Attachment 3

CONSUMER HEALTH CARE RESEARCH AND DEVELOPMENT

PFIZER

CLINICAL PROTOCOL

PROTOCOL NO. 103-0004

PROTOCOL NAME:

Comparative Antiplaque/Antigingivitis Effectiveness of Essential Oil Mouthrinses, with and without Fluoride: A Six-month Clinical Trial

STATUS: Draft
DATE: 25 June 2002

AMENDMENT no.: Not Applicable
STATUS:
DATE:

PROTOCOL SYNOPSIS

Title:
Comparative Antiplaque/Antigingivitis Effectiveness of Essential Oil Mouthrinses, with and without fluoride: A Six-month Clinical Trial

Protocol Identifier: 103-0004

Rationale:

This investigation is being conducted to determine whether the addition of sodium fluoride to an essential oil-containing mouthrinse affects the antiplaque/antigingivitis effectiveness of the mouthrinse.

Objective(s):

Primary: The objective of this controlled clinical study is to compare the efficacy of an essential oil-containing mouthrinse with fluoride to that of an essential oil-containing mouthrinse without fluoride (positive control) in inhibiting the development of supragingival dental plaque and gingivitis in a six-month period.

Secondary: Not applicable.

Subjects and Centers:

A population of 340 evaluable subjects from the Mississauga, Ontario area is expected to complete this single center study.

Inclusion/Exclusion Criteria:
To be eligible for study participation, subjects must meet the following criteria:

1. Males and females between the ages of 18 and 65 in good general and oral health.
2. A minimum of 20 natural teeth with scorable facial and lingual surfaces. Teeth that are grossly carious, fully crowned or extensively restored, orthodontically banded, abutments, or third molars will not be included in the tooth count.
3. A gingival index ≥ 1.75 according to the Modified Gingival Index.
4. A plaque index ≥ 1.95 according to the Turesky modification of the Quigley-Hein Plaque Index scored on six surfaces per tooth.
5. Volunteers must read, sign, and receive a copy of the Informed Consent Form after the nature of the study has been fully explained.

Subjects presenting with any of the following will not be included in the study:

1. History of significant adverse effects following use of oral hygiene products such as toothpastes and mouthrinses.
2. History of uncontrolled diabetes or hepatic or renal disease, or other serious medical conditions or transmittable diseases, e.g. cardiovascular disease or AIDS.
3. History of rheumatic fever, heart murmur, mitral valve prolapse or other conditions requiring prophylactic antibiotic coverage prior to invasive dental procedures.
4. Antibiotic, anti-inflammatory or anticoagulant therapy during the month preceding the baseline exam.
5. Alcoholism, current or recovered.
6. Donation of blood or blood products for transfusion during the 30 days prior to initiation of treatment with study material(s)
7. Participation in any study involving oral care products, concurrently or within the previous 30 days.
8. Self reported pregnancy or lactation (This criterion is due to oral tissue changes related to pregnancy and nursing which can affect interpretation of study results).
9. Significant oral soft tissue pathology, excluding gingivitis, based on a visual examination.
10. Moderate/advanced periodontitis based on a clinical examination (ADA Type III, IV).
11. Any object used for lip, tongue, or other form of oral piercing.
12. Teeth with gross dental caries, large fractured or temporary restorations or severe generalized cervical abrasion and/or enamel abrasion.
13. Fixed or removable orthodontic appliance or removable partial dentures.
14. Use of chemotherapeutic antiplaque/antigingivitis products such as Colgate Total® or chlorhexidine mouthrinse within 2 weeks prior to baseline.

Other Therapy:

ADA-Accepted fluoride toothpaste, ADA-accepted soft textured toothbrush.

Study Design:

This is a single center, double-blind, controlled, parallel-group design clinical trial. Qualified subjects will receive a dental prophylaxis, then rinse twice daily with 20 ml of their assigned mouthrinse for six months while continuing their usual brushing with an ADA-Accepted fluoride toothpaste.

Efficacy Measures:

The primary efficacy variables will be the mean Modified Gingival Index and mean Plaque Index at six months post-baseline.

The secondary efficacy variables will be the mean Bleeding Index at three and six months post-baseline and the mean Modified Gingival Index and mean Plaque Index at three months post-baseline. All indices will be scored at baseline, 3 months and 6 months.

Safety:

An oral soft and hard tissue examination will be performed at baseline, 3 months, and 6 months. At each visit, each subject will be queried in a nonspecific manner to record adverse events.

Decision Points/Statistical Methods/Interim Analysis:

The primary analysis will be based on evaluable subjects, defined as all subjects with no major protocol violations. Demographic and baseline analyses will be performed for randomized as well as evaluable subjects.

For each of the primary and secondary efficacy variables, between-treatment differences at 3 months and 6 months post-baseline will be tested by means of a one-way analysis of covariance model with treatment and smoking status as factors and the corresponding baseline value as the covariate. The treatment-by-baseline interaction will be tested at the 0.05 level to assess heterogeneity of slopes.

The research question is:

> Is the essential oil-containing mouthrinse with fluoride (EOF rinse) (W2194-471) "at least as good as" the essential oil-containing mouthrinse without fluoride (EO rinse) (W2194-395) in inhibiting the development of supragingival plaque and gingivitis?

EOF rinse will be considered "at least as good as" EO rinse in inhibiting the development of plaque and gingivitis if, for each of the primary efficacy variables,

1. The mean for EOF rinse group is statistically significantly lower than the mean for the 5% hydroalcohol control, based on a two-sided 0.05-level test of the null hypothesis that the treatment means are equal versus the alternative hypothesis that the means are different, and
2. The upper limit of the one-sided 97.5% confidence interval for the difference between the means for EOF rinse and EO rinse groups (expressed as a percentage difference relative to EO rinse mean) is below 10%[13]. This procedure is a 0.025 level test of the null hypothesis that the mean for EOF rinse is at least 10% higher than the mean for EO rinse, versus the alternative hypothesis that the mean for EOF rinse is not at least 10% higher than the mean for EO rinse group.

The study will be considered validated if the post baseline six-month means of the primary efficacy variables for EO rinse group are statistically significantly lower than the corresponding means of the 5% hydroalcohol control rinse group based on a two-sided test.

Test Material Regimens:

All subjects will brush with an ADA-Accepted fluoride toothpaste in their usual manner and rinse with assigned mouthrinses twice daily according to label directions (20 ml for 30 seconds, full strength). Although product usage will be unsupervised, subjects will maintain a diary of their product use.

Special Equipment/Measures:

A Qulix™ Color Coded Probe PCPll.5B (Hu-Friedy Mfg. Co., Inc., Chicago, IL, USA) with a 0.5 mm diameter tip.

