CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212520Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	NDA 212520
Priority or Standard	Standard
Submit Date(s)	September 16, 2019
Received Date(s)	September 16, 2019
PDUFA Goal Date	July 16, 2020
Division/Office	Division of Ophthalmology/Office of Specialty Medicine
Reviewer Name(s)	Jennifer Harris, M.D.
Review Completion Date	5/18/2020
Established/Proper Name	Oxymetazoline hydrochloride ophthalmic solution, 0.1%
(Proposed) Trade Name	Upneeq
Applicant	RevitaLid, Inc
Dosage Form(s)	Ophthalmic solution
Applicant Proposed Dosing Regimen(s)	One drop to affected eye in the morning
Applicant Proposed Indication(s)/Population(s)	Patients with blepharoptosis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with acquired blepharoptosis

Table of Contents

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Oxymetazoline is an α-adrenergic agonist that has been used as an ocular vasoconstrictor for over 30 years and as a nasal decongestant for more than 50 years. Oxymetazoline hydrochloride at a 0.025% concentration is the active ingredient in over-the-counter (OTC) eye drops indicated for the relief of redness of the eye due to minor eye irritations (e.g., Visine L.R).

When administered at a 0.1% concentration, oxymetazoline stimulates the α2-adrenergic receptors in Müller's muscle causing it to contract, thereby lifting the upper eyelid and retracting the lower eyelid to a lesser degree. Topical ophthalmic administration of oxymetazoline hydrochloride at lower concentrations (0.01%, 0.025%) results in vasoconstriction and reduction of hyperemia but does not have the pharmacologic effect of raising the upper eyelid.

Oxymetazoline hydrochloride ophthalmic solution, 0.1% is also referred to as RLV-1201 within this review.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Oxymetazoline hydrochloride ophthalmic solution, 0.1% is recommended for approval for the treatment of acquired blepharoptosis. The efficacy of this product was replicated in two adequate and well-controlled trials RVL-1201-201 and RVL 1201-202 that demonstrated that RLV-1201 is statistically superior to placebo (vehicle) in the increase in the number of points seen in the superior visual field as measured using the Leicester Peripheral Field Test (LPFT). The onset in improvement in vision in the upper visual field appears to be approximately 2 hours after dosing and continues for at least 6 hours after dosing. In addition,RLV-1201 showed greater numerical increases in the margin reflex distance compared to placebo.

Safety was assessed in over 350 subjects dosed once a day for six weeks with oxymetazoline 0.1%. Treatment with RVL-1201 is considered safe with a favorable adverse event profile. The adverse events seen where those that are consistent with most topical ophthalmic drops including punctate keratitis, conjunctival hyperemia, dry eye, blurred vision and pain on installation.

1.3. Benefit-Risk Assessment

Patients with acquired ptosis have diminished superior visual fields which may interfere with activities of daily living. Oxymetazoline 0.1% was demonstrated to be superior to placebo in the clinical improvement in the number of points seen in the superior visual field in patients with acquired blepharoptosis. This efficacy was replicated in two adequate and well-controlled trials RVL-1201-201 and RVL 1201-202. The onset in improvement in the upper visual field appears to be approximately 2 hours after dosing and continues for at least 6 hours after dosing.

Patients treated with RVL-1201 for the proposed indication reported few adverse events. The most common (<5%) adverse events experienced with RVL-1201 were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain and headache.

The benefits of using oxymetazoline 0.1% to improve the ability to see in the upper visual field in patients with acquired blepharoptosis outweigh the risks associated with once a day topical administration.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	*Blepharoptosis, or ptosis, can be unilateral or bilateral and usually occurs from a partial or complete dysfunction of the muscles that elevate the upper eyelid.*	*Patients with acquired ptosis may report diminished superior visual fields, which may interfere with activities of daily living and result in reduced quality of life.*
Current Treatment Options	*Treatment for acquired blepharoptosis has predominantly been surgical with the choice of surgical procedure dependent on the severity of ptosis and amount of muscle (levator) function.*	*Pharmaceutical treatment has the potential to replace the need for surgery for lesser degrees of ptosis and mitigate the associated risks of surgery.*
Benefit	*RLV-1201 increases vision in the superior visual field.*	*RLV-1201 has demonstrated a statistically significant increase in vision in the superior visual field in two adequate and well controlled studies. (Study RVL-1201-201 and Study RVL-1201-202)*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	*The most common adverse events experienced with RVL-1201 were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain and headache.*	*Treatment with RVL-1201 for the proposed indication appears safe with few reported adverse events.*

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

√	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	Sec 6.1 Study endpoints
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	√ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Blepharoptosis, or ptosis, is a unilateral or bilateral abnormal drooping of the upper eyelid that usually occurs from a partial or complete dysfunction of the muscles that elevate the upper

eyelid. Ptosis is one of the most common eyelid disorders and is classified as either congenital or acquired.

Acquired ptosis has numerous etiologies but most often is aponeurotic, a result of involutional changes to the levator aponeurosis, a result of stretching or disruption of the muscle during cataract surgery, or as a result of long-term contact lens wear. Patients with acquired ptosis may report blurred vision and diminished superior visual fields, which may interfere with activities of daily living.

2.2. Analysis of Current Treatment Options

There are currently no marketed drugs approved for the treatment of blepharoptosis. Current treatment options for ptosis employ various surgical procedures based on the degree of ptosis.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Oxymetazoline HCL has been approved for marketing in four formulations. Ocular formulations include Ocuclear (NDA 18471) which has been discontinued and Visine L.R. (NDA 19407) which is now over the counter. Both are 0.025% concentrations. Kovanaze (NDA 208032). is a combination product with tetracaine which is approved as a nasal spray. RevitaLid states it is relying on FDA's prior finding of clinical safety for the reference listed drug Rhofade (oxymetazoline cream, 1%) (NDA 208552) with regard to the potential for RVL-1201 to induce genotoxicity, carcinogenicity, and reproductive and developmental toxicity. Rhofade is a dermatological product indicated for the treatment of persistent facial erythema associated with rosacea.

3.2. Summary of Presubmission/Submission Regulatory Activity

12/31/2012 – Initial IND submitted to the Agency
06/19/2014 – End-of-phase 2 meeting
08/24/2018 – Agreed Initial Pediatric Study Plan (iPSP) for partial waiver for all pediatric ages 0 to < 9 years old
06/03/2019 – Pre-NDA meeting

3.3. Foreign Regulatory Actions and Marketing History

RVL-1201has not been approved for marketing.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

N/A – inspections were not conducted as part of this NDA. Investigators with the highest enrollment have been investigated in the recent past.

4.2. Product Quality

The drug product, oxymetazoline HCl ophthalmic solution, 0.1% is a clear, colorless to slightly yellow, aseptically prepared, preservative-free, sterile solution filled into clear, unit dose, (b) (4) single-use containers. The osmolality range of the solution is (b) (4) mOsm/kg, and the pH is adjusted to 5.8-6.8.

Final Formulation Composition

Ingredient	Function	Concentration (mg/mL)
Oxymetazoline Hydrochloride, USP	Active Ingredient	1.00
Sodium Chloride, USP	(b) (4)	(b) (4)
Potassium Chloride, USP		
Calcium Chloride, (b) (4) USP		
Magnesium Chloride (b) (4) USP		
Sodium Acetate (b) (4), USP		
Sodium Citrate, NF		
Hypromellose, USP (b) (4)		
Hydrochloric Acid, NF	pH Adjuster	To adjust pH to (b) (4)
Water for Injection, USP	(b) (4)	q.s.*

(b) (4)

* q.s. – as much as is sufficient.

See Product Quality review for further details.

4.3. Clinical Microbiology

N/A – this is not an anti-infective product.

4.4. Nonclinical Pharmacology/Toxicology

Oxymetazoline systemic exposure after ocular administration of RVL-1201 was substantially lower than that after topical administration of Rhofade; therefore, the Sponsor relied on the Agency's prior finding of nonclinical safety for Rhofade to support this 505(b)(2) application. See Section 4.5. RevitaLid states it is relying on FDA's prior findings of safety for the listed drug Rhofade with regard to the potential for RVL-1201 to induce genotoxicity, carcinogenicity, and reproductive and developmental toxicity.

4.5. Clinical Pharmacology

Summary of Pharmacokinetic Parameters Following Ocular and Topical Administration of Oxymetazoline to Healthy Male and Female Volunteers, Study RVL-1201-PKP01

Parameter	Treatment A: RVL-1201				Treatment B: RHOFADE			
	n	Mean	SD	CV%	n	Mean	SD	CV%
tmax (h)[a]	23	2.00 (0.500 – 12.0)			23	16.0 (8.00 – 24.0)		
Cmax (pg/mL)	23	30.5	12.7	41.8	23	47.6	28.3	59.5
AUC0-tldc (h*pg/mL)	23	400	188	47.1	23	1080	686	63.3
AUCinf (h*pg/mL)	19	468	214	45.7	9	950	476	50.1
kel (h^{-1})	21	0.0841	0.0190	22.6	20	0.0616	0.0148	24.1
t½ (h)[b]	21	8.25	-	-	20	11.3	-	-

AUC0-tldc: area under the plasma concentration-time curve (AUC) from time 0 to the time of the last detectable concentration; AUCinf: AUC from time 0 to infinity; Cmax: maximum plasma concentration; kel: terminal phase rate constant; t½: terminal phase half-life; tmax: time of occurrence of Cmax
Treatment A: one drop of RVL-1201 (oxymetazoline HCl ophthalmic solution, 0.1%) to each eye (Test)
Treatment B: 0.3 g RHOFADE (oxymetazoline HCl, 1%) cream applied to the entire face (Reference)
Note: PK parameters are presented as arithmetic mean, standard deviation (SD), and CV% unless otherwise noted.
AUCinf values with extrapolation > 20% were excluded from summary statistics.
[a] tmax is presented as median (min – max)
[b] t½ is presented as harmonic mean

Source data: Study RVL-1201-PKP01 CSR, Table 14.4.2

See Clinical Pharmacology review for further details.

4.6. Devices and Companion Diagnostic Issues

Not applicable to this application.

