Protocol

Study title: A Phase 1/2a Study of LEV102 Topical Gel in Subjects with Acquired Blepharoptosis
NCT Number:NCT05715346
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TITLE PAGE

Clinical Trial Protocol
LEV102-CS01

Study Title:	A Phase 1/2a Study of LEV102 Topical Gel in Subjects with Acquired Blepharoptosis
Study Number:	LEV102-CS01
Study Phase:	1/2a
Product Name:	LEV102 Topical Gel
IND Number:	156866
Indication:	Acquired Blepharoptosis
Investigators	Multicenter
Sponsor:	Levation Pharma Ltd.
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

	Date
Original Protocol, V 1.0:	09 August 2022
Amendment 1, V 2.0	31 October 2022
Amendment 2, V 3.0	06 December 2022
Amendment 3, V 4.0	17 January 2023
Amendment 4, V 5.0	06 April 2023
Amendment 5, V 6.0	25 May 2023

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 over-the-counter (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 Previous Protocol Amendment: 06 April 2023

Date of Most Recent Protocol Amendment: 25 May 2023

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
BHVI	Brien Holden Vision Institute
CCLRU	Cornea and Contact Lens Research Unit
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
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
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
LogMAR	Logarithm of the Minimum Angle of Resolution
LPFT	Leicester Peripheral Field Test
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MRD1	Margin reflex distance 1
OTC	Over-the-counter
OU	*Oculus uterque* (both eyes)
PK	Pharmacokinetics

PT	Preferred term
QC	Quality control
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
U.S.A.	United States of America
VA	Visual acuity
VAS	Visual Analog Scale
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary
WMA	World Medical Association
WOCBP	Women of child-bearing potential

1 INTRODUCTION

1.1 Background

Blepharoptosis, or ptosis, is a relatively common, abnormal drooping of the upper eyelid with the eye held in primary gaze. This drooping can affect one or both eyes. Based on time of appearance, blepharoptosis is typically classified as either congenital or acquired. Estimates of ptosis prevalence report rates between 4.7% and 13.5% in adult populations, and the incidence of ptosis increases with age. Drooping of the upper eyelid due to ptosis can negatively impact patient well-being, including reduced independence resulting from superior visual field obstruction and increased appearance-related anxiety and depression resulting from ptosis' characteristic 'sleepy' appearance. Functionally, obstruction of the pupil as a result of ptosis can lead to deficits in the superior visual field, detectable via visual field testing and present even in mild cases, with a novel static perimetry test [the Leicester Peripheral Field Test (LPFT)] detecting a visual field deficit in nearly all ptotic eyes (Ho et al., 2011). In large-scale studies of patients with unilateral or bilateral ptosis, improvement in the superior visual field following surgery was associated with significant improvement with respect to activities including performing their occupation, playing sports, and walking without assistance (Bacharach et al., 2021).

The active ingredient in LEV102 Topical Gel is oxymetazoline. Oxymetazoline is an α1- and α2-adrenoceptor agonist. Oxymetazoline was first approved in the United States of America (U.S.A.) in 1964 for the treatment of nasal decongestion (Afrin® Nasal Spray, 1964). Subsequently, numerous additional oxymetazoline-based drugs have been approved by the United States Food and Drug Administration (FDA) for ophthalmic and nasal use, including: Ocuclear® Ophthalmic Solution (1986), Visine® Ophthalmic Solution (1989), Kovanaze® Nasal Spray (2016), Rhofade® Topical Cream (2017), and Upneeq® Eyedrops (2020). Oxymetazoline is also listed in the FDA's over-the-counter (OTC) monograph for nasal use (FDA, 1994).

In addition to oxymetazoline's vasoconstrictor effects, which are therapeutic for the treatment of nasal decongestion and conjunctival hyperemia, oxymetazoline has therapeutic effects in the treatment of acquired blepharoptosis in adults. Presumably, this is due to the stimulation of α-adrenergic receptors in the superior tarsal muscle (also known as Müller's muscle) causing muscle contractions that lift the upper eyelid while retracting the lower eyelid to a lesser degree (Slonim et al., 2020).

The efficacy and safety of an oxymetazoline 0.1% ophthalmic solution approved for the treatment of acquired blepharoptosis in adults (Upneeq™, RVL Pharmaceuticals, Inc., Bridgewater, NJ, U.S.A.) has been reported. Evidence from two phase 3 clinical trials revealed that once-daily use of oxymetazoline 0.1% for 42 days significantly improved the superior visual field and upper eyelid elevation in patients with acquired ptosis and accompanying

superior visual field deficit. Using the LPFT, these studies demonstrated significant improvements in the superior visual field with associated improvements in margin reflex distance 1 (MRD1) measurements. MRD1 is a commonly used assessment in patients with ptosis and is defined as the distance (mm) between the upper eyelid margin and the corneal reflex when the eye is in the primary position. These studies showed that oxymetazoline 0.1% was associated with relatively low adverse event (AE) rates and no tachyphylaxis (Bacharach et al., 2021).

1.2 Study Rationale

The purpose of this study is to determine the ocular and systemic safety and tolerability of a single application of LEV102 Topical Gel on the upper eyelids, as well as to evaluate the effect of a single application of LEV102 Topical Gel on the upper eyelids on superior visual fields and upper eyelid height as measured by MRD1.

Upneeq® is a topical ophthalmic formulation of oxymetazoline (oxymetazoline, 0.1%) approved by the FDA for the treatment of acquired blepharoptosis in adults who report blurred vision and/or diminished superior visual fields (Upneeq® Package Insert 2021; Slonim et al., 2020). The mechanism of action of Upneeq® is presumably stimulating α-adrenergic receptors in the superior tarsal muscle causing it to contract and thereby lift the upper eyelid while retracting the lower eyelid to a lesser degree (Slonim et al., 2020). As Upneeq® and LEV102 Topical Gel share the same active ingredient, Upneeq® validates the mechanism of action in LEV102 Topical Gel.