Comparative Antiplaque/Antigingivitis Effectiveness of Essential Oil Mouthrinses, with and without Fluoride: A Six-month Clinical Trial

Protocol ID: 103-0004

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Date of draft protocol:	25 June 2002
Date(s) of Amendments (if applicable):	Amendment #1: Amendment #2:

TABLE OF CONTENTS

1.0 INTRODUCTION 1
2.0 OBJECTIVES 2
2.1 Primary Objective(s) 2
2.2 Secondary Objective(s) 2
3.0 STUDY DURATION 2
4.0 NUMBER OF SUBJECTS 2
5.0 COMPLIANCE WITH GOOD CLINICAL PRACTICE AND ETHICAL CONSIDERATIONS 2
5.1 Regulatory and Institutional Review 3
5.1.1 Approval/Favorable Opinion of Study Documents 3
5.1.2 Ethical Review of Amendments to Study Documents 3
5.1.3 Variations to the Protocol 4
5.2 Informed Consent 4
6.0 CRITERIA FOR STUDY SUBJECT SELECTION 4
6.1 Inclusion Criteria 4
6.2 Exclusion Criteria 5
7.0 METHODOLOGY 6
7.1 Study Design 6
7.2 Study Schedule 7
7.3 Study Visits 7
7.3.1 Screening Visit 7
7.3.2 Procedures During the Study Treatment Period 7
7.4 Study Evaluations/Procedures 9
7.5 Definition of Efficacy Endpoints 11
7.5.1 Primary Efficacy 11
7.5.2 Secondary Efficacy Variable(s) 11
7.6 Efficacy Analyses 12
7.7 Study Treatment 12
7.7.1 Identity 12
7.7.2 Packaging, Labeling, and Storage 12
7.7.3 Blinding and Breaking the Blind 13
7.7.4 Test Material Dispensing and Accountability 14
7.7.5 Test Material Administration 14

7.7.6 Compliance 14
7.8 Termination of the Study 14
8.0 SAFETY REPORTING 15
8.1 Adverse Event 15
8.2 Serious Adverse Events 16
8.3 Discontinuations 19
9.0 CONCOMITANT THERAPY 19
10.0 STUDY MANAGEMENT AND MATERIALS 19
10.1 Study Materials 19
10.2 Study Documentation 20
10.2.1 Case Report Forms (CRFs) and Source Document Completion and Transfer of Study Data 20
10.2.2 Subjects' Diaries 20
10.2.3 All Other Study Documents/Forms 20
10.2.4 Transfer of Essential Study Documents 20
10.2.5 Archiving of Study Documentation 21
10.3 Monitoring and Quality Assurance 21
11.0 CONFIDENTIALITY 21
12.0 DATA ANALYSIS 22
12.1 Demographic And Baseline Characteristics 22
12.2 Efficacy Evaluation 22
12.3 Safety Data 23
12.4 Sample Size And Power Considerations 23
13.0 FINANCIAL DISCLOSURE 24
14.0 REFERENCES 24
15.0 APPENDICES 25

1.0 INTRODUCTION

In both short term and long term studies there is ample evidence that an essential oil-containing mouthrinse (Listerine® Antiseptic, Pfizer Consumer Healthcare, Morris Plains, NJ) significantly reduces supragingival plaque and gingivitis[1-5]. The six-month studies, designed in accordance with ADA Guidelines[6], consistently showed gingivitis and plaque reductions for those subjects rinsing with Listerine formulations compared to a negative control rinse[2-5]. In these studies, twice-daily rinsing with the essential oil mouthrinse, used adjunctively to the subjects' usual mechanical oral hygiene procedures, reduced gingivitis by as much as 36% and plaque by as much as 56%, compared to a negative control rinse. Furthermore, recent analyses[7] have shown that Listerine mouthrinse is efficacious at interproximal sites as well as facial and lingual sites. The FDA Dental Plaque Products Subcommittee has recommended that the fixed combination of essential oils found in Listerine be classified as Category I for safety and effectiveness in the control of supragingival plaque and gingivitis.

We have recently developed a product in which 0.02% sodium fluoride has been added to the essential oil-containing mouthrinse formulation. Of all the fluoride compounds, only stannous fluoride has been demonstrated to have antiplaque/antigingivitis activity and was recommended for Category I classification by the FDA Dental Plaque Products Subcommittee. While there is no clear scientific rationale for postulating that the addition of **sodium fluoride** would affect the antiplaque/antigingivitis effectiveness of the essential oil rinse, either positively or negatively, the FDA has sought confirmation that, in fact, this is the case. Accordingly, we have compared the antiplaque and antigingivitis activities of essential oil mouthrinses, with and without sodium fluoride, using an experimental gingivitis model[1]. This study was designed based on statistical considerations which would allow for a comparison between the essential oil mouthrinse with fluoride (EOF) and the essential oil-containing mouthrinse (EO) using "at least as good as" criteria[8]. The EOF mouthrinse formulation produced statistically significant ($p<0.001$) reductions in gingivitis and plaque of 12.3% and 30.0%, respectively, relative to the negative control. These reductions were comparable to the reference standard formulation (EO rinse). In addition, the EOF mouthrinse satisfied the "at least as good as" criteria relative to the EO mouthrinse formulation. The results of this study indicate that the incorporation of sodium fluoride into the essential oil-containing mouthrinse formulation did not adversely impact the antiplaque and antigingivitis activity of the Listerine mouthrinse.

An experimental gingivitis model was initially selected to evaluate the relative effectiveness of the EOF and EO mouthrinse formulations based on the acceptance of this model by the Dental Plaque Products Subcommittee for final formulation clinical testing of formulations containing the fixed combination of essential oils. However, in view of the fact that the monograph for antiplaque/antigingivitis ingredients has not yet been developed, the FDA raised questions about the suitability of this model for assessing whether the addition of sodium fluoride affects the activity of the fixed combination of essential oils. In order to

more definitively determine this, we have designed this controlled six-month clinical trial to evaluate the antiplaque and antigingivitis efficacy of twice daily rinsing with an essential oil-containing mouthrinse with 0.02% sodium fluoride compared to an essential oil-containing mouthrinse without fluoride. This six-month study is based on ADA Guidelines and, further, conforms to the study design required by the FDA Plaque Products Subcommittee to determine ingredient effectiveness of antiplaque/antigingivitis formulations.

2.0 OBJECTIVES

2.1 Primary Objective(s)

The objective of this controlled clinical study is to compare the efficacy of an essential oil-containing mouthrinse with fluoride to that of an essential oil-containing mouthrinse without fluoride (positive control) in inhibiting the development of supragingival dental plaque and gingivitis in a six-month period.

2.2 Secondary Objective(s)

Not applicable.

3.0 STUDY DURATION

The maximum and expected duration of exposure to the clinical test material(s) for an individual subject will be six months. The estimated length of time needed to complete the entire study (from enrollment of the first subject to completion of the last subject) is eight months.

4.0 NUMBER OF SUBJECTS

A sufficient number of subjects will be enrolled in this study to ensure that 340 evaluable subjects complete this study. Each subject will receive individually coded 1.0 L. bottles of mouthrinse, an ADA-Accepted soft textured toothbrush and ADA-accepted fluoride toothpaste as needed. Subjects will rinse twice daily for 30 seconds with 20ml of either an essential oil-containing mouthrinse with 0.02% sodium fluoride, an essential oil-containing mouthrinse without fluoride, or 5% Hydroalcohol negative control mouthrinse following regular brushing for 6 months. Subjects who do not complete the study will not be replaced.

