CLINICAL STUDY PROTOCOL

CONFIDENTIAL

A Randomized, Double-Masked, Placebo-Controlled Phase 3 Study of the Safety and Efficacy of RVL-1201 in the Treatment of Acquired Blepharoptosis (Study RVL-1201-202)

Study Phase:	Phase 3
Product Name:	RVL-1201 (oxymetazoline hydrochloride) ophthalmic solution, 0.1%
Document Number:	CLN.RVL-1201.RVL-1201-202.PR.A03
Indication:	Treatment of acquired blepharoptosis
IND:	116915
Sponsor:	RevitaLid Inc. 400 Crossing Boulevard Bridgewater, NJ 08807
Medical Monitor:	Charles Slonim, MD
Protocol Version:	Amendment 3: 09 October 2018 Amendment 2: 10 July 2018 Amendment 1: 08 March 2018 Original Protocol: 12 February 2018

SPONSOR SIGNATURE

Study Title:	A Randomized, Double-Masked, Placebo-Controlled Phase 3 Study of the Safety and Efficacy of RVL-1201 in the Treatment of Acquired Blepharoptosis (Study RVL-1201-202)
Study Number:	Study RVL-1201-202
Document Number:	CLN.RVL-1201.RVL-1201-202.PR.A03

Person authorized to sign the protocol and protocol amendment(s) for the Sponsor, RevitaLid Inc.

INVESTIGATOR'S AGREEMENT

Study Title:	A Randomized, Double-Masked, Placebo-Controlled Phase 3 Study of the Safety and Efficacy of RVL-1201 in the Treatment of Acquired Blepharoptosis (Study RVL-1201-202)
Study Number:	Study RVL-1201-202
Document Number:	CLN.RVL-101.RVL-1201.202.PR.A03

I have received and read the Study RVL-1201-202 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 Council for Harmonisation (ICH) guidelines, and all applicable US federal regulations and local legal and regulatory requirements.

_____

Printed Name of Investigator

_____

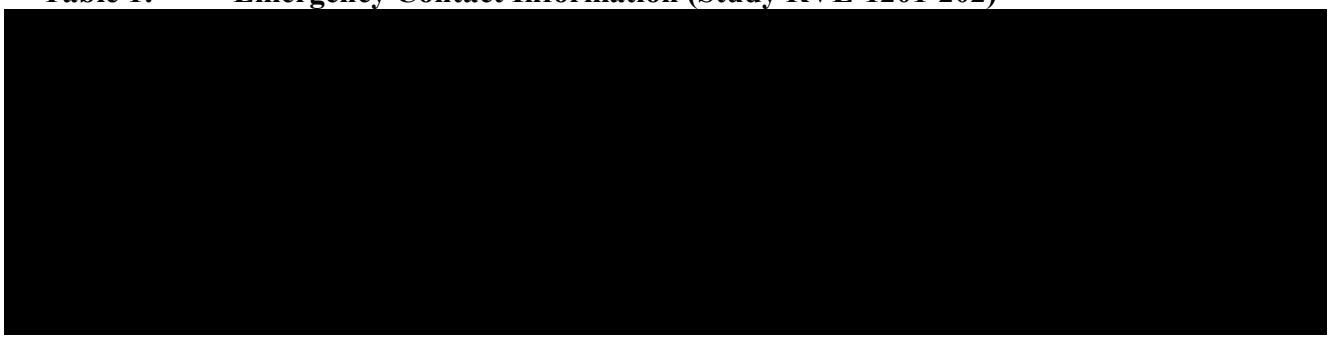
Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information (Study RVL-1201-202)



1. SYNOPSIS

Name of Sponsor/Company: RevitaLid Inc.	
Name of Investigational Product: RVL-1201 Ophthalmic Solution	
Name of Active Ingredient: Oxymetazoline hydrochloride	
Title of Study: A Randomized, Double-Masked, Placebo-Controlled Phase 3 Study of the Safety and Efficacy of RVL-1201 in the Treatment of Acquired Blepharoptosis (Study RVL-1201-202)	
Studied Period (Years): Estimated date first patient enrolled: March 2018 Estimated date last patient completed: February 2019	**Phase of Development:** 3
Objectives: The primary objectives of this study are to evaluate the efficacy of RVL-1201 Ophthalmic Solution in the treatment of acquired blepharoptosis at 2 weeks and to assess the safety of RVL-1201 for a dosing period of 6 weeks.	
Methodology: This will be a randomized, multicenter, double-masked, placebo-controlled study conducted over 42 days (6 weeks). Eligible subjects will be randomized in a 2:1 ratio to one of 2 treatment arms and treated for 42 days: • RVL-1201 Ophthalmic Solution 1 drop in each eye once daily (QD) in the morning (N = 104) • Vehicle (placebo) 1 drop in each eye QD in the morning (N = 52) Both eyes will be treated and assessed, but the more ptotic eye (the eye with the smaller marginal reflex distance (MRD) measurement) will be the study eye. If the MRD = 0 in either eye where both eyes are eligible, the eye with the measurable MRD (≥ 0.5 mm) will be the study eye. If the MRD is the same in both eyes, the eye with the greater visual field defect (the lower Leicester Peripheral Field Test [LPFT] Total Score from Visit 1, Hour 6, based on number of points seen on the top 4 rows) will be the study eye. If the MRD and LPFT are the same in both eyes, the right eye will be the study eye. Following screening evaluations, a determination of eligibility will be made following review of external photographs and LPFT printouts for each subject by the Medical Monitor, who will also designate the study eye. The Medical Monitor will subsequently inform the site whether the subject is eligible and which eye will be the study eye. Eligibility must be confirmed by efficacy evaluations at Baseline, Day 1, Hour 0 (Visit 2), before subjects are randomized to and receive study treatment and undergo efficacy and safety evaluations at specified intervals. Safety and efficacy evaluations will also be conducted at Day 14 (Visit 3), and final safety and tolerability assessments will take place at Day 42 (Visit 4), the last day of study treatment. 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.	
Number of Patients (Planned): Approximately 156 subjects will be enrolled (104 subjects in the RVL-1201 group and 52 subjects in the Vehicle group) at approximately 30 clinical sites.	

Inclusion Criteria:

1. Males or females ≥ 9 years of age.
2. Presence of all the following at Screening:
    a. Loss on a reliable LPFT of ≥ 8 points in the top 2 rows (LPFT Eligibility Score); subjects must see at least 9 total points in the top 4 rows (LPFT Total Score).
        i. This criterion must be met at both the Visit 1 Hour 0 (V1H0) and Visit 1 Hour 6 (V1H6) LPFT assessments
        ii. There must be ≤ 4 points of variance between the V1H0 and the V1H6 LPFT Eligibility Score; AND
    b. The 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 the same eye as Inclusion Criterion #2a; AND
    c. Snellen VA of 20/80 or better in the same eye as Inclusion Criteria #2a and #2b.
3. Presence of all the following at Baseline:
    a. Loss on a reliable LPFT of ≥ 8 points in the top 2 rows (LPFT Eligibility Score) in the same eye as Inclusion Criterion #2a; subjects must see at least 9 total points in the top 4 rows (LPFT Total Score).
        i. These criteria must be met at the Visit 2 Hour 0 (V2H0) LPFT assessment.
        ii. There must be ≤ 4 points of variance between the V1H6 and the V2H0 LPFT Eligibility Score; AND
    b. The 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 the same eye as Inclusion Criterion #2a; AND
    c. Snellen VA of 20/80 or better in the same eye as Inclusion Criteria #2a and #2b.
4. Females must be 1-year postmenopausal, surgically sterilized, or females of childbearing potential (females who have started their menstrual cycles) with a negative urine pregnancy test at Visits 1 and 2. Females 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.
5. Must be able to self-administer study medication or to have the study medication administered by a caregiver throughout the study period.
6. 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 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.

Exclusion Criteria:

In the study eye only

1. Dermatochalasis that extends less than 3 mm above the upper eyelid margin.
2. Pseudoptosis (upper eyelid dermatochalasis that overhangs the upper eyelid margin).

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. Visual field loss from any cause other than ptosis.
11. History of herpes keratitis.
12. History of closed/narrow angle glaucoma (unless patent peripheral iridotomy has been performed > 3 months prior to Visit 1).
13. Periocular neurotoxin (e.g., Botox, Xeomin, Dysport, Myobloc) injections within 3 months prior to Visit 1 and during the study.
14. Topical application of bimatoprost (i.e., Latisse®) to the eyelashes within 7 days prior to Visit 1 and during the study.
15. 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.
16. Intravitreal injections (e.g., Lucentis®, Eylea®, Avastin®, Triesence®) within 7 days prior to Visit 1 and during the study.
17. Current punctal plugs or placement of punctal plugs during the study.
18. 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

19. Resting heart rate (HR) outside the normal range (50–110 beats per minute).
20. Hypertension with resting diastolic blood pressure (BP) > 105 mm Hg or systolic BP > 220 mm Hg.
21. Use of monoamine oxidase inhibitors (MAOIs; e.g., isocarboxazid, phenelzine, tranylcypromine) within 14 days prior to Visit 1 and during the study.

Exclusion Criteria

General (continued):

22. Advanced arteriosclerotic disease or history of cerebrovascular accident (CVA).
23. 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.
24. 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.
25. Pregnancy or lactation.
26. Diagnosed benign prostatic hypertrophy requiring medicinal therapy; previous prostatectomy is allowed.
27. History of contact or systemic allergic reaction to oxymetazoline hydrochloride or other sympathomimetic drugs (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine, fepradinol, or methoxamine).
28. 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.
29. Previous randomization into any previous clinical study of RVL-1201 (Study RVL-1201-001 or Study RVL-1201-201) or into this study (Study RVL-1201-202).

