BAUSCH + LOMB

An Open-Label, Multicenter, Phase 4 Study to Evaluate Early Treatment Outcomes With Miebo™ in Subjects With Dry Eye Disease

CLINICAL STUDY PROTOCOL

STUDY #937

Developmental phase of study:	4
Study design:	Open-label, multicenter trial
Date:	15 Mar 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

ClinicalTrials.gov ID:
NCT06309953

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 US Code of Federal Regulations 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.

Protocol Review and Approvals

An Open-Label, Multicenter, Phase 4 Study to Evaluate Early Treatment Outcomes With Miebo™ in Subjects With Dry Eye Disease

Reviewed and approved:

[redacted]
Executive Director, Global Clinical Operations
Bausch & Lomb Incorporated
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Signature [redacted]

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Personnel Responsible for Conducting the Study

An Open-Label, Multicenter, Phase 4 Study to Evaluate Early Treatment Outcomes With Miebo™ in Subjects With Dry Eye Disease

Contract Research Organization
Sierra Clinical Services

[redacted]

Medical Monitor

[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

An Open-Label, Multicenter, Phase 4 Study to Evaluate Early Treatment Outcomes With Miebo™ in Subjects With Dry Eye Disease

PROTOCOL

STUDY #937

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 (and, if applicable, assent for children) 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:	An Open-Label, Multicenter, Phase 4 Study to Evaluate Early Treatment Outcomes With Miebo™ in Subjects With Dry Eye Disease
Protocol Number:	#937
Number of Clinical Sites:	Up to 8 clinical sites in the United States
Study Phase:	4
Primary Objective:	To evaluate early outcomes with Miebo treatment in subjects with dry eye disease (DED)
Overall Study Design:	
Structure:	This single-arm, open-label, multicenter, prospective study will consist of 4 study visits in subjects with DED. Subjects who sign the informed consent form at the Screening/Baseline Visit (Visit 1; Day 1) will be enrolled in the study and screened for eligibility to participate in the study. [redacted]. Following subjects'confirmation of eligibility and at least 15 minutes after the completion of the Schirmer's test, site staff will instill the first dose of Miebo and dispense Miebo to subjects. [redacted] Subjects will then commence at-home treatment with Miebo 4 times daily (QID) bilaterally and will continue this for approximately 14 days. At Visits 2, 3, and 4 (Days 3, 7, and 14, respectively), subjects will complete 1 [redacted] Follow-up Visit in the clinic at least 30 minutes and no longer than 4 hours post-dose.
Subject Duration:	This study consists of 4 study visits over a period of approximately 14 days.
Study Duration:	The entire duration of the study (from first subject first visit to last subject last visit) is expected to take approximately 5 months.

Dosage Instillation:	Site staff will instill the first dose of Miebo in the clinic at Visit 1. After that, subjects will self-administer Miebo QID bilaterally for approximately 14 days. The last dose prior to Visits 2, 3, and 4 will be instilled at least 30 minutes and no longer than 4 hours prior to the start of the visit.
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
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. Subject-reported history of DED in at least 1 eye for at least 6 months prior to Visit 1 b. Tear-film break-up time ≤5 seconds at Visit 1 c. Total corneal fluorescein staining score ≥4 and ≤11 (ie, sum of inferior, superior, central, nasal, and temporal) according to the National Eye Institute scale at Visit 1 d. Total meibomian gland dysfunction score ≥3 (range, 0–15) e. Unanesthetized Schirmer's test I score ≥5 mm 4. [redacted] 5. Able and willing to follow instructions, including participation in all trial assessments and visits
Exclusion Criteria:	Note: Ocular exclusion criteria are relevant to both eyes, such that meeting a criterion in either eye excludes the subject from the study 1. Had received Miebo as a prescription or as a study treatment in previous Miebo clinical studies 2. Have any clinically significant ocular surface slit-lamp findings at Visit 1 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. Pterygium j. Ocular or periocular rosacea 3. Use of any of the following ocular therapies within 60 days prior to Visit 1: Vuity®, any 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 within 6 months prior to Visit 1 5. Had received or removed a permanent punctum plug within 3 months (6 months for dissolvable 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) 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 within 3 months prior to Visit 1; have undergone refractive surgery 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 study treatment 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. Have corrected visual acuity (VA) worse than or equal to +0.7 logarithm of the minimum angle of resolution (logMAR), as assessed with Snellen chart at Visit 1 18. 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** • Mean change from baseline (CFB) in dry eye symptom severity at Visit 3 (Day 7 ± 1 day) **Exploratory** • [redacted]

	• [redacted]
Safety Outcomes:	• Adverse events (AEs; reported, elicited, and observed) • VA

Statistical Methods:

Continuous variables will be summarized using the mean, standard deviation (SD), 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 subjects who receive at least 1 drop of study treatment.

Per Protocol (PP) Set: The PP Set will consist of all subjects in the FAS with no protocol deviations expected to affect efficacy outcomes.

Primary Efficacy Analysis

[redacted]

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.

Sample Size Calculations:

A sample size of 75 subjects will have 80% power to detect a difference in means of 8.194, assuming a standard deviation of differences of 25, using a paired t-test with a 5% two-sided significance level. To allow for dropouts of up to 25%, approximately 100 subjects will be treated.