4.7. Consumer Study Reviews

Not applicable to this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study Type	Study No.: (eCTD Section)	Study Objective(s)	Study Design Type of Control	Test Product; Dosing Regimen; Route of Administration	Number Enrolled; Healthy Volunteers or Diagnosis of Patients	Duration of Treatment	Study Status; Report Type
BA	RVL-1201-PKP01 (5.3.1.2)	To characterize oxymetazoline bioavailability following ocular administration of RVL-1201 and RHOFADE™ (oxymetazoline hydrochloride) Cream 1% administered transdermally over the entire face in healthy volunteers	Randomized, Open-label Single-center, Single-dose, Two-treatment, Two-period, Two-sequence, Crossover Phase 1	Treatment A (test): one drop of RVL-1201 (lot R80261) per eye Treatment B (reference): 0.3 g Rhofade (oxymetazoline HCl) cream (lot MFBD) 1% applied to the face	24 healthy volunteers: non-smoking, males and females, 18-45 years of age	Single-dose	Completed; Full
Efficacy and Safety	RVL-1201-001 (5.3.5.1)	To demonstrate efficacy and safety of two dosing regimens of RVL-1201 in the treatment of acquired blepharoptosis	Randomized, Placebo-controlled Double-masked, Multi-center, Parallel-design Phase 2	Three treatment groups: RVL-1201 QD: one drop of RVL-1201 (lot 1680614) per eye in the morning; and then one drop of vehicle (lot 1680615) per eye in the afternoon RVL-1201 BID: one drop of RVL-1201 (lot 1680614) per eye twice a day (BID) Placebo BID: one drop of vehicle (lot 1680615) per eye twice a day (BID)	46 blepharoptosis patients: Males and females ≥ 18 years of age with acquired ptosis RVL-1201 QD: 15 RVL-1201 BID: 16 Placebo BID: 15	RVL-1201 QD: 1 x14 days or RVL-1201 BID: 2 x 14 days or Placebo BID: 2 x 14 days	Completed; Full
Efficacy and Safety	RVL-1201-201 (5.3.5.1)	To evaluate the efficacy of RVL-1201 in the treatment of acquired blepharoptosis and to assess the safety and	Randomized in 2:1 ratio, Placebo-controlled Double-masked,	Treatment A: one drop of RVL-1201 (lot RD427) to each eye once daily (QD) in the morning	140 blepharoptosis patients: Males and females ≥ 18 years of age with	1 x 42 days (6 weeks)	Completed; Full

Study Type	Study No.: (eCTD Section)	Study Objective(s)	Study Design Type of Control	Test Product; Dosing Regimen; Route of Administration	Number Enrolled; Healthy Volunteers or Diagnosis of Patients	Duration of Treatment	Study Status; Report Type
		tolerability of RVL-1201	Multi-center, Parallel design Phase 3	Treatment B: one drop of placebo (vehicle) (lot RD425) to each eye once daily (QD) in the morning	acquired ptosis RVL-1201: 94 Placebo: 46		
Efficacy and Safety	RVL-1201-202 (5.3.5.1)	To evaluate the efficacy of RVL-1201 in the treatment of acquired blepharoptosis at 2 weeks and to assess the safety of RVL-1201	Randomized in 2:1 ratio, Placebo-controlled Double-masked, Multi-center, Parallel design Phase 3	Treatment A: one drop of RVL-1201 (R80261) in each eye once daily (QD) in the morning Treatment B: one drop of placebo (vehicle) (lot R80251) in each eye once daily (QD) in the morning	164 blepharoptosis patients: Males and females ≥ 9 years of age with acquired ptosis RVL-1201: 109 Placebo: 55	1 x 42 days (6 weeks)	Completed; Full
Safety	RVL-1201-203 (5.3.5.1)	To demonstrate safety of RVL-1201 in the treatment of acquired blepharoptosis	Randomized in 2:1 ratio, Placebo-controlled Double-masked, Multi-center, Parallel design Phase 3	Treatment A: one drop of RVL-1201 (lot R80261) in each eye once daily (QD) in the morning Treatment B: one drop of placebo (vehicle) (lot R80251) in each eye once daily (QD) in the morning	225 blepharoptosis patients Males and females ≥ 9 years of age with acquired ptosis RVL-1201: 150 Placebo: 75	1 x 84 days (6 weeks) (12 weeks)	Completed; Full

RVL-1201 is code name for oxymetazoline hydrochloride ophthalmic solution, 0.1%.

5.2. Review Strategy

Safety and efficacy for oxymetazoline was supported by two clinical studies RLV-1201-201 and RLV-1201-202. Additional data from study RLV-1201-203 was reviewed to support safety.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. [Study RVL-1201-201]

6.1.1. Study Design

Overview and Objective

The objective of this study was to evaluate the efficacy of RVL-1201 Ophthalmic Solution in the treatment of acquired blepharoptosis and to assess the safety and tolerability of RVL-1201 for a dosing period of 6 weeks.

Trial Design

This was a Phase 3, randomized, multicenter, double-masked, placebo-controlled study designed to evaluate the safety and efficacy of once daily (QD) RVL-1201 compared to Vehicle (placebo) for the treatment of acquired blepharoptosis (ptosis).

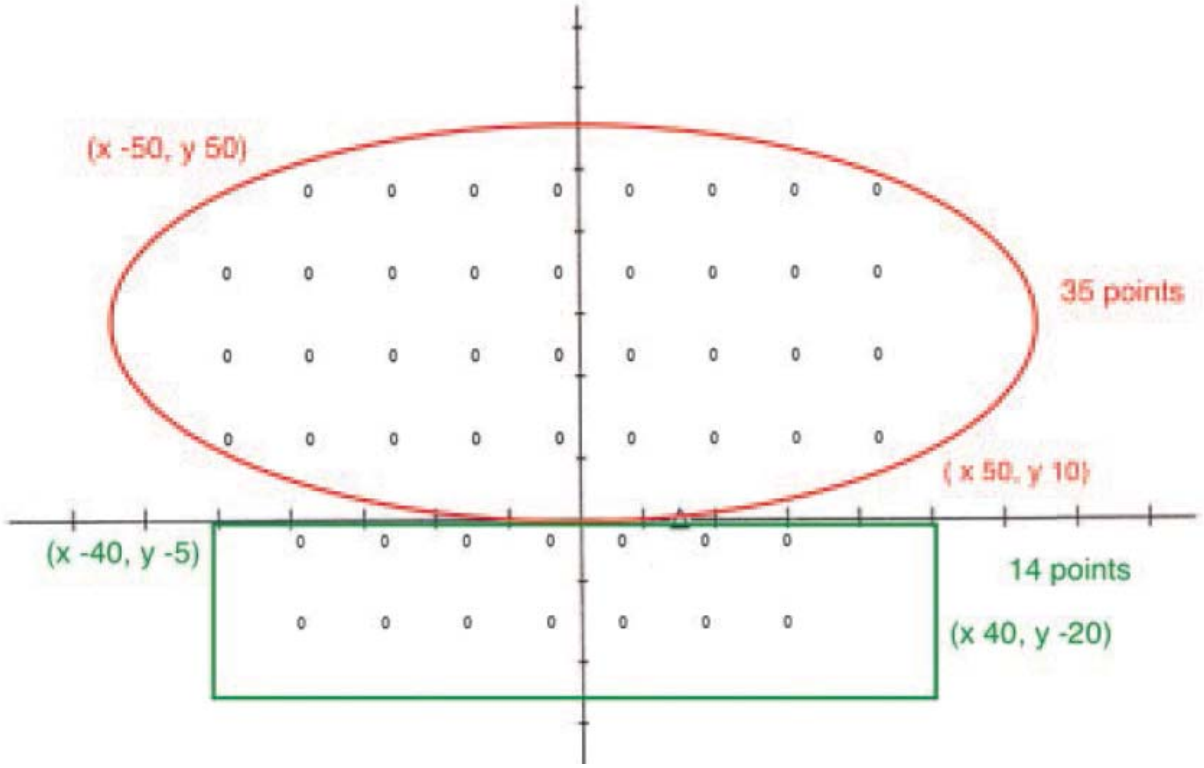
Subjects with acquired ptosis were enrolled and had to have the same qualifying eye at Screening and Baseline with visual field loss on Leicester Peripheral Field Test (LPFT) of ≥ 8 points in the top 2 rows and able to see ≥ 9 total points in the top 4 rows; *and* the distance from the central pupillary light reflex to the central upper lid margin (MRD1) ≤ 2.5 mm; *and* corrected Snellen visual acuity (VA) of ≥ 20/80. Eligible subjects were randomized in a 2:1 ratio to one of two treatment arms and treated for 42 days:

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

Both eyes were treated and followed, but the more ptotic eye (the eye with the smaller marginal reflex distance (MRD1) was deemed the study eye. If the MRD1 was the same in both eyes, the eye with the greater visual field deficit (the lower LPFT Total Score [based on number of points seen in the top 4 rows]) was the study eye. If the MRD1 and LPFT were the same in both eyes, the right eye was the study eye.

Efficacy assessments were the LPFT (performed using the Humphrey Visual Field Analyzer [Carl Zeiss Meditec, Inc]) and photographic measurement of MRD1 and palpebral fissure distance (PFD). All assessments were conducted bilaterally except the LPFT, which was study eye only beginning with Day 1 (Baseline/Randomization).

Leicester Peripheral Field Test Grids



Schedule of Procedures, Study RVL-1201-201

Assessment	Screening Day -7 to -3		Baseline/ Randomization/First Dose Day 1				End: Period 1 Day 14 (± 3 Days)/				End: Period 2 Day 42 (± 3 Days)	Early Discontin-uation
Visit	**1**		**2**				**3**				**4**	
Hour (± 30 minutes)	**0**	**6**	**0**	**2**	**6**	**8**	**0**	**2**	**6**	**8**		
Informed consent	X											
Demographics/medical/ocular history	X											
Urine pregnancy test[a]	X										X	X
Prior/concomitant medications	X		X				X				X	X
Blood pressure/heart rate[b]	X		X	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)[c]	X		X	X	X	X	X	X	X	X	X	X
Palpebral fissure distance (OU)[c]	X		X	X	X	X	X	X	X	X	X	X
Pupil diameter measurement (OU)[c]	X		X	X	X	X	X	X	X	X	X	X
Leicester Peripheral Field Test[d]	X[e]	X[e]	X[e]		X[ef]			X[ef]				
Snellen visual acuity (OU)[g]	X		X			X	X			X	X	X
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									
Dispense/administer study medication[i]			X				X			X		
Comfort assessment											X	X
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X
Study medication accountability							X[j]				X	X

LPFT = Leicester Peripheral Field Test; MRD = marginal reflex distance; OU = Both eyes; PFD = palpebral fissure distance; QD = once daily; VA = visual acuity

[a] Women of childbearing potential only.

[b] Resting blood pressure and heart rate were taken seated after 5 minutes rest.

[c] MRD, PFD, and pupil diameter were measured from external photographs.

[d] LPFT was conducted bilaterally at Screening (Visit 1). All other LPFT examinations were conducted unilaterally on the study eye. For subjects with surgical monovision correction, a neutralizing trial lens could have been put in the lens holder located in front of the chin rest.

[e] Clinical site staff were to instruct the subjects to keep their chin and forehead against the chin and forehead rests, and to keep their brows relaxed. Clinical site staff also were to instruct the subjects to look at the fixation point throughout the test.

[f] The LPFT assessment was to be performed approximately 6 hours post administration of study medication at Visit 2 (Day 1), and approximately 2 hours post administration of study drug at Visit 3 (Day 14). This requirement superseded the order of procedures shown in the table above and in the protocol text in Section 10.2.1 and 10.2.2 (Appendix 16.1.1, Protocol Amendment 3).

[g] If the corrected or uncorrected VA was 20/80 or better, no additional refraction was necessary. If corrected or uncorrected VA was worse than 20/80, then an updated refraction had to be performed. This refraction was to be used for all VA assessments during the study. The subject had to wear the same glasses, if applicable, at each visit. For subjects with surgical monovision correction, VA assessment could have been 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) was to be used for this exam. Phenylephrine hydrochloride (Neosynephrine) was NOT to be used.

[i] Study medication was dispensed at Visit 2 (Day 1) and Visit 3 (Day 14); study medication was administered by the subject at the study site on Visit 2 (Day 1) and Visit 3 (Day 14) at Hour 0. Subjects were to be instructed not to dose before coming for Visit 3 (Day 14); if the subject had dosed, the visit was to be rescheduled. Otherwise subjects (or caregivers, if the subject was not able to self-administer the medication) administered study medication QD in the morning at home daily. Note: Contact lenses had to be removed prior to instillation of study medication and were not to be reinserted for at least 15 minutes after study medication instillation. Contact lenses were not to be worn during study visits. At Visits 3 (Day 14) and 4 (Day 42), subjects brought all study medication materials to the study site, at which time study medication accountability was performed. Study medication Box 1 was collected at Visit 3 (Day 14), and retained at the site. Study medication Box 2 was dispensed on Visit 3 (Day 14) and returned to the site on Visit 4 (Day 42), the last day of dosing.

[j] Study medication accountability procedures were performed AFTER the Hour 0 dose was administered at the study site.

