CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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<u>STATISTICAL REVIEW(S)</u>

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial #:	212520
Drug Name:	RVL-1201 (Oxymetazoline Hydrochloride Ophthalmic Solution, 0.1%)
Indication(s):	Treatment of acquired blepharoptosis
Applicant:	RevitaLid, Inc.
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Biometrics Division:	IV
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Keywords: Blepharoptosis, Leicester Peripheral Field Test, Marginal Reflex Distance, ANCOVA.

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1 EXECUTIVE SUMMARY

In this New Drug Application (NDA), the applicant seeks approval of RVL-1201, a preservative free Oxymetazoline Hydrochloride (HCl) Ophthalmic Solution 0.1%, for the treatment of acquired blepharoptosis (also known as Ptosis). Ptosis is an abnormal drooping of the upper eyelid that occurs due to a partial or complete dysfunction of the muscles that elevate the upper eyelid. Symptoms may include blurred vision, increased tearing, and diminished superior visual fields which may interfere with activities of daily living and result in reduced quality of life. There are no FDA approved pharmacologic therapy for the treatment of ptosis. The current treatment option is surgical procedure.

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.

A total of 140 subjects in Study 201 (94 in RVL-201 and 46 in vehicle) and 164 subjects in Study 202 (109 in RVL-201 and 55 in vehicle) received at least one dose of the study drug and were evaluable for efficacy. Most subjects in both studies were female (76% in 201 and 71% in 202) and white (86% in 201 and 91% in 202). The average age of subjects in both studies was about 64 years (range: 22 – 85 in 201 and 14 – 92 in 201) with most subjects above 50 years of age (88% in 201 and 82% in 201). In both studies, most subjects completed the treatment duration through Day 42 (96% in Study 201 and 98% in Study 202).

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.

The increase in the number of points seen in the superior visual field region of the LPFT from baseline at (1) Hour 6 on Day 1 (duration of action) and (2) Hour 2 on Day 14 (onset of action) were the primary efficacy endpoints in both studies. These endpoints were tested sequentially for superiority in the order listed. The mean change in MRD from baseline at Day 1 Hour 2, Day 14 Hour 2, Day 1 Hour 6, Day 14 Hour 6, Day 1 Minutes 15, Day 14 Minutes 15, Day 1 Minutes 5, and Day 14 Minutes 5 were defined as secondary efficacy variables in Study 202 and tested sequentially for superiority in the order listed. In Study 201, the mean change in MRD at the prespecified timepoints were defined as exploratory variables.

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

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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					Study RVL-1201-202			
Visit	Vehicle (N = 46)	RVL-1201 (N = 94)	Difference[a] (95% CI)	Favor RVL-1201 →	Visit	Vehicle (N = 55)	RVL-1201 (N = 109)	Difference[a] (95% CI)	Favor RVL-1201 →
Baseline	16.9 (5.21)	17.0 (4.41)			Baseline	17.6 (5.48)	17.6 (4.92)		
Day 1, Hour 6	1.5 (3.93)	5.2 (5.97)	3.7 (1.8, 5.6)	3.7	Day 1, Hour 6	2.1 (4.28)	6.3 (6.72)	4.2 (2.4, 6.1)	4.2
Day 14, Hour 2	2.2 (5.80)	6.4 (5.04)	4.2 (2.4, 6.0)	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					-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					Study RVL-1201-202			
Visit	Vehicle (N = 46)	RVL-1201 (N = 94)	Difference (95% CI)	Favor RVL-1201 →	Visit	Vehicle (N = 55)	RVL-1201 (N = 109)	Difference (95% CI)	Favor RVL-1201 →
Baseline	1.03 (0.68)	1.16 (0.66)			Baseline	1.07 (0.70)	1.04 (0.74)		
Day 1, Hour 2	0.50 (0.80)	0.99 (0.78)	0.52 (0.24, 0.79)	0.52	Day 1, Hour 2	0.33 (0.56)	1.05 (0.90)	0.71 (0.45, 0.96)	0.71
Day 14, Hour 2	0.58 (0.88)	1.09 (0.78)	0.54 (0.25, 0.83)	0.54	Day 14, Hour 2	0.43 (0.73)	1.22 (0.93)	0.78 (0.50, 1.06)	0.78
Day 1, Hour 6	0.67 (1.00)	0.94 (0.92)	0.29 (-0.05, 0.63)	0.29	Day 1, Hour 6	0.35 (0.57)	0.98 (0.87)	0.61 (0.37, 0.86)	0.61
Day 14, Hour 6	0.70 (0.99)	1.03 (0.86)	0.36 (0.04, 0.68)	0.36	Day 14, Hour 6	0.47 (0.74)	1.06 (0.90)	0.58 (0.31, 0.85)	0.58
Day 1, Minutes 15					Day 1, Minutes 15	0.32 (0.64)	0.93 (0.81)	0.60 (0.36, 0.84)	0.6
Day 14, Minutes 15					Day 14, Minutes 15	0.41 (0.83)	1.11 (0.92)	0.68 (0.39, 0.97)	0.68
Day 1, Minutes 5					Day 1, Minutes 5	0.20 (0.57)	0.59 (0.72)	0.38 (0.16, 0.59)	0.38
Day 14, Minutes 5					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					-0.5 0.0 0.5 1.0 1.5

Note: By design, MRD measurements were not performed in Study 201 at 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.

In summary, based on the totality of evidence from Studies 201 and 202, the reviewer concludes that the application provided substantial evidence of efficacy of RVL-1201 administered once daily in improving the drooping of the upper eyelid in patients with acquired ptosis.

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2 INTRODUCTION

2.1 Overview

The applicant submitted this NDA for the use of RVL-1201 (Oxymetazoline Hydrochloride Ophthalmic Solution, 0.1%) for the treatment of acquired ptosis.

This NDA contains five clinical studies: one Phase 1 study that characterized the relative bioavailability and pharmacokinetics of oxymetazoline from RVL-1201, a proof-of-concept Phase 1/2a study (Study RVL-1201-001), and three pivotal Phase 3 studies which demonstrate the safety and efficacy of RVL-1201 (Studies RVL-1201-201, -202, and -203). Studies RVL-1201-001, -201, -202, and -203 were completed under IND 116915.

Summaries of studies included in the efficacy and safety analyses

Study ID	Number of Study Centers Location(s)	Study start Enrollment status, date Total enrollment / Enrollment goal	Design Control type	Study & Ctrl Drugs Dose, Route & Regimen	Study Objective	# subjs by arm entered/ completed	Duration	Gender M/F Median Age (Range)	Primary Endpoint(s)
RVL-1201-201	US (16)	29MAY2015-24OCT2016 140 (135)	Randomized, double-masked, placebo-controlled Phase 3, eligible subjects were randomized to 1 of 2 treatment arms and treated for 42 days	• RVL-1201: 1 drop in each eye QD • Vehicle (Placebo): 1 drop in each eye QD	• To evaluate the efficacy of RVL-1201 • To assess the safety and tolerability of RVL-1201	RVL-1201: 94/90 Vehicle (Placebo): 46/45	42 days	34M / 106F 67.0 (22, 85) years	Mean increase from baseline (Day 1, Hour 0) in number of points seen in the top 4 rows on the LPFT at: 1. Hour 6 on Day 1 versus Vehicle in the study eye 2. Hour 2 on Day 14 versus Vehicle in the study eye Tested sequentially in the order specified.
RVL-1201-202	US (27)	26JUN2018-10APR2019 164 (150)	Randomized, double-masked, placebo-controlled Phase 3, eligible subjects were randomized to 1 of 2 treatment arms and treated for 42 days	• RVL-1201: 1 drop in each eye QD • Vehicle (Placebo): 1 drop in each eye QD	• To evaluate the efficacy of RVL-1201 • To assess the safety and tolerability of RVL-1201	RVL-1201: 109/108 Vehicle (Placebo): 55/53	42 days	48M / 116F 67.0 (14, 92) years	Mean increase from baseline (Day 1, Hour 0) in number of points seen in the top 4 rows on the LPFT at: 1. Hour 6 on Day 1 versus Vehicle in the study eye 2. Hour 2 on Day 14 versus Vehicle in the study eye Tested sequentially in the order specified.

Source: Table 1 of Applicant's Summary of Efficacy Report

Summaries of studies included in the safety analysis

Study ID	Number of Study Centers Location(s)	Study start Enrollment status, date Total enrollment / Enrollment goal	Design Control type	Study & Ctrl Drugs Dose, Route & Regimen	Study Objective	# subjs by arm entered/ completed	Duration	Gender M/F Median Age (Range)	Safety Assessments
RVL-1201-203	US (35)	20JUN2018-14MAR2019 234 (225)	Randomized in 2:1 ratio, Placebo-controlled Double-masked, Multi-center, Parallel design	• RVL-1201: 1 drop in each eye QD • Vehicle (Placebo): 1 drop in each eye QD	• To demonstrate safety of RVL-1201 in the treatment of acquired blepharoptosis	RVL-1201: 157/143 Vehicle (Placebo): 77/75	84 days	55M / 179F 66.0 (13, 90) years	Safety was measured by bilateral ophthalmic examinations (Snellen VA, pupil diameter measurement, SLE/CFS, IOP tonometry, dilated ophthalmoscopy/fundus exam), measurement of vital signs (BP/HR), and recording of AEs.

Source: Table 1 of Applicant's Summary of Safety Report

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This statistical review focused on the two pivotal Phase 3 studies for the efficacy summary (Studies 201 and 202) and on the four studies for the safety summary (Studies 001, 201, 202, and 203).

2.2   Data Sources

The primary data source for this review were the clinical study reports (CSR), study protocols including amendments, statistical analysis plans, and the analyses and tabulation datasets. These were provided in an electronic submission located at \\CDSESUB1\evsprod\NDA212520\0001\. The primary analysis datasets are located at \\CDSESUB1\evsprod\NDA212520\0001\m5\datasets\.

