BAUSCH + LOMB

A Phase 4, Multicenter, Open-Label Study to Evaluate the Effect of Miebo® on Preoperative Biometry/Keratometry and Postoperative Refractive Accuracy

CLINICAL STUDY PROTOCOL

STUDY #936

Developmental phase of study:	4
Study design:	Multicenter, open-label study
Date:	06 May 2024 (Version 2.0, Amendment 1)
Sponsor	Bausch & Lomb Incorporated 1400 North Goodman Street Rochester, NY 14609 US Corporate Headquarters Main Office Phone: (908) 927-1400

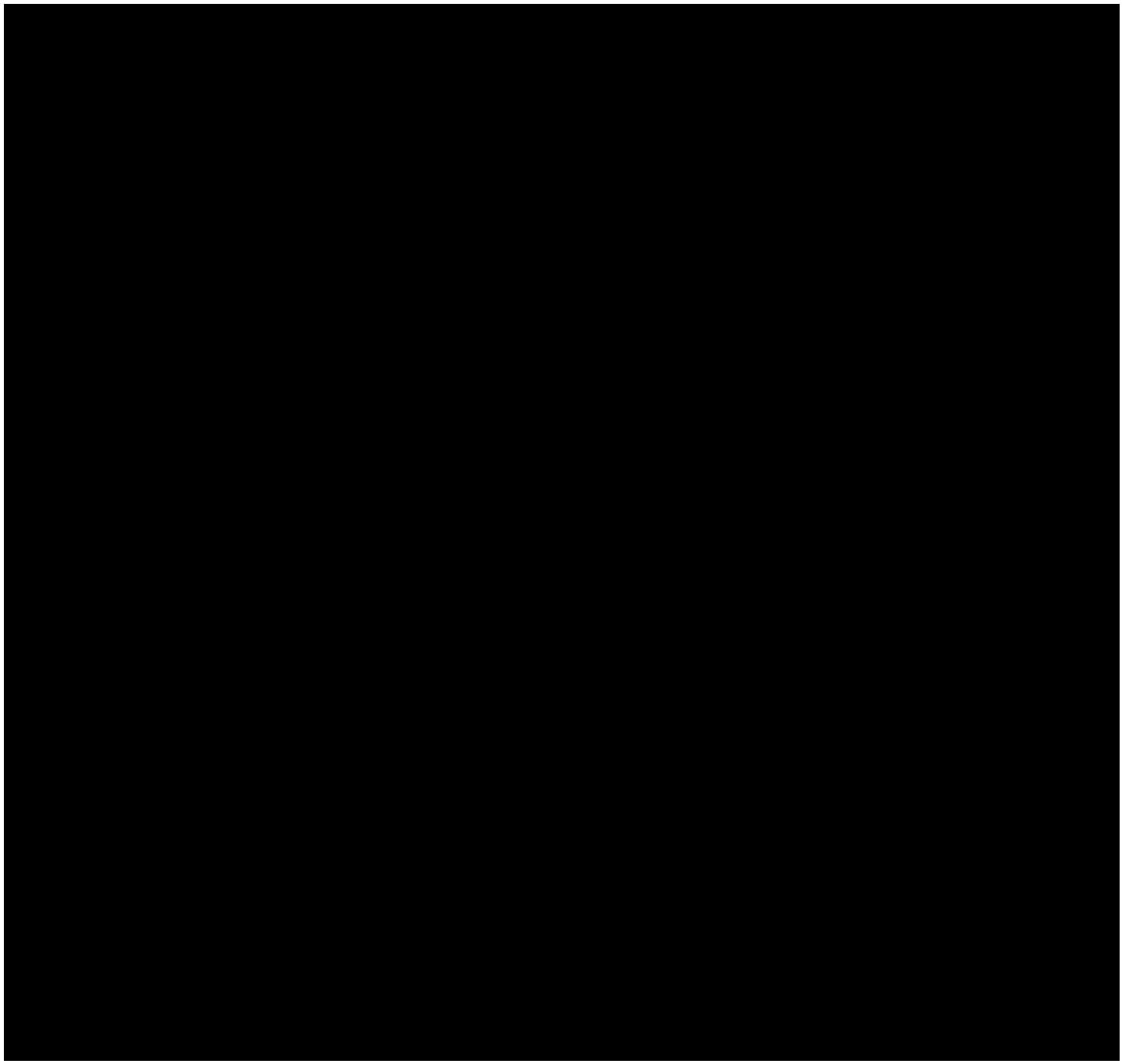
This clinical investigation is being conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and with Good Clinical Practice (GCP), as required by the United States Code of Federal Regulations (CFR) applicable to clinical studies (21CFR Parts 11, 50, 54, 56, 312, 314; 42 USC 282(j); International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline E6(R2): GCP and applicable local regulations.

CONFIDENTIAL

Protocol Review and Approvals

A Phase 4, Multicenter, Open-Label Study to Evaluate the Effect of Miebo® on Preoperative Biometry/Keratometry and Postoperative Refractive Accuracy

Reviewed and approved:



Personnel Responsible for Conducting the Study

A Phase 4, Multicenter, Open-Label Study to Evaluate the Effect of Miebo® on Preoperative Biometry/Keratometry and Postoperative Refractive Accuracy

Contract Research Organization

Sierra Clinical Services

[redacted]

Principal Investigators

A list of Principal Investigators, investigational sites, addresses, and contact details will be kept as a separate document.

Investigator Statement of Agreement

A Phase 4, Multicenter, Open-Label Study to Evaluate the Effect of Miebo® on Preoperative Biometry/Keratometry and Postoperative Refractive Accuracy

PROTOCOL

STUDY #936

I have read the attached protocol and I agree that it contains all information necessary to conduct this study as described and agree to abide by all provisions set forth therein.

I agree to conduct this study properly, ethically, and safely in accordance with internationally recognized code of International Council for Harmonisation Good Clinical Practice (GCP), as required by applicable local laws and regulations. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) and have complied with all financial and administrative requirements of the governing body of the clinical institution and the Sponsor. I will obtain written informed consent from each study subject prior to performing any study specific procedures which are not my routine standard of care.

I understand that my signature/e-signature on a case report form (CRF)/electronic case report form (eCRF) indicates that the data therein has been reviewed and accepted by me. I understand that this document and related information is subject to confidentiality terms found in my signed Confidentiality or Clinical Services Agreement. I agree to protect the confidentiality of my patients, as required by all local privacy regulations, when allowing the Sponsor of this study, and/or relevant regulatory authorities and IRB/ECs, direct access to my medical records for study subjects.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by the Sponsor that is necessary for the proper conduct of this study. I will discuss this material with them to ensure that they are fully informed about the test article and all study-related procedures and required documentation.

_____	_____
Principal Investigator, Printed Name	Date
_____	_____
Signature	Site Number

Upon signing, provide a copy of this page to the Sponsor and retain a copy for your files.

1 Synopsis

Name of Sponsor:	Bausch & Lomb Incorporated
Study Treatment:	Miebo® (perfluorohexyloctane ophthalmic solution)
Study Control:	None (single-arm study)
Protocol Title:	A Phase 4, Multicenter, Open-Label Study to Evaluate the Effect of Miebo® on Preoperative Biometry/Keratometry and Postoperative Refractive Accuracy
Protocol Number:	#936
Number of Clinical Sites:	Up to 10 clinical sites in the United States
Study Phase:	4
Primary Objective:	Determine the effect of preoperative Miebo treatment on the accuracy of preoperative biometry/keratometry and predicted refraction in subjects with dry eye disease (DED) who are already scheduled for cataract surgery
Exploratory Objectives:	• Determine the effect of preoperative Miebo treatment on preoperative signs and symptoms of DED in subjects with DED who are already scheduled for cataract surgery • Determine the effect of preoperative Miebo treatment on preoperative root mean square (RMS) higher-order aberrations (HOAs) in subjects with DED who are already scheduled for cataract surgery • Determine the effect of postoperative Miebo treatment on postoperative signs and symptoms of DED in subjects with DED who received preoperative Miebo treatment before undergoing cataract surgery • Determine the stability of postoperative RMS HOAs after the addition of postoperative Miebo treatment in subjects with DED who received preoperative Miebo treatment before undergoing cataract surgery • Determine the stability of postoperative corneal tomography after the addition of postoperative Miebo treatment in subjects with DED who received preoperative Miebo treatment before undergoing cataract surgery

Overall Study Design:	
Structure:	This single-arm, multicenter, prospective study will consist of 4 study visits in subjects with DED who are already scheduled for cataract surgery. At the Screening/ Baseline Visit (Visit 1; Day 1), subjects who sign the informed consent form (ICF) will be enrolled in the study and screened for eligibility to participate in the study. [redacted] If both eyes are eligible for the study, the eye with the worse central corneal fluorescein staining (CFS) score will be the study eye; if both eyes have the same central CFS score, the eye with the worse total CFS score will be the study eye. If both eyes have the same total CFS score, the Investigator will choose the study eye. While the preference is that the study eye undergoes the second surgery conducted, the Investigator can choose to perform surgery on the study eye as the first or second eye surgery. Eligible subjects will commence treatment with Miebo 4 times daily (QID) bilaterally at Visit 1. Subjects will continue instilling Miebo QID bilaterally for approximately 30 days. [redacted] Subjects will continue dosing Miebo through the bedtime dose the evening before cataract surgery in each eye (but should NOT instill Miebo on the day of surgery). Subjects will undergo cataract surgery on the first eye 0 to 14 days after Visit 2. The first eye surgery can only be performed on the same day as Visit 2 if the surgery is being performed on the non-study eye. Subjects would discontinue Miebo in the non-study eye the night before Visit 2. If both eyes are eligible for the study, subjects will then undergo cataract surgery on the second eye approximately 7 to 14 days following cataract surgery on the first eye. Surgeries, postoperative medications, and timing of postoperative visits will be per the Investigator's standard operating protocol; intraoperative use of aberrometry (eg, ORA or other device) and femtosecond laser are allowed (although use of femtosecond laser or keratome for limbal-relaxing incisions is prohibited). Subjects will have multiple standard postoperative visits per the

	Investigator's standard operating protocol for each eye for approximately 30 days following each surgery. (Note: Cataract surgery and standard postoperative visits are NOT considered part of the study.) As part of the standard follow-up assessments (30 days post-surgery) or at Visit 3, refractive outcome (manifest refraction) for the study eye will be determined. • [redacted] • [redacted] Following Visit 3, subjects will begin a second 30-day regimen of Miebo QID bilaterally. Post-instillation assessment to re-evaluate corneal tomography, HOAs, and DED signs in the study eye, in addition to symptoms of DED, will occur at Visit 4 (Second Eye Postop Day 60 ± 7 days).
Subject Duration:	For subjects receiving bilateral cataract surgery, this study consists of 4 study office visits over as few as approximately 97 ± 10 days and as long as approximately 118 ± 10 days. Visit 1 and Visit 2 occur prior to cataract surgery (Day 1 and Day 30 ± 3 days, respectively). Subjects will undergo cataract surgery on the first eye 0 to 14 days after Visit 2. Subjects will then undergo cataract surgery on the second eye approximately 7 to 14 days after cataract surgery on the first eye. Cataract surgery in the study eye will be performed: • As soon as 31 ± 3 days and a maximum of 44 ± 3 days for limbal-relaxing incisions is prohibited) after initiation of preoperative Miebo treatment if the study eye undergoes first eye surgery • As soon as 37 ± 3 days and a maximum of 58 ± 3 days after initiation of preoperative Miebo treatment if the study eye undergoes second eye surgery

