Clinical Study Protocol

Study Number and Protocol Title	EM-11-050003 A prospective, randomized, blinded, clinical study to evaluate effects of a 3M™ oral rinse on plaque and gingivitis
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1. LIST OF ABBREVIATIONS

Acronym	Definition
AE	Adverse Event
ADE	Adverse Device Effect
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
BI	Bleeding Index
CFR	Code of Federal Regulations
CRF	Case Report Form
DMP	Data Management Plan
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GI	Gingival Index
IRB	Institutional Review Board
FAS	Full Analysis Set
NA	Not Applicable
PI	Plaque Index
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

2. STATEMENT OF COMPLIANCE

This document contains confidential information that is the property of 3M and is subject to all the restrictions on use and disclosure contained in the study contract to which this is appended. Do not copy, disclose, circulate or use for benefit for any third party without written authorization from 3M.

The signatures of the investigator and representative of the sponsor below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted in compliance with 21 CFR 812, Investigational Device Exemptions, 21 CFR 50, Protection of Human Subjects, 21 CFR 56, Institutional Review Boards, 21 CFR 54, Financial Disclosure by Clinical Investigators, 21 CFR 820 Subpart C, Design Controls of the Quality System Regulation, ISO 14155:2011 *Clinical study of medical devices for human subjects – Good Clinical Practice*, in accordance with the Declaration of Helsinki, Guidelines for Good Clinical Practice (ICH E6), and all relevant national guidelines.

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 applicable IRB/Ethics Committee.

It is agreed that all participants in this study will provide written informed consent in accordance with 21 CFR 50, Protection of Human Subjects. All participants will also be informed that their medical records will be kept confidential except for review by representatives of 3M and/or an applicable regulatory body.

Principal Investigator: Yiming Li, DDS, MSD, PhD

Signature: _____ Date: _____

3. PROTOCOL SUMMARY/SYNOPSIS

SYNOPSIS	
Sponsor	3M™ ESPE Dental Products
Study Title	A prospective, randomized, blinded, clinical study to evaluate effects of a 3M™ oral rinse on plaque and gingivitis.
Study ID number	EM # 11-050003
Purpose	The purpose of this study is to assess the performance of the 3M Oral Rinse.
Device Description	The 3M Oral Rinse contains an anti-plaque agent that provides a surface barrier to reduce the adhesion of dental plaque; thereby preventing the accumulation of dental plaque associated with gingivitis.
Device Intended Use	The 3M Oral Rinse is intended to help prevent and reduce plaque and gingivitis.
Treatment Groups	• 3M Oral Rinse • Placebo vehicle control • PerioShield™ Oral Health Rinse predicate device control • Placebo water negative control
Treatment Dose	Products will have identical instructions for use except for the predicate device that has a 10-mL dose rather than a 15-mL dose. Subjects will use the rinse twice a day for 30 seconds after tooth brushing.
Objective **(primary efficacy endpoints)**	To evaluate the effects of the 3M Oral Rinse relative to the placebo vehicle control on plaque and gingivitis levels at 6 months, based on the following two parameters: • Lobene-Soparkar Modification of the Turesky Modified Quigley-Hein Plaque Index (PI) • Löe-Silness Gingival Index (GI)

Objectives **(secondary efficacy and safety endpoints)**	• To evaluate the 3M Oral Rinse: o Versus placebo vehicle control at 3 months using Modified Quigley-Hein Plaque Index (PI) scores. o Versus placebo vehicle control at 3 months using Löe-Silness Gingival Index (GI) scores. o Versus placebo vehicle control at 3 and 6 months using Eastman Interdental Bleeding Index (BI) scores. • To assess the safety of the 3M oral rinse by tracking abnormal changes to soft and hard tissues, and adverse events during the study. • To conduct pairwise comparisons among the four treatment groups, namely, 3M Oral rinse, vehicle control, PerioShield (predicate) and water control, based on the PI and GI scores at 6 months.
Study Design	The study is a prospective, randomized, single center, parallel group, blinded clinical trial. Subjects will be randomly assigned to one of the four treatment groups.
Study Duration	The duration of subject involvement is approximately 6 months. Study duration from the time of first subject enrolled until last subject completed is expected to be approximately 12-15 months.
Sample Size	The sample size was estimated based on GI and PI scores from preliminary clinical study data and the literature. It is estimated that 34 subjects per group will provide 90% power to detect a difference of 0.40 (standard deviation (SD) of 0.5) in the GI and PI scores using a 1-sided 0.025 alpha level. To account for possible dropouts, a sample size of 50 subjects per group will be recruited.

Screening Inclusion criteria:	**Subjects to whom these criteria apply will be entered into the 7-day washout** • Able to understand and willing to sign the Informed Consent • In good general health ages 18 and older • Have at least 20 natural teeth, including at least one molar and one premolar in each quadrant but excluding the third molars • Willing to return to the study facility for scheduled study visits and recalls • Agree not to use other oral hygiene products (non-study toothpaste, dental floss, mouth rinse, chewing gum) • Agree not to brush or floss teeth after 10:00 pm the night before and not eat or drink 4 hours before an appointment • Agree to the study instructions and visit schedule, including no eating or drinking for 4 hours before assessment appointments

Screening Exclusion criteria:	**Subjects to whom these conditions apply will be excluded:** • A history of antibiotic therapy within the previous 30 days or have a condition that is likely to need antibiotic treatment over the course of the study (eg, cardiac conditions requiring antibiotic prophylaxis such as heart murmurs, pacemakers, or prosthetic heart valves, and prosthetic implants) • A history of using antimicrobial oral mouth rinse during the past 3 months • Taking medications which may alter gingival appearance/bleeding • Use of anticonvulsants, calcium channel blockers, or other medications with side effects known to impact oral health • Current participation in any other clinical study within the past 30 days • Reside in the same household with a subject already enrolled in the study • Dry mouth due to head/neck radiation therapy • Orthodontic appliances • Widespread caries or chronic neglect • Gross pathological changes of oral soft tissues • Known history of sensitivity to oral hygiene products • Advanced periodontal disease (purulent exudate, tooth mobility, and/or extensive alveolar bone loss) • Pregnant or nursing or plan to become pregnant within the 6-month study duration • Medical and oral conditions that, in the investigator's judgment, may compromise the subject's safety or interfere with the conduct and outcome of the study • Difficult to be compliant with study visits, such as extensive travel commitments or lack of transportation
Baseline Inclusion/exclusion criteria:	Subjects must meet the screening inclusion criteria and these additional requirements: • Completed the washout period (at least 7 days) using only the study toothbrush, dental floss and toothpaste • A qualifying baseline GI of at least 1.0, as determined by the Löe-Silness Gingival Index (GI) • A qualifying baseline Modified Quigley-Hein (Lobene-Soparkar Modification of Turesky's modification) Plaque

