STATISTICAL ANALYSIS PLAN

Confidential

PROTOCOL TITLE:	A Randomized, Double-Masked, Placebo-Controlled Phase 3 Study of the Safety of RVL-1201 in the Treatment of Acquired Blepharoptosis, Study RVL-1201-203
PROTOCOL NUMBER:	CLN.RVL-1201.RVL-1201-203.PR.A02
Study Phase:	Phase 3
Product Name:	RVL-1201, Oxymetazoline hydrochloride ophthalmic solution, 0.1%
Indication:	Treatment of acquired blepharoptosis
Sponsor:	RevitaLid, Inc. 400 Crossing Boulevard Bridgewater, NJ 08807
Document No:	CLN.RVL-1201-203.SAP.00
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Confidentiality Statement

Approval of Statistical Analysis Plan for Study RVL-1201-203

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATIONS	
Abbreviation	**Explanation**
AE	adverse event
BID	twice daily
BP	blood pressure
CFS	corneal fluorescein staining
CRF	case report form
DOB	date of birth
H	hour
HR	heart rate
IOP	intraocular pressure
IRB	Institutional Review Board
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MRD	marginal reflex distance
OD	oculus dextrus (right eye)
OS	oculus sinister (left eye)
OTC	over-the-counter
OU	oculus uterque (both eyes)
PD	pupil diameter
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SLE	Slit Lamp Exam
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
V	visit

ABBREVIATIONS	
VA	visual acuity
VF	visual field

1. INTRODUCTION

RevitaLid Inc.(RevitaLid) is pursuing the development of RVL-1201 Ophthalmic Solution (oxymetazoline hydrochloride ophthalmic solution, 0.1%) for the treatment of acquired blepharoptosis (ptosis). Ptosis is experienced by approximately 12% of adults over the age of 50 (Sridharan et al, 1995). It is a unilateral or bilateral abnormal drooping of the upper eyelid that usually occurs from a partial or complete dysfunction of the muscle(s) that elevate the upper eyelid: the levator palpebrae superioris and/or Müller's muscle. Patients with ptosis may experience significant superior visual field defects, which can affect daily activities such as driving, crossing streets, and reading.

Treatment for acquired ptosis usually involves surgery, with risks of infection, bleeding, over- or undercorrection, reduced vision, and lagophthalmos (inability to close the eyelids completely) (Finsterer, 2003). Mechanical treatment of ptosis (scleral contact lenses with a bar to lift the eyelid (Shah-Desai et al, 2010), eyelid ptosis crutches attached to glasses, or adhesive tape or putty to affix the upper eyelid to the supraorbital structures) is limited by patient dissatisfaction with physical appearance, contact allergies, or skin irritation. Pharmacologic treatment of ptosis has not been pursued because the agents that have been evaluated (e.g., epinephrine, dipivefrin, apraclonidine, phenylephrine, brimonidine) either caused mydriasis, resulting in blurred vision or photophobia, or unacceptable systemic side effects (Matjucha, 2011; Scheinfeld, 2005; Kass et al, 1979; Fraunfelder and Scafidi, 1978]).

Oxymetazoline hydrochloride is a direct-acting α2-adrenergic agonist that has been used at a 0.025% concentration as an ocular vasoconstrictor for nearly 30 years and at a 0.05% concentration as a nasal decongestant for almost 50 years. When administered at a 0.1% concentration it stimulates the α2 adrenergic receptors in Müller's muscle causing it to contract, thereby lifting the upper eyelid, and retracting the lower eyelid to a lesser degree. Topical ophthalmic administration of oxymetazoline hydrochloride at lower concentrations (0.01%, 0.025%) results in vasoconstriction and reduction of hyperemia but does not have the pharmacologic effect of raising the upper eyelid.

RVL-1201 Ophthalmic Solution contains oxymetazoline hydrochloride 0.1% as the active ingredient, and it is provided in preservative-free unit-dose vials.

Oxymetazoline hydrochloride, a well-characterized and selective α2-adrenergic agonist, was first approved as the active ingredient in the vasoconstrictor/decongestant nasal spray, Afrin® (oxymetazoline hydrochloride, 0.05%) in 1966.