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
CFB	Change from baseline
CFS	Corneal fluorescein staining
CRF	Case Report Form
CRO	Contract Research Organization
DED	Dry eye disease
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDF	Financial disclosure form
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
IRB	Institutional Review Board
MGD	Meibomian gland dysfunction
NEI	National Eye Institute
[redacted]	[redacted]
PP	Per Protocol
QID	4 times daily
SAE	Serious adverse event
TBUT	Tear film break-up time
TEAE	Treatment-emergent adverse event
US	United States
VA	Visual acuity

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

Dry eye disease is defined by the International Dry Eye Workshop as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and is accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[2] Symptoms of DED, such as feeling of dryness, burning, sandy/gritty sensation, foreign body sensation, pain, and itchiness, can be debilitating. In addition, visual function–related symptoms, such as fluctuating vision with blinking, blurred vision, and difficulty with reading despite adequate visual acuity (VA), are an important and underestimated aspect of the disease. Therefore, DED negatively impacts quality of life comparably to other severe diseases,[3] and adverse effects on mental health including depression and anxiety have been observed.[4] Dry eye disease is a serious and chronic disorder that, if left untreated or undertreated, progressively damages the ocular surface and may lead to permanent vision loss due to corneal complications.[5]

Miebo™ is a sterile ophthalmic eye drop formulation, approved for the treatment of the signs and symptoms of DED associated with meibomian gland dysfunction (MGD). It is a single-component product consisting of 100% perfluorohexyloctane. Miebo addresses DED associated with MGD via a new physicochemical mode of action. Due to its low surface tension, it rapidly spreads across the ocular surface and interacts with the lipophilic part of the tear film forming a layer at the tear film air interface. Such a layer prevents excessive evaporation of the aqueous tear film component. In addition, perfluorohexyloctane penetrates meibomian glands, where it potentially interacts with and dissolves the altered, viscous meibum secreted in the glands. As a water-free, single-component product, it is free of excipients like oils, surfactants, and preservatives. Related advantages include convenient handling, improved tolerability, and a decrease in the visual disturbance upon instillations. Due to this mode of action, subjects with DED associated with MGD were considered to experience the greatest benefit from the treatment.[1]

This Phase 4 study is designed to evaluate early Miebo treatment perception and satisfaction in subjects with DED.

In lieu of an Investigator's Brochure, the Investigator is referred to the Miebo prescribing information for risk and benefit details (see Appendix D).[1]

5 Study Objectives and Purpose

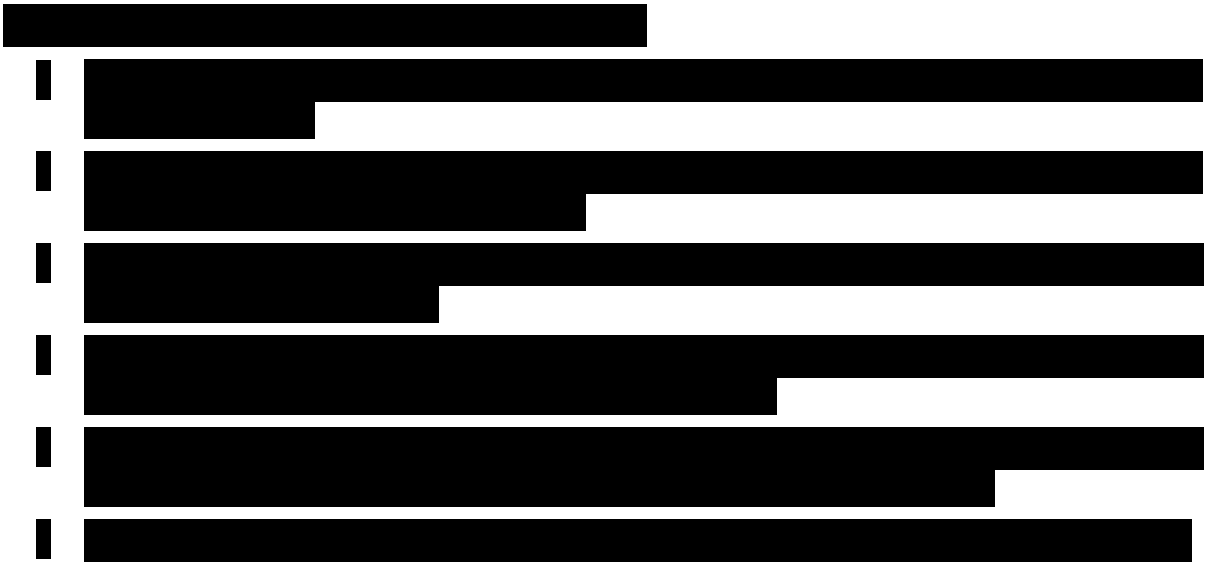
5.1 Objectives

The primary objective of the study is to evaluate early outcomes with Miebo treatment in subjects with DED.

5.2 Endpoints

5.2.1 Efficacy

The primary efficacy endpoint is the mean change from baseline (CFB) in dry eye symptom severity at Visit 3 (Day 7 ± 1 day).