1.3 Risk/Benefit Assessment

1.3.1 Known Potential Risks

LEV102 Topical Gel is a new drug and has not been approved by the FDA for use in any indication. The active ingredient, oxymetazoline, has been used for ophthalmic and nasal indications since the 1960s, and, in that time, pharmacology, pharmacokinetics (PK), and toxicology studies have been conducted on systemic, dermal, and ocular oxymetazoline.

Upneeq® (oxymetazoline, 0.1%) Eyedrops utilizes the same active ingredient as LEV102 Topical Gel in a lower concentration and with a different method of administration. Both Upneeq® and LEV102 Topical Gel are intended to treat acquired blepharoptosis in adults. Upneeq® is intended for direct instillation to the eye, whereas LEV102 Topical Gel is intended for external topical application to the external upper eyelid. The most common AEs reported for Upneeq® (incidence 1-5%) are punctate keratitis, conjunctival hyperemia, dry eye disease, blurry vision, pain at the instillation site, eye irritation, and headache.

Rhofade® (oxymetazoline, 1.0%) Topical Cream and LEV102 Topical Gel both use the same active ingredient and are both intended for topical dermal application to the face. The most common AEs (incidence >1%) for Rhofade® are application site dermatitis, worsening inflammatory lesions of rosacea, pruritis at the application site, erythema at the application site, and pain at the application site.

For additional information about the potential risks associated with LEV102 Topical Gel, please see the Investigator's Brochure (IB).

1.3.2 Known Potential Benefits

This is a first-in-human clinical trial of LEV102 Topical Gel and, therefore, there are no known health benefits. Based on the known effects of Upneeq®, which has the same active ingredient, it is hypothesized that subjects with acquired blepharoptosis may experience an increase in MRD1 values while using LEV102 Topical Gel, with resulting improvement in the superior visual field, increased independent functioning, and higher quality of life and psychosocial functioning.

1.3.3 Assessment of Benefits and Risks

It is the judgement of Levation Pharma Ltd. that there is a favorable benefit-risk ratio for subjects with acquired blepharoptosis. The active ingredient in the investigational product (IP), oxymetazoline, is already approved by the FDA for use in human subjects across multiple indications. Oxymetazoline has been approved and in use since the 1960s. The active ingredient is generally well tolerated in human subjects.

2 STUDY OBJECTIVES

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 AEs • 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 IP comfort questionnaire [Visual Analog Scale (VAS)] at Hour 1

Exploratory:	
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 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 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

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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

Ten (10) 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.

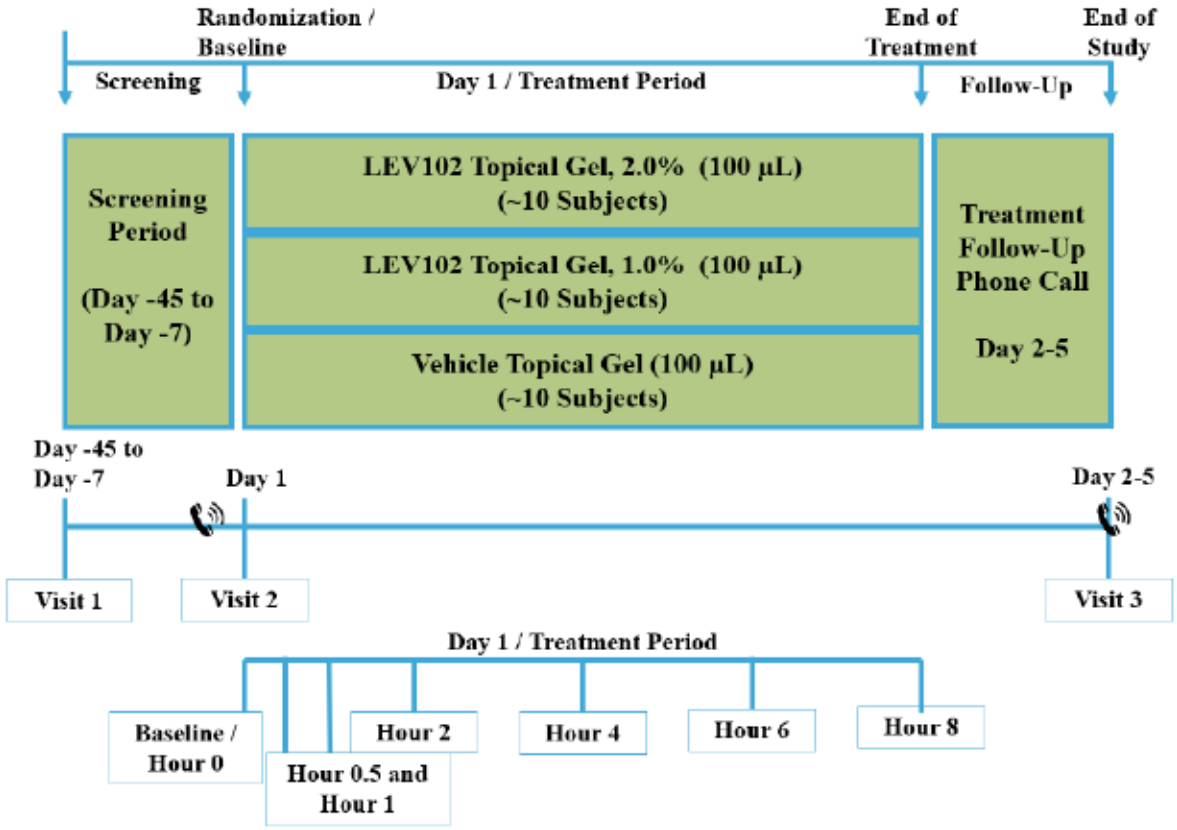
Subjects will undergo study assessments and answer study questionnaires at Baseline, Hour 1, Hour 4, and Hour 8. External photography of the eyes will also be conducted at Baseline, Hour 0.5, Hour 1, Hour 2, Hour 4, Hour 6, and Hour 8. For the purposes of documentation and analysis, Baseline will be 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.