2. STUDY DESCRIPTION

2.1 Objectives

The objective of this study is to evaluate the safety of RVL-1201 Ophthalmic Solution in the treatment of acquired blepharoptosis over 12 weeks.

2.2 Inclusion Criteria

1. Males or females ≥ 9 years of age.
2. Presence of both of the following at Screening/Baseline:
   a. The marginal reflex distance (MRD), the distance from the central pupillary light reflex to the central margin of the upper lid, must be ≤ 2 mm (no visible central pupillary light reflex defaults to 0) in either eye.
   b. Snellen visual acuity (VA) of 20/80 or better in the same eye as Inclusion Criteria #2a.
3. Females must be 1-year postmenopausal, surgically sterilized, or females of childbearing potential with a negative urine pregnancy test at Visit 1. Females of childbearing potential (females who have started their menstrual cycles) 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.
4. Must be able to self-administer study medication or to have the study medication administered by a caregiver throughout the study period.
5. Must be able to understand and sign an informed consent form (ICF) prior to participation in any study-related procedures. For minor subjects, the subject's parent or legal guardian must provide permission by signing the ICF on behalf of the subject and the subject should provide assent, per Institutional Review Board (IRB) guidelines. If a subject becomes 18 years of age during the study, the subject will need to sign an ICF to continue in the study.

2.3 Subject Exclusion Criteria

In both eyes

1. Dermatochalasis that extends less than 3 mm above the upper eyelid margin; dermatochalasis extending < 3 mm above the upper eyelid margin of a single eye is permitted.
2. Pseudoptosis (upper eyelid dermatochalasis that overhangs the upper eyelid margin); pseudoptosis in a single eye is permitted.

In either eye

3. Congenital ptosis.
4. Horner syndrome.
5. Marcus Gunn jaw-winking syndrome.
6. Myasthenia gravis.

7. Mechanical ptosis, including ptosis due to orbital or lid tumor, cicatricial processes affecting the movements of the upper lid, and enophthalmos.
8. Previous ptosis surgery (previous blepharoplasty [only] is allowed provided the surgery took place > 3 months prior to Visit 1).
9. Lid position affected by lid or conjunctival scarring.
10. History of herpes keratitis.
11. History of closed/narrow angle glaucoma (unless patent peripheral iridotomy has been performed > 3 months prior to Visit 1).
12. Periocular neurotoxin (e.g., Botox, Xeomin, Dysport, Myobloc) injections within 3 months prior to Visit 1 and during the study.
13. Topical application of bimatoprost (i.e., Latisse®) to the eyelashes within 7 days prior to Visit 1 and during the study.
14. Use of topical ophthalmic medications (including anti-allergy [e.g., antihistamines], dry eye [i.e., Restasis®, Xiidra®], antimicrobial drugs [e.g., antibiotics and antivirals], and anti-inflammatory drugs [including nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids] other than the assigned study medication within 7 days prior to Visit 1 and during the study. Topical ophthalmic prostaglandin analogues for the treatment of elevated intraocular pressure are permitted if dosed in the evening in accordance with the approved prescribing information. All other topical antiglaucoma medications are prohibited.
15. Intravitreal injections (e.g., Lucentis®, Eylea®, Avastin®, Triesence®) within 7 days prior to Visit 1 and during the study.
16. Current punctal plugs or placement of punctal plugs during the study.
17. Current use of over-the-counter (OTC) vasoconstrictor/decongestant eye medication (e.g., Visine® L.R.®) or any ophthalmic or non-ophthalmic α-adrenergic agonist including OTC products (e.g., Afrin®) at any time during the study; artificial tears are allowed.

General

18. Resting heart rate (HR) outside the normal range (50–110 beats per minute).
19. Hypertension with resting diastolic blood pressure (BP) > 105 mm Hg or systolic BP > 220 mm Hg.
20. Use of monoamine oxidase inhibitors (MAOIs; e.g., isocarboxazid, phenelzine, tranylcypromine) within 14 days prior to Visit 1 and during the study.
21. Advanced arteriosclerotic disease or history of cerebrovascular accident (CVA).
22. History of hyperthyroidism or thyroid eye disease (i.e., exophthalmos, upper eyelid retraction, diplopia secondary to extraocular muscle involvement). Hypothyroidism that is controlled on medication is allowed.