Investigational Product, Dosage and Mode of Administration: RVL-1201 (Oxymetazoline Hydrochloride) Ophthalmic Solution, 0.1%: 1 drop per eye QD, topical ocular administration for 6 weeks

Reference Therapy, Dosage and Mode of Administration: Vehicle (placebo): 1 drop per eye QD, topical ocular administration for 6 weeks

Duration of Treatment: The duration of treatment will be 6 weeks

Study Procedures:

Screening eligibility assessments are obtained on or between Day -7 to Day -3. Key eligibility determinants will be MRD measured from external digital color photographs, 2 LPFTs per subject with ≤ 4 points of variance in the LPFT Eligibility Score between the V1H0 and V1H6 LPFTs as well as between the V1H6 and V2H0 LPFTs, and Snellen VA (if corrected or uncorrected VA is 20/80 or better, no additional refraction is necessary). All assessments of efficacy (LPFT, MRD) and safety (VA, pupil diameter, slit lamp exam [SLE])/corneal fluorescein staining [CFS], intraocular pressure [IOP], dilated ophthalmoscopy/fundus exam) will be conducted in both eyes (OU) at Screening. External photographs and LPFT printouts will be sent to the Medical Monitor for reading/confirmation of eligibility/determination of study eye. Note: Contact lenses must not be worn during study visits.

Study Procedures (continued):

Day -7 to Day -3 (Visit 1): Screening Subjects will provide written informed consent before any study-related screening procedures are conducted. For minor subjects, signed informed consent will be obtained from the subject's parent or legal guardian, and assent will be obtained from the subject following Institutional Review Board (IRB) guidelines. External photographs of the subject's eyes will be taken. The LPFT will be administered twice, with 6 hours intervening. If the Humphrey Visual Field (HVF) Analyzer issues an "XX" for fixation losses, false positives, and/or false negatives, the test will be deemed unreliable. If deemed unreliable, the test must be retaken (once per scheduled test). There must be ≤ 4 points of variance in the LPFT Eligibility Score between the V1H0 and the V1H6 LPFTs. Safety assessments will be conducted. Inclusion/exclusion criteria will be reviewed and the external photograph and LPFT printouts will be sent to the Medical Monitor for reading/confirmation of eligibility/determination of study eye.

Subjects determined by the Medical Monitor as eligible for randomization will be scheduled to return to the clinical site for Visit 2 at Day 1. All LPFT assessments after the study eye has been designated by the medical monitor will be conducted on the study eye ONLY. All assessments will be conducted OU. For subjects with surgical monovision correction where the study eye is the near vision eye, a neutralizing trial lens may be put in the lens holder located in front of the chin rest.

Day 1 (Visit 2): Baseline/Randomization/First Dose/Duration of Action Assessment Subjects will undergo safety and efficacy assessments at Hour 0. An LPFT will be obtained in the study eye and there must be ≤ 4 points of variance in the LPFT Eligibility Score between this test (V2H0) and the V1H6 LPFT performed at Screening. Subjects who meet all eligibility criteria will complete the remainder of baseline assessments and the site will access the Interactive Web Response System (IWRS) to randomize the subject to study treatment and assign the study medication kit to be dispensed. Subjects (or caregivers, if the subject is not able to self-administer the medication) will receive instruction on administration procedures. The first dose will be administered at the clinical site. Safety and efficacy assessments will be conducted at Hours 2, 6, and 8 as specified on the Schedule of Procedures. Site personnel will dispense study medication (Box 1) and conduct study medication accountability procedures.

From Days 2 through 13, study medication will be administered in each eye QD in the morning, and subjects will return to the clinical site on Day 14 ± 3 days in the morning prior to instillation of study medication. Subjects who have dosed prior to arriving at the clinical site must be rescheduled. Note: Contact lenses must be removed prior to instillation of study medication and must not be reinserted for at least 15 minutes after study medication instillation. Contact lenses must not be worn during study visits.

Day 14 ± 3 Days (Visit 3): Onset of Action Assessment Subjects will return all opened and unopened study medication materials and undergo safety and efficacy assessments at Hour 0. Study medication will be administered at the clinical site (using a vial taken from Box 1), and subjects will undergo safety and efficacy assessments at Hours 2, 6, and 8 as specified on the Schedule of Procedures. Site personnel will dispense study medication (Box 2) and conduct study medication accountability procedures.

From Days 15 through 41, randomized study medication will be administered in each eye QD in the morning, and subjects will return on Day 42 ± 3 days in the morning prior to instillation of study medication. Subjects who have dosed prior to arriving at the clinical site must be rescheduled. Note: Contact lenses must be removed prior to instillation of study medication and must not be reinserted for at least 15 minutes after study medication instillation. Contact lenses must not be worn during study visits.

Day 42 ±3 Days (Visit 4): End of Treatment Visit Subjects will return all opened and unopened study medication materials, study medication will be administered at the clinical site (using a vial taken from Box 2), and subjects will undergo final safety and efficacy assessments, and rate the ocular tolerability of study medication as specified on the Schedule of Procedures. Site personnel will conduct final study medication accountability procedures.

Efficacy Assessments: Efficacy will be assessed with the LPFT, a validated visual field test using the HVF Analyzer and photographic measurement of MRD (the distance from the central pupillary light reflex to the central margin of the upper lid). External digital photographs will be used to measure MRD.

Safety and Tolerability Assessments: Safety assessment will include bilateral SLE/CFS, measurement of pupil diameter from external photographs, dilated ophthalmoscopy/fundus examination, tonometry, Snellen VA using recent correction, if applicable, vital signs (BP/HR), and collection of adverse events (AEs). Ocular tolerability will be rated by the subject on a 4-point scale.

Criteria for Evaluation:

Efficacy Endpoints

Primary Efficacy Endpoints:

The primary efficacy endpoints will be the mean change from Baseline (Day 1, Hour 0) in the RVL-1201 group versus the Vehicle group in number of points seen in the top 4 rows on the LPFT test at each of 2 time points:

1. Day 1 Hour 6 (Visit 2)
2. Day 14 Hour 2 (Visit 3)

A hierarchical analysis will be conducted to compare RVL-1201 against Vehicle (placebo) at the 2 time points listed above.

Secondary Endpoints: Secondary endpoints will include the mean observed values and change from baseline values for MRD data in the RVL-1201 group versus the Vehicle group assessed at Day 1 (Visit 2), Day 14 (Visit 3), and at Day 42 (Visit 4).

Safety Endpoints The safety of RVL-1201 will be compared to Vehicle with analysis of safety variables including ophthalmic safety assessments (VA, SLE/CFS, pupil diameter, dilated ophthalmoscopy/fundus examination, and tonometry), vital signs (BP/HR), and AEs. The ocular tolerability of study medication will be rated by the subject.

Statistical Methods:

A detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock.

Analysis Populations:

The primary efficacy analysis of the LPFT endpoints at Day 1 Hour 6 and Day 14 Hour 2 will be conducted on the intent-to-treat (ITT) population (all randomized subjects). Supportive efficacy analysis will also be conducted on the per protocol population (those subjects in the ITT population who had no major protocol deviations). Safety analyses will be performed using the safety population (all randomized subjects who received at least one dose of the randomized study medication).

Sample Size:

A two-group t-test with a 0.05 two-sided significance level will have 90% power to detect a difference in LPFT means of 3.50, assuming that the common standard deviation is 6.0, when the sample sizes in the 2 groups are 94 and 47, respectively (a total sample size of 141). The planned total of 156 subjects will allow for a 10% drop-out rate.

Statistical Methods (continued):

Efficacy Analysis:

The primary efficacy endpoints will be tested sequentially in the order specified. For a claim of statistical significance, the null hypothesis being tested, and all higher ordered null hypotheses must be rejected, i.e., the Day 1 Hour 6 time point will be tested first, and if $P < 0.05$, the Day 14 Hour 2 time point will be tested at a significance level of 0.05. Thus, both hypotheses in the hierarchy will be tested against placebo at a significance level of 0.05. It is important to note that if the Day 1 Hour 6 endpoint is statistically significant (at the 0.05 level) but Day 14 Hour 2 is not statistically significant (at the 0.05 level), the study will still be considered positive.

If both primary efficacy endpoints are significant at the 0.05 significance level, then the secondary efficacy endpoints (MRD) will also be tested sequentially. Testing will stop if a P value ≥ 0.05 for a comparison.

The order of testing for the secondary efficacy endpoints is as follows:

1. Day 1 Hour 2
2. Day 14 Hour 2
3. Day 1 Hour 6
4. Day 14 Hour 6
5. Day 1 Minute 15
6. Day 14 Minute 15
7. Day 1 Minute 5
8. Day 14 Minute 5

All other comparisons are considered exploratory.

The efficacy measures (LPFT and MRD) taken on Day 1, Hour 0 (Visit 2) prior to dosing will serve as baseline. The mean change from baseline (at each corresponding time point) in each efficacy measure after the initial dose will be compared between treatment groups.

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.

A summary of the efficacy endpoints will be prepared at each time point and will include an estimate of the mean change from baseline for each treatment group and of the adjusted treatment difference and 95% confidence interval. The between-treatment comparison will employ ANCOVA with treatment as a fixed factor and baseline as a covariable. A t-test on least square means will be used to compare RVL-1201 to Vehicle with a 2-sided significance level of 0.05. Wilcoxon rank sum tests will also be used to compare treatments at each time point.

All efficacy analyses will be based on observed cases (without imputation). Multiple imputation will be performed only for the primary time points if more than 5% of data are missing for either treatment group; if 5% or fewer data are missing, an analysis with last observation carried forward (LOCF) for missing data will be conducted on the ITT population only.