5.2.2 Safety

The safety outcomes are as follows:

- Adverse events (AEs; reported, elicited, and observed)
- Visual acuity

6 Investigational Plan

6.1 Overall Study Design and Plan: Description

This single-arm, open-label, multicenter, prospective study will consist of 4 study visits in subjects with DED. Subjects who sign the informed consent form (ICF) at the Screening/Baseline Visit (Visit 1; Day 1) will be enrolled in the study and screened for eligibility to participate in the study. Subjects will be asked to complete an Early Outcomes Survey - Baseline Visit 1 (Pre-dosing) to obtain baseline data at the start of Visit 1, after Ocular Surface Disease Index Questionnaire administration. Following subjects'confirmation of eligibility and at least 15 minutes after the completion of Schirmer's test , site staff will instill the first dose of Miebo and dispense Miebo to subjects. Subjects will then complete 2 additional Early Outcomes Surveys - Baseline Visit 1 (Post-dosing) at 5 minutes and 1 hour post-dose.

Subjects will then commence at-home treatment with Miebo 4 times daily (QID) bilaterally and will continue this for approximately 14 days. At Visits 2, 3, and 4 (Days 3, 7, and 14, respectively), subjects will complete 1 Early Outcomes Survey - Follow-up Visit in the clinic at least 30 minutes and no longer than 4 hours post-dose.

6.2 Investigators

The study will be conducted in up to 8 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) also 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 who are enrolled in this study will be followed for approximately 14 days following initiation of study treatment.

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 5 months.

7 Selection and Withdrawal of Subjects

Approximately 100 subjects at up to 8 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 subject. 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 subject prior to performing any study-specific procedures that are not part of the Investigator's routine standard of care. An ophthalmic examination will be done 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. Subject-reported history of DED in at least 1 eye for at least 6 months prior to Visit 1
    b. Tear film break-up time (TBUT) ≤5 seconds at Visit 1
    c. Total corneal fluorescein staining (CFS) score ≥4 and ≤11 (ie, sum of inferior, superior, central, nasal, and temporal) according to the National Eye Institute (NEI) scale at Visit 1
    d. Total MGD score ≥3 (range, 0–15)
    e. Unanesthetized Schirmer's test I score ≥5 mm
4. Ocular Surface Disease Index ≥25 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 (Note: Ocular exclusion criteria are relevant to both eyes, such that meeting a criterion in either eye excludes the subject from the study):

1. Had received Miebo as a prescription or as a study treatment in previous Miebo clinical studies
2. Have any clinically significant ocular surface slit-lamp findings at Visit 1 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. Pterygium
    j. Ocular or periocular rosacea
3. Use of any of the following ocular therapies within 60 days prior to Visit 1: Vuity®, any 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 within 6 months prior to Visit 1
5. Had received or removed a permanent punctum plug within 3 months (6 months for dissolvable 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) 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 within 3 months prior to Visit 1; have undergone refractive surgery 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 study treatment
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. Have corrected VA worse than or equal to +0.7 logarithm of the minimum angle of resolution (logMAR), as assessed with Snellen chart at Visit 1
18. 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 after signing the ICF 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 will be followed according to Section 11.3.5.

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
- 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
- Noncompliance 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 last scheduled study visit. Ongoing AEs will be followed as described in Section 11.3.5. 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, 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

Approximately 100 subjects will receive Miebo (this is a single-arm study).

8.1.1 Treatment Allocation

All subjects will receive Miebo QID bilaterally for approximately 14 days.

8.1.2 Randomization Method

Not applicable; this is a single-arm study.

8.2 Masking

Not applicable; this is an open-label study.

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, are prohibited during the course of the study. 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 12.6.3.2. 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 (100% 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 E).

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 by 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, unused 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 questionnaire
- Early Outcomes Survey
- 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	Visit Time and Window
Visit 1 (Screening/Baseline Visit)	Day 1
Visit 2	Day 3 + 1
Visit 3	Day 7 ± 1
Visit 4	Day 14 ± 2

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

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

The following study measurements will be collected:

- Informed consent/Health Insurance Portability and Accountability Act

- Demographics
- Medical/Surgical history
- Urine pregnancy test (for female subjects of childbearing potential)
- Previous/Concomitant medication
- [redacted]
- [redacted]
- Visual acuity
- Tear film break-up time
- Total CFS score
- Meibomian gland dysfunction (MGD score)
- Schirmer's test
- Inclusion/Exclusion criteria

Following subject's confirmation of eligibility, the following will take place starting from at least 15 minutes after the completion of Schirmer's test:

- Instillation of study treatment (instilled bilaterally by site staff)
- [redacted]
- Dispensation of study treatment
- Dispensation of dosing diary
- Adverse event query

10.1.2 Visit 2: Day 3 + 1 day

The following study measurements will be collected:

- Concomitant medication
- Adverse event query
- Early Outcomes Survey – Follow-up Visit
- Dosing diary review by dedicated team member

10.1.3 Visit 3: Day 7 ± 1 day

The following study measurements will be collected:

- Concomitant medication
- Adverse event query

- [redacted]
- Dosing diary review by dedicated team member

10.1.4 Visit 4: Day 14 ± 2 days

The following study measurements will be collected:

- Concomitant medication
- Adverse event query
- [redacted]
- [redacted]
- Visual acuity
- Dosing diary review by dedicated team member
- Collection of study treatment and dosing diary
- Trial exit

10.1.5 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.