	Subjects will attend multiple standard postoperative visits within the first month post-surgery for both the first and second eye surgeries, which are not part of this study. Visit 3 will occur approximately 30 ± 7 days after the second eye surgery. Visit 4 will occur approximately 60 ± 7 days after the second eye surgery.
Study Duration:	The entire duration of the study (from first subject first visit to last subject last visit) is expected to take approximately 8 months.
Dosage Instillation:	Site staff will instill the first dose of Miebo bilaterally during Visit 1. After this, subjects will begin to self-administer Miebo QID bilaterally up through Visit 2 (instilling Miebo at least 30 minutes and no longer than 4 hours prior to the start of Visit 2). Subjects will continue to self-administer Miebo QID bilaterally through the bedtime dose the evening before cataract surgery (but should not instill Miebo on the day of surgery). • If the first (non-study) eye surgery is being performed the same day as Visit 2, the subject would discontinue Miebo in this eye the night before Visit 2 After Visit 3 (Second Eye Postop Day 30 ±7 days), subjects will self-administer postoperative Miebo QID bilaterally for approximately 30 days (instilling the last dose of Miebo at least 30 minutes and no longer than 4 hours prior to the start of Visit 4).
Measures Taken to Reduce Bias:	Not applicable
Study Population Characteristics:	
Number of Subjects:	Approximately 100 subjects will be treated with Miebo.
Condition/Disease:	Subjects with DED who also have at least 1 visually significant cataract that has been scheduled for cataract surgery
Inclusion Criteria:	1. At least 18 years of age at the time of consent 2. Able to provide written voluntary informed consent 3. The same eye must satisfy the below inclusion criteria (a-e): a. At least 1 eye with a visually significant cataract that has been scheduled for cataract surgery (eligible eye can be a subject's second eye to undergo cataract surgery as long as all eligibility criteria are met in that eye)

	b. Candidate for routine, uncomplicated cataract surgery (phacoemulsification with posterior chamber intraocular lens [IOL] implantation, not combined with any other surgery) c. In the Investigator's opinion, subject has potential postoperative pinhole Snellen visual acuity of at least 20/200 in both eyes d. Tear film break-up time ≤10 sec at Visit 1 e. Total CFS score ≥2 and ≤11 (ie, sum of inferior, superior, central, nasal, and temporal), using the National Eye Institute scale at Visit 1 4. Ocular Surface Disease Index (OSDI) ≥23 at Visit 1 5. Able and willing to follow instructions, including participation in all trial assessments and visits
Exclusion Criteria:	1. Have any clinically significant ocular surface slit-lamp findings in the study eye and/or, in the opinion of the Investigator, have any findings that could interfere with trial parameters, including: a. History of eye trauma b. History of Stevens-Johnson syndrome c. Active blepharitis or lid margin inflammation d. DED secondary to scarring, irradiation, alkali burns, cicatricial pemphigoid, or destruction of conjunctival goblet cells (as with vitamin A deficiency) e. Abnormal lid anatomy causing incomplete eyelid closure f. Abnormal cornea shape (keratoconus) g. Corneal epithelial defect or significant confluent staining or filaments h. History of herpetic keratitis i. Ocular or periocular rosacea 2. Pterygium in either eye 3. Use of any of the following ocular therapies in the study eye within 30 days prior to Visit 1: Vuity®, Qlosi™, topical ocular steroid treatments, prescription dry eye therapy including varenicline nasal spray, or topical anti-glaucoma medication 4. Had a LipiFlow® procedure, intense pulse light procedure, or any kind of other procedure affecting meibomian glands in the study eye within 3 months prior to Visit 1

	5. Had received or removed a permanent punctum plug in the study eye within 1 month (3 months for dissolvable punctum plugs) prior to Visit 1 6. Use of any eye drops (prescription or over-the-counter, such as artificial tears or Lumify®) and/or TrueTear™ device (intranasal tear neurostimulator) in the study eye within 24 hours prior to Visit 1 7. Have active ocular allergies or ocular allergies that are expected to be active during the trial period 8. Have worn contact lenses within 1 month prior to Visit 1 or planned wear during the study 9. Have undergone intraocular surgery or ocular laser surgery in the study eye within 3 months prior to Visit 1; have undergone refractive surgery in the study eye within 2 years prior to Visit 1 10. Have active ocular or systemic infection (bacterial, viral, or fungal), including fever 11. Female subjects who are pregnant, nursing, or planning a pregnancy 12. Female subjects of childbearing potential who are not using an acceptable means of birth control; acceptable methods of contraception include hormonal (oral, implantable, injectable, or transdermal) contraception; mechanical (spermicide in conjunction with a barrier such as a diaphragm or condom) contraception; intrauterine device; or surgical sterilization of partner. For non–sexually active female subjects, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the trial, she must agree to use adequate birth control as defined above for the remainder of the trial 13. Have an uncontrolled systemic disease that, in the opinion of the Investigator, will interfere with the trial 14. Have a known allergy and/or sensitivity to the investigational drug 15. Use of any oral medications known to cause ocular drying (eg, antihistamines, antidepressants, etc.) on a non-stable regimen within 1 month prior to Visit 1 or is expected to be unstable during the trial 16. Have taken isotretinoin (eg, Accutane, Myorisan, Claravis, Amnesteem) within 6 months prior to Visit 1

	17. Are currently enrolled in an investigational drug or device study or had used an investigational drug or device within 60 days prior to Visit 1
Efficacy Endpoints:	**Primary** The primary endpoint will be based on study eye manifest refraction at Visit 3 (Second Eye Postop Day 30 ± 7 days). Comparisons will be made between the IOL calculations based on biometry data collected before and after 30 days of preoperative Miebo treatment and the implanted lens mean difference between absolute deviations from predicted refractive error in the study eye **Exploratory** [redacted]

	[redacted]
Safety Outcomes:	• Adverse events (AEs; reported, elicited, and observed), including complications during cataract surgery

Statistical Methods:

Continuous variables will be summarized using the mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

Analysis Populations

Full Analysis Set (FAS): The FAS will consist of all enrolled subjects who are instilled with study treatment.

Per Protocol (PP) Set: The PP Set will consist of FAS subjects with no protocol violations expected to affect the evaluability of efficacy.

Primary Efficacy Analysis

[redacted]

Safety Analysis

The number and percentage of subjects with specific treatment-emergent adverse events (TEAEs) will be summarized for the FAS. The number of subjects will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term within each system organ class.

Sample Size Calculations

A sample size of 77 subjects will have 80% power to detect an effect size of 0.325 standard deviations using a paired t-test with a 5% two-sided significance level. To accommodate potential missing data of up to 23%, study treatment will be administered to approximately 100 subjects.

Summary of Known and Potential Risks and Benefits to Human Subjects
Refer to Miebo Prescribing Information.

2 Table of Contents

List of Tables

3 List of Abbreviations and Definitions of Terms

Abbreviation or specialist term	Definition or explanation
AE	adverse event
BCDVA	best-corrected distance visual acuity
BCVA	best-corrected visual acuity
CFB	change from baseline
CFR	Code of Federal Regulations
CFS	corneal fluorescein staining
CRF	Case Report Form
CRO	Contract Research Organization
DED	dry eye disease
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDF	financial disclosure form
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HOA	higher-order aberration
ICF	informed consent form
IOL	intraocular lens
IOP	intraocular pressure
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRSE	manifest refraction spherical equivalent
NEI	National Eye Institute
OCT	optical coherence tomography
OSDI	Ocular Surface Disease Index
PP	Per Protocol
QID	4 times daily
RMS	root mean square
SAE	serious adverse event
TBUT	tear film break-up time
TEAE	treatment-emergent adverse event
US	United States
VAS	visual analog scale

4 Introduction

4.1 Indication

Miebo® is indicated for the treatment of the signs and symptoms of dry eye disease (DED).[1]

4.2 Background

Cataract surgery is the most commonly performed surgical procedure worldwide, with favorable outcomes in approximately 98% of cases.[2-4] Visual outcomes are dependent upon accurate intraocular lens (IOL) calculation and selection, which requires, among several factors, a healthy ocular surface.[5-7] A 2018 study performed by Duke University Eye Center and Weill Cornell Ophthalmology examining the prevalence of ocular surface dysfunction in patients presenting for cataract surgery evaluation found that, while 57% of study patients had no previous diagnosis of ocular surface dysfunction, 81% of patients were found to have at least 1 abnormal tear test (tear osmolarity or matrix metalloproteinase 9).[8] In addition, of the 46% of patients in this study who were asymptomatic, 85% had at least 1 abnormal tear test.[8] These findings mirror the results from the Prospective Health Assessment of Cataract Patients' Ocular Surface study, which found that approximately 60% of patients undergoing screening for routine cataract surgery had rapid tear film break-up time (TBUT) and approximately 50% had central corneal staining, both of which are hallmarks of DED.[9]

[redacted]

In this study, we seek to determine if the refractive accuracy of preoperative anterior corneal power readings is improved when Miebo® (perfluorohexyloctane; Bausch & Lomb Incorporated, Bridgewater, NJ) is administered for 1 month to patients who are already scheduled for cataract surgery and who have confirmed DED. This study also examines the impact of Miebo on ocular surface irregularity as measured by higher-order aberrations (HOAs), total and central corneal fluorescein staining (CFS), visual analog scale (VAS) eye dryness, and Ocular Surface Disease Index (OSDI) score.

In lieu of an Investigator's Brochure, the Investigator is referred to the Miebo prescribing information for risk and benefit details (see Appendix D).

5 Study Objectives and Purpose

5.1 Objectives

The primary objective of this study is to determine the effect of preoperative Miebo treatment on the accuracy of preoperative biometry/keratometry and predicted refraction in subjects with DED who are already scheduled for cataract surgery.

[redacted]

- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.2 Endpoints

5.2.1 Efficacy

The primary endpoint will be based on study eye manifest refraction at Visit 3 (Second Eye Postop Day 30 ± 7 days). Comparisons will be made between the IOL calculations based on biometry data collected before and after 1 month of preoperative Miebo treatment and the implanted lens.

- Mean difference between absolute deviations from predicted refractive error in the study eye

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
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- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]

5.2.2 Safety

The safety outcomes are adverse events (AEs; reported, elicited, and observed), including complications during cataract surgery.

6 Investigational Plan

6.1 Overall Study Design and Plan: Description

This single-arm, multicenter, prospective study will consist of 4 study visits in subjects with DED who are already scheduled for cataract surgery. At the Screening/Baseline Visit (Visit 1; Day 1), subjects who sign the informed consent form (ICF) will be enrolled in the study and screened for eligibility to participate in the study. Baseline DED signs and symptoms, along with baseline biometry, corneal tomography, and HOAs, must be conducted at Visit 1.

If both eyes are eligible for the study, the eye with the worse central CFS score will be the study eye; if both eyes have the same central CFS score, the eye with the worse total CFS score will be the study eye. If both eyes have the same total CFS score, the Investigator will choose the study eye. While the preference is that the study eye undergoes the second surgery conducted, the Investigator can choose to perform surgery on the study eye as the first or second eye surgery.

Once subjects are deemed eligible to participate in the study, site staff will instill the first dose of Miebo bilaterally during the Screening/Baseline Visit. After this, subjects will commence treatment with Miebo 4 times daily (QID) bilaterally. Subjects will continue instilling Miebo QID bilaterally for approximately 30 days. Post-instillation assessment to re-evaluate biometry, corneal tomography, HOAs, and DED signs in the study eye, in addition to symptoms of DED, will occur at Visit 2 (Day 30 ± 3 days).

Subjects will continue dosing Miebo through the bedtime dose the evening before cataract surgery in each eye (but should NOT instill Miebo on the day of surgery).

Subjects will undergo cataract surgery on the first eye 0 to 14 days after Visit 2.

The first eye surgery can only be performed on the same day as Visit 2 if the surgery is being performed on the non-study eye. Subjects would discontinue Miebo in the nonstudy eye the night before Visit 2. If both eyes are eligible for the study, subjects will then undergo cataract surgery on the second eye approximately 7 to 14 days following cataract surgery on the first eye. Surgeries, postoperative medications, and timing of postoperative visits will be per the Investigator's standard operating protocol; intraoperative use of aberrometry (eg, ORA or other device) and femtosecond laser are allowed (although use of femtosecond laser or keratome for limbal-relaxing incisions is prohibited). Subjects will have multiple standard postoperative

visits per the Investigator's standard operating protocol for each eye for approximately 30 days following each surgery. (Note: Cataract surgery and standard postoperative visits are NOT considered part of the study.)

