CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212520Orig1s000

SUMMARY REVIEW

Divison Director and Cross-Discipline Team Leader Review for NDA 212520

Date	July 8, 2020
From	Wiley A. Chambers, M.D., William M. Boyd, M.D.
Subject	Division Director and Cross-Discipline Team Leader Review
NDA	212520
Applicant	RVL Pharmaceuticals, Inc.
Date of Submission	September 16, 2019
PDUFA Goal Date	July 16, 2020
Proprietary Name	UPNEEQ
Established or Proper Name	oxymetazoline hydrochloride ophthalmic solution, 0.1%
Dosage Form(s)	Topical ophthalmic solution
Dosing Regimen(s)	Instill one drop of UPNEEQ into one or both ptotic eye(s) once daily
Recommendation on Regulatory Action	Approval
Indication(s)/Population(s)	UPNEEQ is indicated for the treatment of acquired blepharoptosis in adults

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Acting Division Director	Wiley A. Chambers
Medical Officer Review	Jennifer Harris
Statistical Review	Solomon Chefo
Pharmacology Toxicology Review	Muriel Saulnier
OPQ Review incl. Micro	Chunchun Zhang, Sharon Kelly, Yang Nan, Renee A. Marcsisin, Alexander Gontcharov
Clinical Pharmacology Review	Amit A. Somani
OPDP	Carrie Newcomer
OSI	N/A
CDTL Review	William M. Boyd
DMPP	Nyedra W. Booker
DMEPA	Nasim Roosta
DRISK	N/A
Other	N/A

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

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).

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

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.

The efficacy of this product was replicated in two adequate and well-controlled trials RVL-1201-201 and RVL-1201-202 that demonstrated that oxymetazoline hydrochloride ophthalmic solution, 0.1% 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 peak 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, oxymetazoline hydrochloride ophthalmic solution showed greater numerical increases in the margin reflex distance compared to placebo. These trials were conducted under IND 116,915.

Safety was assessed in over 350 subjects dosed once a day for six weeks with oxymetazoline 0.1%. Treatment with oxymetazoline hydrochloride ophthalmic solution 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.

UPNEEQ (oxymetazoline hydrochloride ophthalmic solution), 0.1% will be approved for the treatment of acquired blepharoptosis in adults (b) (4).

Benefit-Risk Assessment Framework

Benefit-Risk Integrated 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 oxymetazoline for the proposed indication reported few adverse events. The most common (<5%) adverse events experienced with oxymetazoline hydrochloride ophthalmic solution 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)
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.

2. Background

The applicant is pursuing an NDA through a 505(b)(2) pathway using supportive information from Rhofade (oxymetazoline HCl) Cream (NDA 2085521) as the reference Listed Drug.

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.

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.

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 marketed without a prescription for relief of ocular redness. Both are 0.025% concentrations. Kovanaze (NDA 208032) is a combination product with tetracaine which is approved as a nasal spray for nasal congestion. Rhofade (oxymetazoline cream, 1%) (NDA 208552) is a dermatological product indicated for the treatment of persistent facial erythema associated with rosacea.

In an April 14, 2020, the applicant submitted a correspondence notifying the Agency that the corporate name and/or address has been changed from

RevitaLid, Inc.
400 Crossing Boulevard
Bridgewater, NJ 08807

to

RVL Pharmaceuticals, Inc
400 Crossing Boulevard
Bridgewater, NJ 08807.

3. Product Quality

From the Product Quality review dated 6/12/2020:

