediately before the visit).

At Baseline visit, the washout dentifrice and the diary will be reviewed to determine compliance. At the Baseline visit, subjects will also undergo, in the following order, a full OST examination, gingival inflammation (MGI), gingival bleeding (BI), supra-gingival plaque (TPI). Subjects with bleeding sites % (derived from BI assessment) or TPI score outside the inclusion criteria range will be discontinued from the study at this visit. 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. The subjects will then be instructed to brush for at least one (timed) minute at site with their assigned study product (supervised brushing) after which they will be instructed to continue using their product twice daily (morning and evening until their next visit), at least one (timed) minute /each time for the next 12 weeks.

After using the study dentifrice for 3, 6, and 12 weeks, subjects will return to the study site (Visits 3, 4, and 5, 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 dentifrice and the diary will be reviewed to determine treatment compliance. Subjects will have a full OST examination and then undergo, in the following order, MGI, BI, and TPI. At Visit 5, subjects will also have a full OHT examination, return all study supplies and will be offered a dental prophylaxis if deemed appropriate by the investigator or examiner.

At Visits 2, 3, 4, and 5, 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 BI assessment, it is not feasible to conduct an accurate repeatability assessment for this index.

Safety and oral tolerability of the study dentifrices will be monitored over the 12-week usage period by review of TEAEs. Medical device incidents will be recorded (the medical device in this study is the manual toothbrush used to apply the study toothpastes) throughout the study.

4.2 Scientific Rationale for Study Design

The goal of this study is to evaluate and compare the efficacy of an on-market dentifrice containing 0.454% w/w SnF₂ to a regular fluoride dentifrice on treating gingival bleeding and gingival inflammation as well as reducing plaque accumulation in a population with clinically measurable levels of gingivitis after 12 weeks use.

This study design follows the FDA guidelines for treatment of gingivitis, where subjects have measurable levels of gingivitis before treatment and do not receive professional dental prophylaxis prior to commencing product usage.

Study subjects with a pre-specified level of gingivitis are stratified according to their sex (male or female) and then randomized to the study product; efficacy is determined after a period of twice-daily brushing, compared to a control/comparator dentifrice.

A 12-week treatment duration has been selected in this study to enable sufficient time to observe product effect ([Parkinson et al., 2014](#); [Parkinson et al., 2018b](#); [Parkinson et al., 2020](#)). The earlier time points, 3 weeks and 6 weeks are considered to help obtain information on the progress of gingivitis resolutions.

Healthy subjects with clinically measurable levels of gingivitis (bleeding sites 10-30%) will be included in this study. The gingivitis status inclusion and exclusion criteria will follow the new classification (2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Condition ([Chapple et al., 2018](#)), and this will help to minimize the risk of an atypical or potential lack of treatment response for subjects with severe gingival health conditions that may otherwise be managed professionally rather than solely via home use of a twice-daily dentifrice. Dental plaque is a pre-requisite for plaque-induced gingivitis. Thus, eligible subjects will be required to have a qualifying minimum level of supra-gingival plaque (overall mean TPI ≥ 1.5) after approximately overnight abstinence from oral hygiene procedures to be randomized to treatment.

The MGI and the BI are established clinical measures of gingival inflammation and gingival bleeding, respectively (i.e., gingival health, [FDA., 2005](#)); the TPI is an established clinical measure of supra gingival plaque accumulation ([FDA., 2005](#)).

The same examiner will perform assessments for the duration of the study to eliminate the possibility of inter-examiner variability.

To assess examiner reproducibility across the treatment period, repeat MGI and TPI assessments will be performed on selected subjects throughout the study. Due to the invasive nature of the index, repeatability assessments are not feasible for the BI.

Based on widely recommended oral hygiene practices and typical consumer habits, all subjects will follow the same dosage regimen of twice-daily treatment (morning and evening). To facilitate compliance with product usage throughout the study and to enable staff to confirm correct dosing, a supervised brushing will be performed on-site at the end of Visits 2-4. Subjects will also be required to record each brushing in the diary provided, including the time of the last brushing before returning for the site assessment visits. During the washout period for this study (14 \pm 3 days), eligible subjects will use a marketed, regular fluoride dentifrice and toothbrush (as provided). Using these products before the Baseline visit will help familiarize subjects with the dosing/diary completion requirements. It will also serve as a 'washout' from any anti-plaque ingredients contained in the subject's own oral hygiene products.

A parallel group design has been selected as most appropriate for this investigation. Anticipated differential changes in clinical variables among treatment groups could lead to carryover effects and an altered oral health state, which makes a crossover design inappropriate for this study. The dosage regimen of twice daily use (morning and evening) will be the same for each treatment group.

