CLINICAL TRIAL PROTOCOL KUR-1301-101

A RANDOMIZED, MULTICENTER, DOUBLE-MASKED, PLACEBO-CONTROLLED, PHASE 3 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF VANCOMYCIN HYDROCHLORIDE OPHTHALMIC OINTMENT 1.1% IN PATIENTS WITH MODERATE TO SEVERE BACTERIAL CONJUNCTIVITIS

Study Phase:	Phase 3
Product Name:	Vancomycin hydrochloride ophthalmic ointment
Indication:	Bacterial conjunctivitis
Sponsor:	Kurobe, LLC 400 N Ashley Drive Suite 2150 Tampa, FL 33602
Medical Monitor:	Charles Slonim, MD
Original Protocol:	10 March 2015
Amendment 1:	03 May 2016
Amendment 2:	15 September 2016

SPONSOR SIGNATURE

Study Title:	A Randomized, Multicenter, Double-Masked, Placebo-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Vancomycin Hydrochloride Ophthalmic Ointment 1.1% in Patients with Moderate to Severe Bacterial Conjunctivitis
Study Number:	KUR-1301-101
Original Protocol:	10 March 2015
Amendment 1:	03 May 2016
Amendment 2:	15 September 2016

Person authorized to sign the protocol and protocol amendment(s) for the sponsor, Kurobe, LLC

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Date

INVESTIGATOR'S AGREEMENT

Study Title:	A Randomized, Multicenter, Double-Masked, Placebo-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Vancomycin Hydrochloride Ophthalmic Ointment 1.1% in Patients with Moderate to Severe Bacterial Conjunctivitis
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I have read the KUR-1301-101 protocol. The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with International Conference of Harmonisation (ICH) Guidelines, and all applicable United States (US) Federal Regulations and local legal and regulatory requirements.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

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Medical Monitor	Charles Slonim, MD Oculos Clinical Research	813-690-0255 (Mobile) 813-443-5865 (Fax) Email: cslonim@pointguardllc.com

1. SYNOPSIS

Name of Sponsor/Company: Kurobe, LLC

Name of Investigational Product: Vancomycin hydrochloride ophthalmic ointment 1.1%

Name of Active Ingredient: Vancomycin hydrochloride

Title of Study: A Randomized, Multicenter, Double-Masked, Placebo-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Vancomycin Hydrochloride Ophthalmic Ointment 1.1% in Patients with Moderate to Severe Bacterial Conjunctivitis.

Studied Period (Years):	**Phase of Development:**
Estimated date first patient enrolled: August 2015 Estimated date last patient completed: November 2016	3

Objectives: The primary objective of this study is to evaluate the safety and efficacy of vancomycin hydrochloride ophthalmic ointment 1.1% dosed 4 times daily (QID) in patients with moderate to severe Gram-positive bacterial conjunctivitis.

Methodology: This will be a randomized, multicenter, double-masked, placebo-controlled study. Eligible subjects will enter the study with clinically diagnosed bacterial conjunctivitis.

At Screening/Visit 1 (Day 1), subjects will undergo AdenoPlus® conjunctival adenovirus screening testing. If the AdenoPlus test result is negative, the subject will undergo microbial culture (including susceptibility testing) and ophthalmic evaluations. If the AdenoPlus® test result is positive, the subject will be considered a screen failure. Subjects confirmed to have met eligibility criteria will be randomized to 1 of 2 treatment arms and will administer the allocated study medication 4 times daily (QID) to the infected eye(s) approximately 4 hours apart for 7 days:

- Vancomycin ophthalmic ointment 1.1% QID
- Vehicle ointment (placebo) QID

If both eyes are being treated, the eye with more severe signs of infection (based on the sum of the 3 grading scales [conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection]) will be considered the study eye. If the sum of the scales for both eyes are equal, the default will be the right eye. If a subject with a unilateral infection develops an infection in the contralateral eye, the subject should contact the clinical site and will be instructed to treat the contralateral eye with the study medication if signs of ocular conjunctival discharge and/or injection are present. The eye originally treated will continue to be considered the study eye. Only the study eye will be assessed for efficacy; safety assessments will be conducted bilaterally.

At Visit 2 (Day 5) subjects will return to the clinical site, and microbial culture and ophthalmic evaluations of safety and efficacy will be conducted.

Methodology (continued):

At Visit 3 (Day 8) subjects will return to the clinical site for final microbial culture, and ophthalmic evaluations of safety and efficacy.

Randomized study medication (vancomycin or vehicle [placebo] ophthalmic ointment) will be provided in identical-appearing tubes. The identity of the study medications will be masked to the subject, Investigator, study personnel responsible for ophthalmic evaluations, and sponsor personnel responsible for medical evaluation of the data.

Number of Patients (Planned): Subjects will be enrolled at approximately 20 clinical sites, until the number of Gram-positive subjects has reached at least 75 per group.

Inclusion Criteria:

1. Age 1 and older
2. Clinical diagnosis of acute bacterial conjunctivitis with at least one eye exhibiting conjunctival discharge graded ≥ 2 as well as palpebral conjunctival injection graded ≥ 2 AND bulbar conjunctival injection graded ≥ 2 with onset ≤ 4 days as reported by the subject.
3. Negative test result on AdenoPlus® adenovirus test.
4. Snellen visual acuity (VA) equal to or better than 20/200 in each eye using current corrective lenses, if required (or if worn) and/or using a pinhole if subject's corrective lenses are not available at the time of exam. Every attempt should be made to obtain a VA measurement in children and, if it is unobtainable, the decision as to whether the criterion is met will be at the investigator's discretion.
5. Female subjects must be 1-year postmenopausal, surgically sterilized, or women of childbearing potential with a negative urine pregnancy test at Visit 1. Women of childbearing potential must use an acceptable form of contraception throughout the study. Acceptable methods include the use of at least one of the following: intrauterine (intrauterine device), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence.
6. Able to self-administer study medication or to have the study medication administered by a caregiver throughout the study period.
7. Must have signed written consent from the subject prior to participation in any study-related procedures if the subject is 18 years of age or older, or from the legally authorized representative/guardian if the subject is under 18 years of age.
8. Must have the signature of the subject on the assent form, as required by Institutional Review Board (IRB) guidelines, if the subject is under 18 years of age.

Exclusion Criteria:

1. Suspected viral or allergic conjunctivitis or suspected fungal or acanthamoeba infections at Screening in either eye.
2. Suspected iritis/uveitis or episcleritis/scleritis at Screening in either eye or history of either condition.
3. Active ulcerative keratitis, specifically any epithelial loss greater than punctate keratitis (eg, confluent epithelial loss or any subepithelial infiltration) in either eye.
4. History of recurrent corneal erosion syndrome, either idiopathic or secondary to previous corneal trauma or dry eye syndrome in study eye.
5. Uncontrolled systemic or debilitating disease (eg, cardiovascular disease, hypertension, diabetes, or cystic fibrosis) in the opinion of the Investigator.
6. Subjects who are immunocompromised (eg, HIV-positive); any use of immunosuppressive therapy (including chemotherapy).
7. Any use of topical ophthalmic medications, including tear substitutes, within 2 hours before Screening and throughout the study period in either eye.
8. Use of topical ophthalmic antimicrobial therapy within 48 hours prior to Screening. Use of topical ophthalmic antimicrobial therapy other than study medication is prohibited throughout the study period in either eye.
9. Use of topical ophthalmic anti-inflammatory agents (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] or steroids, including steroid-antibiotic combinations) within 48 hours prior to Screening and throughout the study period in either eye.
10. Use of systemic antimicrobial therapy for active respiratory tract, urinary tract, skin/soft tissue, or otitis media infection within 72 hours prior to Screening and throughout the study period. Use of a topical dermatologic antibiotic is permitted.
11. Use of systemic steroids within 14 days of screening and throughout the study period. Inhaled, intranasal, and topical dermatological steroids are permitted.
12. Contact lens wear during the study period in study eye. (contact lens wear in an untreated fellow eye is allowed).
13. Ocular surgery (nonlaser or laser) within 6 weeks prior to Screening in study eye.
14. Pregnancy or lactation.
15. Participation in an ophthalmic drug or device research study within 30 days prior to Screening in either eye.
16. Known hypersensitivity to vancomycin, petrolatum, or mineral oil.