Drug Substance

Table 1: Specification for Oxymetazoline Hydrochloride, USP

Test	Method	Specification
Description	USP	White to practically white, fine crystalline powder.
Identification A. By IR B. By HPLC C. Chloride	 A. USP <197M> B. USP / NF C. USP <191>	 A. The IR absorption spectrum of the sample exhibits maxima only at the same wavelengths of the USP standard B. The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the assay C. The filtrate meets the requirements
pH	USP <791>	4.0 – 6.5
Loss on Drying	USP <731>	NMT (b) (4) %
Residue on Ignition	USP <281>	NMT 0.1 %
Assay	USP/NF	98.5 % – 101.5 % on the dried basis
Residual Solvents (b) (4)	(b) (4)	NMT (b) (4)
Organic Impurities A. Related Compound A B. Individual Unspecified C. Other Individual Specified* D. Total Impurities	(b) (4)	 A. NMT 0.15 % B. NMT 0.10 % C. NMT (b) (4) % D. NMT 0.5 %
Microbial Limits A. Total Aerobic Count B. Yeast and Mold Count C. Absence of Listed Pathogens	(b) (4)	 A. NMT (b) (4) cfu/g B. NMT (b) (4) cfu/g C. (b) (4)

Source: Module 3.2.S.4.1 Specification

Oxymetazoline hydrochloride is manufactured by (b) (4) as described in (b) (4) DMF (b) (4). The API is the subject of a USP monograph. The supplier specification meets the monograph requirements and includes the residual solvent (b) (4). An elemental risk assessment is provided in the DMF and the batch analysis data demonstrates it is unnecessary to include testing in the specification. The specifications of the drug product manufacturer, (b) (4) are in alignment with the current USP monograph. They have evaluated all USP and in-house test methods for suitability. Representative batch analysis data

demonstrates comparability between batches analyzed by both [redacted]. [redacted] will re-test for assay [redacted]

Drug Product

COMPOSITION OF THE DRUG PRODUCT

Table 2: Quantitative Composition of Oxymetazoline HCl Ophthalmic Solution, 0.1%

Ingredient	Quantity (% w/v)	Quantity (mg/mL)	Quantity (mg/drop
Oxymetazoline Hydrochloride, USP	0.10	1.00	0.035
Sodium Chloride, USP	[redacted]	[redacted]	[redacted]
Potassium Chloride, USP			
Calcium Chloride, [redacted] USP			
Magnesium Chloride [redacted], USP			
Sodium Acetate, [redacted], USP			
Sodium Citrate, [redacted] NF			
Hypromellose, USP [redacted]			
Water for Injection, USP			
Hydrochloric Acid, NF			
[redacted]			

q.s.- as much as is sufficient, n/a- not applicable
Source: Module 3.2.P.1 Description and Composition of the Drug Product

Container Closure

The container closure system for oxymetazoline hydrochloride ophthalmic solution, 0.1% is a single-use [redacted] vial individually wrapped in a foil pouch. Each individual vial is packaged in a foil pouch comprising of [redacted] The individual foil-pouched vials are further packaged into a child-resistant zipper-pouch (bag). Each child resistant zipper-pouch (bag), will have a label indicating the contents as either 15-count or 30-count of individual foil-pouched vials. This bag will be placed into a labeled carton accordingly.

[redacted]

Source: May 20, 2020 correspondence to NDA 212520

Drug Product

Specifications for Oxymetazoline HCl Ophthalmic Solution, 0.1%

Test	Specification		Test Method
Description	Clear, colorless to slightly yellow solution free of any particulates or crystallization		CTM-SC-AS-6714
Osmolality			SOP-SC-AS-6428
pH	5.8 – 6.8		SOP-SC-AS-6112
Assay	% of the label claim		CTM-SC-AS-6540
Related Substances 6. Each Individual Unknown 7. Total Impurities	At Release 1. NMT % 2. NMT % 3. NMT % 4. NMT % 5. NMT % 6. NMT % 7. NMT %	At Stability 1. NMT % 2. NMT % 3. NMT % 4. NMT % 5. NMT % 6. NMT % 7. NMT %	CTM-SC-AS-6548
Viscosity			CTM-SC-AS-6660
HPLC Identification*	Conforms		USP CTM-SC-AS-6540
UV Identification*	The UV Spectrum of the Oxymetazoline peak of the *Sample solution* corresponds to that of the *Standard solution* as obtained in the *Assay*.		CTM-SC-AS-6540