Inclusion Criteria

For inclusion into the trial, subjects were required to fulfill all of the following criteria:

1. Male or female subjects 18 years of age and older.
2. Presence of all of the following at Screening:
   a. Loss on a reliable LPFT of ≥ 8 points in the top 2 rows (LPFT Eligibility Score); subjects had to see at least 9 total points in the top 4 rows (LPFT Total Score).
      i. This criterion had to be met in both the V1H0 and V1H6 LPFT assessments
      ii. There had to 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 of 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. This criterion had to be met in the V2H0 LPFT assessment.
      ii. There had to 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, ≤ 2 mm (no visible central pupillary light reflex defaults to 0) in the same eye as Inclusion Criterion #2; AND
   c. Snellen VA of 20/80 or better in the same eye as Inclusion Criteria #2a and #2b
4. Female subjects were 1-year postmenopausal, surgically sterilized, or women of childbearing potential with a negative urine pregnancy test at Visit 1. Women of childbearing potential had to use an acceptable form of contraception throughout the study. Acceptable methods included 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. Able to self-administer study medication or to have the study medication administered by a caregiver throughout the study period.
6. Subjects had to be able to understand and sign an IRB-approved ICF prior to participation in any study-related procedures.

Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the trial:

In either eye

1. Congenital ptosis.
2. Presence of either of the following:
    a. Pseudoptosis (upper eyelid dermatochalasis that overhung the upper eyelid margin);

OR

    b. Dermatochalasis that extended less than 3 mm above the upper eyelid margin.
3. Horner syndrome.
4. Marcus Gunn jaw winking syndrome.
5. Myasthenia gravis.
6. Mechanical ptosis, including ptosis due to orbital or lid tumor, cicatricial processes affecting the movements of the upper lid, and enophthalmos.
7. Previous ptosis surgery (previous blepharoplasty [only] was allowed provided the surgery took place > 3 months prior to Visit 1).
8. Lid position affected by lid or conjunctival scarring.
9. Visual field loss from any cause other than ptosis.
10. History of herpes keratitis.
11. History of closed/narrow angle glaucoma (unless patent peripheral iridotomy was performed > 3 months prior to Visit 1).
12. Periocular neurotoxin (e.g., Botox, Xeomin, Dysport, Myobloc) injections within 3 months prior to Visit 1 and during the study.
13. Topical application of bimatoprost (i.e., Latisse) to the eyelashes within 7 days prior to Visit 1 and during the study.
14. Use of topical ophthalmic medications (including anti-allergy [e.g., antihistamines], dry eye [i.e., Restasis] 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 IOP were permitted if dosed in the evening in accordance with the approved prescribing information. All other topical antiglaucoma medications were prohibited.
15. Intravitreal injections (e.g., Lucentis, Eylea, Avastin, Triesence) within 7 days prior to Visit 1 and during the study.
16. Current punctal plugs or placement of punctal plugs during the study.

17. Use of 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 were allowed.
18. History of thyroid eye disease (i.e., exophthalmos, upper eyelid retraction, diplopia secondary to extraocular muscle involvement). Hypothyroidism that was controlled on medication was allowed.

General

19. Resting HR outside the normal range (60–100 beats per minute).
20. Hypertension with resting diastolic BP > 105 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. Patients with diabetic retinopathy could not be enrolled. However, patients with insulin dependent diabetes, diabetes requiring oral hypoglycemic drugs, or diet controlled diabetes were allowed.
24. Pregnancy or lactation.
25. Diagnosed benign prostatic hypertrophy requiring medicinal therapy; previous prostatectomy was allowed.
26. History of contact or systemic allergic reaction to oxymetazoline or other sympathomimetic drugs (e.g., phenylephrine, pseudoephedrine, ephedrine, ropanolamine, fepradinol, or methoxamine).

Study Endpoints

Efficacy

Primary

The mean increase from baseline (Day 1, Hour 0) in number of points seen on the LPFT at:

1. Hour 6 on Visit 2 (Day 1) in the study eye.
2. Hour 2 on Visit 3 (Day 14) in the study eye.

Exploratory

The change from baseline in MRD and PFD at all applicable post-dosing time points

Safety

Safety of RVL-1201 was compared to vehicle with analysis of safety variables including ophthalmic safety assessments (VA, SLE/CF, PD, dilated ophthalmoscopy/fundus examination, and tonometry), vital signs (BP/HR), and AEs. Comfort of study medication was rated by the subject.

Statistical Analysis Plan

A hierarchical analysis was conducted to compare RVL-1201 QD against vehicle (placebo) QD for the ordered primary efficacy endpoints:

Primary efficacy analysis was conducted on the intent-to-treat (ITT) population (all randomized subjects). Analysis was also conducted on the per protocol population (those subjects in the ITT population who had no major protocol violations). Safety analyses was performed using the safety analysis set (all randomized subjects who received at least one dose of the randomized study medication).

The efficacy endpoints were tested sequentially in the order specified. For a claim of statistical significance, the null hypothesis and all higher ordered null hypotheses must be rejected, i.e., the first time point was tested and if $P < 0.05$, the second time point was tested at a significance level of 0.05. Thus, both of the hypotheses in the hierarchy were tested against placebo at a significance level of 0.05.

Protocol Amendments

There were three protocol amendments during the study. The original protocol was issued 12 December 2014, Protocol Amendment 1 was issued 12 March 2015, Protocol Amendment 2 was issued 15 July 2015, and Protocol Amendment 3 was issued 30 November 2015

Key changes in study conduct per Protocol Amendment 1:

- Exclusions based on use of maprotiline, selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants were removed.
- Exclusions based on history of myocardial infarction, angina, arrhythmia, or irregular pulse were removed.
- Exclusions were added for congenital ptosis, and use of periocular neurotoxins, topical application of bimatoprost, and topical ophthalmic medications at specified intervals prior to Screening and during the study.
- Clarification was added to specify that blepharoplasty > 3 months from Visit 1 was allowed, placement of punctal plugs was not allowed, only non-preserved artificial tears were allowed, history of CVA was an exclusion, and that previous prostatectomy was allowed.

Key changes in study conduct per Protocol Amendment 2:

- Revised inclusion criteria allowed 4 points of variance between LPFT tests (instead of 3 points of variance, which had proven too narrow a margin), and specified that this was between specified LPFT Eligibility Scores, not LPFT Total Scores.
- The washout period was eliminated so those subjects who had taken prohibited medication within the specified timeframe were not permitted to enter the study; therefore, the screening visit could be held within 3 to 7 days prior to baseline (Day 1) instead of 7 to 14 days prior to baseline.
- The definition of dermatochalasis sufficient for exclusion was changed from dermatochalasis that extended less than 9-10 mm above the upper eyelid margin to dermatochalasis that extended less than 3 mm above the upper eyelid margin.

Key changes in study conduct per Protocol Amendment 3:

- The inclusion criterion requirement for Snellen VA of 20/40 was changed to 20/80.
- An exclusion criterion was added for intravitreal injections
- Several exclusion criteria were revised:
    - Evening dosing of topical ophthalmic prostaglandin analogues in accordance with approved prescribing information was allowable but administration of any other topical antiglaucoma medications during the study continued to be prohibited.
    - Contact lens wear during the study was allowed if lenses were not worn when RVL-1201 was administered or during study visits.
    - Use of systemic beta-blockers was allowed as it was determined this did not pose a safety concern with once daily dosing of RVL-1201 (oxymetazoline).
    - Patients with hypothyroidism controlled on medication could be considered for enrollment, since it was determined that only hyperthyroidism or thyroid eye disease would pose a safety or efficacy concern.

None of the protocol amendments affected the interpretation of the trial results.

6.1.2. **Study Results**

Compliance with Good Clinical Practices

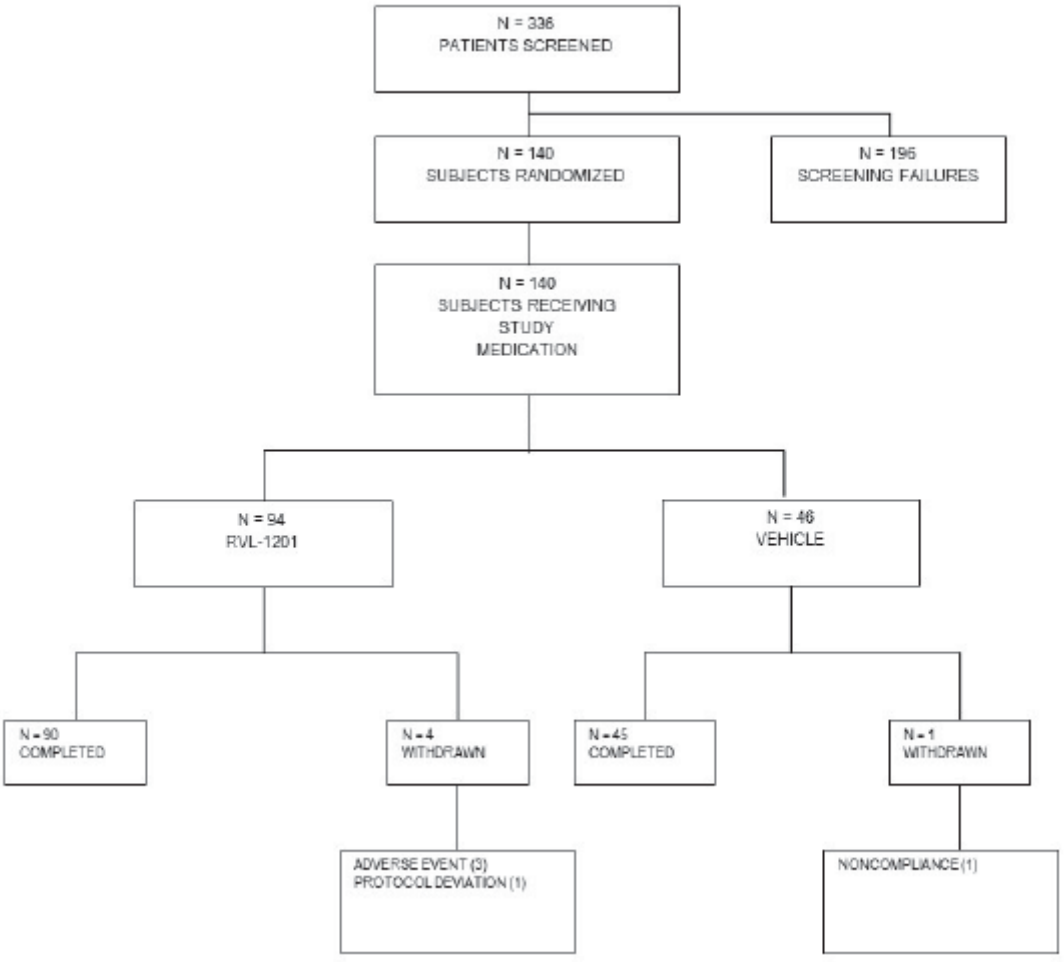
The study was conducted according to all stipulations of the protocol, including all statements regarding confidentiality, to the ethical principles that have their origin in the Declaration of Helsinki, and in compliance with Good Clinical Practice (GCP), International Council for Harmonization (ICH) guidelines, and all applicable US federal regulations and local legal and regulatory requirements.

Financial Disclosure

The sponsor of this NDA certifies that they have not entered into any financial arrangement with the listed clinical investigators and that no investigators of disclosed financial interest with the company. See Appendix 14.2.

Patient Disposition

A total of 336 subjects were screened, of which 140 subjects were randomized and participated in the study from 29 May 2015 (first subject randomized) to 24 Oct 2016 (last subject completed); there were 94 subjects in the RVL-1201 group and 46 subjects in the Vehicle group.