	Index (PI) of at least 1.5 Subjects will be excluded if they do not meet the screening exclusion criteria.
Randomization	200 subjects will be randomized to one of the four treatment groups.
Blinding:	The Principal Investigator and clinical examiners will be blinded to the treatment products. No clinical examiners will see the allocated rinse assigned per the randomization schedule. Due to the rinse packaging differences and to maintain the blind, all study products will be placed in a non-transparent container. Subjects will be told not to open the container until they return to their home and to bring study supplies back to their next scheduled appointment in the same container. Only the study coordinator at the site will know the randomization assignment.
Outcome Measures:	• Modified Quigley-Hein Plaque Index at baseline, 3 and 6 months (± 10 days) • Löe-Silness Gingival Index at baseline, 3 and 6 months (± 10 days) • Eastman Interdental Bleeding Index at baseline, 3 and 6 months (± 10 days) • Oral soft and hard tissue assessment baseline, 3 and 6 months (± 10 days) • Adverse Events
Study Restrictions	Subjects will only use the study toothpaste, toothbrush, dental floss and mouth rinses that are provided by the study staff and will refrain from using any other oral hygiene products or measures such as other toothpaste, mouth rinse, mechanical toothbrush and chewing gum etc. Subjects will not eat or drink 4 hours before clinical exams, and will not brush or floss their teeth the night before and the morning of the clinical exams.
Clinical Safety Assessment	Safety assessments will be completed by a clinical examiner at each clinical visit.

Data Analysis Plan:	Means and standard deviations will be calculated for all clinical measurements and assessments. Categorical variables will be summarized in frequency distributions. Analysis of variance (ANOVA) or (ANCOVA) will be used to test for treatment group differences between the subject groups at 3 and 6 months. GI, PI, and BI scores will be calculated as the average tooth score across all teeth as one score per patient, per visit. All statistical analyses will be performed using SAS version 9.3 or above (SAS Institute, Cary, NC) or another statistical software package.

Study Schedule						
	Screening followed by at least a 7-day washout	Baseline	Interim Visits (Approximately) 1.5 and 4.5 months	3-Month (± 10 days)	6-Month (± 10 days) or upon subject discontinued	Unscheduled visit can occur at any time for any reason
Informed Consent/ Screening Inclusion/ Exclusion Demographics	X					
Baseline Inclusion/ Exclusion/		X				
Oral Exam		X		X	X	X
Concomitant Medications		X	X	X	X	
Randomization		X				
Modified Quigley-Hein Plaque Index		X		X	X	
Löe-Silness Gingival Index		X		X	X	
Eastman Interdental Bleeding Index		X		X	X	
Adverse Events		X	X	X	X	X
Assessment of Compliance		X	X	X	X	
Subject Diary Review/Collection			X	X	X	
Prophylaxis		X				
Review Instructions		X	X	X		X
Blinding Assessment		X			X	
Replenish Study Supplies		X	X	X		

4. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

4.1 Background

Gingivitis is most commonly seen as a plaque-induced, inflammatory condition of the gum tissues that effects approximately 50% to 90% of the population.[1,2] Plaque biofilm can include viruses, fungi, mycoplasma and even protozoa but bacteria are the prominent species.[3] One concern is that gingival inflammation (ie, gingivitis) caused by the plaque biofilm has the potential to spread into the underlying supporting structures of the teeth resulting in the more destructive condition called periodontal disease. Agents that interfere with bacterial adhesion and disrupt biofilm formation may aid in plaque control, thereby reducing the level of inflammation and gingivitis. While they are not meant to replace tooth brushing these rinses could serve as valuable adjuncts to conventional oral hygiene procedures.[3,4] Many oral rinses contain anti-bacterial agents to reduce gingivitis for example chlorhexidine digluconate (CHX), which remains the standard for chemical antiplaque rinses, but is generally not used long-term due to side effects. Ideally, antiplaque methods of preventing and reducing biofilm especially when used long term should not allow opportunistic pathogens to colonize the oral environment.[5]

Gingivitis is diagnosed by dental professionals based on symptoms and an examination of the gingiva or gums for redness, swelling and bleeding. The prevalence and severity of gingivitis was investigated by Dr. Yiming Li, the Principal Investigator, at 3 different locations; Loma Linda University in California: University of Washington in Seattle, Washington; and Boston University in Boston, Massachusetts.[6] In summary, the study showed that overall average GI score was 1.055, with 6% having <0.50, 56% >= 1.00 and 94% >=0.50. The study found a positive correlation between the GI score and age (correlation coefficient 0.308, P<0.001) with a mean of 0.93 for subjects younger than 30 years of age and 1.22 for those older than 59 years. In addition, the study showed that GI scores for males were significantly higher (P<0.001) than that of the females (1.19 vs 0.95); African-Americans showed a significantly higher gingival index scores (P<0.05) than other races except for the Native-Americans (1.18 vs 0.97-1.08). In addition, the study had participants that reflected the 2004 census racial distribution except for having fewer whites (53% vs 67%) and more Asians (14% vs 4%). Subject enrollment is expected to result in a diverse population with proper sex and race compositions representative of the general population experiencing plaque-induced gingivitis.

4.2 Rationale

The 3M Oral Rinse contains an anti-plaque agent that provides a surface barrier to reduce the adhesion of dental plaque. 3M Oral Rinse is intended to help prevent and reduce plaque and gingivitis. The rinse serves as an adjunct to normal mechanical oral hygiene.

The 3M rinse is subject to 21 CFR 872.5580 and the FDA Guidance: *Class II Special Controls Guidance Document: Oral Rinse to Reduce the Adhesion of Dental Plaque.*

The proposed study will have 4 study arms/treatment groups and will assess the performance of the 3M Oral Rinse over a 6- month period.

4.3 Name, Description and Intended Use of the Investigational Product

The 3M Oral Rinse contains a [redacted] surfactant using a proprietary formula. The intended use of the product is to help prevent and reduce plaque and gingivitis.

4.4 Risk/Benefit Summary

4.4.1 Risks and Benefits of the Experimental Device and Clinical Investigation

The anticipated clinical benefit of the 3M Oral Rinse and the predicate oral rinse is control of plaque and gingivitis. Subjects who receive placebos may not receive the same benefit as those who receive active treatment.

Subjects will be instructed to refrain from any dental treatment, including dental prophylaxis, during the study. If necessary, emergency dental treatment may be performed. Subjects will be instructed to inform the investigator as soon as possible if any emergency dental treatment is performed. The investigator will then decide whether the subject should continue in the study. Subjects who receive medical and/or dental treatment with antibiotic management may be dropped from the study.

The following is a list of potential risks associated with this study.

