SAP

Study title: A Phase 1/2a Study of LEV102 Topical Gel in Subjects with Acquired Blepharoptosis
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A Phase 1/2a Study of LEV102 Topical Gel in Subjects with Acquired Blepharoptosis

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Sponsor:	Levation Pharma Ltd. [redacted]
SAP Version:	3.0
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Prepared by:	[redacted].

Confidentiality Statement

SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BHVI	Brien Holden Vision Institute
CCLRU	Cornea and Contact Lens Research Unit
CFR	Code of Federal Regulations
CFB	Change from Baseline
CFH2	Change from Hour 2
CI	Confidence Interval
CRF	Case report form
CS	Clinically significant
eCRF	Electronic case report form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IOP	Intraocular pressure
IRO	Investigator Report Outcome
IP	Investigational product
IRB	Institutional Review Board
LS	Least Square
LogMAR	Logarithm of the Minimum Angle of Resolution
LPFT	Leicester Peripheral Field Test

MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measure
MRD1	Margin reflex distance 1
NCS	Not clinically significant
OD	Oculus dexter
OS	Oculus sinister
OTC	Over-the-counter
OU	Oculus uterque (both eyes)
PT	Preferred term
QC	Quality control
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment Emergent Adverse Events
U.S.A.	United States of America
VA	Visual acuity
VAS	Visual Analog Scale
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary
WOCBP	Women of child-bearing potential

PROTOCOL SYNOPSIS

Sponsor:
Levation Pharma Ltd.

Name of Finished Product:
TBD

Name of Active Ingredient:
Oxymetazoline

Study Title:
A Phase 1/2a Study of LEV102 Topical Gel in Subjects with Acquired Blepharoptosis

Study Number:
LEV102-CS01

Study Phase: 1/2a

Primary Objective and Endpoints:

Objective(s)	Endpoint(s)
Primary:	
1. Assess the ocular and systemic safety and tolerability of a single application of LEV102 Topical Gel on the upper eyelids in subjects with acquired blepharoptosis	• The incidence and severity of systemic and ocular adverse events (AE) • Current corrected visual acuity (VA), using subject's own prescription eyeglasses, if applicable, in both eyes as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) at the Screening visit, Baseline, and Hour 8 • Intraocular pressure (IOP) measured in both eyes at the Screening visit, Baseline, Hour 1, and Hour 8 • Slit lamp examination of both eyes at the Screening visit, Baseline, and Hour 8 • Manual pupillometry of both eyes as measured at the Screening visit, Baseline, Hour 1, Hour 4, and Hour 8 • Heart rate and blood pressure as measured at the Screening visit, Baseline, Hour 1, and Hour 8 • Subject-reported investigational product (IP) comfort questionnaire [Visual Analog Scale (VAS)] at Hour 1

Exploratory Objectives and Endpoints:

Exploratory:	Endpoint(s)
1. Evaluate the effect of a single application of LEV102 Topical Gel on the upper eyelids on superior visual fields and upper eyelid height 2. Gather additional information to guide the development of further clinical studies	• Continuous and categorical analysis in both eyes of change from baseline in margin reflex distance 1 (MRD1) of 1.0, 1.5, 2.0, and 2.5 mm at Hour 0.5, Hour 1, Hour 2, Hour 4, Hour 6, and Hour 8 • Change from baseline in the number of points/dots seen in superior visual field section (top 4 rows) of Leicester Peripheral Field Test (LPFT) at Hour 2 and Hour 6, as well as change from Hour 2 at Hour 6 • Change from baseline in both eyes of ocular hyperemia grade using Brien Holden Vision Institute (BHVI) grading scale [formerly known as the Cornea and Contact Lens Research Unit (CCLRU) grading scale] at Hour 0.5, Hour 1, Hour 2, Hour 4, Hour 6, and Hour 8 • Change from baseline in FACE-Q | Aesthetics© (Satisfaction with Eyes; Appraisal of Upper Eyelids; Appraisal of Lower Eyelids) questionnaires at Hour 4 and Hour 8 • Change from baseline in Investigator-reported outcome questionnaire at Hour 4 and Hour 8

Study Design/Conduct:

This is a Phase 1/2a, multicenter, randomized, vehicle-controlled, double-masked, single-dose, parallel-group study conducted in adult subjects with acquired blepharoptosis. Subjects will receive a one-time application of randomized, double-masked IP.

STUDY ASSESSMENTS

Safety Assessments

- AE monitoring (ocular and non-ocular)
- Current corrected VA
- IOP
- Manual Pupillometry
- Slit Lamp Examination
- Indirect Dilated Ophthalmoscopy
- Conjunctival Hyperemia Evaluation
- Vital Signs
- Urine Pregnancy Test [only for women of child-bearing potential (WOCBP)]

Efficacy Assessments

- Leicester Peripheral Field Test
- FACE-Q | Aesthetics Questionnaires
- Investigator-reported Outcome Questionnaire
- External Photography of Eyes

Other Assessments

- IP Comfort Assessment

Study Population:

This study is expected to enroll approximately 30 adult subjects with acquired blepharoptosis.

Diagnosis and Main Criteria for Inclusion:

The study population will consist of adult subjects who have acquired blepharoptosis. If both eyes qualify for the study, the eye with the lower MRD1 value at Baseline will be designated as the study eye. If MRD1 values are the same for both eyes at Baseline, the right eye will be designated as the study eye. Regardless of study eye or study qualification, all eyes in this study will receive study IP and undergo study assessments.

Inclusion Criteria:

Subjects who meet all the following inclusion criteria will be eligible to participate in the study. Subjects must:

1. Be male or female subjects 25 years of age or older at the time of Screening (Visit 1)
2. Have complaints of aesthetically unacceptable upper eyelid position for both eyes making them desirous for elevation, or have complaints of superior visual field defects in both eyes that impact activities of daily living
3. Present with the following at Screening (Visit 1):
    a. At least one eye that meets both of the following criteria:
        i. MRD1 ≤2.3 mm (no visible central pupillary light reflex defaults to 0)
        ii. Current corrected VA, using subject's own prescription eyeglasses, if applicable, in the qualifying eye(s) of +0.3 LogMAR (Logarithm of the Minimum Angle of Resolution) or better as assessed by ETDRS
    b. Demonstrate upper eyelid elevation ≥0.5 mm change from baseline in MRD1 in both eyes in response to a single drop of Upneeq® (oxymetazoline 0.1% ophthalmic solution) to each eye at Screening

        Note: Upneeq® is preferred but phenylephrine 2.5% ophthalmic solution may be used if Upneeq® is not available in a timely manner.
4. In the judgment of the Investigator, have normal levator palpebrae superioris muscle function of both upper eyelids
5. WOCBP must agree to use an approved method of birth control from the date they sign the informed consent form (ICF) until after the last study visit (Follow-Up Visit)
6. Be able to give informed consent and willing to comply with all study visits and examinations

Exclusion Criteria:

Subjects who meet any of the following exclusion criteria at Screening (Visit 1) or Baseline (Visit 2) will not be eligible to participate in the study. Subjects must not:

Ocular Conditions:

1. Have any other ocular pathology other than ptosis requiring treatment with topical prescription ophthalmic drops in either eye (e.g., glaucoma)

    Note: Subjects who use OTC or prescription topical ophthalmic drops to treat dry eye disease may be allowed with Sponsor approval.
2. Have narrow angles, glaucoma, IOP >23 mmHg or diagnosis of ocular hypertension, cup-to-disc ratio of >0.7, or history of any glaucoma eye surgery in either eye
3. Have any active ocular or peri-ocular infection; any history of recurrent or chronic infection or inflammation in either eye
4. Have a history of herpetic infection in either eye
5. Have a history of corneal disease other than mild to moderate dry eye or surgery in either eye

Note: Subjects with ocular refractive surgery (e.g., laser-assisted *in situ* keratomileusis, photorefractive keratectomy, small incision lenticule extraction) ≥90 days prior to Screening (Visit 1) are allowed.

6. Present with any pupillary abnormality in either eye
7. Present with any manifest strabismus in either eye
8. Present, in the opinion of the Investigator, with clinically significant brow ptosis in either eye
9. Have asymmetry ≥3.0 mm in MRD1 between eyes or interpalpebral distance between both eyes
10. Have any anatomic abnormality of either upper or lower eyelids in either eye that obscures either upper or lower eyelid margin
11. Have any history of ptosis surgery in either eye
12. Have a history of any upper or lower eyelid surgery, including blepharoplasty, skin lesion, or other issue within 3 month of Screening (Visit 1) in either eye
13. Have a history of chronic progressive external ophthalmoplegia, Horner's syndrome, myasthenia gravis, Marcus Gunn jaw winking, congenital ptosis, Kearns-Sayre Syndrome, dermatochalasis, uncontrolled blepharospasm, Ramsay Hunt syndrome, or mechanical ptosis in either eye

    Note: Dermatochalasis (excess eyelid skin) should not be considered exclusionary if, in the opinion of the Investigator, it does not obscure eyelid margins or interfere with quality image capture.