5.0 COMPLIANCE WITH GOOD CLINICAL PRACTICE AND ETHICAL CONSIDERATIONS

This study will be conducted in compliance with Good Clinical Practice (GCPs), including International Conference on Harmonization (ICH) Guidelines, and in general, consistent with

the 1989 version of the Declaration of Helsinki. (See Appendix A) In addition, all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved will be adhered to.

5.1 Regulatory and Institutional Review

5.1.1 Approval/Favorable Opinion of Study Documents

Before the start of the study, documents submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for review and approval/favorable opinion must include:

- Most current version of approved study protocol, signed and dated by Pfizer and the investigator
- Case report form (if applicable)
- Informed consent form
- Advertising and subject recruitment procedures
- Written information to be provided to subjects,
- The Investigator's Brochure (IB)/other safety documents, or locally approved labeling, for approved/marketed drugs or products, in studies with approved indications or dosage forms
- Summary of serious adverse events (saes) or other available safety information including all test material-related serious unexpected aes (e.g., from recent/ongoing non-clinical and clinical studies, toxicology and pharmacokinetic data, etc) which are not included in the IB or locally approved labeling, for approved marketed drugs or products.
- Information about compensation available to subjects
- Investigators' current curriculum vitae and/or other documentation evidencing qualifications

A copy of the IRB/IEC approval/favorable opinion, along with any other documents required under local regulations or standards, must be on file at Pfizer before the first shipment of clinical supply is provided to the study site.

5.1.2 Ethical Review of Amendments to Study Documents

All amendments to the protocol and informed consent form, which require regulatory and/or IRB/IEC approval/favorable opinion, must be reviewed and approved by the sponsor, IRB/IEC and/or local authorities before being implemented. Amendments should not be implemented until all necessary approvals have been obtained, except where necessary to eliminate an immediate hazard(s) to study subjects. Additionally, updates to the IB/other safety documents or locally approved labeling during the study must be submitted to the IRB/IEC for approval/favorable opinion, as appropriate.

5.1.3 Variations to the Protocol

Variations to the protocol are not permitted except where necessary to eliminate an immediate hazard(s) to study subjects. In the event of any deviation from the protocol, the investigator must document the nature of and rationale for the deviation, and promptly notify Pfizer and/or the CRO, as applicable. In addition, the investigator must notify the IRB/IEC, to the extent necessary under GCPs and local requirements.

5.2 Informed Consent

Informed consent must take place before any study specific procedure (including at screening), prior to the initiation of non-routine study-related tests, and prior to administration of clinical test material(s) (either investigational product, comparative product, or placebo). Signed and dated, informed consent will be obtained from each subject (or his/her legally acceptable representative) in accordance with GCPs and with local regulatory and legal requirements. The completed informed consent form must be retained by the investigator as part of the study records.

The informed consent form will be modified, as appropriate (e.g., due to protocol amendment or significant new safety information). If the consent form is revised, it is the investigator's responsibility to ensure that an amended consent is reviewed and approved by Pfizer prior to approval/favorable opinion by the local IRB/IEC, and that it is signed by all subjects subsequently entered in the study and those currently in the study.

Documentation that the informed consent was signed and dated prior to study screening must appear in the study case report form and medical records at the time the informed consent is obtained.

6.0 CRITERIA FOR STUDY SUBJECT SELECTION

Three hundred volunteer subjects will be required to complete the study. Approximately 375 subjects are needed to enter the study so that 340 evaluable subjects could be reasonably expected to complete the study. Volunteers must read, sign, and receive a copy of the Informed Consent Form after the nature of the study has been fully explained. Subjects will be selected by the investigator from a panel of subjects located in the Mississauga, Ontario area.

6.1 Inclusion Criteria

To be eligible for study participation, the subject must meet the following criteria:

1. Males and females between the ages of 18 and 65 in good general and oral health, except gingivitis.

2. A minimum of 20 natural teeth with scorable facial and lingual surfaces. Teeth that are grossly carious, fully crowned or extensively restored, orthodontically banded, abutments, or third molars will not be included in the tooth count.

3. A gingival index ≥ 1.75 according to the Modified Gingival Index.[9]

4. A plaque index ≥ 1.95 according to the Turesky modification of the Quigley-Hein Plaque Index scored on six surfaces per tooth.[10]

5. Volunteers must read, sign, and receive a copy of the Informed Consent Form after the nature of the study has been fully explained.

6.2 Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. History of significant adverse effects following use of oral hygiene products such as toothpastes and mouthrinses.

2. History of uncontrolled diabetes or hepatic or renal disease, or other serious medical conditions or transmittable diseases, e.g. cardiovascular disease or AIDS.

3. History of rheumatic fever, heart murmur, mitral valve prolapse or other conditions requiring prophylactic antibiotic coverage prior to invasive dental procedures.

4. Antibiotic, anti-inflammatory or anticoagulant therapy during the month preceding the baseline exam.

5. Alcoholism, current or recovered.

6. Donation of blood or blood products for transfusion during the 30 days prior to initiation of treatment with study material(s).

7. Participation in any study involving oral care products, concurrently or within the previous 30 days.

8. Self reported pregnancy or lactation (This is an exclusion criterion due to oral tissue changes related to pregnancy and nursing that can influence the study parameters).

9. Significant oral soft tissue pathology, excluding gingivitis, based on a visual examination.

10. Moderate/advanced periodontitis based on a clinical examination (ADA Type III, IV).

11. Any object used for lip, tongue, or other form of oral piercing.

12. Teeth with gross dental caries, large fractured or temporary restorations or severe generalized cervical abrasion and/or enamel abrasion.

13. Fixed or removable orthodontic appliance or removable partial dentures.

14. Use of chemotherapeutic antiplaque/antigingivitis products such as Colgate Total® or chlorhexidine mouthrinse within 2 weeks prior to baseline.

If the subject reports taking medication, a history of allergy, and/or a chronic disease which in the opinion of dental examiner will not affect the clinical parameter(s) being assessed or the safety of the subject, the subject may be enrolled in the study and it will be noted on the Subject Screening Form. The use of any mouthrinse, dentifrice, or any oral hygiene devices other than the test materials supplied is prohibited.

7.0 METHODOLOGY

This is a single center, randomized, controlled, observer blind, parallel group, clinical trial. A 5% hydroalcohol mouthrinse will be used as a negative control and an essential oil-containing mouthrinse without fluoride will serve as the positive control. This study will consist of an initial recruitment phase in which potential subjects will complete health questionnaires an informed consent form and a screening examination. Gingivitis and plaque levels will be determined according to the Modified Gingival Index [9], Turesky modification of the Quigley-Hein Plaque Index[10], and the Bleeding Index[11, 12]. Subjects fulfilling entry criteria will be enrolled and randomly assigned to one of the three mouthrinse groups.