Investigational Product, Dosage and Mode Of Administration: Vancomycin ophthalmic ointment 1.1%, approximately 1 cm of ointment QID, topical ocular administration for 7 days

Reference Therapy, Dosage and Mode Of Administration: Ophthalmic ointment vehicle (placebo), approximately 1 cm of ointment QID, topical ocular administration for 7 days

Duration of Treatment: 7 days

Study Procedures:

Visit 1 (Day 1): Screening/Baseline At Visit 1 subjects will provide informed consent/assent before any study-related procedures are conducted and participate in screening procedures (AdenoPlus® conjunctival adenovirus test, microbial culture, ophthalmic assessments including grading of clinical signs) to establish eligibility for the study**.**

Study Procedures (continued):

Eligible subjects will be randomized into the study, study medication will be dispensed, and subjects (or caregivers) will receive instruction and then administer the first dose of allocated study medication at the site.

All 4 doses should be administered on Day 1 even if the intervals are shorter than 4 hours between doses. On Days 2-7 subjects will continue to administer the randomized study medication QID (approximately 4 hours between doses).

Subjects should be reminded to bring the study diary to the clinical site at Visit 2 (Day 5).

Visit 2 (Day 5): At Visit 2, Day 5 (± 1 day) study site personnel will conduct diary review. Subjects will participate in microbial culture and ophthalmic assessments of safety and efficacy.

Subjects must be reminded not to dose after their fourth dose on Day 7 and to bring all study medication materials and the study diary to the clinical site at Visit 3 (Day 8).

Visit 3 (Day 8): At Visit 3, Day 8 (+ 1 day) subjects will return all study medication to the clinical site. Study site personnel will conduct diary review and study drug accountability procedures. Subjects will participate in final ophthalmic assessments of safety and efficacy.

If the subject continues to show signs of infection in either eye at Day 8, the subject will be treated per the Investigator's standard of care. Study treatment will not be administered after the last dose on Day 7.

Efficacy Assessments: Efficacy will be assessed by the investigator's grading of 3 clinical signs on 4 point scales: Conjunctival discharge on a scale of 0 3 (where 0 is absent and 3 is severe), and bulbar conjunctival injection and palpebral conjunctival injection each graded separately on a scale of 0 3 (where 0 is none and 3 is severe), as well as by microbial culture.

Safety Assessments: Safety will be assessed by Snellen visual acuity, biomicroscopy, and adverse event assessment.

Criteria for Evaluation: The primary endpoints comprise a set of hypotheses that will be tested in a hierarchical fashion.

Primary Efficacy Endpoint: Proportion of subjects at Visit 3 (Day 8) with:

- Clinical resolution of bacterial conjunctivitis (defined as absence of conjunctival discharge, bulbar conjunctival injection and palpebral conjunctival injection)
- Microbial eradication (absence of all Gram-positive bacterial species present at baseline)

The difference in proportion in the two treatment groups will be tested by the chi-square test with a significance level of 0.05. In order to control the Type I error rate these two endpoints will be tested sequentially in the order described above. If the null hypothesis for the clinical resolution endpoint can be rejected at $P \leq 0.05$, the bacterial eradication endpoint will be tested at $P \leq 0.05$

Statistical Methods: Primary efficacy analysis will be conducted on the modified intent-to-treat (mITT) population, which will consist of randomized subjects with Gram-positive bacterial conjunctivitis. Efficacy analysis will also be conducted on the intent-to-treat (ITT) population, which will consist of all randomized subjects. Per protocol (PP) analysis will be conducted on those subjects in the mITT population who are compliant in dosing, meeting study visits, and without significant protocol violations. Safety analyses will be performed using the safety analysis set (all randomized subjects who received at least one dose of the allocated product).

The analysis of continuous and ordinal variables will use the applicable parametric methods (t-test, analysis of variance [ANOVA], and analysis of covariance [ANCOVA]). Descriptive statistics will be used to summarize continuous outcomes (number of subjects [N], mean, standard deviation or standard error of the mean, median, maximum, and minimum) and categorical variables (frequency and percentage) at each assessment time point.

Sample Size: Subjects will be enrolled until the number of subjects with Gram-positive bacterial conjunctivitis has reached at least 75 per group. A two-group chi-square test with a 0.05 two-sided significance level will have 90% power to detect the difference between a Group 1 proportion of 0.75 and a Group 2 proportion of 0.50 (odds ratio of 3.0) when the sample size in each group is 77.

Table 2: Schedule of Procedures

Assessment	**Screening/Baseline**	**Treatment**	**End of Treatment**	**Early Termination**
Day	**Day 1**	**Day 5 (± 1 day)**	**Day 8 (+ 1 day)**	
Visit	**1**	**2**	**3**	
Informed consent	X			
Demographics	X			
Medical/ocular history	X			
Prior/concomitant medications	X	X	X	X
Study diary review		X	X	X
AdenoPlus® conjunctival adenovirus test	X			
Snellen visual acuity	X	X	X	X
Biomicroscopy	X	X	X	X
Grading of conjunctival discharge	X	X	X	X
Grading of bulbar conjunctival injection	X	X	X	X
Grading of palpebral conjunctival injection	X	X	X	X
Microbial culture/susceptibility testing	X	X	X	X
Urine pregnancy test	X		X	X
Inclusion/exclusion review	X			
Randomization	X			
Dispense study medication	X			
Study medication administration at site	X			
Adverse event assessment	X	X	X	X
Collect opened and unopened study medication			X	X

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Table 3: Abbreviations

Abbreviation	Explanation
AE	Adverse event
ADR	Adverse drug reaction
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
CI	Confidence interval
GCP	Good Clinical Practice
eCRF	Electronic case report form
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive web response system
LOCF	Last observation carried forward
mITT	Modified intent-to-treat
MR-CoNS	Methicillin-resistant coagulase-negative staphylococci
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermidis*
NSAID	Nonsteroidal anti-inflammatory drug
QID	Four times daily
SAE	Serious adverse event
SOP	Standard operating procedure
VA	Visual acuity

4. INTRODUCTION

4.1. Background Information

Vancomycin ointment 1.1% is a topical ophthalmic antibiotic ointment being investigated for the treatment of moderate to severe bacterial conjunctivitis, including infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA)/methicillin-resistant *Staphylococcus epidermidis* (MRSE). The initial nonclinical and clinical development of this product was conducted by Toa Pharmaceutical Co., Ltd (Toa), of Toyama, Japan and the product was approved in Japan by the Pharmaceuticals and Medical Devices Agency (PMDA) in 2009. An extensive database comprising 100% of the patients treated with the drug since its approval was maintained by Toa as a post-approval commitment.

4.2. Rationale and Development for the Treatment of Moderate to Severe Bacterial Conjunctivitis

External ocular infections such as those caused by MRSA or MRSE frequently are not serious but in rare cases may be severe enough to threaten vision. Sight-threatening eye infections caused by MRSA, including bilateral blindness from orbital cellulitis, panophthalmitis, and complete corneal flap melt after laser-assisted in situ keratomileusis (LASIK) have been reported (Rutar et al, 2005; Rutar et al, 2006; Rubinfeld and Negvesky, 2001). In a case study of 3 patients with endogenous endophthalmitis caused by MRSA, 2 of the 3 patients experienced blindness in the affected eye and in the third patient, the affected eye had to be enucleated (Ness and Schneider, 2009).