As part of the standard follow-up assessments (30 days post-surgery) or at Visit 3, refractive outcome (manifest refraction) for the study eye will be determined.

- If the first eye is the study eye: Refractive outcome (manifest refraction) will be measured at the 30-Day Postop Standard-of-Care Visit, which occurs prior to Visit 3. Higher-order aberrations, corneal tomography, and DED signs in the study eye, in addition to symptoms of DED, will be measured at Visit 3 (Second Eye Postop Day 30 ± 7 days)
- If the second eye is the study eye (preferred method) or if only 1 eye is undergoing surgery: Refractive outcome (manifest refraction), HOAs, corneal tomography, and DED signs in the study eye, in addition to symptoms of DED, will be measured at Visit 3 (Second Eye Postop Day 30 ± 7 days)

Following Visit 3, subjects will then begin a second 30-day regimen of Miebo QID bilaterally immediately after Visit 3. Post-instillation assessment to re-evaluate corneal tomography, HOAs, DED signs in the study eye, in addition to symptoms of DED, will occur at Visit 4 (Second Eye Postop Day 60 ± 7 days).

6.2 Investigators

The study will be conducted at up to 10 investigative sites in the United States (US).

The study will be conducted by Investigators who are determined by the Sponsor to be suitably qualified by training and experience to conduct this study in compliance with Good Clinical Practice (GCP) and US Food and Drug Administration (FDA) Federal Regulations or local regulations and who are willing to demonstrate use of Miebo, if they have not already done so. Additionally, the Investigator Agreement (on file for each site) verifies Investigator obligations.

In the event that selected sites do not meet expected enrollment rates, the Sponsor may decide to increase enrollment as needed at other currently active sites, replace non-enrolling sites, and/or add additional site(s), to satisfy study enrollment requirements.

6.3 Subject Duration

Eligible subjects receiving bilateral cataract surgeries will attend 4 study office visits over as few as approximately 97 ± 10 days and as long as approximately 118 ± 10 days. Visit 1 and Visit 2 occur prior to cataract surgery (Day 1 and Day 30 ± 3 days, respectively). Subjects will undergo cataract surgery on the first eye 0 to 14 days after Visit 2. Subjects will then undergo cataract surgery on the second eye approximately 7 to 14 days after cataract surgery on the first eye.

Cataract surgery in the study eye will be performed:

- As soon as 31 ± 3 days and a maximum of 44 ± 3 days after initiation of preoperative Miebo treatment if the study eye undergoes first eye surgery
- As soon as 37 ± 3 days and a maximum of 58 ± 3 days after initiation of preoperative Miebo treatment if the study eye undergoes second eye surgery

Subjects will attend multiple standard postoperative visits within the first month post-surgery for both the first and second eye surgeries, which are not part of this study. Visit 3 will occur approximately 30 ± 7 days after the second eye surgery. Visit 4 will occur approximately 60 ± 7 days after the second eye surgery.

6.4 Study Duration

The entire duration of the study (from first subject first visit to last subject last visit) is expected to take approximately 8 months.

7 Selection and Withdrawal of Subjects

Approximately 100 subjects (approximately 100 study eyes) at up to 10 clinical sites in the US will be enrolled and treated with Miebo in this clinical study.

The study purpose, procedures, and subject responsibilities will be explained to the potential participant. The subject's willingness and ability to meet the follow-up requirements will be determined. When it has been established that the subject is willing to participate, written informed consent will be obtained (Section 14.3). In order to determine eligibility, written informed consent must be obtained from each study subject prior to performing any study-specific procedures that are not part of the Investigator's routine standard of care. A complete ophthalmic examination will be conducted at the Screening/Baseline Visit on Day 1.

Subjects will be eligible to participate in this trial if they meet all of the following inclusion criteria and none of the following exclusion criteria.

7.1 Subject Inclusion Criteria

This study will include subjects who meet all of the following inclusion criteria:

1. At least 18 years of age at the time of consent
2. Able to provide written voluntary informed consent
3. The same eye must satisfy the below inclusion criteria (a-e):
    a. At least 1 eye with a visually significant cataract that has been scheduled for cataract surgery (eligible eye can be a subject's second eye to undergo cataract surgery as long as all eligibility criteria are met in that eye)
    b. Candidate for routine, uncomplicated cataract surgery (phacoemulsification with posterior chamber IOL implantation, not combined with any other surgery)
    c. In the Investigator's opinion, subject has potential postoperative pinhole Snellen best-corrected visual acuity (BCVA) of at least 20/200 in both eyes
    d. Tear film break-up time ≤10 sec at Visit 1
    e. Total CFS score ≥2 and ≤11 (ie, sum of inferior, superior, central, nasal, and temporal), using the National Eye Institute (NEI) scale at Visit 1
4. Ocular Surface Disease Index ≥23 at Visit 1
5. Able and willing to follow instructions, including participation in all trial assessments and visits

7.2 Subject Exclusion Criteria

This study will exclude subjects who meet any of the following exclusion criteria:

1. Have any clinically significant ocular surface slit-lamp findings in the study eye and/or, in the opinion of the Investigator, have any findings that could interfere with trial parameters, including:
    a. History of eye trauma
    b. History of Stevens-Johnson syndrome
    c. Active blepharitis or lid margin inflammation
    d. Dry eye disease secondary to scarring, irradiation, alkali burns, cicatricial pemphigoid, or destruction of conjunctival goblet cells (as with vitamin A deficiency)
    e. Abnormal lid anatomy causing incomplete eyelid closure
    f. Abnormal cornea shape (keratoconus)
    g. Corneal epithelial defect or significant confluent staining or filaments
    h. History of herpetic keratitis
    i. Ocular or periocular rosacea
2. Pterygium in either eye
3. Use of any of the following ocular therapies in the study eye within 30 days prior to Visit 1: Vuity®, Qlosi™, topical ocular steroid treatments, prescription dry eye therapy including varenicline nasal spray, or topical anti-glaucoma medication
4. Had a LipiFlow® procedure, intense pulse light procedure, or any kind of other procedure affecting meibomian glands in the study eye within 3 months prior to Visit 1
5. Had received or removed a permanent punctum plug in the study eye within 1 month (3 months for dissolvable punctum plugs) prior to Visit 1
6. Use of any eye drops (prescription or over-the-counter, such as artificial tears or Lumify®) and/or TrueTear™ device (intranasal tear neurostimulator) in the study eye within 24 hours prior to Visit 1
7. Have active ocular allergies or ocular allergies that are expected to be active during the trial period
8. Have worn contact lenses within 1 month prior to Visit 1 or planned wear during the study
9. Have undergone intraocular surgery or ocular laser surgery in the study eye within 3 months prior to Visit 1; have undergone refractive surgery in the study eye within 2 years prior to Visit 1
10. Have active ocular or systemic infection (bacterial, viral, or fungal), including fever
11. Female subjects who are pregnant, nursing, or planning a pregnancy

12. Female subjects of childbearing potential who are not using an acceptable means of birth control; acceptable methods of contraception include hormonal (oral, implantable, injectable, or transdermal) contraception; mechanical (spermicide in conjunction with a barrier such as a diaphragm or condom) contraception; intrauterine device; or surgical sterilization of partner. For non–sexually active female subjects, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the trial, she must agree to use adequate birth control as defined above for the remainder of the trial
13. Have an uncontrolled systemic disease that, in the opinion of the Investigator, will interfere with the trial
14. Have a known allergy and/or sensitivity to the investigational drug
15. Use of any oral medications known to cause ocular drying (eg, antihistamines, antidepressants, etc.) on a non-stable regimen within 1 month prior to Visit 1 or is expected to be unstable during the trial
16. Have taken isotretinoin (eg, Accutane, Myorisan, Claravis, Amnesteem) within 6 months prior to Visit 1
17. Are currently enrolled in an investigational drug or device study or had used an investigational drug or device within 60 days prior to Visit 1

7.3 Subject Disposition Criteria

7.3.1 Subject Enrollment

The subject is considered enrolled in the study at the time the ICF is signed at the Screening/Baseline Visit (Visit 1).

7.3.2 Subject Screen Failures

A subject who fails to meet eligibility criteria will be considered a screen failure.

7.3.3 Subject Completion

For those subjects who are eligible and have consented to participate, Visit 4 will be the final visit to complete their participation.

A subject who has missed visits or is missing study measurements will remain in the study. Subjects who require further follow-up for an AE after study completion will be followed according to Section 11.2.1.5.

7.3.4 Subject Discontinuation

A subject MUST be discontinued prior to the final study visit for any of the following reasons:

- Voluntary withdrawal
- Death
- Any complication during cataract surgery
- A deviation from the IOL chosen at Visit 2
- Inability to finalize manifest refraction at Day 30

- Investigator decision that it is not in the best medical interest of the subject to continue participation in the study

A subject MAY be discontinued (at the discretion of the Investigator, the Sponsor, and/or the Institutional Review Board [IRB]) prior to the final study visit for several reasons, including but not limited to:

- Serious adverse event (SAE) and/or AE occurring during the course of the study that precludes continued follow-up
- Non-compliance with required study procedures
- Occurrence of a relevant exclusion criterion

Prior to discontinuing a subject from the study, every effort should be made to contact the subject, schedule a final study visit, and obtain as much follow-up data as possible. Whenever possible, subjects who have discontinued study treatment should be followed through the next scheduled study visit. Ongoing AEs will be followed as described in Section 11.2.1.5. Subject withdrawals will be documented clearly on the source document and applicable Case Report Form (CRF). Subjects who discontinue from the study should be seen for routinely scheduled visits according to the standard of care by the Investigator or their ophthalmologist.

Notification of subject withdrawals will be made immediately to the Sponsor.

7.3.5 Lost to Follow-Up

Subjects who do not return for scheduled visits, as defined by the visit window, or cataract surgery and cannot be contacted may be considered lost to follow-up. The Investigator will try at least twice to reach the subject by telephone and/or email and will send a follow-up letter by certified mail before considering the subject lost to follow-up. All follow-up attempts will be documented and kept with the subject's source documentation, and the applicable CRFs will be completed. The date a subject will be considered lost to follow-up will be the date of the last completed visit.

Efforts shall be made to keep the number of subjects lost to follow-up to a minimum (below 10% of the number of subjects treated).

8 Treatment Plan

8.1 Methods of Assigning Subjects to Treatment Groups

All subjects will self-administer preoperative Miebo QID bilaterally for approximately 30 days after Visit 1 (Screening/Baseline). Subjects will instill Miebo at least 30 minutes and no longer than 4 hours prior to the on-treatment assessment at Visit 2. Subjects will continue to self-administer Miebo QID bilaterally through the bedtime dose the evening before cataract surgery. Subjects will not instill Miebo on the day of surgery. All subjects will self-administer postoperative Miebo QID bilaterally for approximately 30 days after Visit 3 (Second Eye Postop Day 30 ± 7 days). Subjects will instill Miebo at least 30 minutes and no longer than 4 hours prior to the on-treatment assessment at Visit 4 (Second Eye Postop Day 60 ± 7 days).

8.2 Masking

This is an open-label study; therefore, masking will not be used.

8.3 Concomitant Medications and Treatments

Documentation of all medications and ocular therapies used by the subject within 30 days of informed consent and during the study will be made in study source documents.

Use of any topical ocular therapies, either prescription or over-the-counter, is prohibited during the course of the study (except for those standard ocular therapies used before, during, and after cataract surgery; refer to Section 10.1.3 for additional details). Contact lens wear during the study is prohibited.

8.4 Protocol Deviations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB and agreed to by the Investigator.

The Investigator or designee must document and explain in the subjects' source documentation any deviation from the approved protocol. Protocol waivers will not be allowed under any circumstances. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the IRB for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

Deviation impact on data analysis is described in Section 12.6.4. The date of and reason for deviations in all cases will be documented. Protocol deviations affecting the safety of the subject or the integrity of the study must be reported promptly by the Investigator to the IRB. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB.