Test	Specification	Test Method
Particulate Matter ≥ 10 µm ≥ 25 µm ≥ 50 µm	NMT (b) (4)/mL NMT mL NMT mL	USP <789>
Weight Loss**	NMT (b) (4)%	CTM-SC-AS-6509
Dye Ingress Immersion Test**	No visual evidence of dye ingress and absorbance does not occur at approximately (b) (4) nm	MTM-SC-MB-6380
Sterility	No microbial growth is observed	USP <71> MTM-SC-MB-6308
(b) (4)	All of the drug product formulation components meet the limits of the (b) (4) calculation.	(b) (4)

*Applicable for release testing only. **Applicable for stability testing only.
Source: Module 3.2.P.5.1 Specifications

Facilities

All the facilities are acceptable based on the profile. An overall acceptable cGMP recommendation for all the facilities was issued on 2/4/2020.

(b) (4)

4. Nonclinical Pharmacology/Toxicology

From the Pharmacology Toxicology review dated 6/12/2020:

The proposed clinical dose for RVL-1201 is 1 drop of 35 μL per eye once daily, equivalent to approximately 35 μg/eye/day or 70 μg/2 eyes/day (i.e. 1.16 μg/kg/day equivalent to 43μg/M2/day for a 60 kg subject, Maximum Recommended Human Dose or MRHD). They are pursuing the 505(b)(2) approval pathway proposing the Listed Drug (LD) Rhofade (oxymetazoline HCl) Cream reviewed in NDA 2085521 as the reference compound.

To fulfill the regulatory requirements, the applicant has submitted 2 original toxicity studies in the rabbit, published literature for the pharmacology and toxicology of oxymetazoline, and a comparative bioavailability study in humans that bridges RVL-1201 to Rhofade (Study RVL-1201-PKP01). The systemic exposure to oxymetazoline at the proposed clinical dose of RVL-1201 was less than the exposure at the MRHD for Rhofade, thereby establishing a bridge between the 2 products. [See Clinical Pharmacology review dated 6/10/2020 and Section 5 of this review.]

In vitro functional and binding studies with human cells indicated that oxymetazoline has affinity and potency for several subtypes of alpha adrenoreceptors including α1A- and α2A- adrenoreceptors. These receptors are widely distributed in different tissues in all animal species, including in the eye. In the human eye, α2 adrenergic receptors are the predominant subtype (especially α2A) in the Mueller's muscle of the upper eyelid, and both agonist binding of the α1 and α2 adrenergic receptors at this location can mediate muscle contraction. The α1 adrenergic receptor was also found to play a role in canine and murine models of ptosis.

5. Clinical Pharmacology

From the Clinical Pharmacology review dated 6/10/2020:

The focus of the Clinical Pharmacology review of this NDA was to assess and compare the systemic PK exposure of oxymetazoline for oxymetazoline HCl ophthalmic solution and Rhofade (oxymetazoline hydrochloride) cream, 1% based on the phase 1 study RVL-1201-PKP01. Study RVL-1201-PKP01 is a single-dose, 2-treatment, 2-period, 2-sequence, bioavailability study in which 24 healthy volunteers (i.e., male and female volunteers aged 18 to 45 years) received two separate single-dose administrations of study drug.

The total dose administered to each subject who completed both study periods was 0.07 mg (i.e., 0.035 X 2) of oxymetazoline HCl from one drop of RVL-1201 in each eye and 3 mg of oxymetazoline HCl from 0.3 g Rhofade. Subjects were randomly assigned to one of the 2 treatment sequences. Subjects received either Treatment A or Treatment B on the morning of the first treatment period. In Period 2, subjects received the next treatment in their assigned treatment sequence. The treatment periods were separated by a washout period of 7 days.

Serial blood samples were collected for PK analysis at pre-dose, and 10, 20, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, and 36 hours post-dose. Each subject was scheduled to have 17 blood samples collected per period for PK analysis through 36 hours post-dose. All subjects completed both study periods, and 23 subjects were evaluable for PK analysis. One subject was excluded from PK analysis because pre-dose concentrations of oxymetazoline were observed in both periods that were greater than 5% of their respective C_{max} values.