When ocular infections due to resistant organisms such as MRSA/MRSE do not respond to empiric treatment with approved antibiotics, there are few treatment options, as methicillin resistance has been shown to be a marker for multidrug resistance (resistance to ≥4 antibiotic classes) (Asbell et al, 2008a; Haas et al, 2011). Both MRSA and methicillin-resistant coagulase-negative staphylococci (MR-CoNS, including *Staphylococcus epidermidis*) isolates in one study showed considerable resistance to fluoroquinolones (ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin), macrolides (azithromycin), β-lactams (penicillin), polypeptides (polymyxin B) and aminoglycosides (Asbell et al, 2008a). Trimethoprim was the only agent tested that showed activity against MRSA (vancomycin was not tested in this study). These results are consistent with an earlier analysis of surveillance data that showed an increasing prevalence of MRSA strains resistant to multiple antibiotics, including all available fluoroquinolones (Asbell et al, 2008b). In another study among MRSA and MR-CoNS isolates, 46.5% and 58.3% of isolates, respectively, were resistant to ≥2 antibiotic classes and 11.5% and 6.3%, respectively, were resistant to 5 different drug classes, including the fluoroquinolones. Only vancomycin, a member of the glycopeptides class of antibiotics, was active against all methicillin-resistant isolates (Haas et al, 2011).

The importance of treatment options for multidrug resistant ocular infections is indicated by the increasing incidence of ocular infections caused by MRSA and MRSE (Cavuoto et al, 2007; Blomquist, 2006; Freidlin et al, 2007; Adebayo et al, 2011; Asbell et al, 2008b; Asbell et al, 2008a; Haas et al 2011), including a significant proportion of cases in the community setting

(Klevens et al, 2007; Blomquist, 2006; Miller et al, 2006). In addition to the surveillance study demonstrating the activity of vancomycin against all methicillin-resistant isolates (Haas et al, 2011), other case reports in the literature report successful treatment with vancomycin of several types of external ocular infections due to MRSA or MRSE, including conjunctivitis, corneal ulcers, keratitis, blepharitis, meibomianitis, dacryocystitis, and blepharoconjunctivitis (Brennen and Muder, 1990; Eiferman et al, 1991; Lee et al, 2010; Rubinfeld and Negvesky, 2001; Sotozono et al, 2002; Solomon et al, 2007; Ong et al, 2013; Sotozono et al, 2013; Khan et al, 1984; Fleischer et al, 1986; Goodman and Gottsch, 1988).

Nonclinical studies demonstrated that the bactericidal action of vancomycin against *S. aureus* and the vegetative cells of *Clostridium difficile* results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and ribonucleic acid (RNA) synthesis (Vancocin package insert, 2011).

Antibiotic sensitivity profiles suggest that vancomycin is the drug of choice to treat ocular infections due to MRSA/MRSE, but there currently is no approved ophthalmic formulation of vancomycin in the United States. Current ophthalmic vancomycin treatments must therefore be compounded. The inherent risks of compounding in general were well publicized during 2012, when contaminated methylprednisone acetate from the New England Compounding Center caused an outbreak of fungal meningitis that killed 64 people in 20 states. Furthermore, the solution used for compounding can affect the tolerability of the treatment. For example, Fleischer and colleagues reported treatment of 2 patients with severe MRSE blepharoconjunctivitis with topical vancomycin hydrochloride prepared with sterile water, which they indicated caused significant ocular irritation likely due to the low pH and osmolality values. An alternate solution with phosphate-buffered artificial tears was rated more tolerable than sterile water or saline-based solutions by 10 healthy volunteers, but it retained antimicrobial activity for only 2 weeks (Fleischer et al, 1986).

A more stable vancomycin formulation is particularly desirable for outpatients, who are likely to comprise a substantial proportion of patients seeking treatment for MRSA/MRSE infections. MRSA/MRSE infections were once considered primarily a nosocomial infection. However, MRSA has recently (since at least 2005) been found to be more associated with community onset (~70%) than hospital onset (~30%) (Klevens et al, 2007; Blomquist, 2006). It is therefore anticipated that a substantial number of patients with ocular MRSA/MRSE will be treated in an outpatient setting.

One previous study of the stability of vancomycin ophthalmic solution compounded in artificial tears reported that while the solution was stable for 45 days when stored at -10°C, at room temperature (25°C) it was stable for only 7 days and retained less than 85% of the original vancomycin concentration at 10 days (Fuhrman and Stroman, 1998). Vancomycin eye drops prepared in sodium chloride 0.9% were stable to 21 days at 4°C and 15 days at 25°C (Barbault et al, 1999). Another study demonstrated vancomycin ophthalmic solution in 5% glucose was stable for 3 months when frozen at -20°C (Sautou-Miranda et al, 2002).

The vancomycin ointment 1.1% that is presently being investigated is formulated in a white petrolatum and mineral oil base, common in commercially-available ophthalmic ointments. It is stable for 3 years when stored at 2-8°C in an aluminum tube.

Nonclinical studies of vancomycin ointment 1.1% administered four times daily (QID) suggest a good efficacy and safety profile, Studies in pigmented rabbits show rapid transport of vancomycin to the cornea and conjunctiva, with low-to-no concentrations in the aqueous humor. A published study in pigmented rabbits suggested that vancomycin concentrations were more widely distributed after *Bacillus subtilis*-induced ocular infection as compared with normal rabbits, however, a characteristic which may enhance rapid onset and prolong the duration of the vancomycin antimicrobial effect in infected eyes (Fukuda et al, 2003). Vancomycin was not detected in the serum of either the normal or infected rabbits, however. These results are consistent with a Phase 1 clinical study in healthy volunteers, in which the concentration of vancomycin was below the limits of quantitation (BLQ) in all subjects, after both single-dose and repeated-dose administration. These results suggest that systemic exposure to vancomycin is likely to be low, with few or no systemic effects.

In a Phase 3 clinical study in patients with extraocular bacterial infections due to MRSA and MRSE that were refractory to at least a 3-day course of a topical fluoroquinolone, overall rates of bacterial eradication at end of treatment or discontinuation were 68.8% (11/16) for MRSA and 100% (2/2) for MRSE, in the per protocol set (PPS). In a postmarketing surveillance (PMS) database analysis, among the subset of patients who were culture-positive for MRSA/MRSE and who had documented treatment failure on previous antibiotics and who received vancomycin as monotherapy, overall rates of bacterial eradication were 65.0% (106/163) for MRSA and 80.0% (16/20) for MRSE. The overall clinical response rate was 66.7% and for conjunctivitis (the most common ocular infection studied), the response rate was 71.4%. The safety of vancomycin ointment 1.1% was judged to be satisfactory and no significant tolerability issues were observed.

In the PMS database, comprising 633 patients evaluable for safety and 519 evaluable for efficacy, the clinicians' overall assessment of the clinical effects of treatment resulted in an 82.6% efficacy rate overall, across all types of infections. Across the entire safety database, serious adverse events (SAEs) were uncommon (14/718 patients); with only two SAEs (corneal disorder and corneal erosion) judged to be related to study treatment. Adverse events (AEs) that resulted in discontinuation of drug were also uncommon across the entire safety database (21/718 patients): eyelid edema, eyelid erythema, corneal erosion, and application site pain were the most common AEs leading to discontinuation of drug (each observed in 4/718 patients). The most common treatment-related AEs in the Phase 3 study (defined as AEs for which a causal relationship to the drug could not be ruled out) were eyelid edema and conjunctival hyperemia (each observed in 3/25 patients, 12.0%). The most common adverse drug reactions (ADRs) in the PMS study, defined as AEs considered possibly, probably, or remotely related to drug administration, were punctate keratitis, corneal erosion, and eyelid edema (each reported in 5 patients; 0.8%), followed by eyelid erythema (4/633 patients; 0.6%), application site pain (3/633 patients; 0.5%), and corneal disorder, delayed therapeutic response, and application site discomfort (each reported in 2/633 patients; 0.3%).

The planned Phase 3 clinical trial in the US will evaluate the safety and efficacy of vancomycin ointment 1.1% in subjects with moderate to severe unilateral or bilateral bacterial conjunctivitis.