3   STATISTICAL EVALUATION

3.1   Data and Analysis Quality

The reviewer found the quality of the submitted data and analysis acceptable.

3.2   Evaluation of Efficacy

3.2.1   Study Design and Endpoints

Study Design

The main efficacy support for RVL-1201 for the treatment of acquired ptosis was based on two similarly designed pivotal Phase 3 studies: Study 201 and Study 202.

Both studies were a 6-week, randomized, double-masked, placebo-controlled Phase 3 studies designed to assess the efficacy and safety of RVL-1201 for the treatment of acquired ptosis. Study 201 was conducted at 16 sites in the United States (US); the study was initiated on 29 May 2015 and completed on 24 October 2016. Study 202 was conducted at 27 sites in the US; the study was initiated on 20 June 2018 and completed on 10 April 2019.

In Study 201 and 202, respectively, a total of 140 subjects at least 18 years of age and a total of 164 subjects at least 9 years of age with acquired ptosis who demonstrated the following items in the same qualifying eye at the screening and baseline visits were enrolled: (i) a visual field loss on a reliable LPFT of ≥ 8 points in the top 2 rows and able to see ≥ 9 total points in the top 4 rows (see left panel in Figure below), (ii) MRD of ≤ 2 mm (see right panel in Figure below), and (iii) corrected Snellen visual acuity (VA) of $\geq 20/80$.

The LPFT is a modified visual field test designed to assess how wide an area a patient with an acquired ptosis can see in the superior field region. In this test, 35 points are included in the superior field region (points within the orange color in the figure below) and 14 points are tested in the inferior field region (points within the green color in the figure below). In patients with ptosis, only tests on the superior field region was used for efficacy evaluation.

Regarding the LPFT test, the applicant provided the following additional detail in the NDA:

> "The LPFT is a customized visual field test programmed into the Humphrey Visual Field (HVF) analyzer that is designed to assess the functional disability associated with ptosis and has **98.8% sensitivity to detect the presence of a visual field defect**."

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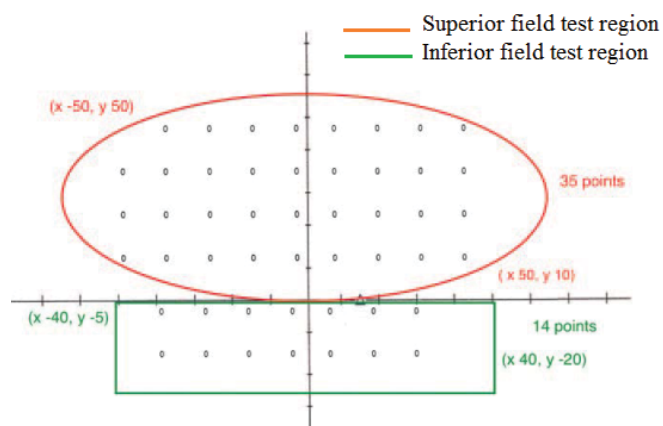
Source: Figure 1 of Study 201 and 202 Clinical Study Reports.

The MRD, the distance from the central pupillary light reflex to the central margin of the upper eyelid, was measured using external photograph (See detail in Appendix).
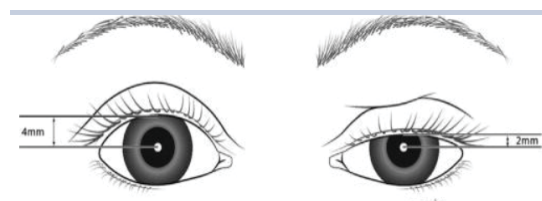
Source: https://eyewiki.aao.org/Margin_to_reflex_distance_1,2,3

An increase in the number of points seen in the superior region of the LPFT test and in the marginal reflex distance is associated with an improvement in the drooping of the upper eyelid.

In both studies, eligible subjects who met all the enrollment criteria were randomized in a 2:1 ratio to one of the two treatment groups and treated for 42 days:

- RVL-1201 Ophthalmic Solution (N = 94 in Study 201 and N = 109 in Study 202)

- Vehicle (placebo) (N = 46 in Study 201 and N = 55 in Study 202)

The total treatment duration in both studies was 42 days. During the treatment period, subjects were to receive one drop of study drug in each eye once daily (QD) in the morning for 42 days and had scheduled visits on Days 1, 14, and 42.

Both eyes were treated and followed in both studies. However, the eye with the smaller MRD measurement was considered as the study eye. If the MRD was the same in both eyes, the eye with the lower LPFT total score (the total number of points seen in the top 4 rows of the LFPT test) was considered as the study eye. The right eye was considered as the study eye if the MRD and LPFT were the same in both eyes.

Efficacy Evaluation

In both studies, key efficacy assessments were made based on LPFT, MRD, and Snellen visual acuity testing. In Study 201, palpebral fissure distance (PFD) – the distance from the upper lid margin to the lower lid margin through the central visual axis – was also assessed for efficacy. As in the MRD assessment, PFD was assessed using external digital photographs (see Appendix for detail).

The LPFT test was performed only on the study eye pre-dose at Hour 0 on Day 1 and post-dose at Hours 2 and 6 on Days 1 and 14. In Study 201, MRD and PFD measurements were taken on both eyes pre-dose at Hour 0 and post-dose at Hours 2, 6, and 8 on Days 1 and 14, and at Hour 0 on Day 42. In Study 202, MRD measurements were taken from both eyes pre-dose at Hour 0 and post-dose at Minutes 5 and 15 and at Hours 2 and 6 on Days 1 and 14, and at Minutes 5 and 15 on Day 42. Snellen visual acuity was measured in both eyes at hours 0 and 8 on Days 1 and 14.

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Efficacy Variables

The primary efficacy variable in both studies was **the mean increase in the total number of points seen in the top 4 of the LPFT test from baseline at (i) hour 6 on Day 1 and (ii) hour 2 on Day 14**. Per the applicant, the two time points were selected to reflect the duration (Hour 6) and onset (hour 2) of improvement in visual field. The applicant further stated that the time points were measured on different days because the number of LPFTs were limited to one per day after the Screening visit.

The mean change in MRD values from baseline assessed at the pre-specified timepoints on Days 1, 14, and 42 were defined as secondary efficacy variables in Study 202. In Study 201, the observed and change in MRD and PFD values from baseline at all measured post-dosing time points were defined as exploratory efficacy variables.

In both studies, measurement collected prior to dosing on Day 1 was considered as baseline.

3.2.2   Statistical Methodology

Primary Efficacy Analysis

The applicant's primary efficacy analysis in both studies was an evaluation of superiority of RVL-1201 in the primary efficacy variable. Superiority was assessed using two sample t-test in Study 201 and analysis of covariance (ANCOVA) with treatment as a fixed factor and baseline value as a covariate in Study 202.

In both studies, superiority of RVL-201 to vehicle in the primary efficacy variable was tested at the two time points sequentially: (i) at hour 6 on Day 1 first and then (ii) at hour 2 on Day 14. That is, Day 1 hour 6 was tested first and if p-value <0.05, then Day 14 hour 2 was tested at a significance level of 5%. The applicant stated that if (i) was statistically significant but (ii) was not, the study would still be considered positive.

The primary efficacy analysis in both studies was based on the intent-to-treat (ITT) population including all randomized subjects who received at least one dose of study medication.

As a sensitivity analysis, the primary efficacy analysis was also performed on the per-protocol (PP) population including all subject in the ITT population without a major protocol violation. As a supporting analysis, the applicant analyzed the primary efficacy data using Wilcoxon rank sum test.

Reviewer's Remark: *For the superiority testing, the applicant used two sample t-test in Study 201 and ANCOVA model adjusting for baseline value in Study 202 without providing a reasonable explanation for the different analysis approaches used in the two studies. In the absence of a reasonable explanation, in this review, ANCOVA model adjusting for baseline value was used in both studies for consistency. It should be noted that the overall conclusion using the two analysis approaches was the same except for minor numerical differences.*

Secondary Efficacy Analysis

In Study 202, the secondary efficacy variable of the mean change in MRD defined at the pre-specified timepoints was tested sequentially in the order listed if the primary efficacy variables were

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to be statistically significant at 5% significance level: *Day 1 Hour 2, Day 14 Hour 2, Day 1 Hour 6, Day 14 Hour 6, Day 1 Minutes 15, Day 14 Minutes 15 , Day 1 Minute 5, and Day 14 Minute 5*.

Superiority evaluations of RVL-201 to vehicle in the MRD measure at these time points were based on ANCOVA model using treatment as a fixed factor and baseline measure as a covariate. Based on the model, 95% CIs were provided. The applicant also analyzed the MRD data using Wilcoxon rank sum test as supporting analysis.

The MRD and PFD measures in Study 201 were analyzed similarly using ANCOVA model using treatment as a fixed factor and baseline measures as covariate. Since the applicant did not specify a formal testing strategy for these measures in Study 201, CIs and p-values presented for these measures were intended for descriptive use only.

Type I error control (Plan for multiplicity adjustment):

The overall study-wise Type I error rate for superiority testing in the primary and key secondary efficacy variables at the pre-specified timepoints were controlled at a significance level of 5%. The primary efficacy variable was tested for superiority at the two timepoints in a sequential manner at a significance level of 5%. Similarly, the key secondary efficacy variable in study 202 was tested for superiority at the pre-specified timepoints in a sequential manner at a significance level of 5% because superiority in the primary efficacy variable was achieved at the two pre-specified timepoints.

Handling of Missing Data

In both studies, the applicant performed the primary and secondary efficacy analyses using observed data (i.e. no missing data imputation) because very few subjects in both studies had missing data: *only three subjects in the RVL-1201 group in Study 201 and two subjects in the vehicle group in Study 202 had missing data in the primary efficacy analysis*. Sensitivity analyses were performed in both studies by imputing missing data using the last observation carried forward (LOCF) approach. Except for minor numerical differences, analyses based on the observed data and the LOCF approach yielded the same conclusion.