- Plaque and gingivitis may not improve
- Subjects may have an increased risk of disease or infection from altered oral mucosal immunity due to potential changes in oral flora
- Potential allergies to product components
- Oral rinses can cause transient mouth/tongue numbness
- Oral rinses can cause mucosal sloughing/irritation
- Oral rinses can cause transient dry mouth
- Oral rinses may cause transient alteration in taste
- Subjects may experience bleeding gums during study visits with clinicians due to probing/gingivitis assessment procedures
- Subjects should avoid rinse contact with skin and eyes. In case of contact with skin, wash thoroughly and in case of contact with eyes, flush with water.

5. Study Design and Study Objectives/Endpoints

5.1 Study Design

This is a prospective, single site, randomized, parallel, blinded clinical trial. Subjects will be randomly assigned to one of four treatment groups identified as Product A, Product B, Product C or Product D.

Subjects will be screened for eligibility and entered into a washout period that is at least 7 days, during which time they will be provided with study toothbrush, toothpaste and dental floss. No oral rinses or medication that alters oral tissue health will be used or taken during the washout period. After randomization, the designated rinse will be placed into a non-transparent container so that other subjects and clinical examiners do not see the allocated rinse per the randomization schedule.

Subjects will be provided with both verbal and written instructions to take home, and a diary for tracking dosing compliance and any side effects from rinse use. Subjects will return the diary along with the empty/used/unused rinse bottles in the original container at their next scheduled visit to monitor for compliance of product use. Subjects that are found to be non-compliant will remain in the study, be re-trained and documented accordingly.

Examinations for the clinical endpoints (PI, GI and BI) will be conducted at the baseline, 3-month (±10 days), and 6-month (±10 days) visits.

Interim visits will be scheduled to review diary, replenish study supplies, check study compliance, etc. Subjects will be provided Colgate Regular toothpaste, dental floss and a soft toothbrush (replaced at 3 months) for use during the 6-month study period.

5.2 Primary Efficacy Objective with 3M Oral Rinse and Vehicle Control

To investigate the effects of the 3M Oral Rinse relative to the placebo vehicle control on plaque and gingivitis levels, at 6 months, based on the Modified Quigley-Hein Plaque Index (PI) and the Löe-Silness Gingival Index (GI) scores.

5.3 Secondary Efficacy Objective with 3M Oral Rinse and Vehicle Control

- To investigate the effects of the 3M Oral Rinse vs. Placebo Vehicle Control on plaque and gingivitis, at 3 months, based on the Modified Quigley-Hein Plaque Index (PI) and the Löe-Silness Gingival Index (GI) scores.
- To investigate the effects of the 3M Oral Rinse vs. Placebo Vehicle Control on Eastman Interdental Bleeding Index (BI) scores at 3 and 6 months

5.4 Secondary Efficacy Objective with All Four Treatment Groups

To investigate the relative efficacy, using pairwise comparisons, of the four treatment groups, namely 3M Oral rinse, vehicle control, PerioShield (predicate) and water control, with respect to the PI and GI scores at 6 months.

5.5 Safety Objectives/Endpoints

- To assess the safety of the 3M oral rinse by tracking abnormal changes to soft and hard tissues, reported side effects and adverse events during the study.

6. SUBJECT SELECTION

Subjects will come in for a screening visit and if they meet the inclusion criteria they will be scheduled for baseline measures after at least a 7-day washout period.

6.1 Subject Inclusion Criteria at Screening

Subjects to whom all of these conditions apply will be eligible for the washout period of this study:

- Able to understand and willing to sign the Informed Consent
- In good general health ages 18 and older
- Have at least 20 natural teeth, including at least one molar and one premolar in each quadrant but excluding the third molars
- Willing to return to the study facility for scheduled study visits and recalls
- Agree not to use other oral hygiene products (eg, non-study toothpaste, dental floss, mouth rinse, chewing gum)
- Agree not to brush or floss teeth after 10:00 pm the night before an appointment
- Agree to the study instructions and visit schedule, including no eating or drinking for 4 hours before assessment appointments

6.2 Subject Exclusion Criteria at Screening

Subjects to whom any of these conditions apply will be excluded:

- A history of antibiotic therapy within the previous 30 days or have a condition that is likely to need antibiotic treatment over the course of the study (eg, cardiac conditions requiring antibiotic prophylaxis such as heart murmurs, pacemakers, or prosthetic heart valves, and prosthetic implants)

- A history of using antimicrobial oral mouth rinse during the past 3-months
- Taking medications which may alter gingival appearance/bleeding
- Use of anticonvulsants, calcium channel blockers, or other medications with side effects known to impact oral health
- Current participation in any other clinical study within the past 30 days
- Reside in the same household with a subject already enrolled in the study
- Dry mouth due to head/neck radiation therapy
- Orthodontic appliances
- Widespread caries or chronic neglect
- Gross pathological changes of oral soft tissues
- Known history of sensitivity to oral hygiene products
- Advanced periodontal disease (purulent exudate, tooth mobility, and/or extensive alveolar bone loss)
- Pregnant or nursing or plan to become pregnant within the 6-month study duration
- Medical and oral conditions that, in the investigator's judgment, may compromise the subject's safety or interfere with the conduct and outcome of the stud
- Difficult to be compliant with study visits, such as extensive travel commitments or lack of transportation

6.3 Baseline Inclusion Criteria at Enrollment

Subjects who meet the screening inclusion criteria and the following baseline inclusion criteria apply will be eligible for treatment randomization:

- Completed the washout period (at least 7 days) using only the study toothbrush, dental floss and toothpaste
- A qualifying baseline Gingival Index of at least 1.0, as determined by the Löe-Silness Gingival Index (GI)
- A qualifying baseline Modified Quigley-Hein (Lobene-Soparkar Modification of Turesky's Modification) Plaque Index (PI) of at least 1.5 (referred to as Modified Quigley-Hein Plaque Index in the following text)

6.4 Baseline Exclusion Criteria at Enrollment

At the baseline visit the same exclusion criteria as the screening visit must be met prior to randomization.

6.5 Recruitment

The clinical site has a racially and ethnically diverse database that may be used to identify potential subjects. In addition, advertisements in publications or the local newspapers may be placed to enhance subject recruitment. The advertisements will provide a brief synopsis of the study and instruct potential subjects to contact the study site for more information. If the subject is interested in participating, he or she will be scheduled for the screening appointment. Subjects who go through the consenting process, meet the Inclusion/Exclusion criteria, and sign an Informed Consent form will be screened for the study and begin the washout. If they qualify at baseline they will be randomized. Multi-language consent forms will be prepared to meet the local IRB requirements, if necessary.

6.6 Withdrawal or Termination of Subjects

A genuine effort will be made to collect all outcome data and keep subjects enrolled in the study. Effort will be made to determine the reason(s) why a subject fails to return to the study site for the necessary visit(s) or has dropped from the study. A subject may withdraw from the study at any time.