14. Have mechanical ptosis, including ptosis due to orbital or eyelid tumor, cicatricial processes affecting the movements of the upper eyelid, and enophthalmos in either eye
15. Have eyelid position affected by eyelid or conjunctival scarring in either eye
16. Have a visual field loss from any cause other than ptosis in either eye
17. Have a history of optic neuropathy in either eye
18. Have used topical application of bimatoprost (i.e., Latisse) to the eyelashes within 7 days prior to Screening (Visit 1) and during the study in either eye
19. Have used topical application of pilocarpine (i.e., Vuity) within 7 days prior to Screening (Visit 1) and during the study in either eye
20. Have concurrent disease in either eye or that could require medical or surgical intervention during the study period
21. Be unwilling to discontinue the use of upper eyelid/eyelash makeup and OTC cosmetic products during the Screening visit and on the day of the study treatment and assessments (Day 1), including but not limited to:
    a. Eyeshadow primer
    b. Eyeshadow
    c. Eyelid moisturizer
    d. Eyeliner
    e. Fake eyelashes (glued or magnetic)
    f. Skin care products applied to the eyelid

    Note: Enhancements that cannot easily be removed should not be considered exclusionary if, in the opinion of the Investigator, they do not obscure eyelid margins or interfere with quality image capture.
    Note: Subjects wearing makeup during the screening visit should remove the makeup on-site before image capture.

22. Have used oxymetazoline topical eye drops (Upneeq®) for treatment of blepharoptosis or as an ocular decongestant (Visine LR) within 7 days prior to Screening (Visit 1) or planned use during the study period in either eye

Note: Eyedrops applied during Screening (Visit 1) to determine study eligibility are exempt from this exclusion.

23. Have had intravitreal injections (e.g., Lucentis, Eylea, Avastin, Triesence) within 7 days prior to Screening (Visit 1) or have plans for an injection during the study in either eye
24. Have a history of thyroid eye disease (i.e., exophthalmos, upper eyelid retraction, diplopia secondary to extraocular muscle involvement) in either eye. Hyperthyroidism that is controlled on medication is allowed

Systemic Conditions:

25. Have a resting heart rate outside normal range of 50-110 beats per minute while sitting during the Screening visit (Visit 1)
26. Have, in the opinion of the Investigator, uncontrolled hypertension, uncontrolled atrial fibrillation, or history of clinical cardiovascular disease including stroke, myocardial infarction, or heart failure
27. Have plans to use a non-ophthalmic α-adrenergic agonist, including OTC products (e.g., Afrin), at any time during the study
28. Have used monoamine oxidase inhibitors (MAOIs; e.g., isocarboxazid, phenelzine, tranylcypromine) within 14 days prior to Screening (Visit 1) or anticipate using MAOIs during the study
29. Subjects with diabetic retinopathy may not be enrolled in this study. However, subjects with insulin-dependent diabetes, diabetes requiring oral hypoglycemic drugs, or diet-controlled diabetes are allowed
30. Have been diagnosed with benign prostatic hypertrophy requiring medicinal therapy; previous prostatectomy is allowed

General:

31. Have participated in other investigational drug or device clinical trials within 30 days prior to Screening (Visit 1), or be planning to participate in any other investigational drug or device clinical trials within 30 days of study completion
32. Have a history of allergic reaction to the investigational drug or any of its components
33. Within 7 days of Screening (Visit 1), or anticipated use during the study, use of any systemic, intranasal, topical dermatologic, or ophthalmic α-adrenergic agonist (including brimonidine) or antagonist including nasal or ocular or oral decongestants including pseudoephedrine, oxymetazoline topical ophthalmic solution, oxymetazoline topical dermatologic cream
34. Subjects who are pregnant or breast-feeding
35. Have used Upneeq® within 7 days of either Screening (Visit 1) or Baseline (Visit 2)

Investigational Product(s); Dose; and Mode of Administration:

- LEV102 Topical Gel, 2.0% (100 µL)
- LEV102 Topical Gel, 1.0% (100 µL)

Reference Therapy; Dose; and Mode of Administration:

- Vehicle Topical Gel (100 µL)

Duration of Treatment:

The duration of the treatment period in this study is 1 day with assessments to be completed at Baseline (before IP administration), Hour 0 (after IP administration), Hour 0.5, Hour 1, Hour 2, Hour 4, Hour 6, and Hour 8.

Duration of Study Participation:

There are 2 clinic visits and 1 telephone follow-up over up to 50 days, (up to 45 days for Screening and 2-5 days after the day of study treatment).

Statistical Methods:

In general, analyses in this study will examine the differences between individual treatment arms, as well as the differences between combined arms of LEV102 Topical Gel compared to vehicle. Continuous measures will be

summarized descriptively by the mean, standard deviation (SD), median, minimum, and maximum values. Categorical measures will be summarized by the frequency and percentage of subjects.

For all exploratory efficacy analyses and all safety analyses performed, Baseline will be defined as the measurement on Day 1 before IP administration and not from any previous visit. If both eyes qualify for the study, the eye with the lower MRD1 value at Baseline will be designated as the study eye. If MRD1 values are the same for OU at Baseline, the right eye will be designated as the study eye. Regardless of study eye or study qualification, all eyes in this study will receive study IP and undergo study assessments.

The sample size of 10 subjects per arm (30 subjects total for a total of 60 eyes) is not based on formal power or precision considerations. Subjects will be analyzed in the group according to the IP treatment received. All endpoints will be analyzed using the Safety Analysis Set and only observed data will be included.

Safety analyses will be performed on all subjects in the Safety Analysis Set. The assessment of safety will be based on the summary of ocular and non-ocular AEs, current corrected VA, IOP, slit lamp biomicroscopy, ocular hyperemia, manual pupillometry, indirect dilated ophthalmoscopy, vital signs, and urine pregnancy test. Summaries will be provided by treatment group, and for ocular assessments separately by eye.

Summary statistics for observed data and changes from baseline (where appropriate) for current corrected VA, IOP, manual pupillometry, vital signs, and the comfort questionnaire will be presented. Abnormalities in slit lamp biomicroscopy will be summarized by frequency and percentage.

Summary statistics for observed data and changes from baseline (where appropriate) for MRD1, LPFT, ocular hyperemia, and subject- and investigator-reported outcome questionnaires at post-dose Visit 2, as well as change from Hour 2 at Hour 6 for LPFT will be presented. Subjects achieving an improvement in MRD1 from baseline of 1.0, 1.5, 2.0, and 2.5 mm will be summarized by timepoint. Summary statistics for observed data and changes from baseline in FACE-Q | Aesthetics questionnaires, as well as the response rates to individual questions, will be presented.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (most current version) and categorized by system organ class (SOC) using preferred terms (PT). Separate summaries of AEs related to treatment and by severity will be presented. The number of deaths and serious adverse events (SAE) will also be presented, and events leading to discontinuation from the study will be listed and tabulated.

All data collected in this study will be presented in data listings for all subjects.

Date of Original Protocol: 09 August 2022

Date of Most Recent Protocol Amendment: 25 May 2023

9.5. EFFICACY AND SAFETY VARIABLES

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

This is a Phase 1/2a, multicenter, randomized, vehicle-controlled, double-masked, single-dose, parallel-group study conducted in adult subjects with acquired blepharoptosis. Subjects will receive a one-time application of randomized, double-masked IP. Approximately 30 subjects will be enrolled in this study. Eligible subjects will be randomized to 1 of the following 3 treatment groups in a 1:1:1 ratio and will receive a single dose of double-masked IP externally on the upper eyelid of both eyes (OU):

- LEV102, 2.0% (100 µL)
- LEV102, 1.0% (100 µL)
- Vehicle (100 µL)

Screening Visit (Visit 1; Day -45 to Day -7)

At the Screening visit (Visit 1), subjects will review and sign the informed consent form (ICF) and begin washout of prohibited medications/procedures not permitted during the study. Subjects will complete study intake and undergo screening assessments, which will include external photography of OU both before and after administration of 1 drop of single-masked Upneeq® (oxymetazoline 0.1% ophthalmic solution) OU. (**Note:** Upneeq® is preferred but phenylephrine 2.5% ophthalmic solution may be used if Upneeq® is not available in a timely manner.) A central reading center will review the images captured during the Screening visit to confirm study eligibility. Subjects wearing makeup during the Screening visit should remove the makeup on-site before image capture.

Subjects should be contacted by telephone on Day -1, the day before Visit 2 (Baseline; Randomization; Day 1), to confirm study visit details and appointment time, or to inform subjects of screen failure. Subjects who remain eligible for study participation at this time should be reminded:

1. If the subject normally wears contact lenses, the subject should not wear contact lenses on study visit days [Visit 1 (Screening); Visit 2 (Baseline; Randomization; Day 1)] and should instead wear prescription eyeglasses.

2. Not to apply any makeup or OTC cosmetic or topical skin care products, including sunscreen or moisturizer, to their eyelids or eyelashes on the day of study treatment (Visit 2; Baseline; Randomization; Day 1).

Day 1/Treatment Period (Visit 2)

Seven (7) to 45 calendar days after the Screening visit, eligible subjects will return to the study site for randomization to 1 of 3 treatment groups in a 1:1:1 ratio. Double-masked IP will be dispensed using a positive-displacement pipette and will be applied smoothly with a gloved finger to the entire external skin of the upper eyelid of each eye by trained study staff.

Note: The Day 1 appointment arrival time must be scheduled for early in the morning to allow sufficient time for the Hour 8 study assessments.