7.1 Study Design

At baseline, the prescreened subjects will present to the clinical site for baseline examinations having refrained from oral hygiene for at least 8 hours, but no more than 18 hours, that day. Subjects will be randomly assigned to one of the three test groups, stratified by smoking status, and receive a complete dental prophylaxis to remove plaque, stain and calculus (confirmed by use of disclosing solution). Subjects will be instructed to brush twice daily with the ADA-Accepted fluoride toothpaste using an ADA-Accepted soft textured toothbrush and to rinse twice daily for 30 seconds with 20 mL of their assigned mouthrinse for 6 months. All daily brushing and rinsing will be unsupervised, however, subjects will be required to maintain a diary to document product use and compliance will be reinforced at each visit by measuring residual volumes of returned mouthrinse bottles. All subjects will be instructed not to rinse, eat or drink for 30 minutes after each mouthrinse use.

Daily rinses will be unsupervised with the exception of the rinse at the baseline visit. Each of the daily rinses shall be separated by at least four hours. During the study, subjects will follow their usual dietary habits but will be instructed to refrain using any oral care products other than the mouthrinse, toothpaste and toothbrush provided to them.

Compliance will be monitored at monthly intervals. Additional study materials will be dispensed as needed at these visits. At the three- and six-month visits, the Modified Gingival Index (MGI), Turesky modification of the Quigley-Hein Plaque Index (PI), and the Bleeding Index (BI) will be scored and the oral tissue examinations performed. At the three- and six-month visits, subjects will not have used their test materials for at least four hours prior to their clinical examinations to avoid potential examiner bias from the odor of the mouthwash formulations. All unused materials will be collected and measured, and daily product use diaries will be assessed.

7.2 Study Schedule

Appendix B, *Study Flow Chart*, contains the schedule of observations and assessments to take place during the study.

7.3 Study Visits

7.3.1 Screening Visit

Prior to entry into this study the following procedures will be performed:

- Informed consent and medical history
- Oral hard and soft tissue examination, MGI, BI and PI scoring
- Identification of subjects with qualifying supragingival plaque and gingivitis

7.3.2 Procedures During the Study Treatment Period

Baseline

Visit 1: Baseline Visit

- Query to update medical and oral health and record adverse events and concomitant medications.
- Oral Exam, MGI, BI and PI scoring

If subject meets entry criteria, the following procedures will be conducted

- Complete prophylaxis
- Randomization to test groups stratifying by smoking status (smokers versus nonsmokers)

- Dispense clinical test materials: fluoride toothpaste and assigned mouthrinse, toothbrush, home care/product use diary,
- Provide verbal and written study instructions and daily home care diary
- Appoint subjects for next visit

Visit 2: One-Month Visit (Compliance Visit)

- Query to update medical and oral health and record adverse events and concomitant medications.
- Assess compliance with use of clinical test material(s) by means of reviewing diaries and measuring returned mouthrinse volumes
- Dispense additional clinical test material(s)
- Schedule next visit

Visit 3: Two-Month Visit (Compliance Visit)

- Query to update medical and oral health and record adverse events and concomitant medications.
- Assess compliance with use of clinical test material(s) by means of reviewing diaries and measuring returned mouthrinse volumes
- Dispense additional clinical test material(s)
- Schedule next visit

Visit 4: Three-Month Exams

- Query to update medical and oral health and record adverse events and concomitant medications.
- Assess compliance with clinical test material(s) by means of reviewing diaries and measuring returned mouthrinse volumes
- Oral hard and soft tissue examination, MGI, PI, and BI scoring
- Dispense additional clinical test material(s)
- Schedule next visit

Visit 5: Four-Month Visit (Compliance Visit)

- Query to update medical and oral health and record adverse events and concomitant medications.
- Assess compliance with use of clinical test material(s) by means of reviewing diaries and measuring returned mouthrinse volumes
- Dispense additional clinical test material(s)
- Schedule next visit

Visit 6: Five-Month Visit (Compliance Visit)

- Query to update medical and oral health and record adverse events and concomitant medications.
- Assess compliance with use of clinical test material(s) by means of reviewing diaries and measuring returned mouthrinse volumes
- Dispense additional clinical test material(s)
- Schedule next visit

Visit 7: Six-Month Visit (Final Exam)

- Query to update medical and oral health and record adverse events and concomitant medications
- Assess compliance with clinical test material(s) by means of reviewing diaries and measuring returned mouthrinse volumes
- Oral examination, MGI, PI, and BI
- Complimentary prophy

7.4 Study Evaluations/Procedures

A single trained dental examiner will perform all examinations and scoring. Prior to initiation of the study, the examiner will review the plaque and gingivitis indices with a representative of the sponsor and an examiner reproducibility exercise will be conducted. The examiner will score at least ten subjects for gingivitis, according to the MGI, and then perform repeat examinations of the same subjects in a random sequence, after a reasonable period of time on day 1, so as to avoid possible recall of scores. On day 2 of the exercise, the examiner will score at least ten subjects for plaque and then perform repeat examinations within the same day of the same subjects in a random sequence so as to avoid possible recall of scores.

Repeatability of mean index scores will be assessed using the intraclass correlation coefficient, R, which will be obtained from the analysis of variance with subject as a factor. The intraclass correlation coefficient, R, will be calculated by dividing the difference of the between- and within-subject mean squares by the sum of the between and within-subject mean squares [4]. The intraclass correlation coefficients for the mean PI and the mean MGI must be > 0.85 to demonstrate examiner reproducibility.

For each scoring assessment, the examiner will call out his/her findings to the recorder who will enter the findings on the appropriate paper case report forms. The examiner will not have access to the case report forms until the completion of the examinations.

Subjects will refrain from oral hygiene for at least 8 hours, but no more than 18 hours, on the day of the baseline examinations and will additionally refrain from use of test products for at least 4 hours prior to the examinations at 3 and 6 months. Separate case report forms will be used at each examination.

Case report forms will be submitted to the sponsor after completion of each examination period. The investigator will retain copies of the case report forms.

The following exams will be conducted at baseline, 3 months, and 6 months in the order presented:

Oral Examination

An oral examination will be conducted at baseline, three months and six months to monitor the effect of the mouthrinse formulations on the soft and hard tissues. Buccal, labial and sublingual mucosae, tongue, hard and soft palate, uvula and oropharynx, and teeth will be examined and findings will be recorded on the Oral Exam CRF. Changes from the baseline and previous visits will be recorded at each subsequent clinic visit. Clinically significant findings will be recorded as adverse events and assessment made regarding relationship to test materials.

Modified Gingival Index

Gingivitis will be assessed at baseline, three and six months by the Modified Gingival Index[9] on the buccal and lingual marginal gingivae and interdental papillae of all scorable teeth:

0 - Normal (absence of inflammation).
1 - Mild inflammation (slight change in color, little change in texture) of any portion of the 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.

