CLINICAL RESEARCH STUDY PROTOCOL

CLINICAL EFFICACY EVALUATION OF THREE DENTIFRICES CONTAINING 35%, 20% AND 0% SODIUM BICARBONATE ON THE REDUCTION OF PLAQUE AND GINGIVITIS

NCT03988374

Church and Dwight
469 N Harrison St,
Princeton, NJ 08540

Sponsor Study Reference Number: ST-7700

Study Site: All Sum Research Center Ltd. [redacted]

Protocol approval date – January 30, 2018

I. PROTOCOL APPROVAL SIGNATURES

The signatures of the Investigator, Examiner, and representative of the Sponsor below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations, clinically and administratively, as detailed in the protocol, including all statements as to confidentiality. It is agreed that the conduct and results of this study will be kept confidential and that the case report forms and other pertinent data will become the property of Church & Dwight Co., Inc.

It is agreed that the protocol contains all necessary information required to conduct the study as outlined in the protocol, and that the study will not be initiated without the approval of the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

It is agreed that all participants in this study will provide written informed consent in accordance with the requirements specified in the U.S. Code of Federal Regulations (21 CFR Parts 50, 56, 312, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and Health Canada regulations. All participants will also be informed that their medical records will be kept confidential by the study site and Sponsor, except for review by representatives of the IRB/IEC, the U.S. Food and Drug Administration, and Health Canada.

Study Site:

CONFIDENTIAL_____

[redacted] Date

[redacted]

All Sum Research Center Ltd.

CONFIDENTIAL_____

[redacted] Date

[redacted]

All Sum Research Center Ltd.

Sponsor: **CONFIDENTIAL**_____

[redacted] Date

[redacted]

Church & Dwight Co., Inc.

II. INTRODUCTION

It is well known that the removal and prevention of bacterial plaque by good oral hygiene is necessary to achieve and maintain oral health. Several studies have shown the role of plaque in the etiology of gingivitis[1-4]. Clinical studies have also shown that effective control of supragingival plaque is important in the prevention of periodontal disease[5].

A series of clinical studies have evaluated the use of [redacted] baking soda dentifrices for their effect on plaque removal. These studies, which include five single-brushing studies[6] and a 4-week plaque removal study[7], have shown the plaque removal benefits of baking soda-containing dentifrices. Brushing with [redacted] toothpaste, containing 20% sodium bicarbonate, was consistently shown to be more effective in enhancing plaque removal as compared to various non-baking soda toothpastes. Therefore [redacted] is interested in exploring the long-term efficacy of brushing with [redacted] toothpaste in subjects with existing plaque and gingivitis.

A double-blind, randomized, 12-week, observational clinical study evaluated and compared the efficacy of two commercially available dentifrices, a baking soda containing dentifrice ([redacted], containing 20% sodium bicarbonate) and a regular non-baking soda dentifrice ([redacted] Regular Paste – negative control), for their ability to reduce gingivitis and enhance supragingival plaque removal. Results showed that [redacted] was significantly ($p<0.001$) more effective in reducing gingivitis, bleeding and plaque than [redacted] Toothpaste following 4-, 8- and 12-weeks of product use.

Based on the results of the 12-week pilot study, this 6-month definitive clinical study will evaluate and compare the efficacy of two [redacted] baking soda-containing dentifrices, containing 20% & 35% baking soda, to a non-baking soda dentifrice for their ability to reduce gingivitis and plaque following 6-months of use.

STUDY OBJECTIVES

The objectives of this 6-month clinical research study are:

1) Primary objective is to evaluate the safety and efficacy of two baking soda dentifrices, containing 20% and 35% baking soda, (test products) compared to that of a non-baking soda dentifrice (negative control) in reducing gingival inflammation and bleeding.

2) Secondary objective is to evaluate the efficacy of two baking soda dentifrices compared to that of a non-baking soda dentifrice in reducing plaque.

III. INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

Approval from an Institutional Review Board/Independent Ethics Committee is required prior to initiation of the study. A copy of the approval letter and approved documents will be provided to the Sponsor. The IRB/IEC will review the protocol, the informed consent, safety information, subject instructions, compliance diary, subject compensation and any amendments.

The investigator shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate in the study prior to obtaining IRB/IEC approval of the study.

All protocol amendments need IRB approval prior to implementation and will not be instituted until the amendment and revised informed consent (if applicable) have been reviewed and received approval/favorable opinion from the local IRB/IEC. A protocol amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately if the IRB/IEC are notified as soon as possible and an approval is requested. Protocol amendments exclusively for logistical or administrative changes may be implemented with notification to the IRB/IEC only.

The constitution of the IRB/IEC must meet the requirements of ICH GCP and of the participating country/countries. A list of IRB/IEC members who attended the meeting when the CTP/CTP amendment was discussed, including the names and qualifications, needs to be provided by the IRB/IEC to the investigator along with a statement from the

IRB/IEC that it is organized per GCP and the applicable laws and regulations. The IRB/IEC must perform all duties outlined by the requirements of ICH GCP and of the participating country/countries.

At the conclusion of the study, the Investigator must submit a study closeout form to the IRB/IEC with a copy forwarded to the Sponsor no later than 60 days after the close of the study. In addition, the response from the IRB/IEC, regarding study closeout will be forwarded to the Sponsor.