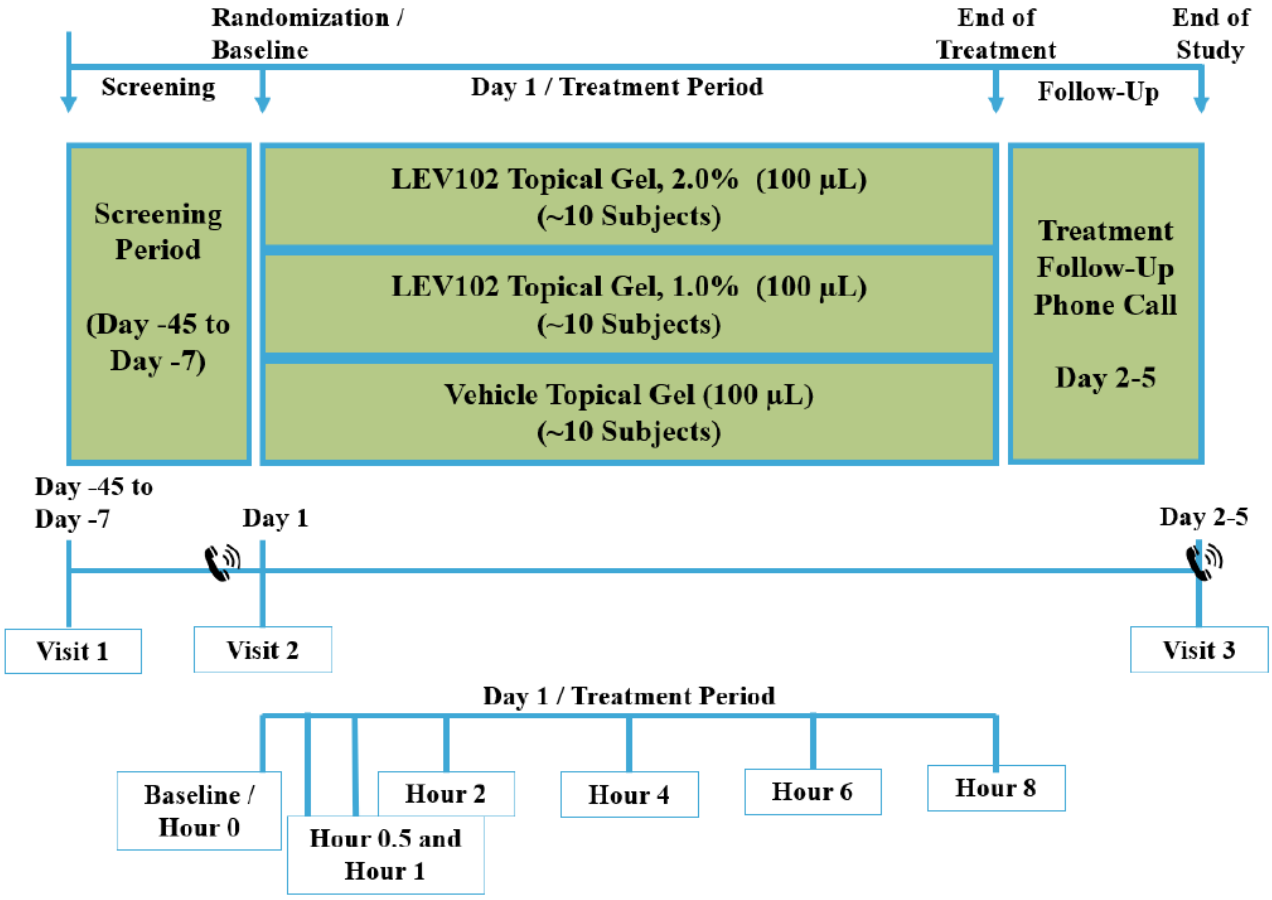
Subjects will undergo study assessments and answer study questionnaires at Baseline, Hour 1, Hour 4, and Hour 8. External photography of the eyes will also be conducted at Baseline, Hour 0.5, Hour 1, Hour 2, Hour 4, Hour 6, and Hour 8. For the purposes of documentation and analysis, Baseline will be defined as the measurements collected at Day 1 before administration of double-masked study IP.

Telephone Follow-Up (Visit 3; Day 2-5)

Subjects will be contacted by clinical site staff for a follow-up telephone interview 2-5 days after the treatment period to collect data on AEs experienced in the days following IP administration and to collect data on concomitant medications.

A diagram of the study design is included below at Figure 1.

Figure 1 Clinical Study Diagram



- Subjects should be contacted by study staff via telephone before study visits to be reminded of the following: 1.) If the subject normally wears contact lenses, the subject should not wear contact lenses on study visit days and should instead wear prescription eyeglasses and 2.) Not to apply any makeup or OTC cosmetic or topical skin care products, including sunscreen or moisturizer, to their eyelids or eyelashes on the day of the screening visit or on the day of study treatment.
- Visit 3 will be a remote visit conducted by telephone.

9.5.1.1. Visit and Procedure Schedule

See Appendix I for a complete visit and procedure schedule.

9.5.1.2. Demographics and Baseline Characteristics

9.5.1.2.1. Demographics and Disease Characteristics

Demographic characteristics including age (years), sex, race, ethnicity, eye color, study eye, and qualifying eyes will be collected at Visit 1 (Screening) and summarized by treatment group and overall.

9.5.1.2.2. Medical History

After providing written informed consent for this study, prospective subjects will be screened to obtain medical history, determine whether they meet enrollment criteria, and capture baseline measurements. Ocular and non-ocular medical and surgical history will be collected at Screening and Baseline and summarized by treatment groups and overall.

9.5.1.2.3. Prior and Concomitant Medications and Therapies

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, OTC medications, and supplements.

All medications that a subject has taken within 30 days of Screening (Visit 1) and through to the end of Visit 3 (End of Study) or discontinuation from the study will be recorded in the eCRF. The generic name of the drug, dose, route of administration, duration of treatment (including start and stop dates), frequency, indication, and whether or not the medication was taken due to an adverse event will be recorded for each medication. Previous and concomitant medications will be coded using the World Health Organization Drug Dictionary (B3 WHO Global, Version September 2022 or later).

Medications specifically prohibited by the protocol are listed in Table 1.

Table 1. Medications and Procedures NOT Permitted

Medication and Procedures Not Permitted	Minimum Washout Period(s)
Glaucoma eye surgery in either eye	Any history
Ptosis surgery in either eye	Any history
Upper eyelid/eyelash makeup and OTC cosmetic products, including but not limited to: a. Eyeshadow primer b. Eyeshadow c. Eyelid moisturizer d. Eyeliner e. Fake eyelashes (glued or magnetic) f. Skin care products applied to the eyelid **Note**: Enhancements that cannot easily be removed should not be considered exclusionary if, in the opinion of the Investigator, they do not obscure eyelid margins or interfere with quality image capture. **Note**: Subjects wearing makeup during the Screening visit should remove the makeup on-site before image capture.	During the Screening visit and for the duration of the treatment period of the study (Day 1)

Medication and Procedures Not Permitted	Minimum Washout Period(s)
Non-ophthalmic α-adrenergic agonist, including OTC products (e.g., Afrin)	Throughout the study
Any upper or lower eyelid surgery, including blepharoplasty, skin lesion, or other issue in either eye	3 months before Screening (Visit 1) and throughout the study
Participated or plan to participate in any other investigational drug or device clinical trials	30 days before Screening (Visit 1), throughout the study, and 30 days after study completion
Oxymetazoline topical eye drops (Upneeq ®) for treatment of blepharoptosis or as an ocular decongestant (Visine LR) in either eye	7 days before Screening (Visit 1) and throughout the study, excluding drops used during Screening to determine study eligibility
MAOIs (e.g., isocarboxazid, phenelzine, tranylcypromine)	14 days before Screening (Visit 1) and throughout the study
Topical application of bimatoprost (i.e., Latisse) to the eyelashes	7 days before Screening (Visit 1) and throughout the study
Topical application of pilocarpine (i.e., Vuity) in either eye	7 days before Screening (Visit 1) and throughout the study
Intravitreal injections (e.g., Lucentis, Eylea, Avastin, Triesence) in either eye	7 days before Screening (Visit 1) and throughout the study
Systemic, intranasal, topical dermatologic, or ophthalmic α-adrenergic agonist (including brimonidine) or antagonist including nasal or ocular or oral decongestants including pseudoephedrine, oxymetazoline topical ophthalmic solution, oxymetazoline topical dermatologic cream, Upneeq®	7 days before Screening (Visit 1) and throughout the study

9.5.1.3. Efficacy Assessments

In general, efficacy analyses will be performed for study eye and for qualified eye. In addition, they will be stratified by abnormal clinically significant and not clinically significant superior visual fields loss. Abnormal clinically significant (CS) superior visual field loss is defined as loss 8 or more points in superior visual field section (top 4 rows) of Leicester Peripheral Field Test (LPFT) at the baseline. If a subject has lost 7 or fewer points in supervisor visual field, then he/she does not have a clinically significant (NCS) superior visual field loss.

Efficacy assessments will be conducted at the timepoints indicated on the Schedule of Procedures and Assessments (Appendix I). They are described below.

9.5.1.3.1 Leicester Peripheral Field Test

The LPFT is a customized visual field test designed to assess ptosis (Ho et al., 2011).

The LPFT will be conducted using a Humphrey Visual Field Analyzer. Clinical study staff will instruct subjects to keep their chin and forehead against the chin and forehead rests, and to ensure that their facial features remain fully relaxed during the assessment. Subjects will be instructed to look at the center of the fixation target throughout the test. Corrective lenses are not necessary with the LPFT.

The LPFT will be scored based on an eligibility score and a total score.

LPFT Eligibility Score = The total number of points missed in the top 2 rows on the LPFT (minimum 0; maximum 17)

LPFT Total Score = The total number of points seen in the top 4 rows on the LPFT (minimum 0; maximum 35)

LPFT assessments will be performed in both eyes separately. Thirty-five points are tested in the superior field while 14 points are included in the inferior field. The inferior field test serves as a reference but should not be used for the analysis.

9.5.1.3.2 FACE-Q | Aesthetics Questionnaires

FACE-Q is a subject-reported outcome measure that has been used successfully in numerous clinical trial settings to evaluate the safety and effectiveness of facial treatments and to inform subject care in clinical practice. FACE-Q can be used to measure subject satisfaction with aesthetic facial procedures and products from the subjects' perspective.