23. Patients with proliferative diabetic retinopathy may not be enrolled. However, patients with insulin dependent diabetes, diabetes requiring oral hypoglycemic drugs, or diet-controlled diabetes, with or without stable background diabetic retinopathy, are allowed.
24. Pregnancy or lactation.
25. Diagnosed benign prostatic hypertrophy requiring medicinal therapy; previous prostatectomy is allowed.
26. History of contact or systemic allergic reaction to oxymetazoline hydrochloride or other sympathomimetic drugs (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine, fepradinol, or methoxamine).
27. Participation in any drug or device clinical investigation within 30 days prior to entry into this study and/or during the period of study participation. Previous screening in Study RVL-1201-202 is allowed.
28. Randomization into any previous clinical study of RVL-1201 (Study RVL-1201-001 or Study RVL-1201-201, or Study RVL-1201-202) or into this study (Study RVL-1201-203).

2.4 Subject Withdrawal Criteria

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

- Withdrawal of subject consent/assent. The subject may request for any reason at any time to be withdrawn from the study.
- The Sponsor terminates the study.

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

If a study subject fails to attend a study visit at any point during the study period, every effort should be made to keep the subject in the study and conduct all study visits as scheduled; all attempts to contact the subject must be documented. If the subject relocates during the study period, Oculos Clinical Research (Oculos), the clinical research organization, should be contacted to determine if there is a possibility that the subject could continue at another clinical site.

2.5 Study Plan/Procedures

This will be a Phase 3, randomized, multicenter, double-masked, placebo-controlled study to evaluate the extended safety of RVL-1201 Ophthalmic Solution compared to Vehicle (placebo) for the treatment of acquired ptosis. The study will be conducted over 84 days (12 weeks).

Eligible subjects will be randomized in a 2:1 ratio to one of 2 treatment arms and treated for 84 days:

- RVL-1201 Ophthalmic Solution 1 drop in each eye QD in the morning (N = 150)
- Vehicle (placebo) 1 drop in each eye QD in the morning (N = 75)

Both eyes will be treated and assessed.

Following screening evaluations at the Screening/Baseline visit (Day 1), a determination of eligibility will be made, and eligible subjects will be randomized and receive study medication.

Study medication, RVL-1201 or Vehicle (placebo), will be provided in identical-appearing unit-dose vials. The identity of the study medications will be masked to the subject, Investigator, study personnel responsible for ophthalmic evaluations, and Sponsor personnel.

Subjects (or their caregiver, if necessary) will administer study medication QD in the morning during the study period.

Safety follow-up visits will be conducted at Day 14 (Visit 2), Day 42 (Visit 3), and Day 84 (Visit 4).

2.6 Randomization and Masking

Study medication will be randomized in a 2:1 ratio (RVL-1201 Ophthalmic Solution [N = 150]; Vehicle [placebo] [N = 75]). A randomized block design will be used, and the randomization will be created by a biostatistician independent of the trial. Randomization will not be stratified by any factors.

If subjects meet eligibility criteria at Screening/Baseline, Day 1 (Visit 1), sites will access the IWRS to randomize subjects to study treatment and assign the study medication kit to be dispensed. The drug kit and randomization number will be recorded in the subject's eCRF. Study medication from the IWRS-assigned kit will be dispensed to the subject after initial dosing at the study site on Day 1 (Visit 1), on Day 14 ± 3 (Visit 2) and on Day 42± 3 (Visit 3).

The study will be double masked. The study medication will be provided in identical-appearing pouches with no labeling indicating the identity of the study group or the contents of the unit-dose vials. The pouches will contain identical-appearing unit-dose vials. Study subjects, Investigators and staff, and study management personnel will be masked to the identity of treatment until after the final database lock.

3. STUDY ASSESSMENTS/ENDPOINTS

3.1 Demographic and Background Characteristics

3.1.1 Demographic/Medical History

A complete medical history will be obtained from each subject. Demographic information including date of birth, gender, race, ethnicity, iris color, and date of informed consent will be recorded.