Statistical Methods (continued):

Safety Analysis

Safety endpoints will be reported on the Safety population. Safety assessments include AEs, vital signs (BP/HR), ophthalmic assessments (Snellen VA, bilateral SLE/CFS, measurements of pupil diameter from external photographs, dilated ophthalmoscopy/fundus examination, and tonometry), and a tolerability assessment. Safety assessment will be based on descriptive statistics utilizing actual and change from baseline values, where appropriate, and individual subject listings.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
α	Alpha
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BID	Twice daily
BP	Blood pressure
CFS	Corneal fluorescein staining
eCRF	Electronic case report form
eDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Heart rate
HVF	Humphrey Visual Field
ICF	Informed consent form
ICH	International Council for Harmonisation
IOP	Intraocular pressure
ITT	Intent-to-treat population
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LOCF	Last observation carried forward
LPFT	Leicester Peripheral Field Test
LPFT Eligibility Score	Total number of points missed in the top 2 rows on the LPFT
LPFT Total Score	Total number of points seen in the top 4 rows on the LPFT
MAOI	Monoamine oxidase inhibitor
MAR	Missing at random
MRD	Marginal reflex distance
OTC	Over-the-counter
OU	Both eyes
NZW	New Zealand White (rabbits)
PP	Per protocol population

Abbreviation	Explanation
QD	Once daily
RVL-1201	Oxymetazoline hydrochloride ophthalmic solution 0.1%
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SE	Study eye
SLE	Slit lamp examination
SOP	Standard operating procedure
US	United States
VA	Visual acuity
V1H0	Visit 1 Hour 0
V1H6	Visit 1 Hour 6
V2H0	Visit 2 Hour 0

4. 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 is a direct-acting α_2-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 α_2 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 α_2-adrenergic agonist, was first approved as the active ingredient in the vasoconstrictor/decongestant nasal spray, Afrin® (oxymetazoline hydrochloride, 0.05%) in 1966.

Detailed information on the nonclinical and clinical studies performed with RVL-1201 may be found in the Investigator's Brochure.

4.1. Justification of Route, Dose, Regimen, and Treatment Period

Topical ocular 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 improving the superior visual field or increasing the marginal reflex distance (MRD). This effect is present at a concentration of 0.1%, the concentration of RVL-1201, based on the results of the Phase 3 study, Study RVL-1201-201. The pilot study,

Study RVL-1201-001, showed that RVL-1201 administered once daily (QD) and twice daily (BID) was more effective at elevating the upper eyelid than Vehicle, but BID dosing did not result in increased upper eyelid elevation compared to QD dosing. The safety profile of RVL-1201 QD in both studies was satisfactory, with AEs that were mild, and did not require treatment. In the pilot study, slightly more subjects in the BID treatment group than in the QD treatment group reported AEs. These were deciding factors in going forward with QD dosing in the first Phase 3 study. The current Phase 3 study, Study RVL-1201-202 will evaluate 1 drop of RVL-1201 in each eye QD for 42 days.

4.2. Good Clinical Practice Statement

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

4.3. Population to Be Studied

Study subjects will be male or female subjects ≥ 9 years of age with acquired blepharoptosis. See Section 7 for inclusion and exclusion criteria. Written informed consent will be obtained prior to enrollment in the trial; for minor subjects, written informed consent from the parent/guardian and assent from the subject will be obtained following Institutional Review Board (IRB) guidelines.

5. TRIAL OBJECTIVES

The primary objectives of this study are to evaluate the efficacy of RVL-1201 Ophthalmic Solution in the treatment of acquired blepharoptosis at 2 weeks and to assess the safety of RVL-1201 for a dosing period of 6 weeks.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This will be a Phase 3, randomized, multicenter, double-masked, placebo-controlled study to evaluate the safety and efficacy of QD treatment with RVL-1201 compared to Vehicle (placebo) for the treatment of acquired ptosis. The study will be conducted over 42 days (6 weeks).

Eligible subjects will be randomized in a 2:1 ratio to one of 2 treatment arms and treated for 42 days:

- RVL-1201 Ophthalmic Solution 1 drop in each eye QD in the morning (N = 104)
- Vehicle (placebo) 1 drop in each eye QD in the morning (N = 52)

Both eyes will be treated and assessed, but the more ptotic eye (the eye with the smaller MRD measurement) will be the study eye. If the MRD = 0 in either eye where both eyes are eligible, the eye with the measurable MRD (≥ 0.5 mm) will be the study eye. If the MRD is the same in both eyes, the eye with the greater visual field deficit (the lower LPFT Total Score from Visit 1, Hour 6 [V1H6] LPFT, based on number of points seen in the top 4 rows) will be the study eye. If the MRD and LPFT are the same in both eyes, the right eye will be the study eye.

Prior to randomization, each subject will attend a screening visit on or between Day -7 to Day -3 (Visit 1). The Visit 1 LPFT will be administered twice, with 6 hours intervening. If the HVF Analyzer issues an "XX" for fixation losses, false positives, and/or false negatives, the test will be deemed unreliable. If deemed unreliable, the test must be retaken (once per scheduled test). There must be ≤ 4 points of variance in LPFT Eligibility Score between the test at Visit 1 Hour 0 (V1H0) and Visit 1 Hour 6 (V1H6). External photographs of the subject's eyes will be taken, and safety assessments will be conducted. Inclusion/exclusion criteria will be reviewed, and the external photograph and LPFT printouts will be sent to the Medical Monitor for reading/confirmation of eligibility/determination of study eye. The Medical Monitor will subsequently inform the site whether the subject is eligible and which eye will be the study eye.

At Day 1, Baseline (Visit 2), subjects will undergo safety and efficacy assessments at Hour 0 beginning with a baseline LPFT in the study eye only. There must be ≤ 4 points of variance in LPFT Eligibility Score between this test at Visit 2 Hour 0 (V2H0) and the V1H6 test performed at Screening. Subjects who meet all eligibility criteria will complete the remaining baseline assessments and the site will access the Interactive Web Response System (IWRS) to randomize the subject to study treatment and assign the study medication kit to be dispensed. The subject (or caregiver, if the subject is not able to self-administer the medication) will then administer the first dose of allocated masked study medication at the clinical site and undergo safety and efficacy assessments at Hours 2, 6 and 8. Site personnel will dispense study medication and conduct study medication accountability procedures.

Study medication, RVL-1201 or Vehicle, 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.

From Days 2 through 13, study medication will be administered in each eye QD in the morning, and subjects will return to the clinical site on Day 14 ± 3 days (Visit 3) in the morning prior to instillation of study medication. Subjects will return all opened and unopened study medication materials and undergo safety and efficacy assessments at Hour 0. After instillation of study medication at the clinical site, the subject will undergo safety and efficacy assessments at Hours 2, 6, and 8. Site personnel will dispense study medication and conduct study medication accountability procedures.

From Day 15 through the morning of Day 42, randomized study medication will be administered QD (in the morning), and subjects will return to the clinic on Day 42 ± 3 days (Visit 4) prior to instillation of study medication. After returning all opened and unopened study medication materials, study medication will be administered, and subjects will undergo safety and efficacy assessments and rate the ocular tolerability of study medication. Site personnel will conduct final study medication accountability procedures.

Table 2 provides a tabular summary of all scheduled visits and procedures to be performed during the clinical study.

Table 2: Schedule of Procedures (Study RVL-1201-202)

	Screening Day -7 to -3		Baseline/Randomization/ First Dose/Day 1					Day 14 (± 3 Days)					End of Treatment Day 42 (± 3 Days)		Early Discontinuation
Visit	1		2					3					4		
Hour (± 30 minutes)	**0**	**6**	**0**	**PD**	**2**	**6**	**8**	**0**	**PD**	**2**	**6**	**8**	**0**	**PD**	
Informed consent/assent	X														
Demographics/medical/ocular history	X														
Urine pregnancy test[a]	X		X										X		X
Collect study medication materials								X					X		X
Prior/concomitant medications	X		X					X						X	X
Adverse event assessment[b]		X	X	X	X	X	X	X	X	X	X	X		X	X
Tolerability assessment														X	X
Blood pressure/heart rate[c]	X		X		X		X	X		X		X		X	X
Snellen visual acuity[g] (OU)	X		X				X	X				X		X	X
External digital photograph	X		X		X	X	X	X		X	X	X		X	X
Marginal reflex distance (OU)[d]	X		X	X[d]	X	X		X	X[d]	X	X			X[d]	X
Pupil diameter measurement (OU)[d]	X		X		X	X	X	X		X	X	X		X	X
Leicester Peripheral Field Test (SE)[e]	X	X	X			X[f]				X[f]					
Slit lamp exam (OU)	X		X				X	X				X		X	X
Corneal fluorescein staining (OU)	X						X					X		X	X
Intraocular pressure tonometry (OU)	X													X	X
Dilated ophthalmoscopy/fundus exam (OU)[h]		X												X	X
Randomization			X												
Administer study medication[i]			X					X					X		
Dispense study medication							X					X			
Study medication accountability							X					X		X	X

LPFT = Leicester Peripheral Field Test; MRD = marginal reflex distance; OU = both eyes; PD = post dose; SE = study eye; 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.

[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. On Day 1 (Visit 2), Day 14 (Visit 3), and Day 42 (Visit 4), the timing of MRD measurements ***must*** be at 5 minutes (+2 minutes) and 15 minutes (+ 2 minutes) **post dose**. For a description of the timing of all MRD measurements, please refer to details of each individual visit in Section 10.

[e] LPFT will be conducted bilaterally at Screening (Visit 1). All other LPFT examinations will be conducted unilaterally on the study eye. For subjects with surgical monovision correction, a neutralizing trial lens may be put in the lens holder located in front of the chin rest of the HVF Analyzer. Instruct the subjects to keep their chin and forehead against the chin and forehead rests, to keep their brows relaxed, and to look at the fixation point throughout the test.