Ref: CSR page 36 Fig2

Discontinued Patients

Treatment Arm	Subject ID	Reason for Discontinuation
RVL-1201	(b) (6)	Protocol deviation – non-compliant with dosing and visits
	(b) (6)	Adverse event – eye irritation and hyperemia
	(b) (6)	Adverse event – eyelid edema
	(b) (6)	Adverse event – instillation site pain and headache
Vehicle	(b) (6)	Noncompliance – patient stopped dosing during trial

Source – CSR Appendix 16.2.1.1

Protocol Violations/Deviations

Protocol deviations were reported for 84 subjects and were balanced between the treatment groups (RVL-1201: 59, Vehicle: 25). The majority of protocol deviations were for not returning all dispensed study medication materials.

Deviation Type	RVL-1201 N = 94 n (%)	Vehicle N = 46 n (%)
Study medication	43 (45.7)	20 (43.5)
Visit procedures	27 (28.7)	10 (21.7)
Visit windows	9 (9.6)	4 (8.7)
Inclusion/exclusion	4 (4.3)	2 (4.3)
Randomization	1 (1.1)	0
Concomitant medications	0	2 (4.3)

ITT = intent-to-treat

Ref. CSR page 38 table 4

Table of Demographic Characteristics

Parameter	RVL-1201 N = 94	Vehicle N = 46	Overall N =140
Age			
Mean (SD)	64.7 (12.22)	63.2 (12.45)	64.2 (12.28)
Median	68.0	65.5	67.0
Min, Max	22, 83	26, 85	22, 85
Sex, n (%)			
Female	74 (78.7)	32 (69.6)	106 (75.7)
Male	20 (21.3)	14 (30.4)	34 (24.3)

Parameter	RVL-1201 N = 94	Vehicle N = 46	Overall N =140
Race, n (%)			
White	78 (83.0)	42 (91.3)	120 (85.7)
Black	12 (12.8)	3 (6.5)	15 (10.7)
Asian	2 (2.1)	1 (2.2)	3 (2.1)
American Indian	2 (2.1)	0	2 (1.4)
Ethnicity, n (%)			
Not Hispanic/Latino	74 (78.7)	35 (76.1)	109 (77.9)
Hispanic/Latino	20 (21.3)	11 (23.9)	31 (22.1)

ITT = intent-to-treat; Min, Max = minimum, maximum; SD = standard deviation

Ref: CSR page 39 Table 5

The overall age and sex characteristics of the subjects enrolled in this study is consistent with the demographics of acquired blepharatosis.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

		RVL-1201 (N=94)	Vehicle (N=46)
Iris Color	Blue	23(24.5%)	14(30.4%)
	Brown	55(58.5%)	22(47.8%)
	Green	4(4.3%)	1(2.2%)
	Hazel	12(12.8%)	9(19.6%)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was measured by counting the returned study medication and comparing it to the amount of dispensed study medication.

% Compliance	RVL-1201 (N = 94)	Vehicle (N = 46)
n	93	46
Mean	97.4	95.7
SD	11.85	15.02
Min, Max	0, 122	0, 103

ITT = intent-to treat; Max = maximum; Min = minimum; SD = standard deviation

Ref. CSR page 40 table 6

There was a high degree of patient compliance throughout the study.

Data Quality and Integrity

Inspections were not be conducted as part of this NDA. Investigators of interest have been investigated in the recent past. There were not data integrity issues uncovered during the review of this NDA.

Efficacy Results – Primary Endpoint

Observed and Change from Baseline in Mean Points Seen in Superior Visual Field on LPFT in the Study Eye at Primary Efficacy Time Points (ITT Population), Study RVL-1201-201

Parameter	Points Seen in Superior Visual Field		Mean Difference, *P*-Value[a] [95% CI] *P*-Value[b]
	RVL-1201 N = 94	Vehicle N = 46	RVL-1201 vs Vehicle
Mean points at baseline (SD)	17.0 (4.41)	16.9 (5.21)	–
Mean points at primary efficacy time points			
n	94	46	
Day 1, Hour 6, observed mean (SD)	22.2 (6.18)	18.4 (6.01)	
Mean change from baseline (SD)	5.2 (5.97)	1.5 (3.93)	3.67, < **0.0001**[a], [2.00, 5.34] **0.0002**[b]
n	91	46	
Day 14, Hour 2, observed mean (SD)	23.4 (5.60)	19.1 (6.13)	
Mean change from baseline (SD)	6.4 (5.04)	2.2 (5.80)	4.20, < **0.0001**[a], [2.30, 6.10] < **0.0001**[b]

CI = confidence interval; ITT = intent-to-treat; LPFT = Leicester Peripheral Field Test; SD = standard deviation
[a] *P*-value = 2-sided t-test
[b] *P*-value = Wilcoxon test

Ref: CSR page 42 Table 7

Study RLV-1201-201 met its primary efficacy endpoint. RLV-1201 is statistically superior to placebo (vehicle) and both day 1 and day 14 in the increase in the number of points seen in the superior visual field as measured using the LPFT. The PP analysis were consistent with the ITT analysis.

Efficacy Results – Secondary and other relevant endpoints

Exploratory efficacy endpoints included the change from baseline in marginal reflex distance (MRD) and palpebral fissure distance (PFD).

Mean Change from Baseline in Marginal Reflex Distance in the Study Eye (ITT Population), Study RVL-1201-201

Parameter	RVL-1201 N = 94	Vehicle N = 46
Mean MRD at baseline, mm (SD)	1.16 (0.661)	1.03 (0.678)
Mean change from baseline in MRD at primary efficacy time points, mm (SD)		
Day 1, Hour 6	n = 94 0.94 (0.924)	n = 46 0.67 (1.001)
Day 14, Hour 2	n = 91 1.09 (0.799)	n = 46 0.58 (0.875)

The results of the MRD endpoint is consistent with the primary efficacy endpoint. RLV-1201 showed greater increases in the margin reflex distance compared to placebo (vehicle). The difference is present at Day 1 and remains consistent at Day 14.

Change from Baseline in Palpebral Fissure Distance in the Study Eye (ITT Population), Study RVL-1201-201

Parameter	RVL-1201 N = 94	Vehicle N = 46
Mean PFD at baseline, mm (SD)	7.46 (1.458)	7.39 (1.329)
Mean change from baseline in PFD at primary efficacy time points, mm (SD)		
Day 1, Hour 6	n = 94 0.80 (1.014)	n = 46 0.80 (1.310)
Day 14, Hour 2	n = 91 0.96 (1.156)	n = 46 0.77 (1.397)

CI = confidence interval; ITT = intent-to-treat; PFD = palpebral fissure distance; SD = standard deviation
[a] *P*-value = 2-sided t-test
[b] *P*-value = Wilcoxon test

Ref: CSR page 44 Table 9

RLV-1201 showed a greater increase in palpebral fissure distance at day 14 but not at day 1. This is inconsistent with the results of the primary efficacy endpoint and margin reflex distance

measurement.

Dose/Dose Response

The relationship of drug dose and drug concentration to efficacy response was not evaluated in Study RVL-1201-201.

Durability of Response

Durability of the clinical effect on was not evaluated in this development program. The onset in improvement in LPFT appears to be approximately 2 hours after dosing and continues for at least 6 hours after dosing ;however, the exact duration is not known.

Persistence of Effect

Persistence of clinical effect was not evaluated in this development program.

Additional Analyses Conducted on the Individual Trial

N/A

6.2. [Study RVL-1201-202]

6.2.1. Study Design

Overview and Objective

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

Trial Design- Same as Study RVL-1201-201

Schedule of Procedures- Same as Study RVL-1201-201

Inclusion Criteria- Essentially same as Study RVL-1201-201

Exclusion Criteria- Essentially same as Study RVL-1201-201

Study Endpoints

Primary- Same as Study RVL-1201-201

Secondary

Mean observed values and change from baseline values for MRD data in the treatment regimen against placebo assessed at Day 1 (Visit 2), Day 14 (Visit 3), and at Day 42 (Visit 4)

Safety- - Same as Study RVL-1201-201

Statistical Analysis Plan

The primary efficacy endpoints were tested sequentially in the order specified: i.e., the mean change from Baseline (Day 1, Hour 0) in the treatment regimen against placebo in number of points seen in the top 4 rows on the LPFT

For a claim of statistical significance, the null hypothesis being tested, and all higher ordered null hypotheses had to be rejected, i.e., the Day 1 Hour 6 time point was tested first and if $P < 0.05$, the Day 14 Hour 2 time point was tested at a significance level of 0.05. Thus, each of the hypotheses in the hierarchy were tested within the treatment regimen against placebo at a significance level of 0.05. If the Day 1 Hour 6 endpoint was statistically significant (at the 0.05 level) but Day 14 Hour 2 was not statistically significant (at the 0.05 level), the study would still be considered positive.

If both primary efficacy endpoints (LPFT) were significant at the 0.05 significance level, then the secondary efficacy endpoints (MRD) were also tested sequentially.

Protocol Amendments

There were 3 protocol amendments during the study. The original protocol was issued 12 February 2018, Protocol Amendment 1 was issued 08 March 2018, Protocol Amendment 2 was issued 10 July 2018, and Protocol Amendment 3 was issued 09 October 2018. None of the protocol amendments contained changes to the analyses planned in the original protocol.

Change in study conduct per Protocol Amendment 1:

- The inclusion criterion related to subject age was changed from > 9 years of age" to "≥ 9 years of age" to correct a typographical error.

Key changes in study conduct per Protocol Amendment 2 included the following:

- Clarification of the definitions of LPFT Eligibility Score (as based on points missed) and LPFT Total Score (as based on points seen) and stipulation that the LPFT Total Score at Visit 1, Hour 6 was to be used by the Medical Monitor to make the study eye designation if the MRD was the same in both eyes.
- Addition of a urine pregnancy test at Baseline, in addition to the test already required at Screening.
- Clarification that only one drop should be administered to each eye daily.

- The dilated ophthalmoscopy/fundus exam at Screening was moved from Hour 0 to Hour 6 so that there was no residual effect from the dilation drops on subsequent visual field testing.

Key changes in study conduct per Protocol Amendment 3 included the following:

- The criteria for designation of the study eye were changed to stipulate that if the MRD = 0 in either eye where both eyes were eligible, the eye with the measurable MRD (≥ 0.5 mm) would be the study eye.
- Clarification that it was mandatory to repeat an unreliable LPFT (once per scheduled test).
- Several exclusion criteria were revised:
    - Presence of dermatochalasis < 3 mm or pseudoptosis was to only exclude the eye that it occurred in, not the opposing upper eyelid.
    - The resting HR range was changed from 60-100 beats per minute to 50-110 beats per minutes to allow enrollment of healthy individuals with heart rates that were normal for them and did not require treatment.
    - Study enrollment was opened to patients with stable background diabetic retinopathy, if otherwise eligible, but patients with proliferative diabetic retinopathy were ineligible for enrollment.