4.3. Justification for Dose, Regimen, and Treatment Period

The 1% concentration of vancomycin was chosen by Toa Pharmaceuticals to go into Phase 3 clinical development. In the Phase 1 clinical study, systemic exposure was greater for subjects

who received repeated administration of 2% versus 1% vancomycin, 9 of 10 subjects in the 2% group had values above the detection limit in the urine as compared to 2 of 10 subjects in the 1% group. Data from nonclinical toxicity studies also supported the 1% concentration. In repeated administration studies in pigmented rabbits, the 3% concentration resulted in conjunctival redness and edema whereas the 1% concentration did not produce these effects. Another nonclinical study showed that corneal concentrations of vancomycin ophthalmic ointment were doubled when administered to *Bacillus subtilis*-infected eyes as compared to normal eyes of Dutch-belted rabbits (Fukuda et al, 2003). Computer simulations predicted QID administration of the 2% concentration to rabbits with infected eyes would result in higher corneal concentrations than administration of the 3% concentration to rabbits with normal eyes. This suggested that administration of the 2% concentration to infected eyes could result in the same sort of mild toxicity as the 3% concentration administered to normal eyes.

The QID dosing regimen utilized in the Phase 3 study conducted by Toa and received by 76% of the patients in the PMS database was well tolerated and was efficacious against bacterial conjunctivitis. The treatment period in the Toa clinical studies was 14 days. This has been modified to 7 days in the current study because the study population will not have refractory bacterial infections. Moreover, the disease is viewed to be self-limiting, and a 7-day study duration has been utilized in previous studies of drugs approved for this indication.

4.4. Good Clinical Practices Statement

This study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with International Conference of Harmonisation (ICH) guidelines, and all applicable US federal regulations and local legal and regulatory requirements.

4.5. Population to Be Studied

Study subjects will be male or female subjects, 1 years of age and older, who have clinically diagnosed moderate to severe bacterial conjunctivitis, and who have tested negative for adenoviral conjunctivitis according to the AdenoPlus® adenovirus test. See Section 7 for inclusion and exclusion criteria. Informed consent will be obtained prior to enrollment in the trial.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of vancomycin hydrochloride ophthalmic ointment 1.1% dosed QID in patients with moderate to severe Gram-positive bacterial conjunctivitis.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This will be a randomized, multicenter, double-masked, placebo-controlled study. Eligible subjects will enter the study with clinically diagnosed bacterial conjunctivitis.

At Screening/Visit 1 (Day 1), subjects will undergo AdenoPlus® conjunctival adenovirus screening testing. If the AdenoPlus test result is negative, the subject will undergo microbial culture (including susceptibility testing) and ophthalmic evaluations. If the AdenoPlus test result is positive, the subject will be considered a screen failure. Subjects confirmed to have met eligibility criteria will be randomized to 1 of 2 treatment arms. The subject (or caregiver) will administer the allocated study medication QID to the infected eye(s) approximately 4 hours apart for 7 days:

- Vancomycin ophthalmic ointment 1.1% QID
- Vehicle ointment (placebo) QID

If both eyes are being treated, the eye with more severe signs of infection (based on the sum of the 3 grading scales [conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection]) will be considered the study eye. If the sum of the scales for both eyes are equal, the default will be the right eye. If a subject with a unilateral infection develops an infection in the contralateral eye, the subject should contact the clinical site and will be instructed to treat the contralateral eye with the study medication if signs of conjunctival discharge and/or injection are present. The eye originally treated will continue to be considered the study eye. Only the study eye will be assessed for efficacy; safety assessments will be conducted bilaterally.

Randomized study medication (vancomycin or vehicle [placebo] ophthalmic ointment) will be provided in identical-appearing tubes. The identity of the study medications will be masked to the subject, Investigator, study personnel responsible for ophthalmic evaluations, and sponsor personnel responsible for medical evaluation of the data.

If the subject continues to show signs of infection in either eye at Visit 3 (Day 8), the subject will be treated per the Investigator's standard of care. Study treatment will not be administered after the last dose on Day 7.

6.2. Number of Subjects

The study will recruit subjects until the number of subjects with Gram-positive bacterial conjunctivitis has reached at least 75 per group.

6.3. Criteria for Study Termination

The study may be terminated at any time by Kurobe, LLC, following appropriate notification.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

1. Age 1 and older
2. Clinical diagnosis of acute bacterial conjunctivitis with at least one eye exhibiting conjunctival discharge graded ≥ 2 as well as palpebral conjunctival injection graded ≥ 2 AND bulbar conjunctival injection graded ≥ 2 with onset ≤ 4 days as reported by the subject.
3. Negative test result on AdenoPlus® adenovirus test.
4. Snellen visual acuity (VA) equal to or better than 20/200 in each eye using current corrective lenses, if required (or if worn) and/or using pinhole if subject's corrective lenses are not available at the time of exam. Every attempt should be made to obtain a VA measurement in children and, if it is unobtainable, the decision as to whether the criterion is met will be at the investigator's discretion.
5. Female subjects must be 1-year postmenopausal, surgically sterilized, or women of childbearing potential with a negative urine pregnancy test at Visit 1. Women of childbearing potential must use an acceptable form of contraception throughout the study. Acceptable methods include the use of at least one of the following: intrauterine (intrauterine device), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence.
6. Able to self-administer study medication or to have the study medication administered by a caregiver throughout the study period.
7. Must have signed written consent from the subject prior to participation in any study-related procedures if the subject is 18 years of age or older, or from the legally authorized representative/guardian if the subject is under 18 years of age.
8. Must have the signature of the subject on the assent form, as required by Institutional Review Board (IRB) guidelines, if the subject is under 18 years of age.

7.2. Subject Exclusion Criteria

1. Suspected viral or allergic conjunctivitis or suspected fungal or acanthamoeba infections at Screening in either eye.
2. Suspected iritis/uveitis or episcleritis/scleritis at Screening in either eye or history of either condition.
3. Active ulcerative keratitis, specifically any epithelial loss greater than punctate keratitis (eg, confluent epithelial loss or any subepithelial infiltration) in either eye.
4. History of recurrent corneal erosion syndrome, either idiopathic or secondary to previous corneal trauma or dry eye syndrome in study eye.

5. Uncontrolled systemic or debilitating disease (eg, cardiovascular disease, hypertension, diabetes, or cystic fibrosis) in the opinion of the Investigator.
6. Subjects who are immunocompromised (eg, HIV-positive); any use of immunosuppressive therapy (including chemotherapy).
7. Any use of topical ophthalmic medications, including tear substitutes, within 2 hours before Screening and throughout the study period in either eye.
8. Use of topical ophthalmic antimicrobial therapy within 48 hours prior to Screening. Use of topical ophthalmic antimicrobial therapy other than study medication is prohibited throughout the study period in either eye.
9. Use of topical ophthalmic anti-inflammatory agents (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] or steroids, including steroid-antibiotic combinations) within 48 hours prior to Screening and throughout the study period.
10. Use of systemic antimicrobial therapy for active respiratory tract, urinary tract, skin/soft tissue, or otitis media infection within 72 hours prior to Screening and throughout the study period. Use of a topical dermatologic antibiotic is permitted.
11. Use of systemic steroids within 14 days of screening and throughout the study period. Inhaled, intranasal, and topical dermatological steroids are permitted.
12. Contact lens wear during the study period in study eye. (contact lens wear in an untreated fellow eye is allowed).
13. Ocular surgery (nonlaser or laser) within 6 weeks prior to Screening in study eye.
14. Pregnancy or lactation.
15. Participation in an ophthalmic drug or device research study within 30 days prior to Screening in either eye.
16. Known hypersensitivity to vancomycin, petrolatum, or mineral oil

7.3. Withdrawal Criteria

The following are the criteria for considering withdrawal from the study:

- Withdrawal of subject consent.
- Subject is lost to follow-up.

If a subject withdraws or is withdrawn from the study, the principal reason for withdrawal will be recorded in the electronic case report form (eCRF).