Gingival Bleeding Index

Bleeding will be assessed at baseline, 3 and 6 months according to the Gingival Bleeding Index .[11, 12] A periodontal probe, (Qulix™ Color Coded Probe PCPll.5B, Hu-Friedy Mfg. Co., Inc., Chicago, IL , USA) with a 0.5 mm diameter tip will be inserted into the gingival crevice, and swept from distal to mesial around the tooth at an angle of approximately 60°, while in contact with the sulcular epithelium. Each of 4 gingival areas (disto-buccal, midbuccal, mesio-buccal and mid-lingual) around each tooth will be assessed. After

approximately 30 seconds, bleeding at each gingival unit will be recorded according to the following scale:

0- Absence of bleeding after 30 seconds
1- Bleeding after 30 seconds
2- Immediate bleeding

Turesky Modification of the Quigley-Hein Plaque Index

Plaque area will be scored at baseline, 3 and 6 months by the Turesky modification of the Quigley-Hein Plaque Index[12], on six surfaces (distobuccal, midbuccal and mesiobuccal, distolingual, midlingual and mesiolingual) of all scorable teeth, following disclosing:

0 - No plaque.
1 - Separate flecks or discontinuous band of plaque at the gingival (cervical) margin.
2 - Thin (up to 1 mm), continuous band of plaque at the gingival margin.
3 - Band of plaque wider than 1 mm but less than 1/3 of surface.
4 - Plaque covering 1/3 or more, but less than 2/3 of surface.
5 - Plaque covering 2/3 or more of surface.

7.5 Definition of Efficacy Endpoints

Antiplaque/antigingivitis efficacy will be determined primarily by evaluation of the amount of supragingival dental plaque and of visual signs of marginal gingivitis, and secondarily by gingival bleeding determinations.

Gingival inflammation will be assessed at baseline, three and six months using the Modified Gingival Index and the gingival Bleeding Index. Supragingival plaque levels will be assessed using the Turesky Modification of the Quigley-Hein Plaque Index.

7.5.1 Primary Efficacy

The primary efficacy variables are whole mouth six-month mean Modified Gingival Index (MGI) scores and whole mouth six-month mean modified Quigley-Hein Plaque Index (PI) scores.

7.5.2 Secondary Efficacy Variable(s)

The secondary efficacy variables are the three and six-month mean Gingival Bleeding Index scores and the whole mouth three-month mean MGI and PI scores.

7.6 Efficacy Analyses

Efficacy analysis will be based on data from evaluable subjects, defined as all randomized subjects with no major protocol violations. Demographic and baseline analyses will be performed both for all randomized subjects and for all evaluable subjects.

7.7 Study Treatment

7.7.1 Identity

Test Material:	**Essential oil-containing Mouthrinse with 0.02% Sodium Fluoride (EOF rinse)**
Formulation Number:	W2194-471
Trade name:	FreshBurst Listerine® Antiseptic Mouthrinse with Fluoride
Dosage form:	20ml rinsed twice a day for 30 seconds
Manufacturer:	Pfizer Consumer Healthcare

Positive Control	**FreshBurst Listerine® Antiseptic Mouthrinse (EO rinse)**
Formulation Number:	W2194-396
Trade name:	FreshBurst Listerine® Antiseptic Mouthrinse
Dosage form:	20ml rinsed twice a day for 30 seconds
Manufacturer:	Pfizer Consumer Healthcare

Negative Control	**5% Hydroalcohol Mouthrinse**
Formulation Number:	W002194-0483P
Dosage form:	20ml rinsed twice a day for 30 seconds
Manufacturer:	Pfizer Consumer Healthcare

7.7.2 Packaging, Labeling, and Storage

At the screening visit, each subject will be given a screening number beginning with S001. Upon qualification, each enrolled subject will be sequentially issued a unique subject number, which determines the treatment assignments according to a randomization schedule.

Pfizer Clinical Consumer and Packaging Operations will package clinical test materials in accordance with applicable regulatory requirements. Mouthrinses will be provided in subject specific bottles utilizing a one-part label containing the following information:

Protocol #	Dosing instructions
Subject #	Warnings
Site identification	Net contents

The test mouthrinses will be supplied in 1.5 L plastic (PET) bottles. The ADA-Accepted toothpaste and soft toothbrushes will be supplied in original marketed packaging. All clinical test supplies will be packed in subject specific boxes/bags containing one bottle of the assigned mouthrinse, one 8.2 oz. tube of ADA-Accepted fluoride and one soft toothbrush.

Labeling of study supplies will be in compliance with regulatory requirements. All test materials must be stored in accordance with the manufacturers' instructions. Until dispensed to the subjects, the test materials will be stored in a securely locked area at 59° - 77°F, accessible only to authorized personnel.

7.7.3 Blinding and Breaking the Blind

The Pfizer Clinical and Consumer Packaging Operations (CCPO) will provide blinded test materials. The clinical examiner will not have access to the treatment code. Personnel dispensing the test products or supervising their use will not participate in the clinical examinations. The randomization will be stratified according to subject's smoking status in the following manner:

- Nonsmokers will be allocated the next sequential number in ascending order starting from 001.
- Smokers will be allocated the next sequential number in descending order starting from the highest number provided to the site.

Once a number has been assigned to a subject, it cannot be reassigned to another subject.

The clinical study coordinator will receive one package containing at least 375 individual envelopes identified by subject numbers. Each numbered envelope will contain the study product identification, formulation codes, and manufacturer's lot number.

Blinding should only be broken for serious, unexpected, and test material-related adverse events, and only for the subject in question, or when required by local regulatory authorities. The investigator must notify Pfizer prior to unblinding of any subject. Expectedness of serious and related adverse event should be assessed using the IB and/or, for marketed products, the locally approved labeling. See Appendix C for complete details on Code Break Guidelines.

7.7.4 Test Material Dispensing and Accountability

Pfizer will provide the investigator with sufficient amounts of the study test material.

The investigator must ensure that deliveries of investigational product from the sponsor are received by a responsible person, that all receipts are recorded in writing and that the product(s) is (are) stored in a secure area under recommended storage conditions. It is also the responsibility of the investigator to ensure that the integrity of packaged Pfizer study product not be jeopardized prior to dispensing. Each individual subject container must be dispensed as provided by Pfizer with no further repackaging or labeling done at the site. The investigator will dispense the test material only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the test material carrying his/her number.

All dispensing will be documented. The investigator is responsible for assuring the retrieval of all study supplies from subjects. All full, partially full and empty test material containers must be returned to Pfizer.

The investigator must maintain accurate and adequate records including dates of receipt and return of test material shipments, and lot number and quantities received/returned from/to Pfizer as well as, dates and amounts dispensed to and returned by the study subjects.

7.7.5 Test Material Administration

At baseline and at each monthly visit, each subject will be provided with his or her assigned mouthrinse and 1-oz. plastic dosage cups marked at the 20 ml level, ADA-accepted fluoride toothpaste, toothbrush and diaries to document compliance with the homecare regimen.

7.7.6 Compliance

The test site will dispense individually coded bottles of mouthrinse for subjects' home use. The bottles will be returned monthly to estimate and compliance will be monitored by measuring the residual volume of mouthrinse and by reviewing the diaries.