This instrument has been used to evaluate the safety and effectiveness of facial aesthetic treatments in numerous clinical trial settings and to inform patient care in clinical practice. The FACE-Q© is composed of a set of 39 independently functioning scales/checklists that measure 3 overarching domains: Facial Appearance, Health-Related Quality of Life, and Adverse Effects. For the purposes of this study a modular approach will be used with the modules listed below.

The different questionnaire modules will be presented separately, and subjects will not have access to the questionnaires they completed at previous clinic visits or at previous timepoints.

FACE-Q |Aesthetics© Scales (Modular Approach)

1. Satisfaction with Eyes (7 items)
2. Appraisal of Upper Eyelids (7 items)
3. Appraisal of Lower Eyelids (7 items)

9.5.1.3.3 Investigator-Reported Outcomes

Principal Investigators will be subjectively assessing the [redacted] photographs in a randomized, masked fashion. After the last subject has completed the study, Principal Investigators will review batched masked/anonymized [redacted] photographs of all subjects' eyes as documented at Baseline, Hour 4, and Hour 8.

[redacted] photographs will be provided to the Principal Investigators in a random manner and should not be organized by site, subject, or timepoint. Each Investigator will assess the photographs based on their subjective impression of various parameters of subjects' eyes, upper eyelids, and lower eyelids.

9.5.1.3.4 External Photography of Eye

Images of subjects' eyes will be captured onsite during the clinic visit and submitted to a central reading center for evaluation. These imaging assessments are common tools within the field of ophthalmology and are generally recognized as reliable, accurate, and relevant.

One of the photography of eye assessments is ptosis evaluation, which measures margin reflex distance 1 (MRD1), defined as the distance from the margin of the upper eyelid to the top of the corneal light reflex when the eye is held in primary position. Subjects will have external photographs taken of both eyes via [redacted] photography for MRD1 measurements and interpalpebral distance measurements by a central reading center at the Screening visit both before and approximately 120 (±30) minutes after instillation of 1 drop of single-masked oxymetazoline in each eye. (**Note**: Upneeq® is preferred but phenylephrine 2.5% ophthalmic solution may be used if Upneeq® is not available in a timely manner.)

Investigators will rate overall bulbar conjunctival hyperemia using the Brien Holden Vision Institute (BHVI) grading scale.

9.5.1.4. Safety Assessments

Safety assessments will be performed at the timepoints indicated in the Schedule of Procedures and Assessments (Appendix I) and as shown below:

- AE monitoring (ocular and non-ocular)
- Current corrected VA
- IOP
- Manual Pupillometry
- Slit Lamp Examination
- Indirect Dilated Ophthalmoscopy
- Conjunctival Hyperemia Evaluation
- Vital Signs

- Urine Pregnancy Test [only for women of child-bearing potential (WOCBP)]

9.5.1.4.1. Adverse Events

An adverse event is any untoward medical occurrence in a subject or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Subject hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly or birth defect

The severity of all AEs will be assessed by the Investigator and graded as follows:

Grade Level	Description
Mild	Requires minimal or no treatment and does not interfere with the subject's daily activities
Moderate	Results in a low level of inconvenience or concern and may cause some interference with functioning
Severe	Interrupts a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe AEs are usually potentially life-threatening or incapacitating. The term "severe" does not necessarily equate to "serious."

All AEs must have their relationship to study intervention assessed by the Investigator who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical study, the IP must always be suspect.

Causality	Definition

Unrelated	no reasonable possibility that the administration of the IP caused the event, no temporal relationship between the IP and event onset, or an alternate etiology has been established
Related	It is known to occur with the IP, there is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB, package insert, or device labeling or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the protocol, as amended. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB, package insert, or device labeling as occurring with a *class of drugs* (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the IP, but are not specifically mentioned as occurring with the particular IP under investigation.

The Investigator will be responsible for initially determining whether an AE is unexpected, i.e., if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IP.

9.5.1.4.2. Current corrected VA

Note: Visual acuity (VA) testing must precede any examination requiring contact with the eye or eyelid and must precede pupil dilation, instillation of study dyes, external photography of the eyes, or application of topical gels as detailed in the order of assessments for the protocol.

Distance VA will be assessed OU with an ETDRS chart at a 4-meter distance using a LogMAR scale. Distance VA should be assessed consistently throughout the study using the same method, equipment, and lighting conditions at each site. Current corrected VA testing will be performed using subjects' own prescription eyeglasses, if applicable; subjects who do not achieve a +0.0 LogMAR score using their prescription eyeglasses, if applicable, will be asked to make their best effort while viewing the ETDRS chart through a pinhole occluder.

Subjects will be instructed to read the letters on the ETDRS chart from the top left-hand corner along each row, one letter at a time then down each row, one at a time. There are no numbers on the chart, only letters.

Subjects will be instructed to read slowly at a rate of about 1 letter/second. At the end of the test, the examiner will count the number of letters incorrectly identified up to and including the last line read

and will record the results on the source document. A VA letter score will be calculated and recorded in the Source Document Worksheets and in the eCRF.

Each letter has a score value of 0.02 log units. Since there are 5 letters per line, the total score for a line on the LogMAR chart represents a change of 0.1 log units. The formula used in calculating the score is:

Calculations: LogMAR VA = Baseline value + (n X 0.02)

where: the baseline value is the LogMAR number of the last line read (at least 1 letter read correctly in this line), and "n" is the total number of letters missed up to and including the last line read, and "0.02" is the value for each letter

9.5.1.4.3. Intraocular Pressure (IOP)

IOP will be measured in mmHg and should be conducted after the slit lamp biomicroscopy exam is completed and before dilation of subjects' eyes.

IOP measurements will be performed utilizing iCare or another tonometer that does not require the use of colored dyes or local anesthetic, and that does not employ an air puff to measure IOP. The same method should be used consistently for the same subject for all visits and IOP assessments. Measurements will be taken with the subject seated. Two consecutive measurements will be taken in each eye and recorded in the source document. The mean of the two measurements will be automatically calculated in EDC. If the two measurements differ by >1.0 mmHg, a third measurement will be taken and recorded in the source document. The median of the three scores will then be automatically calculated in EDC.

9.5.1.4.4. Manual Pupillometry

The pupil size will be measured in ambient room light. The subject should be asked to focus straight ahead on a target at a distance to avoid accommodation while seated in the exam chair. The subject should be instructed not to blink during the measurement. The Investigator should then take the pupil measurement card and place it directly below the pupil while avoiding the line of sight, again to avoid stimulating accommodation. The Investigator should then match the pupil size to the circle size on the card to determine the pupil size. After a brief rest period, the process should be repeated to measure pupil diameter in the fellow eye. Each measurement should be recorded in the eCRF.

If subjects' eyes become dry during the assessment, artificial tears may be administered and recorded as concomitant medication.

9.5.1.4.5. Slit Lamp Biomicroscopy

The slit lamp biomicroscopy exam should be performed with the slit lamp using a beam width and intensity that provides optimal evaluation of the anterior segment. The slit lamp exam should be performed without fluorescein.

The slit lamp examination must be performed before any procedures that would require contact with the eye or eyelids and prior to the instillation of any dilating or anesthetic eye drops or topical gels. The Investigator should use their standard examination technique. This procedure will be performed in the same manner for all subjects observed at the Investigator's site. When possible, the same examiner should conduct all slit lamp biomicroscopy examinations at each visit for a given subject throughout the study.

The Investigator must examine the eyelids, conjunctiva, cornea, anterior chamber, iris/pupil, and the lens of each eye for evidence of erythema and/or edema, opacities or other signs of abnormalities and record a grading for each tissue/structure as specified below. Observations will be documented on the appropriate CRF.

The following aspects of the eye will be evaluated, and corresponding data collected.

Cornea:	Includes all corneal layers
Normal:	Absence of active inflammation, infection, or structural changes/abnormalities
Abnormal:	Presence of active inflammation, infection, or structural changes/abnormalities including focal scarring and fine deposition Clinically significant Not clinically significant

Eyelids:	Includes eyelid edema and eyelid erythema
Normal:	Absence of active inflammatory signs or significant structural changes/abnormalities or discharge
Abnormal:	Presence of active inflammatory signs or significant structural changes/abnormalities or discharge Clinically significant Not clinically significant

Conjunctiva:	Includes periocular tissues, and the bulbar, palpebral and limbal conjunctiva
Normal:	Absence of active inflammatory signs or significant structural changes/abnormalities or discharge

Abnormal:		Presence of active inflammatory signs or significant structural changes/abnormalities or discharge Clinically significant Not clinically significant
Lens	Phakic	
	Pseudophakic	
	Aphakic	

Lens Opacity	***(Phakic only)***
None (0)	None present or less than mild
Mild (1)	Yellow lens discoloration or small lens opacity (axial or peripheral)
Moderate (2)	Amber lens discoloration or medium lens opacity (axial or peripheral)
Severe (3)	Brunescent lens discoloration or complete lens opacification (no red reflex)

9.5.1.4.6. Indirect Dilated Ophthalmoscopy

This procedure will occur after application of dilating eyedrops and upon Investigator confirmation with a pen light OU are fully dilated (recommended time of at least 20 minutes). As dilating drops will be applied, indirect dilated ophthalmoscopy must be performed after external eye and eyelid photography, tests of visual acuity, IOP assessments, and assessments of corneal staining and healing.

