STATISTICAL ANALYSIS PLAN

Confidential

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

PROTOCOL NUMBER: CLN.RVL-1201.RVL-1201-202.PR.A03

Study Phase:	Phase 3
Product Name:	RVL-1201, Oxymetazoline hydrochloride ophthalmic solution, 0.1%
Indication:	Treatment of acquired blepharoptosis
Sponsor:	RevitaLid, Inc. 400 Crossing Boulevard Bridgewater, NJ 08807
Document No:	CLN.RVL-1201-202.SAP.02 Supersedes CLN.RVL-1201-202.SAP.01
Issue Date:	15 April 2019

Confidentiality Statement

Approval of Statistical Analysis Plan for Study RVL-1201-202

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATIONS	
Abbreviation	**Explanation**
α	alpha
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BID	twice daily
BP	blood pressure
CFS	corneal fluorescein staining
CI	confidence interval
CRF	case report form
DOB	date of birth
H	hour
HR	heart rate
HVF	Humphrey visual field
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent-to-treat population
LOCF	last observation carried forward
LPFT	Leicester Peripheral Field Test
MAOI	monoamine oxidase inhibitor
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MRD	marginal reflex distance
OD	oculus dextrus (right eye)
OS	oculus sinister (left eye)
OTC	over-the-counter
OU	oculus uterque (both eyes)
PD	pupil diameter

ABBREVIATIONS	
PP	per protocol population
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SLE	Slit Lamp Exam
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
V	visit
VA	visual acuity
VF	visual field

1. INTRODUCTION

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

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

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

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

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

2. STUDY DESCRIPTION

2.1 Objectives

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

2.2 Inclusion Criteria

1. Male or female subjects ≥9 years of age.
2. Presence of all the following at Screening:
    a. Loss on a reliable LPFT of ≥ 8 points in the top 2 rows (LPFT Eligibility Score); subjects must see at least 9 total points in the top 4 rows (LPFT Total Score).
        i. These criteria must be met in both the V1H0 and V1H6 LPFT assessments
        ii. There must be ≤ 4 points of variance between the V1H0 and the V1H6 LPFT Eligibility Score; AND
    b. The MRD, the distance from the central pupillary light reflex to the central margin of the upper lid, ≤ 2 mm (no visible central pupillary light reflex defaults to 0) in the same eye as Inclusion Criterion #2a; AND
    c. Snellen VA of 20/80 or better in the same eye as Inclusion Criteria #2a and #2b).
3. Presence of all the following at Baseline:
    a. Loss on a reliable LPFT of ≥ 8 points in the top 2 rows (LPFT Eligibility Score) in the same eye as Inclusion Criterion #2a; subjects must see at least 9 total points in the top 4 rows (LPFT Total Score).
        i. These criteria must be met in the V2H0 LPFT assessment.
        ii. There must be ≤ 4 points of variance between the V1H6 and the V2H0 LPFT Eligibility Score; AND
    b. MRD, the distance from the central pupillary light reflex to the central margin of the upper lid, ≤ 2 mm (no visible central pupillary light reflex defaults to 0) in the same eye as Inclusion Criterion #2a; AND
    c. Snellen VA of 20/80 or better in the same eye as Inclusion Criteria #2a and #2b).
4. Females must be 1-year postmenopausal, surgically sterilized, or females of childbearing potential (females who have started their menstrual cycles) with a negative urine pregnancy test at Visits 1 and 2. Females of childbearing potential must use an acceptable form of contraception throughout the study. Acceptable methods include the use of at least one of the following: intrauterine (intrauterine device), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence.
5. Must be able to self-administer study medication or to have the study medication administered by a caregiver throughout the study period.
6. Must be able to understand and sign an informed consent form (ICF) prior to participation in any study-related procedures. For minor subjects, the subject's parent or legal guardian must provide permission by signing the ICF on behalf of the subject and the subject should provide assent, per Institutional Review Board (IRB) guidelines. If a

subject becomes 18 years of age during the study, the subject will need to sign an ICF to continue in the study.