6.2.2. Study Results

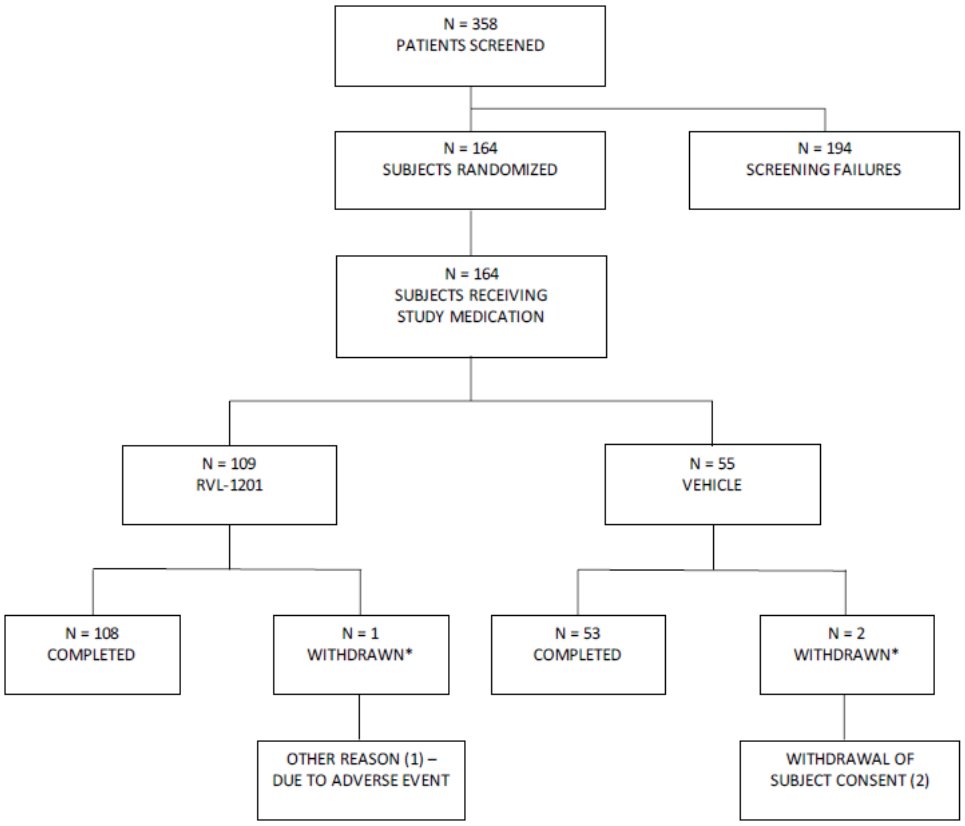
Compliance with Good Clinical Practices

The study was conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with International Council for Harmonization (ICH) guidelines, and all applicable United States (US) federal regulations and local legal and regulatory requirements.

Financial Disclosure

The sponsor of this NDA certifies that they have not entered into any financial arrangement with the listed clinical investigators. See Appendix 14.2.

Patient Disposition



Discontinued Patients

Treatment Arm	Subject ID	Reason for Discontinuation
RVL-1201	(b) (6)	Ocular discomfort OU
Vehicle	(b) (6)	Lower GI bleeding
	(b) (6)	Visit schedule conflict

Protocol Violations/Deviations

Deviation Type	RVL-1201 N = 109 n (%)	Vehicle N = 55 n (%)
Number (%) of subjects with at least one protocol deviation	80 (73.4%)	46 (83.6%)
Protocol Deviations		
IP Accountability issue	34 (31.2%)	22 (40.0%)
Study visit procedure performed outside specified window	26 (23.9%)	20 (36.4%)
Visit outside specified window	16 (14.7%)	9 (16.4%)
Other	16 (14.7%)	4 (7.3%)
Subject does not comply with all inclusion/exclusion criteria	13 (11.9%)	5 (9.1%)
Study visit procedure not performed	13 (11.9%)	4 (7.3%)
Study visit procedure(s) was/were not followed per protocol	12 (11.0%)	5 (9.1%)
Prohibited Medication taken	2 (1.8%)	1 (1.8%)
Informed Consent issue	1 (0.9%)	0
Study Drug not received as assigned*	0	1 (1.8%)

ITT – Intent to treat
IP – Investigative produce
* Subject (b) (6) (Vehicle) reported to the site for Visit 3 and was dispensed Visit 2 kit in error; the subject received the correct treatment but the wrong visit kit. One vial was dispensed from this kit. Per Sponsor, the visit was halted and re-scheduled for one week later, and a new kit was dispensed to the subject. The subject received vehicle throughout the study as per protocol and the randomization schedule.
Ref. CSR page 38 Table 4

Eleven subjects with major protocol deviations were excluded from the PP analysis population, including 10 subjects receiving RVL-1201 (Subjects (b) (6) and 1 subject receiving Vehicle (Subject (b) (6)

The majority of protocol deviations were for not returning all dispensed study medication materials and for visits/procedures performed outside of the specified window.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was measured by counting the returned study medication and comparing it to the amount of dispensed study medication.

	RVL-1201 (N=109)	Vehicle (N=55)
% Compliance	99	99
SD	4.5	4.4

There was a high degree of patient compliance throughout the study.

Data Quality and Integrity

Inspections were not be conducted as part of this NDA. Investigators with the highest enrollment have been investigated in the recent past. There were not data integrity issues uncovered during the review of this NDA.

Demographic Characteristics for Study RVL-1201-202 (ITT Population)

Parameter	RVL-1201 N = 109	Vehicle N = 55	Overall N =164
Age			
Mean (SD)	63.6 (14.31)	63.3 (16.51)	63.5 (15.03)
Median	67.0	67.0	67.0
Min, Max	20, 92	14, 85	14, 92
Sex, n (%)			
Female	77 (70.6%)	39 (70.9%)	116 (70.7%)
Male	32 (29.4%)	16 (29.1%)	48 (29.3%)
Race, n (%)			
White	99 (90.8%)	50 (90.9%)	149 (90.9%)
Black	6 (5.5%)	3 (5.5%)	9 (5.5%)
Asian	4 (3.7%)	2 (3.6%)	6 (3.7%)
Ethnicity, n (%)			
Not Hispanic/Latino	96 (88.1%)	49 (89.1%)	145 (88.4%)
Hispanic/Latino	13 (11.9%)	6 (10.9%)	19 (11.6%)
Iris Color OD			
Brown	46 (42.2%)	18 (32.7%)	64 (39.0%)
Blue	40 (36.7%)	18 (32.7%)	58 (35.4%)
Hazel	15 (13.8%)	15 (27.3%)	30 (18.3%)
Green	7 (6.4%)	3 (5.5%)	10 (6.1%)
Grey	1 (0.9%)	1 (1.8%)	2 (1.2%)
Iris Color OS			
Brown	47 (43.1%)	18 (32.7%)	65 (39.6%)
Blue	40 (36.7%)	18 (32.7%)	58 (35.4%)
Hazel	15 (13.8%)	15 (27.3%)	30 (18.3%)
Green	6 (5.5%)	3 (5.5%)	9 (5.5%)
Grey	1 (0.9%)	1 (1.8%)	2 (1.2%)

ITT = intent-to-treat; Min, Max = minimum, maximum; SD = standard deviation
OD = right eye, OS = left eye

Ref. CSR page 41 Table 5

The overall age and sex characteristics of the subjects enrolled in this study is consistent with the demographics of acquired blepharatosis.

Efficacy Results – Primary Endpoint

Observed and Change from Baseline in Mean Points Seen in Superior Visual Field on LPFT in the Study Eye at Primary Efficacy Time Points (ITT Population), Study RVL-1201-202

Parameter	Points Seen in Superior Visual Field		Mean Difference, *P*-Value[a] [95% CI] *P*-Value[b]
	RVL-1201 N = 109	Vehicle N = 55	RVL-1201 vs Vehicle
Mean points at baseline (SD)	17.6 (4.92)	17.6 (5.48)	–
Mean points at primary efficacy time points			
n	109	55	
Day 1, Hour 6, observed mean (SD)	23.9 (6.67)	19.7 (6.16)	
Mean change from baseline (SD)	6.3 (6.72)	2.1 (4.28)	4.23, < **0.0001**[a], [2.36, 6.09] < **0.0001**[b]
n	109	53	
Day 14, Hour 2, observed mean (SD)	25.3 (6.35)	20.0 (5.84)	
Mean change from baseline (SD)	7.7 (6.41)	2.4 (5.26)	5.30, < **0.0001**[a], [3.45, 7.14] < **0.0001**[b]

CI = confidence interval; ITT = intent-to-treat; LPFT = Leicester Peripheral Field Test; SD = standard deviation
[a] *P*-value = 2-sided t-test from an ANCOVA model with treatment as a fixed factor and baseline score as a covariate
[b] *P*-value = Wilcoxon rank sum test

Study RLV-1201-202 met its primary efficacy endpoint. RLV-1201 is statistically superior to placebo (vehicle) and both day 1 and day 14 in the increase in the number of points seen in the superior visual field as measured using the LPFT. The PP analysis were consistent with the ITT analysis.

Efficacy Results – Secondary and other relevant endpoints

The secondary efficacy endpoint was the change from baseline in MRD at all post-dosing time points.

Mean Change from Baseline in Marginal Reflex Distance in the Study Eye (ITT Population), Study RVL-1201-202

Parameter	RVL-1201 N = 109	Vehicle N = 55	Mean Difference, *P*-Value[a] [95% CI] *P*-Value[b] RVL-1201 vs Vehicle
Mean MRD at baseline, mm (SD)	1.04 (0.735)	1.07 (0.697)	–
Mean change from baseline in MRD at primary efficacy time points, mm (SD)			
Day 1, Hour 6	n = 109 0.98 (0.867)	n = 55 0.35 (0.567)	0.61, < 0.0001[a], [0.37, 0.86] < 0.0001[b]
Day 14, Hour 2	n = 109 1.22 (0.926)	n = 53 0.43 (0.734)	0.78, < 0.0001[a], [0.50, 1.06] < 0.0001[b]

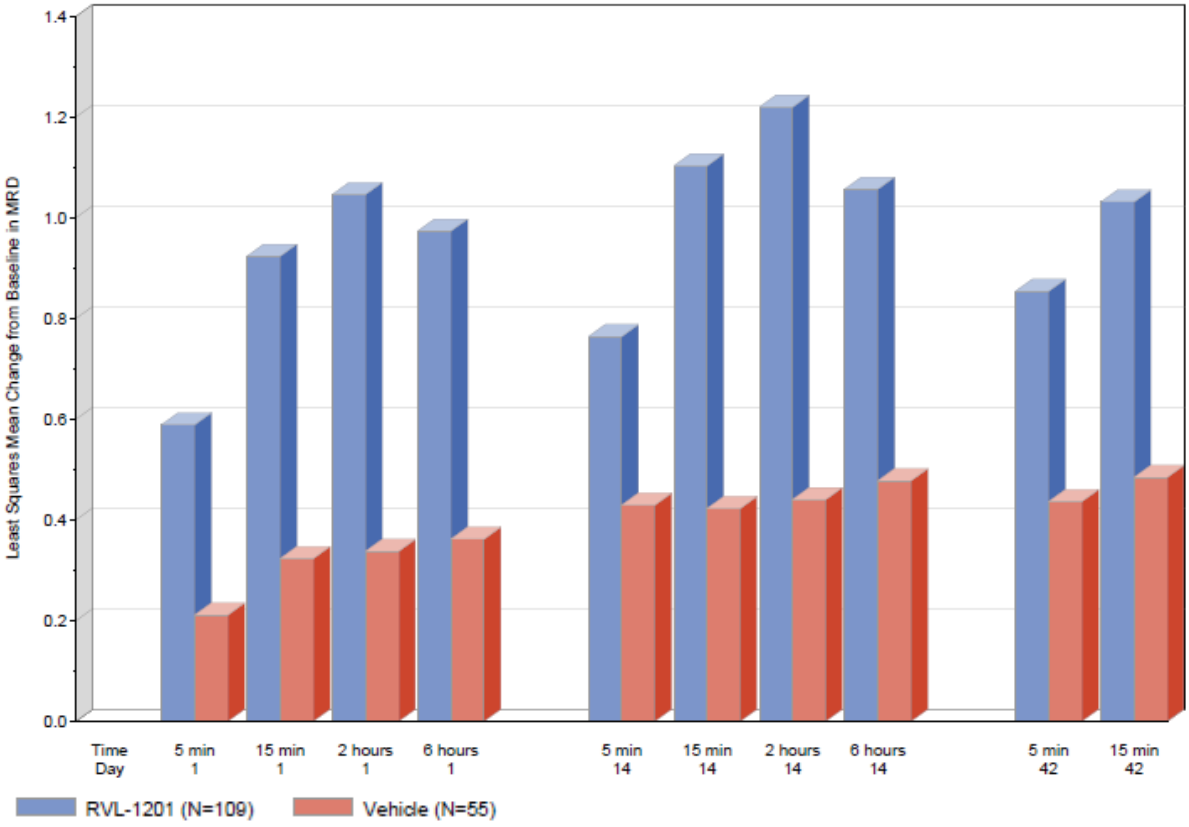
Ref. CSR page 45 Table 8

The results of the MRD endpoint is consistent with the primary efficacy endpoint. RLV-1201 is statistically superior to placebo (vehicle) for increase in the margin reflex distance. The difference is present at Day 1 and remains consistent at Day 14.