Smokers will be excluded from this investigation because of the masking effect of smoking on gum bleeding. Based on the literature, smoking decreases the blood flow within the gingival microvasculature and interferes with neutrophil function, suppressing the inflammatory response to dental plaque and masking the clinical signs of periodontal disease ([Machuca et al., 2000](#); [Obeid and Bercy, 2000](#)).

Gender is a known modifier of the initiation and outcome of gingivitis. Qualified subjects will be stratified by gender to ensure female subjects are balanced between the treatment groups. Hormonal fluctuations through the female menstrual cycle ([Raber Durlacher et al 1994](#)) and hormonal changes during pregnancy may affect the response of the gingival tissue to plaque bacteria and could impact the gingivitis efficacy measurements ([Figuro et al., 2010](#)). Whilst the study products are not contraindicated for pregnancy and breastfeeding, pregnant and/or lactating females will be excluded from this study due to the increased prevalence and severity of gingivitis and periodontal disease observed during pregnancy ([Samant et al., 1976](#)) and breastfeeding ([Aghazadeh et al, 2019](#)) which, together with the increased amounts of calculus and plaque observed during pregnancy, may impact study outcomes.

According to the International Conference on Harmonisation (ICH) guidelines ([ICH, Nov 2016](#)), for a study to be classified as truly double-blind, not only does the examiner (and any appropriate member of staff who may be involved in the dispensing of products, analysis of data etc.) need to be blinded as to the treatment the subject receives, but the products under test must be identical in every way (color, flavor, appearance, packaging). Given it is almost impossible to ensure identical appearance, taste, and packaging for the dentifrices evaluated in this oral care study, the level of blindness for this study is described as “examiner blind.”

4.3 Justification for Dose

The study products are dentifrices, intended for topical oral use, and will be applied by toothbrushing using a manual toothbrush. The dosage regimen of twice daily treatment (morning and evening) will be the same for all subjects and is based on widely recommended oral hygiene practice and typical consumer habit. Study subjects will be instructed to brush for at least one (timed) minute with their assigned study dentifrice on each brushing occasion. After 12 weeks (84±4 days) twice daily treatment, each subject should complete approximately 168 treatment applications. Each subject will complete a supervised brushing with their assigned study dentifrice at the end of study visit 2, 3, and 4 (while still at the study site) to enable staff to check correct dosing and encourage compliance with product usage throughout the study.

4.4 End of Study Definition

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

The end of this study is defined as the date of the last visit of the last subject in the study.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Sufficient subjects will be screened to randomize approximately 160 subjects to ensure approximately 144 evaluable subjects (approximately 72 subjects/group) complete the entire study.

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

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is

considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this protocol.

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

5.2 Inclusion Criteria

Eligible subjects are expected to meet 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/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 BASELINE (Visit 2):

- d. A subject with ongoing hard tissue eligibility and, in the opinion of the clinical examiner, at least 40 evaluable surfaces.
- e. A subject with 10% - 30% bleeding sites (following BI)
- f. A subject with mean whole mouth TPI score ≥ 1.5 .

5.3 Exclusion Criteria

Subjects who meet any of the following exclusion criteria were not eligible for enrollment into the study:

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a sponsor's 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 is intending to become pregnant over the duration of the study.
6. A subject who is a breastfeeding female.
7. A subject who is known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
8. A subject who is unwilling or unable to comply with the lifestyle considerations
9. Subject who is a current smoker or an ex-smoker who stopped within 6 months of Screening.
10. 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 14 days 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, 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).

18. Medication exclusions

At Baseline (Visit 2):

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

19. Periodontal exclusions

- a. A subject who shows signs of active periodontitis (with probing pocket depths > 3 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.

5.4 Randomization Criteria

Subjects who satisfy the study selection criteria will be stratified according to their sex (male or female) and randomized to study treatment.

5.5 Lifestyle Considerations

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

5.5.1 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.

5.5.2 Alcohol, Caffeine and Chewing gum

- Subjects will not be permitted to use chewing gum from screening to the end of the study.

5.5.3 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, mouth rinses) other than those provided during the study.
- Subjects will not be permitted to use any dental floss, toothpicks, waterpicks, or inter-dental brushes (except for the removal of impacted food with non-antimicrobial 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.

5.5.4 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.

For more information on concomitant medications, please refer to [Section 6.8](#).

5.5.5 Contraception

There are no contraception requirements for subjects entered into this study. Females of child-bearing potential should verbally confirm they are not currently pregnant or planning to become pregnant.