If a study subject is lost to follow up at any point during the study period, attempts to contact the subject must be documented.

If a study subject is discontinued from study medication before Day 8 (Visit 3), every effort should be made to keep the subject in the study and conduct all study visits as scheduled or, failing that, to perform all Day 8 procedures at the visit the subject is discontinued.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

Vancomycin ophthalmic ointment is formulated as a white to pale yellow ointment containing a 1.1% concentration of vancomycin hydrochloride in a white petrolatum and mineral oil base containing liquid paraffin and white petrolatum, common in commercially available ophthalmic ointments. It is contained in an aluminum tube.

8.2. Randomization and Masking

Study medication will be randomized in a 1:1 ratio (vancomycin ophthalmic ointment 1.1% QID, or vehicle ophthalmic ointment [placebo]). A randomized block design will be used and the randomization will be created by the biostatistician.

If subjects meet eligibility criteria (see Section 7) at Screening/Baseline, Visit 1 (Day 1), subjects will be randomly assigned to masked study medication. Study sites will assign the next subject kit, taken sequentially, from the lowest to the highest numbered kits from within each shipment of study medication as directed by Oculos Clinical Research (Oculos). A sufficient supply of randomized study medication from the assigned kit to last the duration of the trial will be dispensed to the subject after initial dosing at the study site on Day 1. The drug kit randomization number will be recorded in the subject's eCRF. The perforated portion from the 2-part tear-off label will be affixed to the Study Drug Accountability Log.

The study will be double masked. The study medication will be provided in identical-appearing boxes with no labeling indicating the identity of the study group or the contents of the tube. The boxes will contain identical appearing tubes (see Section 8.1). Study subjects, investigators and staff, and study management personnel will be masked to the identity of treatment until after the final database lock.

8.2.1. Unmasking During the Study Period

Should it be necessary to unmask a subject's treatment assignment in case of emergency, the investigator may obtain the treatment code for a given randomized subject from the 2-part tear-off label from the subject's study medication kit. The randomization code is to be obtained only if a medical emergency exists and knowledge of the medication being taken will influence the medical management of the subject. In the event of emergency or life-threatening condition, the investigator may need to unmask the subject. The following procedure should be followed:

1. The Investigator should contact the Medical Monitor via phone immediately before unmasking a subject, unless it is not possible to do so without risk to the subject.
2. The Investigator should document the SAE and justification for unmasking in the Study Summary and Comments pages of the eCRF.
3. The Subject may continue to participate in the study at the Investigator's discretion. If the subject is to be discontinued from study participation, then ALL procedures described in the Early Discontinuation Visit (Section 10.4) should be completed.

4. The Investigator should contact Oculos at Kurobe-Safety@pointguardllc.com within 24 hours with the randomization number, subject initials, details of the AE or SAE, any action taken, and whether the subject is continuing in the study.

8.3. Concomitant Medications

8.3.1. Permitted Medications and Treatments

Therapy considered necessary for the subject's welfare that will not interfere with the evaluation of the study medication may be given at the discretion of the Investigator. If there is any question as to whether the medication may interfere, the Investigator should contact the Medical Monitor or Sponsor. Whenever possible, medications should be administered in dosages that remain constant throughout the study duration.

8.3.2. Prohibited Medications

The Medical Monitor should be notified before prohibited medication or therapy is administered unless the safety of the subject requires immediate action. The decision to administer a prohibited medication or therapy should be done with the safety of the subject as the primary consideration. The Medical Monitor MUST be contacted to determine the permissibility of a specific medication or therapy and whether or not the subject should continue with study participation.

Prohibited medications and therapies include:

- Immunosuppressive therapies, including chemotherapy
- Topical ophthalmic medications, including tear substitutes, within 2 hours before Screening and throughout the study period.
- Use of topical ophthalmic antimicrobial therapy within 48 hours prior to Screening. (Use of topical ophthalmic antimicrobial therapy other than study medication is prohibited throughout the study period.)
- Use of topical ophthalmic anti-inflammatory agents (eg, NSAIDs or steroids, including steroid-antibiotic combinations) within 48 hours prior to Screening and throughout the study period in either eye. Topical dermatologic steroids are permitted.
- Use of systemic antimicrobial therapy for active respiratory tract, urinary tract, skin/soft tissue, or otitis media infection within 72 hours prior to Screening and throughout the study period. Use of a topical dermatologic antibiotic is permitted.
- Use of systemic steroids within 14 days of screening and throughout the study period. Inhaled, intranasal, and topical dermatological steroids are permitted.

8.4. Treatment Compliance

Treatment compliance will be monitored by subject diaries. At Visit 2 (Day 5), site personnel will review diaries to assess subject compliance. At Visit 3 (Day 8), the diaries will be collected.

Data entry into the clinical database will be performed by a designee of Oculos, the clinical research organization (CRO) responsible for managing the study.

8.5. Discontinuation of Study Medication

Subjects may be discontinued from study medication for any of the following reasons:

- The subject has a clinically significant or serious AE that would not be consistent with continuation in the study, as determined by the Investigator or Medical Monitor
- Pregnancy

If a subject is discontinued from study medication, every effort should be made to encourage the subject to continue to attend study visits to be followed for safety, rather than withdrawing the subject from the study. Reasons for considering subject withdrawal from the study are discussed in Section 7.3.

8.6. Study Medication Materials and Management

8.6.1. Packaging and Labeling

Study medication will be packaged and labeled at a central packaging facility. One kit per subject will be packed. The kit will contain 2 boxes, and each box will contain 1 tube of ointment. Clinical sites are to dispense study medication kits, as directed by Oculos.

8.6.2. Storage

All study medication kits should be stored under refrigeration, 2-8°C (36-46°F), on initial receipt at the clinical site. Once the study medication is dispensed at the Baseline/Screening visit (Day 1), it may be stored at room temperature, 20-25°C (68-77°F), in the original packaging, and should be protected from light. Subjects will retain all opened and unopened study medication materials (tubes and boxes) to return to the site on Day 8.

8.6.3. Administration

Following randomization, site personnel will dispense study medication and instruct the subject (or caregiver, if the subject is not able to self-administer the medication) on administration procedures.

Steps will include:

- Washing the hands.
- Tilting the head back and, pressing the index finger gently on the skin just beneath the lower eyelid, pulling the lower eyelid away from the eye to make a space.
- Squeezing a thin strip of ointment into this space. It should be approximately 1 cm (approximately 1/3 inch).
- Letting go of the eyelid and gently closing the eyes, keeping them closed for approximately 1 minute.
- Avoid touching the applicator tip to any surface (including the eye). After using the study medication, wipe the tip of the tube with a clean tissue and keep the tube tightly closed.
- If both eyes are to be dosed, repeat the process for the second eye, beginning with washing the hands.

Study medication will be applied QID, with approximately 4 hours between each dose.

8.6.4. Study Drug Accountability

The Investigator or designee (eg, study coordinator or pharmacist) will maintain a full accountability record for the study medication and will be responsible for recording the receipt, dispensing, and return of all supplies of the study drug using the inventories supplied by the Sponsor. Each subject's kit will contain sufficient study medication for the duration of the trial. One kit will be dispensed at Screening/Baseline, Visit 1 (Day 1). The Investigator or designee will account for all received and returned study medication. The monitor will review dispensing and study medication accountability records, as well as subject diaries, during site visits and at the completion of the study, and note any discrepancies. All investigational study medication must be stored in a secure facility, with access limited to the Investigator and authorized staff.

9. STUDY ASSESSMENTS

Prior to entry into the study or initiation of any study related procedures, the patient must read, sign, and date the current IRB-approved version of the informed consent form. A full discussion of informed consent and the assent process for minors is presented in Section 13.3 .

9.1. Demographic and Background Characteristics

9.1.1. Demographic/Medical History

Clinically significant/ongoing patient-reported medical/surgical history will be obtained from each subject during Visit 1 (Day 1) as part of the eligibility assessment. Demographic information including date of birth, gender, race, ethnicity, iris color, and date of informed consent will be recorded.