3.2 Rationale for Study Design and Control Group

This study will assess the ocular and systemic safety and tolerability of a single application of LEV102 Topical Gel, 2% (100 µL), LEV102 Topical Gel, 1% (100 µL), and matching vehicle gel (100 µL) on the upper eyelids of subjects with acquired blepharoptosis. The matching vehicle gel is identical in formulation to LEV102, with the exception that the vehicle gel does not contain any active drug.

Subjects will receive 1 drop of single-masked Upneeq® (oxymetazoline 0.1% ophthalmic solution) OU at the Screening visit and will have photography taken of their eyes both before and after single-masked dosing. (**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 these images to ensure all subjects enrolled in the study are oxymetazoline or phenylephrine responders.

Subjects will receive a single dose of double-masked IP on the upper eyelid OU on Day 1 and will undergo study assessments at multiple timepoints on that same day. 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. The treatment period in this study will be on Day 1, and subjects will be contacted by telephone for a follow-up call after IP administration and before being released from the study.

[redacted] The intended clinical dose of LEV102 Topical Gel in this study will be 100 µL per upper eyelid at a formulation strength of either 2% or 1%. Assuming dose proportionality in the systemic exposure to oxymetazoline, the estimated systemic exposure in human subjects should be comparable to the systemic exposure observed with the marketed product, Rhofade®. The maximum dose of LEV102 Topical Gel is calculated as 100 µL of 2% LEV102 for each eyelid (200 µL total) = 2 mg per eyelid or 4 mg per subject for a single dose applied to both upper eyelids.

Based on information obtained from publicly available sources and the data collected to date on LEV102 Topical Gel, Levation Pharma Ltd. believes that the proposed dosing (100 µL of 2% LEV102 administered externally to each upper eyelid, once daily) is within the safety range. Please see the IB for additional details about the nonclinical pharmacology, the preclinical PK, and toxicology studies that informed this evaluation of oxymetazoline.

3.3 End of Study Definition

A subject is considered to have completed the study if they have been randomized to IP, undergone study assessments on Day 1, and been contacted by telephone for their follow-up visit. The end of the study is defined as completion of the last visit or procedure shown in the schedule in the study globally.

4 STUDY POPULATION SELECTION

4.1 Study Population

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.

4.2 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. Women of child-bearing potential (WOCBP) must agree to use an approved method of birth control as outlined in Appendix 16: Women of Child-bearing Potential (WOCBP) from the date they sign the 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

4.3 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)

4.4 Screen/Baseline Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who do not meet the inclusion criteria at the Screening visit and/or are determined unsuitable for the study because they meet exclusion criteria. This includes but is not limited to evaluations completed by the central reading center of images captured during the Screening visit. Baseline failures are defined as subjects who consent to participate in the clinical study and are eligible based on screening criteria but are not eligible based on the Baseline criteria and are therefore not randomly assigned to IP. A minimal set of screen failure information is required to ensure transparent reporting of screen and baseline failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAE).

Rescreening may be permitted a maximum of 1 time 2 weeks after screen failure for subjects with IOP values at Baseline ≥23 mmHg. Rescreening may be permitted a maximum of 1 time after appropriate washout periods for subjects who presented with disqualifying medical conditions at Baseline or previous/concomitant medications prohibited in Table 1. Rescreening may also occur based upon protocol amendments with prior approval from the Medical Monitor and Sponsor. Rescreened subjects should be assigned a new subject number, and the original subject number should be recorded as a screen failure.

5 STUDY TREATMENT(S)

5.1 Description of Investigational Product(s)

LEV102 Topical Gel and its matching vehicle gel are [redacted] gels with high visual viscosity intended for external topical administration to the exterior skin of subjects' upper eyelids. Stability studies of LEV102 show no microscopic changes of note and provide no results indicative of physical instability of the formulation.

The IP components are aseptic; however, it is not possible to terminally sterilize the IP using the current manufacturing method due to loss of drug substance and/or changes in viscosity. The matching vehicle gel in this study is identical in formulation to LEV102 Topical Gel, with the exception that the vehicle gel does not contain any active drug.

The active drug in this study, oxymetazoline, is a commercially available sympathomimetic. [redacted]

5.1.1 Dosage and Administration

Eligible subjects will be randomized to 1 of 3 possible treatment groups in a 1:1:1 ratio. Trained study staff will dispense double-masked IP [LEV102 Topical Gel, 2.0% (100 µL); LEV102 Topical Gel, 1.0% (100 µL); Vehicle Topical Gel (100 µL)] [redacted] will apply the gel smoothly with a gloved finger to the entire external skin of each subject's upper eyelids (OU).

The IP administration in this study must be scheduled for early in the morning in order to accommodate the Hour 8 study assessments. This is a 1-day, single-dose study in which subjects randomized to IP will receive 1 dose of double-masked IP gel (100 µL) per upper eyelid for a total of 200 µL per subject for the duration of the study.

5.2 Preparation/Storage/Handling/Accountability

5.2.1 Acquisition and Accountability

Double-masked IP for this study will be provided to each study site. Once the IP has been delivered to the site, it will be stored in a limited-access area only accessible to trained study staff. Used and unused IP will be maintained at the site for accountability by the clinical study monitor.