[f] The LPFT assessment must be performed approximately 6 hours post-administration of study medication at Day 1 (Visit 2), and approximately 2 hours post-administration of study medication at Day 14 (Visit 3). This requirement supersedes the order of procedures shown in the table above and in the text in Section 10.2.1 and Section 10.2.3.

[g] 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.

[h] Only tropicamide (Mydriacyl) should be used for this exam. Phenylephrine hydrochloride (Neosynephrine) may NOT be used. The dilated ophthalmoscopy/fundus exam at Screening (Visit 1) must be conducted after the LPFT assessment at Hour 6.

[i] Study medication will be administered at the study site at Hour 0 on Day 1 (Visit 2), Day 14 (Visit 3), and Day 42 (Visit 4). Subjects should be instructed not to dose before coming for Day 14 (Visit 3) or Day 42 (Visit 4); if the subject has dosed, the visit must be rescheduled. Otherwise, study medication will be administered QD in the morning at home daily.

6.2. Number of Subjects

The planned sample size is approximately 156 subjects, 104 subjects in the RVL-1201 group, and 52 in the Vehicle group, to be enrolled at approximately 30 clinical sites in the US.

6.3. Criteria for Study Termination

The study may be terminated at any time for any reason by RevitaLid Inc.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Inclusion Criteria

1. Males or females ≥ 9 years of age.
2. Presence of all the following at Screening:
    a. Loss on a reliable LPFT of ≥ 8 points in the top 2 rows (LPFT Eligibility Score); subjects must see at least 9 total points in the top 4 rows (LPFT Total Score).
        i. These criteria must be met in both the V1H0 and V1H6 LPFT assessments
        ii. There must be ≤ 4 points of variance between the V1H0 and the V1H6 LPFT Eligibility Score; AND
    b. The MRD, the distance from the central pupillary light reflex to the central margin of the upper lid, ≤ 2 mm (no visible central pupillary light reflex defaults to 0) in the same eye as Inclusion Criterion #2a; AND
    c. Snellen VA of 20/80 or better in the same eye as Inclusion Criteria #2a and #2b).
3. Presence of all the following at Baseline:
    a. Loss on a reliable LPFT of ≥ 8 points in the top 2 rows (LPFT Eligibility Score) in the same eye as Inclusion Criterion #2a; subjects must see at least 9 total points in the top 4 rows (LPFT Total Score).
        i. These criteria must be met in the V2H0 LPFT assessment.
        ii. There must be ≤ 4 points of variance between the V1H6 and the V2H0 LPFT Eligibility Score; AND
    b. MRD, the distance from the central pupillary light reflex to the central margin of the upper lid, ≤ 2 mm (no visible central pupillary light reflex defaults to 0) in the same eye as Inclusion Criterion #2a; AND
    c. Snellen VA of 20/80 or better in the same eye as Inclusion Criteria #2a and #2b).
4. Females must be 1-year postmenopausal, surgically sterilized, or females of childbearing potential (females who have started their menstrual cycles) with a negative urine pregnancy test at Visits 1 and 2. Females 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.
5. Must be able to self-administer study medication or to have the study medication administered by a caregiver throughout the study period.

6. 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 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.

7.2. Exclusion Criteria

In the study eye only

1. Dermatochalasis that extends less than 3 mm above the upper eyelid margin.
2. Pseudoptosis (upper eyelid dermatochalasis that overhangs the upper eyelid margin).

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. Visual field loss from any cause other than ptosis.
11. History of herpes keratitis.
12. History of closed/narrow angle glaucoma (unless patent peripheral iridotomy has been performed > 3 months prior to Visit 1).
13. Periocular neurotoxin (e.g., Botox, Xeomin, Dysport, Myobloc) injections within 3 months prior to Visit 1 and during the study.
14. Topical application of bimatoprost (i.e., Latisse®) to the eyelashes within 7 days prior to Visit 1 and during the study.
15. 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.
16. Intravitreal injections (e.g., Lucentis®, Eylea®, Avastin®, Triesence®) within 7 days prior to Visit 1 and during the study.

17. Current punctal plugs or placement of punctal plugs during the study.
18. 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

19. Resting heart rate (HR) outside the normal range (50–110 beats per minute).
20. Hypertension with resting diastolic blood pressure (BP) > 105 mm Hg or systolic BP > 220 mm Hg.
21. Use of monoamine oxidase inhibitors (MAOIs; e.g., isocarboxazid, phenelzine, tranylcypromine) within 14 days prior to Visit 1 and during the study.
22. Advanced arteriosclerotic disease or history of cerebrovascular accident (CVA).
23. 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.
24. 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.
25. Pregnancy or lactation.
26. Diagnosed benign prostatic hypertrophy requiring medicinal therapy; previous prostatectomy is allowed.
27. History of contact or systemic allergic reaction to oxymetazoline hydrochloride or other sympathomimetic drugs (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine, fepradinol, or methoxamine).
28. 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.
29. Previous randomization into any previous clinical study of RVL-1201 (Study RVL-1201-001 or Study RVL-1201-201) or into this study (Study RVL-1201-202).

7.3. 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 (see Section 6.3).

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.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Medications

RVL-1201 and Vehicle (placebo) are formulated for topical ocular delivery as aseptically prepared, sterile, non-preserved ophthalmic solutions and contain 0.1% or 0% of the active ingredient, oxymetazoline hydrochloride, respectively. Both RVL-1201 and Vehicle will be packaged in identical unit-dose vials to maintain masking of treatment identity.

8.2. Randomization and Masking

Study medication will be randomized in a 2:1 ratio (RVL-1201 Ophthalmic Solution [N = 104]; Vehicle [placebo] [N = 52]). 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 (see Section 7) at Screening (Visit 1) as well as at Baseline (Visit 2), 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 numbers 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 2) and Day 14 ± 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 (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 IWRS. The treatment 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.

The following procedure should be followed:

1. The Investigator should attempt to contact the Medical Monitor via phone before unmasking a subject unless it is not possible to do so without risk to the subject.
2. The Investigator should document the AE and justification for unmasking in the Study Summary and Comments pages of the eCRF.
3. If the subject is to be discontinued from study medication, then ALL procedures described in the Early Discontinuation Visit (Section 10.3) should be completed.
4. The Investigator should contact Oculos at Revitalid-Safety@oculoscr.com within 24 hours with the subject number and details of the AE or SAE and any action taken.

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. Note: Contact lens wear is permitted during the study. Contact lenses must be removed prior to instillation of study medication and must not be reinserted for at least 15 minutes after study medication instillation. Contact lenses must not be worn during study visits.

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 the subject should continue with study medication.

Prohibited medications and therapies include:

- Periocular neurotoxin (e.g., Botox, Xeomin, Dysport, Myobloc) injections within 3 months prior to Visit 1 and during the study.
- MAOIs (e.g., isocarboxazid, phenelzine, tranylcypromine) within 14 days prior to Visit 1 and during the study.
- Topical application of bimatoprost (i.e., Latisse®) to the eyelashes within 7 days prior to Visit 1 and during the study.
- 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.
- Intravitreal injections (e.g., Lucentis®, Eylea®, Avastin®, Triesence®) within 7 days prior to Visit 1 and during the study.
- Current punctal plugs or placement of punctal plugs during the study.
- 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.

8.4. Treatment Compliance

Treatment compliance will be monitored by study medication accountability. The amount of opened and unopened medication returned at Visits 3 and 4 will be documented in the eCRF to provide an assessment of compliance in the form of percentage compliance for each subject that will be calculated by the electronic data capture (eDC) system.

8.5. Discontinuation of Study Medication

If a subject becomes pregnant during the study, the subject will be withdrawn from study medication and followed through the conclusion of the pregnancy (Section 9.6).

Subjects may be discontinued from study medication because of either of the following:

- Adverse event: A clinically significant or serious AE that in the Investigator's or Medical Monitor's judgment, suggests that continued administration of study medication is not in the subject's best interests for safety reasons. Additionally, if an AE requires treatment, the Investigator in consultation with the Medical Monitor may determine that study medication should not be concurrently administered with a required concomitant medication.
- Subject request: Subject requests to be withdrawn from study medication.

When possible, a decision to discontinue a subject from study medication should first be discussed with the Medical Monitor. 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 or, failing that, to perform all early discontinuation assessment procedures at the visit the subject is withdrawn (Section 10.3). 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. Study sites will utilize the IWRS to assign kits to subjects.

8.6.2. Storage and Administration

Study medication must be stored at room temperature 15°-25° C (59°-77° F). A room temperature log will be maintained at each study site. Subjects should be instructed not to store or place the study medication where it can be exposed to extreme temperatures (e.g., refrigeration or leaving it in a hot car) or light. The study medication will be provided in a child-resistant package. Importantly, subjects MUST store the eye drops out of reach of children at all times. Accidental ingestion by young children can result in serious adverse events. If a child accidentally swallows these eye drops, call the National Capital Poison Center (1-800-222-1222) and seek emergency medical care immediately.

Site personnel will instruct the subject on the proper instillation technique at Day 1 (Visit 2) and the subject (or caregiver, if the subject is not able to self-administer the medication) will administer the first dose at the study site, instilling 1 drop in each eye from the unit-dose vial

The subject should be in a seated position and should tilt his or her head backward for administration of the study medication. The vial of study medication should be held at an almost vertical position above the eye while the lower eyelid is pulled down gently, and 1 drop is placed into the conjunctival cul-de-sac. The tip of the vial should not touch the eye. After a drop is instilled in each eye, the subject should keep the eyes gently closed for approximately 30 seconds. The subject will then empty the remaining contents of the unit-dose vial and place the empty vial in the pouch.