10.1.6 Missed Visits

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.

10.1.7 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 11.3.5 for follow-up of AEs following study exit.

10.2 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).

10.2.1 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

Efficacy will be evaluated using the following assessments:

- [redacted]
- [redacted]

11.2 Evaluation of Safety

Safety will be evaluated using the following assessments:

- Adverse events
- Visual acuity

11.3 Adverse Events

Both eyes must be examined for the presence/absence of AEs at all visits, whether scheduled or not. 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.

11.3.1 Adverse Events Definitions

For the purposes of this study, AEs include all ocular AEs/SAEs, 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

11.3.2 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 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 on the CRF. During the study, the Investigator should treat the study subject as appropriate to ensure his/her safety and welfare. Refer to Section 11.3.5 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)

11.3.3 Evaluations

When evaluating AEs, the Investigator must determine if the event is serious (refer to Section 11.3.1 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

11.3.4 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/Contract Research Organization (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 SAE 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.

11.3.5 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.

11.3.6 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

12.1.1 Efficacy Endpoints

[redacted]

12.1.2 Safety Outcomes

The safety outcomes are detailed in Section 5.2.2.

12.2 Hypotheses

The null hypothesis (H_0) is that the mean difference between the dry eye symptom severity values on Day 7 and at baseline (μ) 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 75 subjects will have 80% power to detect a difference in means of 8.194, assuming a standard deviation of differences of 25, using a paired t-test with a 5% two-sided

significance level. To allow for dropouts of up to 25%, approximately 100 subjects will be treated.

12.4 Analysis Populations

Full Analysis Set (FAS): The FAS will consist of all subjects who receive at least 1 drop of study treatment.

Per Protocol (PP) Set: The PP Set will consist of all subjects in the FAS with no protocol deviations expected to affect efficacy outcomes.

12.5 Statistical Analysis

12.5.1 General Considerations

Summaries for continuous variables will include the sample size (n), mean, standard deviation, median, minimum, and maximum. Summaries for categorical variables will include frequencies and percentages. Missing safety data will not be imputed.

12.5.2 Primary Effectiveness Analyses

[redacted]

12.5.3 Safety Analyses

12.5.3.1 Adverse Events

The number and percent of subjects with specific treatment-emergent adverse events (TEAEs) and the total number of occurrences of each TEAE 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.

12.5.3.2 Subject Demographics and Baseline Characteristics

Race, sex, and age groups will be presented using discrete summary statistics. Age will also be presented using continuous summary statistics. Medical history data will be presented in a listing.

12.5.3.3 Prior and Concomitant Medications

Concomitant medication use will be summarized using the number and percentage of subjects using each type of medication by drug class and preferred term. Ocular and non-ocular medications will be presented in separate tables. Prior medications will be included in a listing but not included in the concomitant medication summary.

12.5.3.4 Subject Disposition

Subject disposition will be summarized using number and percentage of subjects. The reasons for study discontinuation will also be summarized.

12.5.3.5 Treatment Adherence

Treatment adherence will be computed as the number of doses administered divided by the number of doses expected × 100%. Adherence will be summarized using continuous and categorical (less than 80%, 80% to 120%, greater than 120%) summary statistics by treatment group.

12.5.3.6 Treatment Exposure

Duration of treatment exposure will be defined as the total number of days from treatment initiation until last dose date, as recorded at Visit 1 and the study exit CRF page. Duration of exposure to study treatment will be calculated as:

Duration = date of last dose – date of treatment initiation + 1.

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 Multicenter Issues

Data will be collected from multiple sites under the same protocol with the intention of pooling the data.

12.6.3 Multiplicity Issues

No adjustment of the primary endpoint analysis for multiplicity is required.

12.6.3.1 Interim Analysis

No interim analysis is planned for this study.

12.6.3.2 Protocol Deviations

The number of subjects within each type of important protocol deviation will be presented using discrete summary statistics. Important protocol deviations will be identified prior to locking the database.

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 Code of Federal Regulations Parts 11, 50, 54, 56, 312, 314; 42 USC 282(j); ICH GCP E6 (R2) (International Council for Harmonisation, Guidance E6); 42 USC 282(j); 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 noncompliant 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 noncompliant 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 of 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 (eg, 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 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

All study data generated as a result of this study will be regarded as confidential until appropriate analysis and review by the Sponsor or its designee and the Investigator(s) are completed. The results of the study may be published or presented by the Investigator(s) after the review by, and in consultation and agreement with, the Sponsor, and such that confidential or proprietary information is not disclosed.

Prior to any publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Sponsor or its designee, for comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to Bausch & Lomb Incorporated products and activities receive fair, accurate, and reasonable presentation.