Indirect dilated ophthalmoscopy will include assessment of the vitreous, retina, macula, choroid, optic nerve, and vertical optic nerve cup-to-disc ratio. After the ophthalmoscopy procedure, the Investigator will determine if findings are within normal limits or are abnormal. For abnormal findings at Screening (Visit 1), the Investigator will determine whether the abnormality would exclude the subject from study participation. Observations will be documented on the appropriate CRF. Abnormalities should be marked as “clinically significant” or “not clinically significant.”

Vitreous:	
Normal:	Absence of any opacity
Abnormal:	Presence of opacity Clinically significant Not clinically significant
Retina:	
Normal:	Absence of active inflammation or significant structural changes
Abnormal:	Presence of active inflammatory signs or significant structural changes Clinically significant

	Not clinically significant
Macula:	
Normal:	Absence of active inflammation or significant structural changes
Abnormal:	Presence of active inflammatory signs or significant structural changes Clinically significant Not clinically significant

Choroid:	
Normal:	Absence of active inflammation or significant structural changes
Abnormal:	Presence of active inflammatory signs or significant structural changes Clinically significant Not clinically significant
Optic Nerve:	
Normal:	Absence of any damage
Abnormal:	Presence of any damage Clinically significant Not clinically significant

Vertical Optic Nerve Cup-to-Disc Ratio:	—. — —

Other:	Indicate any other dilated fundus ophthalmoscopy findings
	No
	Yes

If yes, specify finding and clinical significance

9.5.1.4.7. Conjunctival Hyperemia Evaluation

Investigators will rate overall bulbar conjunctival hyperemia using the Brien Holden Vision Institute (BHVI) grading scale [formerly known as the Cornea and Contact Lens Research Unit (CCLRU) grading scale]. The following investigator BHVI ratings will be recorded in the eCRF.

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Score	Redness
0	None
1	Very Slight

2	Slight
3	Moderate
4	Severe

9.5.1.4.8. Vital Signs

Subject vital signs will be assessed at the Screening visit (Visit 1), Baseline (Visit 2 before IP administration), and during the study period after IP administration at Hour 1 and Hour 8. Vital signs will include blood pressure while in a seated position and resting heart rate.

9.5.1.4.9. Urine Pregnancy Test (only for women of child-bearing potential (WOCBP))

For the purposes of this study, a woman of child-bearing potential will be defined as a subject with a uterus who is capable of becoming pregnant.

WOCBP must agree to use one of the following methods of birth control from the date they sign the ICF until after the completion of the last study visit (Follow-Up Visit):

a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject, where abstinence may be defined as refraining from sexual contact or defined as engaging in relationships in which it is impossible for sexual contact to result in pregnancy;

b. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (vasectomy procedure must have been conducted at least 60 days prior to the Screening visit or confirmed via sperm analysis);

c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted or injectable) or an intrauterine device or system.

Note: Non-child-bearing potential for the purposes of this study is defined as surgical sterilization (i.e., bilateral oophorectomy, hysterectomy, or tubal ligation), postmenopausal (defined as not having a menstrual period for at least 12 consecutive months prior to Screening), or medical confirmation of infertility.

9.5.1.4.10. IP Comfort Assessment

Subjects will be asked on the day of study treatment to rate the comfort/tolerability of the study IP using a Visual Analog Scale (VAS) after the IP has been applied to their upper eyelids. This assessment will be focused on the comfort of the IP itself, and subjects should be instructed to think about the comfort of

the IP after dosing application and independently from their experience having the IP applied by study staff.

Subjects will be asked to place a single vertical mark along a horizontal 100-mm line to indicate the level of comfort/discomfort they experienced after IP administration. For the VAS, 0 mm represents no comfort at all and 100 mm represents the most comfortable. There may be differences in the length of the line on each CRF page due to photocopy/printing anomalies. Both the subject response and total length of the scale will be measured from the left margin of the scale to the nearest ½ millimeter. The VAS score is the ratio of the patient response to the total length of the scale. Subjects will also be provided with an empty text box to collect any additional notes they would like to share about their experience with the IP in regards to its comfort and tolerability.

9.5.2. Appropriateness of Measurements

All assessments used in this study are widely used and generally recognized as reliable, accurate, and relevant.

9.5.3. Primary Efficacy Variables

9.5.3.1. Efficacy Endpoints

The efficacy endpoint variables are as follows:

- Change from baseline in the number of points seen in supervisor visual field section (top rows) of Leicester Peripheral Field Test (LPFT) at Hours 2 and 6, and as well as change from Hour 2 at Hour 6
- Continuous and categorical analysis in both eyes of change from baseline in margin reflex distance 1 (MRD1) of 1.0, 1.5, 2.0, and 2.5 mm at Hours 0.5, 1, 2, 4, 6, and 8
- Change from baseline on both eyes of ocular hyperemia grade using Brien Holden vision Institute (BHVI) grade scale at Hours 0.5, 1, 2, 4, 6, and 8.
- Change from baseline in FACE-Q | Aesthetics questionnaires at Hours 4 and 8.
- Change from baseline in Investigator-reported outcome questionnaires at Hours 4 and 8.

9.5.3.2. Safety Endpoints

This is primarily a safety and tolerability study with the following safety endpoints.

- The incidence and severity of systemic and ocular adverse events (AE)
- Current corrected visual acuity (VA), using subject's own prescription eyeglasses, if applicable, in both eyes as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) at the Screening visit, Baseline, and Hour 8
- Intraocular pressure (IOP) measured in both eyes at the Screening visit, Baseline, Hour 1, and Hour 8

- Slit lamp examination of both eyes at the Screening visit, Baseline, and Hour 8
- Manual pupillometry of both eyes as measured at the Screening visit, Baseline, Hour 1, Hour 4, and Hour 8
- Heart rate and blood pressure as measured at the Screening visit, Baseline, Hour 1, and Hour 8
- Subject-report investigational product (IP) comfort questionnaire [Visual Analog Scale (VAS)] at Hour 1

9.5.4. Drug Concentration Measurements

Not Applicable.

9.6. DATA QUALITY ASSURANCE

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements (e.g., Good Laboratory Practice [GLP], Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

9.6.1. Training and Education of Investigators and Study Site Personnel

An Investigator Meeting will be held before study initiation and attended by the Investigators and/or Sub-Investigators from each study site, study coordinators from each study site, if possible, and personnel from the sponsor and the Contract Research Organization (CRO), Lexitas Pharma Services, Inc. (hereafter referred to as Lexitas). The purpose of this meeting is to train and instruct the Investigators and the study coordinators on the proper conduct of the clinical trial and ensure that all participants are aware of their obligations set out by the protocol, ICH guidelines, GCP guidelines, and other applicable regulatory requirements.

9.6.2. Monitoring of Study Sites

Lexitas will conduct the clinical monitoring for this study. A Clinical Monitoring Plan (CMP) is to be used, which will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

9.6.3. Data Entry and Verification of Database Used for Analysis and Reporting

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site's Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Merative Clinical Development, a 21 CFR Part 11-compliant data capture system provided by Lexitas Pharma Services, Inc. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

9.6.4. Clinical Study Report

The final clinical study report will be reviewed, audited, and approved by medical, clinical, statistical, and regulatory staff from the sponsor, and key study contributors from Lexitas.

9.6.5. Inter-Laboratory Standardization Methods

Not applicable. There will be no clinical safety laboratory data.

9.7. STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

This section of the analysis plan describes the analyses explicitly mentioned in the protocol as well as additional analyses not explicitly mentioned in the protocol but planned prior to breaking the treatment mask. Section 9.8 describes any changes to analyses that were explicitly mentioned in the protocol or statistical analysis plan.

9.7.1. Statistical and Analytical Plans

General Conventions

Summary statistics for the data collected during this study will be presented to give a general description of the subjects studied. Data from all sites will be combined in the computation of these descriptive summaries. Categorical variables will be summarized by the frequency and percentage of subjects in each category. Continuous variables will be summarized using N, mean, standard deviation (SD), median, minimum, and maximum values.

Number of subjects, minimums, and maximums will be calculated to the same number of decimal places as the source data. Means, medians, other quartiles, and confidence limits will be calculated to one more decimal place than the source data; standard deviations and standard errors will be calculated to two more decimal places than source data. Percentages will be calculated to the nearest one decimal place. Zero count cells will be displayed as "0" with percentage of (0%). Summaries will be performed by the treatment group and presented in the order of LEV102, 2.0%, LEV102, 1.0%, and Vehicle.

In general, analyses will examine the differences between individual treatment arms, as well as the differences between combined arms of LEV102 Topical Gel compared to vehicle. In addition, safety analyses related to ocular endpoints will be performed by study eye and non-study eye. Non-study eye refers to fellow eye.

Study eye is defined as follows:

- If both eyes qualify for the study, the eye with the lower MRD1 value at Baseline will be designated as the study eye.
- If MRD1 values are the same for OU at Baseline, the right eye will be designated as the study eye.

Regardless of study eye or study qualification, all eyes in this study will receive study IP and undergo study assessments.

Summary of safety analysis will be presented by treatment arm:

- LEV102, 2.0%
- LEV102, 1.0%
- Vehicle

In addition, summary of efficacy analysis will be presented by combined arm (LEV102, 2.0% or LEV102, 1.0%) as well.

No formal hypotheses for efficacy have been defined. Summary statistical analyses are exploratory only without any significance testing.

For all exploratory efficacy analyses and all safety analyses performed, baseline assessments are to be performed on Day 1 before the application of IP.

All data collected in this study will be presented in individual subject data listings for all subjects.

Computations for all results will be performed using SAS (Version 9.4, SAS/STAT 15.2 or higher) computer software package (SAS Institute, Inc, 2013, 2020), unless otherwise specified.