Dose/Dose Response

The relationship of drug dose and drug concentration to efficacy response was not evaluated in Study RVL-1201-201.

Summary of Least Squares Mean Change from Baseline in MRD in the Study Eye (ITT Population), Study RVL-1201-202



Ref. CSR page 46 Figure 4

RLV-1201 continues to show a positive effect on margin reflex distance at 6 weeks.

Durability of Response

Durability of the clinical effect on was not evaluated in this development program. The onset in improvement in LPFT appears to be approximately 2 hours after dosing and continues for at least 6 hours after dosing; however, the exact duration is not known.

Persistence of Effect

Persistence of clinical effect was not evaluated in this development program.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The data from studies RVL-1201-201 and RVL-12-1-202 establishes the efficacy of oxymetazoline HCL ophthalmic solution in the treatment of acquired blepharoptosis. See Section 6.0 of this review for the review of effectiveness for these trials.

7.2. Integrated Assessment of Effectiveness

Study RLV-1201-201 and RLV-12021-202 both met their primary efficacy endpoint. RLV-1201was demonstrated to be statistically superior to placebo (vehicle) in the increase in the number of points seen in the superior visual field as measured using the LPFT. The PP analysis were consistent with the ITT analysis. The onset in improvement in the upper visual field appears to be approximately 2 hours after dosing and continues for at least 6 hours after dosing. In addition, RLV-1201 showed greater numerical increases in the margin reflex distance compared to placebo.

8. Review of Safety

8.1. Safety Review Approach

The safety of RVL-1201 was evaluated in 391 subjects in four randomized, double-masked, placebo-controlled studies in patients with acquired blepharoptosis. The safety database included 203 subjects treated for 6 weeks from studies RLV-1201-201 and RLV-1201-202; 157 subjects treated for 12 weeks in safety study RLV-1201-203 and 31 subjects (15 dosed qd/16 dosed bid) treated for 14 days in the proof-of-concepts study RLV-1201-001. A total of 360 subjects were exposed to once daily administration of RVL-1201 for at least 6 weeks.
The Safety population of 375 subjects consists of all subjects who received once a day dosing of the study medication. The Safety population is the analysis population for the evaluation of exposure and safety.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Subject Disposition and Exposure (Randomized Subjects and Safety Population) in RVL-1201 Clinical Studies

Parameter	RVL-1201 QD N=375 n (%)	Vehicle (Placebo) N=193 n (%)
Number Randomized	375 (100.0)	193 (100.0)
Safety Population	375 (100.0)	193 (100.0)
Completed All Visits	356 (94.9)	188 (97.4)
Discontinued Study	19 (5.1)	5 (2.6)
Withdrawal of Subject Consent	6 (1.6)	2 (1.0)
Subject Lost to Follow Up	2 (0.5)	1 (0.5)
Other	11 (2.9)	2 (1.0)
Discontinued Study Medication Prior to Study Completion	19 (5.1)	5 (2.6)
Adverse Event	9 (2.4)	1 (0.5)
Pregnancy	0	0
Subject Non-Compliance	3 (0.8)	2 (1.0)
Other	7 (1.9)	2 (1.0)

Source ISS page 23 table 9

Exposure to Study Medication (Safety Population)

	RVL-1201 QD N=375	Vehicle (Placebo) N=193
Exposure (days)		
Mean (SD)	56 (24)	56 (24)
Median	44	44
Min, Max	1,102	1,91

The exposure and number of subjects who remained in the study and did not discontinue is adequate to assess the safety of this drug product in the clinical trial setting.

8.2.2. **Relevant characteristics of the safety population:**

Demographic and Baseline Characteristics (Safety Population)

Parameter	RVL-1201 QD N=375	Vehicle (Placebo) N=193
Age (years)		
Mean (SD)	63.9 (13.78)	62.9 (14.45)
Median	67.0	65.0
Min, Max	13, 92	14, 90
Age Group, n (%)		
9-17 years	2 (0.5%)	2 (1.0%)
18-50 years	54 (14.4%)	32 (16.6%)
51-64 years	103 (27.5%)	60 (31.1%)
65-75 years	147 (39.2%)	69 (35.8%)
>75 years	69 (18.4%)	30 (15.5%)
Sex, n (%)		
Female	290 (77.3%)	135 (69.9%)
Male	85 (22.7%)	58 (30.1%)
Race, n (%)		
White	329 (87.7%)	170 (88.1%)
Black	30 (8.0%)	16 (8.3%)
Asian	12 (3.2%)	7 (3.6%)
American Indian	2 (0.5%)	0
Pacific Islander	2 (0.5%)	0
Ethnicity, n (%)		
Not Hispanic/Latino	317 (84.5%)	162 (83.9%)
Hispanic/Latino	58 (15.5%)	31 (16.1%)
Iris Color OD, n (%)		
Brown	188 (50.1%)	89 (46.1%)
Blue	101 (26.9%)	60 (31.1%)
Hazel	59 (15.7%)	35 (18.1%)
Green	26 (6.9%)	8 (4.1%)
Grey	1 (0.3%)	1 (0.5%)
Iris Color OS, n (%)		
Brown	189 (50.4%)	89 (46.1%)
Blue	101 (26.9%)	60 (31.1%)
Hazel	59 (15.7%)	35 (18.1%)
Green	25 (6.7%)	8 (4.1%)
Grey	1 (0.3%)	1 (0.5%)
Study Eye, n (%)		
OD	108 (49.5%)	60 (51.7%)
OS	110 (50.5%)	56 (48.3%)

Min, Max = minimum, maximum; SD = standard deviation
OD = right eye, OS = left eye
Source ISS page 24 table 10

The overall age and sex characteristics of the subjects included in the safety population is consistent with the demographics of acquired blepharatosis.

8.2.3. **Adequacy of the safety database:**

The overall exposure to RVL-1201 dosed once per day for at least 6 weeks was over 350 subjects. The size of this database and the clinical evaluations conducted during development were adequate to assess the safety profile of this drug product.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. **Issues Regarding Data Integrity and Submission Quality**

This NDA submission was of sufficient quality to perform a substantive review of this product.

8.3.2. **Categorization of Adverse Events**

The AE's were coded using the MedDRA coding dictionary.

8.3.3. **Routine Clinical Tests**

The routine clinical testing required to evaluate the safety concerns of intraocular administered products (i.e. biomicroscopy, fundoscopy, visual acuity, etc.) were adequately addressed in the design and conduct of the trials for this product.

8.4. Safety Results

8.4.1. **Deaths**

There were no deaths reported in any study in the RVL-1201 clinical development program.

8.4.2. **Serious Adverse Events**

MedDRA System Organ Class **Preferred Term**	**RVL-1201 QD** **N=375** **n (%)**	**Vehicle (Placebo)** **N=193** **n (%)**
Hyperparathyroidism	1 (0.3)	0
Lower gastrointestinal hemorrhage	0	1 (0.5)
Arthralgia	1 (0.3)	0
Cerebrovascular accident	1 (0.3)	0
Nephrolithiasis	1 (0.3)	0

Approximately 1% of subjects in the treatment group had a serious adverse event. All were assessed as being unrelated to the study drug. This assessment is reasonable based on the events noted.

8.4.3. **Dropouts and/or Discontinuations Due to Adverse Effects**

Eight subjects in the RVL-1201 QD treatment group (2.1%) and 2 subjects in the Vehicle treatment group (1.0%) reported adverse events leading to discontinuation from the study and discontinuation of study medication.

Subjects with Adverse Events Leading to Discontinuation of Study Medication and Withdrawal from the Study (Safety Population)

MedDRA System Organ Class **Preferred Term**	**RVL-1201 QD** **N=375** **n (%)**	**Vehicle (Placebo)** **N=193** **n (%)**
Number (%) of Subjects Reporting AEs Leading to Discontinuation from the Study	**8 (2.1)**	**2 (1.0)**
Eye disorders	**6 (1.6)**	**1 (0.5)**
Blepharitis allergic	1 (0.3)	0
Conjunctival hyperemia	1 (0.3)	0
Dry eye	1 (0.3)	0
Eye irritation	1 (0.3)	0
Eyelid edema	1 (0.3)	0
Glare	1 (0.3)	0
Ocular discomfort	1 (0.3)	0
Iritis	0	1 (0.3)
Gastrointestinal disorders	**0**	**1 (0.5)**
Colitis	0	1 (0.5)
Diverticulum	0	1 (0.5)
Hematochezia	0	1 (0.5)
Hemorrhoids	0	1 (0.5)
Lower gastrointestinal hemorrhage	0	1 (0.5)
General disorders and administration site conditions	**1 (0.3)**	**0**
Instillation site pain	1 (0.3)	0
Injury, poisoning and procedural complications	**1 (0.3)**	**0**
Upper limb fracture	1 (0.3)	0
Nervous system disorders	**2 (0.5)**	**0**
Headache	1 (0.3)	0
Migraine	1 (0.3)	0

The majority of adverse reactions leading to discontinuation were ocular events. The type of adverse events seen are commonly associated with topical ophthalmic drops.

8.4.4. Significant Adverse Events

See section 8.4.3 for significant events that lead to either study drug discontinuation or subject withdrawal from the study.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Adverse Events (>1% in Either Treatment Group) by System Organ Class and Preferred Term (Safety Population)

MedDRA System Organ Class Preferred Term	**RVL-1201 QD N=375 n (%)**	**Vehicle (Placebo) N=193 n (%)**
Eye disorders	**74 (20)**	**26 (14)**
Punctate keratitis	13 (4)	4 (2)
Conjunctival hyperemia	11 (3)	1 (1)
Dry eye	9 (2)	1 (1)
Vision blurred	8 (2)	0
Eye irritation	4 (1)	0
Eye pruritus	1 (0)	3 (2)
General disorders and administration site conditions	**13 (4)**	**4 (2)**
Instillation site pain	8 (2)	0
Instillation site complication	1 (0)	3 (2)
Infections and infestations	**16 (4)**	**13 (7)**
Nasopharyngitis	3 (1)	3 (2)
Upper respiratory tract infection	3 (1)	3 (2)
Investigations	**9 (2)**	**6 (3)**
Vital dye staining cornea present	8 (2)	4 (2)
Nervous system disorders	**11 (3)**	**4 (2)**
Headache	8 (2)	2 (1)

The highlighted adverse events are those that occurred more frequently in the treatment group at of rate of > 1%. The most common adverse events experienced with RVL-1201 are punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, and headache.

8.4.6. Laboratory Findings

The only laboratory assessments conducted during the study were urine pregnancy tests for women of childbearing potential. No subjects became pregnant during the study; the results of all urine pregnancy tests conducted were negative.

8.4.7. Vital Signs

There were no overall differences between treatment groups in systolic blood pressure, diastolic blood pressure or heart rate change from baseline during the clinical trials.

8.4.8. Electrocardiograms (ECGs)

N/A – not assessed during this development program.

8.4.9. QT

N/A – not assessed during this development program.

8.4.10. Immunogenicity

N/A – not assessed during this development program.