15 References

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7. Sheppard JD, Kurata F, Epitropoulos AT, Krösser S, Vittitow JL; MOJAVE Study Group. NOV03 for signs and symptoms of dry eye disease associated with meibomian gland dysfunction: the randomized phase 3 MOJAVE study. *Am J Ophthalmol*. 2023;252:265–274.
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9. Protzko E, Segal B, Korenfeld M, Krösser S, Vittitow J. Long-term safety and efficacy of perfluorohexyloctane ophthalmic solution for the treatment of patients with dry eye disease: the KALAHARI study. *Cornea*. 2023 Nov 3. Epub ahead of print.

16 Appendices

16.1 Appendix A Study Flow Chart

Visit Procedure	Screening/Baseline Visit 1 Day 1 [1]	Visit 2 Day 3 (+1 day)	Visit 3 Day 7 (±1 day)	Visit 4 Day 14 (±2 days)
Informed consent/HIPAA	X			
Demographics	X			
Medical/Surgical history	X			
Urine pregnancy test (for female subjects of childbearing potential)	X			
Previous/Concomitant medication	X	X	X	X
AE query	X	X	X	X
[redacted]				
VA [2]	X			X
TBUT [2]	X			
Total CFS score (NEI scale) [2]	X			
Meibomian gland assessment (MGD score) [2]	X			
Schirmer's test [2]	X			
Inclusion/Exclusion criteria	X			
Instillation of study treatment (by site staff)	X[3]			
Early OutcomesSurvey – Baseline Visit 1 (Post-dosing)	X [4]			
Dispensation of study treatment	X			
Dispensation of dosing diary	X			
Review of dosing diary		X	X	X
Collection of study treatment and dosing diary				X
Trial exit				X

AE, adverse event; CFS, corneal fluorescein staining; HIPAA, Health Information Portability and Accountability Act; MGD, meibomian gland dysfunction; NEI, National Eye Institute; [redacted] Disease Index; TBUT, tear film break-up time; VA, visual acuity; VAS, visual analog scale.

[1] Should a subject fail to meet eligibility requirements on Screening, further baseline assessment will be halted.

[2] Assessment to be conducted in the order as depicted in the study flow chart, at applicable visits.

[3] Instillation of study treatment (by study staff) should occur at least 15 minutes after completion of Schirmer's test.

[4] Survey to be completed by subject at 5 minutes and 1 hour post-dose.

[5] Survey to be completed by subject in the clinic at least 30 minutes and no longer than 4 hours post-dose.

16.2 Appendix B Methods of Clinical Evaluations

Any changes to the procedures described in this appendix will be provided under separate cover.

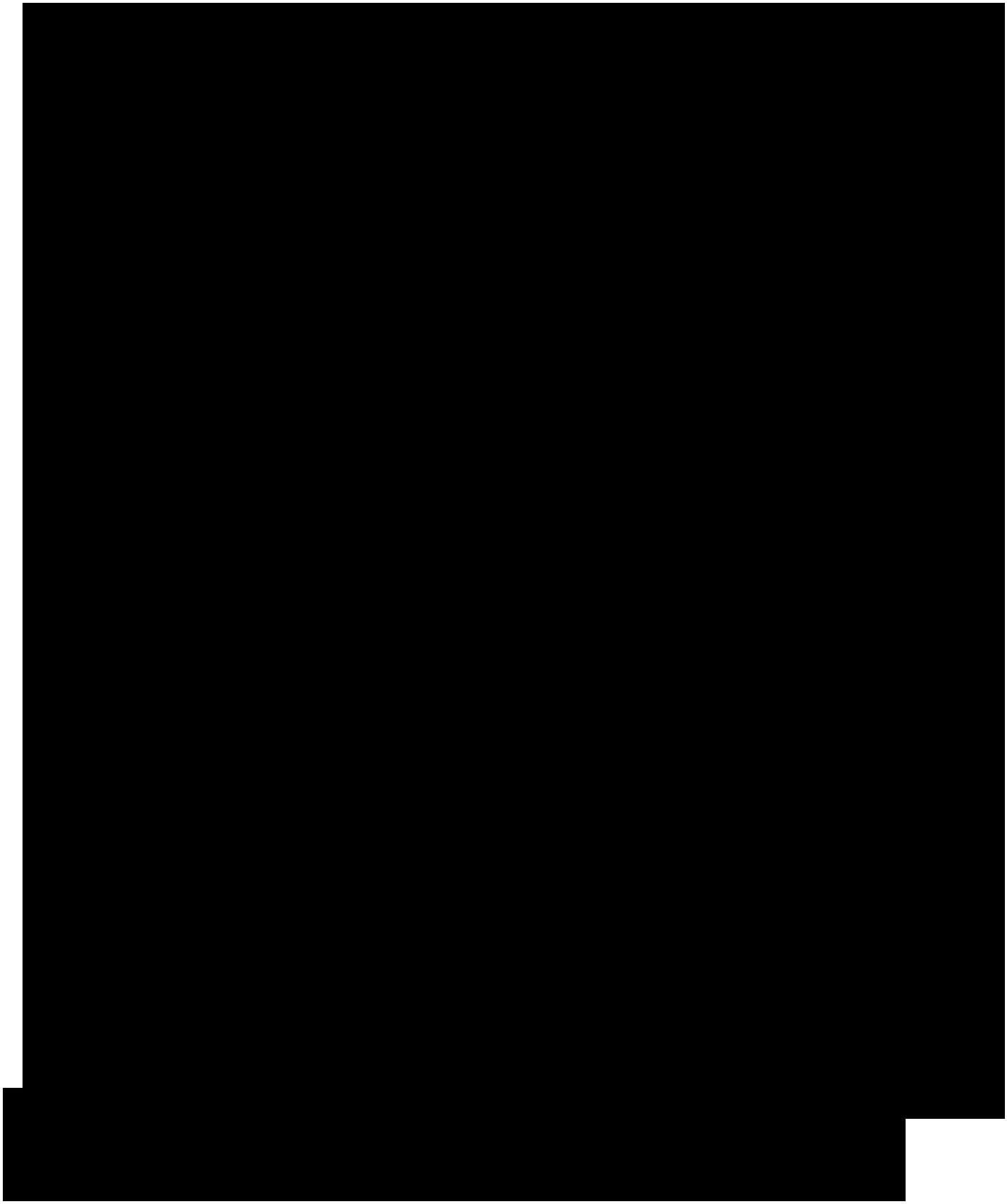
[redacted]