Protocol assessments will continue for a subject until the end of the study, unless the protocol deviation puts the subject at risk or the subject's condition requires that he/she be discontinued from the study.

Scheduled assessments missed or conducted out of window due to Coronavirus Disease 2019 (COVID-19) disruption will be recorded as protocol deviations.

9 Study Materials and Management

9.1 Description of Study Treatment and Intended Use

Miebo® (perfluorohexyloctane ophthalmic solution) is a semifluorinated alkane indicated for the treatment of the signs and symptoms of DED. Each multiple-dose bottle contains 3 mL of 100% perfluorohexyloctane, 1.338 g/mL, as a clear and colorless liquid.

Miebo is manufactured for Bausch & Lomb Incorporated.

9.2 Packaging and Labeling

9.2.1 Packaging

To maintain product integrity and sterility, Miebo will be supplied in its original primary packaging container (bottle) as part of a kit (2 bottles per kit) and labeled per Section 9.2.2.

9.2.2 Labeling

Study treatment labeling will include the following information:

- Protocol number
- Kit number
- Caution statement
- Storage conditions
- Name and address of the Sponsor

9.3 Storage of Study Treatment

Study treatment will be stored at 15ºC to 25ºC (59–77ºF).

9.4 Directions for Use and Administration

Miebo will be used according to the Miebo prescribing information (Appendix D).

9.5 Study Treatment Accountability

A dedicated team member at each site will be responsible for keeping current and accurate records of the study treatment received and dispensed and its disposition. Study treatment must be stored under the appropriate conditions in a secure area and is to be used only in subjects enrolled in the study, in accordance with the conditions specified in this protocol. During the course of the study, the dedicated team member must maintain an inventory of all study treatment, including subject identifiers.

Accountability records will include:

- The batch and kit numbers of the study treatment received, the receipt date, and the quantity received
- The names of all site personnel who received or disposed of the study treatment
- The dates of use, disposal, or return of the study treatment
- A record of each subject treated with the study treatment
- Why and how many bottles of study treatment are returned to the Sponsor
- An explanation for reconciliation of discrepancies

At various time points throughout the study and/or upon completion of the study, the Sponsor or Sponsor's representative will review and verify the dedicated team member's accountability records. Following verification, and as directed by the Sponsor, all unused study treatment and used/partially used bottles of study treatment must be returned to the Sponsor.

9.6 Other Materials

Study materials provided by the Sponsor or Sponsor designee will include:

- Ocular Surface Disease Index (OSDI) questionnaire
- Visual analog scale (VAS) eye dryness
- Dosing diaries

10 Study Procedures and Evaluations

Subjects will be examined and evaluated according to the study flow chart provided in Appendix A.

10.1 Schedule of Evaluations and Procedures

Enrolled subjects who meet eligibility criteria will be seen in the clinic according to the following schedule (Table 1):

Table 1. In-Clinic Visit Details

Visit Name	Eyes Evaluated	Visit Time and Window
Screening/Baseline Visit (Visit 1)	Both eyes	Day 1
Visit 2	Study eye only for corneal biometry, corneal tomography, HOA assessment, IOL power and predicted post-surgical refractive error calculation, IOL finalization, BCVA, slit-lamp biomicroscopy, and CFS scores	Day 30 ± 3 days
Visit 3	Study eye only for corneal tomography, HOA assessment, autorefraction, manifest refraction, BCVA, slit-lamp biomicroscopy, and CFS scores	Second Eye Postop Day 30 ± 7 days
Visit 4	Study eye only for corneal tomography, HOA assessment, BCVA, slit-lamp biomicroscopy, and CFS scores	Second Eye Postop Day 60 ± 7 days

Refer to Appendix A for the study flow chart and Appendix B for methods of clinical evaluation.

10.1.1 Screening/Baseline Visit (Visit 1): Day 1

The following non–eye-specific assessments will be performed:

- Informed consent/HIPAA
- Demographics
- Medical/Surgical history
- Urine pregnancy test (for female subjects of childbearing potential)
- Previous/Concomitant medications
- Inclusion/Exclusion criteria
- Ocular Surface Disease Index
- Visual analog scale eye dryness
- Adverse event query

The following eye-specific assessments will be performed on both eyes:

- Preoperative corneal biometry

- Corneal tomography
- Root mean square HOAs in the central 6.0 mm of the cornea
- Optical coherence tomography assessment of the macula
- Best-corrected visual acuity
- Slit-lamp biomicroscopy
- Meibomian gland assessment (MGD score)
- Tear film break-up time
- Total and central CFS
- Intraocular pressure
- Dilated fundoscopy

Additional activities:

- Determine IOL power calculation and predicted post-surgical refractive error
- Dispensation of dosing diary
- In-clinic instillation of study treatment
- Dispensation of study treatment (subjects will self-administer Miebo QID bilaterally)

10.1.2 Visit 2: Day 30 ± 3 days

The following non–eye-specific assessments will be performed:

- Adverse event query
- Changes in concomitant medications
- Ocular Surface Disease Index
- Visual analog scale eye dryness

The following eye-specific assessments will be performed on study eye only:

- Preoperative corneal biometry
- Corneal tomography
- Root mean square HOAs in the central 6.0 mm of the cornea
- Visual acuity
- Slit-lamp biomicroscopy
- Total and central CFS
- Additional activities:
- Determine IOL power calculation and predicted post-surgical refractive error for the study eye using the biometric data collected at this visit

- Finalize IOL choice for the study eye. Note: Standard monofocal IOL will be the preferred IOL choice, but toric, multifocal, and extended depth-of-focus IOLs are acceptable. The IC-8 lens (pinhole optics) and light-adjustable lenses are not permitted
- Compute the predicted post-surgical refractive error in the study eye using the same IOL power calculation that was used to select the lens and the IOL lens that will be implanted, but with the biometric data collected at Visit 1. Enter this prediction into the CRF
- Review and re-dispense dosing diary
- Subjects will continue to self-administer Miebo QID bilaterally through the bedtime dose the evening before cataract surgery (but should NOT instill Miebo on the day of surgery)
    - If the first (non-study) eye surgery is being performed the same day as Visit 2, the subject would discontinue Miebo in this eye the night before Visit 2

10.1.3 First Eye Cataract Surgery (0–14 Days After Visit 2), Second Eye Cataract Surgery (7–14 Days After First Eye Surgery), and Routine Postop Visits (4 Weeks Postop): NOT Study Visits

- First eye surgery will take place 0 to 14 days after Visit 2 and is NOT considered part of the study, although the Investigator will perform the surgery
- Second eye surgery will take place 7 to 14 days after first eye surgery and is NOT considered part of the study, although the Investigator will perform the surgery
- Study treatment and dosing diary will be brought to the clinic and collected
- Subjects will attend multiple routine postoperative visits that are also NOT considered part of the study and will receive routine postoperative treatment medications per Investigator's standard operating protocol. Routine postoperative visits must be completed prior to Visit 3
- At each of these visits, AEs will be queried (AEs to be recorded at these visits due to potential for postoperative complications following uncomplicated cataract surgery in the study eye)
    - Subjects with the following postoperative AEs must discontinue the study: endophthalmitis, cystoid macular edema, posterior capsular tear/rupture, zonular dehiscence, any complication during surgery that led to a different IOL choice than expected, and any complication that in the opinion of the Investigator would prevent finalization of the subject's manifest refraction at Visit 3
- At each of these visits, changes in concomitant medications will be recorded

10.1.4 Visit 3: Second Eye Postop Day 30 ± 7 days

The following non–eye-specific assessments will be performed:

- Adverse event query
- Changes in concomitant medications
- Ocular Surface Disease Index

- Visual analog scale eye dryness

The following assessments will first be performed on the study eye only:

- Autorefraction
- Manifest refraction
- Best-corrected visual acuity

After establishment of finalized refraction, the following assessments will be performed on the study eye only:

- Corneal tomography
- Root mean square HOAs in the central 6.0 mm of the cornea
- Slit-lamp biomicroscopy
- Total and central CFS
- Additional activities:
- Dispensation and review of dosing diary
- Dispensation of study treatment
- Subjects will restart Miebo regimen (Miebo QID bilaterally) for approximately 30 days after Visit 3

10.1.5 Visit 4: Second Eye Postop Day 60 ± 7 days

The following non–eye-specific assessments will be performed:

- Urine pregnancy test (for female subjects of childbearing potential)
- Adverse event query
- Changes in concomitant medications
- Ocular Surface Disease Index
- Visual analog scale eye dryness

The following assessments will be performed on the study eye only:

- Corneal tomography
- Root mean square HOAs in the central 6.0 mm of the cornea
- Visual acuity
- Slit-lamp biomicroscopy
- Total and central CFS
- Additional activities:
- Review and collect dosing diary
- Collect study treatment

- Exit subjects from the study

10.1.6 Unscheduled Visit(s)

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional examinations should be fully documented in the source documents and on Unscheduled Visit CRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit window will be collected and transcribed to the appropriate visit CRF.

If a subject is seen for multiple visits during a given visit timeframe, the data from the visit that are intended to meet the protocol requirements for the scheduled visit will be captured on the visit CRF. Where such a determination cannot be made, the first visit within the scheduled visit interval will be used for completion of the protocol-required scheduled visit CRF. Data from any additional visits within a scheduled visit interval will be captured on an Unscheduled Visit CRF.

10.1.7 Missed Visit(s)

If a subject misses any scheduled follow-up visit and cannot be seen prior to the start of the visit range for the next scheduled follow-up visit, the visit is considered missed.

10.2 Post-Study Follow-Up

If a subject requires further follow-up upon discontinuation or completion of the study, the Investigator should schedule post-study follow-up visits, as necessary. Refer to Section 11.2.1.5 for follow-up of AEs following study exit.

10.3 Study Completion

The Sponsor or its representative will notify the Investigator or the IRB, as applicable, to inform them when the study is complete (last subject last visit).

10.3.1 Early Study Termination

If during the study it becomes evident to the Sponsor that the study should be stopped prematurely, the study will be terminated and appropriate notification will be given to the Investigators, IRB, and FDA or Local Health Authority, as applicable. The Sponsor or its representative will instruct the Investigators to stop enrolling and dispensing study materials/treatment and to arrange for study closeout at each site as appropriate.

11 Primary and Secondary Safety and Efficacy Variables

11.1 Evaluation of Efficacy

The primary efficacy endpoint is the mean difference between absolute deviations from predicted refractive error in the study eye. There are no secondary efficacy variables.

Efficacy will be evaluated using the following assessments:

- Autorefraction
- Manifest refraction
- Visual acuity

- Slit-lamp biomicroscopy
- Corneal fluorescein staining
- Visual analog scale eye dryness
- Ocular Surface Disease Index
- Higher-order aberrations
- Corneal tomography

11.2 Evaluation of Safety

Safety will be evaluated through recording AEs (reported, elicited, and observed), including complications during cataract surgery.

11.2.1 Adverse Events

Each subject eye treated must be examined for the presence/absence of AEs at all visits, whether scheduled or not and whether part of the study or not (ie, cataract surgery and the standard postoperative visits). If an AE occurs, the first concern will be the safety and welfare of the subject; treatment should be provided as appropriate for the event.

11.2.1.1 Adverse Events Definitions

For the purposes of this study, AEs include all ocular AEs/SAEs in both eyes, and all non-ocular SAEs. Adverse events and SAEs are defined as follows.

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory finding) in a subject, user, or other persons, whether or not related to the study treatment. For users or other persons, this definition is restricted to events related to the study treatment.