8.5. Analysis of Submission-Specific Safety Issues

N/A – there are no submission specific safety issues requiring additional analysis.

8.6. Safety Analyses by Demographic Subgroups

The demographic subgroups analyzed included age, race and ethnicity. Age subgroups were divided into 9-17, 18-50, 51-64, 65-75 and >75 years of age. Race was divided into White and Non-White. Ethnicity was divided into Hispanic/Latino and not Hispanic/Latino.

There were no clinically meaningful safety issues raised in any of the subgroup analyses.

8.7. Specific Safety Studies/Clinical Trials

N/A – there were no safety trials conducted to address a specific safety concern.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

RevitaLid states it is relying on FDA's prior findings of safety for the listed drug Rhofade (NDA 208552) with regard to the potential for RVL-1201 to induce genotoxicity, carcinogenicity, and reproductive and developmental toxicity.

8.8.2. **Human Reproduction and Pregnancy**

No adequate and well-controlled trials of oxymetazoline HCL ophthalmic solution have been conducted in pregnant or lactating women at the concentration proposed for marketing.

8.8.3. **Pediatrics and Assessment of Effects on Growth**

The Applicant made an effort to enroll pediatric patients above the age of 9 years old; however, due to the small number of individuals in this age group with acquired blepharoptosis, adequate numbers could not be enrolled. One subject in Study RVL-1201-202 was 14 years old, three subjects in Study RVL-1201-203 were 13, 15, and 16 years old.

This product was presented at PeRC on March 31, 2020. The PeRC concurred with granting a full waiver of pediatric studies.

8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Overuse has not been studied with oxymetazoline hydrochloride ophthalmic solution 0.1%; however, overuse with the 0.025% solution may produce rebound hyperemia, and overdosage may result in ocular irritation, dryness, mydriasis, and increase in IOP.

In addition, an FDA Drug Safety Communication (10-25-2012) warned of serious adverse events from accidental ingestion by children of over-the-counter eye drops and nasal sprays, including products containing products contain the active ingredients oxymetazoline, tetrahydrozoline, or naphazoline. FDA reviewed 96 cases of accidental ingestion that occurred in children between 1 month and 5 years of age. These cases were reported to the agency between 1985 and October 2012. Serious adverse events included hospitalization, coma, nausea, vomiting, lethargy, tachycardia, decreased respiration, bradycardia, hypotension, hypertension, sedation, somnolence, mydriasis, stupor, hypothermia, drooling, and sedation. Ingestion of only 1-2 mL of the eye drops or nasal spray has resulted in serious adverse events in young children.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There is no post-marketing data available for this oxymetazoline 0.1%. See Section 8.8.4 for safety concerns related to oxymetazoline 0.025%.

8.9.2. Expectations on Safety in the Postmarket Setting

N/A – there are no expected potential safety issues of concern.

8.9.3. Additional Safety Issues From Other Disciplines

N/A – all safety issues have adequately been addressed in this review.

8.10. Integrated Assessment of Safety

Safety was assessed in over 350 subjects dosed once a day for six weeks with oxymetazoline 0.1%. Treatment with RVL-1201 is considered safe with a favorable adverse event profile. The adverse events seen where those that are consistent with most topical ophthalmic drops including punctate keratitis, conjunctival hyperemia, dry eye, blurred vision and pain on installation.

9. Advisory Committee Meeting and Other External Consultations

There were no issues raised during the review of this application that were thought to benefit from discussion at an Advisory Committee meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

11. This "Instruction for Use" has been approved by the U.S. Food and Drug Administration. Approved: Month YYYY Risk Evaluation and Mitigation Strategies (REMS)

N/A/ - there are no recommendations for this product

12. Postmarketing Requirements and Commitments

N/A/ - there are no recommendations for this product

13. Appendices

13.1. References - N/A

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): RVL-1201-201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 16		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details	Yes ☐	No ☐ (Request details from

of the disclosable financial interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Participating Investigators			
Site No.	**Principal Investigator**	**Site Address**	**Sub-Investigators**
02	Douglas Day, MD	Coastal Research Associates 11205 Alpharetta Highway, Suite J-3 Roswell, GA 30076 877-284-0659	Susan Reimbold, OD Susanne Hewitt, MD
03	Gil Epstein, MD	Fort Lauderdale Ey Institute 50 S. Pine Island Road, Plantation, FL 33324 954-741-5555	Stuart Burgess, MD Tirso Lara, MD Natalia Villate, MD
04	John Fezza, MD	Center for Sight 2601 Tamiami Trail Sarasota, FL 34239 941-925-2020	N/A
05	Randall Goodman, MD	Shepard Eye Center 910 East Stowell Road Santa Maria, CA 93454 805-925-2637	Stephen Bylsma, MD Rami Zarnegar, MD
06	Donald Hudak, MD	Apex Eye 7850 Camargo Rd. Cincinnati, OH 45243 513-561-5655	Edward Meier, MD
07	Michael Mercandetti, MD	NuView Aesthetics & Reconstructive Surgery 1499 East Venice Ave. Venice, Florida 34292 941-488-7117	Deborah Fantin, OD

Participating Investigators			
Site No.	**Principal Investigator**	**Site Address**	**Sub-Investigators**
08	Richard Roth, DO	Eye Care Specialists 601 Wyoming Ave. Kingston, PA 18704	Carrie Cardillo, OD
10	David Wirta, MD	Eye Research Foundation Aesthetic Eye Care Institute 520 Superior Avenue, Suite 235 Newport Beach, CA 92663 949-650-1863	Justin Aaker, MD
11	Bradley Kwapiszeski, MD	Heart of America Eye Care, P.A. 8901 W. 74th Street, Suites 285 & 281 Shawnee Mission, KS 66204 913-362-3210	Brenda Edwards, OD
12	Joseph Martel, MD	Martel Medical Eye Group 11216 Trinity River Drive Rancho Cordova, CA 95670 916-712-4179	James Martel, MD
13	Stephen Smith, MD	Eye Associates of Ft. Myers 4225 Evans Ave. Ft. Myers, FL 33901 239-939-0413	Angela Kaplan, OD
14	Lee Shettle, DO	Shettle Eye Research, Inc. 13113 66th Street N. Largo, FL 33773 727-674-2500	N/A
16	Shane Kannarr, OD	Kannarr Eye Care 2521 N. Broadway St. Pittsburg, KS 66762 620-235-1737	Christopher Jacquinot, OD Katherine Painter (Farris), OD Megan Compton, RN
17	Kenneth Sall, MD	Sall Research Medical Center, Inc. 11423 187th St., Suite 101 Artesia, CA 90701 562-804-1974	Julie Kim, OD Jade Davis, OD
18	Damien Goldberg, MD	Wolstan & Goldberg Eye Associates 23600 Telo Ave., Suite 100 Torrance, CA 90505 310-602-5640	Barry Wolstan, MD
19	Steven Rauchman, MD	North Valley Eye Medical Group 1550 Indian Hills Road, #341 Mission Hills, CA 91345 818-365-0606	Robert Smyth-Medina, MD

Covered Clinical Study (Name and/or Number): RVL-1201-202

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 37		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Study RVL-1201-202 Participating Investigators			
Site No.	**Principal Investigator**	**Site Address**	**Sub-Investigators**
201	Dr. Marc Abrams	Abrams Eye Center 2322 East 22nd Street, Suite 102 Cleveland, OH, 44115 216-937-2020 (screened but did not randomize subjects)	Margaret H. Smith, RN
202	Jody G. Abrams, MD	Sarasota Retina Institute 3400 Bee Ridge RD, SUITE 200 Sarasota, FL, 34239 941-921-5335	Marc H. Levy, MD Melvin C. Chen, MD
203	James H. Antoszyk, MD	Charlotte Eye Ear Nose and Throat Associates, P.A. 6035 Fairview Rd. Charlotte, NC, 28210 704-295-3390	Donald H. Stewart III, MD George J. Alter, MD N. Ron Melton, OD
204	Jason Bacharach, MD	North Bay Eye Associates 104 Lynch Creek Way, Suite 12 and 15 Petaluma, CA 94954 707-769-2240	Michael Saidel, MD Roger Weeks, MD Lisa Teel, OD
205	Dr. Robert Benza	Apex Eye, Cincinnati, OH 10615 Montgomery Road, Suite 202 Cincinnati, OH 45242 513-561-5655 Previous address from 04Apr18 to 27Aug18 7850 Camargo Road Cincinnati, OH 45243 (screened but did not randomize subjects)	Radhika L. Kumar, MD
206	Dr. Mark Bergmann	Apex Eye, Cincinnati, OH 6507 Harrison Ave, Suite E Cincinnati, OH 45247 513-661-3566 (screened but did not randomize subjects)	Daniel John Hammer, MD

Study RVL-1201-202 Participating Investigators			
Site No.	**Principal Investigator**	**Site Address**	**Sub-Investigators**
215	Shane R. Kannarr, OD	Kannarr Eye Care 2521 North Broadway Pittsburg, KS, 66762 620-235-1737	Christopher J. Jacquinot, OD Katherine A. Painter, OD Megan Compton, RN
216	Michael S. Korenfeld, MD	Comprehensive Eye Care Ltd. 901 East Third Street Washington, MO, 63090 636-390-3999	Matthew R. Lazarus, OD
217	Bradley Kwapiszski, MD	Heart of America Eye Care, P.A. 8800 West 75th St, Suite 140/141 Shawnee Mission, KS, 66204 913-362-3210	Brenda Edwards, OD
218	Benjamin Knox Lambright, MD	Nature Coast Clinical Research 6122 W. Corporate Oaks Drive Crystal River, FL, 34429 352-563-1865 Satellite site: West Coast Eye Institute 240 North Lecanto Highway Lecanto, FL, 34461 352-563-1865	John W. Rowda, DO Amanda Coppedge, OD Heather Foley, RN Nina Smith, RN, BSN, CCRC
219	Dr. Michelle G. Mijares	South Shore Eye Care 2185 Wantagh Avenue Wantagh, NY, 11793 516-785-3900 (screened but did not randomize subjects)	Jason Todd Flicker, MD Howard Adam Lane, MD Jonathan Wayne Benjamin, MD
220	Joseph Meyer, MD	Round Rock Eye Consultants 1880 Round Rock Ave, Suite # 100 Round Rock, TX, 78681 512-721-8352	N/A
221	Jodi Luchs, MD Matthew D. Paul, MD (took over the site from Dr. Luchs part way through the study)	Danbury Eye Physicians and Surgeons, PC 69 Sand Pit Road, Suite 101 Danbury, CT, 06810 203-791-2020	Katherine J. Zamecki, MD Stephen A. Mathias, MD Margaret A. Marcone, OD
222	Dr. Christopher Pearson	Omega Vision Center PA (DBA: Sabal Eye Care), Longwood, FL (site was initiated but did not screen subjects)	N/A