3.2.3   Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition

In Study 201, a total of 140 subjects (94 in RVL-201 and 46 in vehicle) were enrolled and most of the subjects (96%) completed the study. Only five subjects discontinued early from the study – four subjects in the RVL-201 group (three subjects due to AE and one subject due to protocol deviation) and one subject in the vehicle group (due to noncompliance). In Study 202, a total of 164 subjects (109 in RVL-201 and 55 in vehicle) were enrolled and most of the subjects (98%) completed the study. Only three subjects discontinued early from the study - one subject in the RVL-201 group (due to AE) and two subjects in the vehicle group (due to withdrawal of consent).

Demographic Characteristics

The summaries of the demographic characteristics for all randomized subjects who received at least one dose of study medication are shown in Table 1. As shown, most subjects in both studies were

female (76% in 201 and 71% in 202) and white (86% in 201 and 91% in 202). The average age of subjects in both studies was about 64 years (range: 22 – 85 in 201 and 14 – 92 in 201) with most subjects in both studies above 50 years of age (88% in 201 and 82% in 201).

Table 1: Summary of demographic and baseline disease characteristics
(Randomized Subjects)

| | | Study 201 | | | Study 202 | | |
		Vehicle (N=46)	RVL-1201 (N=94)	Overall (N=140)	Vehicle (N=55)	RVL-1201 (N=109)	Overall (N=164)
Age	Mean (SD)	63.2 (12.45)	64.7 (12.22)	64.2 (12.28)	63.3 (16.51)	63.6 (14.31)	63.5 (15.03)
	Median	65.5	68.0	67.0	67.0	67.0	67.0
	Range	26 - 85	22 - 83	22 - 85	14 - 85	20 - 92	14 - 92
Age Group	9-17 Years	0	0	0	1 (1.8)	0	1 (0.6)
	18-50 Years	5 (10.9)	12 (12.8)	17 (12.1)	10 (18.2)	19 (17.4)	29 (17.7)
	51-64 Years	17 (37.0)	26 (27.7)	43 (30.7)	12 (21.8)	27 (24.8)	39 (23.8)
	65-75 Years	19 (41.3)	39 (41.5)	58 (41.4)	20 (36.4)	43 (39.4)	63 (38.4)
	>75 Years	5 (10.9)	17 (18.1)	22 (15.7)	12 (21.8)	20 (18.3)	32 (19.5)
Sex	Female	32 (69.6)	74 (78.7)	106 (75.7)	39 (70.9)	77 (70.6)	116 (70.7)
	Male	14 (30.4)	20 (21.3)	34 (24.3)	16 (29.1)	32 (29.4)	48 (29.3)
Race	American Indian or Alaska Native	0	2 (2.1)	2 (1.4)	0	0	0
	Asian	1 (2.2)	2 (2.1)	3 (2.1)	2 (3.6)	4 (3.7)	6 (3.7)
	Black or African American	3 (6.5)	12 (12.8)	15 (10.7)	3 (5.5)	6 (5.5)	9 (5.5)
	White	42 (91.3)	78 (83.0)	120 (85.7)	50 (90.9)	99 (90.8)	149 (90.9)
Ethnicity	Hispanic or Latino	11 (23.9)	20 (21.3)	31 (22.1)	6 (10.9)	13 (11.9)	19 (11.6)
	Not Hispanic or Latino	35 (76.1)	74 (78.7)	109 (77.9)	49 (89.1)	96 (88.1)	145 (88.4)

Source: Table 5 of Clinical Study Reports for Study 201 and 202.

The table below shows baseline summary for the key efficacy variables in the two studies: total LPFT, MRD, and PFD (for Study 201 only). As shown, the mean baseline values for these variables were comparable between the treatment groups in both studies. For example, in both studies subjects were able to see a total of about 17 points at baseline in the top 4 superior region of the LPFT. Also, subjects had an average distance from the central pupillary light reflex to the central margin of the upper eyelid of about 1 mm at baseline.

In Study 201, the mean baseline PFD, the distance from the upper lid margin to the lower lid margin through the central visual axis, was about 7.5 mm in each treatment group.

| | | Study 201 | | | Study 202 | | |
	Summary	Vehicle (N=46)	RVL-1201 (N=94)	Overall (N=140)	Vehicle (N=55)	RVL-1201 (N=109)	Overall (N=164)
LPFT	Mean (SD)	16.9 (5.21)	17.0 (4.41)	16.9 (4.67)	17.6 (5.48)	17.6 (4.92)	17.6 (5.09)
	Median	17.0	17.0	17.0	18.0	18.0	18.0
	Range	2.0 – 25.0	8.0 – 27.0	2.0 – 27.0	10.0 – 26.0	8.0 – 27.0	8.0 – 27.0
MRD	Mean (SD)	1.03 (0.678)	1.16 (0.661)	1.12	1.07 (0.700)	1.04 (0.735)	1.049 (0.720)
	Median	1.0	1.0	1.0	1.0	0.0	1.0
	Range	0.0 – 2.0	0.0 – 3.0	0.0 – 3.0	0.0 – 2.0	1.0 – 2.0	0.0 – 2.0
PFD	Mean (SD)	7.4 (1.33)	7.5 (1.46)	7.4 (1.41)	--	--	--
	Median	7.25	7.50	7.5	--	--	
	Range	4.5 – 9.5	5.0 – 11.0	4.5 – 11.0	--	--	--

Source: Based on reviewer analysis. LPFT: Leicester Peripheral Field Test; MRD: Marginal reflex distance.

3.2.4   Efficacy Results and Conclusions

In this section, results of the primary and secondary efficacy variables in both studies are presented and discussed.

Analysis of Primary Efficacy Variable: Change in LPFT

The primary efficacy outcome in both studies was the change in the number of points seen (from a total of 35 points) in the superior field region of the LPFT test from baseline (Day 1 Hour 0) to Day 1 Hour 6 and Day 14 Hour 2. The two time points represent the duration (Hour 6) and onset (Hour 2) of improvement in visual field. An increase in the number of points seen on the visual field test signals an improvement in this parameter.

The efficacy criterion in both studies was demonstration of superiority of RVL-1202 to vehicle in the number of points seen at the two time points tested in a sequential manner.

Figure 3 below shows the mean number of points seen in the superior visual field region of the LPFT test at the three time points: *Day 1 Hour 0 (baseline), Day 1 Hour 6 (duration), and Day 14 Hour 2 (Onset)*. As shown, in both studies, subjects in both treatment groups had a mean baseline LPFT of about 17 points. However, post-treatment (*at Day 1 Hour 6 and at Day 14 Hour 2*), subjects in the RVL-1201 group were able to see 4 to 5 more points than subjects in the vehicle group on the average.

Figure 3: Mean number of points seen in the superior field region of the LPFT test by visit
(All randomized subjects)
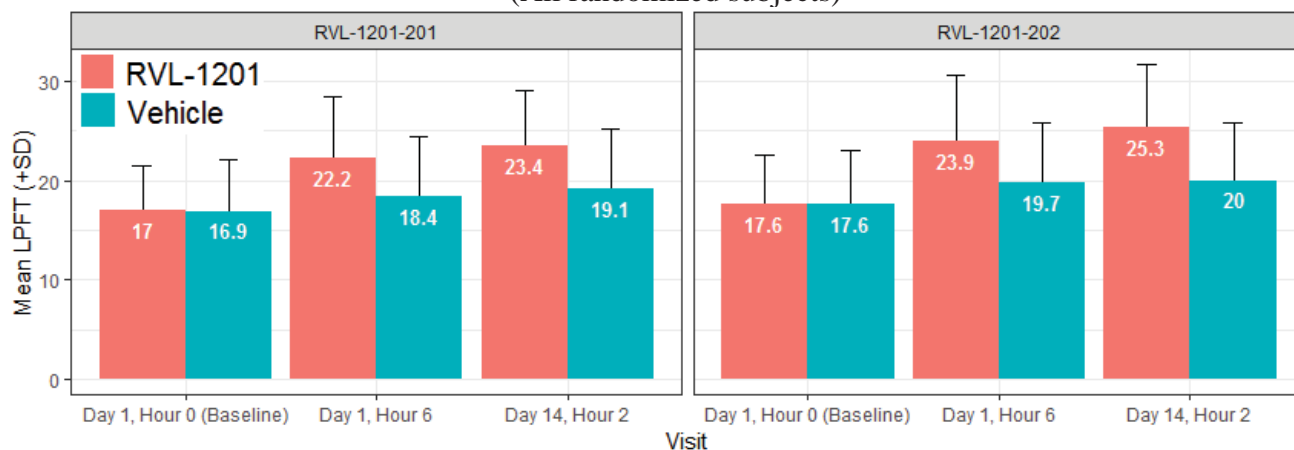
Also, more RVL-1201 treated subjects showed an improvement in the number of points seen in the superior field region of the LPFT test from baseline at Day 1 Hour 6 and at Day 14 Hour 2 compared to vehicle treated subjects.

For example, as shown in Figure 4 below, in Study 201 and 202, respectively, about 51% (**or 20%**) and 62% (**or 24%**) of subjects in the RVL-1201 group improved by at least 5 points (**or at least 10 points**) at Day 1, Hour 6 compared to 20% (**or 2%**) and 27% (**or 6%**) of subjects in the vehicle group (left panel). Similarly, about 62% (**or 21%**) and 67% (**or 28%**) of subjects in the RVL-1201 group were able to see at least 5 points (**or at least 10 points**) at Day 14, Hour 2 compared to 26% (**or 9%**) and 30% (**or 8%**) of subjects in the vehicle group (right panel).