An SAE is an AE that leads to one or more of the following:

- Death
- A life-threatening illness or injury
- A permanent or significant disability/impairment of a body structure or body function (eg, blindness)
- In-patient or prolonged hospitalization
- Medical or surgical intervention to prevent life- or vision-threatening illness or injury or permanent impairment to a body structure or a body function
- Fetal distress, fetal death, or a congenital abnormality or birth defect

11.2.1.2 Identification and Collection

Identification and collection of an AE begins after informed consent has been obtained and documented. Standard sources of identifying AEs include:

- Direct observation by the Investigator

- Asking the study participant a non-specific question (eg, "Have you had any problems since the last visit?")
- Unsolicited volunteering of information by the study participant (eg, "Doctor, I have had blurred vision since I started using this lens.")
- Test results that meet protocol requirements for classification as an AE

Specific to this protocol, ocular AEs in both eyes and all SAEs (ocular and non-ocular) observed or elicited by the Investigator, reported by the subject, or resulting from a test result, etc., occurring during the clinical study must be reported in the CRF. During the study, the Investigator should treat the study subject as appropriate to ensure his/her safety and welfare. Refer to Section 11.2.1.5 for additional information pertaining to ongoing AEs at subject exit.

Pre-existing conditions will not be considered AEs but will be collected at the Screening/Baseline Visit as medical history. A worsening of a pre-existing condition during the study should be documented as an AE and evaluated accordingly.

Hospitalizations for admission without a medical AE should be captured as an SAE until the cause of hospitalization can be identified. However, the following reports of hospitalization without a medical AE should not be considered either serious or an AE:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with worsening of the pre-existing condition (eg, for work-up of persistent pretreatment lab abnormality)
- Social admission (eg, subject has no place to sleep)
- Administrative admission (eg, for yearly physical exam)
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery)

11.2.1.3 Evaluations

When evaluating AEs, the Investigator must determine if the event is serious (refer to Section 11.2.1.1 for criteria), assess the severity of symptoms, and determine the relationship of the event to study treatment, using the following guidelines:

Severity

- **Mild:** Subject awareness of a sign or symptom that is easily tolerated, requires no treatment, and does not interfere with subject's daily activities
- **Moderate:** Subject awareness of a sign or symptom which may be a low level of concern to the subject and may interfere with daily activities but can be relieved by simple therapeutic care
- **Severe:** A sign or symptom that interrupts the subject's daily activity and requires systemic therapy or other treatment

Relationship to Study Treatment

- **Related:** There is at least a reasonable possibility the AE is related to the study treatment. Reasonable possibility means there is evidence to suggest either a causal relationship or association between the study treatment and the AE
- **Not related:** There is little or no reasonable possibility the AE is related to the study treatment. No reasonable possibility means there is no evidence to suggest either a causal relationship or association between the study treatment and the AE

11.2.1.4 Reporting

Actions required by Investigators for reporting non-serious ocular AEs are to record them on AE CRFs only. Neither expedited report to the Sponsor nor report to the IRB is required for non-serious AEs.

Any SAE must be reported to the Sponsor/CRO, independent of the circumstance or suspected cause, within 24 hours from the time the event was reported to the Investigator. All SAEs experienced between the date of consent and 30 days after the last administered dose of study treatment must be reported to the Sponsor/CRO regardless of the relationship to the study treatment or protocol. For events occurring beyond the 30-day period after the last administration of study treatment, or for any timeframe greater than 30 days deemed medically significant, only SAEs considered related to the study treatment should be reported promptly to the Sponsor/CRO.

Within 24 hours of notification, the Investigator will fax or email a completed Serious Adverse Event Form to the Sponsor and CRO contact listed below. For SAEs with fatal outcomes, a summary of available autopsy findings should be submitted as soon as possible.

Care should be taken to ensure that the subject's identity is protected (personal identifiers are redacted) and the date and subject identifier in the clinical study (ie, subject number) are clearly visible on every page/copy of source document provided to the Sponsor. For laboratory results, the laboratory normal ranges should be included.

Investigators should not wait to receive additional information before notifying the Sponsor/CRO of an SAE. If only limited information is initially available, follow-up reports are required.

The Investigator will notify their IRB in writing of any SAE in accordance with the IRB requirements. Sponsor or its designee will be responsible for submitting SAE reports to regulatory authorities based on applicable regulations. The CRO will be responsible to send a notification to all participating Investigators of any SAE that is unexpected and associated with the study. If the Investigator becomes aware of any new information regarding an SAE (eg, resolution, change in condition, or new treatment), a new SAE Form must be completed and faxed/emailed to the Sponsor/CRO within 24 hours. The original SAE Form is not to be altered. The report should be marked as a “follow-up report” and should describe whether the event has resolved or continues and how the event was treated.

Serious AEs that have previously been reported and that continue after the subject’s discontinuation or completion of the study will be followed until their medical endpoints are determined or until no further change in the conditions is expected. The events and endpoints will be reported in writing by the Investigator to the CRO. Following the subject's discontinuation or completion of the study, for any timeframe thereafter deemed medically

significant, any SAEs that are assessed as causally related to study treatment should also be reported to the Sponsor/CRO.

The contacts for reporting SAEs are:

[redacted]

Contact information for the CRO will be provided on the SAE Form.

11.2.1.5 Adverse Events at Subject Exit

Ongoing AEs will be followed until resolution, until no further change in the condition is expected (ie, event stabilized), or as dictated by standard of care. Documentation on the CRF of this follow-up is not required, although subject care should continue as appropriate.

11.2.2 Pregnancy

All female subjects of childbearing potential and male subjects with female partners of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of contraceptive failure is minimized.

Before enrolling a female subject of childbearing potential or a male subject with a female partner of childbearing potential, the Investigator must review the following information about study participation:

- Informed consent requirement
- Contraceptives in current use

By signing the ICF, the Investigator or designee asserts that he/she has discussed this information with the subject and provided appropriate counseling. Following the review of this information, the subject must sign the ICF to enroll in the study.

During the study, all female subjects of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period).

If a subject or Investigator suspects that the subject may be pregnant prior to treatment, the study treatment must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject is considered to be a screen failure, must not continue in the study, and must not receive study treatment. If pregnancy is suspected while the subject is receiving study treatment, the study treatment must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study treatment will be permanently discontinued, and the subject and neonate will be followed until 30 days after the pregnancy comes to term.

Female subjects who become pregnant during the study will be followed until completion of pregnancy. Every effort will be made to obtain the health status of the mother and infant or fetus (in cases of miscarriage or therapeutic abortion) at term. Pregnancy itself is not considered an AE.

All confirmed pregnancies must be immediately reported to the medical monitor, Sponsor, and CRO contact within 24 hours of the Investigator's awareness of the pregnancy. All confirmed

pregnancies must be reported via confirmed facsimile or email transmission and must be submitted on a Pregnancy Report Form to the Sponsor or designee within 24 hours of the Investigator's awareness of the pregnancy. A Pregnancy Report Form will be submitted to the Sponsor, both when pregnancy is confirmed and 30 days after the delivery date. Information provided on the Pregnancy Report Form must include the outcome of the pregnancy and any complications occurring during the pregnancy or the delivery. If a pregnancy is associated with an SAE, an SAE Form should also be submitted to the Sponsor/designee and medical monitor within 24 hours of the Investigator's awareness. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

The contacts for reporting pregnancies are:

[redacted]

Contact information for the CRO will be provided on the Pregnancy Report Form.

12 Statistics

12.1 Study Endpoints

The endpoints are detailed in Section 5.2.

12.2 Hypotheses

The null hypothesis (H_0) is that the mean difference between the absolute deviations from the predicted refractive errors (μ), as determined by the biometry assessment data at Visits 1 and 2, is equal to zero. The alternative hypothesis (H_1) is that the mean difference is not equal to zero.

$$H_0: \mu = 0$$

$$H_1: \mu \neq 0$$

12.3 Sample Size Determination

A sample size of 77 subjects will have 80% power to detect an effect size of 0.325 standard deviations using a paired t-test with a 5% two-sided significance level. To accommodate potential missing data of up to 23%, study treatment will be administered to approximately 100 subjects.

12.4 Analysis Populations

Full Analysis Set (FAS): The FAS will consist of all enrolled subjects who are instilled with study treatment.

Per Protocol (PP) Set: The PP Set will consist of FAS subjects with no protocol violations expected to affect the evaluability of efficacy.

12.5 Statistical Analysis

12.5.1 General Considerations

Continuous variables will be summarized using the mean, standard deviation, median,

minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

12.5.2 Primary Efficacy Analysis

[redacted]

12.5.3 Primary Safety Analyses

The number and percentage of subjects with specific treatment-emergent adverse events (TEAEs) will be summarized for the FAS. The number of subjects will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term within each system organ class.

12.6 Additional Statistical Considerations

12.6.1 Handling of Missing Data

Unless otherwise specified in the statistical analysis plan, missing data will not be imputed.

12.6.2 Multiplicity Issues

No adjustment for multiplicity is required for the primary endpoint.

12.6.3 Interim Analysis

No interim analysis is planned for this study.

12.6.4 Protocol Deviations

Important protocol deviations that affect the evaluation of efficacy will result in exclusion from the PP Set. Protocol deviations will be displayed in a listing.

13 Quality Control and Quality Assurance

13.1 Study Monitoring

The Sponsor and its representatives must be allowed to visit all study site locations to assess the data, quality, and study integrity in a manner consistent with applicable health authority regulations and the procedures adopted by the Sponsor or its representative. If due to unforeseen situations, access to study site locations may be restricted, remote monitoring methods may be implemented to ensure data quality and integrity, as per the monitoring plan.

Prior to the start of the study, member(s) of the Sponsor (or designees) will review the protocol, CRF, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator/sub-Investigator and relevant site personnel.

Monitoring visits and telephone consultations will occur as necessary, as per the monitoring plan, during the course of the study to verify the following:

- The rights and well-being of subjects are protected

- The conduct of the study is in compliance with the currently approved protocol/amendment; 21 CFR Parts 11, 50, 54, 56, 312, 314; 42 USC 282(j); ICH GCP E6 (R2) (International Council for Harmonisation, Guidance E6); and IRB requirements
- The integrity of the data, including adequate study documentation
- The facilities remain acceptable
- The Investigator and site personnel remain qualified and able to conduct the study
- Study treatment accountability

During the study, if the Sponsor (or designee) determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor (or designee) will take remediation action to secure compliance. In addition, the Sponsor may terminate the Investigator's participation in the study, if appropriate, if the Investigator remains non-compliant despite the remediation actions.

13.2 Source Documentation

All medical information obtained at each study visit must be recorded in the subject's record (source documentation) in real time as it is collected. Source documentation consists of original subject documents, as well as data and records with information relevant to the subject and his/her participation in the study.

Source documentation worksheets may be provided by the Sponsor or its designee to record pertinent information. The completed worksheets can then be incorporated into the subject's medical chart. If it is preferred not to use the worksheets in the subject's permanent record, then the worksheets should be used as a reference to determine the type of study data to record in the subject's permanent record.

13.3 Case Report Forms and Data Verification

As used in this protocol, the term CRF should be understood to refer to an electronic data record developed as part of the electronic data capture method utilized in this study.

Subject data required by this protocol are to be recorded on CRFs. The Investigator and site personnel will be responsible for completing the CRFs in a timely manner. The Investigator is required to verify that all of the requested information is accurately recorded on the CRFs. All information requested on the CRFs needs to be supplied, including subject identification and initials, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on CRFs must be traceable to source documents.

The study monitor will be responsible for reviewing and verifying the data recorded on the CRFs, utilizing the original or certified copies of all source documentation and querying discrepant findings.

The Investigator and site personnel will be responsible for answering all queries in a timely manner.

13.4 Recording of Data and Retention of Documents

Subject data recorded on CRFs during the study will be documented in a coded fashion. The subject will only be identified by the unique subject number. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

The Investigator must retain essential documents indefinitely after the completion of the study, unless otherwise notified by the Sponsor.

Essential documents include but are not limited to the following:

- Institutional Review Board approvals for the study protocol, all amendments, ICF(s), and advertisements
- Institutional Review Board annual study review
- Institutional Review Board correspondence and reports (eg, SAE reports, protocol deviations, and safety updates)
- Regulatory documents (eg, financial disclosure and delegation of authority forms)
- All source documents
- Case Report Forms
- Subjects' signed ICFs
- Principal Investigator Protocol Agreement Page
- Accountability records for the study treatment
- Correspondence from and to the Sponsor and CRO
- Any other documents relevant to the conduct of the study

In the event the Investigator withdraws from the study (eg, retirement or relocation), study records will be transferred to a mutually agreed-upon designee (eg, another Investigator or the site IRB). The Investigator will provide notice of such transfer in writing to the Sponsor and/or its representative.

