

Appendix 3
Clinical Protocol 936-9201

“Comparison of Two Dosing Regimens of a Fluoride Mouthrinse Using Salivary Fluoride Clearance”

**Consumer Healthcare Research and Development
Warner Lambert Company**

CLINICAL PROTOCOL

PROTOCOL 936-9201

**Comparison of Two Dosing Regimens of a Fluoride
Mouthrinse Using Salivary Fluoride Clearance**

Investigator: Dr. Domenick Zero

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415 Lansing Street, Indianapolis, Indiana 46202-2876

May 10, 2000

CONFIDENTIAL

CONFIDENTIAL
PROTOCOL FOR CONSUMER HEALTHCARE RESEARCH AND DEVELOPMENT
CLINICAL TRIAL

TITLE: Comparison of Two Dosing Regimens of a Fluoride Mouthrinse Using Salivary Fluoride Clearance

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The above signed confirm herewith to have read and understood this trial protocol and attached appendices, furthermore, to accomplish this study according to the protocol and the Good Clinical Practice guidelines, as well as local regulations, and to accept respective revisions conducted by authorized personnel of Consumer Healthcare Research and Development and by competent authorities.

PROTOCOL FOR CONSUMER HEALTHCARE RESEARCH AND DEVELOPMENT
CLINICAL TRIAL

TITLE: Comparison of Two Dosing Regimens of a Fluoride Mouthrinse Using Salivary Fluoride Clearance

TIME PERIOD AND NUMBER OF SUBJECTS

- A. Anticipated Number of Sites: One
- B. Anticipated Starting Date of the Study: August 1, 2000
- C. Anticipated Completion Date of the Study: October 31, 2000
- D. Anticipated Number of Subjects to Start Study: Ninety
- E. Anticipated Number of Subjects to Finish Study: Eighty-four

Principal Investigator:

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1 STUDY OBJECTIVES

The objective of this study is to assess the comparability of a test dosing regimen (20 ml rinse for 30 seconds) and a reference dosing regimen (10 ml rinse for 60 seconds) by determining salivary fluoride levels over a 120-minute period after rinsing with a fluoride containing mouthrinse (W2194-471).

2 INTRODUCTION

This study will assess the comparability of two dosing regimens for a fluoride mouthrinse by determining salivary fluoride levels over a 120-minute period after rinsing. The fluoride mouthrinse will contain sodium fluoride (0.022% sodium fluoride, or 100 ppm fluoride ion) and the fixed combination of four essential oils found in Listerine® Antiseptic mouthrinse (W2194-471). The two dosing regimens will be a reference regimen (10 ml for 60 seconds) as described in the Anticaries Final Monograph (21 CFR §355.50(d)(2)(ii)) and a test regimen (20 ml for 30 seconds) consistent with Listerine® Antiseptic mouthrinse label directions. FreshBurst Listerine mouthrinse (W2194-396), a non-fluoride mouthrinse, will be used as a negative control. Ninety subjects will be enrolled and a minimum of eighty-four subjects will be expected to complete all three treatment legs of this randomized, observer-blind crossover design study.

Following a medical and dental screening and salivary flow rate screening, all qualifying subjects will use a non-fluoride dentifrice for two to three days prior to each test day, and brush with the non-fluoride dentifrice 30 minutes before collection of baseline saliva samples. After baseline saliva samples are collected, subjects will rinse using one of three treatment regimens: 20 ml fluoride mouthrinse for 30 seconds (test regimen); 10 ml fluoride mouthrinse for 60 seconds (reference regimen); or 20 ml FreshBurst Listerine (non-fluoride negative control) for 30 seconds. Saliva samples will be collected immediately after rinsing and at 7.5 min, 15 min, 30 min, 60 min, and 120 min after rinsing. All saliva samples will be weighed within one hour after collection and analyzed for fluoride concentration using ion selective fluoride electrode. There will be at least a one-week washout period between treatments.

3 ETHICAL AND LEGAL CONSIDERATIONS^a

It is the responsibility of the investigator that this study will be conducted in accordance with the Declaration of Helsinki and according to the guidelines in the attached appendices and in compliance with all applicable laws and regulations of the locale and country where the study is conducted.

It is the responsibility of the investigator that this study will not be initiated until the protocol and a copy of the informed consent document have been reviewed and approved by a duly constituted institutional review board (IRB) or ethics committee (EC), and that any local institutional requirements are satisfied. Current regulations are summarized in Appendix C.

^a Appendices C; Other Administrative and Regulatory Procedures (Section 1.1.2., IRB/EC Review and Approval of Study; 1.1.3., Subject Informed Consent; 1.6.; Confidentiality of Subject Information; and 2.1., Information Required by Consumer Healthcare Research and Development for Regulatory Review) and D; The Declaration of Helsinki

It is the responsibility of the investigator to ensure that each subject and/or his or her legal guardian (or caregiver) will read, understand, and sign a document of informed consent prior to the subject's entrance into the study.

It is the responsibility of the investigator to inform the subject that personal information may be examined during audit or monitoring by properly authorized persons but that personal information will be treated as strictly confidential and will not be publicly available.

Indemnification of the investigator, coworkers, and the institution is provided as specified in the Clinical Study Agreement. It is the responsibility of the investigator to retain the subject log and subject records as detailed in Appendix C.

4 STUDY DESIGN

4.1 Study Design

This controlled, observer-blind, randomized study will utilize a crossover design.

4.2 Randomization

A group randomization code will be provided by the sponsor.

4.3 Washout period

There will be washout period of at least one week between each test session.

5 STUDY POPULATION

5.1 Source and Number of Subjects

Subjects will be recruited from the Indianapolis area. Ninety subjects will be enrolled in the study and a minimum of eighty-four subjects will be required to complete the study.

5.2 Subject Selection Criteria

5.2.1 Inclusion Criteria

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

- Males or females, 18 years or older with good general health and willingness to read and sign the informed consent after the nature of the study has been fully explained.
- Good oral health with normal salivary gland function (unstimulated whole salivary flow rate ≥ 0.3 ml/min and parafilm-stimulated whole salivary flow rate ≥ 1.5 ml/min).
- Normal oral architecture with at least 24 natural teeth and no evidence of a deeply fissured tongue or irregular oral mucosal surfaces.

5.2.2 Exclusion Criteria

Any of the following conditions will exclude subjects from eligibility for study participation:

- History of significant adverse effects following use of oral hygiene products such as dentifrice and mouthrinse.

- An inability to comply with study procedures.
- A condition requiring the use of pre-medication for any dental procedures.

5.2.3 Continuance Criteria

Subjects may be dropped from the study and/or excluded from the efficacy analyses if there is evidence of:

- Use of non-study mouthrinse or other oral care products during the study;
- Non-compliance with the use of study mouthrinse;
- Development of any of the other exclusion criteria.

6 STUDY METHODOLOGY

6.1 Clinical Procedures

6.1.1 Screening Procedure

Prior to study initiation, each subject will be seen at the clinical site to obtain informed consent, a medical history, an oral exam, and a determination of salivary flow rate. For the determination of unstimulated salivary flow rate, subjects will sit quietly for two minutes before start of collection. During the two-minute collection period, they will be instructed to allow their saliva to pool, expectorating into a collection tube whenever they feel the need to swallow. For the determination of stimulated salivary flow rate, subjects will chew on a piece of parafilm for one minute and will be instructed to swallow any pooled saliva during this period. They will then chew the parafilm for a timed two minutes, during which time they will expectorate any pooled saliva into a collection tube. The qualifying unstimulated and stimulated salivary flow rates are ≥ 0.3 ml/min and ≥ 1.5 ml/min, respectively.