3.1.2 Concomitant Medications History

All concomitant medications (prescription and OTC) taken at Visit 1 (Screening/Baseline, 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 (e.g., right eye [OD], left eye [OS], both eyes [OU], 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 be captured in the eCRF but are recorded on a standard procedural medication log provided by Oculos.

3.1.3 Ophthalmic History and Ophthalmic Intervention History

Clinically significant ophthalmic history and ophthalmic intervention history will be documented and will include any previously diagnosed ophthalmic abnormalities and ocular surgeries, including laser procedures.

3.1.4 Urine Pregnancy Test

A urine pregnancy test will be performed at Visit 1 (Screening/Baseline, Day 1) and repeated at Day 84 (Visit 4, End of Treatment) or the Early Discontinuation Visit for women of childbearing potential only.

3.2 External Photography

An external photograph of the subject's face will be taken using the provided digital camera. It is crucial that the same level of ambient lighting be maintained for each photograph throughout the study. The subject will be required to remove mascara and any other eyelid makeup if applicable. The subject will also be asked to relax his/her facial muscles. The photograph will frame the subject's face from mid-forehead to the tip of the nose vertically and from ear-to-ear horizontally. A standardized millimeter ruler label will be placed vertically on the forehead, centered above the eyebrows, as a measurement legend. All measurements (MRD and pupil diameter (PD)) will be made from the digital image or color printed copy of the photograph using a handheld caliper and the millimeter ruler label as the legend.

3.2.1 Marginal Reflex Distance Measurement

The distance from the center pupillary light reflex to the central margin of the upper eyelid is the MRD. The MRD will be measured from the external photograph at Visit 1.

3.3 Safety Assessments

Assessment of the safety and tolerability of RVL-1201 Ophthalmic Solution compared to Vehicle will include bilateral ophthalmic examinations (Snellen VA, PD measurement, SLE/CFS, intraocular pressure (IOP) tonometry, dilated ophthalmoscopy/fundus exam), measurement of vital signs, and recording of adverse events. Subject rating of study medication tolerability will also be obtained. For the timing of all safety assessments, please refer to the Schedule of Procedures.

3.3.1 Vital Signs

Blood pressure (from the same arm, and with the same cuff size, appropriate for arm circumference, throughout study) and heart rate will be measured after at least 3 minutes rest in the sitting position. Vital signs may be repeated once, after at least 5 minutes rest in the seated position, if they are out of range.

3.3.2 Snellen Visual Acuity Assessment

Corrected or uncorrected Snellen VA measurement will be performed with the Snellen eye chart using the subject's current corrective lens prescription, if applicable, at a distance equivalent to 20 feet (6 meters). If the corrected or uncorrected visual acuity is 20/80 or better, no additional refraction is necessary. If corrected or uncorrected visual acuity is worse than 20/80, then an updated refraction must be performed. This refraction must be used for all VA and visual field (if applicable) assessments during the study. The subject must wear the same glasses (if applicable) at each visit. The updated refraction can be placed in a trial frame or phoropter for VA assessments, and the trial frame only for visual field (if applicable) assessments.

For subjects with surgical monovision correction, VA assessment may be conducted in the near vision eye with a near vision reading card held at approximately 14 inches from the subject's eye.

3.3.3 Pupil Diameter Measurement

Pupil diameter will be measured (either horizontally or vertically if top of pupil is not visible in photograph) from the external photograph.

3.3.4 Slit Lamp Exam/Corneal Fluorescein Staining

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

Fluorescein staining of the corneal epithelium will be performed in both eyes according to the Investigator's standard of care.

Staining will be graded on a 5-point scale:

0 = No staining

1 = Trace

2 = Mild

3 = Moderate

4 = Severe

3.3.5 Dilated Ophthalmoscopy/Fundus Exam

Direct dilated ophthalmoscopy will include assessment of the optic nerve head for pallor and cupping. A fundus exam consisting of the vitreous, optic nerve, macula, and peripheral retina will be conducted, and the structures will be graded as normal or abnormal. Only tropicamide (Mydriacyl) should be used for this exam. Phenylephrine hydrochloride (Neosynephrine) may NOT be used.