5.5.6 COVID-19

In accordance with the clinical site procedures, and at the investigator's discretion, subjects will be required to sign the site's consent form for Covid-19. Subjects will need to pass the site's pre-appointment telephone screening and will perform re-assessment prior to or while attending each study visit.

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will 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.

5.7 Sponsor's Qualified Medical Personnel

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

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

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects will be provided with a copy of ICF which has contact number listed.

5.8 Clinical Assessor Qualifications

Clinical examiner(s) involved in the screening, safety and efficacy assessments will be appropriately qualified dental professionals, registered to practice in the US.

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

6 INVESTIGATIONAL/STUDY PRODUCTS

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

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

6.1 Investigational/Study Product Supplies

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

Table 6-1 Investigational/Study Product Supplies

	Test Product	Reference Product (negative control)
Product Name	parodontax Complete Protection (0.454% w/w SnF ₂)	Crest Cavity Protection (0.243% w/w sodium fluoride)
Pack Design	Carton of 6 over-wrapped tubes	Carton of 6 over-wrapped tubes
Dispensing Details	One carton – baseline visit	One carton – baseline visit
Product Master Formulation Code (MFC)	CCI [REDACTED] (Commercial Product)	Commercial Product
Dose/Application	Full ribbon of dentifrice on head of toothbrush provided	Full ribbon of dentifrice on head of toothbrush provided
Route of Administration	Oral	Oral
Usage Instructions	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

Table 6-2 Washout/Acclimatization Product Supplies

	Washout dentifrice
Product Name	Colgate Cavity Protection
Pack Design	One tube
Dispensing Details	One tube – screening visit
Product Master Formulation Code (MFC)	N/A - commercial product
Dose/Application	Apply a full ribbon of dentifrice 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 6-3 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 pack per subject	1 pack at screening. Subjects will use 1 brush during washout period Subjects will use the 2 nd brush during study period	Destroy at site using site disposal procedures	Return
Countdown Timer	Haleon	Individual commercial	Baseline visit	Subject to keep or	Return

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		pack – 1 per subject		destroyed at site using site disposal procedures	
Opaque Bags	Haleon	Commercial Pack	Screening Visit and baseline visit	Subject to keep or destroyed at site using site disposal procedure	Return

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

6.1.1 Medical Devices (if applicable – delete if not needed)

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

The definitions and procedures detailed are in accordance with ISO 14155:2020

6.1.2 Dosage Form and Packaging

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

The washout dentifrices will be supplied in their commercial tubes. The test and reference dentifrices will be supplied in their commercial tubes but over-wrapped in white opaque vinyl in order to mask their identity as much as possible. All investigational samples will have a study label affixed and will be provided in labelled product cartons containing sufficient samples for the duration of the use period. Washout samples will have a study label affixed to each tube.

The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the sponsor Clinical Supplies group. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

Sundry items will be supplied in their commercial packaging for dispensing by study staff as specified in [Table 6-3](#).

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

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

6.1.3 Preparation and Dispensing

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

Study product will be dispensed by qualified site personnel (unblinded) per the dosage/administration instructions. These staff members will not be involved in any safety,

efficacy assessments or other aspects of the study that could be influenced by the knowledge of product a subject has been assigned to use. An additional member of site staff should ensure the dispensing procedures are completed accurately.

The study dentifrice will be dispensed in a blinded fashion to the subject. The study site will be provided with opaque bags in which the study products and product usage instructions will be placed in the bag prior to the subject leaving the dispensing area. Subjects should be advised as to correct product usage in accordance with the Product Usage Instructions at visit 2, 3, and 4. All randomized subjects should receive standard oral care advice at Visit 2 ([section 8.2.1](#)).

6.2 Administration

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

After washout period, subjects will be instructed to self-administer their assigned product per the usage instructions provided to the subject. Subjects will receive a brushing instruction and study diary sheet. This will outline the brushing instructions and will be used to record the date and time of each brushing occasion during the treatment period. Subjects will also be asked to note any missed brushings, and to use the diary to record any changes in medications, or new medications, or to diet. To ensure that subjects understand the dose of dentifrice to be used, staff will demonstrate what is meant by a ‘full ribbon’ (i.e., covering the length of the toothbrush head) and provide detailed oral hygiene instruction during the supervised toothbrushing in agreement with the study schedule and product usage instructions.

6.2.1 Medication/Dosing Errors

Medication/dosing errors may result, in this study, from the administration or consumption of:

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

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

Medication/dosing errors are reportable irrespective of the presence of an associated AE, including:

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

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

6.2.2 Overdose

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

Overdose is not likely to occur in this study.

Limited quantities of the study product(s) will be supplied, and closely monitored by the site for each subject.