A subject may be dropped from the study if any of the following occur:

- Subject fails to show up at the scheduled visits (three attempts will be made to schedule subjects and if they have not responded they will be dropped)
- Subject elects to terminate participation in the study
- Investigator or Study Coordinator elects to withdraw the subject (with written justifications about safety, noncompliance or any other reason)
- Subject experiences a severe adverse reaction to the test product(s)
- Subject begins long-term (12 days or more) treatment with antibiotics
- Subject needs dental therapy that cannot wait until the end of the study
- Subject becomes pregnant

Subjects discontinued from the study for any reason will not be allowed to reenter the study. Subjects withdrawn due to adverse events (AEs) will receive follow-up until the AE is resolved, or is determined by the Investigator to be stable. Final assessments will be completed if possible.

6.7 Blinding and Randomization

6.7.1 Blinding

The Principal Investigator and clinical examiners will be blinded to the treatment product assigned to study subjects. Efforts will be made to ensure that subject blinding is effective as

possible including precautionary measures such as subjects will be told not to open the non-transparent container containing study products until they return to their home and to bring all study supplies back to their next scheduled appointment in the same container. A subject blinding assessment will be completed after the first rinse dose and at the last study visit.

The blind will not be broken during the study unless 3M personnel decide to stop the study or it is necessary to break the blind for subject safety.

6.7.2 Randomization

A total of 200 subjects will be randomized to one of the four treatment groups in a 1:1:1:1 ratio. Random assignment will be provided in sealed envelopes that are to be opened in sequential order at the time the subject qualifies for the study.

7. STUDY PRODUCTS

7.1 3M Oral Rinse

The volume of 15 mL will be swished for 30 seconds followed by expectoration, twice a day (morning and evening), after brushing teeth, for the 6-month duration of the study as described in Appendix 17.1. Subjects will be instructed to use the dosing cup provided by the study team to ensure that the proper dose of rinse is used. They will be instructed not to use the product directly from the bottle (ie, put their mouth on the opening of the container) and to replace the cap after each use. Subjects will be instructed not to eat or drink for 30 minutes after using the rinse and to complete the subject daily diary.

7.2 Vehicle Control Oral Rinse Formulation

The volume of 15 mL will be swished for 30 seconds followed by expectoration, twice a day (morning and evening), after brushing teeth, for the 6-month duration of the study. Subjects will be instructed to use the dosing cup provided by the study team to ensure that the proper dose of rinse is used. They will be instructed not to use the product directly from the bottle (ie, put their mouth on the opening of the container). They will be instructed to replace the cap after each use. Subjects will be instructed not to eat or drink for 30 minutes after using the rinse and to complete the subject daily diary.

7.3 PerioShield Oral Health Rinse Predicate Device Control

PerioShield™ Oral Health Rinse (0.2% delmopinol hydrochloride) is marketed in the US and will be purchased for use in the study. The subjects will follow the product instruction for use using 10 mL for 30 seconds followed by expectoration, twice a day (morning and evening), after brushing teeth, for the 6-month duration of the study. Subjects will be instructed to use the dosing cup provided by the study team to ensure that the proper dose of rinse is used. They will

be instructed not to use the product directly from the bottle (ie, put their mouth on the opening of the container). Subjects will be instructed to replace the cap after each use. Subjects will be instructed not to eat or drink for 30 minutes after using the rinse and to complete the subject daily diary.

This rinse is a marketed product and will be over-labeled by 3M personnel in 3M's Manufacturing Technologies GMP facility, 3M Center, St. Paul, MN.

7.4 Water Control

The water control will be purchased sterile water and over-labeled by 3M personnel in 3M's Manufacturing Technologies GMP facility, 3M Center, St. Paul, MN.

Subjects will rinse with 15 mL for 30 seconds followed by expectoration, twice a day (morning and evening), after brushing teeth, for the 6-month duration of the study. Subjects will be instructed to use the dosing cup provided by the study team to ensure that the proper dose of rinse is used. They will be instructed not to use the product directly from the bottle (ie, put their mouth on the opening of the container). Subjects will be instructed to replace the cap after each use. Subjects will be instructed not to eat or drink for 30 minutes after using the rinse and to complete the subject daily diary.

7.5 Choice of Comparator

The comparators are two negative controls (water and vehicle oral rinse) and a positive control, PerioShield Oral Health Rinse, the predicate medical device.

7.6 Study Product Storage and Accountability

All test materials and study supplies will be provided by the study sponsor. All study products will be stored at the study site in a securely locked area only accessible to authorized personnel until dispensed to subjects.

Access to study products shall be controlled and shall be used only in the clinical study and per the study protocol. The sponsor shall keep records to document shipment of the study supplies to the study site as well as returned study supplies. The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the devices, which shall include:

- Date of receipt
- Identification of each study product
- Expiration date
- Date of distribution
- Subject identification

- Date on which the study product was returned, if applicable, and date of return of unused product

After completion of the study all unused study materials will be returned to 3M.

7.7 Packaging

The label on the rinse containers will be labeled as Product A, B, C or D.

An example of the Rinse Label is shown below.

EM-11-050003
Oral Rinse Study: Product A, B, C or D
500 mL
CAUTION: Investigational Device. Limited by United States Law to Investigational use.
Not for commercial distribution, for clinical investigation use only.
3M ESPE Dental Products, 2510 Conway Ave. St Paul, MN 55144-1000

Pour 15 mL (10 mL on the PerioShield label) into the dosing cup in the am and pm after brushing.
Do not use directly from the bottle.
Replace the bottle cap after each use. Rinse for 30 seconds and spit out.
Do not eat or drink for 30 minutes after rinsing.
Keep Out of Reach of Children - Do Not Swallow.
Store at room temperature. Use as directed.

Call with study concerns: Dr. Yiming Li (909) 558-8069 (*ext.* 88069)

8. STUDY PROCEDURES/EVALUATIONS

8.1 Scheduled Study Visits

8.1.1 Screening Visit

- Informed consent
- Screening inclusion/exclusion criteria
- Demographics
- Distribute study toothbrush, toothpaste and dental floss to use for washout (at least 7-days)

8.1.2 Baseline Visit

- Baseline inclusion/exclusion criteria
- Randomization
- Concomitant medications
- Subject blinding assessment
- Löe-Silness Gingival Index
- Modified Quigley-Hein Plaque Index
- Eastman Interdental Bleeding Index
- Dental prophylaxis
- Test products distribution and training
- Oral hard and soft tissue evaluation (Oral Exam)
- Subject diary, instructions and return appointment
- Adverse events, protocol deviations (if applicable)

8.1.3 Interim Visit (approximately 1.5 months)

- Review of subject diary and visual inspection of product use/compliance
- Replenish study products
- Reinforcement of product use instructions
- Concomitant medications
- Adverse events, protocol deviations (if applicable)

8.1.4 3-Month Visit (± 10 days)