13.5 Audits and Inspections

Audits of clinical research activities in accordance with the Sponsor's internal Standard Operating Procedures to evaluate compliance with the principles of GCP may take place. A regulatory authority also may wish to conduct an inspection during the study or after its completion. If an inspection is requested by a regulatory authority and/or IRB, the Investigator must inform the Sponsor and its representative immediately that this request has been made.

14 Ethics and Administrative Issues

It is the responsibility of the site's Principal Investigator to assure that all aspects of the ethics review are conducted in accordance with ICH GCP E6 (R2). The protocol and any information supplied to the subject to obtain informed consent, including written ICFs, subject recruitment procedures (eg, advertisements), and written information to be provided to subjects (information leaflets), will be reviewed and approved by a qualified IRB prior to enrollment

of participants in the study. Prior to initiation of the study and release of study treatment to a clinical site, the Sponsor or its designee will receive documentation of the IRB approval, which specifically identifies the approved study/protocol and a list of the IRB committee members. Protocol amendments will be reviewed and approved by the IRB prior to implementation of any changes made to the study design in the amendment. Investigators will submit progress reports to the IRB in accordance with the IRB requirements.

14.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and GCP, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki.

14.2 Ethics Review

The Investigator should ensure his/her participation in the study, the protocol, subject recruitment materials (eg, written information or materials including web pages, radio advertisements, television spots, or written text developed to encourage subject enrollment) and the ICF to be used in this study are approved by his/her institution's IRB, or, if not using his/her institution's IRB, by the reviewing central IRB prior to entering any subjects in the study. Documentation of IRB approval of the study protocol and informed consent must be provided to the Sponsor and any designee prior to initiation of the study. In addition, the Investigator must ensure that the reviewing IRB has provided approval for any protocol amendments prior to their implementation. If the amendment necessitates a revision to the ICF, the Investigator should ensure the revised form is also submitted to and approved by the Sponsor or its designee and the IRB prior to its implementation.

14.3 Written Informed Consent

Before entry into the study, the Investigator or an authorized member of the site personnel will explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent will be appropriately recorded by means of either the subject's or his/her legally acceptable representative's dated signature. After having obtained the consent, a copy of the signed and dated ICF will be given to the subject.

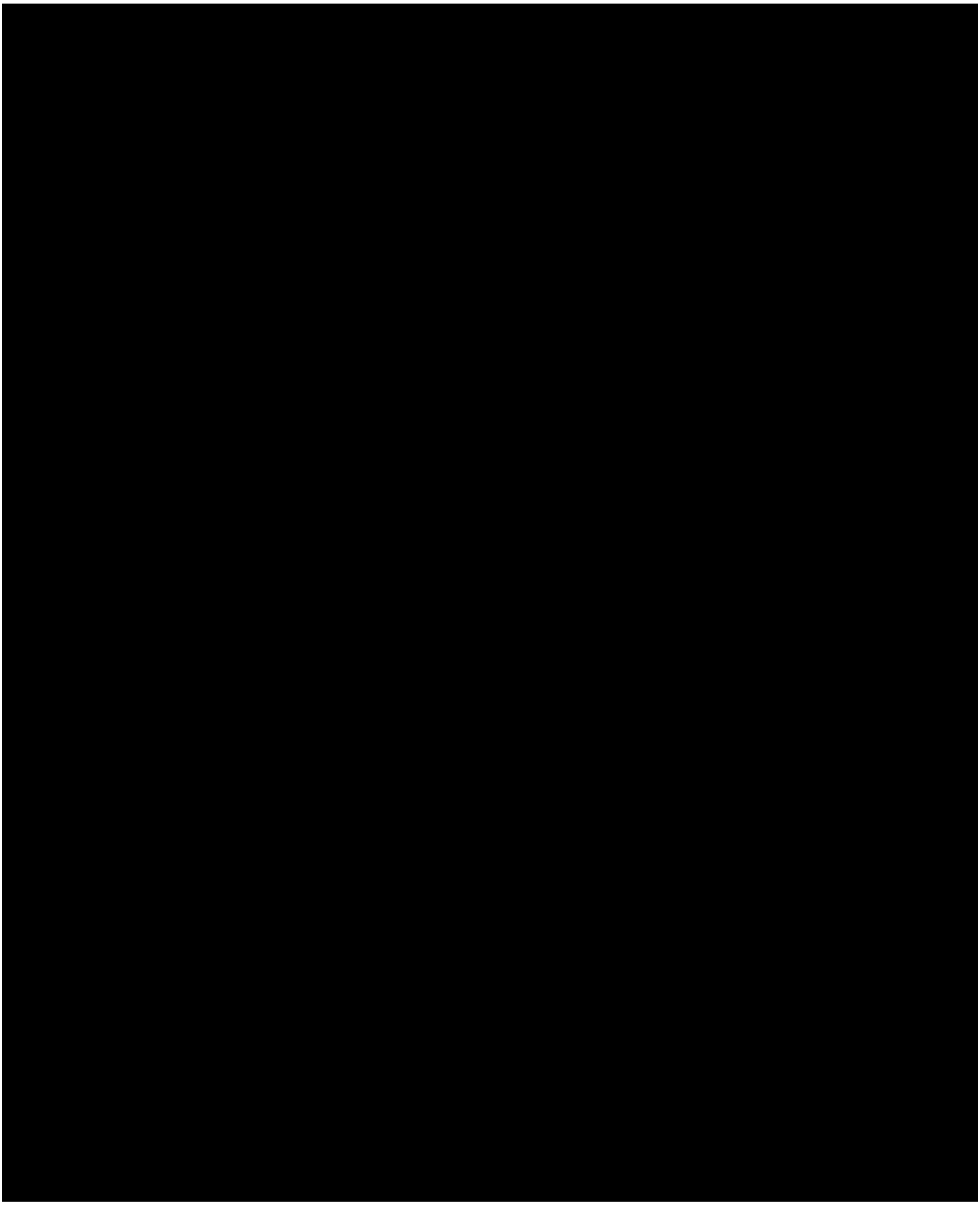
The ICF will be signed before the performance of any study-related activity.

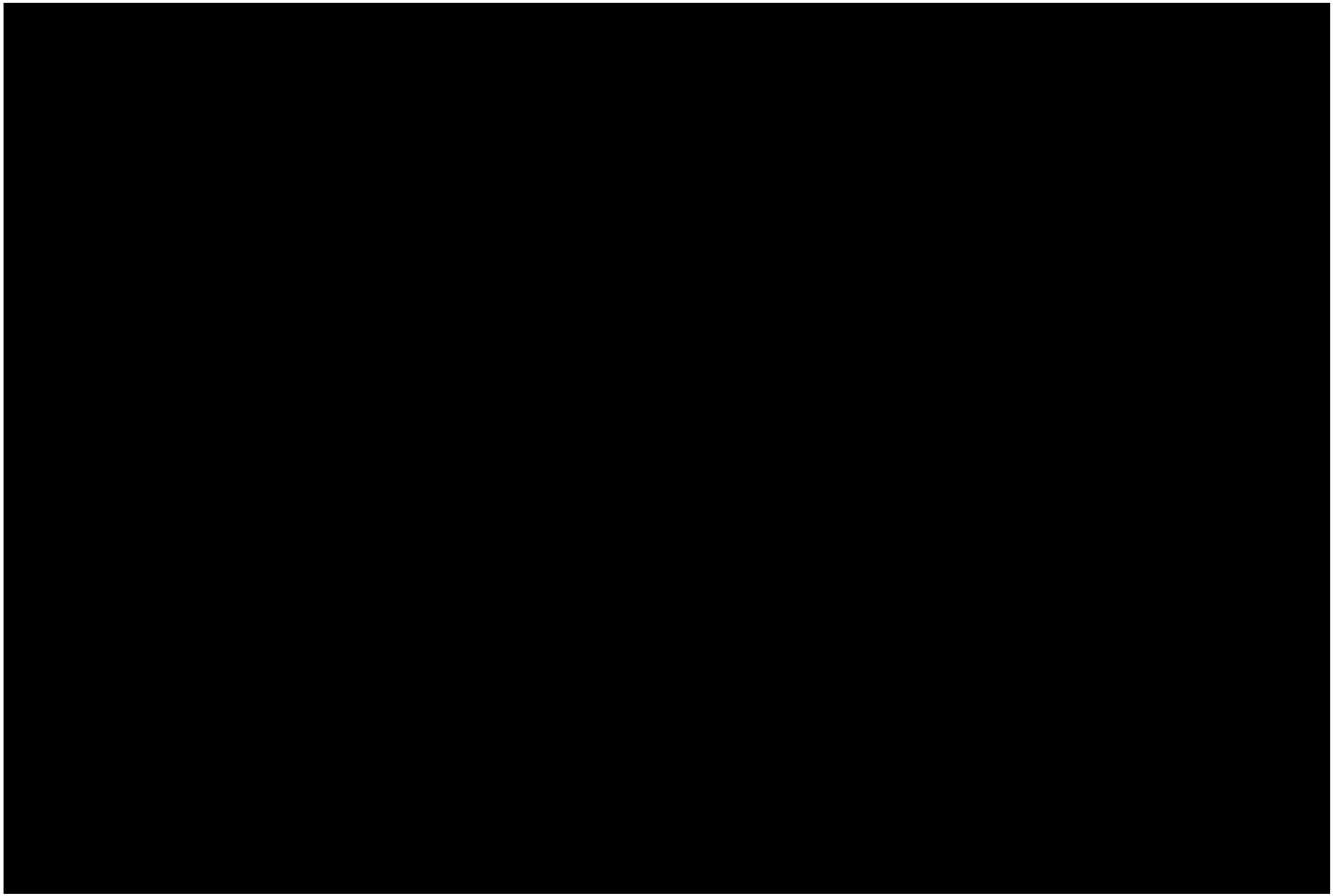
14.4 Financial Disclosure, Clinical Trial Agreements, and Site Contact Information