Strata and Covariates

For analysis of continuous efficacy endpoints, mixed-effect model repeated measure (MMRM) models will model the change from baseline of each endpoint as the dependent variable with the baseline measurement of the corresponding endpoint as a covariate and treatment, time, and treatment by time interaction as fixed effects. A random effect for site will be added to account for site-to-site variability.

Subgroups

All efficacy analysis will be stratified by abnormal clinically significant (CS) superior visual field loss and abnormal not clinically significant (NCS) superior visual field loss based on baseline LPFT values.

Multiplicity

Not applicable because the statistical analyses are exploratory.

Missing Data and Outliers

Every attempt will be made to capture all study data. No imputations will be performed, only observed data will be summarized in general except for imputation of missing responses for items in FACE-Q questionnaires per the standard grading rules.

To score a scale in each of 3 modules i.e. Satisfaction with Eyes, Appraisal of Upper Eyelids, and Appraisal of Lower Eyelids in FACE-Q, the raw scores for the set of items or questions in a module are added together to produce a total raw score for each module. If missing data is less than 50% of the scale's items, replace missing data with the mean of the completed items. The following 3

Conversion Tables below are utilized to convert the raw scale summed score into a score from 0 (worst) to 100 (best).

Table 2. FACE-Q™ – Satisfaction with Eyes Conversion Table

Sum score	Equivalent Rasch Transformed Score (0-100)
7	0
8	10
9	16
10	20
11	24
12	28
13	32
14	35
15	39
16	43
17	47
18	51
19	55
20	59
21	63
22	68
23	72
24	77
25	81
26	86

27	92
28	100

Table 3. FACE-Q™ – Appraisal of Lower Eyelids Conversion Table

Sum Score	Equivalent Rasch Transformed Score (0-100)
7	0
8	10
9	17
10	23
11	28
12	32
13	36
14	39
15	42
16	46
17	49
18	52
19	55
20	58
21	61
22	64
23	68
24	72
25	77

26	82
27	90
28	100

Table 4. FACE-Q™ - Appraisal of Upper Eyelids Conversion Table

Sum Score	Equivalent Rasch Transformed Score (0-100)
7	0
8	8
9	15
10	21
11	26
12	30
13	34
14	38
15	42
16	46
17	49
18	53
19	56
20	59
21	63
22	66
23	70
24	74

25	78
26	83
27	90
28	100

Visit Windows

The nominal visits listed in the eCRF will be used in the summaries. In general, unscheduled visits will not be summarized in tables unless otherwise noted.

Missing Dates

Missing dates that occur for prior or concomitant medications or adverse events will be queried for a date. If no date is obtained, the following imputation rules will apply:

- For start dates, if the given year (or year-month) is the same as study drug administration, the start date will be imputed as study drug administration date; otherwise, missing month-day (or day) will be imputed as ’01-01’ (or ’01’).
- For stop dates, missing months will be imputed as ‘12’ and missing days will be imputed as the last day of the month. If this creates a date after discontinuation/completion, the date of discontinuation/completion will be used.

Imputed dates will only be used to classify events or medications, such as occurring before or after the start of treatment. Imputed dates will only be used in tables. Listings will display the available date data.

Interim Analysis

There is no planned interim analysis.

9.7.1.1. Analysis Populations

The Safety Analysis Set will include all randomized subjects who received at least 1 dose of IP as indicated on the dosing record. Subjects will be analyzed in the group according to the IP treatment received. All endpoints will be analyzed using the Safety Analysis Set and only observed data will be included with the exception noted for the FACE-Q questionnaires.

9.7.1.2. Analysis of Subject Disposition

The number of subjects randomized at each site will be summarized by treatment group and overall.

Subjects' enrollment and disposition during the study will be summarized by treatment groups, and overall. The reasons for discontinuation will be displayed in the order as they appear on the eCRF.

Summary tables will include the following. The percentages will be calculated based on the number of subjects randomized who received at least one dose of study therapy.

- Number of subjects screened;
- Number and percentage of subjects dosed;
- Number and percentage of subjects in Safety Analysis Set;
- Number and percentage of subjects treated who completed the study;
- Number and percentage of subjects treated who discontinued from the study;
- The reasons for study discontinuation;
- Number and percentage of subjects completing each study visit;

A listing of subjects who do not meet all inclusion criteria or meet exclusion criteria will be provided.

A table of protocol deviations will be presented by its classifications and categories, in overall using the Safety Analysis Set. There are three protocol deviation (PD) classifications, i.e. minor, major, and critical, and following 8 PD categories:

- Informed consent
- Inclusion and exclusion criteria
- Study visit schedule
- Study assessment
- Missed procedure
- Investigational product
- Concomitant medication
- Other

9.7.1.3. Analysis of Demographic and Baseline Characteristics

9.7.1.3.1. Demographics and Disease Characteristics

Demographic characteristics including age (years), age group (<55 year old, ≥ 55 year old), sex, race, ethnicity, overall average levator function by study eye and non-study eye will be summarized descriptively by treatment groups and overall using the Safety Analysis Set. Similarly, for categorical parameters, the percentages will be calculated based on the number of subjects with non-missing observations.

9.7.1.3.2. Medical History

Medical history will be coded using MedDRA Version 25.1 or later. The frequency and percentage of subjects with any medical history will be summarized by treatment group and overall using the Safety Analysis Set. System organ class (SOC) will be sorted alphabetically and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to following rules in order:

- Descending frequency within Treatment 1 (LEV102, 2.0%): n = 10
- Descending frequency within Treatment 2 (LEV102, 1.0%): n = 10
- Descending frequency within Control (Topical Gel): n = 10
- PT in alphabetical order

The medical history will include both the ocular and the general (non-ocular) history. Ocular medical history and general (non-ocular) medical history will be summarized separately. Ocular and non-ocular medical histories are identified according to which CRF the event is recorded. Ocular medical history will be summarized if a term occurs for either eye (i.e., at the subject-level).

9.7.1.3.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) (B3 WHO Drug Global, Version Sep 2022 or later) for anatomical therapeutic chemical (ATC) classification and preferred drug name.

The frequency and percentage of subjects with coded medications will be summarized by treatment group and overall using the Full Analysis Set. A subject who used multiple medications will be counted only once for each ATC and preferred drug name. Therapeutic Subgroup (ATC level 3) is sorted alphabetically, and preferred term is sorted by descending frequency overall within each Level 3 term according to following rules in order:

- Descending frequency within Treatment 1 (LEV102, 2.0%): n = 10
- Descending frequency within Treatment 2 (LEV102, 1.0%): n = 10
- Descending frequency within Control (Topical Gel): n = 10
- PT in alphabetical order

Prior and concomitant medications will be summarized separately. Ocular medications are defined as those medications for which an eye has been specified (OD, OS, or OU). Ocular and non-ocular medications will be summarized separately. Ocular medications will be summarized separately for OD, OS, and either eye.

Prior medications are defined as any medications stopped prior to the date of first dose of study medication. Concomitant medications are defined as any medications that (1) start prior to the date of first dose of study medication and are ongoing; or (2) start on or after the date of first dose of study medication; or (3) stop through the end of study (Visit 3). Medications taken after Day 5 or withdrawal from the study are not considered concomitant.

9.7.1.4. Analysis of Study Medication Compliance and Exposure

Because this is a Phase 1/2a single-dose study, compliance and exposure will not be summarized in the table, but they will be presented in a listing.

9.7.1.5. Analysis of Efficacy and Safety Endpoints

The primary objective of this study is to assess the ocular and systemic safety and tolerability of a single application of LEV102 Topical Gel on the upper eyelids in subjects with acquired blepharoptosis; therefore, the study is not powered for the primary efficacy endpoint. However, several exploratory efficacy endpoints are collected and analyzed. All qualifying eyes will be used for analyses of efficacy. For some of those efficacy endpoints, such as LPFT, BHVI, and MRD1, they will be analyzed by study eye and qualified eyes. In addition, it will be stratified by abnormal clinically significant superior visual field loss and not clinically significant superior visual field loss.

All analyses comparing LEV102 to vehicle will be conducted on pooled LEV102 arms versus the vehicle arm. Additional analyses will explore each arm individually against the vehicle arm. Further, treatment estimates and 95% CI will be reported for LEV102 pooled and each dose separately vs. the vehicle arm.

9.7.1.5.1. Efficacy Endpoint Analyses

9.7.1.5.1.1. Leicester Peripheral Field Test (LPFT)

The observed and change from baseline in the number of points seen in superior visual field section (top 4 rows) of LPFT at Hours 2 and 6, as well as change from Hour 2 at Hour 6 will be shown by treatment group. In addition, visual field status, i.e. abnormal clinically significant superior visual field loss and not clinically significant superior visual field loss, change from baseline to both Hour 2 and Hour 6 as well as change from Hour 2 to Hour 6 will be shown by treatment groups.

Moreover, the mean CFB in LPFT score will be analyzed using a MMRM model. The model will include treatment, hour, and treatment by hour interaction as fixed effects, with a random effect for site. An unstructured covariance among repeated measurements between qualifying eyes is assumed. The two primary groups for comparison are all subjects randomized to LEV102 Topical Gel (pooling 2.0% and 1.0% doses) vs. subjects randomized to vehicle. In addition, two dosing

groups will be compared using CFB in LPFT score to determine if there is a significant difference in CFB.