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

6.3 Investigational/Study Product Storage

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

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

The investigator, or designee, will ensure that all study products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and the product label.

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

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

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

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

6.4 Investigational/Study Product Accountability

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

All study products must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only the staff have access. Upon receipt, all study products should be stored according to the instructions specified on the product

labels. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff.

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

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

Subjects will return used and unused tubes of the washout dentifrice to the study site at their Baseline visit (Visit 2). Subjects will return used and unused tubes of their assigned study dentifrice to the study site at their last visits (for most subjects this will be Visit 5). Study product return will be documented using the investigational/study product accountability form/record.

6.4.1 Destruction of Investigational/Study Product Supplies

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

Return and destruction instructions for sundry items are provided in [Table 6-3](#).

6.5 Blinding and Allocation/Randomization

All subjects will be centrally randomized to one of the two study products using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided. Study products will be dispensed according to the instruction received through the IRT at the appropriate study visits.

Returned study products should not be re-dispensed to any subject.

This study is described as examiner-blind (the investigator, clinical examiner and monitor will be blinded to product received). Site staff, the study statistician, data management staff, other employees of the Sponsor and vendors acting on behalf of the sponsor, who may influence study outcomes will also be blinded to the product allocation. To ensure the clinical examiner remains blinded throughout the study:

- site staff involved in the dispensing of study product and the supervision of onsite product usage will work in a separate area;
- the examiner will not be permitted in any area where study product is stored, dispensed, or in use;
- study subjects will be instructed not to remove study product from the opaque bags provided outside of the dispensing room, while at the study site;
- dispensing staff and on-site brushing supervisors will not be involved in any safety/product performance assessments during the study.

6.6 Breaking the Blind

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

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

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

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

6.7 Compliance

Study products will be administered under the supervision of investigator site personnel.

A diary will be supplied to promote compliance and to capture details of product use throughout the study period. Subjects may also record additional information such as AEs or medications used. Any additional details relevant to efficacy or safety should be reviewed by the investigator (or suitably qualified designee) with the subjects and transcribed to the CRF as appropriate.

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

A record of the number of dentifrice tubes dispensed to and taken by each subject must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

Supervised brushings will be carried out at the study site in agreement with the Schedule of Activities, to facilitate subject compliance with dosing and brushing instructions.

6.8 Concomitant Medication/Treatment(s)

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

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

7 INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

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

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

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

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

7.2 Lost to Follow up

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

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

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

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

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

If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be

collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8 STUDY PROCEDURES

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

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

8.1 Visit 1/Screening

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

Subjects will be screened within 14±3 days prior to administration of the investigational/study product to confirm that they meet the subject selection criteria for the study.

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

1. Informed consent
2. Demographics, medical history (including smoking) and prior/concomitant medication/treatment
3. OST examination ([Section 9.3.1](#))
4. OHT examination ([Section 9.3.2](#))
5. Gross gingival assessment ([Section 9.1.1](#))
6. Pocket depth assessment ([section 9.1.2](#))
7. Review of inclusion/exclusion criteria
8. Subject eligibility
9. Dispense washout products/ dentifrice, toothbrush and diary (including instruction on diary completion). Remind subject to use 1 toothbrush during washout and bring both the used and new brushes at baseline visit.
10. Record Adverse events & Incidents ([Section 10](#))

8.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Two copies of the informed consent form (ICF) will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

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

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

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

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Each subject should be provided with a copy of the signed and dated amended consent form. The date of re-consent will be recorded on the CRF.

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

8.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, sex (male or female) and race. Ethnicity and race of subjects will be recorded in accordance with FDA Guidance for Industry: *Collection of Race and Ethnicity Data in Clinical Trials, 2005*.

8.1.3 Medical History and Prior Medication/Treatment

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

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days and prior to signing the informed consent form, will be documented in the eCRF.

8.1.4 Oral Examination/Assessment

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 as described ([Section 9.3.1](#))
- OHT examination as described in ([Section 9.3.2](#))
- Gross assessment of gingival health ([Section 9.1.2](#)).
- Pocket depth assessment ([section 9.1.2](#))

The oral examinations/assessments should be carried out as described in [Section 9](#). All findings will be recorded in the CRF.

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

8.1.5 Inclusion/Exclusion Criteria

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

8.1.6 Subject Eligibility

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

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

8.1.7 Dispense Washout Products

Eligible subjects will be provided with the washout dentifrice, toothbrushes and diary to use during the washout period (14±3 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.