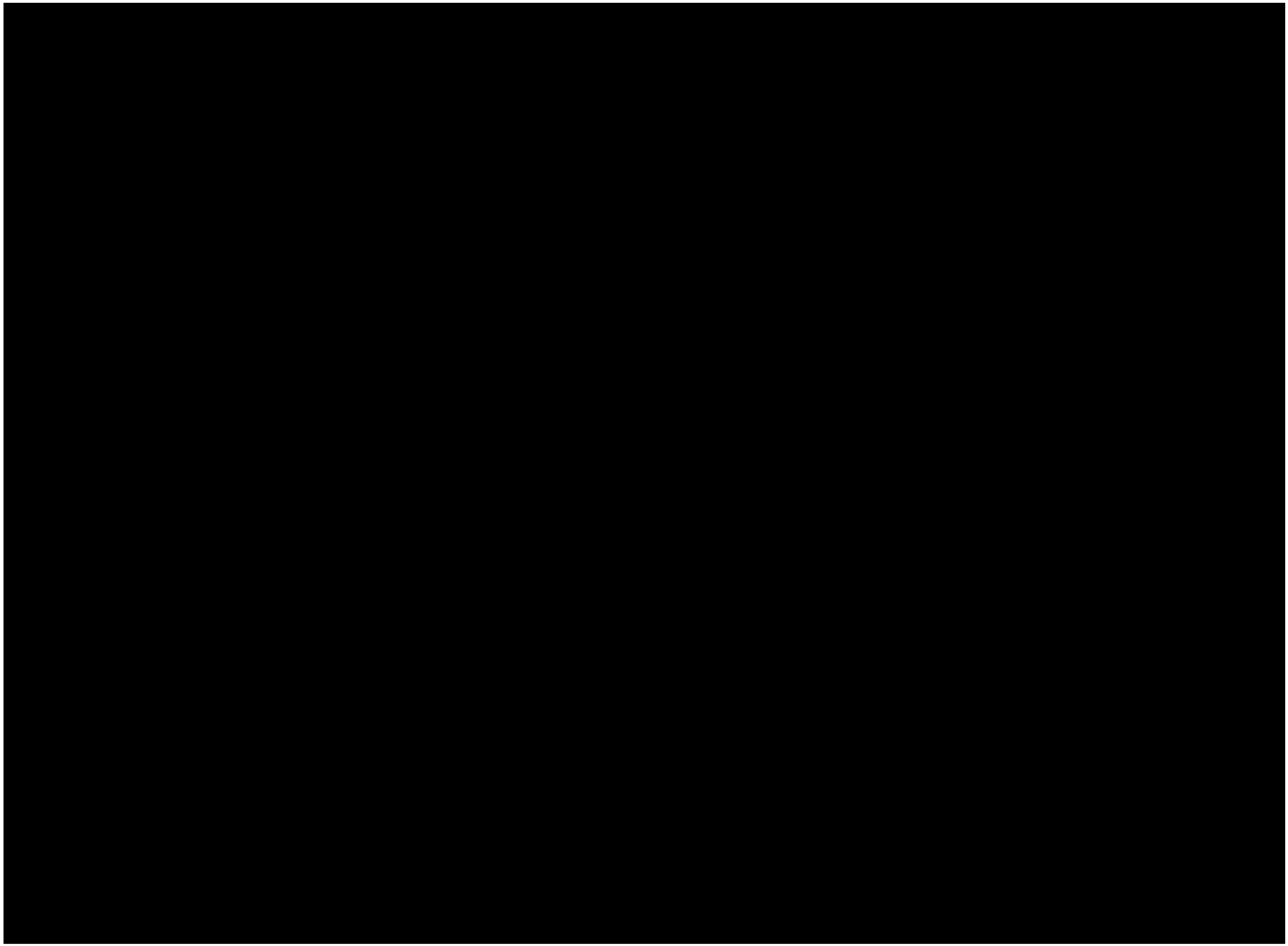
An original financial disclosure form (FDF) must be completed, signed, and dated by the Investigator and any sub-Investigators and study personnel listed on the Delegation of Authority Log. All FDFs will be collected by the Sponsor or its designee and filed in the study Trial Master File. A copy of all FDFs will be retained in the Investigator Site Binder. All contractual and financial agreements between clinical sites and the Sponsor will be administrated by the CRO as designated by the Sponsor and approved at a minimum by both Investigators and the Sponsor in writing. Indemnification information is included in contractual agreements with sites.

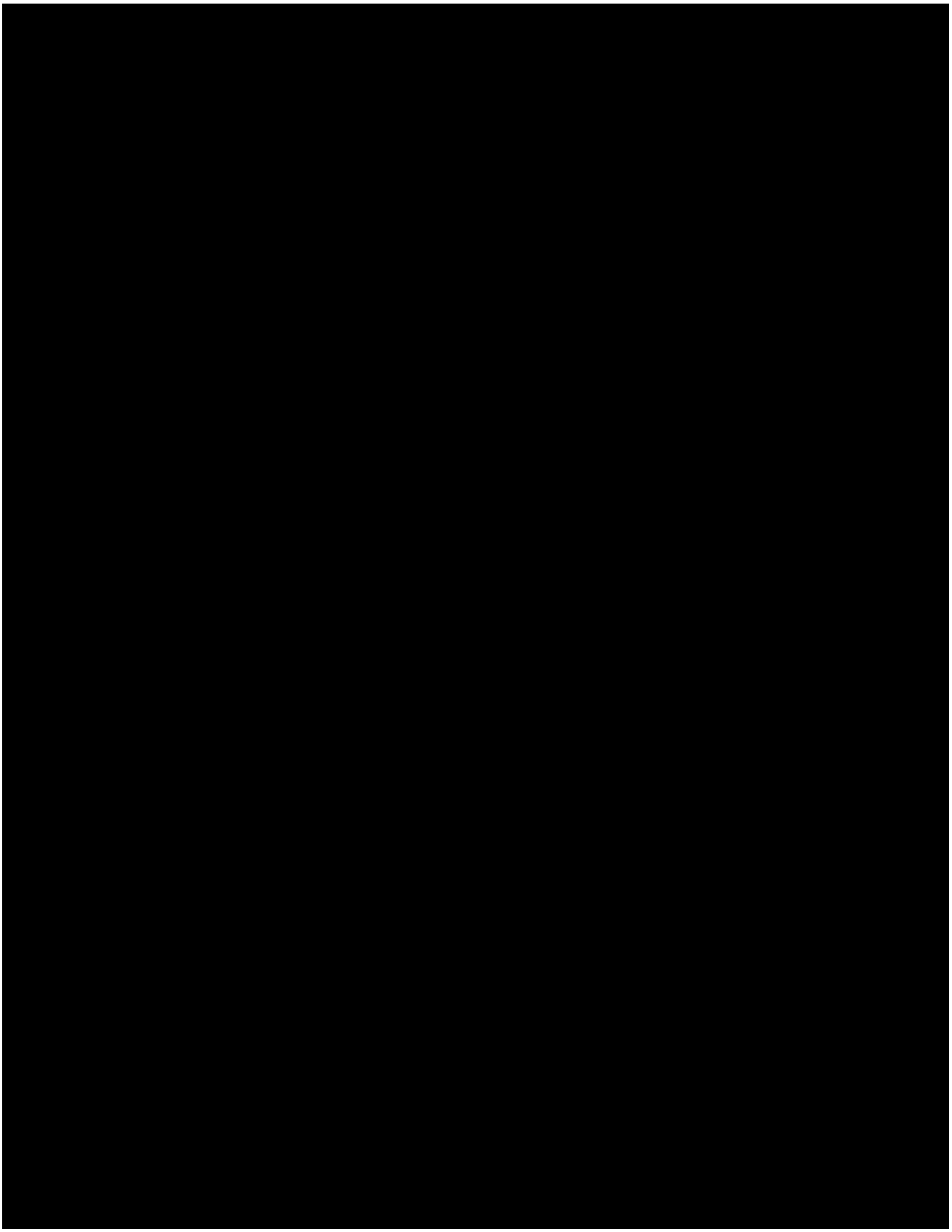
14.5 Confidentiality/Publication of the Study

15 References









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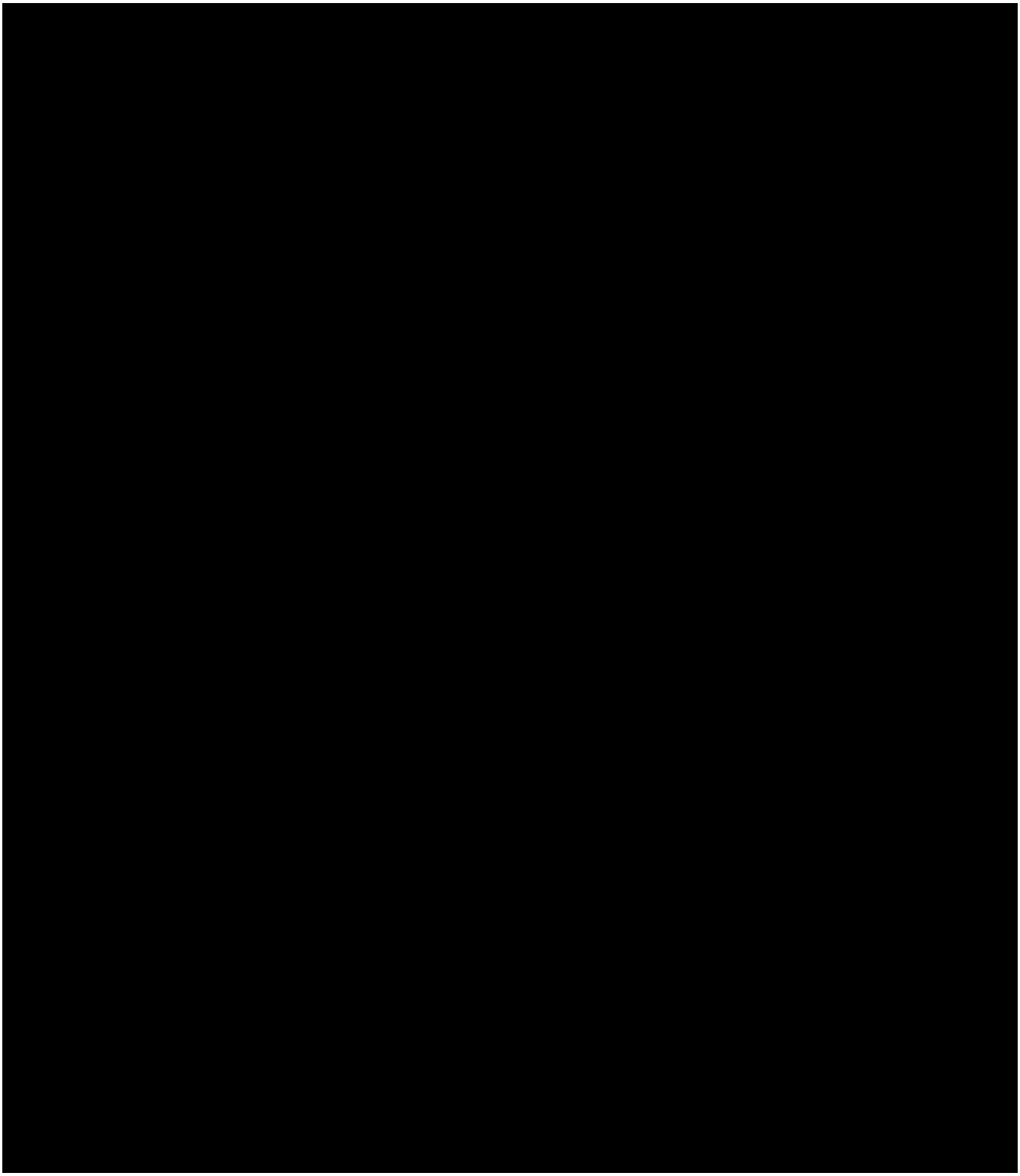
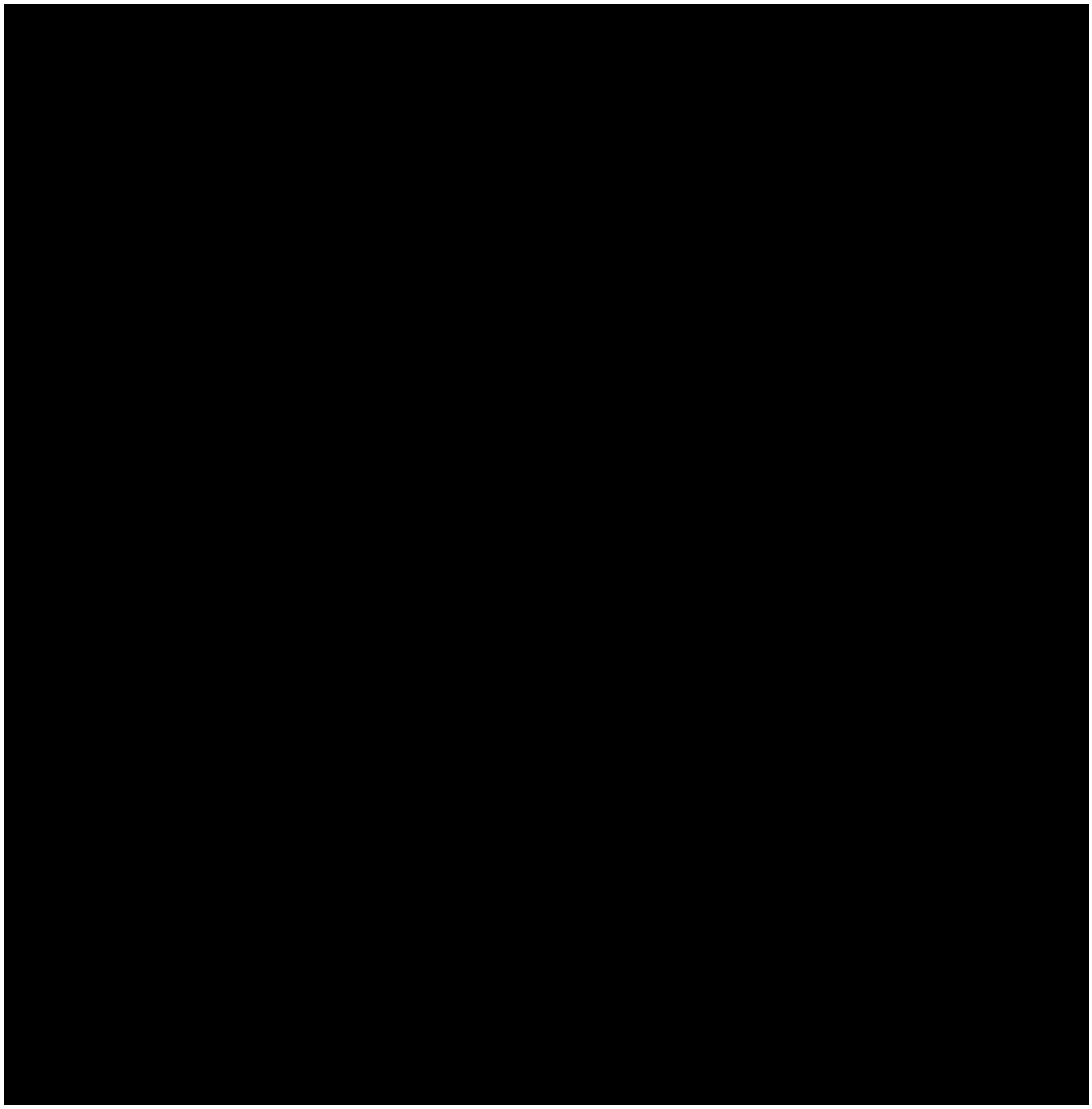