Sample analysis code:

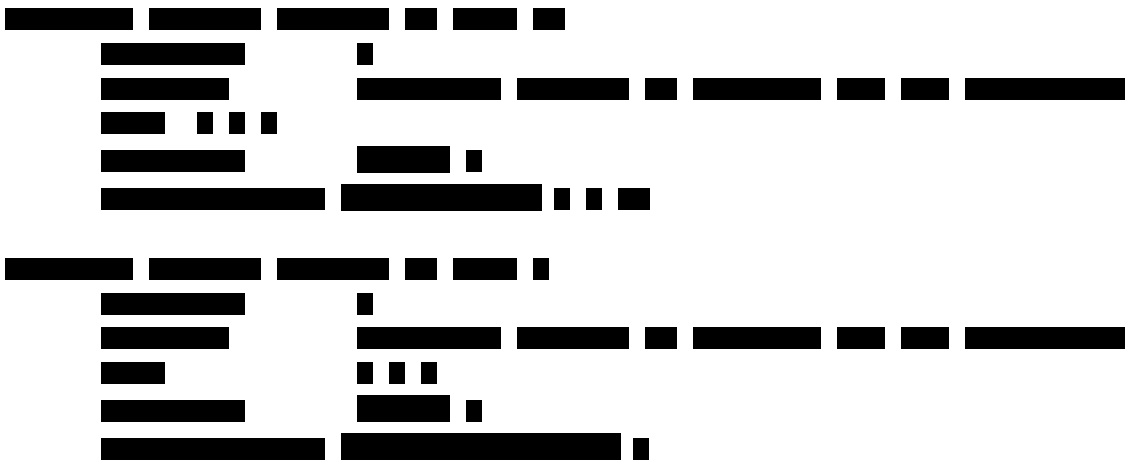
```
proc mixed data = indata;
       class subject center hour treatment;
       model change = baseline hour treatment hour*treatment / solution DDFM = KR;
       repeated / type = un subject = subject;
       random center;
       lsmeans hour*treatment / slice = hour diff cl;
run;
```

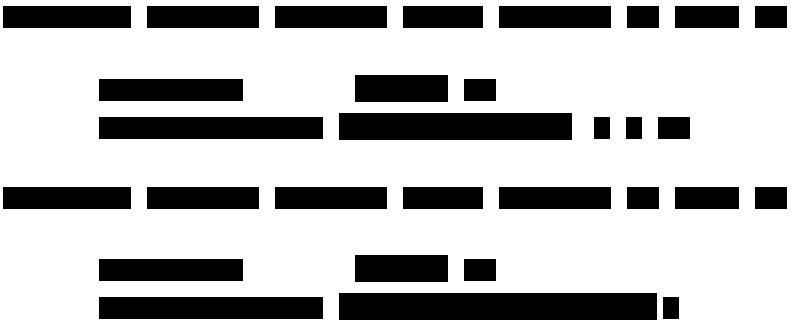
Should the model not converge, compound symmetry will be assumed. Comparisons among individual arms will be obtained from the *lsmeans* statement. Comparisons between the combined active arm and vehicle (least-squares means, treatment differences, 95% confidence intervals) will be obtained using *estimate* statements. Assume treatments are ordered:

1. LEV102, 2.0%;
2. LEV102, 1.0%
3. Vehicle

And baseline, Hour 2, and Hour 6 are ordered numerically. Let $n_{2\%}$ and $n_{1\%}$ be the total number of subjects in LEV102, 2.0% and LEV102, 1.0% arms in the safety analysis set. The percent of subjects in each arm are define as follows:
$p = \frac{n_{1.0\%}}{n_{1.0\%}+n_{2.0\%}}$.

To generate the estimates for the combined LEV102 1.0% and 2.0% for Hour 2 and Hour 6, see the below code.





9.7.1.5.1.2. Margin Reflex Distance 1

First, spaghetti plots of response profiles for margin reflex distance 1 (MRD1) over time will be presented by each subject and across three treatment groups. Means and SD for MRD1 over time will be shown by treatment group in the same Figure. Summary statistics for observed data and changes from baseline for MRD1 of 1.0 mm, 1.5 mm, 2.0 mm, and 2.5 mm at Hour 0.5, Hour 1, Hour 2, Hour 4, Hour 6, and Hour 8 will be shown by treatment group. The mean CFB in MRD1 values will be analyzed using a MMRM model as well. In addition, a comparison between mean maximum MRD1 change from baseline at post-dosing (Visit 2), i.e. maximum mean difference between anytime point tested and hour 0 at Baseline, and mean Upneeq® response values at Screening (Visit 1) after single drop of Upneeq® (oxymetazoline 0.1% ophthalmic solution) to each eye will be performed within each treatment group. Bar graphs of maximum change in MRD1 from Baseline and mean Upneeq® response at Screening will be shown within a treatment group. Furthermore, MMRM model will be utilized to determine if Upneeq® response values at Screening has any impact on MRD1 change from Baseline at each post-dosing hours while controlling baseline covariates.

Moreover, a comparison between MRD1 change at Hour 2 from baseline and Upneeq's response at Hour 2 will be conducted within each treatment group.

9.7.1.5.1.3.Conjunctival Hyperemia Evaluation

Spaghetti plots of response profiles for Brien Holden Vision Institute (BHVI) grading scale over time will be presented by each subject and grouped by Treatment group. The observed and change from baseline in ocular hyperemia grade using the BHVI grading scale at Screening and Hour 0 , Hour 0.5, Hour 1, Hour 2, Hour 4, Hour 6, and Hour 8 at the Baseline visit will be presented by Treatment group. The status of change includes improvement in ≥1 units or worsening ≥1 units in terms of the grading scale.

9.7.1.5.1.4. FACE-Q | Aesthetics

The FACE-Q© is a subject-reported outcome measure that can be used to measure outcomes of facial procedures and products from the subject's perspective. This instrument has been used to

evaluate the safety and effectiveness of facial aesthetic treatments in numerous clinical trial settings and to inform patient care in clinical practice. The FACE-Q© is composed of a set of 39 independently functioning scales/checklists that measure 3 overarching domains: Facial Appearance, Health-Related Quality of Life, and Adverse Effects.

There is no overall or total FACE-Q score. Instead, the FACE-Q in this study is composed of the following three independently functioning scales or modules that are each scored separately and produces each single item visual analogue scale.

1. Satisfaction with Eyes (7 items)
2. Appraisal of Upper Eyelids (7 items)
3. Appraisal of Lower Eyelids (7 items)

To score a scale, the raw scores for the set of items in a scale or modules are added together to produce a total raw score.

Once a total raw score for the scale or module for a patient is computed, the Conversion Table can be used to convert the raw score into a score that ranges from 0 (worst) to 100 (best). If missing data is less than 50% of the scale's items, within person mean for the completed items can be imputed for the missing items prior to computing a total raw score. For example, if there is a 7-item scale or module in this study, and someone has not responded to all the items, but has responded to ≥4 items, all other items for that person can be imputed with a within-person mean (rounded to the nearest integer), and a summed score can be calculated.

Summary statistics for observed data and changes from baseline in each module for FACE-Q | Aesthetics questionnaires will be presented at Screening, baseline, Hours 4 and 8 by treatment group. In addition, MMRM model will be utilized to determine if MRD1 change from Baseline at each post-dosing hours has any impact on FACE-Q from Baseline at each post-dosing hours while controlling baseline covariates. The response to individual questions will be presented in the listing.

9.7.1.5.1.5. Investigator Report Outcome

Spaghetti plots of response profiles for investigator reported outcome (IRO) by each subject over time will be shown across three treatment groups. Frequency and distribution of IRO will be presented across Screening, Baseline, and Visit 2 (Hour 4 and 8). In addition, changes from hour 0 at Baseline in IRO questionnaires will be shown for Hour 4 and Hour 8 by each question and total score for treatment groups. Moreover, Impact of change in MRD1 on IRO will be evaluated by Ordinal Model for Multi-nominal Data to determine the probability for IRO improvement based on change in MRD1 from Baseline.

9.7.1.5.2. Safety Endpoint Analysis

Safety analyses will be performed on all subjects in the Safety Analysis Set. The assessment of safety will be based on the summary of ocular and non-ocular AEs, current corrected VA, IOP, manual pupillometry, slit lamp biomicroscopy, indirect dilated ophthalmoscopy, conjunctival hyperemia evaluation, vital signs, urine pregnancy tests, and a comfort questionnaire. Summaries will be provided by treatment group, and for ocular assessments separately by eye.

9.7.1.5.2.1. Adverse Events

AEs are coded using MedDRA Version 25.1 or later. Ocular AEs are defined as those events for which an eye has been specified (OD, OS, or OU). Treatment-emergent adverse events (TEAEs) will be defined as AEs that start on or after the date of the first dose of double-masked study medication through the end of Visit 3 or early withdrawal. Pretreatment adverse events are events that begin prior to the date of double-masked study medication. Summaries of AE will focus on those events that are treatment-emergent.

Ocular and non-ocular TEAEs are summarized separately. In all summaries of TEAEs, percentages are calculated based on the number of subjects in each treatment group of the Safety Analysis Set. Overall summaries of TEAEs by treatment group will include:

- The number of TEAEs and serious TEAEs reported;
- The number and percentage of subjects who experienced any TEAEs;
- The number and percentage of subjects who experienced any serious TEAEs and the reason for seriousness;
- The number and percentage of subjects with any TEAEs leading to study termination;
- The number and percentage of subjects with any TEAE by worst severity and worst relationship.

Summaries of the frequency and percentage of subjects with TEAEs by SOC and preferred term by treatment group will include:

- All TEAEs by SOC and preferred term;
- All TEAEs by SOC, preferred term, and maximum severity;
- All TEAEs by SOC, preferred term, and maximum relationship.