The systemic exposure (i.e., AUC and C_{max}) to oxymetazoline from the proposed clinical dose of RVL-1201 is lower compared to the exposures following administration of the approved dose of topically applied RHOFADE™ cream, which supports the establishment of a PK bridge between these two products from a clinical pharmacology perspective. See below.

Pharmacokinetic Parameters for Oxymetazoline HCl Ophthalmic Solution, 0.1% and RHOFADE™ (oxymetazoline HCl) Cream 1% in Healthy Adult Subjects

PK Parameter	**Treatment A RVL-1201, Test**		**Treatment B RHOFADE™, Reference**	
	N	**Mean ± SD**	**N**	**Mean ± SD**
T_{max} (hr)[a]	23	2 (0.5 - 12)	23	16 (8 - 24)
C_{max} (pg/mL)	23	30.5 ± 12.7	23	47.6 ± 28.3
AUC_{tlast} (hr*pg/mL)	23	400 ± 188	23	1080 ± 686
AUC_{inf} (hr*pg/mL)[b]	19	468 ± 214	9	950 ± 476
$t_{1/2}$ (hr)[c]	21	8.25 (5.6 - 13.9)	20	11.3 (8.1 - 17.6)

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)
[a] Median (range)
[b] AUC_{inf}: AUC_{inf} values with extrapolation > 20% were excluded from summary statistics.
[c] Harmonic mean (range)

6. Clinical Microbiology

Not applicable. This is not an anti-infective product.

7. Clinical/Statistical- Efficacy

From the Clinical review dated 6/22/2020:

Safety and efficacy for oxymetazoline was supported by two clinical studies RLV-1201-201 and RLV-1201-202.

RLV-1201-201 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)

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. Oxymetazoline 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.

Secondary 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)

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. Oxymetazoline 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)

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.

RLV-1201-202 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)

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

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.

Secondary Endpoints

Mean Change from Baseline in Marginal Reflex Distance in the Study Eye (ITT Population)

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.

Efficacy Summary Statement

Study RLV-1201-201 and RLV-12021-202 both met their primary efficacy endpoints. Oxymetazoline was 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, oxymetazoline showed greater numerical increases in the margin reflex distance compared to placebo. 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.

8. Safety

From the Clinical review dated 6/22/2020:

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.

Overall Exposure

Subject Disposition and Exposure (Randomized Subjects and Safety Population)

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

Deaths - There were no deaths reported in any study.

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 by the applicant as being unrelated to the study drug. This assessment is reasonable based on the events noted.

Dropouts and/or Discontinuations Due to Adverse Effects

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

MedDRA System Organ Class **Preferred Term**	**Oxymetazoline** **N=375** **n (%)**	**Vehicle** **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**

MedDRA System Organ Class **Preferred Term**	**Oxymetazoline** **N=375** **n (%)**	**Vehicle** **N=193** **n (%)**
Upper limb fracture	1 (0.3)	0
Nervous system disorders	**2 (0.5)**	**0**
Headache	1 (0.3)	0
Migraine	1 (0.3)	0

Eight subjects in the RVL-1201 QD treatment group (2%) and 2 subjects in the Vehicle treatment group (1%) reported adverse events leading to discontinuation from the study and discontinuation of study medication.

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**	**Oxymetazoline** **N=375** **n (%)**	**Vehicle** **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.

Safety Summary Statement

Safety was assessed in over 350 subjects dosed once a day for six weeks with oxymetazoline 0.1%. Treatment with oxymetazoline 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

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

10. Pediatrics

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.

11. Other Relevant Regulatory Issues

BIOSTATISTICS

Per the original Biostatistics review dated 6/10/2020:

This NDA is based on two similarly designed Phase 3 efficacy and safety studies (Study 201 and Study 202) and a Phase 3 safety study (Study 203). Study 201 and 202 were a 6-week, multicenter, randomized, double-masked, vehicle-controlled, superiority studies. In both studies, eligible subjects with acquired ptosis were randomized in a 2:1 ratio to either RVL-1201 or vehicle and were to receive one drop of study drug in each eye once daily (QD) in the morning for 42 days. Follow-up assessments were made on Days 1, 14, and 42.