Appendix D MIEBO PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MIEBO safely and effectively. See full prescribing information for MIEBO.

MIEBO™ (perfluorohexyloctane ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
MIEBO (perfluorohexyloctane ophthalmic solution) is a semifluorinated alkane indicated for treatment of the signs and symptoms of dry eye disease. (1)

----------DOSAGE AND ADMINISTRATION----------
Instill one drop of MIEBO four times daily into each eye. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution: 100% perfluorohexyloctane. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------ADVERSE REACTIONS----------
Most common ocular adverse reaction was blurred vision. Blurred vision was reported in less than 4% of individuals. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-553-5340 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

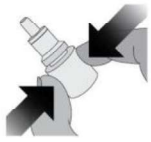
1 INDICATIONS AND USAGE
MIEBO™ (perfluorohexyloctane ophthalmic solution) is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage
Instill one drop of MIEBO four times daily into affected eye(s).

Contact lenses should be removed prior to and for at least 30 minutes after the administration of MIEBO.

2.2 Administration Instructions



Step 1. Remove the cap from eye drop bottle.

Step 2. Holding the bottle upright, gently squeeze the bottle.

Step 3. While squeezing, turn the bottle upside down and release the pressure (drawing air into the bottle).

Step 4. Keeping the bottle upside down, place the bottle above your eye and squeeze it again to release a drop into your eye.
Repeat steps 1 - 4 for the second affected eye.

3 DOSAGE FORMS AND STRENGTHS
MIEBO (perfluorohexyloctane ophthalmic solution) is a sterile, clear and colorless ophthalmic solution containing 100% perfluorohexyloctane.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Use with Contact Lenses
MIEBO should not be administered while wearing contact lenses. Advise patients that contact lenses should be removed prior to and for at least 30 minutes after administration of MIEBO.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In patients with DED, 614 patients received at least one dose of MIEBO in two randomized controlled clinical trials across 68 sites in the United States. The most common ocular adverse reaction was blurred vision. Blurred vision and conjunctival redness were reported in 1-3% of individuals.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well controlled studies with MIEBO in pregnant women.

In animal reproduction studies with oral administration of perfluorohexyloctane during the period of organogenesis, no adverse maternal or developmental effects were observed in rats at doses up to 162 times the recommended human ophthalmic dose (RHOD) (*see Data*). Maternal toxicity, miscarriages and reduced fetal weights were observed in rabbits at all doses tested, with the lowest dose as 41 times the RHOD.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

An embryofetal study was conducted in pregnant rabbits administered perfluorohexyloctane by oral gavage on gestation days 6 to 19, to target the period of organogenesis. Perfluorohexyloctane produced maternal toxicity, characterized by reduced body weight gain and food consumption, and miscarriages at all doses tested, with the lowest dose as ≥ 250 mg/kg/day (41 times the RHOD based on body surface area). Reduced fetal weights were also observed at ≥ 250 mg/kg/day but no fetal mortality or malformations. A no observed adverse effect level (NOAEL) for maternal toxicity was not established in rabbits.

An embryofetal study was conducted in pregnant rats administered perfluorohexyloctane by oral gavage on gestation days 6 to 17, to target the period of organogenesis. There was no evidence of embryofetal toxicity or teratogenicity at doses up to 2,000 mg/kg/day (162 times the RHOD).

8.2 Lactation

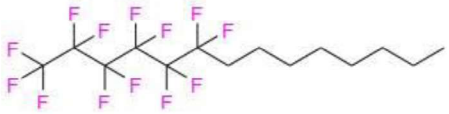
There are no data on the presence of perfluorohexyloctane in human milk, the effects on the breastfed infant, or the effects on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of MIEBO to an infant during lactation; however, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MIEBO.

8.4 Pediatric Use
The safety and effectiveness of MIEBO in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION
MIEBO™ (perfluorohexyloctane ophthalmic solution) is a sterile, clear and colorless liquid containing 100% perfluorohexyloctane, for topical ophthalmic use.

The active ingredient is 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorotetradecane and is a semifluorinated alkane. It has a molecular formula of $C_{14}H_{17}F_{13}$ and a molecular weight of 432.26 g/mol. The chemical structure is:



Perfluorohexyloctane is practically immiscible with water. It is miscible with ethanol and most organic solvents. Each multiple-dose bottle contains 3 mL of perfluorohexyloctane, 1.338 g/mL as a clear and colorless liquid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Perfluorohexyloctane, a semifluorinated alkane, contains 6 perfluorinated carbon atoms and 8 hydrogenated carbon atoms. Perfluorohexyloctane forms a monolayer at the air-liquid interface of the tear film which can be expected to reduce evaporation. The exact mechanism of action for MIEBO in DED is not known.

12.3 Pharmacokinetics
The pharmacokinetics of perfluorohexyloctane following topical ocular administration of MIEBO has not been quantitatively characterized in humans. A single pharmacokinetic (PK) study was conducted that showed low systemic perfluorohexyloctane blood levels after topical ocular administration. Perfluorohexyloctane was not metabolized by human liver microsomes in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of perfluorohexyloctane.

Perfluorohexyloctane was not mutagenic or clastogenic in a standard battery of genotoxicity tests, including a bacterial mutagenicity assay (Ames assay), an in vitro chromosome aberration assay using human peripheral lymphocytes, and an in vivo bone marrow micronucleus assay in rats.

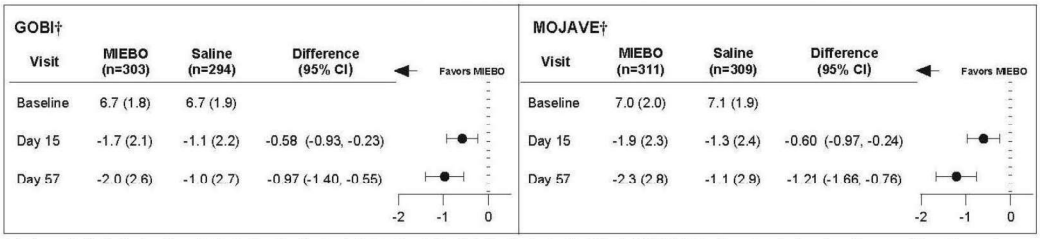
14 CLINICAL STUDIES

In two randomized, multicenter, double-masked, saline-controlled trials (GOBI and MOJAVE), a total of 1,217 patients with a history of DED and clinical signs of meibomian gland dysfunction were randomized to MIEBO or saline 0.6% (1:1 ratio) to evaluate safety and efficacy after receiving MIEBO four times daily (QID) for 57 days.The mean age of the 614 patients who received MIEBO was 57 years (range, 19-87 years). The majority of patients were female (76%).

Effects on Signs of Dry Eye Disease

Total corneal fluorescein staining (tCFS) was recorded at each study visit using a standardized grading system of 0-3 for each of the five areas on the cornea (inferior, superior, central, nasal, and temporal), totaling a maximum tCFS score for each eye of 15. The average baseline tCFS was approximately 6.7 in GOBI and 7.0 in MOJAVE. At Days 15 and 57, a statistically significant reduction in tCFS favoring MIEBO was observed in both studies (Figure 1).

Figure 1: Mean Change (Standard Deviation) from Baseline and Treatment Difference (MIEBO-Saline) in Total Corneal Fluorescein Staining (Study Eye) in 8-Week Study in Patients with Dry Eye Disease

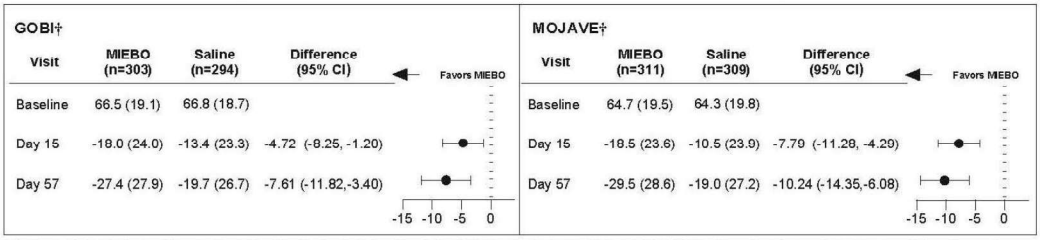


† A Phase 3, Multi-Center, Randomized, Double-Masked, Saline-Controlled Trial to Evaluate the Effect of NOV03 (Perfluorohexyloctane) on Signs and Symptoms of Dry Eye Disease Associated with Meibomian Gland Dysfunction

Effects on Symptoms of Dry Eye Disease

Eye dryness score was rated by patients using a visual analogue scale (VAS) (0=no discomfort, 100=maximal discomfort) at each study visit. The baseline VAS eye dryness average score was approximately 67 in GOBI and 65 in MOJAVE. At Days 15 and 57, a statistically significant reduction in VAS eye dryness score favoring MIEBO was observed in both studies (Figure 2).

Figure 2: Mean Change (Standard Deviation) from Baseline and Treatment Difference (MIEBO-Saline) in Eye Dryness Score (Study Eye) in 8-Week Study in Patients with Dry Eye Disease



† A Phase 3, Multi-Center, Randomized, Double-Masked, Saline-Controlled Trial to Evaluate the Effect of NOV03 (Perfluorohexyloctane) on Signs and Symptoms of Dry Eye Disease Associated with Meibomian Gland Dysfunction

16 HOW SUPPLIED/STORAGE AND HANDLING

MIEBO™ (perfluorohexyloctane ophthalmic solution) is supplied as a sterile, clear and colorless liquid in multiple-dose 5 mL polypropylene bottles with dropper tips and screw caps, packaged in a carton - NDC 24208-377-05.

Storage
Store MIEBO at 15ºC to 25ºC (59ºF to 77ºF). After opening, MIEBO can be used until the expiration date on the bottle.

17 PATIENT COUNSELING INFORMATION

Use with Contact Lenses
Advise patients that contact lenses should be removed prior to and for at least 30 minutes after administration of MIEBO.

Administration Instructions
Advise patients to instill one drop of MIEBO four times daily into each eye as depicted in the Administration Instructions *[see Dosage and Administration (2.2)]*.

Distributed by:
Bausch & Lomb Americas Inc.
Bridgewater, NJ 08807 USA

Patented. See https://patents.bausch.com for US patent information.

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