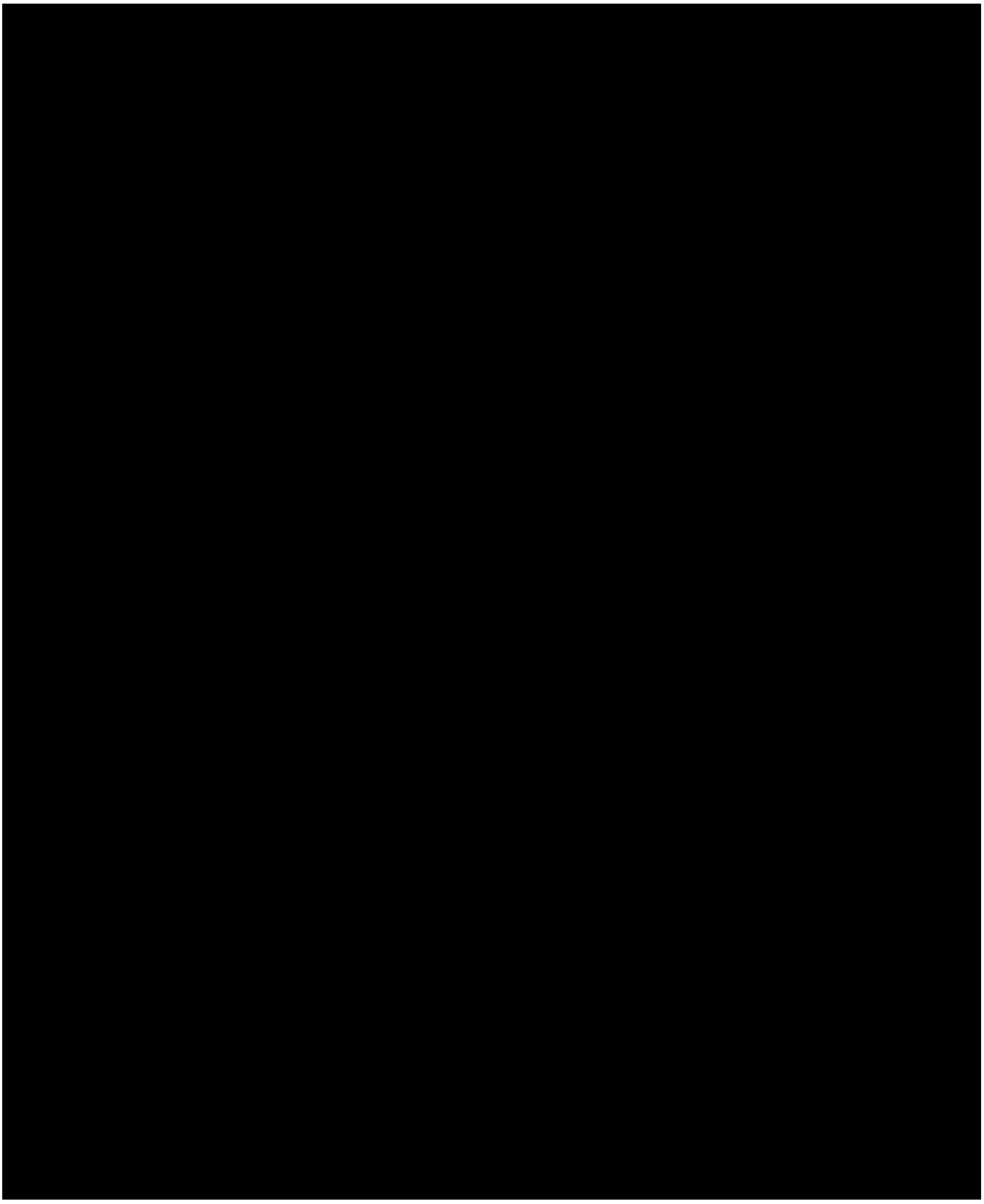
[redacted]