8.2 Study Period

8.2.1 Baseline: Visit 2 (Day 0)

Subjects will visit the clinical study site 14 ±3 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/ compliance checks including diary review
2. Confirm that 2nd toothbrush has not been used
3. Review of concomitant medication or non-drug treatments/procedures, adverse events, incidents and lifestyle restrictions.
 - Concomitant medications/ treatments ([Section 6.8](#))
4. OST examination ([Section 9.3.1](#))
5. MGI assessment ([Section 9.2.1](#))
6. Gingival bleeding
 - BI assessment ([Section 9.2.2](#)) (including bleeding sites % which is derived from BI assessment)
7. Plaque disclosure ([Section 9.2.3](#))
8. TPI assessment ([Section 9.2.4](#))
9. Inclusion/exclusion criteria
10. Subject eligibility
11. MGI repeatability assessment (where applicable) ([Section 9.2.1](#))
12. TPI repeatability assessment (where applicable) ([Section 9.2.4](#))
13. Randomization
14. Dispense study dentifrice, study instructions & diary and timer
15. Oral hygiene instructions and/ including diary completion instructions
16. Supervised brushing at site using the 2nd toothbrush

17. Record Adverse events & Incidents ([Section 10](#))

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.

8.2.2 Visit 3 and 4 (Day 21 ±3 day and 42 ±4 day)

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

1. Collect study dentifrice, toothbrush & diary from subject
2. Review of concomitant medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions
 - Concomitant medications/ treatments ([Section 6.8](#))
3. Compliance checks including diary review
4. Subject continuance
5. OST examination ([Section 9.3.1](#))
6. MGI assessment (& repeatability assessment, where applicable) ([Section 9.2.1](#))
7. BI assessment ([Section 9.2.2](#))
8. Plaque disclosure ([Section 9.2.3](#))
9. TPI assessment (& repeatability assessment, where applicable) ([Section 9.2.4](#))
10. Return study dentifrice, toothbrush, study instructions and diary to subject
11. Oral hygiene instruction review / compliance checks including diary completion review with subject
12. Supervised brushing at site
13. Record Adverse events & Incidents ([Section 10](#))

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.

8.2.3 Visit 5 (Day 84 ±4 day)

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

1. Collect study dentifrice, toothbrush, diary & timer (all study supplies) from subject
2. Review of concomitant medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions
 - Concomitant medications / treatments ([Section 6.8](#))

3. Compliance checks including diary review
4. Subject continuance
5. OST examination ([Section 9.3.1](#))
6. OHT examination ([Section 9.3.2](#))
7. MGI assessment (& repeatability assessment, where applicable) ([Section 9.2.1](#))
8. BI assessment ([Section 9.2.2](#))
9. Plaque disclosure ([Section 9.2.3](#))
10. TPI assessment (& repeatability assessment, where applicable) ([Section 9.2.4](#))
11. Complete optional dental prophylaxis (as/ if deemed necessary by examiner)
12. Record Adverse events & Incidents ([Section 10](#))
13. Study conclusion ([Section 8.4](#))

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.

8.3 Diary Review

The diary should be reviewed at every visit by the investigator, or suitably qualified designee, and the subject. Any subject comment captured in the diary which is considered an adverse event will be assessed and reported as per the defined procedure in this protocol. Adverse event reporting procedures are summarized in [Adverse Event and Serious Adverse Events](#).

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

Additional and missed product applications will be considered deviations from the protocol and will be recorded on the Deviations Log.

8.4 Study Conclusion

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

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

8.5 Follow-up Visit/Phone Call

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

9 STUDY ASSESSMENTS

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

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the [Study Procedures](#) section of this protocol. A single examiner will be responsible for the conduct of the clinical measures of gingivitis/ plaque accumulation for the duration of the study.

Eligible tooth assessments will be accomplished by oral examination and will evaluate dentition exclusions along with a gross gingival assessment in relation to the general dentition inclusion/exclusion criteria.

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

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

9.1.1 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).

9.1.2 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.

9.2 Efficacy Assessments

The following 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.

The same examiner will be used throughout the study for each clinical index to eliminate the possibility of inter-examiner variability.

At Baseline visit, subjects with bleeding sites % (derived from BI assessment) or TPI score outside the inclusion criteria range will be discontinued from the study.

9.2.1 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 facial and lingual surfaces of each scorable tooth (second permanent molar to second permanent molar in each arch) by an appropriately qualified examiner. Two scores will be recorded buccally/labially (papilla and margin) and two 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 9-1 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.