Study RVL-1201-202 Participating Investigators			
Site No.	**Principal Investigator**	**Site Address**	**Sub-Investigators**
207	James D. Boyce, MD	Orange County Ophthalmology Medical Group 12665 Garden Grove Blvd. Suite 401 Garden Grove, CA 92843 714-534-8373	Norman H. Liu, MD Ryan Taban, MD
208	Leonard Robert Cacioppo, MD	Hernando Eye Institute 14543 Cortez Blvd. Brooksville, FL, 34613 352-596-4030	James Richard Jachimowicz, MD
209	Douglas G. Day, MD	Coastal Research Associates 11205 Alpharetta Highway, Suite J3 Roswell, GA, 30076 770-777-1928	Susanne Michele Hewitt, MD
210	Shane Foster, OD	Drs. Quinn, Foster & Associates 416 West Union Street Athens, OH, 45701 740-594-2271	Thomas G. Quinn, OD, MS Rachel LeFebvre, OD
211	Ronald E. P. Frenkel, MD	East Florida Eye Institute 509 SE Riverside Drive, Suite 302 Stuart, FL, 34994 772-287-9000	Julia Nemiroff, MD Kathleen Gold, RN
212	Bradley S. Giedd, OD, MS, FAAO	Maitland Vision Center 668 North Orlando Ave, Suite 1007 Maitland, FL, 32751 407-647-2020 Previous address from 06Apr2018 to 12Jun2018: 600 S. Orlando Ave. Suite 300 Maitland, FL 32751 407-456-7440	Ryan Schott, OD
213	Alan H. Gruber, MD	Rochester Ophthalmological Group 2100 S. Clinton Ave Rochester, NY 14618 585-244-6011	Paul James Hartman, MD Gerard Cairns, OD, PhD
214	Dr. Gary Jerkins	Advancing Vision Research, LLC., 4306 Harding Pike, Suite 206B Nashville, TN 37205 615-297-6591 Suite number changed 04Jan19 4306 Harding Pike, Suite 202 Nashville, TN 37205 (screened but did not randomize subjects)	N/A

Study RVL-1201-202 Participating Investigators			
Site No.	**Principal Investigator**	**Site Address**	**Sub-Investigators**
223	Robert B. Pendelton, MD, PhD	Pendelton Eye Center 3637 Vista Way Oceanside, CA, 92056 760-758-2008	N/A
224	Eugene E. Protzko, MD	Seidenberg Protzko Eye Asssociates 2023 Pulaski Highway Havre de Grace, MD, 21078 443-643-4506	Jonathan A. Seidenberg, MD Kimberly Ann Neutze-Heaney, DO Candice Rovecamp Giordano, MD Scott M. Smearman, OD David D. Reed, OD Daniel C. Byron, OD Rachna Dilip Shah, OD Salina Kanji, OD Amber Christine Huleva, OD Carine M. Tata, OD
225	Dr. Charles Reilly	R and R Eye Research 5430 Fredericksburg Road San Antonio, TX 78229 210-424-2584 (screened but did not randomize subjects)	Edward R. Rashid, MD William J. Flynn, MD Robert A. Rice, MD Gregory Brunin, MD
226	Kyle Rhodes, MD	Lake Travis Eye and Laser Center 401 Ranch Road 620 S, Suite 210 Lakeway, TX, 78734 512-721-8352	Tam "Tommy" Q. Dang, MD
227	Dr. William Schiff	Barnet Dulaney Perkins Eye Center, 4800 North 22nd Street Phoenix, AZ, 85016 602-955-1000 (screened but did not randomize subjects)	Josh Perkins, OD David Coulson, OD
228	Philip Lee Shettle, DO	Shettle Eye Research 13113 66th Street North Largo, FL, 33773 727-674-2500	N/A
229	Steven M. Silverstein, MD	Silverstein Eye Centers 4240 Blue Ridge Blvd., Suite 1000 Kansas City, MO 64133 816-358-3600	Jeff L. Lookhart, OD
230	Robert John Smyth-Medina, MD	North Valley Eye Medical Group 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345 818-365-0606	Steven Howard Rauchman, MD

Study RVL-1201-202 Participating Investigators			
Site No.	**Principal Investigator**	**Site Address**	**Sub-Investigators**
231	James D. Sutton, MD	Mississippi Eye Associates 3631 Bienville Boulevard Ocean Springs, MS, 39564 228-875-2020	N/A
232	Dr. Michael Tepedino	Cornerstone Eye Center 1400 E. Hartley Drive High Point, NC 27262 336-802-2255 (screened but did not randomize subjects)	Robert J. DaVanzo, MD J. Zachary Forsey, MD Michael W. Evans, MD
233	Michael Khanh Le Tran, MD	Michael K. Tran, MD Inc. 15355 Brookhurst St., Suite 104 Westminster, CA, 92683 714-839-2077	Elizabeth Vu Nguyen, DO
234	Thomas Richard Walters, MD	Keystone Research, Ltd. located at Texan Eye, PA 5717 Balcones Drive Austin, TX, 78731 512-451-4400	Robert Edward Marquis, MD Yen Dang Nieman, MD Blythe Elizabeth Monheit, MD Tanya Tabassum Khan, MD
235	David L. Wirta, MD	Eye Research Foundation 520 Superior Avenue, Suite 235 Newport Beach, CA, 92663 949-650-1863	David Salvay, MD
236	Richard M. Evans, MD	Keystone Research Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX, 78240 210-696-9706	Jason D. Burns, MD Daniel P. Nolan, DO Michael A. Orozco, OD Angela M. Rowden, MD

Covered Clinical Study (Name and/or Number): RVL-1201-203

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 36		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Study RVL-1201-203 Participating Investigators			
Site No.	**Principal Investigator**	**Site Address**	**Sub-Investigators**
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302	Jody G. Abrams, MD	Sarasota Retina Institute 3400 Bee Ridge RD, SUITE 200 Sarasota, FL, 34239 941-921-5335	Marc H. Levy, MD Melvin C. Chen, MD
303	James H. Antoszyk, MD	Charlotte Eye Ear Nose and Throat Associates, P.A. 6035 Fairview Rd. Charlotte, NC, 28210 704-295-3390	Donald H. Stewart III, MD George J. Alter, MD N. Ron Melton, OD
304	Jason Bacharach, MD	North Bay Eye Associates 104 Lynch Creek Way, Suite 12 and 15 Petaluma, CA 94954 707-769-2240	Michael Saidel, MD Roger Weeks, MD Lisa Teel, OD
305	Robert Benza, MD	Apex Eye, Cincinnati, OH 10615 Montgomery Road, Suite 202 Cincinnati, OH 45242 513-561-5655 Previous address from 04Apr18 to 27Aug18 7850 Camargo Road Cincinnati, OH 45243	Radhika L. Kumar, MD
306	Dr. Mark T. Bergmann	Apex Eye, Cincinnati, OH 6507 Harrison Ave, Suite E Cincinnati, OH 45247 513-661-3566	Daniel John Hammer, MD
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309	Douglas G. Day, MD	Coastal Research Associates 11205 Alpharetta Highway, Suite J3 Roswell, GA, 30076 770-777-1928	Susanne Michele Hewitt, MD
310	Shane Foster, OD	Drs. Quinn, Foster & Associates 416 West Union Street Athens, OH, 45701 740-594-2271	Thomas G. Quinn, OD, MS Rachel LeFebvre, OD
311	Ronald E. P. Frenkel, MD	East Florida Eye Institute 509 SE Riverside Drive, Suite 302 Stuart, FL, 34994 772-287-9000	Julia Nemiroff, MD Kathleen Gold, RN
312	Bradley S. Giedd, OD, MS, FAAO	Maitland Vision Center 668 North Orlando Ave, Suite 1007 Maitland, FL, 32751 407-647-2020 Previous address from 06Apr2018 to 12Jun2018: 600 S. Orlando Ave. Suite 300 Maitland, FL 32751 407-456-7440	Ryan Schott, OD
313	Alan H. Gruber, MD	Rochester Ophthalmological Group 2100 S. Clinton Ave Rochester, NY 14618 585-244-6011	Paul James Hartman, MD Gerard Cairns, OD, PhD
314	Dr. Gary Jerkins	Advancing Vision Research, LLC., 4306 Harding Pike, Suite 206B Nashville, TN 37205 615-297-6591 Suite number changed 04Jan19 4306 Harding Pike, Suite 202 Nashville, TN 37205	N/A
315	Shane R. Kannarr, OD	Kannarr Eye Care 2521 North Broadway Pittsburg, KS, 66762 620-235-1737	Christopher J. Jacquinot, OD Katherine A. Painter, OD Megan Compton, RN
316	Michael S. Korenfeld, MD	Comprehensive Eye Care Ltd. 901 East Third Street Washington, MO, 63090 636-390-3999	Matthew R. Lazarus, OD
317	Bradley Kwapisezski, MD	Heart of America Eye Care, P.A. 8800 West 75th St, Suite 140/141 Shawnee Mission, KS, 66204 913-362-3210	Brenda Edwards, OD

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Site No.	**Principal Investigator**	**Site Address**	**Sub-Investigators**
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319	Michelle G. Mijares, MD (Formerly Jodi Ian Luchs, MD)	South Shore Eye Care 2185 Wantagh Avenue Wantagh, NY, 11793 516-785-3900	Jason Todd Flicker, MD Howard Adam Lane, MD Jonathan Wayne Benjamin, MD
320	Joseph Meyer, MD	Round Rock Eye Consultants 1880 Round Rock Ave, Suite # 100 Round Rock, TX, 78681 512-721-8352	N/A
321	Matthew D. Paul, MD	Danbury Eye Physicians and Surgeons, PC 69 Sand Pit Road, Suite 101 Danbury, CT, 06810 203-791-2020	Katherine J. Zamecki, MD Stephen A. Mathias, MD Margaret A. Marcone, OD
322	Dr. Christopher Pearson	Omega Vision Center PA (DBA: Sabal Eye Care), Longwood, FL	N/A
323	Robert B. Pendelton, MD, PhD	Pendelton Eye Center 3637 Vista Way Oceanside, CA, 92056 760-758-2008	N/A
324	Eugene E. Protzko, MD	Seidenberg Protzko Eye Asssociates 2023 Pulaski Highway Havre de Grace, MD, 21078 443-643-4506	Jonathan A. Seidenberg, MD Kimberly Ann Neutze-Heaney, DO Candice Rovecamp Giordano, MD Scott M. Smearman, OD David D. Reed, OD Daniel C. Byron, OD Rachna Dilip Shah, OD Salina Kanji, OD Amber Christine Huleva, OD Carine M. Tata, OD
325	Charles D. Reilly, MD	R and R Eye Research 5430 Fredericksburg Road San Antonio, TX 78229 210-424-2584	Edward R. Rashid, MD William J. Flynn, MD Robert A. Rice, MD Gregory Brunin, MD
326	Kyle Rhodes, MD	Lake Travis Eye and Laser Center 401 Ranch Road 620 S, Suite 210 Lakeway, TX, 78734 512-721-8352	Tam "Tommy" Q. Dang, MD

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328	Philip Lee Shettle, DO	Shettle Eye Research 13113 66th Street North Largo, FL, 33773 727-674-2500	N/A
329	Steven M. Silverstein, MD	Silverstein Eye Centers 4240 Blue Ridge Blvd., Suite 1000 Kansas City, MO 64133 816-358-3600	Jeff L. Lookhart, OD
330	Robert John Smyth-Medina, MD	North Valley Eye Medical Group 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345 818-365-0606	Steven Howard Rauchman, MD
331	James D. Sutton, MD	Mississippi Eye Associates 3631 Bienville Boulevard Ocean Springs, MS, 39564 228-875-2020	N/A
332	Michael E. Tepedino, MD	Cornerstone Eye Center 1400 E. Hartley Drive High Point, NC 27262 336-802-2255	Robert J. DaVanzo, MD J. Zachary Forsey, MD Michael W. Evans, MD
333	Michael Khanh Le Tran, MD	Michael K. Tran, MD Inc. 15355 Brookhurst St., Suite 104 Westminster, CA, 92683 714-839-2077	Elizabeth Vu Nguyen, DO
334	Thomas Richard Walters, MD	Keystone Research, Ltd. located at Texan Eye, PA 5717 Balcones Drive Austin, TX, 78731 512-451-4400	Robert Edward Marquis, MD Yen Dang Nieman, MD Blythe Elizabeth Monheit, MD Tanya Tabassum Khan, MD
335	David L. Wirta, MD	Eye Research Foundation 520 Superior Avenue, Suite 235 Newport Beach, CA, 92663 949-650-1863	David Salvay, MD

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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