System organ class (SOC) will be sorted alphabetically, and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

- Descending frequency within Treatment 1 (LEV102 , 2.0%): n = 10
- Descending frequency within Treatment 2 (LEV102, 1.0%): n = 10

- Descending frequency within Control (Vehicle), n=10
- PT in alphabetical order.

Subjects are counted only once for each SOC and PT. In summaries of maximum severity and maximum relationship, subjects with multiple occurrences of events will only be counted once at the maximum severity/relationship per SOC and PT.

Any TEAEs that have a missing severity will be presented as severe in the summary table but will be presented with a missing severity in the data listing. Any AEs that have a missing study relationship will be presented with a relationship of "Related" in the summary table but will be presented with a missing relationship in the data listing.

All TEAEs are displayed in listings. In addition, separate listings will be provided for:

- Subjects with any adverse event leading to study termination;
- Subjects with any serious adverse event;
- Subject deaths.

9.7.1.5.2.2. Current Corrected Visual Acuity

Summary statistics for observed and change from Baseline for current corrected visual acuity for study eye and non-study eye will be presented by treatment groups.

9.7.1.5.2.3. Intraocular Pressure (IOP)

Descriptive summaries of the observed values at each scheduled visit as well as the change from baseline at each post-baseline visit will be shown by treatment groups.

9.7.1.5.2.4. Manual Pupillometry

Descriptive summaries of the observed values in pupil diameter at each scheduled visit as well as the change from baseline at each post-baseline visit for study eye and non-study eye will be presented by treatment groups.

9.7.1.5.2.5. Slit Lamp Biomicroscopy

The frequency and percentage of subjects with observed values of normal and abnormal as well as the categorical shift from baseline at each post-baseline visit will be tabulated for each parameter at each scheduled visit by eye and treatment group.

9.7.1.5.2.6. Indirect Dilated Ophthalmoscopy

Indirect dilated ophthalmoscopy will be presented in a listing.

9.7.1.5.2.7. Vital Signs

Descriptive summaries of the observed values of vital signs at the Screening, Baseline, and at Hours 1 and 8 will be presented for each parameter by treatment group. Vital signs include heart rate (bpm), systolic, and diastolic blood pressure.

9.7.1.5.2.8. Investigational-Product (IP) Comfort Assessment

Investigational-Product (IP) comfort assessment will be conducted at 1 hour after dosing. Descriptive summaries of the observed scores of Comfort/Tolerability Rating Scale of the IP at 1 hour after dosing will be presented for each treatment group.

9.7.2. Determination of Sample Size

The sample size of 10 subjects per arm (30 subjects total for a total of 60 eyes) is not based on formal power or precision considerations.

9.8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1. Protocol Amendments

Date	Description	Substantive/Non-Substantive
25 May 2023	**Protocol Amendment 5 (Version 6.0)**	Revise Investigator-reported exploratory outcome endpoint as described in Protocol Clarification Memo_12Apr2023 - signed • Revise screening window • Add a note to exclusion criterion #1 • Add a note to exclusion criterion #5 • Revise exclusion criterion #9 • Revise exclusion criterion #10 • Revise exclusion criterion #13 • Revise exclusion criterion #21 • Revise exclusion criterion #22 • Revise exclusion criterion #24 • Remove exclusion criterion #27 • Additional updates were made for consistency with the changes outlined above or changes administrative in nature.
12 April 2023	Protocol Clarification Memo_12Apr2023 - signed	Investigator Reported Outcome visit changes from Baseline, Hour 1, and Hour 8 to Baseline. Hour 4, and Hour 8.
06 April 2023	Protocol Amendment 4 (Version 5.0)	• Revise threshold for MRD1 from 2.0 mm to 2.3 mm • Rescreening may also occur based upon protocol amendments with prior approval from the Medical Monitor and Sponsor. • MRD1 is defined as the distance from the margin of the upper eyelid to the top of the corneal light reflex when the eye is held in

		primary position (normal MRD1 is 4.0-4.5 mm).
17 January 2023	Protocol Amendment 3 (Version 4.0)	• Revise the timing of the Leicester Peripheral Field Test to occur at Screening, Baseline, Hour 2, and Hour 6 • Clarify that exclusionary ophthalmic α-adrenergic agonist includes brimonidine • Additional updates were made for consistency with the changes outlined above or changes administrative or stylistic in nature or as clarifications
06 December 2022	Protocol Amendment 2 (Version 3.0)	• Update the Safety Analysis section in the protocol to include pregnancy details. This section provides details on the data collection and follow-up activities that will occur if a subject becomes pregnant during the study or up until 30 days after study completion. Additional details have been added to describe follow-up procedures and how the data will be utilized. • Revise and update list of procedures in Section 7 (Study Activities) to include Bulbar Conjunctival Hyperemia to match Appendix 1: Schedule of Visits and Procedures • Revise and update Appendix 11: Slit Lamp Biomicroscopy to remove "anesthetic drops" as these are not permitted in the study. • Revise and update Appendix 11: Slit Lamp Biomicroscopy to add "Anterior Chamber" and "Iris/Pupil" assessment tables.

		• Revise and update Appendix 13: Indirect Dilated Ophthalmoscopy to remove " assessments of corneal staining and healing " as this is not applicable. • Additional updates were made for consistency with the changes outlined above or changes administrative or stylistic in nature
30 August 2022	Protocol Amendment 1 (Version 2.0)	This is a substantiative amendment; changes were made based on FDA comments on 26 July, 01 August, 03 August and 18 August 2022. Details can be found in the corresponding Summary of Changes document.
19 May 2022	Original Protocol (Version 1.0)	N/A

9.8.2. Changes from Protocol-Specified Analyses

There are no changes from protocol-specific analyses.

9.8.3. SAP Amendments

There were five (5) amendments made to the SAP since the original protocol was approved.

REFERENCES

1. Ho SF, Morawski A, Sampath R, Burns J. Modified visual field test for ptosis surgery (Leicester Peripheral Field Test). *Eye (Lond)* 2011;25(3):365-369.
2. Levation Pharma Ltd., 2023. A Phase 1/2a Study of LEV 102 Topical Gel in Subjects with Acquired Blepharoptosis. The Study Protocol. Version 6.
3. SAS Institute Inc. (2020). SAS/STAT User's Guide. SAS Institute Inc., Cary, NC, USA.

APPENDIX I: SCHEDULE OF PROCEDURES AND ASSESSMENTS

Days/Weeks	**Screening (Day -45 to Day -10)**	**Baseline/Randomization/Day 1**								**Day 2-5 (Telephone Follow-Up)**
Visit	**1**	**2**								**3**
Time (Hours)	---	**Baseline[1]**	**Hour 0 (IP Dosing)**	**0.5 hour (±10 minutes)**	**1 hour (±15 minutes)**	**2 hours (±15 minutes)**	**4 hours (±15 minutes)**	**6 hours (±15 minutes)**	**8 hours (±60 minutes)**	
Informed consent	X									
Inclusion/Exclusion criteria	X	X								
Randomization			X[2]							
IP administration OU			X[2]							
Demographics	X									
Medical/Ocular/Surgical history	X	X								
Vital signs[3]	X	X			X				X	
Urine pregnancy test[4]	X	X								

Note: All ophthalmic assessments must be conducted on both eyes at each timepoint.

[1] Baseline assessments are to be performed on Day 1 before the application of IP by the study staff.

[2] Study-eligible subjects only.

[3] Vital signs will include resting heart rate and sitting blood pressure.

[4] Women of child-bearing potential only; urine pregnancy test

Days/Weeks	**Screening (Day -45 to Day -10)**	**Baseline/Randomization/Day 1**								**Day 2-5 (Telephone Follow-Up)**
Visit	**1**	**2**								**3**
Time (Hours)	---	**Baseline[1]**	**Hour 0 (IP Dosing)**	**0.5 hour (±10 minutes)**	**1 hour (±15 minutes)**	**2 hours (±15 minutes)**	**4 hours (±15 minutes)**	**6 hours (±15 minutes)**	**8 hours (±60 minutes)**	
Current corrected VA	X	X							X	
IOP	X	X			X				X	
Leicester Peripheral Field Test	X	X				X		X		
Levator function	X									
FACE-Q | Aesthetics questionnaires	X	X					X		X	
BHVI assessment	X	X		X	X	X	X	X	X	
[redacted] external photography of eyes[5, 6]	X	X		X	X	X	X	X	X	
Manual pupillometry	X	X			X		X		X	
IP comfort assessment					X					

[5] To include MRD1 and interpalpebral distance measurements by central reading center. Only MRD1 values at Screening will be used for determining study eligibility. MRD1 values at Baseline will be used for assessing efficacy.

[6] Photography will be taken of subjects' eyes during the Screening visit: 1.) Before the instillation of oxymetazoline OU or phenylephrine OU and 2.) Approximately 120 (±30) minutes after the administration of eye drops. Only responders will be eligible for continuation in the study.

Days/Weeks	**Screening (Day -45 to Day -10)**	**Baseline/Randomization/Day 1**								**Day 2-5 (Telephone Follow-Up)**
Visit	**1**	**2**								**3**
Time (Hours)	---	**Baseline[1]**	**Hour 0 (IP Dosing)**	**0.5 hour (±10 minutes)**	**1 hour (±15 minutes)**	**2 hours (±15 minutes)**	**4 hours (±15 minutes)**	**6 hours (±15 minutes)**	**8 hours (±60 minutes)**	
Administration of 1 drop of oxymetazoline OU or phenylephrine OU	X									
Slit lamp examination and external eye exam	X	X							X	
Indirect dilated ophthalmoscopy	X									
AE assessment			X	X	X	X	X	X	X	X
Record concomitant medications	X	X							X	X
Exit study										X