9.1.2. Concomitant Medications History

All concomitant medications (prescription and over-the-counter [OTC]) taken at Visit 1 (Day 1) and for 3 months prior to Visit 1 and throughout the course of the study will be recorded in the Concomitant Medications page of the eCRF. Information regarding the dates of first and last dose, site of dosing (eg, right eye, left eye, both eyes, systemic), and the reason the concomitant medication is being taken must be recorded in the eCRF. When a concomitant medication has been taken at a stable dose for longer than 6 months, an estimation of the start date is adequate. Standard procedural medications will not go into the eCRF but are recorded on a standard procedural medication log provided by Oculos.

9.1.3. Ophthalmic History and Ophthalmic Intervention History

Clinically significant/ongoing ophthalmic and ophthalmic intervention history will be documented and will include previously diagnosed ophthalmic abnormalities and ocular surgeries, including laser procedures, as well as previous ocular infections.

9.1.4. Urine Pregnancy Test

A urine pregnancy test will be performed at Screening/Baseline, Visit 1 (Day 1) and repeated at End of Treatment Visit 3 (Day 8) or the Early Discontinuation Visit for women of childbearing potential only.

9.2. Efficacy Assessments

9.2.1. Assessment of Clinical Resolution

9.2.1.1. Ocular Discharge

Conjunctival discharge will be graded on a 4-point scale where 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

9.2.1.2. Bulbar Conjunctival Injection

Bulbar conjunctival injection will be graded using the scale below.

0	None. May appear blanched to reddish pink without perilimbal injection. Vessels of bulbar conjunctiva easily observed
1	Mild. A flush, reddish color, predominantly confined to the bulbar conjunctiva
2	Moderate. Bright red color of the bulbar conjunctiva
3	Severe. Deep, bright diffused redness of the bulbar conjunctiva

9.2.1.3. Palpebral Conjunctival Injection

Palpebral conjunctival injection will be graded using the scale below.

0	None. May appear blanched to reddish pink without perilimbal injection. Vessels of palpebral conjunctiva easily observed
1	Mild. A flush, reddish color, predominantly confined to the palpebral conjunctiva
2	Moderate. Bright red color of the palpebral conjunctiva
3	Severe. Deep, bright diffused redness of the palpebral conjunctiva

9.2.1.4. Bulbar and Palpebral Conjunctival Injection

Injection will be graded in both the palpebral and bulbar conjunctiva using the scale below.

0	None. May appear blanched to reddish pink without perilimbal injection. Vessels of palpebral or bulbar conjunctiva easily observed
1	Mild. A flush, reddish color, predominantly confined to the palpebral or bulbar conjunctiva
2	Moderate. Bright red color of the palpebral or bulbar conjunctiva
3	Severe. Deep, bright diffused redness of the palpebral or bulbar conjunctiva

9.2.2. Assessment of Bacterial Eradication

A microbial culture will be taken from the study eye at baseline to identify the bacterial species present and at each subsequent study visit to assess bacterial eradication, defined as absence of all Gram-positive bacterial species that were present at baseline.

9.3. Safety Assessments

9.3.1. Snellen Visual Acuity Assessment

Snellen VA measurement will be performed at all study visits with the Snellen eye chart using the subject's current corrective lens prescription or pinhole, as applicable, at a distance equivalent to 20 feet (6 meters).

9.3.2. Biomicroscopy

A routine biomicroscopic examination will be performed to evaluate the anterior segment of the eye, including lids, cornea, conjunctiva, anterior chamber, iris, and lens. Abnormalities will be documented.

9.4. Diagnostic Assessments

9.4.1. AdenoPlus® Test

RPS AdenoPlus® conjunctival adenovirus test will be performed at the beginning of Visit 1 (Screening/Baseline). A positive result on the AdenoPlus® test will automatically render the subject a screen failure.

9.5. Adverse and Serious Adverse Events

9.5.1. Definition of Adverse Events

9.5.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a study medication (pharmaceutical/biological product) that does not necessarily have a causal relationship to this medication. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the study medication, whether or not related to the study medication. Study medication includes the investigational drug under evaluation and the comparator product or vehicle placebo that is given during any phase of the study.

Medical conditions/diseases present before starting the investigational treatment are only considered AEs if they worsen after starting the investigational treatment. Abnormal test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by open-ended questioning of the subject at each visit during the study. At each clinic visit, study personnel should ask the following question: "Have you had any problems since your last visit?" AEs also may be detected when they are volunteered by the subject during or between visits or through study assessments.

9.5.1.2. Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

Note: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Results in persistent or significant disability/incapacity (excluding progression/outcome of the disease under study);

- Is a congenital anomaly/birth defect,
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Is medically significant; ie, defined as an event that jeopardizes the health of the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Treatment on an outpatient emergency basis that does not result in hospital admission, or a hospitalization that is elective or is a preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the study, is not considered an SAE.

All SAEs that are ongoing at the time of completion or discontinuation from the study will be followed until stabilization or resolution of the event.

9.6. Relationship to Study Drug

The relationship of AEs to the study medication should be assessed by the Investigator using the definitions below.

Not suspected: The temporal relationship of the event to the study medication makes a causal relationship unlikely, or, other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Suspected: The temporal relationship of the event to the study medication makes a causal relationship possible or other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study medication and the occurrence of the AE, then the AE should be considered “suspected.”

If the relationship between the AE/SAE and the investigational product is determined by the Sponsor to be “suspected” the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting (see Section 9.8).

9.7. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation, regardless of severity or potential association with the study medication or study procedures, will be recorded in the eCRF. Clinically significant changes in blood pressure and heart rate should be reported as AEs. All AEs that occur after a subject has signed the informed consent form until the final study visit, Visit 3 (Day 8), should be collected and recorded on the AE eCRF page. Serious adverse events will be followed until the event is resolved or stabilized.

Medical conditions/diseases occurring before the first dose of study medication during Visit 1 (Day 1) should be collected on the medical/ocular history pages of the eCRF.

The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the following:

- Onset (date and time);
- Resolution (date and time);
- Severity grade (mild, moderate, severe);
- Relationship to study medication (not suspected, suspected);
- Action taken (none, study medication temporarily interrupted, study medication permanently discontinued; concomitant medication taken; hospitalization/prolonged hospitalization; other);
- Serious outcome (yes/no).

The severity grade should be determined by the Investigator using the definitions below.

- Mild: Discomfort noticed but no disruption of normal daily activity
- Moderate: Discomfort sufficient to cause interference with normal daily activity
- Severe: Incapacitating, with inability to perform normal activities

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity (as defined directly above) whereas seriousness is defined by the criteria under Section 9.5.1.2 . An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on the pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

9.8. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from signing of informed consent until the final study visit, Visit 3 (Day 8), following the end of treatment exposure. Any SAEs "suspected" to be related to the investigational product and discovered by the Investigator at any time after the study should be reported to Oculos.

Any SAE that occurs must be reported to Oculos within 24 hours of its occurrence or within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported to Oculos as follow-up to the original episode within 24 hours of the Investigator receiving the information. Information about all SAEs will be collected and recorded on the SAE form. All pertinent medical records and information collected during the treatment and follow-up of the subject should be maintained at the site with a copy emailed to Kurobe-Safety@pointguardllc.com. The Investigator must assess the SAE relationship and complete the SAE form. Oculos may request additional information. Follow-up information (eg, discharge summary) will be retained in the subject's chart and a copy will be emailed to Kurobe-Safety@pointguardllc.com.

In addition, all SAEs should be recorded on the Adverse Event eCRF page with the serious question marked "Yes".

It is the investigator's responsibility to notify the approving IRB of any SAEs on a timely basis as instructed by the Sponsor following the Sponsor's determination of causality.

All subjects who experience an SAE should be followed clinically and undergo the appropriate diagnostic evaluations until stabilization or resolution of the event.