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Figure 4: Cumulative distribution of the change in LPFT from baseline by visit and timepoint
(All Randomized Subjects)
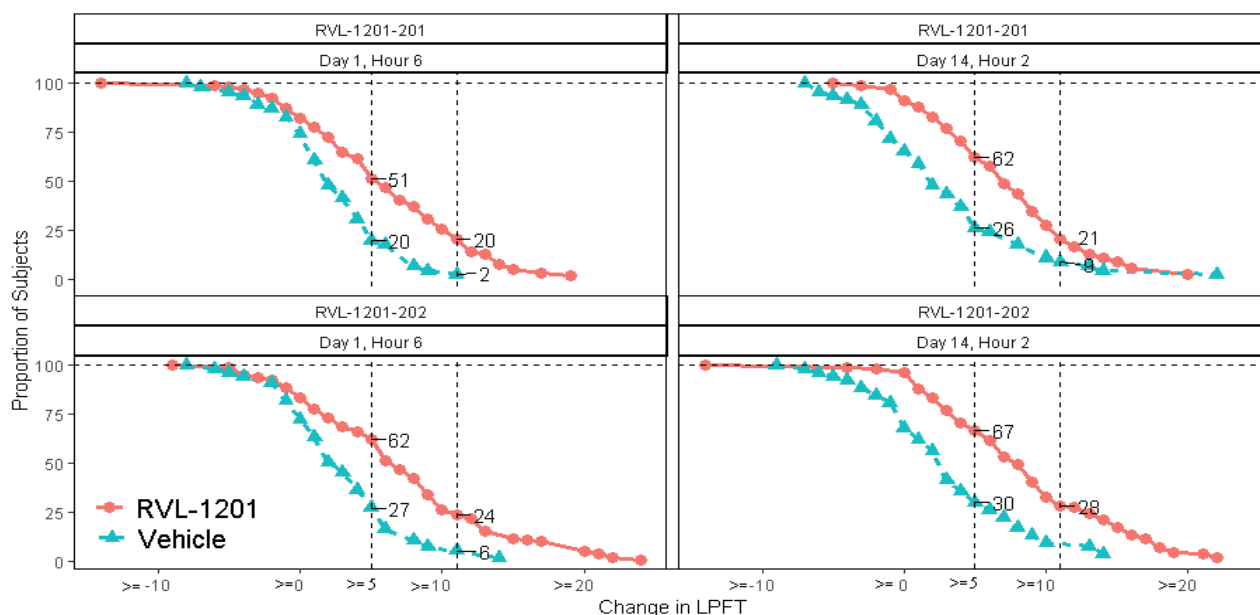
Treatment comparison in the mean change in the number of points seen in the superior field region of the LPFT test was made using ANCOVA model. Table 2 below shows the summary of the mean change from baseline (Day 1 Hour 0) at Day 1 Hour 6 and at Day 14 Hour 2 in the two studies. The table also shows the treatment differences (*RVL-1201 minus Vehicle*) and the corresponding 95% confidence intervals (CIs) including p-values based on the ANCOVA model.

Table 2: Summary of mean change in LPFT point from baseline at Day 1 Hour 6 and Day 14 Hour 2
(All randomized subjects)

		Study 201		Study 202	
		Vehicle	RVL-1201	Vehicle	RVL-1201
Day 1, Hour 0 (Baseline)	N	46	94	55	109
	Mean (SD)	16.9 (5.21)	17.0 (4.41)	17.6 (5.48)	17.6 (4.92)
	Median	17.0	17.0	18.0	18.0
	Range	2.0 - 25.0	8.0 - 27.0	10.0 – 26.0	8.0 – 27.0
Change from Baseline					
Day 1, Hour 6	**N**	46	94	55	109
	Mean (SD)	1.5 (3.93)	5.2 (5.97)	2.1 (4.28)	6.3 (6.72)
	Median	1.0	5.0	2.0	6.0
	Range	-8.0 – 11.0	-14 – 19.0	-8.0 – 14.0	-9.0 – 24.0
	Difference in LS Means (95% CI)		**3.7 (1.8, 5.6)**		**4.2 (2.4, 6.1)**
	P-value		**<0.001**		**<0.001**
Day 14, Hour 2	N	46	91	53	109
	Mean (SD)	2.2 (5.80)	6.4 (5.04)	2.43 (5.26)	7.70 (6.40)
	Median	1.0	6.0	2.0	7.0
	Range	-7.0 – 22.0	-5.0 – 20.0	-9.0 – 14.0	-14.0 – 22.0
	Difference in LS Means (95% CI)		**4.2 (2.4, 6.0)**		**5.3 (3.5, 7.1)**
	P-value		**<0.001**		**<0.001**

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Based on the model, subjects in the RVL-1201 group displayed a statistically superior increase in the number of points seen at the two time points from baseline compared to subjects in the vehicle group. In Study 201, the increase in the number of points seen in the RVL-1201 group was higher than in the vehicle group by 3.7 points (95% CI: 2.0 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, in Study 202, the increase in the number of points seen in the RVL-1201 group was higher than 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**.

Reviewer's Remark

i)   *Three subjects in the RVL-1201 group and two subjects in the vehicle group had missing data at Day 14 Hour 2. Analysis based on the LOCF imputation approach yielded the same conclusion except for minor numerical differences.*

ii) *Due to the discrete nature of the LPFT data, the change from baseline in the number of points seen at the two time-points were also analyzed using Wilcoxon rank-sum test and similar conclusion was achieved.*

Analysis of Secondary Efficacy Variable: Change in MRD

In both studies, MRD was measured using external photograph at pre-specified timepoints. An increase in MRD signals an improvement in the drooping of the upper eyelid.

Figure 5 below shows the mean MRD at the various time points on Days 1, 14, and 42. As shown, in Study 202 (bottom panel), the mean baseline MRD value (at Day 1 Hour 0) was comparable between the treatment groups (about 1.1 mm) whereas, in Study 201 (top panel), the mean baseline MRD values in the RVL-1201 group was slightly higher than in the vehicle group (1.16 mm vs 1.03 mm).

Figure 5: Summary of mean (+SD) MRD over time
(All randomized Subjects)
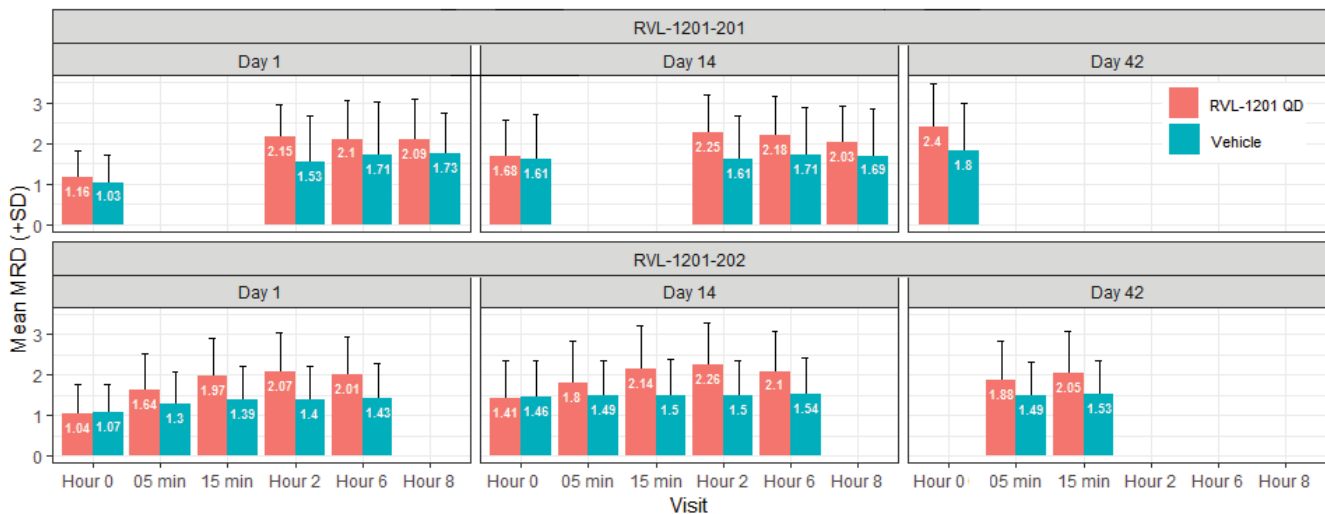
Note 1: By design, MRD values were not measured post-dose at 5 and 15 minutes on Days 1, 14, and 42 in Study 201 and at Hours 0 and 8 on Day 1 in Study 202. Measurements at Day 1 and 14 Hour 0 were taken prior to instillation of study medication while on Day 42 Hour 0 was taken after instillation of study medication.

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Regarding MRD measures post-dose at Days 1, 14 and 42, subjects in both treatment groups (in both studies) displayed an improvement from baseline although the improvement was numerically better for subjects in the RVL-1201 group than in the vehicle group.

The summary of the mean change in MRD from baseline (Day 1 Hour 0) at pre-specified post-dose timepoints on Days 1, 14, and 42 are shown In Table 3 and Figure 6 for Study 201 and in Table 4 and Figure 7 for Study 202. The tables also display the treatment differences (*RVL-1201 minus Vehicle*) for the mean change in MRD at the pre-specified timepoints and the corresponding 95% CI including p-values based on ANCOVA model.

As shown in Table 3 and Figure 6, in Study 201, subjects in the RVL-1201 group yielded numerically greater improvement in MRD from baseline than in the vehicle group. However, statistically significant differences were achieved only at Day 1 Hour 2, Day 14 Hour 2 and Hour 6, and Day 42 Hour 0. It should be noted that since the change in MRD variable was defined as an exploratory variable in Study 201, p-values and CIs presented in the table were intended for descriptive use only.