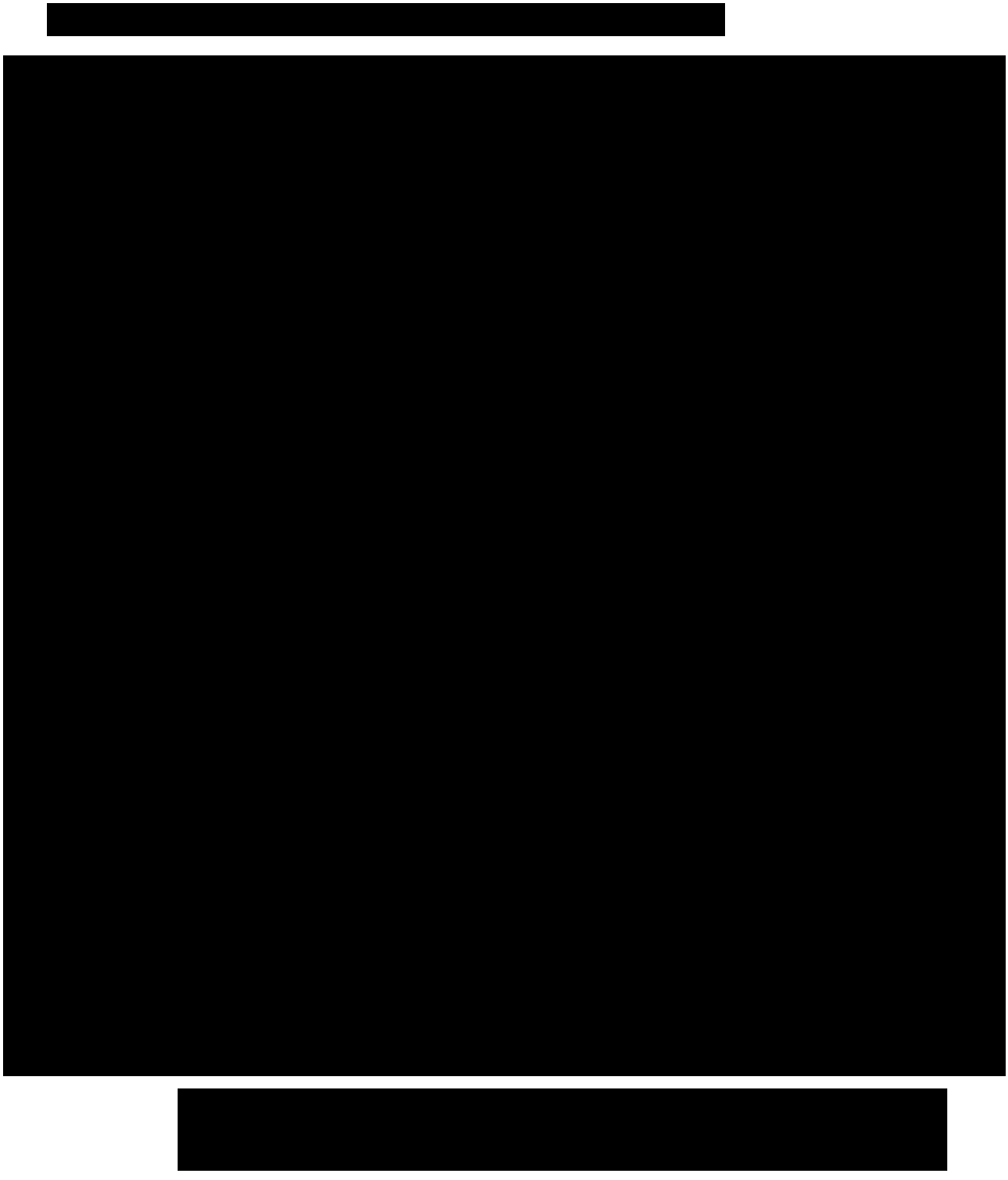
[redacted]