Kurobe will report all SAEs to the US Food and Drug Administration (FDA) on the appropriate schedule depending if the event is drug related or not drug related, expected, unexpected (based on the available information in the Investigator's Brochure).

Any death occurring during the study and follow up period should be reported as an SAE. For any death occurring through the end of the study, regardless of the degree of relationship to study drug, the SAE resulting in the death must be reported to Oculos. A death occurring after completion of the study at Visit 3 (Day 8) that is not reasonably associated with study drug administration, does not require completion of the SAE form.

10. STUDY ACTIVITIES

10.1. Visit 1 (Day 1)/Screening/Baseline

At Visit 1 (Day 1) subjects will provide informed consent/assent before any study-related procedures are conducted and participate in screening procedures (AdenoPlus® conjunctival adenovirus test, microbial culture, ophthalmic assessments including grading of clinical signs) to establish eligibility for the study**.** Subjects deemed eligible (subjects who are clinically diagnosed with bacterial conjunctivitis, and who have met the inclusion/exclusion criteria) will be randomized into the study and dispensed medication. Subjects (or caregivers) will receive instruction and then administer the first dose of allocated study medication at the site. Visit 1 procedures include:

- Informed consent
- Demographics information
- Medical/ocular history
- Prior/concomitant medication review
- AdenoPlus conjunctival adenovirus test
- Snellen VA using current corrective lenses and/or pinhole as applicable
- Biomicroscopy
- Grading of conjunctival discharge
- Grading of bulbar conjunctival injection
- Grading of palpebral conjunctival injection
- Microbial culture / susceptibility testing
- Urine pregnancy test (for females of childbearing potential only)
- Inclusion/exclusion review
- Randomization
- Dispense study medication
- Study medication administration at site
- Adverse event assessment

All 4 doses should be administered on Day 1 even if the intervals are shorter than 4 hours between doses. On Days 2-4 subjects will continue to administer the randomized study medication QID (approximately 4 hours between doses). On Day 5, subjects will return to the site for Visit 2. Subjects should be reminded to bring the study diary to the clinical site at Visit 2 (Day 5).

10.2. Visit 2/Treatment

At Visit 2 (Day 5 [± 1 day]), study site personnel will conduct diary review. Subjects will participate in microbial culture and ophthalmic assessments of safety and efficacy. Microbial culture results (including Gram-positive and MRSA/MRSE status) will be reviewed and noted in the eCRF.

Visit 2 procedures include:

- Concomitant medication review
- Study diary review
- Snellen VA using current corrective lenses and/or pinhole as applicable
- Biomicroscopy
- Grading of conjunctival discharge
- Grading of bulbar conjunctival injection
- Grading of palpebral conjunctival injection
- Microbial culture
- Adverse event assessment

Subjects should administer all 4 doses on Day 5 even if the intervals are shorter than 4 hours between doses. On Days 6-7 subjects will administer the randomized study medication QID (approximately 4 hours between doses). On Day 8, subjects will return to the site for Visit 3. Subjects are to be reminded not to dose after their fourth dose on Day 7 and to bring all study medication materials and the study diary to the clinical site at Visit 3 (Day 8).

10.3. Visit 3/End of Treatment

At Visit 3, Day 8 (+ 1 day) subjects will return all study medication to the clinical site. Study site personnel will conduct diary review and study drug accountability procedures. Subjects will participate in final ophthalmic assessments of safety and efficacy.

Visit 8 procedures include:

- Concomitant medication review
- Study diary review
- Snellen VA using current corrective lenses and/or pinhole as applicable
- Biomicroscopy
- Grading of conjunctival discharge
- Grading of bulbar conjunctival injection
- Grading of palpebral conjunctival injection
- Microbial culture
- Urine pregnancy test

- Adverse event assessment
- Collect opened and unopened study medication

If the subject continues to show signs of infection in either eye at Visit 3 (Day 8), the subject will be treated per the Investigator's standard of care. Study treatment will not be administered after the last dose on Day 7.

10.4. Early Discontinuation

If a study subject is discontinued from study medication before Visit 3 (Day 8) but after Visit 1 (Day 1), every effort should be made to perform all of the following procedures that were not previously conducted at the visit during which the subject was discontinued:

Early termination procedures include:

- Concomitant medication review
- Study diary review
- Snellen VA using current corrective lenses and/or pinhole as applicable
- Biomicroscopy
- Grading of conjunctival discharge
- Grading of bulbar conjunctival injection
- Grading of palpebral conjunctival injection
- Microbial culture
- Urine pregnancy test
- Adverse event assessment
- Collect opened and unopened study medication

11. STATISTICS

11.1. General Considerations

This will be a randomized, multicenter, double-masked, active- and placebo-controlled study. Eligible subjects will enter the study with unilateral or bilateral moderate to severe bacterial conjunctivitis. At Screening/Baseline, Visit 1 (Day 1), subjects will undergo AdenoPlus® conjunctival adenovirus screening testing. If the AdenoPlus test result is negative, the subject will undergo microbial culture (including susceptibility testing) and ophthalmic evaluations. If the AdenoPlus test result is positive, the subject will be considered a screen failure. Subjects confirmed to have met eligibility criteria will be randomized to 1 of 2 treatment arms and will administer the allocated study medication QID to the infected eye(s) approximately 4 hours apart for 7 days:

- Vancomycin ophthalmic ointment 1.1% QID
- Vehicle ointment (placebo) QID

A biostatistician will perform statistical analyses as agreed with the Sponsor according to the Statistical Analysis Plan. Any additional or supplemental data analysis performed independently by an investigator shall be submitted to the Sponsor for review.

The analysis of continuous and ordinal variables will use the applicable parametric methods (t-test, analysis of variance [ANOVA], analysis of covariance [ANCOVA]). Descriptive statistics will be used to summarize continuous outcomes (number of subjects [N], mean, standard deviation or standard error of the mean, median, maximum, and minimum) and categorical variables (frequency and percentage) at each assessment time point. (The time points at which data are collected are specified in the schedule of observations—see Table 2) Within-group changes for continuous and categorical outcomes will be assessed using 95% confidence intervals (CIs).

All subjects with clinically diagnosed bacterial conjunctivitis will be treated and followed, but only those eyes with Gram-positive bacterial conjunctivitis will be included in the primary analysis of efficacy.

11.2. Determination of Sample Size

A two group chi-square test with a 0.05 two-sided significance level will have 90% power to detect the difference between a Group 1 proportion of 0.75 and a Group 2 proportion of 0.50 (odds ratio of 3.0) when the sample size in each group is 77. The mITT population of the active treatment group will be compared to the mITT population of the vehicle group.

11.3. Analysis Populations

11.3.1. Populations for Efficacy Analysis

11.3.1.1. Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) population is defined as all randomized subjects. An ITT analysis with LOCF for missing data will be conducted as a secondary efficacy analysis for all efficacy endpoints.

11.3.1.2. Modified Intent-to-Treat (mITT) Population

The modified intent-to-treat (mITT) population consists of those subjects in the ITT population who have Gram-positive bacterial conjunctivitis.

11.3.2. Per Protocol Analyses

The per protocol population will consist of those subjects in the mITT who are compliant in dosing, meeting study visits and without significant protocol violations.

11.3.3. Population for Safety Analysis

The safety analysis population is defined as all randomized subjects who received at least one dose of the allocated study medication. Both eyes will be analyzed.

11.4. Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized for the ITT analysis population; however, should there be a reasonable difference in the size of the ITT and safety analysis populations, demographic and baseline characteristics will be summarized for both. The comparability of groups used in comparison analyses will be characterized in tables of demographic data. Summary tables will be supported with individual subject data listings.

11.5. Efficacy Analysis

Efficacy analyses will be performed on Visit 3 (Day 8).

Efficacy data will be presented in tables of descriptive statistics and frequency distribution. All summary tables will be supported with individual subject data listings.

For the primary efficacy analysis, those who require rescue interventions or who are lost to follow up will be considered treatment failures.

11.5.1. Primary Endpoint

The primary endpoints comprise a set of hypotheses that will be tested in a hierarchical fashion.