9.2.2 BI Assessment ([Saxton and van der Ouderaa, 1989](#))

The BI assesses the number of bleeding points elicited on probing as a measure of gingival condition. The gingivae will be air dried and then the examiner will use PCP11.5B Hu-Friedy Qulix Color Coded probe to assess bleeding. The probe will be gently inserted into the gingival crevice to a depth of approximately 1 millimeter (mm) and then run around the tooth (at angle of ~ 60° to the long axis of the tooth), gently stretching the epithelium while sweeping from interproximal to interproximal along the sulcular epithelium. Minimum force should be used to avoid damage to the gingival tissue. The BI will be assessed on the facial and lingual gingival surfaces of each scorable tooth (second molar to second molar). Three scores (according to the scale below) should be recorded buccally/labially (distal, body, mesial sites) and three scores lingually/palatally. All scorable teeth in one quadrant should be probed first (approximately 30 seconds) before recording the number of gingival units which bleed.

The BI scoring system will be as follows:

Table 9-2 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 BI 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 BI.

9.2.3 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 rediscovered between the TPI and repeat assessments at the discretion of the clinical examiner.

9.2.4 TPI Assessment ([Lobene et al, 1982](#))

The Turesky Modification of the Quigley Hein Plaque Index ([Lobene et al, 1982](#)) 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 9-3 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 \geq 1/3 but < 2/3 of the tooth surface
5	Plaque covering \geq 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.

9.2.5 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 - 5. 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.

9.3 Safety and Other Assessments

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

9.3.1 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.

9.3.2 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.

9.3.3 Pregnancy Testing

For this study, the individual 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 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.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

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

10.1 Definition of an Adverse Event (AE)

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

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

Events Meeting the AE Definition:

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

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medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE if they fulfill the definition of an AE.

Events NOT meeting the AE definition:

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

10.2 Definition of a Serious Adverse Event (SAE)

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

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

- **Results in death**
- **Is life-threatening**
 - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
 - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for

observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

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

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

10.3 Time Period and Frequency for Collecting AE and SAE Information

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

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

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

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

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be

reasonably related to the study product or study participation, the investigator must promptly notify the sponsor.

10.4 Reporting Procedures

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

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

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

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

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

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

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

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

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

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

10.4.1 Reporting of an Adverse Event

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

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE CRF page, an SAE form should be completed, as fully as possible. Hard copies of the 'paper' SAE form will be provided in the investigator study master file. Original SAE forms will be retained in the investigator study master file. PI will be responsible for notifying the IRB/IEC of SAEs that occur during the study.

It is essential to enter the following information:

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

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

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

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

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

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

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.5.2 Assessment of Causality

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

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

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

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

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

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

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

10.6 Follow-up of AEs and SAEs

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

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

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by Haleon to elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory

tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

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

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

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

10.7 Withdrawal Due to an Adverse Event

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

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

10.8 Regulatory Reporting Requirements for SAEs

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

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

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

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

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

10.9 Pregnancy

10.9.1 Time Period for Collecting Pregnancy Information

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

10.9.2 Action to be Taken if Pregnancy Occurs

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

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

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

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

10.10 Medical Device Incidents

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

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

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

10.10.1 Definition of an Incident

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

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

It is sufficient that:

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

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

- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents:

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

10.11 Reporting of Incidents and Malfunctions

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

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

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

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

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

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

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

10.12 Follow-up of Medical Device Incidents

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

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

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

10.13 Regulatory Reporting Requirements for Medical Device Incidents

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

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

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

11 DATA MANAGEMENT

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

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

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

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

11.1 Case Report Form

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

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

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

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

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

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

11.2 Data Handling

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

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

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, WHO Drug.

11.2.1 Data Queries

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

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

The primary endpoint for this study is “Change from Baseline in NBS at Week 12 for the test product (containing 0.454% w/w SnF₂)”. There were no previous similar studies where the same active ingredient in the test product was used without pre-prophylaxis. Thus, due to the uncertainty of what would be expected in terms of change from baseline for the test product given the aforementioned parameters, treatment efficacy estimates for the key secondary objective (test dentifrice compared to the reference dentifrice) were used instead. Two sponsor clinical studies that included pre- prophylaxis ([Parkinson et al. 2014](#) and [Haleon Study 212537](#)) were used as reference to estimate efficacy of test dentifrice (0.45% w/w SnF₂) compared to reference dentifrice (negative control). In these two studies, the mean difference (SD) between the test and reference product reported a mean difference in BI of 0.07 between groups with standard deviation ranging from 0.04 to 0.128 at 12 weeks. Due to the uncertainty of what would be expected in terms of the range of mean differences when subjects do not undergo a pre-prophylaxis, a higher SD of 0.128 was used to calculate the sample size for this study.

The percent differences from control in the reference studies remained consistent (~ 40% - 60% in favor of the test dentifrice) in the studies mentioned above, thus an assumption was made that these numbers would not fall far from that range in this study.