IV. SUBJECT INFORMATION AND CONSENT

The clinical investigation, including the consent form, will be reviewed by an IRB/IEC in accordance with Title 21 of the Code of Federal Regulations, Parts 50 and 56 and in accordance with local regulatory and legal requirements of Health Canada. Subjects must sign and date an Informed Consent consistent with requirements specified in the U.S. Code of Federal Regulations (21 CFR Parts 50, 56, 312, the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) guidelines and any local regulatory and legal requirements of Health Canada prior to participation in the trial. Subjects will be given ample opportunity to read the consent form and to have all questions regarding study conduct answered prior to signing and dating the consent form. Each subject will be provided with an exact copy of the informed consent form to retain for his or her records.

Informed consent means the knowing consent of an individual, to exercise free power of choice without undue inducement or constraint or coercion. The elements of information necessary for such consent include: a statement that the study involves research; an explanation of the procedures to be followed and their purpose; identification of any procedures that are experimental; any expected discomforts, risks or benefits; approximate number of subjects involved in the study; any appropriate alternative procedures or treatments; description of the confidentiality of subject records; name and phone number of the individual to contact with inquiries concerning the research; explanation of compensation or free medical treatment available for research-related injury; statement that the subject is free to withdraw consent and to discontinue participation at any time; statement that participation is voluntary; indication of any additional costs to the subject; assurance that the subject will be notified of new findings relevant to the subject's participation; statement that it is within the Investigator's discretion to drop the subject from participation at any time.

In addition, the informed consent should include no exculpatory language by which the subject is made to waive, or appear to waive, any of his/her legal rights or to release the institution from liability or negligence.

V. SUBJECT POPULATION

Number of Subjects

Approximately 320 subjects will be enrolled to ensure that 100 subjects per group (300 total) will be expected to complete the 6-month study. Subjects will be selected from the study site's database of subjects located in the Mississauga, Ontario area. Volunteers must read and sign the Informed Consent Form after the nature of the study has been fully explained.

Inclusion Criteria

Individuals may be included in the study provided they meet all the following inclusion criteria:

- Have provided written informed consent prior to being entered into the study.
- Be between 18 and 70 years of age, male or female.
- Have at least eighteen (18) natural teeth with scorable facial and lingual surfaces as determined by the Examiner. Teeth that are grossly carious, orthodontically banded, exhibiting general cervical abrasion and/or enamel abrasion, or third molars will not be included in the tooth count.
- Have a mean baseline plaque index score ≥ 1.95 as determined by the Soparkar Modification[10] of the Turesky Modification[11] of the Quigley-Hein[12] Plaque Index (PI).
- Have a mean baseline gingival index score of ≥ 1.70 and ≤ 3.0 as determined by the Modified Gingival Index[8] (MGI).
- Presence of ≥ 10 bleeding sites upon probing.
- Agree not to have a dental prophylaxis or any other elective, non-emergency dental procedures any time during the study.

- Agree to abstain from the use of chewing gum, mouth rinses, any toothpaste other than the study toothpaste, tooth whitening products (either professional or at home use) and all other oral hygiene other than the study procedures for the duration of the study.
- Agree to refrain from all oral hygiene on the morning of each evaluation visit and to refrain from eating, drinking and smoking for 4 hrs. prior to each evaluation visit.
- Agree to comply with the conditions and schedule of the study.

Exclusion Criteria

Individuals are not eligible for participation in this study if any of the following are noted:

- Physical limitations or restrictions that might preclude normal tooth brushing.
- Evidence of gross oral pathology, including widespread caries or chronic neglect, extensive restoration, pre-existing gross plaque or soft or hard tissue tumor of the oral cavity.
- Heavy supra- or subgingival calculus that might interfere with evaluations as determined by the Investigator/Examiner.
- Evidence of major oral hard or soft tissue lesions or trauma at the baseline visit as determined by the Investigator/Examiner.
- Conditions requiring antibiotic treatment prior to dental procedures.
- History of uncontrolled diabetes or hepatic or renal disease, or other serious conditions or transmittable diseases, (e.g. cardiovascular disease, AIDS).
- Subjects with grossly carious, fully crowned, or extensively restored teeth, orthodontic appliances, peri/oral piercings, or removable partial dentures.
- Treatment with antibiotics within the 1-month period before the baseline examination, or a condition that is likely to require antibiotic treatment over the course of the trial.
- Chronic treatment (2 weeks or more) with any medication known to affect periodontal status (including phenytoin, calcium antagonists, cyclosporine, coumarin, nonsteroidal anti-inflammatory drugs, and aspirin) within 1 month of the baseline examination. All other medications for chronic medical conditions must have been initiated at least 3 months before enrollment.
- Have severe periodontal disease or being actively treated for periodontal disease.
- Having history of early-onset periodontitis or acute necrotizing ulcerative gingivitis.
- Concomitant periodontal therapy other than prophylaxis in the last 6 months.
- Professional prophylaxis within 1 month prior to the baseline clinical evaluation.
- Subjects who participated in a gingivitis study in the past month.
- Daily use of chemotherapeutic antiplaque/antigingivitis products such as [redacted] within the past 4 months.
- History of significant adverse effects following use of oral hygiene products such as toothpastes and mouthrinses.
- Subjects who are allergic to any ingredients in the test or control product, as listed on the IRB Safety Assessment.
- Self-reported pregnancy and nursing since hormonal changes can exaggerate gingival response to dental plaque.