Efficacy evaluation in both studies was based on: (i) the number of points seen (range 0-35 points) in the superior field region of a modified visual field test (also known as a Leicester Peripheral Field Test [LPFT]) and (ii) the distance from the central pupillary light reflex to the central margin of the upper eyelid (also known as marginal reflex distance [MRD]). An increase in both efficacy measures from baseline signals an improvement in the drooping of the upper eyelid.

In both studies, subjects in the RVL-1201 group demonstrated a statistically superior increase in the number of points seen in the superior visual field region of the LPFT at the two time points and in the MRD at the pre-specified points from baseline compared to subjects in the vehicle group. As shown in Figure 1, the increase in the number of points seen in the RVL-1201 group from baseline in Study 201 was higher than in the vehicle group by 3.7 points

(95% CI: 1.8 to 5.6; p<0.001] at Day 1 Hour 6 and by 4.2 points (95% CI: 2.4 to 6.1; p < 0.001) at Day 14 Hour 2. Similarly, the increase in the number of points seen in the RVL-1201 group in Study 202 was higher than in the vehicle group by 4.2 points (95% CI: 2.4 to 6.1; p-value < 0.001) at Day 1 Hour 6 and by 5.3 points (95% CI: 3.5 to 7.1; p-value < 0.001) at Day 14 Hour 2.

Figure 1: Summary of the mean change (SD) in the number of points seen on the LPFT at the two timepoints (All randomized subjects [b])

Study RVL-1201-201

Visit	Vehicle (N = 46)	RVL-1201 (N = 94)	Difference [a] (95% CI)	Favor RVL-1201 →
Baseline	16.9 (5.21)	17.0 (4.41)		
Day 1, Hour 6	1.5 (3.93)	5.2 (5.97)	3.7 (1.8, 5.6)	3.7
Day 14, Hour 2	2.2 (5.80)	6.4 (5.04)	4.2 (2.4, 6.0)	4.2

-2 0 2 4 6 8

Study RVL-1201-202

Visit	Vehicle (N = 55)	RVL-1201 (N = 109)	Difference [a] (95% CI)	Favor RVL-1201 →
Baseline	17.6 (5.48)	17.6 (4.92)		
Day 1, Hour 6	2.1 (4.28)	6.3 (6.72)	4.2 (2.4, 6.1)	4.2
Day 14, Hour 2	2.4 (5.26)	7.7 (6.40)	5.3 (3.5, 7.1)	5.3

-2 0 2 4 6 8

[a] Least square means differences and corresponding 95% confidence intervals (CI) were based on ANCOVA model adjusted for baseline number of points.
[b] Included all randomized subjects who received at least one dose of study medication.

RVL-1201 treated eyes also displayed a significant increase in MRD from baseline at the pre-specified timepoints compared to vehicle treated eyes. As shown in Figure 2 below, in Study 202, the increase in MRD from baseline in the RVL-1201 group was statistically significantly higher than in the vehicle group by 0.4 mm to 0.8 mm at all the pre-specified timepoints. The largest difference was achieved at Day 14 Hour 2 (0.8 mm) and the smallest difference was achieved at Day 1 Minutes 5 (0.4 mm). Study 201 also provided supporting evidence regarding the treatment benefit of RVL-1201 compared to vehicle in MRD increase from baseline at the measured timepoints.