When authorized by the Sponsor and after the clinical study monitor has verified drug accountability is complete and accurate, used and unused double-masked IP will either be

returned to the Sponsor or designee, or will be disposed/destroyed by the sites in accordance with the requirements of applicable local authorities and regulatory bodies to ensure disposal of IP does not expose human beings to risks from the drug.

5.2.2 Product Formulation, Appearance, Packaging and Labeling

LEV102 Topical Gel and Vehicle Topical Gel will be packaged in identical [redacted] vials and labeled in accordance with federal regulations for investigational new drugs. Labels will include verbatim the following statement: "Caution: New Drug – Limited by Federal law to investigational use."

Additional details may also be included on the label, provided that these details do not pose a risk to study masking. This may include but is not limited to the protocol number, IP volume per container, storage requirements, manufacturer, and lot number.

5.2.3 Product Storage and Stability

The double-masked IP for this study will be stored upright in a limited-access area accessible only to trained study staff at a controlled room temperature between 20°C-25°C (68°F-77°F) and protected from direct sunlight. Temperature excursions experienced in warehouses and during shipping [not to exceed 30°C (86°F)] are permitted.

Once a vial of double-masked IP has been opened, it must only be used for dosing a single subject. Opened and unopened vials will be maintained at the site for accountability by the clinical study monitor.

5.3 Measures to Minimize Bias: Randomization and Masking

Eligible subjects will be randomized in the electronic data capture (EDC) system in a 1:1:1 ratio to double-masked IP [LEV102 Topical Gel, 2.0% (100 µL); LEV102 Topical Gel, 1.0% (100 µL); Vehicle Topical Gel (100 µL)] without stratification by study site. The double-masked IP will be dispensed and administered to subjects by trained study staff only.

The randomization schedule will be computer-generated in the EDC, and all IP will be masked to the Sponsor, study personnel, and study subjects throughout the study until after the final database has been locked. Appropriate precautions must be taken to prevent unauthorized access to the randomization scheme. Unless the subject's safety requires otherwise and if time permits, the decision to unmask a treatment assignment is to be made jointly by the Investigator and the study's medical monitor after consultation with the Sponsor.

If unmasking is required during the study, the integrity of the study assessments and collected data will be maintained by limiting access to the unmasked data.

5.4 Concomitant Therapy

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 electronic case report form (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 (WHODrug).

Unless specifically prohibited by the exclusion criteria detailed in 4.3, concomitant medications may be taken as prescribed or as needed throughout this study and recorded in the eCRF.

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.	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)
Note: Subjects wearing makeup during the Screening visit should remove the makeup on-site before image capture.	
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

6 STUDY PROCEDURES

6.1 Dispensing Study Drug

This is a double-masked, single-dose study in subjects with acquired blepharoptosis. Subjects will not have any IP dispensed to them. 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. The gloved study staff will carefully rub the IP into subjects' upper eyelid skin until the IP has been fully absorbed into the eyelid skin. Care will be taken to ensure IP is not accidentally instilled into subjects' eyes.

6.2 Adverse Events Assessments

AEs will be monitored throughout the study. Subjects will be encouraged to report any adverse findings during the study whether or not they are related to IP. These can be collected either in an unsolicited fashion without any prompting or in response to a general question such as: "Have you noticed anything different since you started the study; began the IP, etc.?"

All AEs will be captured on the appropriate case report form (CRF). Information to be collected at minimum includes event description, onset, assessment of severity, relationship to IP, and outcome.

6.2.1 *Definitions*

An AE is any untoward medical occurrence in a clinical study subject 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 IP.

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
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment,

they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.2.2 *Timing*

The Investigator will record all AEs with start dates occurring any time after informed consent is obtained until 7 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE but will be recorded as Medical History. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

6.2.3 *Severity*

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

- **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."

6.2.4 *Relationship*

All AEs must have their relationship to study intervention assessed by the Investigator who examines and evaluates the subject based on temporal relationship and the Investigator's 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.

- **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**: Is known to occur with the IP, 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.

6.2.5 *Expectedness*

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 Investigator's Brochure, 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 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.

6.2.6 *Adverse Event Reporting Requirements*

According to federal regulations, an Investigator must immediately report (i.e., within 24 hours) to the Sponsor any SAE, whether or not considered drug related, including those listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the IP caused the event. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the IP and the event (e.g., death from anaphylaxis). In that case, the Investigator must immediately report the event to the Sponsor (See 21 Code of Federal Regulations (CFR) 312.64(b)).

According to federal regulations, the Sponsor must notify the FDA and all participating Investigators as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that a potential serious risk arising from a clinical study qualifies for reporting. The Sponsor must report any suspected adverse reaction that is both serious and unexpected. The Sponsor must report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event (See 21 CFR 312.32(c)(1)).

Furthermore, the Sponsor must also notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information (See 21 CFR 312.32(c)(2)).

6.2.7 *Clinical Laboratory Adverse Events*

Not applicable. Clinical laboratory tests and pharmacokinetics are not being conducted for this study.

6.2.8 *Treatment-Emergent Adverse Events*

Treatment-emergent adverse events will be defined as AEs that occur in a subject after informed consent has been signed and after the subject has received IP on Day 1.

6.3 Removal of Subjects from the Study or Study Drug

Subjects are free to withdraw from participation in the study at any time upon request. An Investigator may discontinue or withdraw a subject from the study for any of the following reasons:

- Pregnancy
- Significant study treatment/intervention non-compliance
- If any clinical adverse event, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- The Sponsor or Investigator terminates the study
- The subject requests to be discontinued from the study.

The reason for subject discontinuation or withdrawal from the study will be recorded on the CRF. Subjects who sign the informed consent form and do not receive IP on Day 1 may be replaced. Subjects who sign the informed consent form, are randomized, have been dosed with IP on Day 1, and subsequently withdraw, or are withdrawn or discontinued from the study, may not be replaced.