VI. STUDY DESIGN

This parallel group, double-blind, randomized, single center, IRB/IEC-approved study will enroll approximately 320 subjects to ensure that approximately 100 subjects per group (300 subjects total) will complete the 6-month study. The Study Examiner will screen for subjects that meet the enrollment criteria. Subject group stratification will be based on smoking and tobacco use. Subjects will be randomly assigned to one of three dentifrice treatment groups. Oral soft and hard tissue examinations, gingivitis, bleeding and plaque assessments will be done at baseline and after 6 weeks and 3- and 6-months. Following an initial supervised tooth brushing, subjects will brush unsupervised with their assigned toothpaste at home for the 6-month treatment phase of the study, 2 times daily for 1 minute per brushing. Subjects will be provided with a timer and will maintain a daily diary of their brushing and record any oral effects they experience. Compliance will be assessed by subject diary and weight-loss of returned test products at each visit. The examiner will be blinded to the product codes/identification and product assignments.

Study Schedule:

Events	Screening Baseline	2-weeks*	6-weeks	3-months	18-weeks**	6-Months
Informed Consent, Demographics, Inclusion/Exclusion Criteria, Medical History, Conmeds	X					
Demographics/Product Use Questionnaire	X					
Dentifrice Distribution	X		X	X	X	
Diary Disbursement/Review	X		X	X	X	X
Update of Inclusion/Exclusion Criteria, Medical History and Conmeds			X	X	X	X
Oral Soft/Hard Tissue Exam	X		X	X		X
Gingival Exam (MGI)	X		X	X		X
Bleeding Exam (GBI)	X		X	X		X
Plaque Exam (PI)	X		X	X		X
Subjective Sensory Evaluation	X		X	X	X	X
Supervised Brushing	X					
Compliance Check		X	X	X	X	X
Product assessment Questionnaire						X
Adverse Events			X	X	X	X
Product Weights	X		X	X	X	X

* At 2-weeks, subjects will receive a post-baseline compliance call to reinforce product use instructions and study instructions.

** The 18-week visit will include only: Diary review, product weights, product distribution, sensory evaluation, adverse events, update of inclusion/exclusion and any medical changes.

VII. SUBJECT ASSIGNMENT TO TREATMENT GROUPS

At the baseline visit, following the clinical assessments, the study population will be evenly distributed into three treatment groups of approximately equal size and equivalence. Qualified subjects will be randomly assigned to the three treatment groups based on a randomization scheme developed using the baseline plaque and gingival assessment scores and age for stratification. The study staff responsible for random assignments will be blinded to the product treatments. Allowance will be made for members of the same household co-habiting at one address to receive the same products to prevent inadvertent switch-over.

VIII. TEST PRODUCTS AND CLINICAL SUPPLIES

Test Products

Two baking soda-containing dentifrices:

1. [redacted] containing 20% baking soda ([redacted])
2. [redacted] dentifrice with 35% baking soda minus amorphous calcium phosphate (ACP)

Negative Control

[redacted] with 0% baking soda

Clinical Supplies The sponsor will provide the following items to the study site:

- 3916-23A - Toothpaste
- 3916-23B - Toothpaste
- 3916-23C - Toothpaste

[redacted] Toothbrushes – 2 per subject to be dispensed at the baseline and 3 month visits.

Packaging and Labeling

The dentifrice products will be provided in white labeled 6.0 oz. tubes to protect the blind. The assigned dentifrice product, along with a toothbrush, timer, subject diaries and instructions will be distributed to subjects in a white bag (provided by All Sum Research) to protect the blinding of the examiner/study personnel and subjects.

The dentifrice front- and back-panel labels will include the following information:

Front Panel Label	Back Panel Label
Subject #: _____ Tube #: _____ Product Code: XXXX-XX Gimgivitis Study#: ST-7700 Anti-Cavity Toothpaste Not For Sale Study Participant Use Only Investigational natural health product to be used only by a qualified investigator for the purpose of this Clinical Study. MFG Date: XXXX Lot# XXXXXX Exp. Date: 01/2019 Net contents: 6.0 oz	Product contains: 0.24% Sodium Fluoride (inactives will be listed for each test article) **Warnings: Keep out of reach of children.** If more than used for brushing is accidently swallowed, get medical help or contact a Poison Control Center right away. **Directions:** Do not swallow. See enclosed instruction sheet. Store at room temperature. **Dist. By:** All Sum Research Center Ltd [redacted] Questions / Problems [redacted] (Days) Evening emergencies please call [redacted] **Manufactured by :** [redacted]

Study Supplies Accountability

Delivery and Inventory: Immediately upon receipt of study supplies at the clinical site, study personnel will account for all products and return the designated copy of "Test Supply Delivery Form" to the Sponsor acknowledging receipt of the test materials. The Investigator shall assure that appropriate records are maintained of: number of study products received, distribution to study participants, or other disposition, including dates, type of test articles, and product code numbers. The Investigator must account for any significant discrepancy and/or deficiency.

Any interim shipments will be inventoried by the Investigator or his / her designee. For all interim shipments, Test Supply Delivery Forms will be completed. The original will be returned to the Sponsor and the Investigator will retain a copy.

Storage: Study supplies will be maintained under secure, dry, room temperature conditions, until assignment to subjects.

Return of Study Supplies: At the conclusion of the study, All Sum Research will collect and inventory all dispensed products and complete the "Test Supply Delivery and Return Form" for returned study products. All used and unused products will then be returned to the Sponsor Clinical Study Coordinator listed on the study protocol at the following address: [redacted].