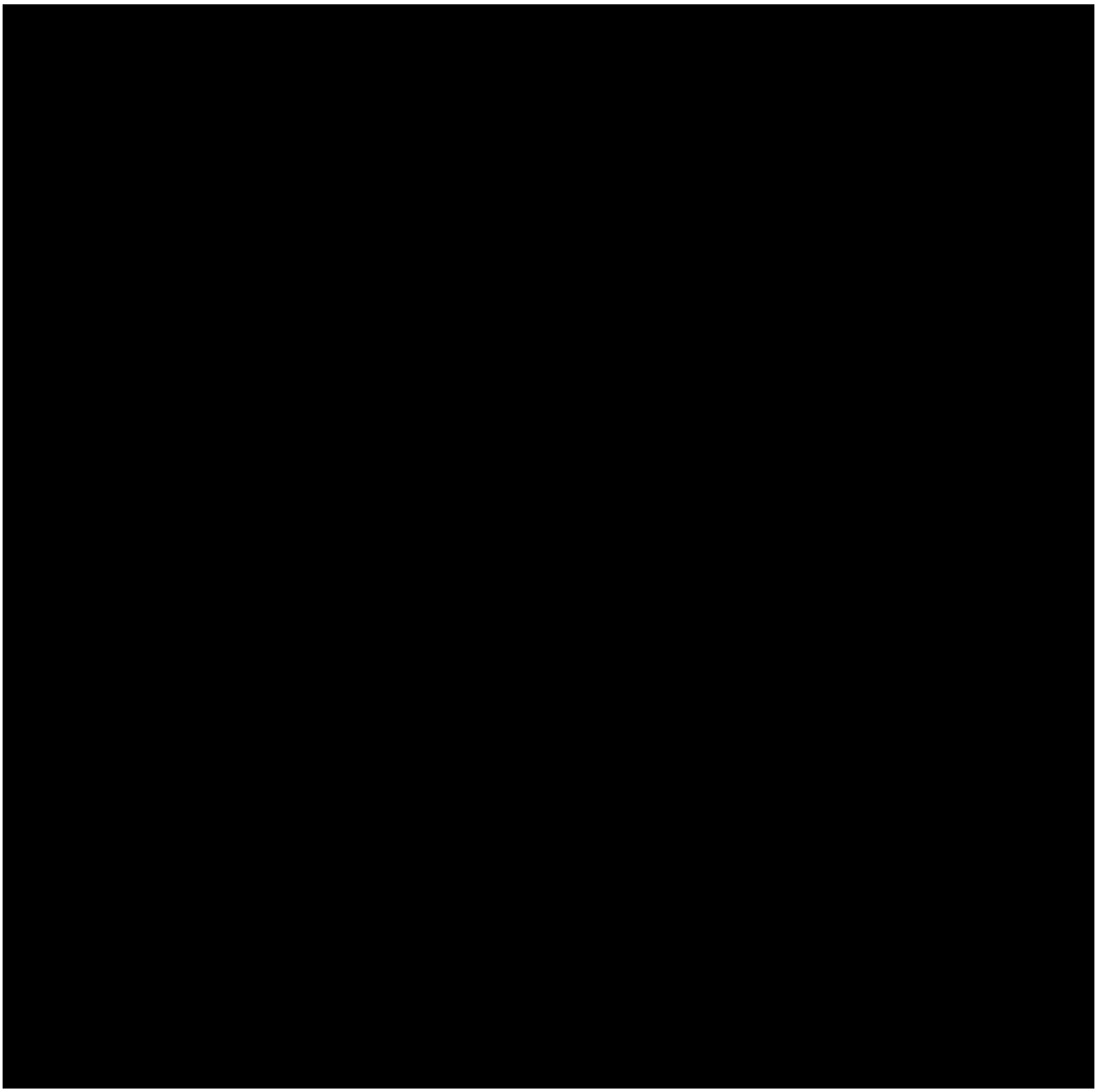
[redacted]

[redacted]









16.5 Appendix E 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

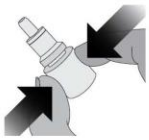
1 INDICATIONS AND USAGE
MIEBO™ (perfluorohexyloctane ophthalmic solution) is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

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

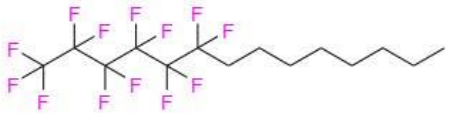
There are no data on the presence of perfluorohexyloctane in human milk, the effects on the breastfed infant, or the effects on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of MIEBO to an infant during lactation; however, the developmental and 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.

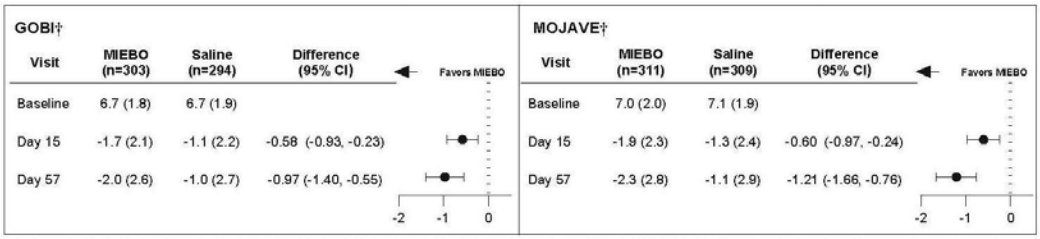
14 CLINICAL STUDIES

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

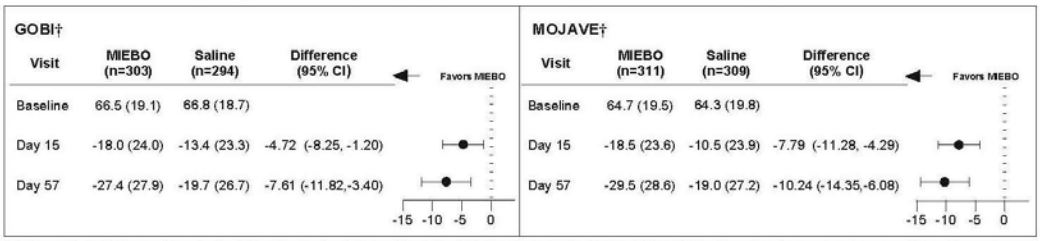


† A Phase 3, Multi-Center, Randomized, Double-Masked, Saline-Controlled Trial to Evaluate the Effect of NOV03 (Perfluorohexyloctane) on Signs and Symptoms of Dry Eye Disease Associated with Meibomian Gland Dysfunction

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



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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

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