Table 3: Summary of mean change in MRD from baseline (Day 1 Hour 0) over time (Study 201)
(All randomized subjects)

| Visit | Time | Vehicle | | | | RVL-1201 | | | | Difference in LS Means (95% CI) | p-value |
		N	Mean (SD)	Median	Range	N	Mean (SD)	Median	Range		
Day 1	Hour 0	46	1.03 (0.678)	1.0	0.0 - 2.0	94	1.16 (0.661)	1.0	0.00 - 3.00	--	--
	Hour 2	46	0.50 (0.803)	0.0	-1.0 - 3.0	94	0.99 (0.776)	1.0	-1.0 - 3.0	0.52 (0.24, 0.79)	0.0003
	Hour 6	46	0.67 (1.001)	0.5	-1.0 - 4.0	94	0.94 (0.924)	1.0	-1.0 - 4.5	0.29 (-0.05, 0.63)	0.0905
	Hour 8	46	0.70 (0.771)	0.5	-0.5 - 3.0	94	0.93 (0.958)	1.0	-1.0 - 4.0	0.27 (-0.05, 0.59)	0.0956
Day 14	Hour 0	46	0.58 (0.943)	0.5	-1.0 - 4.0	94	0.52 (0.820)	0.5	-1.0 - 3.5	-0.02 (-0.32, 0.28)	0.9051
	Hour 2	46	0.58 (0.875)	0.5	-1.0 - 3.0	91	1.09 (0.799)	1.0	-1.0 - 3.0	0.54 (0.25, 0.83)	0.0004
	Hour 6	45	0.70 (0.985)	0.5	-1.0 - 4.0	92	1.03 (0.856)	1.0	-0.5 - 4.0	0.36 (0.04, 0.68)	0.0296
	Hour 8	45	0.68 (1.023)	0.5	-2.0 - 4.0	91	0.88 (0.857)	1.0	-1.0 - 3.0	0.25 (-0.07, 0.57)	0.1280
Day 42	Hour 0	45	0.79 (1.020)	1.0	-1.0 - 4.5	91	1.25 (1.036)	1.0	-1.0 - 4.0	0.50 (0.13, 0.87)	0.0087

Note: Measurements at Day 1 and 14 Hour 0 were taken prior to instillation of study medication while on Day 42 Hour 0 was taken after instillation of study medication.

Figure 6: Summary of the mean change in MRD from baseline at each visit and timepoint (Study 201)
(All randomized subjects)
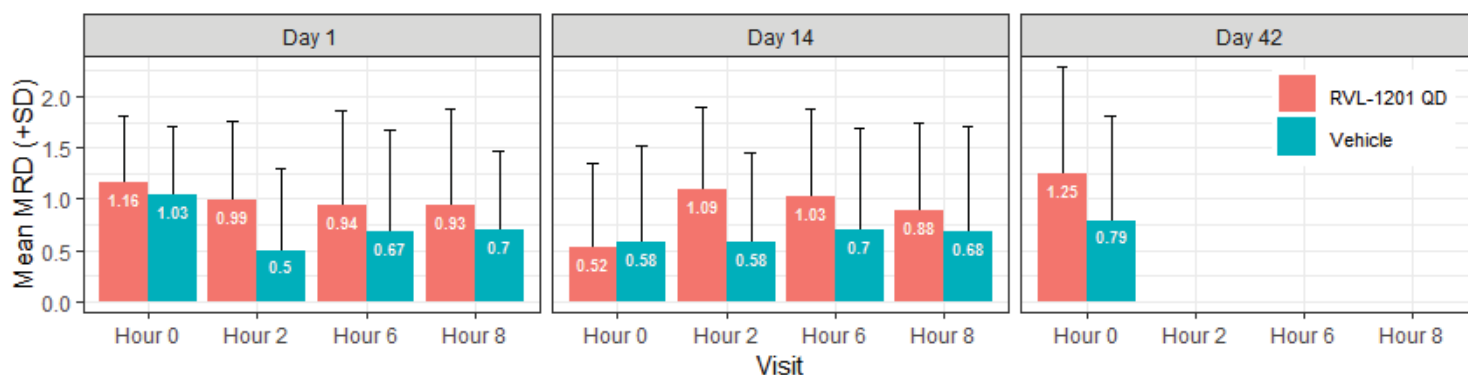
In Study 202, the change in MRD was defined as the key secondary efficacy variable. The sponsor tested superiority of RVL-1201 to vehicle in the secondary efficacy variable at the pre-specified timepoints sequentially at 5% significance level in the following order because the primary efficacy variable was determined statistically significant at 5% significance level: *Day 1 Hour 2, Day 14 Hour*

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2, Day 1 Hour 6, Day 14 Hour 6, Day 1 Minutes 15, Day 14 Minutes 15 , Day 1 Minutes 5, and Day 14 Minutes 5. Superiority was assessed using ANCOVA model based on all randomized subjects. The ANCOVA model included treatment and baseline MRD as a covariate.

Based on the model, subjects in the RVL-1201 group yielded a superior marginal reflex distance increase at all the pre-specified timepoints from baseline compared to subjects in the vehicle group. As shown in Table 4 and Figure 7 below, the mean increase in MRD in the RVL-1201 group was higher than in the vehicle group by 0.7 mm (95% CI: 0.45 to 0.96; p<0.001] at Day 1 Hour 2 and by 0.78 mm (95% CI: 0.50 to 1.06 mm; p < 0.001) at Day 14 Hour 2. Similarly, the mean increase in MRD in the RVL-1201 group was higher than in the vehicle group by 0.61 mm (95% CI: 0.37 to 0.86 mm; p<0.001] at Day 1 Hour 6 and by 0.58 mm (95% CI: 0.31 to 85 mm; p < 0.001) at Day 14 Hour 6. Superiority was also achieved at the earliest timepoints (post-dose 5 minutes and 15 minutes) although the magnitude of the treatment difference was slightly lower at 5 minutes post-dose.

Table 4: Summary of mean change in MRD from baseline (Day 1 Hour 0) over time (Study 202)
(All randomized subjects)

Visit	Time	Vehicle				RVL-1201				Difference in LS Means (95% CI)	p-value [a]
		N	Mean (SD)	Median	Range	N	Mean (SD)	Median	Range		
Day 1	Hour 0	55	1.07 (0.697)	1.0	0.00 - 2.00	109	1.04 (0.735)	1.0	0.00 - 2.00	--	--
	5 minutes	54	0.20 (0.571)	0.0	-1.00 - 1.50	108	0.59 (0.721)	0.5	-1.00 - 3.00	0.38 (0.16, 0.59)	0.0007 [7]
	15 minutes	55	0.32 (0.641)	0.0	-1.00 - 2.00	108	0.93 (0.811)	1.0	-1.00 - 3.00	0.60 (0.36, 0.84)	<0.0001 [5]
	Hour 2	55	0.33 (0.555)	0.0	-0.50 - 2.00	107	1.05 (0.903)	1.0	-1.00 - 4.00	0.71 (0.45, 0.96)	<0.0001 [1]
	Hour 6	55	0.35 (0.567)	0.5	-0.50 - 1.50	109	0.98 (0.867)	1.0	-1.00 - 3.50	0.61 (0.37, 0.86)	<0.0001 [3]
Day 14	Hour 0	53	0.40 (0.743)	0.5	-1.00 - 2.50	108	0.37 (0.805)	0.5	-2.00 - 3.00	-0.04 (-0.29, 0.22)	0.7800
	5 minutes	53	0.42 (0.775)	0.5	-1.00 - 2.50	107	0.77 (0.853)	1.0	-1.00 - 2.50	0.33 (0.07, 0.60)	0.0151 [8]
	15 minutes	52	0.41 (0.833)	0.5	-1.00 - 3.00	107	1.11 (0.922)	1.0	-1.00 - 3.50	0.68 (0.39, 0.97)	<0.0001 [6]
	Hour 2	53	0.43 (0.734)	0.5	-1.00 - 2.00	109	1.22 (0.926)	1.0	-1.00 - 3.50	0.78 (0.50, 1.06)	<0.0001 [2]
	Hour 6	53	0.47 (0.737)	0.5	-0.50 - 2.00	109	1.06 (0.902)	1.0	-1.00 - 3.50	0.58 (0.31, 0.85)	<0.0001 [4]
Day 42	5 minutes	53	0.42 (0.799)	0.5	-1.50 - 2.00	107	0.86 (0.849)	1.0	-1.00 - 3.50	0.42 (0.15, 0.68)	0.0020
	15 minutes	52	0.47 (0.926)	0.5	-2.00 - 2.50	106	1.04 (0.912)	1.0	-1.00 - 4.00	0.55 (0.26, 0.84)	0.0003

[a] Sequential order of testing of the change in MRD.
Note: MRD measurements at Day 1 and 14 Hour 0 were taken prior to instillation of study medication.

Figure 7: Summary of the mean change in MRD from baseline over time (Study 202)
(All randomized subjects)
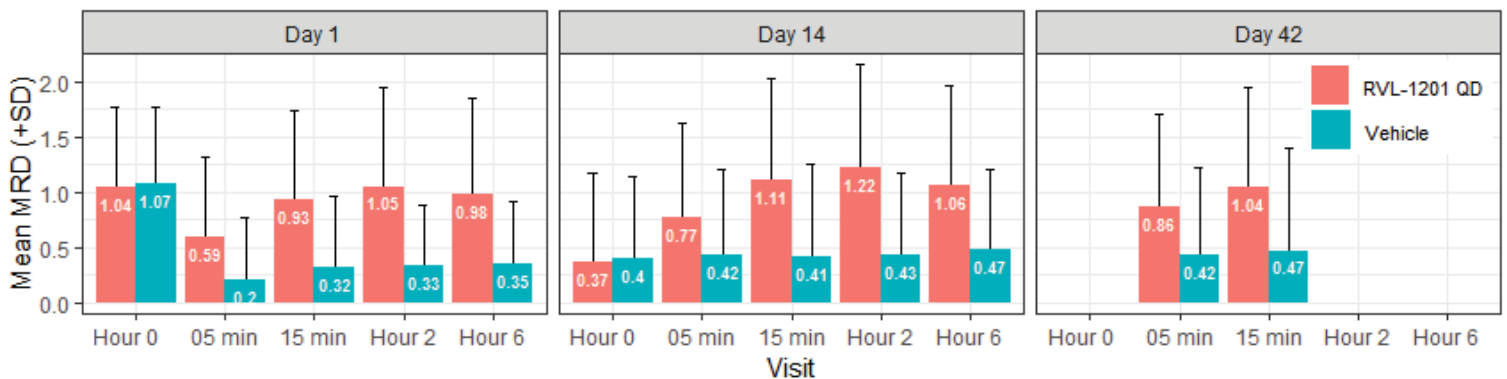
Analysis of Exploratory Efficacy Variable: Change in PFD

The change in palpebral fissure distance (PFD) – *the distance from the upper lid margin to the lower lid margin through the central visual axis* – was also assessed as an exploratory efficacy variable in Study 201 only. An increase in the PFD measure signals an improvement in the drooping of the upper eyelid.