IX. TREATMENT REGIMEN

Qualified subjects meeting all inclusion and exclusion criteria will be provided with their assigned dentifrice, a manual toothbrush, a timer, a subject diary, and a subject instruction sheet at baseline. Subjects will be instructed to apply a full-brush length of the toothpaste and to brush in their usual manner for 1 minute (using the timer provided by the study site), 2 times daily (morning and evening), using only the assigned dentifrice and the toothbrush provided for the 6-month duration of the study. Subjects will be instructed on the use of the timer and must

demonstrate understanding of use while at the study site. After tooth brushing, subjects may rinse their mouth with tap water if they normally do so. The first 1 minute brushing at the baseline visit will be supervised at the study site to ensure that the subject understands the instructions. All subsequent brushings will be at home and unsupervised.

PRODUCT USE COMPLIANCE

To ensure compliance with product use, each subject will complete a daily diary indicating the time of each tooth brushing for the 6-month duration of the study. The diary will also provide space for voluntary comments about the products and any effects the subject experiences.

The subjects will be requested to return their dentifrice, toothbrush, timer and diary at each exam visit for a compliance check. The dentifrice products will be weighed at initial dispensation and at all subsequent visits to assess product use and subject compliance with study requirements. Based on product weights, subjects who appear to be out of compliance will again be shown how to apply a full ribbon of product to their toothbrush and will be reminded to brush two times daily. To maintain blinding, each subject's dentifrice tube will be inspected to confirm that the over-label has not been removed. The subjects will also be questioned at each site visit to confirm they have not removed the label and identified the product being used.

Following 2-weeks of product use, subjects will be contacted by phone to remind them of the product use instructions and study instructions.

X. STUDY PROCEDURE

Screening/Baseline Visit

Male and female subjects selected from the study site's database and prescreened potential subjects will report to the study site where they will read and sign the informed consent prior to enrollment. Subjects will be asked about demographics, medical history, general health status and current medication usage, and the information will be recorded. Prior to exam visit, subjects will refrain from oral hygiene the morning of their visit and will refrain from eating, drinking and smoking for approximately 4 hours prior to their visit.

The subjects will provide a sensory evaluation for safety purposes and they will fill out a product use questionnaire. They will be asked if they are currently experiencing any problems such as burning, stinging, irritation, etc., and if so, the nature of the effect, severity and onset time (if known) will be recorded on the CRF.

A qualified dental examiner will first perform an oral soft and hard tissue examination (OST), followed by a gingival assessment (Lobene Modified Gingival Index[8] (MGI)), gingival bleeding assessment (Gingival Bleeding Index[9] (GBI)) and plaque assessment (Soparkar Modification[10] of the Turesky Modification[11] of Quigley-Hein Plaque Index[12] (PI)).

Next, qualified subjects will be given one tube of their randomly assigned dentifrice (baseline weight recorded), a toothbrush, timer, Subject Diary, and a Subject Instruction Sheet. They will be instructed to apply a ribbon of dentifrice along the entire length of the toothbrush bristles, and to brush 2 times daily (morning and evening) for 1 minute per brushing. Subjects will be given a timer to use for a timed 1 minute at home brushing and a diary to record the time of each brushing and any comments they may have about their brushing experience. To ensure that the subjects understand the use instructions, the subjects will do the first brushing at the site under supervision.

The subjects will be instructed not to use any other oral hygiene products. However, subjects who currently use dental floss will be able to continue use, whereas non-flossers will be instructed not to start flossing during the study. Subjects will be scheduled to return in approximately 6 weeks and will be instructed to refrain from any oral hygiene procedures the morning of their visit and to refrain from eating, drinking and smoking for approximately 4 hours prior to their visit. They will be advised to follow the instructions carefully and return to the 6-week visit with their assigned toothpaste, toothbrush, timer and diary for their next examination. Subjects will receive a reminder call prior to their 6-week visit.

2-week (±3 days) Compliance Phone Contact

Approximately 2 weeks after the baseline visit, study personnel will contact each subject by phone. Study personnel will reinforce the product use instructions and study instructions and will remind the subject of the 6-week visit.

6-Week Visit (± 7 Days) &
3-Month Visit (± 7 Days)

Subjects will report to the study site with their dentifrice, toothbrush, diary and timer, having refrained from all oral hygiene procedures that morning and from eating, drinking and smoking for approximately 4 hours prior to their appointment time. Their medical history, current medication usage and inclusion/exclusion criteria will be updated and recorded. The dentifrice products will be weighed to assess product use and the diary entries will be reviewed to determine compliance with study requirements. The subject will be questioned about dentifrice use compliance by asking "Your brushing schedule is twice daily (morning and evening), for 1 minute per brushing, using only the toothpaste and toothbrush provided by All Sum Research. Have you deviated from that schedule at all?" (e.g. made any changes or forgotten to use the toothpaste). A "yes" or "no" answer to the question must be obtained. For all "yes" answers, the study site staff must determine what changed. Subjects will be assessed for any AEs they may have experienced since the previous visit.

The subjects will provide a post-baseline sensory evaluation. They will be asked if they have experienced any problems such as burning, stinging, irritation, etc., and, if so, the nature of the effect, severity and onset time (if known) will be recorded. A qualified dental examiner will perform an oral soft and hard tissue examination (OST), followed by gingival, bleeding, and plaque assessments.

The subjects will be provided with one additional tube of toothpaste.

The subjects will be reminded not to use any other oral hygiene products for the duration of the study. Subjects will be scheduled for their next visit and will be instructed to refrain from any oral hygiene procedures the morning of their next visit and to refrain from eating, drinking and smoking for approximately 4 hours prior to their next visit. They will be advised to follow the instructions carefully and return to the study site with their assigned toothpaste, toothbrush, timer and diary for their next appointment. Subjects will be scheduled for their next visit and will receive a reminder call prior to the visit.