- Any change in medical/dental history
- Concomitant medications
- Oral hard and soft tissue evaluation (Oral Exam)
- Löe-Silness Gingival Index
- Modified Quigley-Hein Plaque Index
- Eastman Interdental Bleeding Index
- Review of subject diary and visual inspection of product use/compliance
- Replenish study products
- Reinforcement of product use instructions

- Adverse events, protocol deviations (if applicable)

8.1.5 Interim Visit (approximately 4.5 months)

- Review of subject diary and visual inspection of product use/compliance
- Replenish study products
- Reinforcement of product use instructions
- Concomitant medications

8.1.6 End of Study visit or 6-Month Visit (± 10 days)

- Any change in medical/dental history
- Concomitant medications
- Subject blinding assessment
- Oral hard and soft tissue evaluation (Oral Exam)
- Löe-Silness Gingival Index
- Modified Quigley-Hein Plaque Index
- Eastman Interdental Bleeding Index
- Review of subject diary and visual inspection of product use/compliance
- Adverse events, protocol deviations (if applicable)
- Collection of study products

8.2 Study Procedures

8.2.1 Screening Visit

Prior to entering the study, the Investigator/Study Coordinator or designated assistant will explain to each subject the elements of informed consent including, nature of the study, the purpose, procedures and expected duration; and the benefits and possible risks involved in study participation.

A screening oral examination will be conducted to determine study eligibility. If eligible, subjects will be scheduled for the baseline visit and they will receive the study toothpaste, tooth brush and dental floss for the washout period. Subjects will be instructed not to brush or floss their teeth after 10:00 pm the night before assessments and not to eat and drink for 4 hours prior to the scheduled clinical examinations.

8.2.2 Baseline Visit

The clinical examinations will be conducted by calibrated examiners. The same examiner will perform the same clinical examination throughout the study. See Appendix 17.2 on training and calibration procedures of the clinical examiners. A subject blinding assessment question will be completed at the baseline visit after the first dose is taken. Professional cleaning by a dental hygienist will be completed at end of the baseline visit so all subjects start the study with a plaque free status.

8.2.3 Assessment of Efficacy Methods

8.2.3.1 Oral Tissue Examination

The oral hard and soft tissue examination findings will be recorded as normal (oral tissue is what is expected by visual inspection) or abnormal. Hard tissue is defined as the visible tooth surface above the gum line (gingival area). Soft tissue refers to gingiva, oral mucosa and tongue. All abnormal findings will be described on the case report form. Examples of abnormal oral clinical findings:

Hard tissue: changes including discoloration/staining, erosion, white spots etc.

Soft tissue: changes in gingiva, oral mucosa, tongue, swelling and redness (inflammation), vesicles, ulcers, desquamation, white or red lesions, fungal overgrowth or bleeding tissue.

8.2.3.2 Gingival Index

The method of Löe-Silness will be used for evaluating gingivitis according to the following criteria: [7,8]

Löe-Silness Gingival Index

0 = Absence of inflammation.

1 = Mild inflammation: slight change in color and little change in texture.

2 = Moderate inflammation: moderate glazing, redness, edema, hypertrophy. Tendency to bleed upon probing.

3 = Severe inflammation: marked redness and hypertrophy. Tendency to spontaneous bleeding.

The gingival surface surrounding each tooth (all natural teeth) will be scored on six surfaces: 1) mesio-facial; 2) mid-facial; 3) disto-facial; 4) mesio-lingual; 5) mid-lingual; and 6) disto-lingual.

Third molars and those teeth with cervical restorations or prosthetic crowns will be excluded from the scoring procedure. The GI score of the individual can be obtained by adding the scores of all surfaces and dividing by the number of surfaces examined.

8.2.3.3 Plaque Index

The Lobene-Soparkar modification of Turesky's modified Quigley-Hein Plaque Index will be used for evaluating dental plaque according to the following criteria: [9,10,11]

Modified Quigley-Hein Plaque Index

0 = No plaque

1 = Separate flecks of plaque at the cervical margin of the tooth

2 = A thin, continuous band of plaque (up to one mm) at the cervical margin of the tooth.

3 = A band of plaque wider than 1 mm, but covering less than 1/3 of the crown of the tooth.

4 = Plaque covering at least 1/3, but less than 2/3 of the crown of the tooth.

5 = Plaque covering 2/3 or more of the crown of the tooth.

Prior to examination, Vaseline will be applied to the subject's lips, a plaque disclosing solution is put into a medicine cup and a cotton tip applicator is used to apply solution to all surfaces of teeth. The subject's mouth is then rinsed with water and the examiner then records the plaque index.

Each tooth is scored for supragingival plaque on six surfaces: 1) mesio-facial; 2) mid-facial; 3) disto-facial; 4) mesio-lingual; 5) mid-lingual; and 6) disto-lingual. Third molars and those teeth with cervical restorations or prosthetic crowns will be excluded from the scoring procedure. The PI score of the individual can be obtained by adding the scores of all surfaces and dividing by the number of surfaces examined.

8.2.3.4 Bleeding Index

Gingival bleeding on probing will be examined using the Eastman Interdental Bleeding Index according to the following criteria and will be recorded on the case report form: [12] The Bleeding Index (BI) will determine the extent of interdental inflammation.

Eastman Interdental Bleeding Index

0 = Absence of bleeding.

1 = Presence of bleeding

The interdental cleaner is inserted between two teeth from the facial aspect, depressing the interdental tissues 1 to 2 mm. This is repeated four times and the presence or absence of bleeding within 15 seconds is recorded. The absence or presence of bleeding will be recorded for each examined site (between two teeth), and a score will be calculated as the number of bleeding sites out of the number of examined sites for each evaluation on a subject.

9. ASSESSMENT OF SAFETY

9.1 Safety Parameters

The principal measure of safety will be the incidence of adverse events reported during the study.

9.2 Unscheduled Visits

An unscheduled visit can occur any time during the study if the investigator believes the subject should be evaluated. The subjects will be instructed to notify the Study Coordinator or Principal Investigator with any medical/dental issues (cannot tolerate the rinse, oral issues, adverse events etc.) If the subject is requested to return to the clinic for an assessment/examination, this visit will be collected on the "unscheduled visit" form.

9.3 Adverse Events

An adverse event (AE) can be identified via visual examination by the dental examiner or reported by the subject. The Investigator is responsible for identifying AEs throughout the study. An AE may occur at any time during the conduct of the study, in any phase of the study or after the study is completed.

Examples of AEs that are considered expected during the conduct of the study include the following: mucosal sloughing, taste alteration, mouth or tongue numbness or tingling, and dry mouth. In addition, irritated or bleeding gums may occur due to probing during the dental examination.