Table 5 below shows the summary of the change in PFD from baseline (Day 1 Hour 0) at the pre-specified timepoints. As shown, the mean PDF at baseline was comparable between the treatment groups (~7.5 mm). The table also shows the treatment differences (*RVL-1201 minus Vehicle*) for the mean change in PFD at the pre-specified timepoints and the corresponding 95% CIs including p-values based on ANCOVA model.

As shown in the table, subjects in the RVL-1201 group showed a slight numerical increase in PFD at each post-dose timepoints compared to subjects in the vehicle group. However, statistically significant difference in the mean change in PFD was not achieved between the treatment groups at each of the specified timepoints on Days 1, 14, and 42 except at Day 1 Hour 2. It should be noted that since the change in PFD variable was defined as an exploratory variable in Study 201, p-values and CIs presented in the table were intended for descriptive use only.

Table 5: Summary of the mean change in PFD from baseline over time (Study 201)
(All randomized subjects)

Visit	Time	Vehicle				RVL-1201				Difference in LS Means (95% CI)	p-value
		N	Mean	Median	Range	N	Mean	Median	Range		
Day 1	Hour 0	46	7.39 (1.329)	7.3	4.50 - 9.50	94	7.46 (1.458)	7.5	5.00 - 11.0	--	
	Hour 2	46	0.50 (1.278)	0.3	-2.00 - 4.00	94	0.97 (1.026)	1.0	-1.00 - 4.00	0.47 (0.07, 0.86)	0.0210
	Hour 6	46	0.80 (1.310)	1.0	-2.00 - 4.00	94	0.80 (1.014)	1.0	-1.50 - 4.00	-0.00 (-0.40, 0.40)	0.9954
	Hour 8	46	0.74 (1.031)	0.5	-1.00 - 3.50	94	0.94 (1.196)	1.0	-2.00 - 5.00	0.20 (-0.20, 0.61)	0.3276
Day 14	Hour 0	46	0.63 (1.280)	1.0	-2.00 - 4.00	94	0.36 (1.208)	0.0	-2.50 - 4.00	-0.27 (-0.71, 0.17)	0.2274
	Hour 2	46	0.77 (1.397)	1.0	-2.00 - 5.00	91	0.96 (1.156)	1.0	-2.00 - 3.50	0.18 (-0.26, 0.63)	0.4134
	Hour 6	45	0.86 (1.417)	1.0	-1.00 - 5.00	92	0.93 (1.163)	1.0	-1.50 - 3.50	0.08 (-0.37, 0.53)	0.7284
	Hour 8	45	0.71 (1.494)	0.5	-3.00 - 5.50	92	0.86 (1.059)	1.0	-1.50 - 3.00	0.15 (-0.29, 0.59)	0.4910
Day 42	Hour 0	45	0.81 (1.482)	1.0	-2.00 - 6.00	91	1.13 (1.170)	1.0	-2.00 - 4.00	0.32 (-0.15, 0.78)	0.1792

Reviewer's Note:

In Study 201, the treated group showed numerically greater increase in MRD (distance from the center of the eye to the center of the upper eyelid) compared to the vehicle group at all visits and timepoints (See Table 3). However, as shown in Table 5, the same effect was not observed for the PFD measure (distance from the center of the upper eyelid to the center of the lower eyelid). What that mean is, on the average, subjects in the treated group may have shown a decrease in the distance from the center of the eye to the center of the lower eyelid. Table 6 in Appendix shows the summary of the mean change in the distance from center of the eye to center of the lower eyelid over time. As shown, the distance from center of the eye to the center of the lower eyelid over time in the treated group was numerically lower compared to the vehicle group. The reviewer defers to the medical review team for any possible clinical explanation.

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3.2.5 Efficacy Conclusion

Based on the collective efficacy evidences in Study 201 and Study 202, the RVL-1201 group displayed a statistically superior improvement in the number of points seen in the superior field region of the LPFT test from baseline at post-dose timepoints on Day 1 Hour 6 (duration) and on Day 14 Hour 2 (onset) compared to the vehicle group.

In addition, in Study 202, the RVL-1201 group was statistically superior to the vehicle group with respect to the increase in the marginal reflex distance (MRD) at all the pre-specified post-dose timepoints on Days 1 and 14. Study 201 also provided supporting evidences regarding the treatment benefit of RVL-1201 compared to vehicle in improving the marginal reflex distance from baseline.

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3.3 Safety Evaluation

In this section, a high-level summary of the integrated safety data is presented and discussed. For a comprehensive study level safety evaluation, see the FDA medical review.

The integrated safety summary report was based on the four completed studies: A Phase 2 proof-of-concept study (RVL-1201-001 – here after referred to as Study 001), the two efficacy and safety studies (Studies 201 and 202), and a Phase 3 safety study (Study 203).

Study 001 was a 2-week randomized, multi-centered, double-masked, vehicle-controlled Phase 1/2a study deigned to assess the safety and efficacy of two dosing regimens of RVL-1201 in subjects with acquired ptosis. In this study, 46 eligible subjects were randomized in a 1:1:1 ratio and were to receive one of the three treatments for 2 weeks: RVL-1201 QD (N=15), RVL-1201 twice daily (BID, N=16), and vehicle (N=15). Both eyes were treated and assessed in the study. Only the QD dosing regimen was included in the integrated safety summary.

Study 203 was a 12-week randomized, multicentered, double-masked, placebo-controlled Phase 3 study designed to evaluate the safety of RVL-1201 compared to vehicle in subjects with acquired ptosis. In this study, 255 eligible subjects were randomized in a 2:1 ratio and were to receive one of the two treatments in each eye once a day (in the morning) for 84 days: RVL-1201 (N=157) or Vehicle (N=75). Both eyes were treated and assessed in the study.

In the integrated safety summary (ISS), a total 568 subjects who received at least one study medication were included (193 subjects in the vehicle group and 375 subjects in the RVL-1201 group). Most subjects in both treatment groups completed all study visits (95% in the RVL-1201 group and 97% in the vehicle group). About 4% of subjects discontinued study medication prior to study completion (5% in the RVL-1201 group and 3% in the vehicle group) and less than 2% of subjects in both treatment groups discontinued study medication due to an adverse event.

Summary of Treatment Exposure

The median duration of treatment exposure for subjects included in the ISS was 44 days (range: 1 to 102). The duration of exposure was comparable between the treatment groups.

Exposure to Study Medication

Parameter	RVL-1201 QD N=375	Vehicle (Placebo) N=193	Overall N=568
Exposure (days)	n=375	n=193	n=568
Mean (SD)	56.4 (24.01)	56.4 (24.02)	56.4 (23.99)
Median	44.0	44.0	44.0
Min, Max	1, 102	1, 91	1, 102

Source: Table 11 of Integrated Summary of Safety Report.

Summary of Treatment Emergent Adverse Events (TEAEs)

Based on the sponsor's integrated safety summary report, the number and percentage of subjects reporting any TEAEs were similar between the treatment groups (31.2% in the RVL-1201 group and 30.6 in the vehicle group). Four subjects (1.1%) in the RVL-1201 group reported serious TEAEs

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(hyperparathyroidism, arthralgia, cerebrovascular accident, and nephrolithiasis) whereas only one subject in the vehicle group reported serious TEAEs (lower gastrointestinal hemorrhage). Nine subjects (2.4%) in the RVL-1201 group (3 in 201, 1 in 202, and 5 in 203) and three subjects (1.6%) in the vehicle group (1 each in study 201, 202, and 203) discontinued study drug due to TEAEs. No death was reported in the four studies included in the safety summary.

Table below shows summary of the most frequent ocular and non-ocular TEAEs (>1%) reported by system organ class and preferred term based on all subjects who received at least one study medication (safety population). Punctate keratitis and conjunctival hyperemia were most frequent ocular TEAEs reported in the RVL-1201 group whereas punctate keratitis and eye pruritus were most frequent ocular TEAEs reported in the vehicle group.