18-Week Compliance Visit (±7 Days)
At Week 18, subjects will report to the study site with their dentifrice, toothbrush, diary and timer for a compliance visit. Products will be weighed and diaries will be reviewed. Subjects will provide a sensory evaluation as described at the 6-week visit. The subjects will be provided with one additional tube of toothpaste.

The subject will be questioned about dentifrice use compliance by asking "Your brushing schedule is twice daily (morning and evening), for 1 minute per brushing, using only the toothpaste and toothbrush provided by All Sum Research. Have you deviated from that schedule at all?" (e.g. made any changes or forgotten to use the toothpaste). A "yes" or "no" answer to the question must be obtained. For all "yes" answers, the study site staff must determine what changed. Subjects will be assessed for any AEs they may have experienced since the previous visit and any changes to inclusion/exclusion criteria or medical updates.

The subjects will be reminded not to use any other oral hygiene products for the duration of the study. Subjects will be scheduled for their next visit and will be instructed to refrain from any oral hygiene procedures the morning of their next visit and to refrain from eating, drinking and smoking for approximately 4 hours prior to their visit. They will be advised to follow the instructions carefully and return to the study site with their assigned toothpaste, toothbrush, timer and diary at their next appointment. The study personnel will reinforce the product use instructions and study instructions and will schedule subjects for the 6-month visit. Subjects will receive a reminder call prior to their next visit.

6-Month (± 7 Days)
Subjects will report to the study site with their dentifrice, toothbrush, diary and timer, having refrained from all oral hygiene procedures that morning and refraining from eating, drinking and smoking for approximately 4 hours prior to their appointment time. Their medical history, current medication usage and inclusion/exclusion criteria will be updated and recorded.

Subjects will provide a sensory evaluation as described at the 6-week visit. A qualified dental examiner will perform an oral soft and hard tissue examination (OST), followed by a gingival, bleeding and plaque assessments.

The subject will be questioned about dentifrice use compliance by asking "Your brushing schedule is twice daily (morning and evening), for 1 minute per brushing, using only the toothpaste and toothbrush provided by All Sum Research. Have you deviated from that schedule at all?" (e.g. made any changes or forgotten to use the toothpaste). A "yes" or "no" answer to the question must be obtained. For all "yes" answers, the study site staff must determine what changed. Subjects will be assessed for any AEs they may have experienced since the previous visit.

The dentifrice products will be weighed to assess product use and the diary entries will be reviewed to determine compliance with study requirements. All test products will be collected.

At the 6-month visit, subjects will complete a product questionnaire for informational purposes. This visit completes the subjects' participation in the study.

XI. STUDY ASSESSMENTS

A qualified examiner will evaluate the oral soft and hard tissues, gingival index (MGI[8]), bleeding index (GBI[9]) and plaque index (PI) (Soparkar Modified Turesky[10-12]) for all subjects at all visits except the 18-week compliance visit. The examiner will be blinded to the treatment randomization assignments.

Oral Soft and Hard Tissue Examination

At each evaluation visit an examination of the oral hard and soft tissues will be conducted. Examination of the oral cavity will include lips, tongue, gingiva, sublingual area, buccal mucosa, muco-buccal and muco-labial folds, hard and soft palate, and pharyngeal area and cervical areas of all teeth. Assessments are to include color, texture, soft tissue abrasion, and any irregularities. Any effects and changes from the baseline will be recorded.

Sensory Evaluation

At all visits, the subjects will be asked if they have experienced any problems with their product during the study and the response will be recorded for safety purposes. If the subjects experience any effects such as burning, stinging, irritation, etc., the effect and severity and duration (if known) will be recorded. (At the baseline visit, subjects will be asked if they are currently experiencing any of the effects listed above.)

Clinical efficacy assessments will be performed by a single examiner at Baseline, 6 weeks and 3 and 6 months in the following sequence: MGI, GBI, PI.

Gingival Inflammation (MGI)

Gingival inflammation will be assessed at each evaluation visit, according to the Modified Gingival Index (MGI),[8] and will be scored on buccal and lingual marginal gingivae and interdental papillae (four gingival areas: buccal, mesiobuccal, lingual and mesiolingual) of all scorable teeth using a scale of 0 – 4 as noted below:

0 = Normal (absence of inflammation).
1 = Mild inflammation (slight change in color, little change in texture) of any portion of the entire gingival unit.
2 = Mild inflammation of the entire gingival unit.
3 = Moderate inflammation (moderate glazing, redness, edema, and/or hypertrophy) of the gingival unit.
4 = Severe inflammation (marked redness and edema/hypertrophy, spontaneous bleeding, or ulceration) of the gingival unit.

Whole mouth MGI scores will be calculated by summing all scores and dividing by the number of scorable sites examined.

Gingival Bleeding Index (GBI)

Gingival bleeding tendency will be assessed at each evaluation visit according to the Bleeding Index (BI) described by Saxton and van der Ouderaa.[9] The gingiva will be lightly air-dried and a periodontal probe with a 0.5 mm diameter tip will be inserted into the gingival crevice to a depth of approximately 1 mm. The probe will be moved gently around the tooth at an angle of approximately 60 degrees to the long axis of the tooth, stroking the inner surface of the sulcular epithelium. Each of four gingival areas (distobuccal, midbuccal, mesiolingual, and midlingual) of the scorable

teeth will be probed in a likewise manner, waiting approximately 30 seconds before recording the number of gingival units which bleed, according to the following scale:

0 = absence of bleeding after 30 seconds;
1 = bleeding observed after 30 seconds; and
2 = immediate bleeding observed.