9.3.1 Definitions

- Adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or any untoward clinical sign (including a laboratory abnormality) in human subjects or users, whether or not considered related to the subject's participation in the research.
- Serious Adverse Event (SAE) is an adverse event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in disability or permanent damage, or results in congenital anomaly or birth defect. In addition, and AE may be considered a SAE if based on appropriate medical judgment,

may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

- Adverse Device Effect (ADE) is an AE that is considered by the Investigator to have a reasonable likelihood of being related to the use of the investigational device.
- Serious Adverse Device Effect (SADE) is an ADE that resulted in any of the consequences of an SAE.
- Unanticipated Adverse Device Effect (UADE) is any adverse device effect which by its nature, incidence, severity, or outcome was not previously identified in the protocol, clinical investigation plan, Investigator's Brochure, or risk analysis report.
- Unanticipated Serious Adverse Device Effect (USADE) is any serious adverse device effect which by its nature, severity or outcome was not previously identified in the protocol, clinical investigation plan, Investigator's Brochure, or risk analysis report, or any other unanticipated serious problem associated with a device that relates to rights, safety and welfare of subjects.

9.3.2 Recording and Reporting

The site personnel record each AE occurring in the study, including those not thought to be associated with the device, on the AE CRF. Documentation includes the AE description, severity, seriousness, date of onset and resolution, relationship to the investigational device, action taken and outcome.

If the AE is considered by the Investigator to be related to the study device, the event is considered an adverse device effect. The site personnel must promptly report all adverse device effects to the 3M study monitor. If the adverse device effect is also considered by the Investigator to be serious and/or unanticipated the Investigator must report it to the IRB as soon as possible and within 10 working days.

3M reports a serious, unanticipated adverse device effect to the FDA within 10 working days of notification.

10. CLINICAL MONITORING

The study monitor is responsible for ensuring the proper conduct of the study in regards to ethics, protocol adherence and data validity of the data recorded on the Case Report Forms (CRFs). The CRFs will be verified by the monitor at the study site at regular intervals throughout the study. The Investigator must allow the monitor and/or representative of the Sponsor, and any regulatory body to review and inspect the study files, patient medical records and other related study documents as required. CRFs will be reviewed for completeness and clarity. Missing or unclear data will be investigated by the monitor and will be clarified throughout the study.

In order to perform this role, the monitor must be given direct access to all subject's source documents (e.g., general charts, appointment books, enrollment and follow-up forms) that supports data on the CRFs. The study personnel must make available such records to monitor and to regulatory personnel for inspection including:

- Informed consent forms and HIPAA forms
- All study related IRB correspondence
- Protocol amendments, IRB approval
- Protocol deviations
- Accounting of all medical devices and other supplies
- Adverse events/adverse device effects

The progress of the study will be monitored by:

- EDC review
- Periodic on site visit
- Telephone communications
- Review of source documents

10.1 Monitor Training

The designated monitor will be qualified by experience including knowledge of Good Clinical Practices.

10.1.1 Site/Investigator Training

The Sponsor will be responsible for providing training to the investigator and appropriate clinical site study personnel.

11. STATISTICAL METHODS

11.1 General Statistical Considerations

Means and standard deviations will be calculated for all clinical measurements and assessments. Categorical variables will be summarized in frequency distributions. Analysis of variance (ANOVA) or (ANCOVA) will be used to test for treatment group differences between the subject groups over the visits. When appropriate, alternative statistical methods such as normalizing transformations or nonparametric tests may be used to analyze the data.

The GI, PI, and BI scores will be calculated as the average tooth score across all measures and teeth surfaces as one score per patient, per visit. For example, a patient with 28 evaluable teeth will have 168 data points (6 per tooth) averaged per tooth and then averaged over all teeth to

produce one score per patient per visit. The subject indices computed will range between 0 and 3 (GI), or 0 and 5 (PI), or 0 and 1 (BI).

All statistical analyses will be performed using SAS version 9.3 or above (SAS Institute, Cary, NC) or another statistical software package.

11.2 Analysis Data Sets

The intent-to-treat (ITT) data set will be the primary dataset and will include ideally all subjects randomized with subjects analyzed in the group to which they were randomly assigned.

A second per-protocol (PP) data set will be defined excluding any subjects with major deviations or lack of compliance with taking their assigned study treatment. These major deviations will be defined in a blinded fashion prior to completion of any analyses and will include violating the PI and GI entry criterion and a compliance of < 80% of planned doses.

All subjects randomized will be included in the safety analyses. In addition, subjects participating in the washout period before randomization will be summarized.

11.3 Primary Efficacy Analyses with 3M Oral Rinse and Vehicle Control

Performance of the 3M Oral Rinse (3M OR) will be assessed based on two primary endpoints. Statistical analysis will be performed on the PI and GI scores at 6-months using an ANCOVA with treatment as the factor and baseline score as a covariate.

The success criterion for the study will be based on the single comparison between the 3M Oral Rinse group and the vehicle control group. The primary efficacy dataset will exclude data from the other two treatment groups, namely, the PerioShield (predicate) and the water control groups.

Significance of the overall treatment effect will be assessed by the p-value associated with the F-test statistic for the treatment group. The level of significance will be two-sided alpha of 0.05.

The main null hypothesis of interest to support that 3M Oral Rinse reduces plaque and gingivitis is as follows:

$$H_0: \mu_{\text{3M Oral Rinse}} \geq \mu_{\text{Vehicle}} \text{ versus } H_A: \mu_{\text{3M Oral Rinse}} < \mu_{\text{Vehicle}}$$

Both primary endpoint comparisons will be based on the intent-to-treat (ITT) data set. The study will be considered successful if both primary endpoints are met.

11.4 Secondary Efficacy Analyses with 3M Oral Rinse and Vehicle Control

Secondary efficacy hypotheses will be tested in a fixed sequential order, conditional on the expected significance of the primary analyses. The fixed-sequence testing of a subsequent

hypothesis will be conditional on the significant testing of the previous hypotheses. The sequential order of testing will preserve the one-sided alpha of 0.025 and is outlined as follows:

1. Modified Quigley-Hein Plaque Index (PI) at 3 months between the 3M Oral Rinse and the Placebo Vehicle Control
2. Löe-Silness Gingival Index (GI) at 3 months between the 3M Oral Rinse and the Placebo Vehicle Control
3. Eastman Interdental Bleeding Index at 6 months between the 3M Oral Rinse and the Placebo Vehicle Control
4. Eastman Interdental Bleeding Index at 3 months between the 3M Oral Rinse and the Placebo Vehicle Control

11.5 Secondary Efficacy Analyses with All Four Treatment Groups

All pairwise comparisons involving the four treatment groups, namely the 3M Oral Rinse, vehicle control, PerioShield predicate and water control groups, will be carried out with the PI and GI endpoints at 6 months. Analyses will be performed using the ANCOVA model and the p-values will be adjusted using the Tukey method.