Based on the assumptions outlined above, a sample size of approximately 160 subjects (approximately 80 per group) will be randomized to ensure approximately 144 evaluable subjects (approximately 72 per group) complete the study (assuming a 10% dropout rate); this will provide sufficient power (90%) to achieve statistical significance (at the 5%, two-sided level) for the key secondary outcome.

12.2 Populations for Analysis

- The Safety population will comprise all randomized subjects who receive at least one dose of the study product. This population will be based on the product the subject actually received.
- The modified Intent-To-Treat (mITT) population will include all randomized subjects who complete at least one use of study product and have at least one post baseline clinical performance assessment. This population will be based on the study product to which the subject was randomized. Any subject who receives a randomization number will be considered to have been randomized.
- The Per-Protocol (PP) population will include all randomized subjects who do not have any 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.

12.3 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical reporting and analysis plan (SAP), which will be written following finalization of the protocol and prior to study unblinding/analysis (as appropriate). This section is a summary of the planned

statistical analyses of the most important endpoints including primary and key secondary endpoints.

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

Statistical analyses of the endpoints will be performed using the change from baseline, in order to present direct estimates for the within-treatment mean changes from baseline (e.g., the primary endpoint). Descriptive summary statistics will be presented for the actual and change from baseline values at each time point.

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 multiplicity for the comparison between test and reference products in the number of bleeding sites at week 12. This will only be assessed for confirmatory evidence if the primary endpoint (change from baseline within the test product at week 12) achieves a statistically significance reduction. There will be no further adjustments for multiplicity for any other secondary endpoints.

12.3.1 Primary Analysis(es)

A mixed model with repeated measures (MMRM) will be performed on the change from baseline with product (test or reference), time point and product by time point interaction as fixed effects, and baseline NBS as a covariate. Subject will be fitted as a repeated measure with unstructured covariance. Kenward-Roger degrees of freedom will be used.

For the primary objective, to test the null hypothesis (H_0 : There is no Mean Change from Baseline for the test dentifrice ($\Delta=0$)) vs. the alternative hypothesis (H_1 : There is Mean Change from baseline for the test Dentifrice ($\Delta \neq 0$)), the results from the MMRM model at Week 12 for the test product group will be used. P-values and 95% confidence intervals (CI) will be provided.

12.3.2 Secondary Analysis(es)

The key secondary objective is to evaluate the efficacy of a dentifrice containing 0.454% w/w SnF₂, compared to negative control, as measured by NBS, after 12 weeks twice daily toothbrushing. The key secondary endpoint is the NBS at 12 weeks and will be analyzed using the same MMRM from the primary analysis.

Other secondary timepoints (week 3 and 6) for NBS will be analyzed using the same MMRM from the primary analysis. Estimates of treatment effect (changes from baseline at 3, 6 and 12 weeks) and treatment comparisons will be based on least squares means (LS means) generated by appropriate contrast statements. P-values and 95% confidence intervals (CI) will be provided.

In addition to NBS, other secondary endpoints include change from baseline assessments after 3, 6, and 12 weeks for BI, MGI, and TPI.

For the change from baseline for each endpoint above, the same MMRM as applied for the NBS (in primary objective) will also be applied but including the respective baseline as covariate instead of the baseline NBS. Results within and between treatments at each time point will also be obtained and presented in the same manner.

12.3.3 Exploratory Analysis(es)

Results between treatments (mean difference from baseline for treatment vs mean difference from baseline for reference) at each time point will also be obtained and presented in a similar manner as in the primary objective in the low and high baseline MGI subgroups:

- Low: $MGI \leq 2$
- High: $MGI > 2$

Estimates of treatment comparisons will be based on least squares means (LS means) generated by appropriate contrast statements. P-values and 95% confidence intervals (CI) will be provided.

12.3.4 Safety Analysis(es)

The Safety population will be used for safety analyses. Safety analyses will be performed according to product received. All AEs will be reviewed by the Clinical Research Scientist, or designee, prior to database lock and unblinding and will be coded using the MedDRA. During this review stage, AEs will be further categorized as oral or non-oral. AEs will be listed and summarized by product received. SAEs will also be listed. AEs will be regarded as ‘treatment’ emergent if they occur on or after the first product use at the Baseline visit.

The following AEs tables will be produced, presented by product group:

- listing of all AEs (randomized subjects and non-randomized subjects);
- summary of AEs;
- treatment emergent AEs by Oral/Non-Oral and Preferred Term (PT);
- treatment emergent AEs by System Organ Class (SOC) and PT;
- treatment related AEs by Oral/Non-Oral and PT;
- listing of serious AEs (if there are no SAEs, a null listing will be produced; if there are more than 5 treatment emergent serious AEs (SAEs), a table will be produced in place of the listing by SOC and PT);
- non-serious treatment emergent AEs by SOC and PT (only produced if there are more than 5 AEs).