Soparkar Modification of the Turesky Modified Quigley-Hein Plaque Index (PI)
Plaque will be scored at each evaluation visit using the Soparkar modification[10] of the Turesky Modification[11] of the Quigley-Hein Plaque Index[12] (PI), on all scorable buccal and lingual surfaces. Plaque is first stained with a disclosant and scored according to a 6-point interval scale in which the higher value denotes a quantitative increase in plaque.

Each tooth is visually divided into 6 areas for scoring: 1) mesio-facial, 2) mid-facial, 3) disto-facial, 4) mesio-lingual, 5) mid-lingual, and 6) disto-lingual. Thus, the maximum score per tooth is 30.

Plaque is quantified according to the following criteria:
0=No visible plaque
1=Separate flecks of plaque at the cervical margin of the tooth
2=A thin, continuous band of plaque (up to 1mm wide) at the cervical margin
3=A band of plaque wider than 1mm but covering less than one-third of the crown
4=Plaque covering at least one-third but less than two-thirds of the crown.
5=Plaque covering two-thirds or more of the crown.

A plaque index score for each subject is calculated by adding all the individual plaque scores (six per tooth), and dividing this sum by the total number of measurements.

XII. ADVERSE EXPERIENCES

Adverse Event Definition and Handling
An adverse event (AE) is any unexpected or serious medical occurrence in a clinical investigation subject during the study, whether or not related to the study product. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the investigational product summary.

Adverse events will be reported to the sponsor within 24 hours and the sponsor will be notified immediately of any serious adverse event.

All adverse events observed by the Investigator and/or reported by the subject will be recorded throughout the entire study and documented. The Investigator will be asked to make a judgment on all adverse events as to their severity and possible relation to the study treatments.

More specifically, adverse events would include:

- Any unexpected event not seen before study initiation.
- Any pre-existing event that recurs with increased intensity or increased frequency subsequent to initial product treatment.

All adverse events should be recorded on the appropriate case report form, including date of onset, severity, duration, treatment and follow-up observation.
The following definitions will be used for grading severity of adverse events:

- Mild - Either asymptomatic, or subject is aware of the sign, symptom or event, but it is easily tolerated.
- Moderate - Discomfort enough to cause interference with usual activity and may warrant intervention.
- Severe - Incapacitating with inability to do usual activities.

The Investigator will assess the likelihood that there is a reasonable possibility of a causal relationship between a study product and the adverse event. This will be captured using the following criteria: product related, non-product

related, non-product related but protocol related. The causal relationship to the product will be assessed as: definitely related, probably related, possibly related, probably not related or definitely not related.

Serious Adverse Event

A serious adverse event is any adverse event that:

- Results in death.
- Is life threatening (i.e., immediate risk of death as the event occurred). A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.
- Results in persistent or significant disability or incapacity (i.e., a substantial, persistent disruption in a subject's ability to conduct normal life functions).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (hospitalization is official admission to a hospital). Hospitalization or prolongation of a hospitalization constitutes criteria for an adverse event to be serious; however, it is not in itself considered a serious adverse event. In the absence of an adverse event, a hospitalization or prolongation of a hospitalization should not be reported as a serious adverse event by the participating Investigator. This is the case in the following situations:
    - The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
    - The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the study file.

  In addition, a hospitalization for a pre-existing condition that has not worsened does not constitute a serious adverse event.
- Results in cancer.
- Results in a congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event(s) may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include: Allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. If there is any doubt whether the adverse event constitutes a serious adverse event, the information will be treated as a serious adverse event.

Adverse Event Recording and Reporting

All adverse events, whether serious or not, will be recorded on source documents and adverse event case report form. The recording period for all serious adverse events starts at the time the subject signs the informed consent. This includes events that emerge during screening. The recording period for a non-serious adverse event starts at the time the subject takes the first dose of study product. The recording period for serious adverse events lasts for 30 days and at least 7 days for non-serious adverse events after the subject's last administration of study product, regardless of relationship to the study product or protocol. The Investigator must follow up as medically necessary on all adverse events, serious adverse events, and other reportable events until the event has subsided or values have returned to baseline, or in the case of permanent impairment, until the condition stabilizes. For serious adverse events, the Investigator will provide all documentation pertaining to the event (*e.g.,* additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc.) to the Sponsor in a timely manner.

Information about all adverse events, serious and non-serious, including the event's severity, start and stop times/dates, chronicity, relatedness to study product, and any actions taken, must be recorded on the appropriate case report forms. The information recorded will be based on the signs and symptoms detected during the physical

examination and clinical evaluation of the subject as well as information recorded in the subject's diary, when applicable.

Serious Adverse Event Reporting
Any **serious adverse event**, regardless of causal relationship, must be reported immediately to Sponsor no later than 24 hours after the Investigator becomes aware of the serious adverse event) by emailing a pdf of the completed Adverse Event case report form and then confirming by telephone that the email was received. Along with a completed and signed case report form, the Investigator may include the following documentation: pertinent

supporting records such as assessment of the AE/drug relationship, the action(s) taken by the Investigator, case report forms, hospital records, and diagnostic test results.

Follow-up information relating to a serious adverse event must be reported to the Sponsor within 24 hours of receipt by the Investigator by emailing a completed Adverse Event case report form and confirming by telephone that the email was received. The subject will be observed and monitored carefully until the condition resolves, stabilizes, or its cause is identified. The Investigator will also promptly notify the IRB/IEC about the serious adverse event in accordance with IRB/IEC requirements.

