Title: THE ROLE OF TOPICAL ANTIBIOTIC PROPHYLAXIS IN EYELID SURGERY

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UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
Clinical Research Protocol
THE ROLE OF TOPICAL ANTIBIOTIC PROPHYLAXIS IN EYELID SURGERY

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Version Date:	9/9/2018
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Development Phase:	
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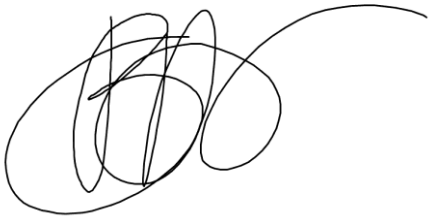
Approval:



9/9/18

PI or Sponsor Signature (Name and Title)

Date

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Dr. Robert Kersten with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 17-22309

Protocol Title: The Role of Topical Antibiotic Prophylaxis in Eyelid Surgery

Protocol Date: 9/9/18

9/9/18

Investigator Signature *Date*

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LIST OF ABBREVIATIONS

AE	adverse event
CFR	Code of Federal Regulations
CRF	case report form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
PI	Principal Investigator
SAE	serious adverse experience

PROTOCOL SYNOPSIS

TITLE	The Role of Topical Antibiotic Prophylaxis in Eyelid Surgery
SPONSOR	UCSF
FUNDING ORGANIZATION	n/a
NUMBER OF SITES	1
RATIONALE	As antibiotic resistance, antibiotic-related complications (e.g. contact dermatitis), and healthcare costs are on the rise, the routine use of post-operative topical antibiotic prophylaxis should be examined. After all, the rates of postoperative infections involving Class I and Class II surgical wounds (as defined by the CDC, or Centers for Disease Control and Prevention), including those associated with eyelid surgery, are known to be low. Despite a lack of evidence supporting the use of prophylactic topical antibiotic therapy after eyelid surgery, the practice remains widespread both nationally and internationally. As such, we propose a randomized control trial testing the hypothesis that routine topical antibiotic prophylaxis does not significantly reduce the rate of infection after eyelid surgery.
STUDY DESIGN	This is a prospective randomized control trial.
PRIMARY OBJECTIVE	To determine if there is a role for topical prophylactic topical antibiotic therapy after eyelid surgery.
SECONDARY OBJECTIVES	To determine of rates of wound infection after eyelid surgery both with and without topical post-operative antibiotic prophylaxis; to determine if rates of wound infection after eyelid surgery are different among healthy and immunocompromised patients; to determine the type and frequency of adverse reactions resulting from topical antibiotic use.
NUMBER OF SUBJECTS	400
SUBJECT SELECTION CRITERIA	<u>Inclusion Criteria</u>: Patients aged 18 and older who are undergoing various eyelid procedures in an office, ambulatory care center, or operating room including but not limited to: • blepharoplasty (upper and lower lids); • ectropion repair;

	• entropion repair; • external dacrocystorhinostomy; • external levator resection; • eyelid lesion removal and/or biopsy; • eyelid reconstruction and defect repair including after Mohs surgery; • fat pad excision (upper and lower lids); • gold or platinum weight implantation; • internal levator resection; • lateral tarsal strip; • orbital fracture repair requiring periorbital incisions; • orbitotomy requiring periorbital incisions; • tarsorrhaphy; • wedge excision. • Patients undergoing repeat procedures will also be included. <u>Exclusion Criteria</u>: • Patients aged younger than 18 years old who are undergoing the above eyelid procedures in an office, ambulatory care centers, operating rooms; • patients undergoing chalazion removal; • patients who have had previous wound infections at the site of the procedure; • patients with oral or IV antibiotic use within 10 days prior to procedure; • patients requiring IV antibiotics during the procedure; • patients with grossly contaminated or inflamed wounds; • patients with human or animal bites, • patients with wounds resulting from trauma • patients allergic to all study drug options.

TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Topical Ophthalmic Antibiotic Ointment (e.g. poly-bacitracin, bacitracin). Apply a thin ribbon to surgical wounds 4 times a day (while awake) for 7 days.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Artificial Tear Ointment (e.g. Refresh PM). Apply a thin ribbon to surgical wounds 4 times a day (while awake) for 7 days.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 14 days. **Screening:** During pre-operative assessment. **Treatment Duration:** 7 days **Follow-up:** 7-14 days The total duration of the study is expected to be 2 years with ongoing subject recruitment. Each subject will have a final follow-up at post-operative week 1 and/or post-operative week 2 unless a post-operative infection occurs. In the event of a post-operative infection, final follow-up will occur upon infection resolution.
CONCOMMITANT MEDICATIONS	Allowed: All non-antimicrobial medications. Prohibited: Antibiotics taken by IV or by mouth.
PRIMARY ENDPOINT	• To determine the rates of eyelid surgical site infections (SSIs) with and without topical antibiotic therapy.
SECONDARY ENDPOINTS	• To determine the rate of eyelid SSIs in patients with compromised immune status (e.g. patients with diabetes, those who smoke, those on chronic high-dose steroids, etc.) • To classify the types of complications related to antibiotic ointment and artificial tear ointment use; to determine their respective rates.
SAFETY EVALUATIONS	Adverse events will reported according to the UCSF IRB reporting requirements. Risks of participating in this study are not greater than the risks involved in current post-operative standard of care regimens.
PLANNED INTERIM ANALYSES	Serious adverse events will be monitored on an ongoing basis throughout the study. Study data from each subsequent set of 25 patients enrolled will be reviewed regularly by a Data Safety Monitoring Committee (DSMC).

STATISTICS **Primary Analysis Plan**	We will plan to use a T-test or a linear regression model (with no covariates other than study arm).
Rationale for Number of Subjects	We aim to recruit 200 people for each arm of the study, totaling 400 subjects. These numbers are commensurate to our regular surgical patient volume over the course of two years and as such, detected rates of infection will be clinically relevant.

1 BACKGROUND AND RATIONALE

Despite a lack of evidence supporting the use of routine topical antibiotic therapy (e.g. poly-bacitracin, bacitracin, erythromycin, etc.) after eyelid surgery, it is currently standard of care to provide patients with post-operative antibiotics in order to prevent surgical site infections (SSIs). For instance, a 2014 survey of oculoplastic surgeons from 43 countries revealed that while rates of prophylactic oral and perioperative intravenous antibiotic use varied considerably, topical antibiotic use was common across all geographic regions (85.2%).[1]

The rates of postoperative infections involving Class I: Clean and Class II: Clean-Contaminated* surgical wounds, including those associated with eyelid surgery, are known to be low. For instance, while the rate of infection after blepharoplasty is 0.2% with antibiotic ointment use [2] and the rate of infection after external dacrocystorhinostomy is 1% with antibiotic use,[3] the rates of infection without topical antibiotics in a range of dermatological procedures such as Mohs surgery are as low as 0.7%.[4] There is currently no literature on the rates of infection after blepharoplasty and other eyelid-specific procedures in the absence of prophylactic antibiotic ointment.

As antibiotic resistance, antibiotic-related complications (e.g. contact dermatitis), and healthcare costs are on the rise, it has been advocated that topical antibiotic prophylaxis be withheld in eyelid surgery except in certain high risk cases. As such, we propose a randomized control trial testing the hypothesis that routine topical antibiotic prophylaxis does not significantly reduce the rate of infection after eyelid surgery. The hope is to reduce rates of antibiotic resistance, antibiotic-related complications, and healthcare costs.

*Under CDC surgical wound classification system, Class I/Clean wounds include “an uninfected operative wound in which no inflammation is encountered and…[is] primarily closed and, if necessary, drained with closed drainage…Class II/Clean-Contaminated wounds include those …without unusual contamination… [and] no evidence of infection or major break in technique.”