3.3.6 Intraocular Pressure Tonometry

Intraocular pressure will be measured utilizing a Goldmann, Tono-Pen, or iCare tonometer (whichever is chosen, it must be used for the duration of the trial; no combination is permitted) and using the standard of care. If possible, the same calibrated instrument should be used for a given subject throughout the study.

3.3.7 Study Medication Tolerability Assessment

Subjects will be asked to rate the ocular tolerability of the medication according to the following 4-point scale:

0 = No discomfort

1 = Mild discomfort

2 = Moderate discomfort

3 = Severe discomfort

3.3.8 Adverse Events

An adverse event (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.

Adverse events will be evaluated and classified for:

- Serious Adverse Events (SAE)
- Relationship to Study Drug
- Severity of Adverse Event
- Outcome

4. SAMPLE SIZE AND POWER CONSIDERATIONS

The sample size for this study is not based on statistical calculations. The sample size was based on the need to obtain sufficient safety data to meet regulatory obligations for the development of RVL-1201.

5. ANALYSIS POPULATIONS

Safety Population:

The safety population includes all subjects who receive at least one dose of double-masked study treatment and have at least one post-dose visit. All analyses will be performed using the safety population according to the treatment received.

6. DATA HANDLING

6.1 Study Data

Study data identified in the schedule of procedures are collected, and source verified, in eCRFs at the site conducting the study. All relevant study data will be formulated into data sets to provide transparency, traceability, and integrity of trial analysis results from collection source.

Observed study data will be mapped to the CDISC Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture.

6.1.1 Clinical Data – CDISC Study Data Tabulation Model (SDTM)

Domains will be mapped to CDISC SDTM version 3.2. The SAP will not be amended to provide information on additional SDTM domains. All SDTM domains will be fully documented with define documents (DEFINE.XML) and a study data reviewer's guide (SDRG) after database lock and final analyses are completed.

6.1.2 Analysis Data – CDISC Analysis Data Model (ADaM)

All planned and exploratory analyses will be completed using the ADaM data sets derived from the SDTM domains for this study. Analysis data sets will contain all derived study endpoints required for analysis. All analysis data sets will be fully documented with define documents (DEFINE.XML) and an analysis data reviewer's guide (ADRG) after database lock and final analyses are completed.

Additional analysis data sets may be developed to support unplanned analyses after database lock. The SAP will not be amended for additional analysis data sets defined for the study and these additional data sets will be documented in the define documentation completed after all analyses are completed for the trial and the clinical study report is written.

6.2 Handling of Early Termination Visit Information

If a patient is terminated early from this study the early termination visit data will be analyzed at the closest scheduled visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

6.3 Handling of Missing Data

All analyses will be based on observed cases (without imputation).

If the intensity of an AE is missing, the event will be considered severe. If relationship of the AE to study drug is missing, the event will be counted as related.

Adverse events will be considered treatment emergent unless it can be determined from the onset or end date information that the event cannot have been treatment emergent.

7. STATISTICAL ANALYSIS

7.1 General Considerations

This is a Phase 3 study to evaluate the safety of daily treatment with RVL-1201 Ophthalmic Solution (oxymetazoline hydrochloride ophthalmic solution, 0.1%) compared to Vehicle (placebo) for the treatment of acquired ptosis over an extended dosing period of 12 weeks.

Subjects will be randomized in a 2:1 ratio of RVL-1201 Ophthalmic Solution to Vehicle into 2 treatment groups and treated for 84 days:

- RVL-1201 Ophthalmic Solution 1 drop in each eye QD in the morning (N = 150)
- Vehicle (placebo) 1 drop in each eye QD in the morning (N = 75)

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.

All data collected in the study database will be presented in the listings.

All statistical analyses and reporting will be performed using the SAS® System Version 9.4 or later.

7.1.1 Definition of Baseline

Measures collected prior to dosing on Day 1 will serve as baseline.