Figure 2: Summary of the mean change (SD) in the marginal reflex distance (MRD) at pre-specified timepoints (All randomized subjects)

Study RVL-1201-201

Visit	Vehicle (N = 46)	RVL-1201 (N = 94)	Difference (95% CI)	Favor RVL-1201 →
Baseline	1.03 (0.68)	1.16 (0.66)		
Day 1, Hour 2	0.50 (0.80)	0.99 (0.78)	0.52 (0.24, 0.79)	0.52
Day 14, Hour 2	0.58 (0.88)	1.09 (0.78)	0.54 (0.25, 0.83)	0.54
Day 1, Hour 6	0.67 (1.00)	0.94 (0.92)	0.29 (-0.05, 0.63)	0.29
Day 14, Hour 6	0.70 (0.99)	1.03 (0.86)	0.36 (0.04, 0.68)	0.36
Day 1, Minutes 15				
Day 14, Minutes 15				
Day 1, Minutes 5				
Day 14, Minutes 5				

-0.5 0.0 0.5 1.0 1.5

Study RVL-1201-202

Visit	Vehicle (N = 55)	RVL-1201 (N = 109)	Difference (95% CI)	Favor RVL-1201 →
Baseline	1.07 (0.70)	1.04 (0.74)		
Day 1, Hour 2	0.33 (0.56)	1.05 (0.90)	0.71 (0.45, 0.96)	0.71
Day 14, Hour 2	0.43 (0.73)	1.22 (0.93)	0.78 (0.50, 1.06)	0.78
Day 1, Hour 6	0.35 (0.57)	0.98 (0.87)	0.61 (0.37, 0.86)	0.61
Day 14, Hour 6	0.47 (0.74)	1.06 (0.90)	0.58 (0.31, 0.85)	0.58
Day 1, Minutes 15	0.32 (0.64)	0.93 (0.81)	0.60 (0.36, 0.84)	0.6
Day 14, Minutes 15	0.41 (0.83)	1.11 (0.92)	0.68 (0.39, 0.97)	0.68
Day 1, Minutes 5	0.20 (0.57)	0.59 (0.72)	0.38 (0.16, 0.59)	0.38
Day 14, Minutes 5	0.42 (0.78)	0.86 (0.85)	0.42 (0.15, 0.68)	0.42

-0.5 0.0 0.5 1.0 1.5

Note: By design, MRD measurements were not performed in Study 201at Minutes 5 and 15 on Days 1 and 14.
[a] Least square mean differences and corresponding 95% confidence intervals (CI) were based on ANCOVA model adjusted for baseline MRD values.
[b] Included all randomized subjects who received at least one dose of study medication.

Biostatistics concluded that the application provided substantial evidence of the efficacy of RVL-1201 administered once daily in improving the drooping of the upper eyelid in patients with acquired blepharoptosis.

FINANCIAL DISCLOSURE
The applicant certifies that they have not entered into any financial arrangement with the clinical investigators for the following two studies:

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 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) 16		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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) 37		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

OSI
Office of Scientific Investigations (OSI) inspections were not conducted as part of this NDA. Investigators with the highest enrollment have been investigated in the recent past.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of proposed proprietary name, UPNEEQ, and granted conditional acceptance on 6/15/2020. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

(b) (4) were previously evaluated as proposed proprietary names but received proprietary name denied letters from DMEPA.

OPDP
The Office of Prescription Drug Promotion (OPDP) completed a review of the substantially complete label on 6/25/2020.

DMPP
The Division of Medical Policy Programs (DMPP) completed a review of the substantially complete patient instructions for use on 6/29/2020.

12. 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:	Clinical M.O. Review Section where discussed, if applicable
	■ Clinical outcome assessment (COA) data, such as	Section 6.1.1, 6.1.2 and 6.2.1 and 6.2.2
	■ 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	[e.g., Sec 2.1 Analysis of Condition]
	□ 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	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

13. Regulatory Action

NDA 212520 UPNEEQ (oxymetazoline hydrochloride ophthalmic solution), 0.1% will be approved for for the treatment of acquired blepharoptosis in adults. There are no recommended postmarketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

14. Labeling

Labeling was submitted on 7/7/2020 following discussion and recommendations from the Agency. The final submitted labeling was found to be consistent with 21 CFR 201.57. The application will be approved with the submitted labeling with one minor edit – the word (b) (4) on the first page of the Patient Instructions for Use should be deleted. The applicant is in agreement with this edit.

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/

WILLIAM M BOYD
07/08/2020 02:17:41 PM

WILEY A CHAMBERS
07/08/2020 02:29:09 PM