7.8 Termination of the Study

Every effort within the bounds of safety and subject choice should be made to have each subject complete the study. The reason for a subject discontinuation from the study will be reported in the case report form. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must attempt to determine the primary reason for discontinuation. Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response according to the definition of adverse event noted earlier. A discontinuation must be immediately reported to the Pfizer clinical monitor or his/her designated representative if

it is due to a serious adverse event. The final evaluation required by the protocol will be performed at the time of study discontinuation. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for subjects, and document the course of the subject's condition.

Additionally, any subject may be discontinued from the study at any time at the discretion of the investigator if he/she feels it is in the best interest of the subject.

8.0 SAFETY REPORTING

Clinical research center personnel will ask subjects about the occurrence of any adverse events during their participation in this study. Adverse events will be recorded from the day the subject signs the informed consent form through the end of the study.

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to study product will be recorded on the adverse event page(s) of the case report form.

8.1 Adverse Event

Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre-existing illnesses should be recorded. Exacerbation of pre-existing illness, including the disease under study, is defined as a manifestation (sign or symptom) of the illness that indicates a significant increase in the severity of the illness as compared to the severity noted at the start of the trial. It may include worsening or increase in severity of signs or symptoms of the illness, increase in frequency of signs and symptoms of an intermittent illness, or the appearance of a new manifestation/complication. Exacerbation of a pre-existing illness should be considered when a patient/subject requires new or additional concomitant drug or non-drug therapy for the treatment of that illness during the trial. Lack of or insufficient clinical response, benefit, efficacy, therapeutic effect, or pharmacologic action, should not be recorded as an adverse event. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., laboratory, x-ray, ECG) should also be recorded as adverse events. The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

1) test result is associated with accompanying symptoms, and/or
2) test result requires additional diagnostic testing or medical/surgical intervention, and/or
3) test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or

4) test result leads to any of the outcomes included in the definition of a serious adverse event, and/or
5) test result is considered to be an adverse event by the investigator or sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not meet condition #2 above for reporting as an adverse event.

Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it did meet one of the above conditions except for condition #4.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative (see section 1.2). For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event (i.e., study product or other illness). The investigator is required to assess causality and indicate that assessment on the CRF. Follow-up of the adverse event, after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and the Pfizer clinical monitor or his/her designated representative.

8.2 Serious Adverse Events

All serious adverse events (as defined below) regardless of treatment group or suspected relationship to study product must be reported immediately by telephone to **Sylvia L. Santos, RDH, MS. at 973-385-5357.**

Outside of normal working hours, serious adverse events should be reported to **Sylvia L. Santos, RDH, MS at 973-808-6809.**

A serious adverse event is any adverse drug experience occurring at any dose that:

1) results in death;
2) is life-threatening;
3) results in inpatient hospitalization or prolongation of existing hospitalization;
4) results in a persistent or significant disability/incapacity; or
5) results in congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug experiences when, based upon appropriate medical judgment, they may jeopardize the patient/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 inpatient hospitalization, or the development of drug dependency or drug abuse.

Regardless of the above criteria, any additional adverse experiences which Pfizer personnel or an investigator considers serious should be immediately reported to Pfizer and included in the Corporate adverse events database system.

A **life-threatening adverse event** is any adverse drug experience that places the patient/subject at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Initial **hospitalization** is defined as any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit (e.g., from the psychiatric wing to a medical floor, from a medical floor to the coronary care unit, from the neurological floor to the tuberculosis unit).

1) Inpatient admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to Pfizer. For example:

   i. Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (e.g., for work-up of persistent pretreatment lab abnormality)
   ii. Social admission (e.g., subject has no place to sleep)
   iii. Administrative admission (e.g., for yearly physical exam)
   iv. Protocol-specified admission during a clinical trial (e.g., for a procedure required by the study protocol)
   v. Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery)

   However, if a hospitalization for an unknown event occurs, it should be considered as a serious adverse event.

2) Inpatient admission does not include the following:

   i. Emergency Room/Accident and Emergency/Casualty Department visits
   ii. Outpatient/same-day/ambulatory procedures
   iii. Observation/short-stay units
   iv. Rehabilitation facilities
   v. Hospice facilities
   vi. Respite care (e.g., caregiver relief)
   vii. Skilled nursing facilities
   viii. Nursing homes
   ix. Custodial care facilities

x. Clinical research/Phase I units

Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the investigator or treating physician**. For protocol-specified hospitalizations in clinical trials, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical adverse event (i.e., not associated with the development of a new adverse event or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to Pfizer .

Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient/subject.

Disability is a substantial disruption of a person's ability to conduct normal life functions.

Any serious adverse event or death must be reported immediately independent of the circumstances or suspected cause if it occurs or comes to the attention of the investigator at any time during the study through the last follow-up visit required by the protocol or 30 days after the last administration of study product, whichever comes later. Any serious adverse event occurring at any other time after completion of the study must be promptly reported if a causal relationship to study product is suspected. The only exception to these reporting requirements are serious adverse events that occur during a pre-randomization/washout run-in period, during which either placebo alone is administered, or no active study product or no protocol-specified background product is administered.

For all serious adverse events, the investigator is obligated to pursue and provide information as requested by the Pfizer clinical monitor or designated representative in addition to that on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, including concomitant medications and illnesses must be provided. The investigator's assessment of causality must also be provided. If causality is unknown and the investigator does not know whether or not study product caused the event, then it should be attributed to study product. If the investigator's causality assessment is "unknown but not related to study product", this should be clearly documented on study records. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative. The investigator should ensure that information reported immediately by telephone or other means and information entered in the case report form are accurate and consistent.

8.3 Discontinuations

The reason for a subject discontinuing from the study will be recorded in the case report form. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response according to the definition of adverse event noted earlier. A discontinuation must be reported immediately to the Pfizer clinical monitor or his/her designated representative if it is due to a serious adverse event. The final evaluation required by the protocol will be performed at the time of study discontinuation. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition.

9.0 CONCOMITANT THERAPY

Any medication the subject takes other than the study drugs specified in the protocol, is considered concomitant medication. All concomitant medications must be recorded in the subject's medical record and on the CRFs. All non-drug therapy (i.e. tooth extraction, endodontic treatment, etc.) will be recorded on the appropriate CRF.

Subjects will be considered non-evaluable if any of the following classes of medication are taken within three weeks of the clinical examinations: systemic antibiotics, anti-inflammatory drugs, or anticoagulants. In addition, subjects are prohibited from using any other oral hygiene products other than the test materials provided.

10.0 STUDY MANAGEMENT AND MATERIALS

10.1 Study Materials

The tube of ADA-Accepted fluoride toothpaste and ADA-Accepted soft textured toothbrushes will be supplied in original marketed packaging. Case Report Forms (CRFs) will be provided to the study site by Pfizer. The following study documents will be supplied by Pfizer: subject diaries, test materials dispensing log, subject screening log. All unused study supplies will be returned to Pfizer.