7.2 Subject Disposition

Subject disposition, including the number of subjects randomized, treated, and completing the study (and completing each study visit), will be tabulated by treatment group. The percentage of subjects treated and completing the study will be based on the total number randomized. Discontinuations and the reasons for discontinuation will be summarized. Discontinuations of study medication prior to study completion will also be summarized. Subject disposition will also be summarized by study site.

Eligibility criteria exemptions and protocol deviations will be summarized by treatment group and presented in a listing.

The total number and percentage of subjects included in the safety population will be summarized by treatment group, with percentages based on the total number randomized subjects.

7.3 Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized using descriptive statistics for the safety population.

Demographic information including age, gender, race, ethnicity and iris color will be summarized. MRD captured at Visit 1 (Screening/Baseline, Day 1) will also be summarized by eye (left eye (OS) and right eye (OD)). Such tables will be supported with individual subject data listings.

Age will be determined as the whole integer number of years from the date of birth (DOB) to the date of the screening visit, i.e., the truncated integer difference between the DOB and Visit 1.

Prior medications will be tabulated. A prior medication is defined as any mediation that starts and stops prior to first dose of study medication.

Medical and surgical history classified using the Medical Dictionary for Regulatory Activities (MedDRA) will be summarized descriptively and presented in a listing.

7.4 Concomitant Medications

All concomitant medications listed on the case report form will be provided in data listings in the clinical study report. The frequency distribution based on the generic drug name of all prior and concomitant medications used during the study will be provided for each treatment group.

7.5 Treatment Compliance and Exposure

The amount of opened and unopened medication returned at Visits 2, 3 and 4 will be documented in the CRF to provide an assessment of compliance in the form of percentage compliance for each subject. Compliance is determined by counting opened/unopened bottles. The percent of opened bottles to the total that should have been used during the treatment period will be tabulated.

8. SAFETY MEASURES

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

8.1 Intraocular Pressure

Descriptive statistics of the observed and change from baseline IOP will be tabulated by visit and treatment group. The descriptive statistics will be presented by eye (left eye (OS) and right eye (OD)).

8.2 Snellen Visual Acuity

The Snellen fraction will be converted to an equivalent logMAR value. The logMAR value is calculated by taking the $\log_{10}$ of the reciprocal of the Snellen fraction. For example, if the Snellen fraction is 20/60, the log MAR value is $\log_{10}(60/20) = 0.477$.

Descriptive statistics of the observed and change from baseline logMAR will be tabulated by visit and treatment group. The descriptive statistics will be presented by eye (left eye (OS) and right eye (OD)). Note that any repeat tests due to refraction issues will be utilized in the analyses.

8.3 Pupil Diameter

Descriptive statistics of the observed and change from baseline pupil diameter will be tabulated by visit and treatment group. The descriptive statistics will be presented by eye (left eye (OS) and right eye (OD)).

8.4 Corneal Fluorescein Staining

The status of the cornea epithelium will be graded on a 5-point scale (no staining, trace, middle, moderate, and severe) and will also be assessed for clinical significance (yes or no). The clinical significance results will be tabulated (n, %) by visit and treatment group.

8.5 Slit Lamp Examination

The status of the anterior segment of the eye, including lids, cornea, conjunctiva, anterior chamber, iris, and lens with respect to normalcy, non-clinically significant or clinically significant changes will be tabulated (n, %) by visit and treatment group.

8.6 Ophthalmoscopy and Fundus Exam

The status of the fundus with respect to normalcy, non-clinically significant or clinically significant changes will be tabulated (n, %) by visit and treatment group. The summaries will be presented by eye (left eye (OS) and right eye (OD)).

8.7 Tolerability Assessment

Tolerability assessments will be summarized in frequency tables based on the ordinal scale for each treatment group at the Day 84 assessment.

8.8 Vital Signs: Heart Rate and Blood Pressure

Descriptive statistics of the observed and change from baseline HR and BP will be tabulated by visit and treatment group.

8.9 Adverse Events

Treatment-emergent adverse events (TEAE) are those with onset after randomization or if occurring prior to randomization worsened after randomization. Only treatment-emergent events will be summarized. All events in the clinical database regardless of when they occurred will be provided in data listings. Adverse events will be classified according to the MedDRA system to the levels of system organ class (SOC) and primary preferred term (PT).