6.1.2 Lead-in Procedures

Two to three days before the start of the first test leg, all subjects will receive a professional supragingival tooth cleaning by a dental hygienist to remove all hard and soft deposits. Manual instrumentation (if required) and a low abrasion non-fluoride toothpaste will be used. To minimize any carry-over effect from normal usage of fluoride-containing dental products, subjects will be provided a non-fluoride dentifrice with which to clean their teeth for the two to three days prior to each test day. Subjects will be instructed to maintain their normal diet during the lead-in period with the exception that they will be instructed not to drink tea or eat canned sardines because of their high levels of fluoride.

6.1.3 Treatment Procedure

- a All tests will be started at least 2 hours after consumption of any food or beverage.
- b All experimental procedures will be conducted under direct supervision of research personnel.
- c All subjects will brush with the non-fluoride dentifrice 30-min before the start of a test.
- d For each test period, saliva samples will be collected prior to treatment, and the subjects will then rinse with one of the following three randomly assigned dosing regimens: 20 ml fluoride rinse for 30 seconds; 10 ml fluoride rinse for 60 seconds; or 20 ml FreshBurst Listerine® mouthrinse for 30 seconds.

6.1.4 Sample Collection and Handling

- a Unstimulated saliva samples will be collected prior to rinsing, immediately after rinsing, and at 7.5 min, 15 min, 30 min, 60 min, and 120 min after rinsing.
- b Subjects will be asked to sit quietly for two minutes before saliva collection.
- c Saliva collection will be initiated by having the subjects swallow all the residual saliva in their mouth, then letting saliva pool in their mouths for a two-minute period while their heads are tilted forward.
- d As the subjects feel the need to swallow, they will expectorate into a plastic pre-weighed re-sealable collection vial.
- e At the end of the two-minute collection period, all remaining saliva will be expectorated into the plastic vial.
- f Subjects will be instructed not to eat or drink during the two-hour sample collection period and will be requested to keep conversation to a minimum.

6.2 Laboratory Procedures

6.2.1 Sample Treatment and Fluoride Analysis

- a Saliva samples will be weighed within one hour after collection. Salivary flow rate (mL/min) will be determined by dividing the sample weight (1 g = 1 mL) by the collection time (2 min)
- b Saliva samples will be centrifuged (10,000 g, 4° C, 10 min) and the supernatant will be stored at -20° C for later fluoride analysis (see below).
- c The saliva sample will be transferred into a microdiffusion dish of a Taves diffusion apparatus (60x15 mm petri dish with top half of a 17 mm polyethylene cap secured in the bottom center as a diffusion trap).
- d The total volume of the samples will be adjusted to 3.0 mL with DDW and 0.1 mL of 1.65 N NaOH added to the central trap. The dish will be closed and sealed with petroleum jelly (Vaseline).
- e One mL of 6 N HCl saturated with hexamethyldisiloxane^b will be added to the sample through the small hole in the lid of the petri dish and then the hole immediately sealed with petroleum jelly. The samples will be rotated for 18 hours on an orbital shaker at 80 rpm.
- f At the end of the diffusion period, the NaOH traps will be removed. The samples containing the traps will be dried at 65 °C for two hours, allowed to cool to room temperature, and buffered with 0.4 mL of 0.66 N acetic acid (final pH, 5.0). Samples will be then mixed vigorously by vortexing to assure complete dissolution of dried sample in cap.
- g The fluoride will be measured using a fluoride combination electrode (Orion 94-09) and pH/mVmeter. The fluoride content (µg F) of the samples will be calculated from a standard curve constructed from fluoride standards (0.1, 0.5, 1.0, 5.0, 10, 50 and 100 ppm F) microdiffused at the same time as the samples.

^b 6N HCl/HMD: Place 200 mL of 6N hydrochloric acid in a separatory funnel and mix with 25 mL of hexamethyldisiloxane (HMD, Aldrich Chemical Company) for 2 minutes. Discard the HMD layer, and mix the acid with fresh HMD for 2 minutes. Discard the HMD layer again. Mix the acid with a third fresh HMD for 2 minutes. The acid is stored with this last HMD layer on top, and the HCl/HMD is drawn off from the bottom of the separatory funnel as needed.

- h The amount of total fluoride in the saliva samples will be calculated based on the amount of fluoride divided by the volume of the sample and expressed as $\mu\text{g F/mL}$ of saliva.

6.3 Efficacy Assessments

The primary efficacy variable will be salivary fluoride content, expressed as area under the curve (AUC), from 0 to 120 minutes post-treatment. AUC values will be \log_{10} transformed prior to statistical analysis.

6.4 Safety Assessments

An oral hard and soft tissue examination will be performed on each subject prior to and following each test period, as described in Appendix E. All subjects will be questioned at the beginning and end of each treatment period regarding general health or oral complaints they may have experienced since entering into the study. Any complaints and/or adverse effects will be documented on the adverse effects clinical record form described in appendix B.

6.5 Adverse Event Reporting^c

Any new or continuing signs or symptoms will be recorded for each subject at each study visit as detailed in Appendix B.

6.5.1 Serious Adverse Events

Report immediately to Consumer Healthcare Research and Development any serious adverse event defined as any adverse event at any dose that results in any of the following outcomes:

- Death;
- Life-threatening adverse event;
- In-patient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect; and
- Medically significant event (includes clinical laboratory abnormalities)

IN CASE OF SERIOUS OR LIFE-THREATENING ADVERSE EVENTS, OR IN THE EVENT OF DEATH, THE INVESTIGATOR AND A CONSUMER HEALTHCARE R&D COLLEAGUE MUST BE CONTACTED IMMEDIATELY.^d

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Warner-Lambert Company
170 Tabor Road
Morris Plains, NJ
Phone: (973)-385-3345

If any serious adverse event occurs, interrupt or discontinue study treatment at your (the physician investigator) discretion. If in acute medical emergency the Consumer Healthcare Research and Development colleague cannot be contacted, you may break the

^c Appendix B, Administrative Procedures for Reporting Adverse Events

^d Appendix B, Administrative Procedures for Reporting of Adverse Events (Section 4.1, Immediately Reportable Adverse Events)

randomization code only if this is required for proper treatment of the subject.^e Notify the Consumer Healthcare Research and Development colleague of emergency code breaks as soon as possible.

6.5.2 Lack of Efficacy

Lack of efficacy should not be captured as an adverse event.

6.5.3 Adverse events follow-up

In following up adverse events, attempts should be made to obtain as much information as possible about event evolution and outcome. The documentation of this follow-up should be maintained with the subject's study records.

6.6 Removal of Subjects From the Study

Every effort within the bounds of safety and subject choice should be made to have each subject complete the study. Subjects will be encouraged to complete the study, although they may withdraw at any time without prejudice. Termination should be reported to the monitor in a timely manner the reason for all dropouts and the time of their occurrence are to be specified and recorded on the appropriate case record form. Subjects removed from the study will not be replaced.

6.7 Study Completion^f

The study will be terminated when all subjects complete all three test legs.

7 STUDY TREATMENT

7.1 Test Mouthrinse and Dosing Regimens

All test products will be provided by the sponsor.

Study Materials	Dosing Regimens	Product Number
FreshBurst Listerine [®] with 0.02% NaF (100 ppm F ⁻)	1. Rinse with 20 ml for 30 seconds (test regimen), or 2. Rinse with 10 ml for 60 seconds (reference regimen)	W2194-471
FreshBurst Listerine [®]	Rinse with 20 ml for 30 seconds	W2194-396
Fresh'n Brite [®] non- fluoride toothpaste*	1. Brush for one minute, BID, for 3 days prior to each test day; 2. Brush for one minute, 30 minutes before sampling on test day.	W9979-18

* Fresh'n Brite denture toothpaste is a commercially available non-fluoride toothpaste and is safe for use on natural teeth.

^e Appendix C, Other Administrative and Regulatory Procedures (Section 1.6, Emergency Information)

^f Appendix C, Other Administrative and Regulatory Procedures (Section 3.3, Study Termination)

7.2 Labeling

A label will be affixed to the mouthrinse supplies. Each label will contain protocol number, patient #, group code letter, dosing instructions, and site identification.

7.3 Shipment and Storage

All study materials will be shipped to the investigator from the Warner-Lambert Company. The contents of the shipment should be reconciled with the shipping invoice. All study test supplies should be stored in a secure, locked area at room temperature, and be available for accountability during scheduled visits by the study monitor.

7.4 Maintenance of Product Dispensing Records

The mouthrinse dispensing record should be kept current and be available for inspection by the Warner-Lambert monitor.

7.5 Return of Unused Study Materials

The Consumer Healthcare Research and Development Division of Warner-Lambert Company requires that the investigator collect all original containers, whether empty or containing unused study materials, and retain these for the clinical study monitor to conduct an inventory of supplies prior to releasing material for appropriate disposal by the study site. The responsible location is:

Clinical & Consumer Packaging Operations Department
Warner-Lambert Company
175 Tabor Road
Morris Plains, NJ 07950
Tel: 973-385-4389

8 DATA COLLECTION AND MONITORING PROCEDURES

Case Report Forms (Appendix G) will be supplied by Consumer Healthcare Research and Development. These are to be completed as instructed. Original CRFs and other required study documentation will be returned to Warner Lambert Company.

Monitoring will be performed by Consumer Healthcare Research and Development or its designee. At each monitoring visit, subject records will be inspected for completeness and accuracy, dispensing records and drug inventory will be examined and a monitor's report prepared. Completed hard copies of the individual test response tracings will be forwarded to Warner-Lambert after completion of the study.

9 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1 Data Analysis

Data management and statistical analyses will be performed by the Statistics and Data Management Department of the Warner-Lambert Consumer Healthcare Research & Development Division.

9.2 Data Sets Analyzed

The primary efficacy analyses will be based on evaluable subjects, defined as all randomized subjects with no major protocol violations who have evaluable data for each treatment period. Efficacy analyses will also be performed using all randomized subjects.

Demographic analysis will also be performed both for evaluable subjects and for randomized subjects.

9.3 Statistical Power and Sample Size Considerations

The planned sample size of eighty four completed subjects for this study will provide 85% power to show the test regimen to be "at least as good as" the reference regimen, given that the true ratio between test and reference averages (test/reference) is at least 95% (see Success Criteria section for definition of "least as good"). This calculation is based on a standard deviation on the log scale of 0.17, estimated from a pilot study. (Kingman: J Periodont Res 1992, 27:378)

9.4 Efficacy Variables

The primary efficacy variable is post-treatment salivary fluoride content, expressed as area under the fluoride concentration curve (AUC), from 0 to 120 minutes post-treatment. AUC values will be \log_{10} transformed prior to statistical analysis.

9.4.1 The Primary Research Question

Does rinsing using the test regimen (20 ml for 30 seconds) provide at least as much fluoride in saliva as rinsing using the reference regimen (10 ml for 60 seconds)?

9.4.2 Analysis

AUC from 0 to 120 minutes will be analyzed using a mixed model, with subject considered random, with sequence, treatment, period, and carryover considered fixed, and with pre-treatment fluoride concentration as the covariate. Using this model, the lower limit of the one-sided 95% confidence interval for the ratio of test to reference will be calculated by computing the lower limit for the confidence interval on the log scale, and then by taking the antilog.

The assumption of normally distributed errors will be evaluated by Shapiro-Wilk test and an examination of the normal probability plots. Treatment-by-baseline interaction will be examined to evaluate equality of slopes.

9.5 Success Criteria

The test dosing regimen (20ml for 30 seconds) will be considered at least as good the reference regimen (10 ml for 60 seconds) if the lower limit of the one-sided 95% lower confidence interval for the ratio of the test dosing regimen to reference dosing regimen averages is at least 0.8 (i.e., 80%).

9.6 Fluoride Concentration at Each Sampling Period

Summary statistics will be provided for fluoride concentration at each sampling period.

9.7 Interim Analysis

No interim analyses will be performed.

10 LIST OF APPENDICES

- A. Timetable of Visits and Procedures
- B. Administrative Procedures for the Reporting of Adverse Events
- C. Other Administrative and Regulatory Procedures
- D. Declaration of Helsinki
- E. Detailed Study Safety Procedures

F. Case Report Forms

APPENDIX A**Timetable of Visits & Procedures**

Visit	Day	Procedures
1, Leg 1	One	Screening, OST, Cleaning, Study Material Distribution
2, Leg 1	Two to Three days after Visit 1	Saliva Collection and Analysis, OST
3, Leg 2	At Least One Week After Visit 2	Cleaning, Study Material Distribution
4, Leg 2	Two to three Days after Visit 3	Saliva Collection and Analysis, OST
5, Leg 3	At Least One Week after Visit 4	Cleaning, Study Material Distribution
6, Leg 3	Two to three Days after Visit 5	Saliva Collection and Analysis, exit OST

APPENDIX B
Administrative Procedures for Reporting of Adverse Events

APPENDIX B

Administrative Procedures for the Reporting of Adverse Events

INTRODUCTION

The administrative procedures for reporting adverse events described in this appendix are to be followed during the conduct of this protocol.

If you have any questions concerning adverse event reporting, please contact the Consumer Healthcare Research and Development colleague or representative who is monitoring your site or a Consumer Healthcare Research and Development colleague whose name, address, and telephone number appears on the cover sheet to this protocol.

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1. ADVERSE EVENTS DURING THE STUDY

Each subject will be observed and queried in a nonspecific fashion by the investigator or study coordinator at each visit during baseline, study treatment, and protocol-defined follow-up for any new or continuing adverse events (AEs) since the previous visit. Any new AEs or ones changing in character, frequency, or in intensity reported by the subject or caregiver or noted by the investigator or study coordinator after the signing of the informed consent will be recorded on the AE Case Report Form (CRF).

The investigator will review any clinical laboratory test results in a timely fashion when received from the laboratory. Those results qualifying as AEs as defined in Sections 2 of Appendix B. This appendix will be recorded on the AE CRF and will be handled according to these administrative procedures for reporting AEs.

The investigator will review concomitant medications being taken by the subject. The AE that led to the administration of any new concomitant medications (not specified in the protocol) will be reported on the AE CRF.

2. DEFINITIONS

Pre-Existing Conditions

A pre-existing condition is one that is present at the start of study treatment.

Baseline

Defined by the Therapeutic Group for each program.

Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Related Adverse Event

An AE where there is a reasonable possibility that the event may have been caused by drug (Unknown is also considered related).

Serious Adverse Event (SAE)

Any adverse event occurring at any dose that results in any of the following outcomes:

- Death;
- Life-threatening adverse event;
- In-patient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect; and
- Medically significant event (includes laboratory abnormalities).

Medically significant events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse, or laboratory abnormalities.

The following hospitalizations are not considered SAEs:

- For diagnostic or elective surgical procedures for a pre-existing condition;
- For therapy of the target disease(s) of the study if the protocol explicitly anticipated and defined the symptoms or episodes;
- For study efficacy measurement, as defined in the protocol.

Life-Threatening Adverse Event

Any adverse event that places the subject or subject, in the view of the investigator, 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.

Unexpected Adverse Event

Any adverse event, the specificity or severity of which is not consistent with the current Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an AE that has not been previously observed (e.g., included in the Investigator's Brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the product.

Clinical Laboratory Adverse Event

A clinical laboratory abnormality that is regarded as an AE if it has been confirmed by at least 1 repeat test and suggests a disease and/or organ toxicity of a severity that requires active management, e.g., change of dose, discontinuation of drug, more frequent follow-up, diagnostic investigation, etc.

Treatment-Emergent Signs and Symptoms (TESS)

Any AE that was not evident during baseline as defined by the study protocol or that increases in intensity or frequency, or changes in character during treatment.

Post-Treatment Adverse Event

Any AE that occurs after study treatment is discontinued. Post-treatment follow-up and post-treatment adverse events of interest to the study will be defined per protocol.

Lack of Efficacy

A worsening of the disease being studied or lack of desired effect of the study drug (not reported as an AE if defined as an efficacy parameter in the protocol).

2.1. Attributes of Adverse Events

2.1.1. Treatment-Emergent Signs and Symptoms (TESS)

Any condition/diagnosis that meets the definition of a TESS event is captured as such on the AE CRF.

2.1.2. Serious Adverse Events

All SAEs, as defined in Section 2, are immediately reportable to the Sponsor within 24 hours of the Investigator's first knowledge of the event (see Section 4.1 of this appendix).

If there is an exception to the SAE definition, it is described in the protocol.

2.1.3. Intensity

The following criteria are used to assess the intensity of each AE:

Mild: The subject is aware of the sign or symptom, but finds it easily tolerated.

Moderate: The subject has discomfort enough to cause interference with or change usual activities.

Severe: The subject is incapacitated and unable to work or participate in many or all usual activities.

Not Applicable:

Note: For oncology studies, in lieu of these criteria, standardized coding criteria may be used as defined in the protocol.

2.1.4. Relationship to Study Drug—Physician's Assessment

Causality will be captured by the investigator on the CRF Adverse Events as one of the following choices:

(a) Probable

A clinical event, including a laboratory test abnormality, which meets **all** of the following criteria:

- i. Occurs within a reasonable time sequence to administration of the drug.
- ii. Is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- iii. There is a positive dechallenge; that is, the event follows a clinically reasonable response on withdrawal.
- iv. Rechallenge information is not required, or may be unclear or not applicable. However, if the information is available, rechallenge is positive; that is, the event recurs upon reintroduction.

(b) Possible

A clinical event, including a laboratory test abnormality, which meets **all** of the following criteria:

- i. Occurs within a reasonable time sequence to administration of the drug.
- ii. Could also be explained by the presence of concurrent disease or other drugs or chemicals.
- iii. Dechallenge information is not required, or may be unclear or not applicable. However, if the information is available, dechallenge may be positive or negative; that is, the event may or may not follow a clinically reasonable response on withdrawal.
- iv. Rechallenge information is not required, or may be unclear or not applicable. However, if the information is available, rechallenge may be positive or negative; that is, the event may or may not recur upon reintroduction.

(c) Unlikely

A clinical event, including a laboratory test abnormality, which meets **one** of the following criteria:

- i. The temporal relationship (time sequence to drug administration) makes a causal relationship improbable or
- ii. Other drugs, chemicals, underlying disease, or other factors provide more plausible explanations.

2.1.5. Clinical Outcome

The following categories are used to assess the clinical outcome of each AE:

Recovered (with or without residual effects):

The subject has fully recovered from the AE with or without observable residual effects.

Not Yet Recovered:

The subject is still being treated for the residual effects of the original AE. This does not include treatment for pre-existing conditions including the indication for the study drug.

Died Due to This Adverse Event

Died, Other Causes

Unknown

Surgery/Procedure

3. CAPTURING ADVERSE EVENTS

3.1. Pre-Existing Condition

A pre-existing condition should be reported as an AE if the frequency, intensity, or the character of the condition worsens during study treatment.

3.2. Lack of Efficacy

Signs or symptoms defined in the protocol as lack of efficacy or collected as efficacy parameters should not be reported as AEs.

3.3. Clinical Laboratory Adverse Event

A clinical laboratory abnormality should be reported as an AE only if the conditions are met as defined in Section 2.

3.4. Hospitalization or Surgery/Procedure

Any AE that results in hospitalization (i.e., subject admitted—not just an emergency room visit) should be reported as an SAE except as described in Section 2 of Appendix D or unless specifically instructed otherwise in the protocol. Any condition/diagnosis responsible for surgery/procedure should be reported as an AE if it meets the criteria for an AE. The surgery/procedure itself will be reported as a Clinical Outcome of the underlying event.

Events that prolong any hospitalization are reported as SAEs.

3.5. Death

The cause of death should be reported as an AE. Death should not be reported as an AE, but as a Clinical Outcome. The only exception is “Sudden Death” when the cause of death is unknown, which is reported as an AE with death as the Clinical Outcome.

3.6. General Physical Examination Findings

At screening, any clinically significant finding should be recorded on the General Medical History CRF. After the signing of the informed consent document, any new clinically significant finding that meets the definition of an AE must be documented as such.

4. RECORDING AND REPORTING

All AEs that occur at any time during the study including the posttreatment period as defined in the protocol, are to be reported in the subject’s CRFs. The investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms.

If the event meets the definition of a “serious” adverse event, a photocopy or fax of the Warner-Lambert Serious Adverse Event Report, the Adverse Event Case Report Form, and Concomitant Medication Case Report Form, and/or other pertinent information must be provided within 24-hours to the clinical monitors. Warner-Lambert Company will monitor the completeness and accuracy of these forms.

At each visit, after the subject has had an opportunity to spontaneously mention any problems, the investigator should inquire about adverse events by asking the following standard questions:

- a. “Have you had any (other) medical problems since your last visit?”
- b. “Have you taken any new medications, other than those given to you in this study, since your last visit?”

All unresolved adverse events observed at the last study visit should be followed by the investigator until the events are resolved, stabilized, the subject is lost to follow-up, or the

events are otherwise explained. All follow-up information should be reported to Warner-Lambert Company.

Adverse events will be recorded at each clinic visit. All adverse events should be recorded on the Adverse Events page of the Case Report Form including date of onset and cessation, intensity and relationship to study drug. The action taken and clinical outcome of SERIOUS adverse events must be reported to the Clinical Monitor without delay. All medical problems occurring since the previous visit which were not present at the initial must be recorded. If there is worsening of a medical condition that was present at the initial visit, this should also be reported. This information is obtained by questioning the subject and/or caregiver and/or examining the subject.