The results of the OST and OHT examinations will be listed and the results of the OST examinations will be tabulated.

12.3.5 Other Analysis(es)

For descriptive purposes only, the percent change from baseline at weeks 3, 6 and 12, in each arm separately, will be calculated and reported for each primary and secondary outcome variable. Additionally, the number and percent of patients improving, remaining the same, or worsening (compared to baseline) at weeks 3, 6 and 12, in each arm separately, will be calculated and reported for each primary and secondary outcome variable. These analyses will only use the observed data and not the LOCF imputed data.

Repeatability of the examiner

The repeatability of the examiner in conducting the MGI and TPI assessments will also be performed. The repeat plaque and MGI assessments will be compared to the original assessments. The repeat assessment is not to be used in any efficacy analysis. The first

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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).

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 the analysis of only complete cases using ANCOVA are biased ([Baron et al, 2008](#); [Ashbeck et al, 2016](#)). 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 visit would have obtained a similar efficacy result at that visit compared to a subject using the same study product with similar non-missing results at other timepoints (Baseline and the other post-Baseline visit). Sensitivity analyses will present results from the separate ANCOVA models using only non-missing values at each single time point. Additional sensitivity analyses may be added to the SAP prior to unblinding in case of high drop-out rates and/or exclusion from PP population.

Exclusion of Data from Analysis

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

12.3.6 Demographic and Baseline Characteristics

Age and other continuous variables will be summarized using descriptive statistics including mean, standard deviation, median, minimum, and maximum. Gender, race and other categorical variables will be summarized using frequency counts and percentages for the safety and mITT populations. Medical history and current medical conditions will be listed.

12.3.7 Study Drug/Product Compliance

Number of brushings, brushing compliance (%), number of missed brushings, number of additional brushings over 12 weeks will be summarized using descriptive statistics.

Number of brushings is defined as: [(date of Visit 5 – date of Visit 2) multiplied by 2 – number of missing brushings + number of additional brushings].

Brushing compliance (%) is defined as: [100 x (Number of brushings / Expected number of brushings)], where expected number of brushings is defined as: [(date of Visit 5 – date of Visit 2) multiplied by 2].

12.3.7.1 Prior and Concomitant Medications

Prior and Concomitant Medications will be listed only.

12.3.8 Handling of Dropouts and Missing Data

Subjects who withdraw from the study early will be included in the statistical analysis up to the point of withdrawal. Subjects who withdraw will not be replaced. For the primary analyses, no data will be imputed in the case of dropouts or missing data. However, sensitivity analyses using LOCF are planned as detailed in section 12.3.5.

12.3.9 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

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

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

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

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

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

13.2 Quality Assurance

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

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

The investigator(s) will notify Haleon or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Haleon or its agents to prepare the study site for the inspection and will allow Haleon or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply

copies of the inspection finding to Haleon or its agent. Before response submission to the regulatory authority, the investigator will provide Haleon or its agents with an opportunity to review and comment on responses to any such findings.

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

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

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

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (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, applicable portion of EU MDR 2017/745, ISO 14155:2011 and ISO 14155:2020, and applicable local regulatory requirements and laws.

13.3.3 Subject Information and Consent

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

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

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

The informed consent documents must be in compliance with ICH GCP, applicable portion of ISO 14155, local regulatory requirements, and legal requirements, including applicable privacy laws.

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

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

13.3.4 Subject Recruitment

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

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

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

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

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

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

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

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

13.5 Provision of Study Results to Investigators

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

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

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

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

13.6 Records Retention

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

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

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

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

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

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

No study document should be destroyed without a prior written agreement between Haleon and the investigator. The investigator must 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.

13.7 Conditions for Terminating the Study

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

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

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investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

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

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

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15 APPENDICIES

15.1 ABBREVIATIONS

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

Table 15-1 Abbreviations

Abbreviation	Term
AE	Adverse event
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
EC	ethics committee

Abbreviation	Term
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
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
NBS	number of bleeding sites
No.	Number
OH	Oral health
OHT	Oral hard tissue
OST	Oral soft tissue
PI	Principal investigator
PI	Personal information
PP	Per protocol
PRO	Patient reported outcome
RAP	Reporting and analysis plan
REC	Research ethics committee

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Abbreviation	Term
SAE	serious adverse event
SD	Standard deviation
SE	Standard error
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

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