6.4 Lost to Follow-Up

A subject will be considered lost to follow-up if the subject fails to return to the clinic for scheduled visits and if the subject cannot be contacted by the study site staff. Subjects will similarly be considered lost to follow-up if the subject does not respond to phone calls for the Visit 3 telephone follow-up (Day 2-5) in a timely manner.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study;

- Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.

Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study with a primary reason of Lost to Follow-Up.

6.5 Appropriateness of Measurements

6.5.1 Safety Assessments

The safety assessments selected for this study are all common tools within the field of ophthalmology and are generally recognized as reliable, accurate, and relevant in assessing the health and safety of subjects' eyes. Safety assessments in this study include:

- AE monitoring (ocular and non-ocular)
- Current Corrected VA (Appendix 2: Current Corrected Visual Acuity)
- IOP (Appendix 4: Intraocular Pressure (IOP))
- Manual Pupillometry (Appendix 9: Manual Pupillometry)
- Slit Lamp Examination (Appendix 11: Slit Lamp Biomicroscopy)
- Conjunctival Hyperemia Evaluation (Appendix 12: Bulbar Conjunctival Hyperemia [Brien Holden Vision Institute (BHVI) Grading Scale (Formerly Known as the CCLRU)])
- Indirect Dilated Ophthalmoscopy (Appendix 13: Indirect Dilated Ophthalmoscopy)
- Vital Signs (Appendix 15: Vital Signs)
- Urine Pregnancy Test [only for WOCBP (Appendix 16: Women of Child-bearing Potential (WOCBP))]

6.5.2 Efficacy Assessments

The efficacy assessments selected for this study are a mix of common tools within the field of ophthalmology generally recognized as reliable, accurate, and relevant and novel approaches to assessing ptosis. Efficacy assessments in this study include:

- Leicester Peripheral Field Test (Appendix 5: Leicester Peripheral Field Test (LPFT))

The LPFT is a novel, modified visual field test developed by Ho et al. (2011) to evaluate superior visual field defects in advance of ptosis surgery. The resulting literature confirms that ptosis can be considered both a functional issue and a cosmetic issue. The LPFT was selected for this study because of its FDA-approved use in clinical trials for Upneeq®.

- FACE-Q | Aesthetics Questionnaires (Appendix 6: 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.

- Investigator-Reported Outcomes (Appendix 8: Investigator-Reported Outcomes)
  Principal Investigators will be subjectively assessing the [redacted] photographs in a randomized, masked fashion.

- External Photography of Eyes (Appendix 3: Ptosis Evaluation; Appendix 7: [redacted] External Photography)
  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. Please see the Manual of Procedures for additional information about the central reading center's role, operations, and qualifications.

6.5.3 Other Assessments

This study will also include an IP Comfort Assessment (Appendix 14: Investigational Product Comfort/Tolerability Assessment).

7 STUDY ACTIVITIES

Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization will be obtained from all subjects before any study-related procedures are performed. The procedures and assessments that should occur at each study visit are detailed at Appendix 1: Schedule of Visits and Procedures.

Unless otherwise noted, procedures and assessments should occur in the order listed. The Screening visit involves Upneeq® or phenylephrine instillation and use of dilating eye drops. Subjects who normally wear contact lenses should instead use prescription eyeglasses during all study visits.

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

- Subject provides informed consent and HIPAA authorization
- Collect demographic information and medical, ocular, and surgical histories
- Record any concomitant medications
- Vital signs
- Urine pregnancy test (WOCBP only)
- FACE-Q | Aesthetics Questionnaires
- Current corrected VA
- Bulbar Conjunctival Hyperemia - (BHVI) Grading Scale
- LPFT
- Slit lamp examination and external eye exam
- Manual pupillometry
- Levator function test
- 1st [redacted] external photography of eyes
- Administration of 1 drop of 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.

- Wait 120 (±30) minutes
- 2nd [redacted] external photography of eyes
- IOP
- Administration of dilating eye drops
- Wait at least 20 minutes
- Indirect dilated ophthalmoscopy
- Confirm initial study eligibility based on inclusion and exclusion criteria
- Schedule the Baseline visit (Visit 2) for at least 5 calendar days from the Screening visit to allow Upneeq® or phenylephrine washout and central reading center processing of images

7.2 Baseline/Randomization (Visit 2; Treatment Period; Day 1)

Subjects should be contacted by site study staff via telephone before their Day 1 visit to confirm study eligibility as confirmed by the central reading center. Subjects should be reminded during this call 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 study treatment.

7.2.1 Baseline Assessments (Before IP Administration)

- Collect new medical, ocular, and surgical histories
- Record concomitant medications
- Vital signs
- Urine pregnancy test (WOCBP only)
- FACE-Q | Aesthetics Questionnaires
- Bulbar Conjunctival Hyperemia - (BHVI) Grading Scale
- Current corrected VA
- LPFT

- Slit lamp examination and external eye exam
- Manual pupillometry
- [redacted] external photography of eyes (submitted for Baseline measurement only, not for study eligibility)
- IOP
- Confirm continued study eligibility based on inclusion and exclusion criteria

7.2.2 IP Administration and Hour 0 Procedures (After IP Administration)

- Randomization
- Double-masked IP administration OU
- Record AEs (immediately after IP administration)

7.2.3 Hour 0.5 Procedures (±10 minutes)

- Record AEs
- [redacted] external photography of eyes
- Bulbar Conjunctival Hyperemia - (BHVI) Grading Scale

7.2.4 Hour 1 Procedures (±15 minutes)

- Record AEs
- Vital signs
- Manual pupillometry
- [redacted] external photography of eyes
- IOP
- IP comfort assessment
- Bulbar Conjunctival Hyperemia - (BHVI) Grading Scale

7.2.5 Hour 2 Procedures (±15 minutes)

- Record AEs
- LPFT

- [redacted] external photography of eyes
- Bulbar Conjunctival Hyperemia - (BHVI) Grading Scale

7.2.6 Hour 4 Procedures (±15 minutes)

- Record AEs
- FACE-Q | Aesthetics Questionnaires
- Manual pupillometry
- [redacted] external photography of eyes
- Bulbar Conjunctival Hyperemia - (BHVI) Grading Scale

7.2.7 Hour 6 Procedures (±15 minutes)

- Record AEs
- LPFT
- [redacted] external photography of eyes
- Bulbar Conjunctival Hyperemia - (BHVI) Grading Scale

7.2.8 Hour 8 Procedures (±60 minutes)

- Record AEs
- Record concomitant medications
- Vital Signs
- FACE-Q | Aesthetics Questionnaires
- Current corrected VA
- Bulbar Conjunctival Hyperemia - (BHVI) Grading Scale
- Slit lamp examination and external eye exam
- Manual pupillometry
- [redacted] external photography of eyes
- IOP

7.3 Treatment Follow-Up Phone Call [Visit 3; Day 2 to Day 5]

- Record AEs
- Record concomitant medications
- Release subjects from study

7.4 Study Withdrawal/Early Termination Procedures

The duration of the treatment period in this study is 1 day with assessments to be completed at Baseline, Hour 0 (after IP administration), Hour 0.5, Hour 1, Hour 2, Hour 4, Hour 6, and Hour 8. Windows for these timepoints are described in Appendix 1: Schedule of Visits and Procedures.

Subjects who withdraw from the study or who are terminated from the study before the Telephone Follow-Up (Visit 3) may be released after AEs and concomitant medications have been assessed. The reason for early withdrawal/termination will be recorded in the subject's CRF.

8 QUALITY CONTROL AND 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 may be developed to describe a site's quality management.

Quality control (QC) procedures will commence with the beginning of data entry and QC checks on the database will be generated throughout the study. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures, the study monitors will verify that the clinical study 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 study-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor or their designee, and inspection by local and regulatory authorities.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

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.

A separate Statistical Analysis Plan (SAP) will be prepared before unmasking of study data. Any amendments or changes to the planned analyses will be described in the SAP and the language in the final SAP will supersede the language in this protocol in the event of a discrepancy.

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.

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.

9.2 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.

9.3 Analysis Populations

The Safety Analysis Set will include all 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.

9.4 Demographics and Baseline Characteristics

Demographic characteristics, including age (years), sex, race, and ethnicity, will be summarized by treatment group and overall. Medical history [coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA)], and prior and concomitant medications (coded using the most recent version of the WHODrug) will be summarized by treatment group and overall.

The number of subjects who were enrolled and completed each visit of the study will be provided, as well as the reasons for all enrollment discontinuations, grouped by major reason (e.g., lost to follow-up, adverse event, poor compliance, rescue due to lack of efficacy). A list of discontinued subjects and protocol deviations will be provided.

9.5 Safety 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, 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.

9.5.1 Adverse Events

AEs will be coded using 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 SAEs will also be presented, and events leading to discontinuation from the study will be listed and tabulated.

9.5.2 Other Safety Endpoints

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.

9.5.3 Pregnancy

Individuals who are pregnant are not permitted to participate in the study. All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period.

If a subject becomes pregnant during the study or up until 30 days after study completion, the Investigator must notify Levation Pharma, Ltd, or their pharmacovigilance designee, within 24 hours of learning its occurrence by completing a Pregnancy Report Form.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days after delivery.

Any complications during pregnancy should be recorded as an AE and complications such as spontaneous abortion/miscarriage or congenital abnormality should be considered SAEs. AEs and SAEs must be reported to Levation Pharma, Ltd, or their pharmacovigilance designee,

using the Serious Adverse Event Form within 24 hours of knowledge of the event. Note: An elective abortion is not considered an SAE.

9.6 Exploratory Efficacy Assessments

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.

9.7 Tabulation of Individual Subject Data

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Study Administrative Structure

Title/Role	Contact Information
Sponsor	[redacted]
Chief Medical Officer	
Medical Monitor	
Contract Research Organization	

10.2 Institutional Review Board (IRB) Approval

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained from the IRB before any subject is enrolled in this study. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent form needs to be obtained from subjects who provided consent using a previous version of an approved consent form. Investigators are not to deviate from the study protocol except when necessary for the protection of subjects' health, safety, or welfare.

10.3 Ethical Conduct of the Study

This study will be conducted in compliance with the study protocol and in accordance with GCP, as described in the ICH Harmonized Tripartite Guideline: Guideline for Good Clinical Practice; the ethical principles established in the World Medical Association's (WMA) Declaration of Helsinki; and applicable local regulations.

10.4 Subject Information and Consent

Informed consent is a process that is initiated before subjects agree to participate in a study, and the informed consent process continues throughout subjects' study participation. Consent forms will be approved by the Institutional Review Board (IRB) and subjects will be asked to read and review the document. Before any study-specific procedures are performed, the Investigator (or designee) will provide subjects the ICF and explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subjects' comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions before signing it. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it before agreeing to participate in the study. The subject will sign and date the ICF and provide HIPAA authorization before any study-specific procedures are done. Subjects will receive a copy of the fully signed and dated ICF.

The Investigator (or designee) will explain to subjects that they are completely free to refuse to enter the study or to withdraw from the study at any time, without giving a reason. Similarly, the Investigator and Sponsor will be free to withdraw subjects at any time for safety or administrative reasons. Other requirements necessary for the protection of the human rights of subjects will also be explained according to current ICH GCP guidelines and the WMA Declaration of Helsinki in its revised edition. The content of the ICF will adhere to U.S.A. FDA regulations and ICH guidelines. Once the Investigator (or designee) is assured that subjects understand the implications of study participation, subjects will provide written informed consent to participate in the study.

10.5 Subject Confidentiality

Subject confidentiality and privacy will be strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their interventions. This confidentiality will be extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study subjects' contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Lexitas Pharma Services, Inc. This will not include the subjects' contact information or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Lexitas Pharma Services, Inc. staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Lexitas Pharma Services, Inc.

10.6 Study Monitoring

Lexitas Pharma Services, Inc. will conduct the clinical monitoring for this study. A clinical monitoring plan will be used and 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.

10.7 Case Report Forms and Study Records

Data collection is the responsibility of the clinical study 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.

Copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each subject enrolled in the study. Data recorded in the 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 any clinical laboratory data will be entered into IBM Clinical, 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.

10.8 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

10.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of protocol deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1 Quality Assurance and Quality Control, section 5.1.1
5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site's Investigator to use continuous vigilance to identify and report protocol deviations. All protocol deviations must be addressed in study source documents and reported to the Sponsor and reviewing IRB per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.10 Access to Source Documentation

The Study Monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product will be able to inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (i.e., office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records. Data and study integrity will be maintained by limiting access to unmasked data.

10.11 Publication Policy

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. The institution and Investigators

participating in this trial shall have no right to publish or present the results of this study without the prior written consent of the Sponsor.

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12 APPENDICES

12.1 Appendix 1: Schedule of Visits and Procedures

Days/Weeks	Screening (Day -45 to Day -7)	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								
Current corrected VA	X	X							X	
IOP	X	X			X				X	
Leicester Peripheral Field Test	X	X				X		X		
Levator function	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 -7)	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)**	
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					
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

[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 as defined in Appendix 7: [redacted] External Photography will be eligible for continuation in the study.

12.2 Appendix 2: Current Corrected Visual Acuity

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. If a subject reads a number, the examiner should remind the subject that the chart contains no numbers, and the examiner should then request a letter instead of a number from the subject. Subjects should be encouraged to guess if a letter appears unclear. If a subject identifies a letter as 1 of 2 possible letters, the examiner should ask the subject to pick 1 letter only.

Subjects will be instructed to read slowly at a rate of about 1 letter/second. If at any point the subject reads too quickly, the examiner should stop the subject and remind the subject to read slowly in order to achieve the best identification of each letter. If a subject loses their placement in the chart, the examiner should ask the subject to go back to the line where the place was lost. The subject should not proceed to the next letter until they have given a definite response. If a subject changes a response before moving on to the next letter, the examiner must accept the change.

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

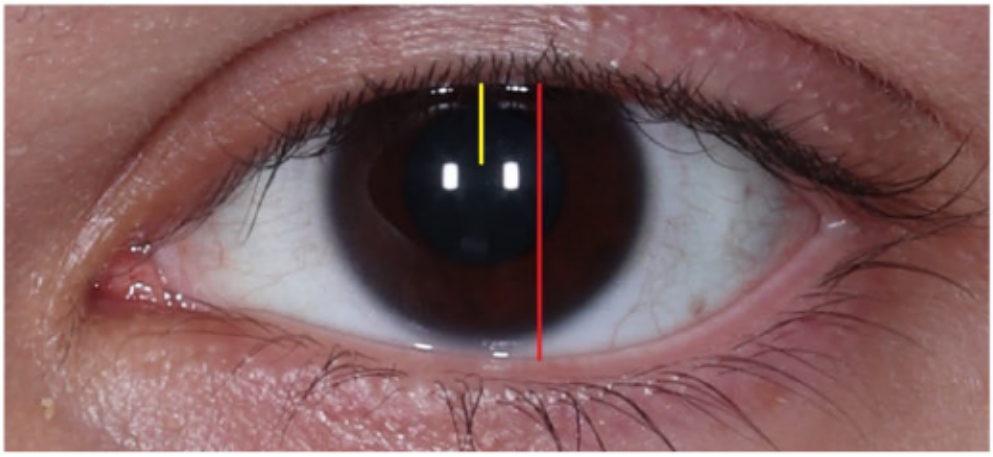
"n" is the total number of letters missed up to and including the last line read, and
"0.02" is the value for each letter

12.3 Appendix 3: Ptosis Evaluation

The MRD1 in millimeters will be used to determine study eligibility at the Screening visit. Changes in ptosis throughout Visit 2 will also be measured by MRD1 using external photography of the eyes at Baseline (before IP administration), Hour 0.5, Hour 1, Hour 2, Hour 4, Hour 6, and Hour 8. External photography of MRD1 and palpebral fissure will be captured at each timepoint and submitted to a central reading center.

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, shown by the yellow line in Figure 2 (normal MRD1 is 4.0-4.5 mm). Additionally, changes in the palpebral fissure may also be evaluated. The palpebral fissure is the distance between the upper and lower eyelid margins while the subject is in primary gaze (normal range can vary from 7-12 mm), shown by the red line in Figure 2.

Figure 2 MRD1 Ptosis Evaluation



Method adapted from *Aesthet Surg J*, Volume 30, Issue 3, May/June 2010, Pages 320-328.