Each subsequent morning of dosing, the subject will open a pouch from the box, administer one drop to each eye from a single new unit-dose vial and close the eyes gently for 30 seconds, empty the remaining contents of the unit-dose vial, then store the opened vial in the foil pouch, and place it in the box for return to the study site. On Day 14 ± 3 days (Visit 3), subjects will return all opened and unopened study medication materials, and site personnel will conduct study medication accountability procedures and dispense study medication for the remaining study period. On Day 42 ± 3 days (Visit 4) the box, complete with opened unit-dose vials/pouches and any unopened study medication will be returned to the study site, and final study medication accountability will be conducted. The Day 42 visit will be the last day of study treatment; no further study medication will be dispensed at this visit.

Note: Contact lens wear is permitted during the study. Contact lenses must be removed prior to instillation of study medication and must not be reinserted for at least 15 minutes after study medication instillation. Contact lenses must not be worn during study visits.

8.6.3. Study Medication Accountability

The Investigator or clinical site staff 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 medication using the inventories supplied by the Sponsor. Each subject's kit will contain sufficient study medication for the duration of the trial. Final study medication accountability will be conducted at Day 42 ± 3 days (Visit 4); study medication will not be re-dispensed at this visit. The Investigator or clinical site staff will account for all received and returned study medication. The monitor will review dispensing and study medication accountability records 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 subject must read, sign, and date the current IRB-approved version of the informed consent form. For minor subjects, the subject's parent or legal guardian must provide permission by signing the ICF on behalf of the subject, and assent from the minor subject should also be obtained following 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. A full discussion of informed consent is presented in Section 13.3. Procedures must be performed in the order specified in Table 2.

9.1. Demographic and Background Characteristics

9.1.1. 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.

9.1.2. Concomitant Medications History

All concomitant medications (prescription and OTC) taken at Visit 1 (Screening) 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, left eye, 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.

9.1.3. 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.

9.1.4. Urine Pregnancy Test

A urine pregnancy test will be performed for females of childbearing potential only (females who have started their menstrual cycles).

9.2. Efficacy Assessments

The efficacy of RVL-1201 Ophthalmic Solution compared to the Vehicle for the pharmacologic treatment of acquired blepharoptosis will be measured by improvement in visual field (as determined by LPFT assessment) and increase in MRD.

9.2.1. Leicester Peripheral Field Test

The LPFT, a customized visual field test designed specifically to assess ptosis (Ho et al, 2011), will be performed using a Humphrey Visual Field Analyzer. It is an age-corrected screening test with a three-zone strategy. Thirty-five points are tested in the superior field while 14 points are tested in the inferior field. A maximum of 48° is tested in the superior visual field. The center of fixation is shifted 15° inferiorly to allow for maximum superior field testing (Ho et al, 2011). The inferior field test serves as a reference but is not used in the analysis.

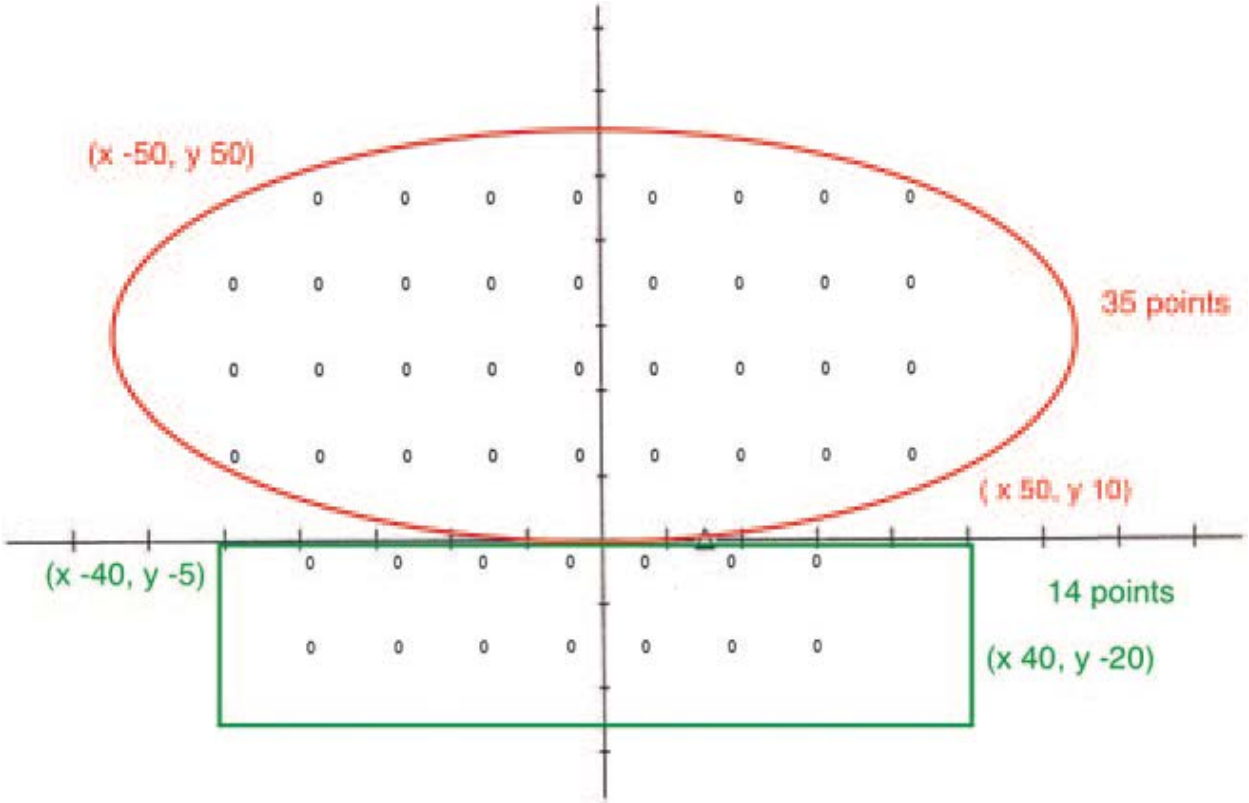


Figure 1: Leicester Peripheral Field Test Grids

Clinical site staff must instruct the subjects to keep their chin and forehead against the chin and forehead rests, and to keep their brows relaxed. Clinical site staff must also instruct the subjects to look at the fixation target throughout the test. A corrective lens is not necessary on the LPFT UNLESS the subject would have a difficult time seeing the target without it (e.g., high myope, high hyperope, or high astigmat).

There are two types of scores for the LPFT assessment:

LPFT Eligibility Score: The total number of points missed in the top 2 rows on the LPFT.

LPFT Total Score: The total number of points seen in the top 4 rows on the LPFT.

Leicester Peripheral Field Test assessments will be performed OU until the point of study eye designation by the medical monitor. After designation, LPFT assessments will be performed only on the study eye. For subjects with surgical monovision correction where the study eye is the near vision eye, a neutralizing trial lens may be put in the lens holder located in front of the chin rest of the HVF Analyzer.

The HVF Analyzer will determine if the LPFT test is reliable. If the HVF Analyzer issues an "XX" for fixation losses, false positives, and/or false negatives, the test will be deemed unreliable. If deemed unreliable, the test must be retaken (once per scheduled test). If the outcome of the repeated test is reliable it will be used in the efficacy analysis, and if the repeated test is unreliable it will be included in the ITT analysis set but excluded from the PP analysis set.

9.2.2. 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) 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.

9.2.2.1. 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.

9.3. Safety Assessments

Assessment of the safety and tolerability of RVL-1201 Ophthalmic Solution compared to Vehicle will include bilateral ophthalmic examinations (Snellen VA, pupil diameter 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.

9.3.1. 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.

9.3.2. 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.

9.3.3. 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 (see Section 9.2.2).

9.3.4. 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

9.3.5. 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.

9.3.6. 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.

9.3.7. 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

9.4. Adverse and Serious Adverse Events

9.4.1. Definition of Adverse Events

9.4.1.1. 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.

9.4.1.2. 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; i.e., 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.

9.5. 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.

9.6. 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. Changes from baseline assessments that are part of the disease being studied will not necessarily be recorded as adverse events unless the Investigator deems them as such. Clinically significant changes in blood pressure and heart rate should be reported as AEs. All AEs that occur following consent and until the final study visit (Day 42, Visit 4) should be collected and recorded on the AE eCRF page. Serious adverse events will be followed until the event is resolved or stabilized.

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);
- Resolution (date);
- 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 9.4.1.2. 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 subject will be withdrawn from study medication and followed through conclusion of pregnancy. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

9.7. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded following consent and until the final study visit, Day 42 (Visit 4), 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.

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 [redacted]. The Investigator must assess the SAE relationship and complete the SAE form. Oculos/RevitaLid Inc. may request additional information. Follow-up information (e.g., discharge summary) will be retained in the subject’s chart and a copy will be emailed to [redacted].

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.

RevitaLid Inc. 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 or 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 medication, the SAE resulting in the death must be reported to Oculos. A death occurring after completion of the study does not require completion of the SAE form.

10. STUDY ACTIVITIES

Table 2 provides a tabular summary of all scheduled visits and procedures to be performed during the clinical study.

Hour number (when not "0") refers to hours passed since administration of study medication.

10.1. Screening Visit

Screening eligibility assessments are obtained during the Screening Visit conducted on or between Day -7 to Day -3 (Visit 1). Key eligibility determinants will be MRD measured from external digital color photographs, 2 LPFTs per subject with ≤ 4 points of variance in the LPFT Eligibility Score between the V1H0 and V1H6 LPFTs, and Snellen VA. All assessments of efficacy (LPFT and MRD) and safety (VA, pupil diameter, SLE)/CFS, IOP, dilated ophthalmoscopy/fundus exam) will be conducted in both eyes (OU) at Screening. External photographs and LPFT printouts will be sent to the Medical Monitor for reading/confirmation of eligibility/determination of study eye.