2.3 Subject Exclusion Criteria

In the study eye only

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

In either eye

3. Congenital ptosis.
4. Horner syndrome.
5. Marcus Gunn jaw-winking syndrome.
6. Myasthenia gravis.
7. Mechanical ptosis, including ptosis due to orbital or lid tumor, cicatricial processes affecting the movements of the upper lid, and enophthalmos.
8. Previous ptosis surgery (previous blepharoplasty [only] is allowed provided the surgery took place > 3 months prior to Visit 1).
9. Lid position affected by lid or conjunctival scarring.
10. Visual field loss from any cause other than ptosis.
11. History of herpes keratitis.
12. History of closed/narrow angle glaucoma (unless patent peripheral iridotomy has been performed > 3 months prior to Visit 1).
13. Periocular neurotoxin (e.g., Botox, Xeomin, Dysport, Myobloc) injections within 3 months prior to Visit 1 and during the study.
14. Topical application of bimatoprost (i.e., Latisse®) to the eyelashes within 7 days prior to Visit 1 and during the study.
15. Use of topical ophthalmic medications (including anti-allergy [e.g., antihistamines], dry eye [i.e., Restasis®, Xiidra®], antimicrobial drugs [e.g., antibiotics and antivirals], and anti-inflammatory drugs [including nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids] other than the assigned study medication within 7 days prior to Visit 1 and during the study. Topical ophthalmic prostaglandin analogues for the treatment of elevated intraocular pressure are permitted if dosed in the evening in accordance with the approved prescribing information. All other topical antiglaucoma medications are prohibited.
16. Intravitreal injections (e.g., Lucentis®, Eylea®, Avastin®, Triesence®) within 7 days prior to Visit 1 and during the study.
17. Current punctal plugs or placement of punctal plugs during the study.

18. Current use of over-the-counter (OTC) vasoconstrictor/decongestant eye medication (e.g., Visine® L.R.®) or any ophthalmic or non-ophthalmic α-adrenergic agonist including OTC products (e.g., Afrin®) at any time during the study; artificial tears are allowed.

General

19. Resting heart rate (HR) outside the normal range (50–110 beats per minute).
20. Hypertension with resting diastolic blood pressure (BP) > 105 mm Hg or systolic BP > 220 mm Hg.
21. Use of monoamine oxidase inhibitors (MAOIs; e.g., isocarboxazid, phenelzine, tranylcypromine) within 14 days prior to Visit 1 and during the study.
22. Advanced arteriosclerotic disease or history of cerebrovascular accident (CVA).
23. History of hyperthyroidism or thyroid eye disease (i.e., exophthalmos, upper eyelid retraction, diplopia secondary to extraocular muscle involvement). Hypothyroidism that is controlled on medication is allowed.
24. Patients with proliferative diabetic retinopathy may not be enrolled. However, patients with insulin dependent diabetes, diabetes requiring oral hypoglycemic drugs, or diet-controlled diabetes, with or without stable background diabetic retinopathy, are allowed.
25. Pregnancy or lactation.
26. Diagnosed benign prostatic hypertrophy requiring medicinal therapy; previous prostatectomy is allowed.
27. History of contact or systemic allergic reaction to oxymetazoline hydrochloride or other sympathomimetic drugs (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine, fepradinol, or methoxamine).
28. Participation in any drug or device clinical investigation within 30 days prior to entry into this study and/or during the period of study participation.
29. Previous randomization into any previous clinical study of RVL-1201 (Study RVL-1201-001 or Study RVL-1201-201) or into this study (Study RVL-1201-202).

2.4 Subject Withdrawal Criteria

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

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

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

If a study subject fails to attend a study visit at any point during the study period, every effort should be made to keep the subject in the study and conduct all study visits as scheduled; all attempts to contact the subject must be documented. If the subject relocates during the study

period, Oculos Clinical Research (Oculos), the clinical research organization, should be contacted to determine if there is a possibility that the subject could continue at another clinical site.