An overall summary will be presented which gives the number and percentage of subjects within each treatment group who experienced any TEAE, experienced any TEAE by maximum severity, experienced any TEAE by greatest relationship, discontinued early from the study due to a TEAE, permanently discontinued treatment due to a TEAE, experienced a treatment-emergent serious adverse event (TESAE), and who died.

In summary tables, TEAEs occurring in both eyes will be counted once at the greater intensity and relationship to study drug. When counting events, bilateral ocular events are counted twice, i.e., once for each eye. Bilateral ocular events are listed separately in the eCRF (they will be identified as OD and OS).

The number and percentage of subjects experiencing one or more events within a MedDRA system organ class and preferred term class without regard to intensity, relationship, or seriousness will be tabulated by treatment group. In addition, tabulations will display events by SOC, PT, and maximum intensity or greatest relationship to treatment.

The number of deaths and TESAEs will also be presented, and TEAEs leading to premature discontinuation from the study and TEAEs leading to discontinuation of study medication will be listed and tabulated.

A glossary listing that shows the verbatim terms assigned to each SOC and PT will be provided.

A listing of TEAEs by treatment group ordered by subject, SOC, PT, and onset date will be provided.

A listing of serious TEAEs by treatment group ordered by subject, SOC, PT, and onset date will be provided.

9. INTERIM ANALYSIS

No interim analyses are planned.

10. TABLES, LISTINGS AND FIGURES

Table, listing and figure shells will be prepared.

11. REFERENCES

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12. SCHEDULE OF PROCEDURES

Assessment	Screening/Baseline Randomization Day 1	Day 14 (± 3 Days)	Day 42 (± 3 Days)	Day 84 (± 3 Days)	Early Discontinuation
Visit	**1**	**2**	**3**	**4**	
Informed consent	X				
Demographics/medical/ocular history	X				
Collect study medication materials		X	X	X	X
Urine pregnancy test[a]	X			X	X
Prior/concomitant medications	X	X	X	X	X
Adverse event assessment[b]	X	X	X	X	X
Tolerability assessment				X	X
Blood pressure/heart rate[c]	X	X	X	X	X
External digital photograph	X	X	X	X	X
Marginal reflex distance (OU)[d]	X				
Pupil diameter measurement (OU)[d]	X	X	X	X	X
Snellen visual acuity (OU)[e]	X	X	X	X	X
Slit lamp exam (OU)	X	X	X	X	X
Corneal fluorescein staining (OU)	X	X	X	X	X
Intraocular pressure tonometry (OU)	X		X	X	X
Dilated ophthalmoscopy/fundus exam (OU)[f]	X			X	X
Review inclusion/exclusion criteria / Randomize eligible participants	X				
Dispense/administer study medication[g]	X	X	X		
Study medication accountability	X	X	X	X	X

MRD = marginal reflex distance; OU = both eyes; VA= Visual acuity

[a] Females of childbearing potential only (females who have started their menstrual cycles).

[b] For precise timing of adverse events at each visit, please refer to details of each individual visit in Section 10 of the protocol.

[c] Resting blood pressure and heart rate are taken seated after 3 minutes rest.

[d] MRD and pupil diameter will be measured from the external photograph.

[e] If the corrected or uncorrected VA is 20/80 or better, no additional refraction is necessary. If corrected or uncorrected VA is worse than 20/80 an updated refraction must be performed, which must be used for all VA assessments during the study. The subject must wear the same glasses, if applicable, at each visit. For subjects with surgical monovision correction, VA assessment may be conducted in the near vision eye with a near vision reading card held at approximately 14 inches from the subject's eye.

[f] Only tropicamide (Mydriacyl) should be used for this exam. Phenylephrine hydrochloride (Neosynephrine) may NOT be used.

[g] Study medication will be dispensed at Day 1 (Visit 1), Day 14 (Visit 2), and Day 42 (Visit 3). Study medication will be administered at the study site on Day 1. Otherwise, study medication will be administered QD in the morning at home daily.

13. REVISION HISTORY

Not applicable.