10.1.1. Day -7 to Day -3 (Visit 1): Screening

At Screening, Day -7 to Day -3 (Visit 1), subjects will provide informed consent before any study-related procedures are conducted. For minor subjects, permission will be obtained from the subject's parent or legal guardian by signing the ICF on behalf of the subject, and assent will be obtained from the minor subject following IRB guidelines. Subjects will then participate in screening procedures to establish eligibility for the study. At the end of the visit, inclusion/exclusion criteria will be reviewed and external photograph and LPFT printouts will be sent to the Medical Monitor for reading/confirmation of eligibility/determination of study eye.

Screening procedures include the following:

- Informed consent/assent
- Demographics
- Medical and ocular histories
- Urine pregnancy test (females of childbearing potential only)
- Prior and concomitant medications/therapies
- BP/HR
- Snellen visual acuity (OU)
- MRD (OU) (from external photograph)
- Pupil diameter measurement (OU) (from external photograph)
- LPFT (OU); administered twice, with 6 hours intervening. If the HVF Analyzer issues an "XX" for fixation losses, false positives, and/or false negatives, the test will be deemed unreliable. If deemed unreliable, the test must be retaken (once per scheduled test).

- SLE (OU)
- CFS (OU)
- IOP (OU)
- Dilated ophthalmoscopy/fundus exam (OU); must be conducted after the LPFT assessment at Hour 6
- AE assessment

At the end of the visit, inclusion/exclusion criteria will be reviewed and external photographs and LPFT printouts will be uploaded through the eDC system to the Medical Monitor for reading/confirmation. The Medical Monitor will subsequently inform the site whether the subject is eligible and which eye will be the study eye.

If both eyes qualify, the more ptotic eye (the eye with the smaller MRD measurement), will be the study eye. If the MRD = 0 in either eye where both eyes are eligible, the eye with the measurable MRD (≥ 0.5 mm) will be the study eye. If the MRD is the same in both eyes, the eye with the greater visual field defect (the lower LPFT Total Score from the V1H6 LPFT, based on the number of points seen in the top 4 rows) will be the study eye. If the MRD and LPFT are the same in both eyes, the right eye will be the study eye.

10.2. Treatment Visits

For all treatment visits, LPFT assessments will be performed in the study eye; safety assessments (VA, pupil diameter, SLE/CFS, IOP, dilated ophthalmoscopy/fundus exam) and efficacy assessment from external photography (MRD) will be conducted OU. The window for each hourly assessment time point is ±30 minutes.

10.2.1. Day 1 (Visit 2): Baseline/Randomization/First Dose/Duration of Action Assessment

On Day 1 (Visit 2), subjects determined to be eligible after review by the Medical Monitor will be given a confirmatory LPFT (in the study eye), randomized into the study if the LPFT in the chosen study eye conforms to inclusion criteria (see Section 8.2 for randomization procedures, and Section 7.1 for inclusion criteria), receive a dose of allocated masked study medication, and undergo safety and efficacy assessments over approximately 8 hours.

Day 1 procedures include the following:

Hour 0

- Urine pregnancy test (females of childbearing potential only)
- AE assessment
- Concomitant medication review
- BP/HR
- Snellen VA (OU)
- MRD (from external photograph) (OU)

- Pupil diameter measurement (from external photograph) (OU)
- LPFT test (study eye only)
- Compare V2H0 LPFT Eligibility Score with V1H6 LPFT Eligibility Score
- SLE (OU)
- Randomize the subject to double-masked study medication (see Section 8.2)

Administer Study Medication

- Instruct the subject on use and storage of study medication (see Section 8.6.2)
- The subject (or caregiver, if the subject is not able to self-administer the medication) will administer allocated study medication, 1 drop in each eye. After a drop is instilled in each eye, the subject should keep the eyes gently closed for approximately 30 seconds.

Post Dose

- MRD (from external photograph) (OU) at 5 minutes (+ 2 minutes) and 15 minutes (+ 2 minutes) post dose
- AE assessment at approximately10 to 30 minutes post dose

Hour 2

- AE assessment
- BP/HR
- MRD (from external photograph) (OU)
- Pupil diameter measurement (from external photograph) (OU)

Hour 6

- AE assessment
- MRD (from external photograph) (OU)
- Pupil diameter measurement (from external photograph) (OU)
- LPFT test (study eye only) (this test must be performed approximately 6 hours post administration of study medication. This requirement supersedes the order of procedures provided here and in the schedule of procedures)

Hour 8

- AE assessment
- BP/HR
- Snellen VA (OU)
- Pupil diameter measurement (from external photograph) (OU)
- SLE (OU)

- CFS (OU)
- Dispense study medication Box 1
- Study medication accountability

10.2.2. Days 2 through 13

From Days 2-13, study medication will be administered QD (in the morning) and subjects will return on Day 14 ± 3 days (Visit 3) BEFORE instillation of study medication. Subjects will be instructed to bring Box 1 with all study medication materials (opened and unopened unit-dose vials and pouches) to the study site at Visit 3 (Day 14) for study medication accountability/treatment compliance determination.

10.2.3. Day 14 ± 3 (Visit 3): Onset of Action Assessment

On Day 14 ± 3 (Visit 3), confirm the subject did not instill their morning dose of study medication. Subjects who dosed prior to the morning visit MUST be rescheduled.

Day 14 procedures include the following:

Hour 0

- Collect Box 1, containing all opened and unopened study medication materials (unit-dose vials and pouches), from the subject
- Concomitant medication review
- AE assessment
- BP/HR
- Snellen VA (OU)
- MRD (from external photograph) (OU)
- Pupil diameter measurement (from external photograph) (OU)
- SLE (OU)

Administer Study Medication

- The subject (or caregiver, if the subject is not able to self-administer the medication) will administer allocated study medication from Box 1, 1 drop in each eye. After a drop is instilled in each eye, the subject should keep the eyes gently closed for approximately 30 seconds.

Post Dose

- MRD (from external photograph) (OU) at 5 minutes (+ 2 minutes) and 15 minutes (+ 2 minutes) post dose
- AE assessment at approximately 10 to 30 minutes post dose

Hour 2

- AE assessment
- BP/HR
- MRD (from external photograph) (OU)
- Pupil diameter measurement (from external photograph) (OU)
- LPFT test (study eye only) (this test will must be performed approximately 2 hours post administration of study medication. This requirement supersedes the order of procedures provided here and in the schedule of procedures)

Hour 6

- AE assessment
- MRD (from external photograph) (OU)
- Pupil diameter measurement (from external photograph) (OU)

Hour 8

- AE assessment
- BP/HR
- Snellen VA (OU)
- Pupil diameter measurement (from external photograph) (OU)
- SLE (OU)
- CFS (OU)
- Dispense study medication Box 2
- Study medication accountability

10.2.4. Days 15 through 41

From Days 15-41, subjects (or caregivers, if the subject is not able to self-administer the medication) will administer study medication QD (administered in the morning) and return on Day 42 (Visit 4) in the morning BEFORE instillation of study medication. Subjects will be instructed to bring all study medication materials (opened and unopened unit-dose vials and pouches) to the study site for study medication accountability/treatment compliance assessment.

10.2.5. Day 42 ± 3 (Visit 4): Last Day of Treatment

At Day 42 ± 3 (Visit 4), confirm the subject did not instill their morning dose of study medication. Subjects who dosed prior to the morning visit MUST be rescheduled.

Subjects will undergo final efficacy and safety assessments and rate the ocular tolerability of study medication.

Visit 4 procedures include the following:

Hour 0

- Collect Box 2, containing all opened and unopened study medication materials (unit-dose vials and pouches), from the subject
- Urine pregnancy test (females of childbearing potential only)

Administer Study Medication

- The subject (or caregiver, if the subject is not able to self-administer the medication) will administer allocated study medication from Box 2, 1 drop in each eye. After a drop is instilled in each eye, the subject should keep the eyes gently closed for approximately 30 seconds.

Post Dose

- MRD (from external photograph) (OU) at 5 minutes (+ 2 minutes) and 15 minutes (+ 2 minutes) post dose
- Pupil diameter measurement (from external photograph) (OU)
- Concomitant medication review
- AE assessment
- Study medication tolerability assessment (rating by subject)
- BP/HR (taken after 3 minutes at rest)
- Snellen VA (OU)
- SLE (OU)
- CFS (OU)
- IOP (OU)
- Dilated ophthalmoscopy/fundus exam (OU)
- Final study medication accountability

10.3. Early Discontinuation Assessment Procedures

If a study subject is discontinued from study medication before Day 42 (Visit 4) but after Day 1 (Visit 2), procedures performed will include the following:

- Collect all opened and unopened study medication materials (opened and unopened unit-dose vials and pouches) from the subject
- Concomitant medication review
- AE assessment
- Study medication tolerability assessment (rating by subject)
- Urine pregnancy test (females of childbearing potential only)
- BP/HR (taken after 3 minutes at rest)

- Snellen VA (OU)
- MRD (from external photograph) (OU)
- Pupil diameter measurement (from external photograph) (OU)
- SLE (OU)
- CFS (OU)
- IOP (OU)
- Dilated ophthalmoscopy/fundus exam (OU)
- Study medication accountability

11. STATISTICS

11.1. General Considerations

This is a Phase 3 study to evaluate the efficacy and safety of QD treatment with RVL-1201 Ophthalmic Solution (oxymetazoline hydrochloride ophthalmic solution, 0.1%) compared to Vehicle (placebo) for the treatment of acquired ptosis.

Subjects will be randomized in a 2:1 ratio of RVL-1201 Ophthalmic Solution to Vehicle into 2 treatment groups and treated for 42 days:

- RVL-1201 Ophthalmic Solution 1 drop in each eye QD in the morning (N = 104)
- Vehicle (placebo) 1 drop in each eye QD in the morning (N = 52)

All efficacy variables will be compared between the RVL-1201 QD treatment regimen and placebo.