2.5 Study Plan/Procedures

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

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

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

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

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

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

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

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

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

2.6 Randomization and Masking

Study medication will be randomized in a 2:1 ratio (RVL-1201 Ophthalmic Solution [N = 104]; Vehicle [placebo] [N = 52]). A randomized block design will be used, and the randomization will be created by a biostatistician independent of the trial. Randomization will not be stratified by any factors.

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

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

3. STUDY ASSESSMENTS/ENDPOINTS

3.1 Demographic and Background Characteristics

3.1.1 Demographic/Medical History

A complete medical history will be obtained from each subject during Visit 1 (Screening) as part of the eligibility assessment. Demographic information including date of birth, gender, race, ethnicity, iris color, and date of informed consent will be recorded.

3.1.2 Concomitant Medications History

All concomitant medications (prescription and OTC) taken at Visit 1 (Screening) and for 3 months prior to Visit 1 and throughout the course of the study will be recorded in the Concomitant Medications page of the eCRF. Information regarding the dates of first and last dose, site of dosing (e.g., right eye [OD], left eye [OS], both eyes [OU], systemic), and the reason the concomitant medication is being taken must be recorded in the eCRF. When a concomitant medication has been taken at a stable dose for longer than 6 months, an estimation of the start date is adequate. Standard procedural medications will not be captured in the eCRF but are recorded on a standard procedural medication log provided by Oculos.

3.1.3 Ophthalmic History and Ophthalmic Intervention History

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

3.1.4 Urine Pregnancy Test

A urine pregnancy test will be performed at Visit 1 (Screening) and repeated at Day 42 (Visit 4, End of Treatment) or the Early Discontinuation Visit for women of childbearing potential only.

3.2 Efficacy Assessments

The efficacy of RVL-1201 Ophthalmic Solution compared to the Vehicle for the pharmacologic treatment of acquired blepharoptosis will be measured by improvement in visual field (as determined by LPFT assessment) and increase in MRD. For the timing of all efficacy assessments, please refer to the Schedule of Procedures.

3.2.1 Leicester Peripheral Field Test

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

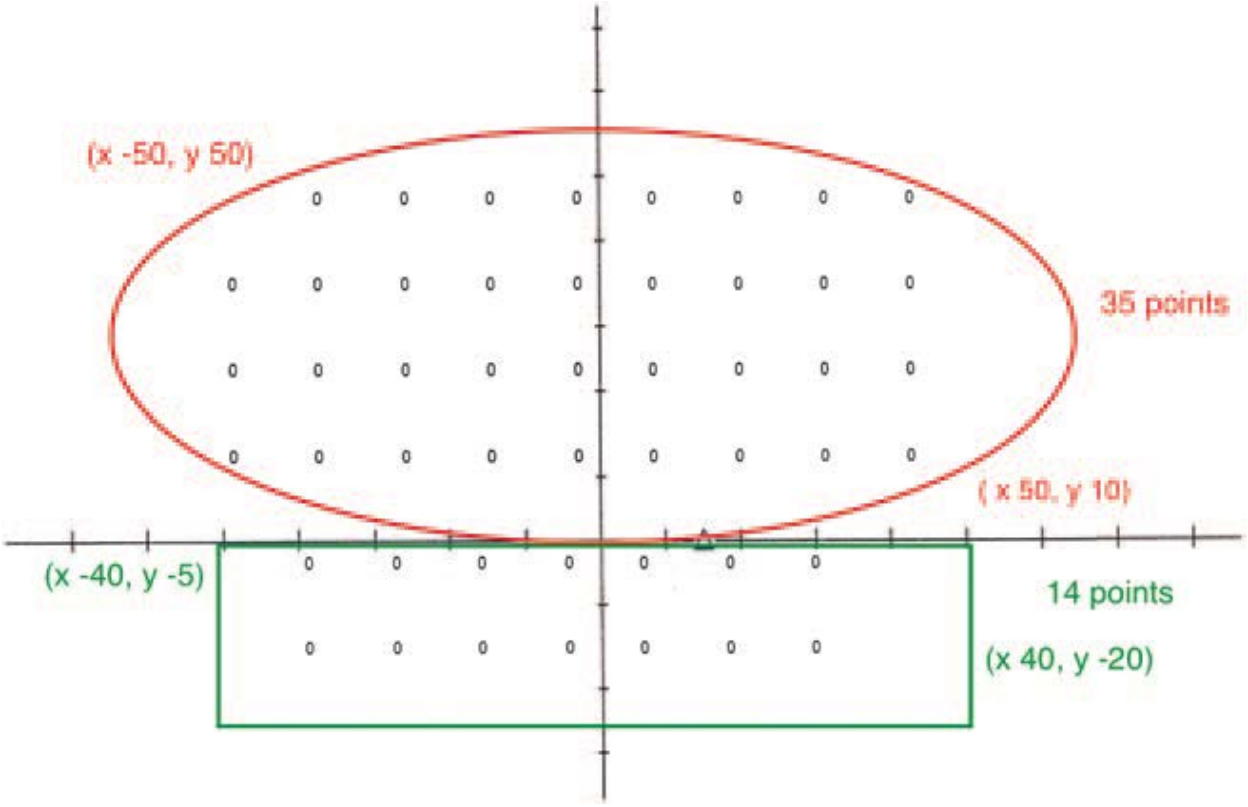

Figure 1: Leicester Peripheral Field Test Grids

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

There are two types of scores for the LPFT assessment:

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

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

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

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

3.2.2 External Photography

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

3.2.3 Marginal Reflex Distance Measurement

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

3.3 Safety Assessments

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

3.3.1 Vital Signs

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

3.3.2 Snellen Visual Acuity Assessment

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

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

3.3.3 Pupil Diameter Measurement

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

3.3.4 Slit Lamp Exam/Corneal Fluorescein Staining

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

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

Staining will be graded on a 5-point scale:

0 = No staining

1 = Trace

2 = Mild

3 = Moderate

4 = Severe

3.3.5 Dilated Ophthalmoscopy/Fundus Exam

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

3.3.6 Intraocular Pressure Tonometry

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

3.3.7 Study Medication Tolerability Assessment

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

0 = No discomfort

1 = Mild discomfort

2 = Moderate discomfort

3 = Severe discomfort

3.3.8 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject administered a study medication (pharmaceutical/biological product) that does not necessarily have a causal relationship to this medication. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the study medication, whether or not related to the study medication. Study medication includes the investigational drug under evaluation and the comparator product or vehicle placebo that is given during any phase of the study.

Adverse events will be evaluated and classified for:

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

4. SAMPLE SIZE AND POWER CONSIDERATIONS

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

5. ANALYSIS POPULATIONS

Intent-to-treat (ITT) Population:

The intent-to-treat (ITT) population is defined as all randomized subjects who received at least one dose of the allocated study medication. The primary efficacy analysis of the LPFT endpoints at Day 1 Hour 6 and Day 14 Hour 2 will be conducted on the ITT population.

Per-protocol (PP) Population:

The per-protocol (PP) population consists of those subjects in the ITT population who had no major protocol deviations that may impact efficacy. The PP population will be used as a supportive analysis of efficacy using only observed data.

Safety Population:

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

6. DATA HANDLING

6.1 Study Data

Study data identified in the schedule of procedures are collected, and source verified, in electronic Case Report Forms (eCRFs) at the site conducting the study. All relevant study data will be formulated into data sets to provide transparency, traceability, and integrity of trial analysis results from collection source. Observed study data will be mapped to the CDISC Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture.

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

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

6.1.2 Analysis Data – CDISC Analysis Data Model (ADaM)

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

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

6.2 Handling of Early Termination Visit Information

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

6.3 Handling of Missing Data

All efficacy analyses will be based on observed cases (without imputation). If more than 5% of data in any treatment group are missing, multiple imputation will be employed to analyze incomplete data sets under the assumption that the mechanism responsible for the missing data is at worst characterized as missing at random (MAR). The reasons for missing data will be recorded and the impact of these reasons and any treatment group imbalance on the assumption of MAR will be evaluated. See Section 6.4 for more details on the multiple imputation analysis. If 5% or fewer data are missing, an analysis with last observation carried forward (LOCF) for

missing data will be conducted on the ITT population only. LOCF imputation will be performed for LPFT and MRD variables only.

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

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

6.4 Multiple Imputation Details

Multiple imputation is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed datasets can then be analyzed using standard analysis methods. Rubin (1987) presented rules for how to combine the multiple sets of estimates to produce overall estimates, confidence intervals, and tests that adequately incorporate missing data uncertainty.

Missing values for LPFT and MRD will be imputed simultaneously based on an underlying joint normal distribution using a Markov Chain Monte Carlo (MCMC) method.

The imputations will be done separately for each treatment group and will include the following variables in the imputation model: LPFT at baseline, LPFT at Day 1 Hour 6, LPFT at Day 14 Hour 2, MRD at baseline, MRD at Day 1 (5 Minutes, 10 Minutes, 15 Minutes, 2 Hours, 6 Hours, and 8 Hours), MRD at Day 14 (pre-dose, 5 Minutes, 10 Minutes, 15 Minutes, 2 Hours, 6 Hours, and 8 Hours), and MRD at Day 42 (5 Minutes, 10 Minutes, and 15 Minutes).

The number of imputations will be set to 500. The outcomes of interest (change from baseline) will be calculated from these imputed datasets. The treatment difference for each imputed dataset will be evaluated using ANCOVA models. See Section 11.5.3 for details on these models. The estimates and standard errors of the differences in LS means based on the 500 imputed datasets are then combined by applying Rubin's rules for multiple imputed datasets. T-tests are also provided. SAS Proc MI, Proc GLM, and Proc MIANALYZE will be utilized for these analyses. The averaged difference in LS means with the corresponding 95% confidence interval will also be presented.

Example SAS code is provided below:

PROC MI:

```
proc mi data=original out=imputed seed=1223 nimpute=500;
   mcmc initial = EM;
   var LPFT0 LPFTD1_6 LPFTD14_2
   MRD0 MRDD1_M5 MRDD1_M10 MRDD1_M15 MRDD1_H2 MRDD1_H6 MRDD1_H8
   MRDD14_0 MRDD14_M5 MRDD14_M10 MRDD14_M15 MRDD14_H2 MRDD14_H6 MRDD14_H8
   MRDD42_M5 MRDD42_M10 MRDD42_M15;
   by treat;
   ods output misspattern=msgpat varianceinfo=varinfo
   parameterestimates=param;
run;
```

PROC GLM:

```
proc glm data=imputed;
   by _imputation;
class trtname;
model lpftd1_6_c=trtname lpft0;
estimate 'RVL-1201 - Placebo' trtname -1 1;
lsmeans trtname/pdiff;
ods output estimates=est_ds;
run;
```

PROC MIANALYZE;

```
proc mianalyze data=est_ds;
   by parameter;
modeleffects estimate;
   stderr stderr;
   ods select ParameterEstimates;

run;
```

7. STATISTICAL ANALYSIS

7.1 General Considerations

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

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

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

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

The analysis of continuous and ordinal variables will use the applicable parametric methods (t-test, analysis of variance [ANOVA], and analysis of covariance [ANCOVA]). Descriptive statistics will be used to summarize continuous outcomes (number of subjects [N], mean, standard deviation or standard error of the mean, median, maximum, and minimum) and categorical variables (frequency and percentage) at each assessment time point.

Final analyses of efficacy will be conducted when all subjects complete Day 42 (Visit 4) and the data base has been locked.

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

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

7.1.1 Definition of Study Eye

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

Only the study eye will be used in the analysis of efficacy, but the data for both eyes will be included in the analysis of safety.

7.1.2 Definition of Baseline

Measures collected prior to dosing on Day 1 will serve as baseline. For measures not collected on Day 1 the measure taken prior to Day 1 but closest in time to Day 1 will serve as baseline.

7.2 Subject Disposition

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

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

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

7.3 Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized using descriptive statistics for the ITT population. The comparability of groups used in comparison analyses will be characterized in tables of demographic data.

Demographic information including age, gender, race, ethnicity and iris color will be summarized. Such tables will be supported with individual subject data listings.

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

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

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

7.4 Concomitant Medications

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

7.5 Treatment Compliance and Exposure

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

8. EFFICACY ANALYSES

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

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

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

8.1 Hypothesis Testing

The primary efficacy endpoints will be tested sequentially in the order specified. For a claim of statistical significance, the null hypothesis being tested, and all higher ordered null hypotheses must be rejected, i.e., the Day 1 Hour 6 time point will be tested first and if $P < 0.05$, the Day 14 Hour 2 time point will be tested at a significance level of 0.05. Thus, each of the hypotheses in the hierarchy will be tested within the treatment regimen against placebo at a significance level

of 0.05. It is important to note that if the Day 1 Hour 6 endpoint is statistically significant (at the 0.05 level) but Day 14 Hour 2 is not statistically significant (at the 0.05 level), the study will still be considered positive.

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

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

All other MRD comparisons are to be considered exploratory and informative of efficacy.

8.2 Primary Efficacy - LPFT

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

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

Descriptive statistics of the observed and change from baseline in the number of points detected will be tabulated by visit and treatment group. The difference between treatment groups will be compared using an ANCOVA model with treatment as a fixed factor and baseline score as a covariate. The 95% confidence limits on the difference will be provided. Wilcoxon rank sum tests will also be used to compare treatments on change from baseline at each time point.

8.3 Secondary Efficacy - MRD

Descriptive statistics of the observed and change from baseline in MRD will be tabulated by visit, time point, and treatment group. The difference between treatment groups will be compared using an ANCOVA model with treatment as a fixed factor and baseline score as a covariate. The 95% confidence limits on the difference will be provided. Wilcoxon rank sum tests will also be used to compare treatments on change from baseline at each time point. The analyses will be performed for both the study eye and the non-study eye.

9. SAFETY MEASURES

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

9.1 Intraocular Pressure

Descriptive statistics of the observed and change from baseline IOP will be tabulated by visit and treatment group. The descriptive statistics will be presented for both the study eye and the non-study eye.

9.2 Snellen Visual Acuity

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

Descriptive statistics of the observed and change from baseline logMAR will be tabulated by visit and treatment group. The descriptive statistics will be presented for both the study eye and the non-study eye. Note that any repeat tests due to refraction issues will be utilized in the analyses.

9.3 Pupil Diameter

Descriptive statistics of the observed and change from baseline pupil diameter will be tabulated by visit and treatment group. The descriptive statistics will be presented for both the study eye and the non-study eye.

9.4 Corneal Fluorescein Staining

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

9.5 Slit Lamp Examination

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

9.6 Ophthalmoscopy and Fundus Exam

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

9.7 Tolerability Assessment

Tolerability assessments will be summarized in frequency tables based on the ordinal scale for each treatment group at the Day 42 assessment.

9.8 Vital Signs: Heart Rate and Blood Pressure

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

9.9 Adverse Events

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

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

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

Events that are possibly or probably related will be counted as an event related to study drug.

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

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

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

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

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

10. INTERIM ANALYSIS

No interim analyses are planned.

11. TABLES, LISTINGS AND FIGURES

Table, listing and figure shells will be prepared.

12. REFERENCES

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13. SCHEDULE OF PROCEDURES

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

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

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

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

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

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

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

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

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

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

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

14. REVISION HISTORY

Changes from CLN.RVL-1201-202.SAP.00 to CLN.RVL-1201-202.SAP.01: The SAP was revised to incorporate changes corresponding to the revised Protocol CLN.RVL-1201.RVL-1201-202.PR.A03.

A section was added to describe the multiple imputation methodology (Section 6.4 Multiple Imputation Details).

Changes from CLN.RVL-1201-202.SAP.01 to CLN.RVL-1201-202.SAP.02: The SAP was revised to clarify that subjects with major protocol deviations that may impact efficacy will be excluded from the per-protocol population and removed sentences about using t-tests to test efficacy endpoints to make it clear that ANCOVA models will be utilized. In section 5 Analysis Populations, for the per protocol population “protocol violation” was revised to “protocol deviation”.