1. Fay A, Nallasamy N, Bernardini F, et al. Multinational Comparison of Prophylactic Antibiotic Use for Eyelid Surgery. JAMA Ophthalmol. 2015 Jul; 133(7):778-84.
2. Carter SR, Stewart JM, Khan J, et al. Infection after blepharoplasty with and without carbon dioxide laser resurfacing. Ophthalmology. 2003 Jul; 110(7):1430-2.
3. Yazici B, Meyer DR. Selective antibiotic use to prevent postoperative wound infection after external dacryocystorhinostomy. Ophthal Plast Reconstr Surg. 2002; 18:331
4. Saco M, Howe N, Nathoo R, et al. Topical antibiotic prophylaxis for prevention of surgical wound infections from dermatologic procedures: a systematic review and meta-analysis. J Dermatolog Treat. 2015 Apr; 26(2):151-8.

2 STUDY OBJECTIVES

2.1 Primary Objective

The objective is to conclusively determine whether or not topical post-operative antibiotic use has a meaningful prophylactic role after eyelid surgery.

2.2 Secondary Objectives

To determine of rates of wound infection after eyelid surgery both with and without topical post-operative antibiotic prophylaxis; to determine if rates of wound infection after eyelid surgery are different among healthy and immunocompromised patients; to determine the type and frequency of adverse reactions resulting from topical antibiotic use.

3 STUDY DESIGN

3.1 Study Overview

This is a single center, placebo-controlled, randomized trial. 400 subjects are planned. Subjects will be randomly assigned to a study drug or to a placebo. Each subject will apply a single dose of topical study drug or placebo four times daily to their surgical wounds over the course of one week.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following treatment regimens will be used:

- Experimental treatment: topical ophthalmic antibiotic ointment (e.g. erythromycin, bacitracin or polybac)
- Placebo: artificial tear ointment (e.g. Refresh PM)

Total duration of subject participation will be from the time of approval for eyelid surgery to post-operative visit #1 (either one or two weeks after surgery). Total duration of the study is expected to be 2 years.

4 CRITERIA FOR EVALUATION

4.1 Primary Efficacy Endpoint

The primary endpoint will be the rate of superficial incisional and deep incisional surgical site infection (SSI) of clean and clean-contaminated wounds at postoperative visit week 1 and/or postoperative visit week 2. Superficial and deep incisional SSI will be defined per CDC surgical site infection criteria, slightly modified for the eyelid area, and will be evaluated by one of two observers (RV or RK):

Modified Eyelid Superficial Incisional SSI:[4]

(1) Infection occurs within 14 days after the operation,
(2) AND infection involves only skin and subcutaneous tissue of the incision,

(3) AND at least one of the following criteria is met:
- purulent drainage from the incision
- organisms isolated from an aseptically obtained culture of fluid or tissue from the incision
- at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness or heat
- diagnosis of superficial incisional SSI by a surgeon or attending physician

Modified Eyelid Deep Incisional Surgical Site Infection:[4]

(1) Infection occurs within 14 days after the operation (or one year in case of implants)
(2) AND infection involves deep soft tissues, such as the fascia and muscles,
(3) AND at least one of the following criteria is met:
- purulent drainage from the incision but not from the organ/space of the surgical site
- a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness - unless the culture is negative
- an abscess or other evidence of infection involving the incision is found on direct examination or by histopathologic or radiological examination
- diagnosis of a deep incisional SSI by a surgeon or attending physician.

5. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Hospital Infection Control Practices Advisory Committee. Guideline for prevention of surgical site infection, 1999. Infect Control Hosp Epidemiol. 1999; 20(4):250–278.

4.2 Secondary Efficacy Endpoints

- The rate of superficial and deep SSI in high infection-risk groups such as patients with diabetes, those who smoke, those on chronic high-dose steroids, etc.
- The classification of types of complications (e.g. allergic dermatitis) related to antibiotic ointment and artificial tear ointment use as well as their respective rates.