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

A detailed SAP will be finalized prior to database lock. 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 (the time points at which data are collected are specified in the schedule of observations—see Table 2).

Final analyses of efficacy will be conducted when all subjects complete Day 42 (Visit 4).

11.1.1. Handling of Missing Data

All efficacy analyses will be based on observed cases (without imputation). If more than 5% of data in any treatment group are missing, multiple imputation will be employed to analyze incomplete data sets under the assumption that the mechanism responsible for the missing data is at worst characterized as missing at random (MAR). The reasons for missing data will be recorded and the impact of these reasons and any treatment group imbalance on the assumption of MAR will be evaluated. If 5% or fewer data are missing, an analysis with last observation carried forward (LOCF) for missing data will be conducted on the ITT population only.

11.2. Determination of Sample Size

A two-group t-test with a 0.05 two-sided significance level will have 90% power to detect a difference in LPFT means of 3.50, assuming that the common standard deviation is 6.0, when the sample sizes in the 2 groups are 94 and 47, respectively (a total sample size of 141). The planned total of 156 subjects will allow for a 10% drop-out rate.

11.3. Analysis Populations

Three populations will be used for analysis, as described below.

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 who received at least one dose of the allocated study medication. The primary efficacy analysis of the LPFT endpoints at Day 1 Hour 6 and Day 14 Hour 2 will be conducted on the ITT population.

11.3.1.2. Per-Protocol (PP) Population

The per-protocol (PP) population consists of those subjects in the ITT population who had no major protocol deviations. Supportive efficacy analysis will be conducted on the PP population.

11.3.2. Safety Population

The safety population is defined as all randomized subjects who received at least one dose of the allocated study medication. All safety analyses will be performed using the safety population.

11.4. Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized for all analysis populations. Summary tables will be supported with individual subject data listings.

11.5. Efficacy Analysis

Efficacy analyses will be performed on the ITT population for the primary efficacy variables. Analysis of the hierarchical efficacy variables will also be conducted with the PP population using only observed data.

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

The efficacy measures (LPFT and MRD) taken on Visit 2 (Day 1, Hour 0) prior to dosing will serve as baseline.

11.5.1. Hypothesis Testing

The primary efficacy endpoints will be tested sequentially in the order specified. For a claim of statistical significance, the null hypothesis being tested, and all higher ordered null hypotheses must be rejected, i.e., the Day 1 Hour 6 time point will be tested first, and if $P < 0.05$, the Day 14 Hour 2 time point will be tested at a significance level of 0.05. Thus, each of the hypotheses in the hierarchy will be tested within the treatment regimen against placebo at a significance level of 0.05. It is important to note that if the Day 1 Hour 6 endpoint is statistically significant (at the 0.05 level) but Day 14 Hour 2 is not statistically significant (at the 0.05 level), the study will still be considered positive.

If both primary efficacy endpoints are significant at the 0.05 significance level, then the secondary efficacy endpoints (MRD) will also be tested sequentially. Testing will stop if a P value ≥ 0.05 for a comparison. The order of testing is as follows:

1. Day 1 Hour 2
2. Day 14 Hour 2
3. Day 1 Hour 6
4. Day 14 Hour 6
5. Day 1 Minute 15
6. Day 14 Minute 15
7. Day 1 Minute 5
8. Day 14 Minute 5

All other comparisons are considered exploratory.

11.5.2. Primary Efficacy Endpoints

The primary efficacy endpoints will be the mean change from Baseline (Day 1, Hour 0) in the RVL-1201 group versus the Vehicle group in number of points seen in the top 4 rows on the LPFT test at:

1. Day 1 Hour 6 (Visit 2)
2. Day 14 Hour 2 (Visit 3)

11.5.3. Primary Efficacy Analysis

A summary of the efficacy endpoints will be prepared at each time point and will include an estimate of the mean change from baseline for each treatment group and of the adjusted treatment difference and 95% confidence interval. The between-treatment comparison will employ ANCOVA with treatment as a fixed factor and baseline as a covariable. A t-test on least squares means will be used to compare RVL-1201 to Vehicle with a 2-sided significance level of 0.05. Wilcoxon rank sum tests will also be used to compare treatments at each time point.

11.5.4. Secondary Efficacy Endpoints

Secondary endpoints will include the mean observed values and change from baseline values for MRD data in the RVL-1201 group versus the Vehicle group assessed at Day 1 (Visit 2), Day 14 (Visit 3), and at Day 42 (Visit 4).

11.5.5. Secondary Efficacy Analysis

The same analysis methods that are used for the primary efficacy endpoints will be utilized for the secondary efficacy endpoints.

11.6. Safety Analyses

The safety of RVL-1201 will be compared to Vehicle with analysis of safety variables including bilateral ophthalmic examinations (Snellen VA, SLE/CFS, measurement of pupil diameter from external photographs, dilated ophthalmoscopy/fundus examination, and tonometry), vital signs (BP/HR), and AEs. The ocular tolerability of study medication will be rated by the subject. 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/RevitaLid Inc. 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 ensure compliance with GCP and all applicable regulatory requirements, RevitaLid 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/assent 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, 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 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/Assent

A sample ICF 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 form and minor assent form must be submitted to and approved by the IRB. The informed consent must be written in a language in which the subject is fluent. 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 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, the assent form must be signed and dated per IRB guidelines. If subjects become 18 years of age during the study, they will need to sign an ICF to continue in the study. The original informed consent 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/RevitaLid Inc., 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 on behalf of RevitaLid Inc. 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, interim monitoring visits, and a study close-out visit. Training will be provided for key investigative personnel in all aspects of study conduct. The Investigator will be responsible for making sure that clinical site personnel are provided adequate training on conducting their designated tasks.

The sites will record data directly into the eCRF in order to optimize the eCRF source verification process with limited hand-written source documentation. Monitors will review e-source data and overall study data/consistency remotely and query discrepancies based upon eCRF entries (eCRF initial entry is the source). During this monitoring, data are reviewed as entered by the site, and the monitors will flag any abnormalities, trends, or safety signals for Medical Monitor review and monitor follow-up onsite, if necessary.

During visits to the clinical site, the monitor may review the source documents including but not limited to LPFT tests, signed informed consent forms, 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/RevitaLid Inc., 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 medication 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 Oculos 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 onto eCRFs provided by Oculos. The eCRF is the first place the majority of the study data will be recorded and therefore considered to be the source document. In general, paper source documents will not be created, but when generated, source documents (e.g., discharge summaries, etc.) will be retained at the study site.

13.7. Protocol 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.

All protocol deviations will be documented. A significant protocol deviation must be reported to Oculos upon discovery. A reportable protocol deviation is defined as nonadherence to the protocol that involves inclusion/exclusion criteria, affects subject safety, or has the potential to affect the integrity of the data. Protocol deviations should be reported to the IRB in accordance with IRB guidelines. If there is any question as to whether the deviation is reportable, Oculos and the IRB should be contacted.

All changes to the protocol will be made by the Sponsor/Oculos 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 (Section 12). 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 ICFs; 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 Oculos or their designee.

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

The Investigator must maintain essential study documents (protocol and amendments, source documentation corresponding to all information contained in the CRFs/eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years after the formal discontinuation of clinical development of the investigational product. If the principal Investigator moves from the current study site, RevitaLid Inc. 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 RevitaLid Inc. as soon as possible in the event of accidental loss or destruction of any study documentation.

If it becomes necessary for Oculos/RevitaLid Inc. 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 RVL-1201 and the operations of RevitaLid Inc., 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 RevitaLid Inc. 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 RevitaLid Inc.

The publication policy is addressed in a separate agreement.

14. REFERENCES

Finsterer J. Ptosis: causes, presentation, and management. Aesthetic Plast Surg. 2003 May-Jun;27(3):193-204.

Fraunfelder FT, Scafidi AF. Possible adverse effects from topical ocular 10% phenylephrine. Am J Ophthalmol. 1978;85(4):447-53.

Ho SF, Morawski A, Sampath R, Burns J. Modified visual field test for ptosis surgery (Leicester Peripheral Field Test). Eye (Lond). 2011 Mar;25(3):365-9. doi:10.1038/eye.2010.210. Epub 2011 Jan 21

Kass MA, Mandell AI, Goldberg I, Paine JM, Becker B. Dipivefrin and epinephrine treatment of elevated intraocular pressure: a comparative study. Arch Ophthalmol. 1979 Oct;97(10):1865-6.

Matjucha IC. The nonsurgical treatment of ptosis. In: Cohen AJ, Weinberg DA, editors: Evaluation and management of blepharoptosis. New York: Springer, 2011. p. 155-61.

Scheinfeld N. The use of apraclonidine eyedrops to treat ptosis after the administration of botulinum toxin to the upper face. Dermatol Online J. 2005 Mar 1;11(1):9.

Shah-Desai SD, Aslam SA, Pullum K, Beaconsfield M, Rose GE. Scleral contact lens usage in patients with complex blepharoptosis. Ophthal Plast Reconstr Surg. 2011 Mar-Apr;27(2):95-8.

Sridharan GV, Tallis RC, Leatherbarrow B, Forman WM. A community survey of ptosis of the eyelid and pupil size of elderly people. Age Ageing. 1995 Jan;24(1):21-4.