4.1. Immediately Reportable Adverse Events

The investigator or designee must report the occurrence of any serious adverse event to the Warner-Lambert Company within 24 hours, regardless of the causal assessment to study medication, and followed up with a detailed written explanation of the event within 3 days.

A photocopy or fax of the Warner-Lambert Serious Adverse Event Report, the Adverse Event Case Report Form, and Concomitant Medication Case Report Form, and/or other pertinent information must be provided within 24-hours to:

Jane Zhang
Oral Care Technology Development
Warner-Lambert Company
170 Tabor Road
Morris Plains, NJ 07950
Tel: 973-385-3345
Fax: 973-385-4300

The investigator is responsible for continuing to report to Warner-Lambert Company, within 24 hours, any new or relevant follow-up information on the serious adverse event as the information becomes known to the investigator. All unresolved serious adverse events should be followed by the investigator until the event has resolved, stabilized, the subject is lost to follow-up, or the event is otherwise explained.

4.2. Other Adverse Events

AEs that are not immediately reportable according to the definitions in this appendix will only be recorded on the standard AE CRF. These forms will be collected by the sponsor after the event is resolved, or if the event is continuing, at approximately 12- to 16-week intervals until after the AE ends or if the AE does not end, until the subject completes the study or the protocol-specified follow-up period.

4.3. Follow-Up Period

For SAEs, the subject must remain under observation until the SAE has subsided or stabilized and all serious pathological values and findings have returned to normal or stabilized.

Follow-up information will not be collected for "not yet recovered" or continuing nonserious AEs unless time frames are specifically written in the protocol.

APPENDIX C
Other Administrative and Regulatory Procedures

APPENDIX C

Other Administrative and Regulatory Procedures

INTRODUCTION

This appendix provides information necessary to administer this study in compliance with global GCPs, government regulations, and the policy and procedures of Consumer Healthcare Research and Development Pharmaceutical Research, Warner-Lambert Company.

If you have any questions concerning the conduct of the study, contact one of the Consumer Healthcare Research and Development Medical/Dental Colleagues whose name, address, and telephone number appears on the signature sheet to this protocol.

Your signature on this protocol, any subsequent amendments and addenda, and the Clinical Study Agreement confirms that you:

Have been given appropriate information on the study drug;

Have read and understood the protocol and appendices;

Agree to conduct the study in accordance with the provisions of the protocol and applicable regulations;

Acknowledge Consumer Healthcare Research and Development' ownership of the data and results obtained from the conduct of this protocol; and

Agree to maintain the confidentiality of certain information (see Section 1.8.1)

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1. ADMINISTRATIVE PROCEDURES

1.1. Ethics and Informed Consent

1.1.1. Declaration of Helsinki

This study will be conducted in accordance with the Declaration of Helsinki.

1.1.2. Institutional Review Board (IRB) or Ethics Committee (EC) Review and Approval of the Study

An IRB/EC, that is organized and operates according to GCP and applicable laws and regulations, should safeguard the rights, safety, and well being of all trial subjects. No subject should be admitted to a trial before the IRB/EC issues its written approval/favorable opinion of the trial.

The investigator is responsible for:

- Promptly reporting to the IRB/EC all changes in the research activity, and all unanticipated problems involving risks to human subjects or others;
- Not making any changes in the research without IRB/EC approval, except when absolutely necessary to eliminate apparent immediate hazards to human subjects;
- Submitting a progress report describing the status of the clinical investigation to the IRB/EC at appropriate intervals not exceeding 1 year; and
- Submitting a final report when required by the IRB/EC within 3 months following completion, termination, or discontinuation of the study. Copies of these reports will also be provided to Consumer Healthcare Research and Development.

In general, all communications with the IRB/EC regarding the study of a Consumer Healthcare Research and Development drug will be handled by the principal investigator (or coordinating investigator, if applicable) of the study. Consumer Healthcare Research and Development personnel may directly contact the IRB/EC if necessary but must not attempt to influence the IRB/EC in any way. A copy of all communications from the IRB/EC to the investigator regarding its review of and initial approval of the study and its reapprovals at intervals must be provided to the Consumer Healthcare Research and Development Site Monitor/Clinical Research Associate by the investigator.

1.1.3. Subject Informed Consent

The investigator must fully explain the purpose of the study to the subject or his/her guardian prior to entering the subject into the study. The investigator is responsible for obtaining written informed consent from each subject. For subjects under the legal age of consent or unable to provide written consent, written informed consent must be obtained from his/her legal guardian, or legal representative. Also, the assent of a child to participate in the study must be obtained when appropriate, e.g., in consideration of the child's age and maturity.

Consumer Healthcare Research and Development requires that informed consent be obtained orally and on a written form prepared by the investigator and approved by the IRB/EC. Although a sample Informed Consent Document (ICD) may be provided to international investigators or a template to US investigators, the investigator is ultimately responsible for the content of the document.

The person signing the consent form will receive a copy of the signed form. The signed consent form will be filed at the site with the investigator's copies of the Case Report Forms (CRFs) for each subject.

1.2. Clinical Evaluations Not Specified in the Protocol

Procedures not specified in the protocol can be conducted only if required for the successful management of a subject or they will not affect the conduct or results of the study and each procedure should be approved by the Consumer Healthcare Research and Development Medical/Dental Colleague.

1.3. Monitoring the Study

Frequent contact between the principal investigator and Consumer Healthcare Research and Development will be maintained by the Medical/Dental Colleague and/or the Site Monitor/Clinical Research Associate, or comparable persons from a designated Contract Research Organization appointed by Consumer Healthcare Research and Development, to assure that this study is conducted according to the protocol and that all forms are accurate and complete prior to being forwarded to Consumer Healthcare Research and Development.

1.3.1. Pre-study Visit

Representatives from Consumer Healthcare Research and Development, usually those who will monitor the site, will visit the investigator, site staff, and study facility prior to initiation of the clinical study to:

Review the key elements of the available information on the investigational drug and the protocol;

Determine the site's ability to conduct the study based on, for example, experience, adequacy of physical facilities;

Assess availability of an adequate, suitable subject population; and

Assess IRB/EC involvement and accessibility for Site Monitor/Clinical Research Associate visits including source document verification against medical records.

If the prospective investigator has conducted a study for the Company within the last 12 months with the same investigational drug, a telephone interview may be used to replace an on-site visit at the discretion of the Senior Director.

1.3.2. Investigators' Meeting

Principal investigators must not enroll subjects into a study unless they have received training on all aspects of a clinical study. For multicenter studies, this training is typically provided at an Investigators' Meeting. A prestudy Investigators' meeting is a formal meeting between the sponsor and the investigators and their staff to review all aspects of a clinical study prior to study initiation. The main purposes of this meeting is to:

- Review the study protocol and procedures;
- Resolve any questions regarding the purpose(s) and conduct of the study;
- Instruct all participants in the administrative and regulatory (i.e., GCP) procedures to be followed.

For some studies, the Senior Director may waive the Investigator's Meetings if the goals have been accomplished via a Prestudy Visit and/or Investigators' Meeting or the site has participated in other similar studies for Consumer Healthcare Research and Development within the past 12 months.