10.2 Study Documentation

10.2.1 Case Report Forms (CRFs) and Source Document Completion and Transfer of Study Data

The investigator is required to prepare and maintain adequate and accurate case histories (i.e., medical records or dental records) designed to record all observations and other data pertinent to the study for each study participant. This includes accurate documentation of test material accountability as described in section 7.7.4, *Test Material Dispensing and Accountability*, of this protocol. The subject's records must contain adequate information to allow for verification of subject identity throughout the study. Investigators must retain a subject identification code list, should they need to contact subjects after the study.
A CRF will be completed for each subject enrolled in the study. A subject screening log, noting reasons for screen failure, where applicable, will be maintained for all subjects. All information recorded on the CRFs for this study must be consistent with the subject's source documentation (i.e., dental records).

The original CRFs for each subject will be periodically checked against the subject's source documents at the study site by the Pfizer site monitor. Instances of missing or unclear data will be discussed with the investigator for resolution. 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 to Pfizer. The CRF data will be entered into a computerized database and a quality assurance audit will be performed on the database by Pfizer.
Data on all paper study documents (e.g., subject exclusion records, source documents, study medication inventory/accountability forms) should be typed or printed using a ballpoint pen. If an error is made, cross it out with a single horizontal line, clearly record the new information next to the error, and initial and date the correction. Do not use correction fluid at any time.

10.2.2 Subjects' Diaries

Diary information will be collected during this study for the purposes of tracking subject compliance with the home care regimen.

10.2.3 All Other Study Documents/Forms

Not Applicable.

10.2.4 Transfer of Essential Study Documents

All completed original CRFs, dated and signed by the investigator, and any data clarification forms (DCFs), dated and signed by the investigator or designee, will be returned promptly to Pfizer at the completion of the study. A copy of each completed CRF and DCF must be retained at the site.

10.2.5 Archiving of Study Documentation

Study data and other essential documents should be retained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements. Pfizer will inform the investigator, in writing, as to when these documents no longer need to be maintained.

10.3 Monitoring and Quality Assurance

An investigator meeting will be held to introduce investigators and their personnel to the study protocol, CRFs, procedures and regulatory requirements. During the course of the study, a monitor will make routine site visits to review protocol compliance, compare CRFs with individual subject's original source documents, assess test material accountability and ensure that the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner to ensure that subject confidentiality is maintained.

Regulatory authorities of certain countries and/or Pfizer quality assurance staff may carry out source data checks and/or on-site inspections/audits. Direct access to original source data will be required for inspections/audits, which will be carried out giving due consideration to data protection and subject confidentiality.

11.0 CONFIDENTIALITY

All personal study subject data collected and processed for the purposes of this study will be managed by the investigator and his staff with adequate precautions to ensure the confidentiality of those data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors and other authorized agents of Pfizer, the IRB approving this research, and the United States (US) Food and Drug Administration, as well as, that of any other applicable government agency will be granted direct access to the study subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentations of the results of this study at meetings or in publications, the subjects' identity will remain confidential.

12.0 DATA ANALYSIS

The Statistical and Data Management Department at Pfizer Consumer Healthcare Research and Development will be responsible for the data management and statistical analysis of this data.

The primary analysis will be based on data from evaluable subjects, defined as all subjects with no major protocol violations. Demographic and baseline analyses will be performed for both randomized and evaluable subjects. No imputations will be made for missing data points.

12.1 Demographic And Baseline Characteristics

The three treatment groups will be compared with respect to baseline age, and whole-mouth mean Modified Gingival Index, mean Plaque Index and mean Bleeding Index by means of a one-way analysis of variance model with treatment as the factor, and with respect to gender, race, and smoking status using a chi-square test or Fisher's exact test if cell sizes are small.

12.2 Efficacy Evaluation

For each of the primary and secondary efficacy variables, between-treatment differences at 3 months and 6 months will be tested using a one-way analysis of covariance model with treatment and smoking status as factors and the corresponding baseline value as the covariate. The treatment-by-baseline interaction will be tested at the 0.05 level to assess heterogeneity of slopes.

The following pairwise comparisons will be tested for each of the primary and secondary efficacy variables at 3 months and 6 months:

- EOF rinse (test product) versus the 5% hydroalcohol negative control rinse
- EOF rinse versus EO rinse (positive control)
- EO rinse versus the 5% hydroalcohol negative control rinse

The research question is:

> Is the essential oil-containing mouthrinse with fluoride (EOF rinse) (W2194-471) "at least as good as" the essential oil-containing mouthrinse without fluoride, positive control (EO rinse) (W2194-395), in inhibiting the development of plaque and gingivitis?

EOF rinse will be considered "at least as good as" EO rinse in inhibiting the development of plaque and gingivitis if, for each of the primary efficacy variables,

1. The mean for EOF rinse is statistically significantly lower than the mean for the 5% hydroalcohol control, based on a two-sided 0.05-level test of the null hypothesis that the treatment means are equal versus the alternative hypothesis that the means are different, and

2. The upper limit of the one-sided 97.5% confidence interval for the difference between the means for EOF rinse and EO rinse (expressed as a percentage difference relative to EO rinse mean) is below 10%[13]. This procedure is a 0.025 level test of the null hypothesis that the mean for EOF rinse is at least 10% higher than the mean for EO rinse, versus the alternative hypothesis that the mean for EOF rinse is not at least 10% higher than the mean for EO rinse.

The study will be considered validated if the post baseline means of the primary efficacy variables for EO rinse are statistically significantly lower than the corresponding means of the 5% hydroalcohol control rinse based on a two-sided test.

Within treatment comparisons will be performed for each efficacy variable on the change from baseline after 3 months and 6 months of treatment by means of a paired t-test.

Each comparison will be tested at the 0.05 level, two-sided tests.

Summary statistics will be provided for each efficacy variables by treatment group at baseline, 3 months and 6 months post-baseline.

12.3 Safety Data

Safety data will be summarized by treatment group.

12.4 Sample Size And Power Considerations

The planned sample size of 340 (68 per negative control rinse and 136 per test rinse and positive control rinse group) completed, evaluable subjects is based on estimates of variability and adjusted means from Studies #931-838, #931-939, #931-1176, #931-1244, #931-1305 and #951-9075. The sample size provides at least 80% probability that the upper 97.5% confidence limit for the difference between means for test rinse and positive control rinse is less than 10% of positive control mean. This assumes an underlying mean no more than 0.5% higher for test than for positive control rinse, and coefficients of variation (c.v.) of 15% and 25%, as percentages of the positive control means, for mean Modified Gingival Index and mean Plaque Index, respectively. The c.v.'s of 15% and 25% are the second largest c.v. observed in these six studies. This sample size also provides greater than 80%

power to detect a 10% difference between negative control and active treatments, assuming a 20% c.v., at the 0.05 level of significance, two-sided.

Any changes in the planned statistical methods will be documented in the integrated clinical/statistical report.

13.0 FINANCIAL DISCLOSURE

Not Applicable.