4.3 Safety Evaluations

- Adverse events will be monitored throughout the study and will be reported according to the UCSF IRB reporting requirements.
- The DSMC will receive regular updates, including information such as: number of patients screened, number of participants enrolled, number of participants randomized/receiving treatment, number of participants lost to follow-up,

number of participants meeting the outcome definition, and number of participants with an adverse event. These updates will be made after each consecutive set of 25 participants has been enrolled.

- Stopping rule for the trial: As part of the regular DSMC review process detailed above, the DSMC will make a determination at each review whether the study can continue.

5 SUBJECT SELECTION

5.1 Study Population

Subjects requiring or electing to undergo eyelid surgery and meet the inclusion criteria will be eligible for participation in this study.

5.2 Inclusion Criteria

Patients aged 18 and older who are undergoing various eyelid procedures in an office, ambulatory care center, or operating room including but not limited to:

- blepharoplasty (upper and lower lids);
- ectropion repair;
- entropion repair;
- external dacrocystorhinostomy;
- external levator resection;
- eyelid lesion removal and/or biopsy;
- eyelid reconstruction and defect repair including after Mohs surgery;
- fat pad excision (upper and lower lids);
- gold or platinum weight implantation;
- internal levator resection;
- lateral tarsal strip;
- orbital fracture repair requiring periorbital incisions;
- orbitotomy requiring periorbital incisions;
- tarsorrhaphy;
- wedge excision.
- Patients undergoing repeat procedures will also be included.
- Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

5.3 Exclusion Criteria

- Patients aged younger than 18 years old who are undergoing the above eyelid procedures in an office, ambulatory care centers, operating rooms;
- patients undergoing chalazion removal;
- patients who have had previous wound infections at the site of the procedure;
- patients with oral or IV antibiotic use within 10 days prior to procedure;

- patients requiring IV antibiotics during the procedure;
- patients with grossly contaminated or inflamed wounds;
- patients with human or animal bites,
- patients with wounds resulting from trauma
- patients who are allergic to all study drug options.

6 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

The following medications are prohibited during the study and administration will be considered a protocol violation:

- Intravenous antibiotics.
- Oral antibiotics.

7 STUDY TREATMENTS

7.1 Method of Assigning Subjects to Treatment Groups

Patients will be randomly assigned to topical antibiotic ointment or placebo treatment groups in a 1:1 ratio using a computer-generated randomization scheme developed by the study statistician. Randomization will be performed at the time of study recruitment.

7.2 Blinding

Neither subjects nor investigators will be blinded.

7.3 Formulation of Test and Control Products

Test:

Erythromycin Ophthalmic Ointment USP, 0.5%, 3.5g, Akorn

OR

Bacitracin Zinc Ophthalmic Ointment USP, 3.5g, Bausch+Lomb

OR

Bacitracin Zinc and Polymyxin B Sulfate Ophthalmic Ointment USP, 3.5g, Bausch +Lomb

Control:

Refresh PM Lubricant Eye Gel, 3.5g

7.3.1 Packaging and Labeling

Study drug will be supplied in single 3.5 g tubes and will be labeled per the manufacturer.

7.4 Supply of Study Drug at the Site

Study drug supply (or placebo) will be obtained at an outpatient pharmacy on or before day of surgery.

7.4.1 Dosage/Dosage Regimen

Topical Ophthalmic Antibiotic Ointment (e.g. poly-bacitracin, bacitracin). Apply a thin ribbon to surgical wounds 4 times a day (while awake) for 7 days.

OR

Artificial Tear Ointment. Apply a thin ribbon to surgical wounds 4 times a day (while awake) for 7 days.

7.4.2 Dispensing

Study drug or placebo will be dispensed by an outpatient pharmacist.