1.3.3. Study Initiation Visit

This visit, which is conducted by the Site Monitor/Clinical Research Associate, typically occurs after the Investigators' Meeting and after written study materials and clinical supplies are at the site, and before subject enrollment. The purpose of this visit is to ensure that both Consumer Healthcare Research and Development and the investigator have fulfilled all necessary obligations before treating subjects in a clinical trial. During the visit, the Site Monitor/Clinical Research Associate reviews with the investigator and

appropriate site staff the key elements of study documents and supplies and their study obligations and roles.

1.3.4 Monitoring Visits and Phone Contacts

Routine monitoring visits, at appropriate intervals detailed in the monitoring guidelines, will be scheduled based on the design and complexity of the protocol and the timelines for obtaining study results to:

- Verify that the rights and well-being of human subjects are protected (e.g., signed informed consent document, IRB/EC approvals, etc);
- Ensure study conduct in accordance with the protocol (and any amendments), local regulatory requirements, Consumer Healthcare Research and Development procedures, and GCPs;
- Verify the accuracy and timely ensure completion of the recorded data (e.g., CRFs) with respect to source documents (see Section 1.3.4.1 below);
- Resolve data queries;
- Verify that data and biological samples are collected in a timely manner;
- Maintain an accurate record of study progress;
- Account accurately for clinical drug supplies;
- Ensure continued acceptability of facilities for study conduct;
- Ensure appropriate maintenance of required documents;
- Prepare the site for audits.

In addition, both Consumer Healthcare Research and Development and the site are responsible for documenting substantive telephone conversations (e.g., those about inclusion/exclusion criteria in the protocol, medication dosing procedures, adverse events, and emergency code breaks).

1.3.4.1. Source Data Verification

The purpose of Source Data Verification (SDV; also known as Source Document Verification) is to ensure as much as possible the accuracy, quality, and reality of the data recorded on CRFs via a comparison to source documents. Source documents are the original documents or records where raw/source data concerning a subject have been first recorded, e.g., medical charts, hospital records, clinical laboratory reports, X-rays, automated instrument tracings, signed and dated informed consent documents.

1.3.5. End-of-Study Visit

The final on-Site Monitor visit is conducted when:

- The investigator completes the study or requests to discontinue participation in the study; or
- Consumer Healthcare Research and Development decides to discontinue the study for all investigators in a trial (e.g., due to adverse events or study enrollment being reached) or for an individual investigator (e.g., due to poor subject enrollment).

Purposes of the End-of-Study Visit include:

- Reviewing and ensuring completeness of required documentation and documentation retention policies;
- Collecting completed CRFs;
- Ensuring that all adverse events have been identified, documented and reported to Warner Lambert;
- Ensuring final returning/disposition of any remaining clinical drug supplies;
- Ensuring that the investigator has notified the IRB/EC of study completion or discontinuation;
- Reviewing processes that occur after the End-of-Study Visit; and
- Finalizing payment issues.

1.3.6. Communicating Deficiencies

The Consumer Healthcare Research and Development Site Monitor/Clinical Research Associate will inform the site of any deficiencies related to the conduct of the study noted during monitoring visits or audits conducted by Consumer Healthcare Research and Development QA colleagues.

1.4. Randomization Code

The Statistics and Data Management Department of Consumer Healthcare Research and Development or designee generates the randomization code, and then Consumer Healthcare Research and Development or other designated facility will provide product assembled based on a randomization code.

1.5. Medical Intervention and Code Breaking

If any adverse event requires medical intervention, the study medication may be discontinued and the subject treated at the discretion of the physician investigator. In an acute medical emergency, the product assignment code may be broken if this is considered essential for subject management. For this purpose, the product assignment code will be provided to the investigator in a sealed envelope. However, **before breaking the code**, an attempt must be made to contact the Warner-Lambert Monitor. If not possible, contact should be made at the first opportunity. If the code is broken, a record of the time and reason must be put in writing and sent to the Warner-Lambert Monitor. This letter will become part of the permanent study record. The investigator's copy of the sealed product assignment code must be returned to Warner-Lambert at the end of the study.

1.6. Confidentiality of Subject Information

All subjects will be assigned a study subject number. Subsequently, subjects will be identified in the CRFs only by their initials and that number. Any information published as a result of the study will be such that it will not permit identification of any subject. The information from this study will be available within Consumer Healthcare Research and Development and may be shared with the regulatory authorities. It may also be the subject of an audit by a regulatory agency (e.g., FDA) within the local government. The subject's identity will remain protected except as required for legal or regulatory inquiries.

1.7. Publication or Presentation of Results

Upon written permission from Warner-Lambert, the investigator shall be free to publish, present or use any results arising out of the performance of the study for their own instructional, research or publication objectives. Any proposed oral or written use of such results by the investigator shall be submitted to Warner-Lambert for review at least forty-five (45) days prior to submission for publication, presentation or use. This condition is stated so that Warner-Lambert will be aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use.

Warner-Lambert shall reserve the right to deny publication or presentation of the data or to request modification of any publication, presentation or use of study results if such publication, presentation or use will jeopardize a patent application or patent. If the investigator does not consent to such modification, independent patent counsel will be consulted at Warner-Lambert's option; provided that the decision of such patent counsel shall serve only as guidance to, and shall not be binding upon, the investigator.

Further, if there are medical reasons justifying submission for publication, presentation or use sooner than 45 days after submission to Warner-Lambert, Warner-Lambert Company will use its best efforts to expedite review and reduce the 45-day period.

1.7.1. Intellectual Property Rights

By signing a Clinical Study Agreement, the investigator agrees to keep in confidence and use only for completion of the study:

- Information provided to him/her by or on the behalf of Consumer Healthcare Research and Development; and
- Data, inventions, and discoveries, generated as a result of the study.

The investigator also agrees to return all copies of such information to Consumer Healthcare Research and Development at the sponsor's request and that data, inventions, and discoveries generated during the course of this study shall be the property of Consumer Healthcare Research and Development and will sign any documents, if requested, to transfer such ownership. This obligation will not apply to any information or data that later becomes public knowledge.

1.8. Restriction for Subject Inclusion

Study site personnel and immediate family are excluded from enrollment.

2. DOCUMENTATION PROCEDURES

2.1. Information Required by Consumer Healthcare Research and Development for Regulatory Review

This study will not start in any country until the requirements of Consumer Healthcare Research and Development and all regulatory requirements for the country in which the trial will be conducted have been satisfied. The following documents and information must be provided by the principal investigator to Consumer Healthcare Research and Development:

2.1.1. Prior to Study Initiation

2.1.1.1. New Product Application (IND)

Signed protocol (and amendments, if applicable);

A completed, signed FDA Statement of Investigator (FDA Form 1572) for each principal investigator and co-principal investigator;

Current curriculum vitae for the principal investigator, co-principal investigators, and subinvestigators listed on 1572s;

Current and dated laboratory reference ranges for any laboratory listed on 1572s;

Current and dated laboratory certifications for any laboratory listed on 1572s;

IRB or EC approvals of the study protocol; amendments, when applicable; ICDs; and advertisements used to recruit subjects, if applicable. IRB/EC approvals should include specific reference to document approved, the formal name of the IRB/EC issuing the approval, and the signature of the chairperson of the IRB/EC or designate. If the IRB/EC reviewed a specific outline or abridgment of the protocol prepared by the investigator instead of the complete protocol, a copy of the document actually reviewed should also be supplied to Consumer Healthcare Research and Development.

Signed clinical study agreement and

Institutional review board/ethics committee membership list.

2.1.1.2. Non - IND Application

- Signed protocol (and amendments, if applicable);
- IRB/EC approvals of the study protocol; amendments, when applicable; ICDs; and advertisements used to recruit study subjects, if applicable
- Regulatory approval of protocol (and amendments), if dictated by local law;
- Current curriculum vitae for each principal investigator and co-principal investigator ;
- Current laboratory reference ranges and certifications
- Signed clinical study agreement and
- Institutional review board/ethics committee membership list.

2.1.2. During the Study

Revisions or updates to any documents listed in Section 2.1.1;

Completed CRFs for each subject entered into the study;

All documents related to all serious adverse events and pregnancies and any reports to the IRB/EC describing serious adverse events or deaths either caused by or during use of the investigational drug; and

Investigator's annual progress report to the IRB/EC, and a copy of the annual IRB/EC reapproval of the study upon which the report is based, if dictated by local law.

2.1.3. End-of-Study

Further revisions or updates to any documents listed in Section 2.1.1;

Completed subject CRFs not yet retrieved;

Investigator's final report of the study, if applicable;

Investigator's written notification to IRB/EC regarding study completion or discontinuation, if dictated by local law;

Signed Statement of Clinical Study Close-Out;

Signed Investigator Authorization of Data Clarification Letter.

2.2. Document Storage and Retention

Warner-Lambert policy requires that, following completion of a clinical study, the Principal Investigator must maintain all study records, including source documents, until otherwise notified by Warner-Lambert.

RECORDS MAY NOT BE DESTROYED OR DISCARDED WITHOUT THE WRITTEN PERMISSION OF WARNER-LAMBERT COMPANY.

Each completed original CRF, dated and signed by the investigator, and any data clarification forms (DCFs), dated and signed by the investigator, will be returned promptly to Warner-Lambert. A copy of each completed CRF and DRF must be retained at the site.

In order to assure the accuracy of data collected in the CRFs, it is mandatory that representatives of Warner-Lambert Company have access to original source documents. Source documents include subject records, subject charts, study records/worksheets, laboratory reports, etc. During the review of these documents, the anonymity of the subject will be respected, with strict adherence to professional standards of confidentiality. Warner-Lambert Company reserves the right to terminate the study for refusal of the investigator to supply source documentation of work performance for this study.

2.3. Guidelines for Recording Data in the Case Report Forms

The completed CRF is a legal document as it may be intended for submission to a federal regulatory agency as part of a regulatory submission. Therefore, the following guidelines must be followed in its completion.

All data entered on the CRF must be in black or blue ink. No data entry in the original CRF may be deleted or corrected by either erasure, use of ink eradication fluid, liquid paper, adhesive correction tape, or any other means. When a data entry is in error, draw a single line through the erroneous entry (the original data must remain discernible) and indicate the correct data in whatever way is appropriate. All correction(s) with reason(s) for corrections (e.g., entry error) must be initialed and dated by one of the investigators or his/her designee. Usually the initials should be near the corrected data, clearly associated with the specific correction being made;

Validity of data recorded on CRFs during each subject visit will be attested to by a dated signature. As indicated on each CRF, some must be signed by an investigator, others can be signed by a study coordinator;

All questions should be answered. If information cannot be provided, appropriately enter or mark a single line; NA for Not Applicable/Available; ND for Not Done; or UNK for Unknown;

Each page of the CRF must contain the subject's initials, the subject's ID number, as well as the study number in the spaces provided. In the interest of subject privacy, initials rather than full names should be used for identification. For the same reason, the social security number, address, or home telephone number of a subject should not be entered in the CRF.

The investigator is responsible for providing the completed original CRF for each subject to the Consumer Healthcare Research and Development Site Monitor/Clinical Research Associate. If the subject is hospitalized, the information in the CRF may be compared with the subject's hospital records by the Consumer Healthcare Research and Development Site Monitor/Clinical Research Associate to verify its accuracy. If, because of institutional policy, only a copy of certain hospital records can be included in the CRF, the copy must be completely legible and either be signed or initialed in ink by the investigator. Since this verified copy will be considered as and dated the original by Consumer Healthcare Research and Development, the investigator is responsible for informing Consumer Healthcare Research and Development of any change that may be made in the "true" original that will be in the subject's hospital records.

2.4. Review of Case Report Forms

The completed CRFs will be reviewed by Consumer Healthcare Research and Development Medical/Dental Colleagues, Site Monitor/Clinical Research Associates, and Clinical Data Management, or equivalent persons in a designated Contract Research Organization. The investigator will be contacted if any corrections or additions are necessary. The investigator is responsible for cooperating fully with Consumer Healthcare Research and Development personnel or its designee in correcting any erroneous or contradictory data entries.

2.5. Investigator's Responsibility for Clinical Product Supply Accountability

All clinical product supplies, i.e., new or marketed product, any corresponding placebo, and any active product control (including marketed formulations) in finished dosage form, provided by Consumer Healthcare Research and Development to the investigator for use in the clinical study must be accounted for in written documentation (i.e., records of receipt, dispensing, and return/destruction) that must be maintained and retained by the investigator and that will be monitored by Consumer Healthcare Research and Development personnel. Note: if applicable, the investigator may designate a pharmacist to be responsible for clinical product supply accountability.

2.5.1. Receipt of Clinical Product Supplies

The investigator must verify and acknowledge the receipt of clinical product supplies and retain related documentation.

2.5.2. Storage

Product drug supplies must be maintained as specified in the protocol (e.g., environmental conditions required for stability) under secure (locked) conditions. Access to the stored study product should be limited to the investigators, the study coordinator, and the pharmacist (when applicable).

2.5.3 Dispensing of Clinical Product Supplies

Product Dispensing records must be maintained. The investigator must assure completion of the product dispensing records with appropriate information (e.g., amount dispensed and returned by the subject, etc). The product dispensing records must be retained by the investigator along with the subject's study records.

2.5.4. Return of Clinical Product Supplies

As specified in the protocol, all product containers and all unused products remaining at the termination or completion of the study must be returned to the address shown in the protocol or with the product shipment.

Used product containers should be maintained separately and returned periodically during the trial. The Consumer Healthcare Research and Development Site Monitor/Clinical Research Associate will assist in returning product and containers as required. The investigator must document on appropriate forms the quantity of containers returned. All returned products provided by Consumer Healthcare Research and Development will be counted by Clinical and Consumer Packaging Operations or designee.

When applicable, any on-site product destruction must be pre-approved by Consumer Healthcare Research and Development, and actual product destruction must be documented.

3. PROTOCOL AMENDMENTS AND ADDENDA

Definitions

A *protocol amendment* is any systematic change (e.g., revision, addition, deletion) that is made to the Final Protocol for all sites from a clinical study and is identified by consecutive Arabic numerals (e.g., Amendment 1, Amendment 2, etc). Amendments can be made regardless of whether the protocol has been signed by the investigator or whether or not the protocol has been implemented at a site.

An *Urgent Protocol Amendment* is one that must be instituted quickly, usually to eliminate an apparent immediate hazard to subjects and may be implemented prior to eventual IRB/EC review (within 5 working days) and submission to regulatory authorities.

The principal investigator, Study Monitor/CRA working on the study and the senior member of each of the following departments or their designee, must approve all amendments to the protocol: Medical/Dental Affairs, Statistics & Data Management, and Regulatory Affairs. The VP Medical/Clinical Research and Development Affairs/ VP Oral Care, may sign if deemed appropriate. The investigator is responsible for submitting any proposed change in the approved protocol in writing to the IRB/EC for review and approval and for sending a copy of the approval to Consumer Healthcare Research and Development. The Regulatory Affairs Departments of Consumer Healthcare Research and Development will file all amendments to studies that have been filed with a regulatory agency with the FDA or appropriate regulatory authorities.

With the exception indicated in Section 3.1 below, the amendment/addendum will apply to all subjects entered into the study (or all subjects in affected sites for addenda) after it has gone through the applicable procedure described above and been approved by the IRB/EC. Any amendments proposed in a multicenter protocol must be approved by the IRB/EC at the individual study site before it can be placed in effect at that site.

Protocol modifications or amendments fall into one of the following categories.

3.1. Urgent Protocol Amendment

If the amendment eliminates an apparent immediate safety hazard to the subject (urgent protocol amendment), it may be implemented immediately. Consumer Healthcare Research and Development will promptly notify the FDA and/or appropriate regulatory

authorities of the amendment while the investigator will notify his/her IRB/EC of the change in writing within 5 working days of its implementation.

3.2. Other Amendments

Examples of protocol modifications requiring amendments to the Final Protocol and thus prior IRB/EC approval include:

- Changes in the drug dosage or formulation;
- Increases in subjects'/subjects' duration of exposure to drug;
- Increases in subject numbers;
- Significant changes in protocol design (e.g., drop/add control group)
- Addition of a test/procedure that better monitors/reduces risk of side effects/adverse events;
- Elimination of test intended to monitor safety;
- Specific request from a regulatory agency;
- Modification in entry (ie, inclusion/exclusion) or evaluability criteria;
- Significant change in safety/efficacy status of the clinical test product;
- Ambiguity (scientific or grammatical) in the protocol that needs clarification;

3.3. Study Termination

Warner Lambert Company may terminate the Study at any time in the exercise of its sole discretion upon fifteen- (15) days prior written notice to Institution. The Study may be terminated by Institution upon fifteen- (15) days prior written notice to Warner because of significant subject safety concerns or for other material and significant reasons. Upon receipt or giving of notice, as the case may be, Institution agrees to promptly terminate conduct of the Study to the extent medically permissible for all subjects. In the event of termination hereunder, other than as a result of a material breach by Institution, the total sums payable by Warner pursuant to this Agreement shall be equitably pro-rated for actual work performed to the date of termination with any unexpended funds previously paid by Warner to Institution being refunded to Warner.

3.4. Deviations from Protocol

A copy of the approved protocol will be kept on file at Warner-Lambert Company and the study site. Neither the investigator nor the sponsor are permitted to deviate from the protocol.

Apart from regulatory requirements, it is vital to the success of the study that the investigator adheres to the details of the protocol and thus, holds to a minimum the number of cases later classified as 'incomplete' or 'unusable.'

When a situation occurs that requires departure from the protocol, the investigator will contact the study monitor. Contact with the study monitor will be made as soon as possible in order to discuss the situation and to agree on an appropriate course of action.

Warner-Lambert Company reserves the right not to compensate the investigator for evaluation of cases in which the procedures and evaluations are conducted in a manner other than that specified by the protocol.

APPENDIX D
The Declaration of Helsinki

The Declaration of Helsinki

Recommendations Guiding Physicians in Biomedical Research
Involving Human Subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964,

and amended by
the 29th World Medical Assembly, Tokyo, Japan, October 1975;
the 35th World Medical Assembly, Venice, Italy, October 1983;
the 41st World Medical Assembly, Hong Kong, September 1989;

and the

48th General Assembly, Somerset West, Republic of South Africa, October 1996

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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

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

- L. 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 E

Detailed Study Safety Procedures

The oral hard and soft tissues will be examined at screening and subsequent examinations. Aberrations will be recorded and their severity assessed.

Aberrations may include, but are not limited to cheek bites, food burns, mechanical trauma such as toothbrush or floss abrasion, amalgam tattoos, geographic tongue, corrugated tongue, Fordyce granules, linea alba, traumatic ulcers, aspirin burns, tooth stain. Such conditions will typically be recorded as soft or hard tissue aberrations and not as adverse events.

An expected outcome for some subjects during brushing or rinsing may be a transient burning or tingling sensation on the oral soft tissues, which has been reported with use of essential oil-containing products. If there is no observed clinical aberration in those subjects reporting this sensation, then it will not be considered an adverse event and the comment will be captured by the subject on his/her diary, and/or as a comment on a clinical CRF. All oral complaints require a clinical diagnosis to be recorded as an adverse event.

**APPENDIX F
CASE REPORT FORM
I. SCREENING PROCEDURES**

Subject's initial _____ Subject's number _____
 Race _____ Date of Birth _____
 Sex Male Female Smoker Yes No

General and Oral Health Screening

Informed Consent: Yes No
 Medical History Information Provided: Yes No (use attached forms)
 Pre-medication for dental procedure: Yes No
 General Health Condition: Pass Fail
 Number of natural teeth _____ (minimum 24)
 Oral Examination: Yes No (use oral soft tissue exam form)
 Oral Health Condition: Pass Fail
 History of adverse effects to oral hygiene products: Yes No

Collect Saliva Samples for Screening:

Sample	Container wt. (g)	Saliva + container (g)	Saliva wt. (g)	Flow Rate (ml/min)
Unstimulated Saliva				
Stimulated Saliva				

Subject accepted: Yes No
 If not, explain: _____

Dental Prophylaxis Yes No
Written Instructions Provided: Yes No
Product Distribution: Toothbrush Yes No
 Non-fluoride toothpaste Yes No

Any Adverse Reactions _____

Signature of Examiner _____ Date _____

APPENDIX F
CASE REPORT FORM
II. ORAL SOFT TISSUE EXAM

Subject's Initials _____ Subject's No. _____

Visit Number: _____ Date of Exam _____

Condition of:	Normal	Describe abnormality
lips	_____	_____
buccal mucosa	_____	_____
labial mucosa	_____	_____
sublingual mucosa	_____	_____
attached gingivae	_____	_____
tongue	_____	_____
hard/soft palate	_____	_____
uvula	_____	_____
oropharynx	_____	_____
teeth	_____	_____
other	_____	_____

Abnormality attributable to experimental oral rinses? Yes _____ No _____ NA _____

=====
Comments:

Examiner's Signature _____ Date _____

**APPENDIX F
CASE REPORT FORM
III. SALIVA COLLECTION**

Subject Initial: _____

Subject Assignment #: _____ Test Leg: _____

Date: _____ Examiner: _____

	Sample No.	Time	Container wt. (g)	Saliva + container (g)	Saliva wt. (g)	Flow Rate (ml/min)
Pre-rinse (baseline)	1					
Immediately after rinse	2					
7.5 min	3					
15 min	4					
30 min	5					
60 min	6					
120 min	7					

Remarks _____

Any Adverse Reactions _____

Signature of Examiner _____