XIII. SUBJECT COMPLETION AND WITHDRAWAL

Subject Completion
Only subjects who complete all procedures and comply with all areas of the protocol will be deemed to have completed the study. Subjects will be compensated for their time and travel and for successfully completing all provisions and procedures of the study. If a subject voluntarily withdraws from the study, or if withdrawn by the Investigator for any reason, he/she will be compensated as agreed upon with All Sum Research. Subject compensation will be documented in the Informed Consent and will be approved by the IRB/IEC.

Subject Withdrawal
Subjects are free to withdraw at any time during the clinical trial. Subjects may also be withdrawn from the study at any time at the discretion of the Investigator and/or the Sponsor. All subject withdrawals will be documented in the study file. Where possible, the reason for the withdrawal will be documented. Any withdrawals as the result of an adverse event will be followed-up at the discretion of the Study Investigator. Withdrawn subjects will not be replaced.

Subject Discontinuation
A subject will be considered discontinued from the study at any time under the following circumstances:

- Any subject who violates any condition of the entrance criteria after having been entered the study.
- Any subject who develops a confounding concomitant illness (as determined by the subject, Research Coordinator or Investigator) or a serious adverse event.
- Any subject who becomes uncooperative, does not adhere to the requirements of the study protocol, or refuses to complete the study.

XIV. STATISTICAL ANALYSIS AND DATA MANAGEMENT

Data analysis will be performed by the Sponsor's Statistician; the contract lab will summarize Oral Soft and Hard Tissue findings, Sensory Responses and Adverse Events by product and time point.

Demographic Data and Baseline Comparability
The table of demographic information will include the count and percent for each gender and for each ethnic group, as well as descriptive statistics (mean, median, standard deviation, minimum and maximum) for age. Comparisons between the treatment groups with respect to gender and ethnic group will be performed using chi-squared tests. The comparison between the treatment groups with respect to age will be performed using a t-test.

Sample Size

The planned sample size for this study is to complete with at least 100 evaluable subjects per treatment group (300 total subjects). Approximately 320 subjects will be enrolled, to assure that at least 100 evaluable subjects per group complete the study. Based on a 3-month pilot clinical study, in which the coefficient of variation for the plaque index (PI) was 18.1%, the coefficient of variation for the gingival index (MGI) was 7.2%, and the coefficient of variation for the bleeding index (GBI) was 61.3%, 100 subjects per group will give a power of over 95% for detecting a 20% difference between groups.

Efficacy Analysis

The primary analysis will be conducted on the population of subjects who complete all study visits. A secondary analysis will be conducted on the intent to treat population; that is, at each time point, all subjects who completed both the baseline evaluation and that evaluation will be included in the analysis. Additional subsets of the subject

population may be analyzed for informational purposes only. Other than the subject inclusion criterion, all analyses will be conducted identically as follows:

For each examination and each index, subjectwise mean Index scores will be obtained by calculating the average of the index scores evaluated at all individual measurement sites within the mouth. In addition to these 'whole-mouth' scores, subjectwise scores will also be obtained by calculating the average index scores over selected subsets of sites within the mouth. These subsets will include: Proximal sites; Marginal sites (MGI and GBI only); Gingival sites (PI only); Facial sites; Lingual sites; Posterior sites; Anterior sites; Posterior Facial sites; Posterior Lingual sites; Anterior Facial sites; and Anterior Lingual sites.

All statistical analyses will be based on the subjectwise Index scores. Separate analyses will be performed based on the subjectwise whole-mouth scores, as well as the subjectwise scores obtained from each of the selected subsets of the mouth.

The primary endpoints employed for the treatment comparisons in this study will be the month 6 Index scores. Additional analyses will be conducted on the Index scores collected at other time points. The comparison of the study treatments will employ an analysis of covariance (ANCOVA) model, with the associated baseline Index score included as a covariable. The ANCOVA model will include the factors: subject, treatment, and baseline Index score. Post-ANCOVA pairwise treatment comparisons of the adjusted means will be performed using t-tests utilizing Tukey's adjustment for multiple comparisons. Within-treatment comparisons of the mean baseline Index scores to the mean month 6 (or other post-baseline time point) Index scores will be performed using paired t-tests.

The comparison of the study treatments at baseline for each index will be performed using the same model described above, without the inclusion of the covariable.

All statistical tests of hypotheses will be two-sided, and employ a level of significance of $\alpha = 0.05$.

Safety Analysis

The safety population will consist of all randomized subjects. Safety parameters will include oral soft and hard tissues and subjective reports as well as any AEs. The analysis will include all observed effects which initially occurred, or worsened following treatment. Any adverse effects will be summarized and classified according to their intensity (mild, moderate, or severe) and relationship (definitely related, probably related, possibly related, probably not related or definitely not related) to study product.

XV. STUDY ADMINISTRATION

Investigator Study Binder

The Investigator will maintain a study binder at the study site. Included in this binder will be tabbed sections for maintaining the following: Study protocol, monitor sign in sheet for any monitoring visits, protocol amendments/administrative changes, Form FDA 1572, curricula vitae, IRB/IEC documentation, sample IRB/IEC approved informed consent form, product accountability forms, correspondence, master subject log and any other documentations as deemed necessary. This binder must be kept current and be available for review by representatives of the Sponsor.

Subject Identification

Date of birth and subject initials count as personally identifiable information (PII) and should not appear on CRFs. For purposes of confidentiality and to maintain anonymity, subjects will be assigned identification numbers (ie.001-330). Subjects should be identified to the Sponsor only by their assigned identification number and gender. The Investigator will maintain a complete list of all subjects enrolled in the study with their current mailing address on the master subject log. This list is necessary should contact of subjects be required in the future. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify subjects. The Investigator will maintain a complete list of all subjects enrolled in the study with their current mailing address on the master subject log. This list is necessary should contact of subjects be required in the future.

Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol and Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the subject, subset of subjects or all subjects, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the Sponsor and must be addressed in study subject source documents. In addition, protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff are responsible for knowing and adhering to their IRB requirements.

Protocol Amendments

No amendment to the protocol will be permitted without approval from the study Sponsor, Investigator, and IRB. Such changes will be documented in writing. Approval by the IRB must be obtained prior to initiation of the amendment.

Data Handling

All Sum Research will supply case report forms. All case report forms will be completed in a timely manner in black ink to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Data will be manually recorded on Case Report Forms (CRFs). All requested information must be entered on the case report form. All Sum Research will be responsible for data entry and will submit data to Sponsor Representative, in an Excel spreadsheet, for statistical analysis of the data.

The investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject participating in the study. Data captured in source documents includes subject information, original records of clinical findings, observations, medical histories, prior and concomitant medication records, inclusion/exclusion eligibility checklist, records of subject visits and phone calls, progress notes, subjects' diaries or evaluation checklists, test product dispensing and accountability records.

A Case Report Form (CRF) will be developed by the clinical investigator site and will be completed for each subject enrolled in the study. The CRF will include documenting subject demographics and subject's study completion status. All information recorded on the CRFs for this study must be consistent with the subject's source documentation records. The efficacy CRF pages may also serve as source documents. The Investigator or designee must review all entries for completeness and correctness.

The Investigator or designee agrees to make all CRFs and source documents available to the Sponsor's Study Monitor for full inspection. After resolution of the monitor's queries, a copy of the final CRF will be placed in the investigator's study file and the original will be taken by the site monitor for the Sponsor's Trial Master File (TMF).

The sponsor will review the CRFs and additional source documents for completeness and adherence to the protocol.

Report

At the termination of the study, a report which includes but is not limited to the following information will be prepared and submitted:

- A description of the test products
- A description of the test system
- Dates
- Protocol amendments/deviations
- Results
- Copy of protocol
- Statistical report
- Data tables
- Product weight tables (electronic)

Records of Inventory and Retention

All documentation will be stored in a lockable, restricted access facility for the duration of the study. Study personnel will be reminded of the confidential nature of personal information.

All Sum Research shall maintain all the records relating to this study, including case report forms and source documents (original records from which the case report forms were prepared), for a period of at least 7 years after completion of the study, per Health Canada regulatory requirements. If at any time All Sum Research is no longer able to maintain the required study records, the Sponsor must be notified in writing as soon as possible. In any case, the Sponsor retains the right to reclaim all study records. If the Sponsor reclaims the study records, the master subject log, which contains confidential information identifying and how to contact the study subjects, will be provided to the Sponsor in a sealed envelope labeled "confidential."

The Investigator assumes the responsibility of retaining the following records: Signed and dated protocol and amendments; records of receipt and disposition of test supplies; IRB/IEC approval, correspondence and final study summary; signed informed consent for each subject; completed case report forms, diaries and questionnaires; subject screening records; master subject log; medical histories; correspondence; adverse events; roster of study personnel; monitoring visit record.

Disclosure of Data/Publications

All information obtained during the conduct of the study will be regarded as confidential. All Sum Research will not seek to arrange publication of any of the information or results from the study in any scientific journal or other publications or by way of lecture without Church & Dwight's written consent.

Monitoring of Study

Qualified representatives of the Sponsor will conduct periodic on-site visits to the clinical site over the course of the study to assess adherence to the protocol, proper documentation, and to ensure that the study is conducted in accordance with current Good Clinical Practice Guidelines. Communication by telephone and facsimile may also supplement on-site visits.

A representative of the Sponsor will inspect all case report forms, informed consents, source documents and the study binder. These inspections are for the purpose of verifying adherence to the protocol and determining the completeness and exactness of the data entered on the case report forms and study product log.

As part of monitoring and inspection of this study, the Investigator agrees that the Sponsor, its employees, or representatives, IEB/IEC, as well as representatives of the Food and Drug Administration, Health Canada and other regulatory authorities will have the right to inspect and review pertinent records relating to this trial. In addition, informed consent documents signed by study participants will indicate approval to release their records for review while maintaining their confidentiality.

Responsibility of Investigator/Study Director

In agreeing to conduct this study, the Investigator/Study Director assumes certain responsibilities mandated by federal regulations: An Investigator/Study Director is responsible for ensuring that an investigation is conducted according to study protocol, and applicable regulations; for protecting the rights, safety, and welfare of subjects; and for the control

of the products under investigation. An Investigator/Study Director will, in accordance with the appropriate federal regulations, obtain the informed consent of each human subject to whom the product is administered. The Investigator/Study Director will retain all study documents as stipulated in "Records Storage/Retention." The Investigator/Study Director certifies that he has not been disbarred by the FDA from conducting clinical trials. The Investigator will comply with the requirements outlined in 21 CFR 54, Financial Disclosure by Clinical Investigators. Since the study takes place in Canada, the Investigator/Study Director will assume the responsibility of conducting this study in accordance with all applicable Canadian regulations.

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