11.6 Safety Analysis

Safety variables will include adverse events, abnormal soft and hard oral tissue, and reported side effects. First, an overall test will be carried out to compare each safety parameter among all four treatment groups. If this overall test is significant (p-value ≤ 0.05), pairwise comparisons will be carried out to compare the 3M Oral Rinse and the vehicle control. Each active vs vehicle comparison will be carried out at an alpha level of 0.05.

11.7 Missing Data

Subjects with missing PI and/or GI data will be included in the ITT analysis using appropriate input data sets and imputation methods. It is assumed that the data will be missing at random, and Expectation-Maximization (EM) algorithm will be used. If this assumption proves to be unreliable, other methods will be considered. In addition, a sensitivity analysis using alternative imputation methods to handle the missing data, namely last observation carried forward and using group means, will be conducted to examine the robustness of the primary analysis.

If a subject becomes pregnant during the study, the subject will be dropped and assessments completed.

11.8 Sample Size

The sample size was estimated based on GI and PI scores from the preliminary data (CR 14-006) and from the FDA approval documents obtained under Freedom of Information for the predicate

device, Decapinol Oral Rinse, manufactured by Sinclair Pharmaceuticals (identical product now marketed as PerioShield Oral Health Rinse in the US by Sunstar Americas, Inc.)[13]

It is estimated that 34 subjects per group will provide 90% power to detect a difference of 0.40 (standard deviation (SD) of 0.5) in the GI and PI scores using a 1-sided 0.025 alpha level. To account for possible dropouts, a sample size of 50 subjects per group will be recruited.

It is anticipated that 200 subjects enrolled, with 50 subjects in each of the four groups will provide adequate power for the study endpoints. Subjects who drop out will not be replaced. Each subject will be asked to return to the study clinic around the middle of the two recalls (1.5 and 4.5 months) for study product replenishment, assessment of diaries, concomitant medications and reinforcement of product use instructions.

11.9 Study Termination

3M may suspend or prematurely terminate the study at any time or for any reason.

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Institutional Review Board (IRB)

Prior to the initiation of the study, the protocol, informed consent form, HIPAA form, and other IRB required documentation will be submitted to the Loma Linda University Institutional Review Board (IRB) for review and approval. The Informed Consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization form will be signed by subject.

The Investigator is required to forward the Sponsor a copy of the written and dated IRB approval. Study products will not be shipped to the clinical trial site until a copy of written and dated approval have been received by the Sponsor.

The investigator is required to ensure compliance with all applicable laws and regulations governing patient privacy and maintain confidentiality and use coded patient identifying information.

During the clinical study, any amendment or modification to the protocol or informed consent form should be sent to the IRB, FDA and the Sponsor for review and approval.

12.2 Informed Consent

Prior to entering the study, the Investigator/Study Coordinator or designated assistant will explain to each subject the elements of informed consent including, nature of the study, the purpose, procedures and expected duration; and the benefits and risks involved in study participation etc. Each subject will be provided a consent document and will have the opportunity to ask questions. Each subject will be informed of his/her right to withdraw from the

study at any time without prejudice. After this explanation and before any study-specific procedures have been performed, the subject will voluntarily sign and date an informed consent form.

The Investigator or designated study coordinator must ensure that written authorization for use and disclosure of protected health information (HIPAA) is obtained before including any individual as a subject in the study.

The original signed consent and authorization forms will be maintained in the Investigator study documentation file.

13. DATA MANAGEMENT

13.1 Case Report Forms

The data will either be directly recorded into an Electronic Data Capture (eDC) system or will be recorded on data collection sheets and transferred into the eDC system.

In accordance with the Clinical Research Agreement, the Investigator shall allow the Sponsor to have access to the clinical study documents. The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data reported.

The Study Site will be trained on the completion of data collection forms and the use of the eDC system. The Study Coordinator, or designated data entry personnel will complete the data entry and query resolution in the eDC system promptly.

The Investigator is responsible for verification of the study data. The Investigator will:

- Ensure that the data collecting during the study conforms to the requirements for completeness, accuracy and reliable data.
- Maintain all study documentation and/or control and institute measures to prevent accidental or premature destruction of a data and/or documents related to the study

3M™ intends to use electronic data capture (eDC) software for this study. The site will be trained on the eDC software prior to study enrollment. They will be provided with a manual, including instructions on how to complete the eCRFs and how to make eCRF corrections. Data may be recorded onto data collection sheets prior to data entry or may be entered directly into the eDC system. Once the forms are completed, the monitor will review the eCRFs to assure accuracy and completeness. The Investigator must review and sign the eCRFs for each subject in a timely fashion following completion.

On resolution of all data queries and after completion of electronic signatures by the Investigator, the database will be closed and data listings, summary tables, graphical output and descriptive

statistics produced. Once all the subject data has been collected, the analysis and reporting will be conducted.

Any data existing for subjects who were randomized, who withdraw voluntarily or who are withdrawn from the clinical investigation, will be used in the final analysis. The inclusion of partial data will be documented in the final report.

13.2 Study Final Report

3M is responsible for writing a final report for the study which will be submitted to the FDA. The Investigator for the study will review and provide their signatures indicating their approval of the report.

13.3 Protocol Deviations

A deviation is a departure from the protocol that will likely affect the safety, rights or welfare of subjects, the scope of the investigation or the scientific quality of the study. A protocol deviation is only for an individual subject. Any deviation(s) will be documented using the Protocol Deviation Form. The form will include a description of the circumstances surrounding and the reason for the deviation as well as any actions taken. If the deviation affects subject safety, rights or welfare a copy is sent to the study monitor within 24 hours of identifying the occurrence.

Any finding that is considered to have a significant impact on the study objectives or integrity of the study as assessed by the Principal Investigator will be reported to 3M within 24 hours.

Deviations, which are made to protect the life or physical well-being of a subject in an emergency, must be reported by the Investigator to the IRB/IEC within 5 working days of occurrence and by 3M to the FDA within 5 working days after 3M learns of the occurrence.

13.4 Protocol Amendments

Amendments to the protocol or informed consent will be documented by the Investigator using an Amendment/Administrative Revision form and submitted to 3M. 3M will submit protocol amendments to the FDA and Investigator for submission to the IRB. 3M will notify the Investigator when a protocol amendment may be implemented.

14. RECORD KEEPING

14.1 Study Personnel Requirements

Prior to study initiation, the Investigator must provide CVs, Statement of Investigator and Financial Disclosure. The Investigator will provide a log of signatures/initials of staff participating in the study.

14.2 Pre-Study Documentation Requirements

Prior to study start, the Investigator must provide 3M with the following documents:

- Signed protocol including any amendments in place prior to study initiation
- Curriculum vitae for the Investigator and any sub-investigators
- IRB approved consent/authorization form
- IRB study approval letter
- IRB name, location, chairperson, and membership list
- Financial disclosure documents
- Signed research agreement

14.3 Records, Reports and Retention Requirements

Study records must be kept until 3M provides notification that the documents can be destroyed. To comply with regulatory requirements, the Investigator must arrange for the retention of all study records for 2 years following the date a marketing application is cleared, or if no application is filed, until 2 years after completion/termination of the study.