7.4.3 Administration Instructions

See 7.4.1

7.5 Supply of Study Drug at the Site

n/a

7.5.1 Storage

n/a

7.6 Study Drug Accountability

n/a

7.7 Measures of Treatment Compliance

Subjects will be asked to keep a patient diary noting the day and date they take their study drug and any adverse events. They will be asked to bring their patient diary to each study visit along with all used and unused study drug containers.

8 STUDY PROCEDURES AND GUIDELINES

Patients will be recruited at their pre-operative visits and be randomized to study drug vs placebo at that time **(Visit 1).** Study enrollment and randomization group will be recorded under the Apex smartphrase, ".RKRVEYELIDPRE" before being transferred to REDCap. Primary and secondary endpoints will assessed at postoperative week #1 **(Visit 2)** and recorded under the Apex smartphrase, ".RKRVEYELIDPOST" before being transferred to REDCap.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

8.1 Clinical Assessments

8.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Visit 1 and 2 and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

8.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Visit 1.

8.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Visit 1.

8.1.4 Physical Examination

A complete eye examination will be performed by either the investigator or a subinvestigator who is a physician at Visit 1. New abnormal eye exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

8.1.5 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9 EVALUATIONS BY VISIT

9.1 Visit 1

1. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Record demographics data (e.g. age, sex, race).
3. Record ophthalmologic and medical history, including current and recent antibiotic use.
4. Perform eye exam.
5. Randomize subject.
6. Document randomization using Apex smartphrase, ".RKRVEYELIDPRE"
7. Assign surgery date.

9.2 Visit 2 (Post-operative week 1)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Concomitant medications review.
3. Perform abbreviated eye examination.
4. Determine presence or absence of surgical site infection.
5. Determine presence or absence of drug/placebo allergies.
6. Determine if patient is immunocompromised.
7. Start treatment if infection present.
8. Document findings using Apex smartphase, ".RKRVEYELIDPOST"

9.3 Visit 3 (Only if surgical site infection present at Visit 2.)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Record changes to concomitant medications.
3. Perform abbreviated eye examination.
4. Note duration of treatment and if infection resolved.

9.4 Early Withdrawal Visit

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and exclusionary medication use.
2. Record changes to concomitant medications.
3. Perform complete eye examination.

10 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events

will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.

Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

10.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

10.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

10.3 Medical Monitoring

The DSMC will receive regular updates, including information such as: number of patients screened, number of participants enrolled, number of participants randomized/receiving treatment, number of participants lost to follow-up, number of participants meeting the outcome definition, and number of participants with an adverse event. These updates will be made after each consecutive set of 25

participants has been enrolled. As part of this regular review process, the DSMC will make a determination at each review whether the study can continue.

Dr. Jeremy Keenan should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: 415-476-6323

11 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

11.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 9.4 for early termination procedures.

11.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 2) should have an early discontinuation visit. Refer to 9.4 for early termination procedures.

11.3 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

Subjects who withdraw from the study will not be replaced.

12 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Non-compliance with study drug regimen

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

13 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

13.1 Data Sets Analyzed

All randomized subjects who have completed one week of study drug or placebo will be included in data analysis.

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

13.2 Demographic and Baseline Characteristics

Age

Gender
Race
Smoker (Y/N)

13.3 Analysis of Primary Endpoint

T-test or a linear regression model (with no covariates other than study arm).

13.4 Analysis of Secondary Endpoints

T-test or a linear regression model (with no covariates other than study arm).

Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

13.5 Interim Analysis

The DSMC will make determinations for interim analysis during their regular review of study data.

13.6 Sample Size and Randomization

200 patients will be randomized to the topical antibiotic group and 200 patients will be randomized to the artificial tear ointment group.

14 DATA COLLECTION, RETENTION AND MONITORING

14.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject number and initials.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

14.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

14.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

14.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

14.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

14.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or

designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

14.7 Subject Confidentiality

In order to maintain subject confidentiality, only subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

15 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

15.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

15.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator

to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

15.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

15.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws,

including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

15.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical