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Study LL-BMT10001

A Phase 2a Study of Safety, Tolerability, and Efficacy of Drug-Delivering Contact Lens LL-BMT1 in Patients With Primary Open-Angle Glaucoma or Ocular Hypertension

Protocol V 1.2
Date: 21 December 2020

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A Phase 2a Study of Safety, Tolerability, and Efficacy of Drug-Delivering Contact Lens LL-BMT1 in Patients With Primary Open-Angle Glaucoma or Ocular Hypertension

Protocol Number:	**LL-BMT10001**
Investigational Device Exemption	
Sponsor:	**Leo Lens Technology Co., Inc.** **9899 Hibert Street, Suite A** **San Diego, CA 92131** **Phone:** [redacted]
Version Number:	**v1.2**
Date:	**21 December 2020**

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TECHNOLOGY

Protocol Signature Page

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the applicable Declaration of Helsinki and in accordance with 21 CFR's 50, 54, 56, 812 or the applicable guidelines for good clinical practices or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual.

I agree to maintain all information supplied by Leo Lens Technology Co., Inc. in confidence and when this information is submitted to an Institutional Review Board, Independent Ethics Committee, or other review board, it will be submitted with a designation that the material is confidential.

DAVID WONG MD		29 DEC 2020
Investigator Printed Name	Signature	Date

Acknowledged by:

Praful Doshi		12/21/2020
Sponsor Representative Name	Signature	Date

Return signed page to Trial Runners

Version 1.2
21 December 2020

No subjects enrolled.
No effect on subject exposure or safety.

Based upon input from the Investigational Review Board, best corrected visual acuity and slit lamp exam were added to all visits prior to the baseline visit. This impacts several sections of the protocol including the Schema and Schedule of Activities section.

STUDY TITLE

A Phase 2a Study of Safety, Tolerability, and Efficacy of Drug-Delivering Contact Lens LL-BMT1 in Patients With Primary Open-Angle Glaucoma or Ocular Hypertension

PROTOCOL NUMBER

LL-BMT10001

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), applicable United States (US) Code of Federal Regulations (CFR), the Health Insurance Portability and Accountability Act (HIPAA), and local regulatory guidelines. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) Sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial patients. 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 patient 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 patient 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 patients who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Phase 2a Study of Safety, Tolerability, and Efficacy of Drug-Delivering Contact Lens LL-BMT1 in Patients With Primary Open-Angle Glaucoma or Ocular Hypertension
Study Description:	This will be an open-label, phase 2a clinical study. Beginning 2 weeks prior to the Baseline Visit, all patients will have a 2-week run-in acclimation screening with a nonmedicated contact lens in each eye to ensure contact lens tolerability. Five patients with treated or treatment-naïve primary open-angle glaucoma (POAG) or ocular hypertension (OHT) in both eyes who have successfully passed the acclimation screening will be enrolled. All previously treated eyes will have a washout period prior to enrollment. At least one eye (called the study eye) will have untreated (after washout, if applicable) intraocular pressure (IOP) between 22 mmHg and 34 mmHg (inclusive). If the fellow eye does not meet this IOP criterion, it must have an untreated IOP (following washout, if applicable) within 5 mmHg of the study eye without exceeding the 34-mmHg maximum. Five patients will be enrolled to receive LL-BMT1 (medicated) contact lenses placed in a packaging solution containing [redacted]. During the 7-day treatment period, patients will be assessed for safety and IOP reduction. Adverse events (AEs) and treatment-related serious adverse event [SAE] will be monitored, as will other safety measures, including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, and contact lens protein deposit. The study hypothesis is that no safety concerns are revealed.
Objectives:	The primary objective of this study is to evaluate the safety of LL-BMT1 in patients with POAG or OHT. Additional objectives of this study are to evaluate the tolerability and IOP-lowering effects of LL-BMT1 in patients with POAG or OHT.
Endpoints:	*Primary safety endpoint:* AE rate *Secondary safety endpoints*: percent of patients with ≥5-mmHg increase from baseline in IOP at each visit; abnormal slit-lamp biomicroscopy findings at the Baseline, Day 1, and Day 7 Visits; contact lens protein deposits at the Day 7 Visit; and change from baseline in Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) results at the Day 7 Visit *Secondary efficacy endpoints:* change from baseline in IOP at each visit

Study Population:	Five patients who are at least 18 years of age of either sex with POAG or OHT in both eyes
Phase:	2a
Description of Site Enrolling Patients:	Up to 2 sites within the United States (US)
Description of Study Intervention:	LL-BMT1 is a US Food and Drug Administration (FDA)-classified Group 4 extended-wear contact lens that has bimatoprost printed onto the anterior surface of the contact lens in one set concentration. The coating of the anterior surface does not obstruct the optic zone, and the bimatoprost elutes from both the concave and convex surfaces of the lens. LL-BMT1 is designed to lower the IOP of patients with POAG or OHT and be worn for 1 week (7 days, 6 nights). Patients will wear LL-BMT1 lenses for 1 week.
Study Duration:	3 to 4 months
Patient Treatment Duration:	1 week for each patient

1.2 SCHEMA

Day -45 to -14 (Visit 1): Screening

- Total n=5 to 7 (If all 7 patients successfully complete the acclimation screening, only 5 patients will be enrolled to receive LL-BMT1. If dropouts occur during acclimation screening resulting in less than 5 patients successfully completing the acclimation screening, then that patient(s) will be replaced until at least 5 patients have been enrolled to receive LL-BMT1)
- Obtain informed consent
- Screen potential patients by inclusion and exclusion criteria, including:
    - Ultrasound pachymetry to assess corneal thickness
    - Humphrey visual field to assess visual field loss *(If Humphrey visual field assessment has been completed within 6 months of Screening Visit, it does not have to be repeated at the Screening Visit)*
- Obtain medical history
- Concomitant medications - *Systemic treatments that the patient has been receiving for at least 30 days prior to study initiation will be collected*
- If on any IOP-lowering medication, start washout according to the period required for the current medication, timed to end at the Baseline Visit
- Two weeks prior to the Baseline Visit, start 2-week acclimation screening with insertion of nonmedicated lenses

Day -14 (Visit 2): Acclimation (first nonmedicated lens insertion)

- Concomitant medications - *The medical monitor should be informed of any new systemic medications that cannot be delayed until the end of the study to determine if the patient can participate and/or continue in the study*
- AEs
- BCVA
- Biomicroscopy
- Nonmedicated lens insertion

Day -7 (Visit 3): Acclimation (first nonmedicated lens removal)

- Concomitant medications
- AEs - The patient will also be questioned about AEs related to the contact lens wear by the investigator. Eligibility for the treatment portion of the study will be at investigator's discretion.
- Nonmedicated lens removal
- BCVA
- Biomicroscopy

Day -6 (Visit 4): Acclimation (second nonmedicated lens insertion)

- Concomitant medications
- AEs
- BCVA
- Biomicroscopy
- Nonmedicated lens insertion (new lens)

Day 0 (Visit 5): Baseline

- Concomitant medications
- AEs - The patient will also be questioned about AEs related to the contact lens wear by the investigator. Eligibility for the treatment portion of the study will be at investigator's discretion.
- Remove nonmedicated lenses
- Verify inclusion/exclusion criteria
- CLDEQ-8
- Heart rate and blood pressure
- Urine pregnancy test for women of childbearing potential
- BCVA
- Biomicroscopy
- IOP (measured at 9 am ±1 hour)
- IOP (measured at 4 pm ±1 hour)

Day 1 (Visit 6): Lens insertion

- Concomitant medications
- AEs
- Heart rate and blood pressure - *procedure should be performed before study intervention*
- BCVA - *procedure should be performed before study intervention*
- Biomicroscopy - *procedure should be performed before study intervention*

- IOP (measured at 8 am ±1 hour) - *procedure should be performed before study intervention*
- LL-BMT1 insertion of new lens
- Contact lens assessment
- LL-BMT1 removal (directly before 4 pm IOP assessment) - *If a lens is damaged during removal, a new lens cannot be inserted in the patient's eye. Patients can remain on the study if at least one LL-BMT1 lens is able to be reinserted.*
- IOP (measured at 4 pm ±1 hour)
- LL-BMT1 reinsertion (directly after 4 pm IOP assessment)

Day 4 (Visit 7): On-treatment assessment

- Concomitant medications
- AEs
- Heart rate and blood pressure
- BCVA
- Biomicroscopy
- LL-BMT1 removal (directly before 8 am IOP assessment) - *If a lens is damaged during removal, a new lens cannot be inserted in the patient's eye. Patients can remain on the study if at least one LL-BMT1 lens is able to be reinserted.*
- IOP (measured at 8 am ±1 hour)
- LL-BMT1 reinsertion (directly after 8 am IOP assessment)

Day 7 (Visit 8): End of treatment assessment

- Concomitant medications
- AEs
- Heart rate and blood pressure
- BCVA
- Biomicroscopy
- LL-BMT1 removal - *Lens will be removed prior to IOP assessment, but the lens will not be reinserted*
- Contact lens protein deposit assessment
- IOP (measured at 4 pm ±1 hour)
- CLDEQ-8

Day 8 (Visit 9): Follow-up assessment / End of study

- Concomitant medications
- AEs
- BCVA
- Heart rate and blood pressure
- IOP (measured at 8 am ±1 hour)
- If patient's IOP is decreased by ≥3 mmHg from baseline, schedule Visit 10. If not, Visit 9 is the end of the study

Day 9 (Visit 10): Conditional follow-up assessment (If a patient's IOP is decreased from baseline by ≥3 mmHg at the Day 8 Visit) / End of study

- Concomitant medications
- AEs

- Heart rate and blood pressure
- IOP (measured at 8 am ±1 hour)

1.3 SCHEDULE OF ACTIVITIES

Procedures	Screening Visit 1 Day -45 to -14	Acclimation Visit 2 Day -14	Acclimation Visit 3 Day -7	Acclimation Visit 4 Day -6	Baseline Visit 5 Day 0	Lens Insertion Visit 6 Day 1	On-Treatment Visit 7 Day 4	End of Treatment Visit 8 Day 7	Follow-Up Visit 9 Day 8	Conditional Follow-Up/ End of Study Visit 10 Day 9	Early Termination Visit
Informed consent	X										
Inclusion/exclusion criteria	X				X						
Ultrasound pachymetry	X										
Humphrey visual field assessment[a]	X										
Demographics	X										
Medical history	X										
Insertion of nonmedicated lenses[b,c]	X	X		X							
Removal of nonmedicated lenses[b]			X		X						
Heart rate and blood pressure	X				X	X[d]	X	X	X	X	X
Urine pregnancy test[e]	X				X						
BCVA	X	X	X	X	X	X[d]	X	X	X		X
Biomicroscopy	X	X	X	X	X	X[d]	X	X			X
IOP[f,q]	X				X[g]	X[d,h]	X[i]	X[j]	X[i]	X[i]	X
CLDEQ-8					X[k]			X			X
Insertion of new LL-BMT1 lens[b,c]						X[l]					
Removal/reinsertion of LL-BMT1 lens[c]						X[m]	X[m]	X[n]			X
CL assessment[o]						X		X			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X[p]	X	X[p]	X	X	X	X	X	X

Abbreviations: AEs, adverse event; BCVA, best-corrected visual acuity; CL, contact lens; CLDEQ-8, Contact Lens Dry Eye Questionnaire-8; IOP, intraocular pressure.
[a]If Humphrey visual field assessment has been completed within 6 months of Screening Visit, it does not have to be repeated at the Screening Visit.
[b]All lens insertions and removals will be conducted by the investigator.
[c]At the discretion of the investigator, topical anesthesia can be applied to patient's eyes prior to lens insertion.
[d]These procedures should be performed before study intervention.
[e]Urine pregnancy test will be performed on women of childbearing potential.

[f]IOP will be assessed 3 minutes after lens removal, with the goal of reinserting the lens within 2-3 minutes after IOP assessment. Three measurements will be taken at each visit and these results will be averaged.
[g]IOP will be performed at 9 am ±1 hour and 4 pm ±1 hour.
[h]IOP will be performed at 8 am ±1 hour and 4 pm ±1 hour.
[i]IOP will be performed at 8 am ±1 hour.
[j]IOP will be performed at 4 pm ±1 hour.
[k]Questionnaire to be given at the end of the acclimation screening.
[l]Lens will be inserted by the investigator after all assessments (except 4 pm IOP assessment) are complete.
[m]Lens will be removed prior to and reinserted following IOP assessment. If a lens is damaged during removal, a new lens cannot be inserted in the patient's eye. Patients can remain on the study if at least one LL-BMT1 lens is able to be reinserted.
[n]Lens will be removed prior to IOP assessment, but the lens will not be reinserted.
[o]Assessments will include contact lens centration, movement with blinking, and lens surface wettability/deposits, as described in ISO 11980:2012.
[p]The patient will also be questioned about AEs related to the contact lens wear by the investigator. Eligibility for the treatment portion of the study will be at investigator's discretion.
[q]Should the IOP at any time during the study be elevated 10 mmHg above baseline (after washout, if applicable), the lens will be removed and a different IOP-lowering medication should be prescribed at the discretion of the investigator. The patient will be discontinued from study intervention but will continue in the study

2 INTRODUCTION

2.1 STUDY RATIONALE

Therapy for glaucoma and ocular hypertension today includes pharmaceuticals, laser trabeculoplasty, and surgery. Each of these treatments has been shown to be effective in lowering elevated IOP as well as to slow the progression of glaucomatous visual field loss (Kass 2002; Lichter 2001; AGIS Investigators 2000; CNTGSG 1998).

Pharmacotherapy with eye drops requires patients, or their care givers, to be adherent to the dosing schedule, as well as to be able to appropriately instill eyedrops. Even experienced patients at a private practice clinic are less than perfect in both adherence and performance (Robin 2007; Stone 2009).

In order to optimize therapy, a wide range of drug delivery technologies have been evaluated in ophthalmology (Novack 2009). Recently, an intracameral drug delivery system using bimatoprost (Durysta®, Allergan) was approved by the US FDA (Craven 2020; Lewis 2017). While providing ocular hypotensive efficacy for at least 3 months, use of this product has been associated with concerns about the health of the corneal endothelium (Durysta prescribing information [PI]).

Thus, there is a continuing need for safe and effective pharmacotherapeutic delivery systems for the treatment of elevated IOP.

2.2 BACKGROUND

Leo Lens Technology Co., Inc. has developed the MediPrint™ process that allows active pharmaceutical ingredients to be inkjet printed onto FDA-approved, Group 4 extended-wear contact lenses (eg, BIOMEDICS® 55 [ocufilcon D] soft [hydrophilic] contact lenses). Currently, Leo Lens Technology is developing a lens that has bimatoprost digitally printed onto the anterior surface of the contact lens at one strength. This product, called LL-BMT1, is designed to reduce elevated IOP in patients with open-angle glaucoma (OAG) or OHT. LL-BMT1 is a preservative-free, continuous wear (7-day and 6-night) contact lens that delivers sustained-release bimatoprost to the eye. This product is intended to provide a novel, sustained delivery mechanism for bimatoprost and has the potential to reduce progression of glaucoma and the rate of vision loss in patients with glaucoma or OHT, compared to the current standard of care.

Bimatoprost has been approved by the FDA as bimatoprost ophthalmic solution (Lumigan® New Drug Application [NDA] 021275 and NDA 022184; Lumigan PI), several abbreviated NDAs, Latisse® NDA 022369, and Durysta® NDA 211911. NDA 021275 has been discontinued by its Sponsor, Allergan. However, it is Sponsor's understanding that this was not for safety or efficacy reasons.

The bimatoprost in LL-BMT1 is printed on a contact lens that is an FDA-approved, Group 4 extended-wear contact lenses (eg, BIOMEDICS® 55 [ocufilcon D] soft [hydrophilic] contact

lenses). The contact lens used in LL-BMT1 was approved by the US FDA as PMA P890023. Information on this product is provided in the instructions for use (Biomedics 55 PI).

[redacted]

2.3 POTENTIAL RISKS AND BENEFITS TO HUMAN PATIENTS

Adverse reactions of greatest concern reported with bimatoprost eyedrops include pigmentation (including blepharal pigmentation and iris hyperpigmentation), eyelash changes, intraocular inflammation, macular edema, and hypersensitivity. In controlled clinical trials, the most common adverse reaction was conjunctival hyperemia (31%). Approximately 1.6% of patients discontinued therapy due to conjunctival hyperemia. Other adverse drug reactions (reported in 1% to 4% of patients) with Lumigan® 0.01% included conjunctival edema, conjunctival hemorrhage, eye irritation, eye pain, eye pruritus, erythema of eyelid, eyelids pruritus, growth of eyelashes, hypertrichosis, instillation site irritation, punctate keratitis, skin hyperpigmentation, vision blurred, and visual acuity reduced. In post-marketing use, AEs reported also include asthma-like symptoms, dizziness, dry eye, dyspnea, eye discharge, eye edema, foreign body sensation, headache, hypersensitivity (including signs and symptoms of eye allergy and allergic dermatitis), lacrimation increased, and periorbital and lid changes (including deepening of the eyelid sulcus; Lumigan PI).

The bimatoprost in LL-BMT1 is printed on Group 4 extended-wear contact lenses. Risks to patients in the present study are those typical of contact lenses.

[redacted]

The potential benefit to patients in this study is the lowering of IOP without the use of daily eyedrops.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Justification for Endpoints
Primary safety		
To evaluate the safety of LL-BMT1 in patients with POAG or OHT	AE rate	AE collection is necessary to determine the safety of this intervention. AEs will be collected at each visit to maximize safety during the study.
Secondary safety		
To evaluate the safety and tolerability of LL-BMT1 in patients with POAG or OHT	The secondary safety endpoints are: • Percent of patients with ≥10-mmHg increase from baseline in IOP at each visit • Abnormal slit-lamp biomicroscopy findings at the Baseline, Day 1, and Day 7 Visits • Contact lens protein deposits at the Day 7 Visit • Change from baseline in CLDEQ-8 results at the Day 7 Visit	These safety endpoints will provide additional safety information during the course of the study.
Secondary efficacy		
To evaluate IOP-lowering effects of LL-BMT1 in patients with POAG or OHT	The secondary efficacy endpoint is: • Change from baseline in IOP at each visit	IOP assessment is necessary to determine the efficacy of an IOP-lowering device.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This will be an open-label, phase 2a clinical study. Five patients with treated or treatment-naïve POAG or OHT in both eyes will be enrolled. All previously treated eyes will have a washout period prior to enrollment. At least one eye (called the study eye) will have untreated (after washout, if applicable) IOP between 22 mmHg and 34 mmHg (inclusive). If both eyes meet this criterion, then the eye with the higher IOP will be selected as the study eye. If the IOP in both qualified eyes is the same, then the right eye will be selected as the study eye. If the fellow eye does not meet this IOP criterion, it must have an untreated IOP (following washout, if applicable) within 5 mmHg of the study eye without exceeding the 34-mmHg maximum. For all enrolled patients, both eyes will be treated, and all tests will be performed separately on both eyes, but only the study eye will be included for efficacy analysis.

Beginning 2 weeks prior to the Baseline Visit, all patients will have a 2-week run-in acclimation period with a nonmedicated contact lens in each eye to ensure contact lens tolerability. The patient will be questioned about AEs related to the contact lens wear. The patient must have experienced no contact lens-related AEs in order to be eligible for the study. If a patient does not successfully complete the 2-week acclimation screening, that patient will be replaced until at least 5 patients successfully complete the acclimation screening. Those patients who have completed acclimation screening will be enrolled as patients for dosing with LL-BMT1. After insertion of the LL-BMT1 (medicated) lens, patients will be followed for 7 or 8 days for assessments of safety and IOP reduction.

Five (5) patients will receive LL-BMT1 contact lenses [redacted] inserted into each eye at the Day 1 visit, where they will remain until the Day 7 Visit, at which time the lenses will be removed. Patients will not remove the lenses themselves during the study. During the 7-day treatment period, patients will be assessed for safety and IOP reduction which requires removal and reinsertion of LL-BMT1 on Day 1 and Day 4. AEs will be monitored, as will other safety measures, including BCVA, slit-lamp biomicroscopy, and contact lens protein deposit. Patients will attend a follow-up visit on Day 8, during which heart rate/blood pressure, BCVA, and IOP will be assessed. If a patient's IOP is decreased from baseline by ≥3 mmHg at the Day 8 Visit, a Day 9 Visit will be performed in order to reassess IOP.

The primary focus of this safety study will be a comprehensive descriptive assessment of safety endpoints. No formal study hypothesis will be tested.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is designed to examine the use of bimatoprost delivered via extended-wear contact lenses and assess the safety and efficacy of this drug device in a sample of patients. Both bimatoprost and the contact lens (as a nonmedicated lens) are FDA-approved, long-standing commercial products with well-characterized safety and effectiveness profiles. All patients will attend a follow-up visit on Day 8, and if IOP at that visit is decreased from baseline by ≥3 mmHg, patients will attend a conditional follow-up visit on Day 9 in order to reassess IOP.

4.3 JUSTIFICATION FOR DOSE

LL-BMT1 is an investigational device composed of an FDA-approved Group 4 extended-wear contact lens that has been has had bimatoprost coated onto the anterior surface of the lens via an inkjet printer. Once LL-BMT1 is inserted in the eye, the bimatoprost will elute uniformly from both the concave and convex surfaces of the lens. In vitro studies have shown that the LL-BMT1 lens [redacted] releases approximately 26 µg bimatoprost over the 7-day wearing period. Given the fact that over a 7-day period, patients using bimatoprost eye drops would receive approximately 105 µg of bimatoprost, LL-BMT1 releases approximately 25% of the total amount of bimatoprost compared with the eye drops. However, because of the continuous elution of drug from the lens, the LL-BMT1 lens is expected to have increased bioavailability compared with topical bimatoprost administration, possibly resulting in a safer, more efficacious treatment.

4.4 END OF STUDY DEFINITION

A patient is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities, Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the Schedule of Activities, Section 1.3, in the last patient.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Male or female, at least 18 years of age at the Screening Visit
2. Diagnosed with POAG or OHT in both eyes
3. At least one eye (called the study eye) must have an untreated IOP between 22 mmHg and 34 mmHg (inclusive) as measured at 9 am during the Baseline Visit. For eyes receiving IOP treatment, untreated IOP will be assessed following a required washout period as outlined below:
    - 4 days washout for parasympathomimetic and topical or systemic carbonic anhydrase inhibitors
    - 2 weeks washout for sympathomimetics and alpha agonists
    - 4 weeks washout for beta adrenergic blocking agents, combination product, Rho kinase (ROCK) inhibitors, and prostaglandin agonists
4. If the fellow eye does not meet inclusion criterion #3 above, it must have an untreated IOP (following washout, if applicable) within 5 mmHg of the study eye without exceeding the 34 mmHg maximum (eg, a study eye IOP of 22 mmHg and a fellow eye IOP of 17 mmHg are allowed).
5. BCVA of Early Treatment Diabetic Retinopathy Study (ETDRS) of 50 letters or better (Snellen equivalent of 20/100 or better) in each eye
6. Women of child-bearing potential must not be pregnant or lactating, must have a negative pregnancy test at screening and must be practicing an adequate method of birth control, including intrauterine device (IUD); oral, dermal (“patch”), implant or injected contraceptives; tubal ligation; or barrier methods with spermicide
7. No adverse reactions to nonmedicated contact lenses during the 2-week acclimation screening
8. Score of 0-11 on CLDEQ-8, administered at the end of the 2-week acclimation screening
9. Willing and able to comply with the study procedure and sign a written informed consent

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Glaucoma or optic neuropathy due to anything other than POAG or OHT
2. Cup-to-disc ratio of >0.8 in either eye
3. Corneal thickness <480 or >620 μm
4. IOP >34 mmHg in either eye at the Screening Visit or Baseline Visit
5. Significant visual field loss, in the opinion of the investigator
6. Uncontrolled systemic disease, such as poorly controlled hypertension or poorly controlled diabetes
7. An active ocular infection (ie, bacterial, viral, parasitic, or fungal) in either eye at the Screening Visit
8. Current contact lens use for vision correction (unless willing to switch to glasses for the duration of the study)
9. Current contact lens use for cosmetic purposes (unless willing to discontinue use for the duration of the study)
10. Clinically significant dry eye
11. History of treated allergic, vernal, or atopic conjunctivitis
12. History of contact lens intolerance, corneal scarring, corneal neovascularization, giant papillary conjunctivitis, or any other corneal pathology that is deemed by the investigator to constitute a contraindication for applying contact lenses
13. Aphakia or presence of anterior chamber intraocular lens in either eye
14. History of clinically significant macular pathology (ie, progressive age-related macular degeneration, diabetic macular edema, proliferative diabetic retinopathy, etc.)
15. History of corneal refractive surgery (ie, laser-assisted in situ keratomileusis [LASIK], photorefractive keratectomy [PRK], radial keratotomy [RK], small incision lenticule extraction [SMILE], or corneal inlay, etc.)
16. History of prior incisional glaucoma surgery (ie, bleb, shunt, seton, etc.)
17. History within past 6 months of any ocular anterior segment laser or other intraocular surgery
18. Use of laser of any type on retina in either eye within 3 months prior to the Screening Visit
19. History of punctal cautery or planned use of punctal plugs during the study
20. Cataract surgery in either eye within 3 months, or other intraocular surgery in either eye within 6 months prior to the Screening Visit or planned during the course of the study

21. Anticipated need for ocular surgery in either eye during the study period
22. Required chronic use of topical or injectable ocular medications other than IOP-lowering medication, including artificial tears, or currently receiving chronic intravitreal injections
23. Known allergy or hypersensitivity to the study medications or its components
24. Treatment with an investigational drug within 60 days prior to the Baseline Visit (when treatment is given)
25. Any participation in a clinical trial within 30 days of the Screening Visit or during the course of the study
26. Patient has a condition or is in a situation that, in the investigator's opinion, will interfere with the patient's ability to comply with the dosing and visit schedules and the protocol evaluations or may not be suitable for this study

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants will be instructed to refrain from using a sauna, hot tub, and partaking in any water-related activities, including swimming, snorkeling and scuba diving. All participants will be instructed to avoid consuming fluids for 1 hour prior to each study visit.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. Screen failures can be identified at the Screening Visit, at either of the Acclimation Visits, or at the Baseline Visit. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, 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 SAEs.

Individuals who do not meet the criteria for participation in this trial (screen failure) may not be rescreened.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Because this study will enroll only 5 patients with a duration of less than 6 weeks (including washout), no particular recruitment or retention strategies are expected to be necessary. Enrolled patients who fail acclimation screening will be replaced until at least 5 patients successfully complete the acclimation screening. Enrolled patients who exit the study early due to related or unrelated reasons will not be replaced.

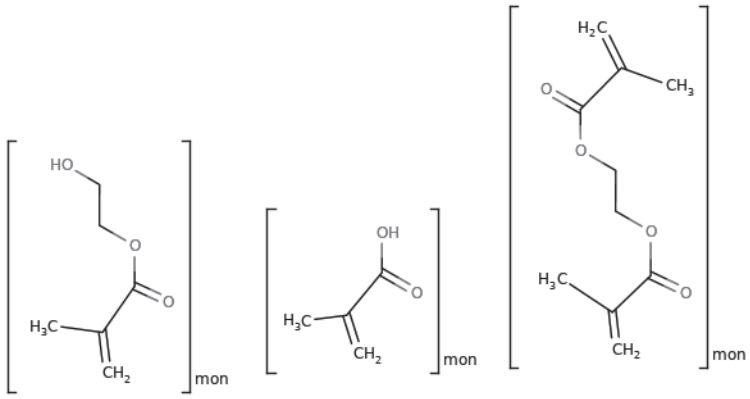
6 STUDY INTERVENTION

6.1 STUDY INTERVENTIONS ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

LL-BMT1 is an investigational device composed of an FDA-approved Group 4 extended-wear contact lens (marketed as ocufilcon D; Figure 1) that has had bimatoprost coated onto the anterior surface of the lens via an inkjet printer.

Figure 1. Ocufilcon D Chemical Structure



Chemical Formula: C_{10}-H_{14}-O_4.C_6-H_{10}-O_3.C_4-H_6-O_2)x-

Before printing, the unmodified Group 4 lens has the following parameters (Table 1):

Table 1. Parameters of the nonmedicated Group 4 lens

Base Curve	8.6 ± 0.2 mm
Diameter	14 ± 0.2 mm
Water Content	55%
Spherical Power	+10.00 to -10.00
Optic Zone	6 mm to 9 mm
Lens Thickness	60 μm to 150 μm

In order to coat the lens, bimatoprost is diluted in a proprietary mixture, which is then placed in an inkjet cartridge and printed onto the contact lens surface, without obstructing the optic zone.

The LL-BMT1 lenses are supplied freely floating in individual vials of basic saline solution [redacted]. Once the LL-BMT1 lens is inserted in the eye, the bimatoprost will elute from both the concave and convex surfaces of the lens at a descending release rate over the next 7 days.

The Sponsor has determined the dosing of LL-BMT1 [redacted]. For this study, there will be one dose [redacted]. In vitro studies have shown

that an LL-BMT1 lens releases approximately 26 µg bimatoprost over the 7-day wearing period.

After the printing process, the LL-BMT1 lens was tested to verify that it maintained its integrity through physical, chemical, and biological (toxicity) testing. Results are shown below (Table 2).

Table 2. Parameters of the LL-BMT1 (medicated) Group 4 lens

Base Curve	8.6 ± 0.2 mm
Diameter	14 ± 0.2 mm
Power	Labeled power ± 0.125
Refractive Index	1.41
Water Content	56.7%
Light Transmission	97%
ISO-3993 Cytotoxicity	Non-toxic
ISO-3993 Systemic toxicity	Non-toxic
ISO-3993 Ocular irritation	Non-toxic
ISO-3993 Histopathology	Non-toxic

6.1.2 DOSING AND ADMINISTRATION

Patients will have LL-BMT1 lenses inserted by the investigator at the Day 1 Visit, and they will remain in the patients' eyes (except during IOP assessment) until the Day 7 Visit (end of treatment), at which time the investigator will remove the lenses. Patients will not remove the lenses themselves during the study.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

LL-BMT1 lenses will be shipped to the investigator from the Sponsor's manufacturing site. The lenses should be handled according to normal Group 4 lens procedures

[redacted]

If a LL-BMT1 lens is damaged during removal from the storage vial or during the thorough rinsing procedure, then a new LL-BMT1 lens can be used by the investigator.

When lenses are removed and handled during the study period while the patient's IOP is measured, the lens should be held by the Principal Investigator or staff with a sterile plastic tweezer with a soft tip. When the lens is reinserted in the patient's eye, one drop of sterile saline solution should be added to the bowl of the lens prior to reinsertion in the eye.

Investigator should take care with lens handling, especially during removal of the lens for IOP assessment. If a lens is damaged during removal, a new lens cannot be inserted in the patient's eye. Patients can remain on the study if at least one LL-BMT1 lens is able to be reinserted in one of the patient's eyes.

Any unused contact lenses should be returned to the Sponsor at the completion of the study.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The LL-BMT1 lenses, manufactured by Leo Lens Technology Co., Inc., are supplied freely floating in individual vials of basic saline solution [redacted]. The peel-off cap and rubber stopper will be removed from the vial prior to use. The extended-wear contact lenses have had bimatoprost coated onto the anterior surface of the lens.

6.2.3 PRODUCT STORAGE AND STABILITY

The study lenses must be stored in a secure, locked location accessible only to authorized study personnel and maintained at a temperature of 2˚-8˚C (35.6˚-46.4˚F), with excursion permitted to 25˚C (77˚F). The lenses should also be kept away from light when stored.

6.2.4 PREPARATION

Not applicable.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Not applicable.

6.5 CONCOMITANT THERAPY

Aside from study medication, antihistamines and all topical ocular medications are prohibited during the study. In addition, marijuana and any other recreational drugs are prohibited. Systemic treatments that the patient has been receiving for at least 30 days prior to study initiation are

acceptable. The medical monitor should be informed of any new systemic medications that cannot be delayed until the end of the study to determine if the patient can participate and/or continue in the study. Prior to study treatment initiation, any current glaucoma medications must be washed out using the below schedule (but washout should not commence until after written informed consent has been obtained):

- 4 days washout for parasympathomimetic and topical or systemic carbonic anhydrase inhibitors
- 2 weeks washout for sympathomimetics and alpha agonists
- 4 weeks washout for beta adrenergic blocking agents, combination product, ROCK inhibitors, and prostaglandin agonists

6.5.1 RESCUE MEDICINE

The Sponsor will not supply rescue medication. Should the IOP at any time during the study be elevated 10 mmHg above baseline (after washout, if applicable), the lens will be removed and a different IOP-lowering medication should be prescribed at the discretion of the investigator. The patient will be discontinued from study intervention but will continue in the study.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the electronic Case Report Form (eCRF).

7 STUDY INTERVENTION DISCONTINUATION AND PATIENT DISCONTINUATION

7.1 DISCONTINUATION OF STUDY INTERVENTION

Patients may be discontinued from study intervention for any of the following reasons:

- Investigator decision: The investigator can decide that the patient should be discontinued from study intervention for any reason.
- Patient decision: Patients who decide to discontinue study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing. The patient is lost to follow-up after a reasonable number of attempts to contact the patient (including documented phone calls and/or emails, and a certified letter) have been completed.
- Sponsor decision: The Sponsor or its designee can stop the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.
- Pregnancy: If a patient becomes pregnant during the study, the patient will be immediately discontinued from study intervention. Only pregnancies considered by the

investigator as related to study drug (e.g., resulting from an interaction between study drug and a contraceptive drug) are considered AEs unto themselves. However, all pregnancies with an estimated conception date that occurred during the study must be recorded in the AE section of the eCRF and investigators must actively follow up, document, and report on the outcome of all pregnancies.

- AE: If the investigator decides that the study intervention should be discontinued because of an AE, the investigational product is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately.

- Damage to both LL-BMT1 lenses: The investigator should take care with lens handling, especially during removal of the lens for IOP assessment. If a lens is damaged during removal, a new lens cannot be inserted in the patient's eye. Patients can remain on the study if at least one LL-BMT1 lens is able to be reinserted in one of the patient's eyes. If both lenses are damaged during removal, then the patient will not be allowed to continue with study procedures.

In all of these circumstances, patients should continue to attend all remaining study visits and undergo all scheduled testing.

7.2 PATIENT DISCONTINUATION FROM THE STUDY

Patients will be discontinued from the study in the cases of patient death or lost to follow-up.

Patients may decide to discontinue participation in the study; any such patient withdrawing from the study will be asked to complete the Early Termination Visit assessments. The reason for patient discontinuation from the study will be recorded on the eCRF. No patients who discontinue from the study will be replaced under any circumstances.

7.3 LOST TO FOLLOW-UP

A patient will be considered lost to follow-up per Principal Investigator discretion and upon consultation with the Sponsor upon failure to adhere to the protocol.

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

- The site will attempt to contact the patient and reschedule the missed visit on the following day and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the patient (where possible, 3 telephone calls and a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record or study file.

- Should the patient continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

- **Goldmann applanation tonometry.** Intraocular pressure will be measured with a Goldmann applanation tonometer that is calibrated pre-study and monthly during study participation.

8.2 SAFETY AND OTHER ASSESSMENTS

Abnormal findings that are of clinical significance will be recorded as AEs on the eCRFs.

- **Ultrasound pachymetry.** Corneal thickness will be measured using an ultrasound pachymeter.
- **Humphrey visual field assessment.** Visual field (perimetry) will be assessed using a Humphrey Field Analyzer. If Humphrey visual field assessment has been completed within 6 months of Screening Visit, it does not have to be repeated at the Screening Visit
- **Contact Lens (CL) Assessment:** Assessments will include contact lens centration, movement with blinking, and lens surface wettability/deposits, as described in ISO 11980:2012.
- **Heart rate and blood pressure.** Heart rate and blood pressure will be measured by a manual or automated sphygmomanometer.
- **Pregnancy testing.** Pregnancy testing will be performed using a human chorionic gonadotropin pregnancy urine dipstick test on women of childbearing potential.
- **Best-corrected visual acuity.** BCVA will be quantified using the ETDRS visual acuity protocol (at a distance of 3 m) and the number of letters read correctly will be recorded on the eCRF.
- **Biomicroscopy.** Biomicroscopy will be performed by slit-lamp examination of conjunctiva, cornea, and iris with findings reported on a scale of 0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe. The status of the lens will be assessed using the Age-Related Eye Disease Study scale.
- **Goldmann applanation tonometry.** IOP will be measured with a Goldmann applanation tonometer. During the study, the LL-BMT1 contact lens will be removed in order to perform IOP assessment. Of particular significance, all lens insertions and removals will be conducted by the investigator. IOP will be assessed 3 minutes after lens removal, with the goal of reinserting the lens within 5 minutes of removal. Two consecutive IOP measurements of each eye were obtained. If the 2 measurements differed by more than 2 mmHg, a third measurement was obtained. For each eye, IOP was analyzed as the mean

of 2 measurements or as the median of 3 measurements. For each patient, change from baseline IOP was determined by averaging the values for each eye (Sherwood 2006).

- **Conjunctival hyperemia.** The Efron Grading Scales for Contact Lens Complications will be performed using a conjunctival hyperemia scale.

Unscheduled visits can be included if safety concerns arise. Additional examinations may be performed as necessary to ensure the safety and wellbeing of patients during the study. eCRFs should be completed for each unscheduled visit.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to that product. Worsening of the pterygium is not an AE, unless the lesion growth is greater than expected.

Treatment-emergent AEs are any AEs with an onset date equal to or after the date of the first insertion of the study lens and during the treatment. A pre-existing event that worsens after the first treatment date is considered a treatment-emergent event.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. See Section 8.3.6 for procedures for reporting an SAE.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild:** Event requires minimal or no treatment and do not interfere with the patient's daily activities
- **Moderate:** Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning

- **Severe:** Event interrupts a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious"

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

A determination will be made of the relationship (if any) between an AE and the study drug. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the drug and/or the lens.

- **Unrelated:** A causal relationship can be excluded and another documented cause of the AE is most plausible
- **Unlikely related:** A causal relationship is improbable, and another documented cause of the AE is most plausible
- **Possibly related:** A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the study drug
- **Probably related:** A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the study drug, and there is a reasonable response on withdrawal

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Any medical condition that is present at the time that the patient is screened will be considered as medical history and not reported as an AE. However, if the study patient's condition deteriorates at any time after enrollment, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator or qualified designee will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Patient will be told to call and notify the investigator of such events that occur during this period after the end of study visit. Events will be followed for outcome information until resolution or stabilization.

AEs will be monitored throughout the study beginning at the time the patient signs the informed consent for this study. At each post-Baseline visit, the investigator will begin by querying for AEs by asking each patient a general, non-directed question, such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported AEs will be documented on the appropriate eCRF, including seriousness, severity, relationship to study drug, action taken, and outcome (including date of resolution or stabilization, if AE is not ongoing). If AEs occur, the first concern will be the safety of the study patients.

If a patient becomes pregnant during the study, the investigator must inform the Sponsor and collect follow-up data regarding the pregnancy, birth, and status of the child. The Sponsor will provide special CRFs for data collection in the case of pregnancy. Follow-up should be continued until study close-out at the study center. After close-out, the Sponsor's Safety designee will continue to obtain follow-up information. Pregnancy should be recorded as a protocol deviation. Pregnancy is not an AE; however, any complication related to pregnancy would be considered an AE.

8.3.5 ADVERSE EVENT REPORTING

Any AE should be recorded on the appropriate eCRF.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Any SAE occurring during the study period should be immediately (ie, within 24 hours of learning of the event) reported to a Trial Runners representative listed on the protocol cover page. The SAE is recorded on the appropriate eCRFs. In the event of an early termination within 8 days after study drug administration, the occurrence of an SAE within 8 weeks from Baseline (Day 0) should be reported immediately to Trial Runners personnel. All patients with an SAE that is related to study drug must be followed for at least 30 days and the outcomes reported until the event is resolved or stabilized. The investigator should supply the Sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

In the event of an SAE, the investigator must:

- Notify the Trial Runners safety office and the medical monitor immediately by fax using the SAE reporting forms provided by Trial Runners (see first page of the protocol for the SAE fax number). Emergency phone numbers and relevant personnel contacts are below:
  - [redacted]
    - [redacted]
    - [redacted]
  - [redacted]
    - [redacted]
    - [redacted]
- Obtain and maintain in the patient’s files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient
- Provide Leo Lens Technology with a complete, written case history (AE report form) which includes a statement as to whether the event was or was not related to the use of the investigational drug
- Promptly inform the governing IRB of the SAE if it is drug-related. For other SAEs, notify the governing IRB as required by the IRB, local regulations, and the governing health authorities

Adverse drug reactions that are both serious and unexpected (suspected unexpected serious adverse reactions) will be subject to expedited reported to the IRB as required by the relevant regulations. Reporting must occur within 15 calendar days of first knowledge, or for fatal or life-threatening events, an initial or full report must be made within 7 calendar days and a follow-up report must be made, if necessary, within the 15-calendar day timeframe.

8.3.7 REPORTING EVENTS TO PATIENTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

If a female patient becomes pregnant during the study, the investigator will notify Trial Runners and the medical monitor immediately after the pregnancy is confirmed and the patient will be exited from the study. The investigator will (1) notify the patient's physician that the patient was being treated with LL-BMT1 or bimatoprost, as appropriate, and (2) follow the progress of the pregnancy to term on the patient providing written informed consent for release of this data. The investigator should document the outcome of the pregnancy and provide a copy of the documentation to Leo Lens Technology.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to patients or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the patient population being studied
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or

application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems or events as outlined in the Safety Management Plan. The unanticipated problem report will include the following information:

- Protocol identifying information: protocol title and number, Principal Investigator's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an unanticipated problem
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are SAEs will be reported to the IRB and to the study Sponsor within 24 hours of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to the study Sponsor within 7 days of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the OHRP within 10 days of the IRB's receipt of the report of the problem from the investigator.

An investigator shall submit to the Sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)). A Sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the FDA and to all reviewing IRB's and participating investigators within 10 working days after the Sponsor first receives notice of the effect. Thereafter the Sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PATIENTS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

There are no formal study hypotheses to be tested in this study. We hypothesize that no safety concerns are revealed in eyes receiving LL-BMT1.

9.2 SAMPLE SIZE DETERMINATION

Due to the exploratory nature of this study, no formal power sample size calculation has been performed. An empirical sample size of at least 5 evaluable patients is planned. Assuming a 10%-20% drop-out non-evaluable rate, up to 7 patients (7 study eyes) will be consented to begin acclimation screening. Those who are consented but fail acclimation screening will be replaced until at least 5 patients successfully complete the acclimation screening. Five patients who pass acclimation screening will be enrolled as patients for study treatment.

9.3 POPULATIONS FOR ANALYSES

The following populations will be analyzed:

- Safety population: Includes all patients whose eyes are in contact with LL-BMT1 lenses.
- Intent-to-treat (ITT) population: Includes all patients who have LL-BMT1 lenses successfully inserted.
- Modified intent-to-treat (mITT) population: Includes all patients who have LL-BMT1 lenses successfully inserted and complete at least 1 on-therapy follow-up assessment; only the study eye from each patient will be included in this analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The database will be locked after all patients exit the study and all data clarification forms or queries have been resolved. Prior to database lock, a detailed Statistical Analysis Plan (SAP) will be finalized and approved. Final analysis will occur after database lock.

Wherever appropriate, summary statistics will include the frequency, mean, standard deviation, median, minimum, and maximum for continuous and ordinal variables, and frequency counts and percent for categorical variables. Graphical representations of the results may also be provided.

In general, unless otherwise specified, eyes will be the analytical unit and a formal statistical test will only be conducted for exploratory purposes when sample size is deemed appropriate. All testing will be two-sided with a 95% confidence level. Due to the small sample size in this study, nonparametric approach will be applied. For quantitative variables, within-eye before-and-after comparisons will be assessed using one-sample Wilcoxon test. For qualitative variables, Fisher's Exact test will be used.

9.4.2 SAFETY ANALYSES

Analysis of treatment-emergent AEs will be conducted based on the safety population. Safety endpoints include:

- AEs
- Concomitant medications
- Heart rate and blood pressure
- BCVA
- IOP
- Biomicroscopy
- Conjunctival hyperemia

Ocular events will be reported on an eye level, while non-ocular events will be on a patient level.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each AE reported, the number and percent of patients/eyes will be tabulated based on the preferred term and ocular and non-ocular AEs will be reported separately. The tables will be generated by relationship to treatment as well as by system organ class and severity.

The primary safety endpoint is the AE rate (100 × [number of AEs / number of eyes exposed to treatment]). The modified safety set will be used for a sensitivity analysis of the primary safety endpoint.

Secondary safety endpoints:

- Percent of patients with ≥5-mmHg increase from baseline in IOP at each visit
- Abnormal slit-lamp biomicroscopy findings at the Baseline, Day 1, and Day 7 Visits
- Contact lens protein deposits at the Day 7 Visit
- Change from baseline in CLDEQ-8 results at the Day 7 Visit

Pre-existing AEs, those identified after enrollment but before treatment with LL-BMT1, will be tabulated for all consented patients.

9.4.3 EFFICACY ANALYSES

The secondary efficacy endpoint is the change from baseline in IOP at each visit.

The efficacy analyses will be based on the mITT population and only the study eyes will be used. Statistical analyses will be performed using methods described in Section 9.4.1.

9.4.4 BASELINE DESCRIPTIVE STATISTICS

Baseline and demographic assessments will be presented descriptively.

9.4.5 PLANNED INTERIM ANALYSES

No interim analysis will be performed.

9.4.6 SUB-GROUP ANALYSES

No subgroup analyses are planned.

9.4.7 TABULATION OF INDIVIDUAL PATIENT DATA

Line listings will be provided for each patient.

9.4.8 OTHER EXPLORATORY ANALYSES

No other exploratory analyses are planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PATIENTS

Consent forms describing in detail the study intervention, study procedures, and risks, that have been reviewed and approved by the relevant IRB, will be given to the patient and written documentation of informed consent will be required prior to starting study intervention. An informed consent form will be submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved, and the patient will be asked to read and review the document. The investigator will explain the research study to the patient and answer any questions that may arise. A verbal explanation will be provided in terms suited to the patient's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research patients. Patients will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patients should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. Patients must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice.

A copy of the informed consent document will be given to the patients for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the patient undergoes any study-specific procedures. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

Recruitment may be halted by the site investigator at any time for safety reasons. If this occurs, the IRB and any other investigators will be immediately notified.

Leo Lens Technology may stop the study (and/or the study site) for any reason with appropriate notification. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study patients, the IRB, and Sponsor and will provide the reason(s) for the termination or suspension. Study patients will be contacted, as applicable, and be informed of changes to study visit schedule.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB, and/or FDA.

10.1.3 CONFIDENTIALITY AND PRIVACY

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to Leo Lens Technology, the governing health authorities, or the FDA if they inspect the study records as required by law. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

In accordance with HIPAA requirements, additional purposes of this study include (1) the publishing of anonymous patient data from the study, and (2) the creation and maintenance of a data repository.

All study-related correspondence, patient records (ie, source documents listed in Section 11.4.1), informed consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and patient questionnaires, correspondence with IRB, and other essential documents should be maintained on file. Local regulatory requirements should be followed regarding the retention of clinical study documentation.

Leo Lens Technology requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Medical Monitor
[redacted]
[redacted]

[redacted]

10.1.6 SAFETY OVERSIGHT

No internal data review committee will be used during this study.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial patients are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by an employee of Trial Runners on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations, such as the objective, purpose, design, complexity, masking, size, and endpoints of the study.
- An employee of Trial Runners or regulatory authority representatives will conduct on-site visits to review, audit, and copy study-related documents. These representatives will meet with the investigator and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion.

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

Following written Standard Operating Procedures, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (eg, Good Laboratory Practices, Good Manufacturing Practices).

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site 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.

- Clinical data will be entered into eCRFs. Data entered into the eCRF will correspond with and be supported by source documentation maintained at the site. A final report of all patient data will be provided to each site at the end of the study to serve as eCRF documentation.

Source documents may include a patient's medical records, diaries, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests and laboratory tests. The investigator's copy of the eCRFs serves as part of the investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record:

- Patient’s name (this information will not be included in the study database)
- Patient’s contact information (this information will not be included in the study database)
- Date that the patient entered the study, patient number, and patient medication kit number
- Study title and/or the protocol number of the study and the name of Leo Lens Technology
- Statement that informed consent was obtained (including the date) prior to any study procedures being performed and that the patient was provided a copy of the signed informed consent. A statement that country and local patient privacy-required documentation for this study has been obtained (including the date)
- Dates of all patient visits
- All concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- Occurrence and status of any AEs (including any procedure-related AEs)
- The date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation
- The results, if applicable, of any procedures performed to confirm eligibility criteria
- Documentation of the patient’s medical history
- Heart rate and blood pressure
- Results of biomicroscopy/ophthalmoscopy exams
- Documentation of whether any procedure, including study treatment administration, was performed according to the protocol, noting any deviations (if applicable)
- Study drug accountability and reconstitution records

10.1.9.2 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.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Project Management Plan requirements. The noncompliance may be either on the part of the patient, the investigator, or the study site staff. As a result of 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 investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study medical records, reported to Leo Lens Technology or its designee. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the Project Management Plan.

10.1.11 PUBLICATION AND DATA SHARING POLICY

Leo Lens Technology, as the Sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between the Principal Investigator and Leo Lens Technology personnel. Authorship will be established prior to the writing of the manuscript. No individual publications will be allowed prior to completion of the final report of the study, except as agreed with Leo Lens Technology.

This study will be registered on the ClinicalTrials.gov registry.

10.1.12 CONFLICT OF INTEREST POLICY

Due to potential conflict of interest, patients or members of the patient's household who are employees of the investigative site are not eligible for enrollment in the study.

10.2 ADDITIONAL CONSIDERATIONS

Investigational site staff will be instructed to follow their institutional infection control standard procedures and to consider additional measures during periods of community transmission of conditions, such as COVID-19. These additional measures may include:

- Contacting patients the day before a scheduled appointment for a number of reasons, including:
    - To determine if they are experiencing any signs or symptoms of possible infections. Such COVID-19-related symptoms include fever, cough, shortness of breath, and sore throat
    - To determine if the patient has tested positive for COVID-19, been in contact with someone who is known or suspected to be positive for COVID-19, or traveled to an area of in which there is or has been an outbreak of COVID-19 cases
    - To reschedule patients who are experiencing respiratory symptoms and instructing them to seek appropriate medical attention. This requires removal of the LL-BMT1 contact lenses if they are in the on-treatment portion of the study. Removal under these circumstances can done by the subject or by site personnel.
    - To remind patients to contact the investigational site if they develop respiratory or other COVID-related symptoms on the morning before a scheduled examination of if they have had changes to their health status since their last visit

Upon arrival at the investigational site, patients should be assessed for fever and provided with proper protective equipment (PPE; eg, face masks), if they are not already using PPE.

Equipment that is meant to be used on more than one person should be draped to prevent possible contamination and appropriately cleaned before and after each use. Additional measures should also be considered, including:

- Posting guidelines for the reduction of risk of coronavirus transmission
- Reminding patients of the need for social distancing/ consider having patients wait outside of the investigational site (eg, in their vehicles until they are ready to be seen)
- Restricting non-essential individuals accompanying patients from patient areas
- Providing supplies for respiratory hygiene and cough etiquette, including 60% to 95% alcohol-based hand sanitizer, no-touch receptacles for waste disposal, face masks, and tissues at healthcare facility entrances, waiting rooms, patient check-ins, etc.
- Reminding patients to wash hands and/or use hand sanitizer frequently

Study visits and assessments should be rescheduled at the discretion of the Investigator when there is a perceived increased risk of coronavirus transmission to patients and/or investigational site staff.

10.3 ABBREVIATIONS

AE	adverse event
BCVA	best-corrected visual acuity
CFR	Code of Federal Regulations

CLDEQ-8	Contact Lens Dry Eye Questionnaire-8
CONSORT	Consolidated Standards of Reporting Trials
eCRF	electronic Case Report Forms
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
[redacted]	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IFU	instructions for use
IND	Investigational New Drug
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IWRS	interactive web response system
LASIK	laser-assisted in situ keratomileusis
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
OAG	open-angle glaucoma
OHRP	Office for Human Research Protections
OHT	ocular hypertension
PI	prescribing information
POAG	primary open-angle glaucoma
PP	per-protocol
PPE	proper protective equipment
PRK	photorefractive keratectomy
ROCK	Rho kinase
QC	quality control
RK	radial keratotomy
SAE	serious adverse event
SAP	statistical analysis plan
SMILE	small incision lenticule extraction
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.1	11/19/20	Based upon input from the U.S. Food and Drug Administration, the numbers of subjects to be entered and dosed in the study was changed FROM “5-7” TO “5”. This impacts several sections of the protocol including the Synopsis, Schema, Overall Design, and Sample Size Determination section. Further, clarifications were added to the Schema and Safety and Other Assessment sections to assist the Investigator.	Amendment based on input from U.S. Food and Drug Administration.

1.2	12/21/20	Based upon input from the IRB, the protocol was amended to include best corrected visual acuity and slit lamp exam to all visits prior to the baseline visit.	Amendment based on input from IRB.

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12 ATTACHMENTS

Patient/Subject #:_____

Date:__/___/____Time:_____

CONTACT LENS QUESTIONNAIRE-8 (CLDEQ-8)

1. Questions about **EYE DISCOMFORT**:

   a. During a typical day in the past 2 weeks, **how often** did your eyes feel discomfort while wearing your contact lenses?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

   When your eyes felt discomfort with your contact lenses, **how intense was this feeling of discomfort…**

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	1	2	3	4	5

2. Questions about **EYE DRYNESS**:

   a. During a typical day in the past 2 weeks, **how often** did your eyes feel dry?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

   When your eyes felt dry, **how intense was this feeling of dryness**…

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	1	2	3	4	5

3. Questions about **CHANGEABLE, BLURRY VISION:**

   a. During a typical day in the past 2 weeks, **how often** did your vision change between clear and blurry or foggy while wearing your contact lenses?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

   When your vision was blurry, **how noticeable was the changeable, blurry, or foggy vision** …

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	1	2	3	4	5

4. Question about **CLOSING YOUR EYES:**
   During a typical day in the past 2 weeks, **how often** did your **eyes bother you so much that you wanted to close them**?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

5. Question about **REMOVING YOUR LENSES:**
   How often during the past 2 weeks, did your eyes *bother you so much* while wearing your contact lenses that you felt as if you needed to stop whatever you were doing and **take out your contact lenses**?

   1 Never
   2 Less than once a week
   3 Weekly
   4 Several times a week
   5 Daily
   6 Several times a day