Records to be retained by the Investigator include, but are not restricted to:

- Study protocol, amendments, deviations
- IRB approval of protocol, consent form, authorization form, waiver of consent and/or authorization and amendments to any of these documents
- Applications to the IRB
- Signed consent/authorization forms
- eCRFs
- Records of receipt, use or disposition of the investigational drug
- Correspondence relating to the study
- Investigator Brochure
- Financial disclosure documents
- Sponsor Final Report

15. STUDY ADMINISTRATION

The following personnel will be responsible for the study administration:

Study Sponsor 3M ESPE Dental Products
2510 Conway Avenue

St. Paul, MN 55144-1000 USA

Principal Investigator	Yiming Li, DDS, MSD, PhD Associate Dean for Research Professor and Director, Center for Dental Research Loma Linda University School of Dentistry Professor of Microbiology and Molecular Genetics Loma Linda University School of Medicine 11175 Campus Street CSP-A1008A Loma Linda, CA 92350 Office Phone: (909) 558-8069 Fax (909) 558-0328 Email: yli@llu.edu
Sub-investigator	Sean Lee, DDS Professor and Director, Clinical Research Center for Dental Research Loma Linda University School of Dentistry 11175 Campus Street CSP-A1008A Loma Linda, CA 92350 Office Phone: 909-558-3221 Fax (909) 558-0328 Email: seanlee@llu.edu
3M Medical Monitor	Lois Duerst, DDS 3M ESPE Dental Products Staff Dentist 2510 Conway Avenue St. Paul, MN 55144-1000 USA Phone: 651- 733-0625 Email: lduerst@mmm.com
Study Coordinator	Michele Arambula, DA Clinical Research Coordinator Center for Dental Research Loma Linda University School of Dentistry 11175 Campus Street CSP-A1008A

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16. REFERENCES

1. American Academy of Periodontology. Parameter on plaque-induced gingivitis. *J Periodontol* 2000; 71: 851-852.
2. National Institute of Health and Clinical Excellence (NICE). Dental recall interval between routine dental examinations. *http://guidance.nice.org.uk/CG19 Clinical Guideline 19*; 2004.
3. Baehni PC, Takeuchi Y. Anti-plaque agents in the prevention of biofilm-associated oral disease. *Oral Diseases* 2003; 9 (Suppl 1): 23-29.
4. Moran JM. Chemical plaque control – prevention for the masses. *Periodontol 2000*, 1997; 15: 109-117.
5. Steinberg D, Feldman M, Ofek I, Weiss EI. Effect of a high-molecular weight component of cranberry on constituents of dental biofilm. *J Antimicrob Chemother* 2004; 54: 86-89.
6. Li Y. Lee S. Hujoel P. et al. Prevalence and severity of gingivitis in American adults. *American Journal of Dentistry*, 23 (1), Feb 2010, 9-13
7. Löe H, Silness J (1963). Periodontal disease in pregnancy. *Acta Odont Scand* 21:533-537.
8. Talbott K, Mandel ID, Chilton NW. Reduction of baseline gingivitis scores with repeated prophylaxis. *J Prev Dent* 1977; 4: 28-29.
9. Quigley GA, Hein JW. Comparative cleaning efficacy of manual and power brushing. *J Am Dent Assoc* 1962; 65:26-29.
10. Turesky S, Gilmore ND, Glickman I. Reduced plaque formation by the chloromethyl analogue of Vitamin C. *J Periodontol* 1970; 41:41-43.
11. Lobene RR, Soparkar PM, Newman MB. Use of dental floss. Effect on plaque and gingivitis. *Clin Prev Dent*. 1982; Jan-Feb; 4(1):5-8.
12. Caton JG, Polson AM. The interdental bleeding index: a simplified procedure for monitoring gingival health. *Compend Cont Ed Dent* 1985; 6:88, 90-92.
13. FDA FOI, 510(k) for Sinclair Pharmaceuticals PMA for Decapinol, Retrieved from *http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHFOIAElectronicReadingRoom/UCM237296.pdf*

17. APPENDICES

17.1 Appendix 1: Subject Instructions

Subject Instructions

Use only the study products provided. Do not use any other toothpaste, chewing gum, toothbrush, dental floss or mouth rinses during the study.

Rinse Instructions:

- Brush teeth in the morning and evening using the study toothpaste and toothbrush.
- After brushing pour 10 or 15 mL (study coordinator to circle dose) of the rinse into the dosing cup (do not use directly from the bottle)
- Replace the cap after each rinse dose
- Rinse for 30 seconds and spit out
- Do not eat or drink for 30 minutes after using the rinse
- Use one bottle of a rinse at a time (one bottle should last about 3 weeks)
- Avoid skin and eye contact
- Store at room temperature

Call with any study concerns: Dr. Yiming Li (909) 558-8069 (*ext.* 88069), or the Study Coordinator, Michele Arambula, DA at (909)-558-8170 or Email: marambula@llu.edu

Your next interim visit appointment is on _____

- Bring back all study supplies including the empty rinse bottle, toothpaste, floss and brush in the container provided at the start of the study

Your next clinical examination and assessments is on _____

- Do not brush or floss your teeth after 10 pm the night before
- Do not eat or drink for 4 hours before this visit for your clinical exam
- Do not brush your teeth the night before and the morning of this appointment for clinical exams
- Bring back all study supplies in the container provided at the start of the study

17.2 Appendix 2: Training and Calibration of Clinical Examiners

Training and Calibration of Gingival Index (GI) and Plaque Index (PI) Examination

The clinical examination of the GI and PI will be performed by experienced examiners who have publications on the GI and PI evaluation, and the examiners will perform the same clinical examination throughout the study. To ensure adequate reliability and consistency, a training and calibration session on the GI and PI evaluation will be conducted for the examiners prior to the baseline, 3-month, and 6-month visits.

The training and calibration will be conducted using digital dental photographs of 15 historical subjects selected from a library at the study site. The digital dental photographs of 15 subjects will be selected to provide adequate representation of the full range of the GI (0 to 3) and PI (0 to 5) scales. In addition, the goal will be to achieve a sample that is representative of the study population in terms of race, age and sex. The digital dental photographs instead of subjects are used for training and calibration because clinical examination of the GI and PI on the same subject by multiple examiners will produce significant variations between evaluations as well as discomfort to the subject.

The Principal Investigator will review the criteria of the GI and PI with the examiner, who will then determine the initial score; after one week, the examiner will again reevaluate the same set of the digital dental photographs in a random order. The two-way random, single measure reliability of the Intraclass Correlation Coefficient (ICC) will be computed and ICC values ≥ 0.85 will signal acceptable calibration of the study examiner.