MedDRA System Organ Class Preferred Term	RVL-1201 QD N=375 n (%)	Vehicle (Placebo) N=193 n (%)
Eye disorders	**74 (19.7)**	**26 (13.5)**
Punctate keratitis	13 (3.5)	4 (2.1)
Conjunctival hyperaemia	11 (2.9)	1 (0.5)
Dry eye	9 (2.4)	1 (0.5)
Vision blurred	8 (2.1)	0
Eye irritation	4 (1.1)	0
Eye pruritus	1 (0.3)	3 (1.6)
General disorders and administration site conditions	**13 (3.5)**	**4 (2.1)**
Instillation site pain	8 (2.1)	0
Instillation site complication	1 (0.3)	3 (1.6)
Infections and infestations	**16 (4.3)**	**13 (6.7)**
Nasopharyngitis	3 (0.8)	3 (1.6)
Upper respiratory tract infection	3 (0.8)	3 (1.6)
Investigations	**9 (2.4)**	**6 (3.1)**
Vital dye staining cornea present	8 (2.1)	4 (2.1)
Nervous system disorders	**11 (2.9)**	**4 (2.1)**
Headache	8 (2.1)	2 (1.0)

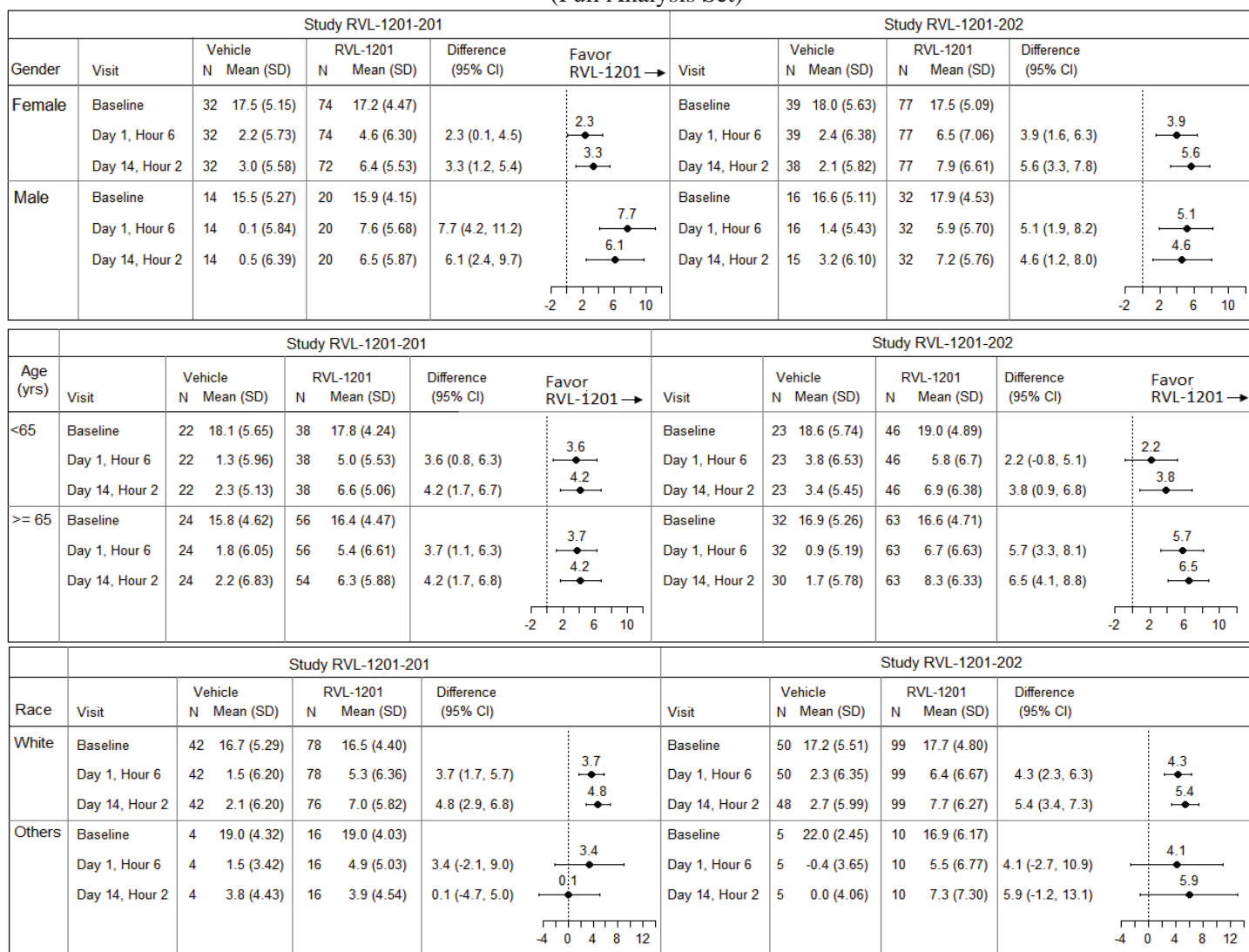Source: Table 17 of Integrated Summary of Safety Report.

Based on the overall safety evaluation, the applicant stated that the safety profiles for subjects treated with RVL-1201 and vehicle group were comparable, and as such, RVL-1201 administered once daily was well tolerated.

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4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, the primary efficacy variable of the change in LPFT from baseline at the two timepoints was summarized by the subgroups of Age Group (<65 versus >=65 years), Gender, and Race (White versus Other). It should be noted that the race categories of '*American Indian or Alaska Native*', '*Asian*', and '*Black or African American*' were pooled as 'Others' due to small sample sizes.

Figure 8 below shows summary of the mean change in LPFT over time by the subgroups of Gender, Age, and Race. As shown below, within the levels of each subgroup variables, subjects in the RVL-1201 group were able to see numerically more points than subjects in the vehicle group. The efficacy results in the levels of these subgroup variables were consistent with the overall population (See Figure 1). It should be noted that in some subgroups (example 'Race: Others') there were only few subjects and results for these subgroup levels may not be indicative of the overall treatment effects.

Figure 8: Change in LPFT over time by the subgroups of Gender, Age Group, and Race
(Full Analysis Set)

Study RVL-1201-201

Gender	Visit	Vehicle N Mean (SD)	RVL-1201 N Mean (SD)	Difference (95% CI)	Favor RVL-1201 →
Female	Baseline	32 17.5 (5.15)	74 17.2 (4.47)		
	Day 1, Hour 6	32 2.2 (5.73)	74 4.6 (6.30)	2.3 (0.1, 4.5)	2.3
	Day 14, Hour 2	32 3.0 (5.58)	72 6.4 (5.53)	3.3 (1.2, 5.4)	3.3
Male	Baseline	14 15.5 (5.27)	20 15.9 (4.15)		
	Day 1, Hour 6	14 0.1 (5.84)	20 7.6 (5.68)	7.7 (4.2, 11.2)	7.7
	Day 14, Hour 2	14 0.5 (6.39)	20 6.5 (5.87)	6.1 (2.4, 9.7)	6.1

Study RVL-1201-202

Visit	Vehicle N Mean (SD)	RVL-1201 N Mean (SD)	Difference (95% CI)	
Baseline	39 18.0 (5.63)	77 17.5 (5.09)		
Day 1, Hour 6	39 2.4 (6.38)	77 6.5 (7.06)	3.9 (1.6, 6.3)	3.9
Day 14, Hour 2	38 2.1 (5.82)	77 7.9 (6.61)	5.6 (3.3, 7.8)	5.6
Baseline	16 16.6 (5.11)	32 17.9 (4.53)		
Day 1, Hour 6	16 1.4 (5.43)	32 5.9 (5.70)	5.1 (1.9, 8.2)	5.1
Day 14, Hour 2	15 3.2 (6.10)	32 7.2 (5.76)	4.6 (1.2, 8.0)	4.6

(x-axis: -2 2 6 10)

Study RVL-1201-201

Age (yrs)	Visit	Vehicle N Mean (SD)	RVL-1201 N Mean (SD)	Difference (95% CI)	Favor RVL-1201 →
<65	Baseline	22 18.1 (5.65)	38 17.8 (4.24)		
	Day 1, Hour 6	22 1.3 (5.96)	38 5.0 (5.53)	3.6 (0.8, 6.3)	3.6
	Day 14, Hour 2	22 2.3 (5.13)	38 6.6 (5.06)	4.2 (1.7, 6.7)	4.2
>= 65	Baseline	24 15.8 (4.62)	56 16.4 (4.47)		
	Day 1, Hour 6	24 1.8 (6.05)	56 5.4 (6.61)	3.7 (1.1, 6.3)	3.7
	Day 14, Hour 2	24 2.2 (6.83)	54 6.3 (5.88)	4.2 (1.7, 6.8)	4.2

Study RVL-1201-202

Visit	Vehicle N Mean (SD)	RVL-1201 N Mean (SD)	Difference (95% CI)	Favor RVL-1201 →
Baseline	23 18.6 (5.74)	46 19.0 (4.89)		
Day 1, Hour 6	23 3.8 (6.53)	46 5.8 (6.7)	2.2 (-0.8, 5.1)	2.2
Day 14, Hour 2	23 3.4 (5.45)	46 6.9 (6.38)	3.8 (0.9, 6.8)	3.8
Baseline	32 16.9 (5.26)	63 16.6 (4.71)		
Day 1, Hour 6	32 0.9 (5.19)	63 6.7 (6.63)	5.7 (3.3, 8.1)	5.7
Day 14, Hour 2	30 1.7 (5.78)	63 8.3 (6.33)	6.5 (4.1, 8.8)	6.5

(x-axis: -2 2 6 10)

Study RVL-1201-201

Race	Visit	Vehicle N Mean (SD)	RVL-1201 N Mean (SD)	Difference (95% CI)	
White	Baseline	42 16.7 (5.29)	78 16.5 (4.40)		
	Day 1, Hour 6	42 1.5 (6.20)	78 5.3 (6.36)	3.7 (1.7, 5.7)	3.7
	Day 14, Hour 2	42 2.1 (6.20)	76 7.0 (5.82)	4.8 (2.9, 6.8)	4.8
Others	Baseline	4 19.0 (4.32)	16 19.0 (4.03)		
	Day 1, Hour 6	4 1.5 (3.42)	16 4.9 (5.03)	3.4 (-2.1, 9.0)	3.4
	Day 14, Hour 2	4 3.8 (4.43)	16 3.9 (4.54)	0.1 (-4.7, 5.0)	0.1

Study RVL-1201-202

Visit	Vehicle N Mean (SD)	RVL-1201 N Mean (SD)	Difference (95% CI)	
Baseline	50 17.2 (5.51)	99 17.7 (4.80)		
Day 1, Hour 6	50 2.3 (6.35)	99 6.4 (6.67)	4.3 (2.3, 6.3)	4.3
Day 14, Hour 2	48 2.7 (5.99)	99 7.7 (6.27)	5.4 (3.4, 7.3)	5.4
Baseline	5 22.0 (2.45)	10 16.9 (6.17)		
Day 1, Hour 6	5 -0.4 (3.65)	10 5.5 (6.77)	4.1 (-2.7, 10.9)	4.1
Day 14, Hour 2	5 0.0 (4.06)	10 7.3 (7.30)	5.9 (-1.2, 13.1)	5.9

(x-axis: -4 0 4 8 12)

Note: Difference and corresponding 95% CI were based on ANCOVA model adjusted for baseline number of points read on the LPFT test.

5   SUMMARY AND CONCLUSIONS

5.1   Statistical Issues

There are no major statistical issues in the submission.

5.2   Collective Evidence

In the pivotal Phase 3 efficacy and safety studies (Study 201 and Study 202), the applicant assessed the improvement in the drooping of the upper eyelid using (i) the number of points seen in the superior field region of the LPFT test and (ii) the marginal reflex distance (MRD). An improvement in these efficacy parameters signals an improvement in the drooping of the upper eyelid.

In Studies 201 and 202, RVL-1201 treated eyes displayed a statistically superior improvement in the number of points seen in the superior field region of the LPFT test from baseline at Day 1 Hour 6 (duration) and at Day 14 Hour 2 (onset) compared to vehicle treated eyes. For example, at the two time points, RVL-1201 treated eyes were able to see **four to five** more points from baseline than vehicle treated eyes on the average (Figure 1). Also, at the two timepoints, 55% to 65% of RVL-1201 treated eyes showed **at least five points** improvement in the LFPT test compared to 20% to 30% of vehicle treated eyes (Figure 4).

Additionally, in Study 202, RVL-1201 treated eyes displayed a statistically superior increase in the marginal reflex distance from baseline at all the pre-specified post-dose timepoints on Days 1 and 14 compared to vehicle treated eyes (Figure 2 right panel). For example, at the pre-specified timepoints, the increase in MRD in the RVL-1201 treated eyes were higher than in the vehicle treated eyes by **0.4 mm to 0.8 mm** where the largest difference was achieved at Day 14 Hour 2 (0.8 mm) followed by Day 1 Hour 2 (0.7 mm). Study 201 also provided supporting evidences regarding the treatment benefit of RVL-1201 compared to vehicle in improving the marginal reflex distance from baseline.

In this NDA submission, safety was assed based on four completed studies (Studies 001, 201, 202, and 203). Based on the applicant's integrated assessment of the safety data, the safety profiles for RVL-1201 and vehicle treated eyes were comparable. No death was reported in the four studies included in the safety summary. Four subjects in the RVL-1201 group and one subject in the vehicle group reported serious adverse events (AEs). Nine subjects in the RVL-1201 group (3 in 201, 1 in 202, and 5 in 203) and three subjects in the vehicle group (1 each in study 201, 202, and 203) discontinued study drug due to AE. Punctate keratitis (3.5%) and conjunctival hyperemia (2.9%) were most frequent ocular AEs reported in the RVL-1201 group and punctate keratitis (2.1%) and eye pruritus (1.6%) were most frequent ocular AEs reported in the vehicle group.

5.3   Conclusion and Recommendation

Based on the totality of evidence from Studies 201 and 202, the reviewer concludes that the application provided substantial evidence of efficacy of RVL-1201 administered once daily in improving the drooping of the upper eyelid in patients with acquired ptosis.

5.4 Labeling Recommendation

In Section 14 of the draft labeling, the applicant proposed to include the text below (RE: 14 Clinical Studies) including the primary efficacy results from Study 201 and Study 202 (RE: Table 2 below) and the secondary efficacy results from Study 202 (RE: Table 3 below).

14. CLINICAL STUDIES

PROPRIETARY NAME was evaluated for the treatment of acquired blepharoptosis ▓▓▓▓ (b) (4) in two ▓▓▓▓ (b) (4) randomized, double-masked, vehicle-controlled, parallel-group clinical efficacy trials. Both studies were randomized in an approximate 2:1 ratio of active versus vehicle. Efficacy was assessed with the Leicester Peripheral Field Test (LPFT) (primary) and photographic measurement of Marginal reflex distance 1 (MRD1). The primary efficacy endpoints were ordered in a hierarchy to compare PROPRIETARY NAME to vehicle on the mean increase from baseline (Day 1 Hour 0) in number of points seen on the top 4 rows of the LPFT in the study eye at Hour 6 on Day 1 and Hour 2 on Day 14.

In Trial 1 a total of 140 subjects were randomized 94 patients to the PROPRIETARY NAME group and 46 patients to the vehicle group. Treatments were administered once daily to each eye for 42 days (6 weeks). The mean age of the subjects was 64 ▓(b)(4) years.

In Trial 2 a total of 164 subjects were randomized 109 patients to the PROPRIETARY NAME group and 55 patients to the vehicle group. Treatments were administered once daily to each eye for 42 days (6 weeks). The mean age of the subjects was 63 ▓(b)(4) years.

▓▓▓▓▓▓▓▓▓▓▓▓ (b) (4) ▓▓▓. The results from both trials on the primary endpoint for Hour 6 on Day 1 and Hour 2 on Day 14 are presented in Table 2.

Table 2 - 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)

	Trial 1			Trial 2		
	Points Seen (SD) in Superior Visual Field		Mean Difference, p-value[a] [95% CL] p-value[b]	Points Seen (SD) in Superior Visual Field		Mean Difference, p-value[a] [95% CL] p-value[b]
	PROPRIETARY NAME N = 94	Vehicle N = 46	PROPRIETARY NAME vs Vehicle	PROPRIETARY NAME N = 109	Vehicle N = 55	PROPRIETARY NAME vs Vehicle
Baseline	17.0 (4.41)	16.9 (5.21)		17.6 (4.29)	17.6 (5.48)	
Day 1, Hour 6,						
Observed mean	22.2 (6.18)	18.4 (6.01)		23.9 (6.67)	19.7 (6.16)	
Mean change from baseline	5.2 (5.97)	1.5 (3.93)	3.67, (b) (4) [2.00, 5.34] (b) (4)	6.3 (6.72)	2.1 (4.28)	4.23 (b) (4) [2.36, 6.09], (b) (4)
Day 14, Hour 2,						
Observed mean	23.4 (5.60)	19.1 (6.13)		25.3 (6.35)	20.0 (5.84)	
Mean change from baseline	6.4 (5.04)	2.2 (5.80)	4.20, (b) (4) [2.30, 6.10] (b) (4)	7.7 (6.41)	2.4 (5.26)	5.30 (b) (4) [3.45, 7.14] (b) (4)

CL = confidence limit; LPFT = Leicester Peripheral Field Test; ITT = intent-to-treat; SD = standard deviation
a ▓(b) (4)
b ▓▓▓▓▓▓

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Marginal reflex distance 1 (MRD1), ▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓ (b) (4) showed a positive effect with PROPRIETARY NAME treatment. Greater MRD1 increases were observed for the PROPRIETARY NAME group than the vehicle group ▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓ (b) (4) 6 hours post-dose.

▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓ (b) (4)

Reviewer's Remark:

Overall, the applicant proposed text and tables included in Section 14 of the draft label appear acceptable. The reviewer has the following recommendations regarding Table 2 and Table 3 above:

    i)   *In Table 2, the mean difference (95% CI) column was based on the 2-sample test for Study 201 (Trial 1) and based on ANCOVA model adjusted for baseline LFPT points for Study 202 (Trial 2). For consistency reason, we recommend that the mean difference (95% CI) and p-value be based on the ANCOVA model for both studies. The reviewer recommends that* ▓▓▓ (b) (4) ▓▓▓▓▓▓▓▓▓▓▓

▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓ (b) (4)

    iii) *In* ▓▓▓ (b) (4) *the applicant should describe the ITT population in the footnote.*

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Appendix: External Photography (Source: Section 9.5.1.1.2 of the CSR)

An external photograph of the subject's face was taken at all study visits using the provided digital camera. At each site, the same level of ambient lighting was to be maintained for each photograph throughout the study. The subject was required to remove mascara and any other eyelid makeup, if applicable. The subject was also asked to relax his/her facial muscles. The photograph framed the subject's face from mid-forehead to the tip of the nose vertically and from ear-to-ear horizontally. A standardized millimeter ruler label was placed vertically on the forehead, centered above the eyebrows, as a measurement legend. All measurements were made from the digital image or color printed copy of the photograph using a handheld caliper and the millimeter ruler label as the legend.

Table 6: Summary of the mean change in the distance from center of the eye to
the center of the lower eyelid over time (Study 201)
(All Randomized Subjects)

| Visit | Time | Vehicle | | RVL-1201 | | Difference in LS Means | |
		N	Mean (SD)	N	Mean (SD)	(95% CI)	p-value
Day 1	Hour 0	46	6.36 (1.177)	94	6.30 (1.285)	--	
	Hour 2	46	0.00 (0.960)	94	-0.02 (0.852)	-0.02 (-0.34, 0.29)	0.8943
	Hour 6	46	0.13 (0.951)	94	-0.14 (0.993)	-0.27 (-0.62, 0.08)	0.1296
	Hour 8	46	0.04 (0.855)	94	0.01 (0.939)	-0.03 (-0.36, 0.29)	0.8418
Day 14	Hour 0	46	0.05 (0.979)	94	-0.16 (0.937)	-0.21 (-0.55, 0.12)	0.2132
	Hour 2	46	0.20 (1.046)	91	-0.14 (1.041)	-0.33 (-0.71, 0.04)	0.0798
	Hour 6	45	0.16 (1.117)	92	-0.09 (0.871)	-0.25 (-0.59, 0.10)	0.1571
	Hour 8	45	0.03 (1.052)	91	-0.01 (0.864)	-0.04 (-0.37, 0.30)	0.8192
Day 42	Hour 0	45	0.02 (1.050)	91	-0.12 (0.914)	-0.14 (-0.49, 0.20)	0.4151

Note: Based on reviewer analysis. Distance from center of the eye to the center of the lower eyelid for each subject was calculated by subtracting the PFD data from the MRD data.

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/s/

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