The primary efficacy endpoints are: proportion of subjects at Visit 3 (Day 8) with:

- Clinical resolution of bacterial conjunctivitis (defined as absence of conjunctival discharge, bulbar conjunctival injection and palpebral conjunctival injection)

- Microbial eradication (absence of all Gram-positive bacterial species present at baseline)

The difference in proportion in the two treatment groups will be tested by the chi-square test with a significance level of 0.05. In order to control the Type I error rate these two endpoints will be tested sequentially in the order described above. If the null hypothesis for the clinical resolution endpoint can be rejected at $P \leq 0.05$, the bacterial eradication endpoint will be tested at $P \leq 0.05$

11.6. Safety Analyses

Safety assessments will include VA using current corrective lenses and/or pinhole, if applicable, slit lamp examination (both conducted bilaterally), urine pregnancy test (for women of childbearing potential only), and collection of adverse events.

Safety data will be presented in tables of descriptive statistics and frequency distribution. All summary tables will be supported with individual subject data listings.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Oculos Clinical Research/Kurobe, LLC and/or their contracted agents utilize standard operating procedures (SOPs) designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs require compliance with FDA regulations and the ICH Good Clinical Practice (GCP) guidance.

The study will be monitored by Oculos to verify that the rights and well-being of human subjects are being protected, the reported data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol, with ICH GCP, and with the applicable regulatory requirements.

To insure compliance with GCP and all applicable regulatory requirements, Kurobe or its agent may conduct a quality assurance audit at any time during or after completion of a study. The investigator will be given adequate notice if he/she is selected for an audit. The audit will include, but is not limited to: a review of all informed consent forms, medical records, and regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the investigational drug product receipt, storage, and administration. At the conclusion of an audit, the auditor will conduct a brief meeting with the investigator to review the findings of the audit.

13. ADMINISTRATIVE CONSIDERATIONS

13.1. Institutional Review Board (IRB)

The IRB must review, approve, and provide continuing review of the clinical study protocol, protocol amendments, the informed consent documents, subject recruitment advertisements, and any other written information to be provided to the subjects. Initial IRB approval is an affirmative decision that the clinical study has been reviewed and may be conducted at the study site within the constraints set forth by the IRB, the institution, GCP, and applicable regulatory requirements. A copy of the IRB approval letter for the protocol, the informed consent, minor assent, the intended advertising, and any written material to be provided to the subject must be submitted to Oculos prior to release of investigational supplies to the study site. Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines. The IRB must be notified of completion or termination of the study. The study site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB concerning this protocol.

13.2. Ethical Conduct of the Study

The study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with ICH guidelines, and all applicable US federal regulations and local legal and regulatory requirements.

13.3. Written Informed Consent

A sample informed consent form containing the required elements of informed consent will be provided by Oculos. Sample minor assent form(s) will be provided as required by IRB guidelines. Any changes made to these samples must be approved by Oculos prior to submission to the IRB. After approval by Oculos, the informed consent and minor assent forms must be submitted to and approved by the IRB. The informed consent must be written in a language in which the subject is fluent. The minor assent form(s) will be written as required by IRB guidelines. Regulations require that foreign language informed consent and assent forms be submitted to the IRB for approval. The foreign language translation is required to contain a statement of certification of the translation. The investigator must forward a copy of the consent and assent forms, the certified foreign language translation, and an IRB approval letter to Oculos.

It is the responsibility of the Investigator to inform each subject of the purpose of this clinical trial, including possible risks and benefits, and to document the informed consent/assent process. Prior to undergoing any study-related procedures, the subject must read, sign, and date the current IRB-approved version of the informed consent form. For minor subjects ages 7-17, the assent form must be signed and dated per IRB guidelines. The original informed consent/assent form is to be retained by the study site, and a copy is to be given to the subject.

13.4. Subject Confidentiality and Confidentiality of Data

Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the study site, Oculos/Kurobe, LLC, the IRB, and FDA/relevant regulatory

agencies. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. No information that can be related to a specific individual subject will be released or used in any fashion without the signed written consent of that subject. All reports and communications relating to study subjects will identify subjects only by initials and subject identification number. Complete subject identification will be kept by the Investigator for purposes of long-term follow-up, if needed. This information will be treated with strict adherence to professional standards of confidentiality.

13.5. Study Monitoring

The study will be monitored by Oculos to assure compliance with the study protocol and the quality of the data collected. Monitoring visits may occur as required and could include a study initiation visit, a monitoring visit, and a study close-out visit. Training will be provided for key investigative personnel in all aspects of study conduct.

During visits to the study site, the monitor may review the source documents including but not limited to signed informed consent forms, patient diaries, study medication accountability and storage, and the reporting procedures for AEs and SAEs. All data generated during this study and the medical records/documents from which they originated are subject to inspection by Oculos, the study Sponsor, the FDA, and other regulatory agencies. The investigator must notify Oculos promptly of any inspections scheduled by regulatory authorities.

Upon completion of the study, the clinical monitor will conduct a final visit (closeout) to the site. The objectives of this visit are to ascertain that all regulatory records and reports are complete, verify that the study drug and other supplies have been accounted for, and ensure that the investigators are aware of their responsibilities once the study ends.

The Investigator is responsible for permitting the Sponsor direct access to any study documents for monitoring and auditing purposes, for providing adequate space for monitoring, and for addressing any questions or issues that might be raised by the monitor or auditor on a timely basis.

13.6. Case Report Forms and Study Records

All data relating to study procedures will be entered by site personnel directly onto eCRFs provided by Oculos. The eCRF is the first place the majority of the study data will be recorded; therefore, the electronic data captured will be the source. In general, paper source documents will not be created, but when generated, source documents (eg, original patient diaries, discharge summaries, etc.) will be retained at the study site.

13.7. Protocol Violations/Deviations

The Investigator should not deviate from the requirements of this protocol without prior written approval of the Medical Monitor at Oculos, with the exception of a medical emergency.

A significant protocol violation must be reported to Oculos upon discovery. Protocol deviations should be reported to the IRB in accordance with IRB guidelines.

All changes to the protocol will be made by Kurobe, LLC, or designee as an approved amendment to the protocol, submitted to the FDA, and approved by the IRB prior to implementation.

13.8. Access to Source Documentation

A trial-related monitoring audit, review by the IRB, and/or regulatory inspection may be conducted at any time during or after completion of a study. The Investigator will be given adequate notice if he/she is selected for an audit and must provide direct access to study documentation. The audit may include, but is not limited to, a review of all informed consent forms; a review of medical records; a review of regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the investigational drug product receipt, storage, and administration.

13.9. Data Generation and Analysis

Management of data and the production of the clinical study report will be the responsibility of Kurobe.

During the course of the trial, data queries will be generated for data items that are potentially erroneous and require appropriate clarification or correction. Such clarifications and corrections will be discussed with and approved by study site personnel and appropriately documented. Prior to database lock, data listings will be generated and anomalous values investigated.

13.9.1. Retention of Data

All study-related records must be maintained for at least 2 years after a marketing application is approved for the drug. If an application is not approved for the drug, all study-related records must be maintained until at least 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA or regulatory agencies have been so notified. The investigator will not discard any records without notifying Kurobe. If the principal investigator moves from the current study site, Kurobe should be notified of the name of the person who will assume responsibility for maintenance of the records at the study site or the new address at which the records will be stored. The investigator will notify Kurobe as soon as possible in the event of accidental loss or destruction of any study documentation.

If it becomes necessary for Oculos/Kurobe or the FDA or relevant regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

13.10. Publication and Disclosure Policy

All information concerning KUR-1301 and the operations of Kurobe, LLC, such as patent applications, formulas, manufacturing processes, basic scientific data or formulation information not previously published, are considered CONFIDENTIAL and shall remain the sole property of Kurobe, LLC The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent of Kurobe, LLC

The publication policy is addressed in a separate agreement.

14. LIST OF REFERENCES

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