Procedure steps:

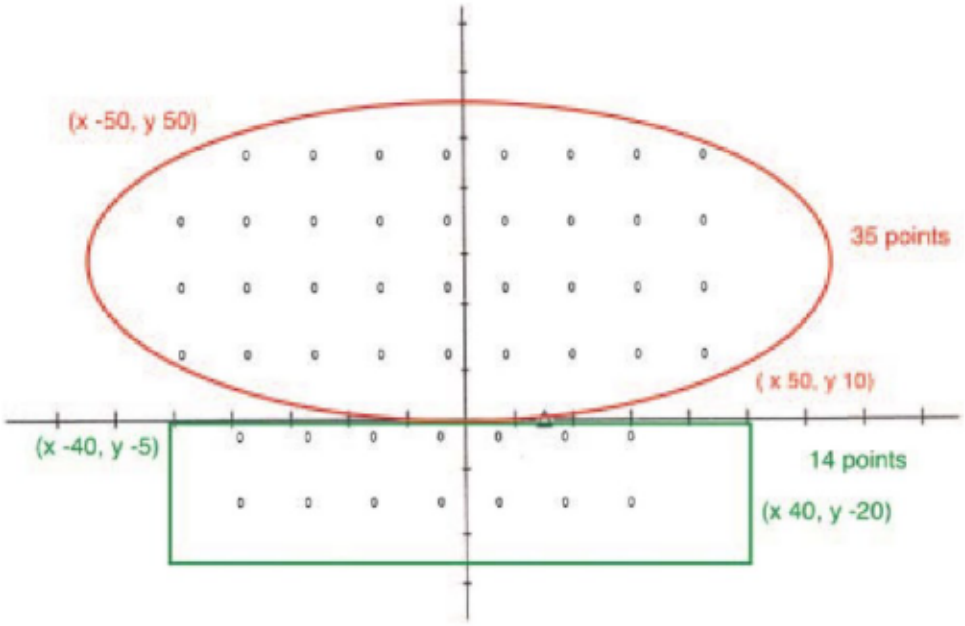
1. External photography of both of a subjects' eyes will be captured via [redacted] photography and submitted to a central reading center for evaluation of masked photographs.
2. The reading center will calculate the MRD1 value as measured from the lower margin of the upper eyelid to the top of the corneal light reflex.
3. MRD1 values will be recorded in the EDC in millimeters.

12.4 Appendix 4: 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.

12.5 Appendix 5: Leicester Peripheral Field Test (LPFT)



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.

12.6 Appendix 6: FACE-Q | Aesthetics Questionnaires

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. 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)

12.7 Appendix 7: [redacted] External Photography

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.) Subjects wearing makeup during the Screening visit should remove the makeup on-site before image capture.

The subjects will be asked to maintain a neutral expression to ensure that their facial features remain fully relaxed for all image assessments. A central reading center will review the images captured during the Screening visit to determine study eligibility. Only subjects who demonstrate a positive shift in upper eyelid elevation (MRD1) ≥0.5 mm in response to a single drop of oxymetazoline ophthalmic solution or phenylephrine ophthalmic solution will be eligible for study participation.

Throughout the day of Visit 2 (Baseline; Randomization; Day 1; Treatment Period), subjects will have additional external photographs taken of their eyes at Baseline (before IP administration), Hour 0.5, Hour 1, Hour 2, Hour 4, Hour 6, and Hour 8.

12.8 Appendix 8: Investigator-Reported Outcomes

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.

Additional details for this Investigator-reported assessment may be found in the Manual of Procedures.

12.9 Appendix 9: 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.

12.10 Appendix 10: Levator Palpebrae Superioris Function

Levator palpebrae superioris function of each subject will be assessed by Investigators at the Screening visit. Investigators will place a single finger firmly on the subject's brow to isolate the levator muscle and negate the mechanical activity of the frontalis muscle.

The subject will be instructed to gaze downward. Investigators will place a ruler at the upper eyelid margin and instruct subjects to shift their gaze from staring downward to staring upward. The new position of the upper eyelid will be noted and the difference between the two measurements will be recorded as the levator palpebrae superioris function. Normal levator function is typically 13-17mm.

12.11 Appendix 11: 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 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

Anterior Chamber:	Includes Anterior Chamber
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

Iris/Pupil:	Includes all Iris and Pupil
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)

12.12 Appendix 12: Bulbar Conjunctival Hyperemia [Brien Holden Vision Institute (BHVI) Grading Scale (Formerly Known as the CCLRU)]

Investigator-Rated Assessment of Bulbar Conjunctival Hyperemia

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]. Investigator BHVI ratings will be recorded in the eCRF.

Score	Redness
0	None
1	Very Slight
2	Slight
3	Moderate
4	Severe

12.13 Appendix 13: 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, and IOP assessments.

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

12.14 Appendix 14: Investigational Product Comfort/Tolerability 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 line to indicate the level of comfort/discomfort they experienced after IP administration. 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.

Comments (Optional): Please provide any additional comments you would like to share about your experience today with the investigational product related to the product's comfort/tolerability	

12.15 Appendix 15: 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.

12.16 Appendix 16: 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.

12.17 Appendix 17: Compliance Statement and Sponsor Approval

Study Title:	A Phase 1/2a Study of LEV102 Topical Gel in Subjects with Acquired Blepharoptosis
Study Number:	LEV102-CS01
Final Date:	25 May 2023

This study will be conducted in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP), with the United States of America Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), and as stipulated in the Declaration of Helsinki with respect to the use of human subjects in clinical studies and investigations.

Sponsor's Representative:

Name (printed) Chief Medical Officer	Signature	Date

Medical Monitor:

Name (printed)	Signature	Date

12.18 Appendix 18: Investigator's Signature

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

LEV102-CS01

Version No.: 6.0

Issue Date: 25 May 2023

I have read the clinical trial protocol and understand it. I agree to conduct the study as outlined in this document and in accordance with Good Clinical Practice Guidelines, all local and federal requirements and regulations, and in compliance with those precepts set forth in the Declaration of Helsinki with respect to the use of human subjects in clinical studies and investigations.

The Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the study subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

Further, I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Investigator:

Name (printed)	Signature	Date