14.0 REFERENCES

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15.0 APPENDICES

A. World Medical Association Declaration of Helsinki
B. Study Flow Chart
C. Code Break Guidelines

Appendix A: World Medical Association Declaration Of Helsinki

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
and the
41st World Medical Assembly
Hong Kong, September 1989

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subjects."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic, and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic, or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a subject, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical

Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil, and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

A. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

B. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment, and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

C. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

D. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

E. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

F. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

G. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

H. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

I. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits, and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

J. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

K. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

L. Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

M. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

A. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health, or alleviating suffering.

B. The potential benefits, hazards, and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

C. In any medical study, every subject - including those of a control group, if any - should be assured of the best-proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

D. The refusal of the subject to participate in a study must never interfere with the physician-subject relationship.

E. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.(I,B)

F. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the subject.

III. NONTHERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (NON-CLINICAL BIOMEDICAL RESEARCH)

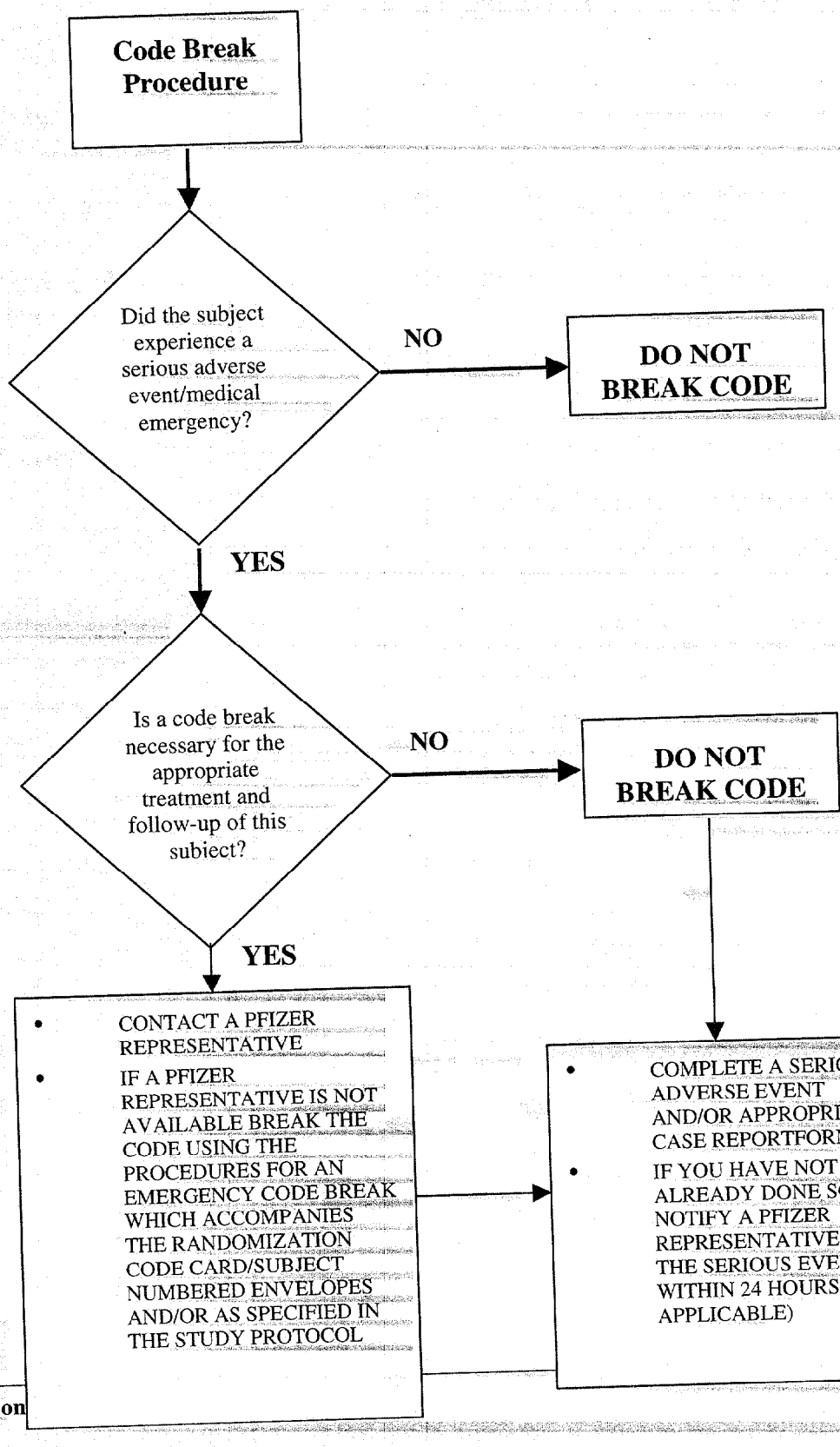
A. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

B. The subjects should be volunteers - either healthy persons or subjects for whom the experimental design is not related to the subject's illness.

C. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

D. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Appendix B: Study Flow Chart		
TIME	EVENT	PROCEDURES
Prior to Day 1	Screening	• Informed Consent, Med/Dent History, Assess subject entry qualification • Oral exam for # of teeth, presence of diseased sites • Record Concomitant medications. • Schedule appointment for next Visit.
Day 1	Visit 1, Baseline	• Query subject & record for adverse events and Concomitant medications. • Oral Exam, MGI, BI, PI • Complete prophylaxis • Randomization to treatment • Dispense clinical test material(s) • Provide study instructions and daily home care diary • Schedule appointment for next Visit.
Month 1	Month One, Visit 2, Compliance Visit	• Query subject & record for adverse events and Concomitant medications. • Update of medical and oral history • Assess compliance • Dispense clinical test material(s) • Schedule next visit
Month 2	Month 2, Visit 3, Compliance Visit	• Query subject & record for adverse events and Concomitant medications. • Update of medical and oral history • Assess compliance • Dispense clinical test material(s) • Schedule next visit
3 Months	Interim 3-Month Exams, Visit 4	• Query subject & record for adverse events and Concomitant medications. • Update of medical and oral history • Oral Exam, MGI, BI, PI • Assess compliance • Dispense clinical test material(s) • Schedule next visit
Month 4	Month 4, Visit 5, Compliance Visit	• Query subject & record for adverse events and Concomitant medications. • Update of medical and oral history • Assess compliance

Appendix B: Study Flow Chart		
TIME	EVENT	PROCEDURES
		• Dispense clinical test material(s) • Schedule next visit
Month 5	Month 5, Visit 6, Compliance Visit	• Query subject & record for adverse events and Concomitant medications. • Update of medical and oral history • Assess compliance • Dispense clinical test material(s) • Schedule next visit
6 Months	Final 6-Month Exams, Visit 12	• Query subject & record for adverse events and Concomitant medications. • Update of medical and oral history • Oral Exam, MGI, BI, PI • Assess compliance • Dispense clinical test material(s) • Complimentary Prophy

Appendix C: Code Break Guidelines