15. SUMMARY OF CHANGES

15.1. Changes Implemented in Protocol RVL-1201-202 Amendment 1

The following changes were made to the original protocol:

Location	Description of Change	Rationale for Change
Synopsis Inclusion Criteria; 4.3. Population to be Studied; 7.1. Inclusion Criteria	Change "> 9 years of age" to "≥ 9 years of age"	To correct a typographical error

15.2. Changes Implemented in Protocol RVL-1201-202 Amendment 2

The following changes were made to Amendment 1:

Location	Description of Change	Rationale for Change
Synopsis Methodology; 6.1. Overall Study Design; 10.1.1. Day -7 to Day -3 (Visit 1): Screening	Change "If the MRD is the same in both eyes, the eye with the greater visual field defect (the ~~higher~~ Leicester Peripheral Field Test [LPFT] Total Score, based on number of points ~~not~~ seen on the top 4 rows) will be the study eye." to "If the MRD is the same in both eyes, the eye with the greater visual field defect (the **lower** Leicester Peripheral Field Test [LPFT] Total Score **from Visit 1, Hour 6,** based on number of points seen on the top 4 rows) will be the study eye."	To clarify that the LPFT Total Score is based on points seen (rather than points missed) and indicate that the LPFT Total Score at Visit 1, Hour 6 is used by the Medical Monitor to make the study eye designation if the MRD is the same in both eyes.

Location	Description of Change	Rationale for Change
Synopsis Inclusion Criteria; Table 2: Schedule of Procedures; 7.1. Inclusion Criteria; 10.2.1. Day 1 (Visit 2): Baseline/Randomization/First Dose/Duration of Action Assessment	Change (Synopsis and 7.1) "4. Females must be 1-year postmenopausal, surgically sterilized, or females of childbearing potential (females who have started their menstrual cycles) with a negative urine pregnancy test at Visit 1." to "4. Females must be 1-year postmenopausal, surgically sterilized, or females of childbearing potential (females who have started their menstrual cycles) with a negative urine pregnancy test at Visit**s** 1 **and 2**." Add (to 10.2.1) Hour 0 • "**Urine pregnancy test (females of childbearing potential only)**"	To add a urine pregnancy test to Baseline procedures to ensure that female subjects of childbearing potential continue to have a negative result following the -7 to -3 days between Screening and Baseline.
Synopsis Study Procedures; 8.6.2. Storage and Administration; 10.2.1. Day 1 (Visit 2): Baseline/Randomization/First Dose/Duration of Action Assessment; 10.2.5. Day 42 ± 3 (Visit 4): Last Day of Treatment	Change "~~full~~ drop" to "drop" Delete ~~if a full drop is not instilled into the eye, the subject should wait approximately 10-15 seconds and administer a second drop~~	To clarify that only one drop should be administered to each eye at each dose.
3. List of Abbreviations and Definitions of Terms; 9.2.1. Leicester Peripheral Field Test	Change "LPFT Eligibility Score: Total number of ~~missed points~~ in the top 2 rows on the LPFT. LPFT Total Score: The total number of ~~missed~~ points in the top 4 rows on the LPFT." to "LPFT Eligibility Score: Total number of **points missed** in the top 2 rows on the LPFT. LPFT Total Score: Total number of points **seen** in the top 4 rows on the LPFT."	To clarify that the LPFT Eligibility Score is based on points missed while the LPFT Total Score is based on points seen.

Location	Description of Change	Rationale for Change
Table 2: Schedule of Procedures, Footnote h; 10.1.1. Day -7 to Day -3 (Visit 1): Screening	Change (to Schedule of Procedures) "X" was moved from Screening Hour 0 to Screening Hour 6. Add (to Schedule of Procedures, Footnote h) "Only tropicamide (Mydriacyl) should be used for this exam. Phenylephrine hydrochloride (Neosynephrine) may NOT be used. **The dilated ophthalmoscopy/fundus exam at Screening (Visit 1) must be conducted after the LPFT assessment at Hour 6."** Add (to 10.1.1) • "Dilated ophthalmoscopy/fundus exam (OU)**; must be conducted after the LPFT assessment at Hour 6**"	To clarify that the dilated ophthalmoscopy/fundus exam should be conducted after the Visit 1, Hour 6 LPFT. This is to avoid any possible residual effect from the dilation drops during the visual field testing.
8.2.1. Unmasking During the Study Period; 9.7. Reporting Adverse Events	Change "Revitalid-Safety@oculos.com" to "Revitalid-Safety@oculos**cr**.com"	To correct a typographical error
9.6. Recording Adverse Events	Change "For each AE, the Investigator will evaluate and report the following: • Onset (date ~~and time~~); • Resolution (date ~~and time~~);" to "For each AE, the Investigator will evaluate and report the following: • Onset (date); • Resolution (date);"	Time of onset and resolution of AEs will not be collected.

Location	Description of Change	Rationale for Change
10.1.1. Day -7 to Day -3 (Visit 1): Screening	Change "At the end of the visit, inclusion/exclusion criteria will be reviewed and external photographs and LPFT printouts will be uploaded to the Medical Monitor for reading/confirmation ~~at eslonim@pointguardllc.com~~." to "At the end of the visit, inclusion/exclusion criteria will be reviewed and external photographs and LPFT printouts will be uploaded **through the eDC system** to the Medical Monitor for reading/confirmation."	The external photographs and LPFT printouts will not be emailed to the Medical Monitor, they will be uploaded through the eDC system.
10.2. Treatment Visits	Change "The window for each hourly assessment time point is +30 minutes." to "The window for each hourly assessment time point is ±30 minutes."	To clarify that the window for the hourly assessment time points is "±"30 minutes, not "+"30 minutes.
Table 2: Schedule of Procedures 10.2.1. Day 1 (Visit 2): Baseline/Randomization/First Dose/Duration of Action Assessment; 10.2.3. Day 14 ± 3 (Visit 3): Onset of Action Assessment; 10.3. Early Discontinuation Assessment Procedures	Change order of procedures from • "BP/HR (taken after 3 minutes at rest) • MRD (from external photograph) (OU) • Pupil diameter measurement (from external photograph) (OU) • ~~Snellen VA (OU)"~~ to • "BP/HR (taken after 3 minutes at rest) • **Snellen VA (OU)** • MRD (from external photograph) (OU) • Pupil diameter measurement (from external photograph) (OU)"	To create a more efficient flow of procedures for the clinical site.

15.3. Changes Implemented in Protocol RVL-1201-202 Amendment 3

The following changes were made to Amendment 2:

Location	Description of Change	Rationale for Change
Synopsis Methodology; 6.1. Overall Study Design; 10.1.1. Day -7 to Day -3 (Visit 1): Screening	**Add** Both eyes will be treated and assessed, but the more ptotic eye (the eye with the smaller marginal reflex distance (MRD) measurement) will be the study eye. **If the MRD = 0 in either eye where both eyes are eligible, the eye with the measurable MRD (≥ 0.5 mm) will be the study eye.** If the MRD is the same in both eyes, the eye with the greater visual field defect (the lower Leicester Peripheral Field Test [LPFT] Total Score from Visit 1, Hour 6, based on number of points seen on the top 4 rows) will be the study eye. If the MRD and LPFT are the same in both eyes, the right eye will be the study eye.	Potential improvements in MRD can be more accurately determined if the eligible eye has a measurable MRD.
Synopsis Exclusion Criteria; 7.2. Exclusion Criteria	Change from In ~~either~~ eye ~~2. Presence of either of the following:~~ ~~a.~~ Pseudoptosis (upper eyelid dermatochalasis that overhangs the upper eyelid margin) ~~*or*~~ ~~b.~~ Dermatochalasis that extends less than 3 mm above the upper eyelid margin to In **the study** eye **only** 1. Dermatochalasis that extends less than 3 mm above the upper eyelid margin. 2. Pseudoptosis (upper eyelid dermatochalasis that overhangs the upper eyelid margin).	Dermatochalasis of < 3 mm or pseudoptosis should only exclude the eye that it occurs in, not the opposing upper eyelid that might otherwise be eligible for the study.
Synopsis Exclusion Criteria; 7.2. Exclusion Criteria	Change from 18. Resting heart rate (HR) outside the normal range (60–100 beats per minute). to 18. Resting heart rate (HR) outside the normal range (**50**–1**10** beats per minute).	To allow enrollment of healthy individuals with heart rates that are normal for them and do not require treatment.

Location	Description of Change	Rationale for Change
Synopsis Exclusion Criteria; 7.2. Exclusion Criteria	24. Patients with diabetic retinopathy may not be enrolled. However, patients with insulin dependent diabetes, diabetes requiring oral hypoglycemic drugs, or diet controlled diabetes are allowed. 24. 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.	To allow patients with stable background diabetic retinopathy to participate in the study, if otherwise eligible.
Synopsis Study Procedures; 6.1. Overall Study Design 9.2.1. Leicester Peripheral Field Test 10.1.1. Day 7 to Day 3 (Visit 1): Screening	Change from If the Humphrey Visual Field (HVF) Analyzer issues an "XX" for fixation losses, false positives, and/or false negatives, the test will be deemed unreliable. If deemed unreliable, the test ~~may~~ be retaken once per scheduled test. to If the Humphrey Visual Field (HVF) Analyzer issues an "XX" for fixation losses, false positives, and/or false negatives, the test will be deemed unreliable. If deemed unreliable, the test **must** be retaken **(**once per scheduled test**)**.	To clarify that it is not optional to repeat an "unreliable" test once, it is mandatory.
Table 2: Schedule of Procedures Footnote d	Change from [d] MRD and pupil diameter will be measured from the external photograph. For a description of the ~~precise~~ timing of MRD measurements, please refer to details of each individual visit in Section 10. [d] MRD and pupil diameter will be measured from the external photograph. **On Day 1 (Visit 2), Day 14 (Visit 3), and Day 42 (Visit 4), the timing of MRD measurements must be at 5 minutes (+2 minutes) and 15 minutes (+ 2 minutes) post dose.** For a description of the timing of **all** MRD measurements, please refer to details of each individual visit in Section 10.	To establish consistency between the description of the timing of assessments between the schedule and Section 10.