TITLE PAGE

Clinical Trial Protocol: 922

Protocol Title:	Effects of NOV03 on the Tear Film in Subjects with Dry Eye Disease
Protocol Number:	922
Study Phase:	4
Investigational Product Name:	Perfluorohexyloctane (NOV03; MIEBO™)
IND Number:	130558
Indication:	Signs and symptoms of dry eye disease
Investigator:	[redacted]
Sponsor:	Bausch & Lomb Incorporated 400 Somerset Corporate Boulevard Bridgewater, NJ 08807
Contract Research Organization:	NA
IRB/IEC:	Miami VA Institutional Review Board

	Date
Original Protocol:	23rd Jan 2023
Amendment 2:	16th Oct 2023

Confidentiality Statement

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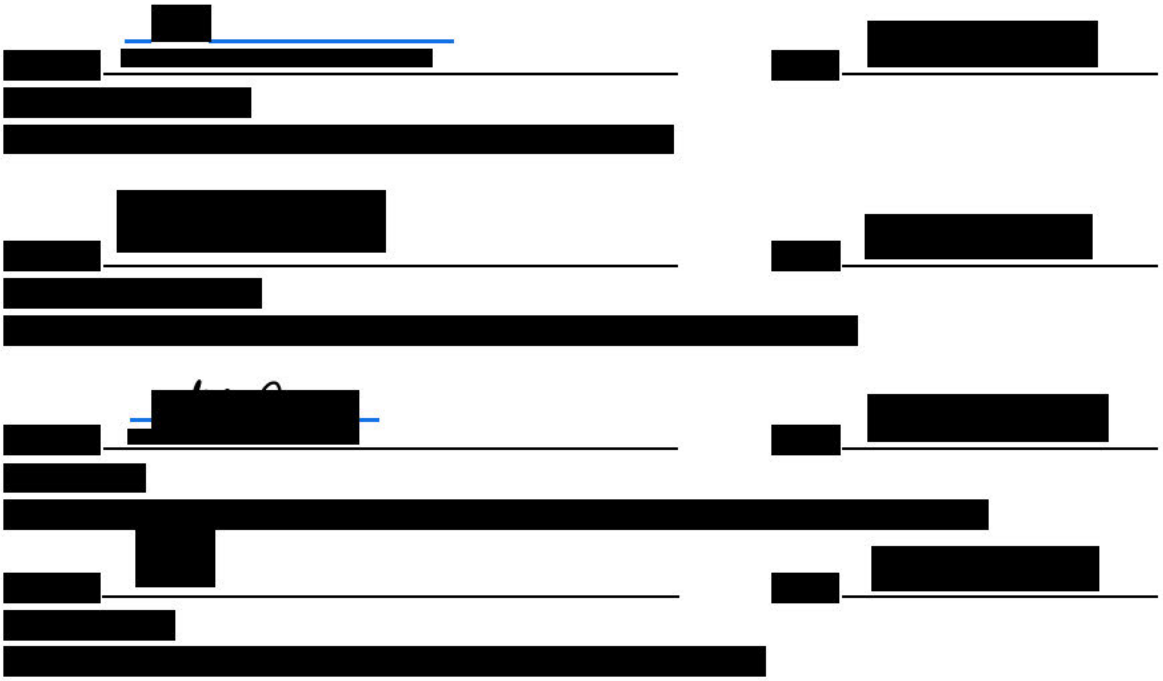
SPONSOR APPROVAL PAGE

Protocol Title:	Effects of NOV03 on the Tear Film in Subjects with Dry Eye Disease
Protocol Number:	922
Final Date:	16th Oct 2023

This clinical study protocol was authored by [redacted].

The following personnel approve this protocol.



INVESTIGATOR'S SIGNATURE

Protocol Title:	Effects of NOV03 on the Tear Film in Subjects with Dry Eye Disease
Protocol Number:	922
Final Date:	16th Oct 2023

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by Ora and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

[redacted]

[redacted]

SPONSOR PERSONNEL

Sponsor:	Bausch & Lomb Incorporated 400 Somerset Corporate Boulevard Bridgewater, NJ 08807
Sponsor Representative:	[redacted]

MEDICAL MONITOR

Medical Monitor:	[redacted]

SYNOPSIS

Protocol Title:	Effects of NOV03 on the Tear Film in Subjects with Dry Eye Disease
Protocol Number:	922
Investigational Product:	Perfluorohexyloctane (PFHO; MIEBO™; NOV03)
Study Phase:	4
Primary Objective(s):	Determine the effect of a single instillation of PFHO on the thickness and evaporation rate of the mucus-aqueous layer of the tear film
Exploratory Objective(s):	[redacted]
Overall Study Design:	
Structure:	This pilot, open label, single-arm, single-center study will consist of 2 study visits in subjects with dry eye disease associated with MGD. A Screening Visit will occur to verify subjects are eligible to participate followed by an Assessment Visit to evaluate tear film parameters at baseline and over approx. 4 hours following a single instillation of PFHO. *Screening Visit:* At Visit 1, the subjects will complete the informed consent process followed by a screening visit to determine the presence of dry eye and associated MGD, which will include slit-lamp exam, visual acuity (VA), intraocular pressure (IOP), meibomian gland dysfunction (MGD) assessment, Schirmer test, tear film break up time (TFBUT), corneal fluorescein staining (CFS), and ocular surface disease index (OSDI). *Assessment Visit:* At Visit 2, a slit lamp examination and two baseline tear film assessments will be performed (tear film parameters: mucus-aqueous layer thickness (MALT); mucus-aqueous thinning rate (MALTR); [redacted] Then 1 drop of PFHO will be instilled into both eyes (the study eye will be the eye with the highest corneal fluorescein staining). The above assessments will be repeated at multiple time points up to 4 hours post-instillation (time points: 5±1 min, 15±2 min, 30±2 min, 60±5 min, 120±10 min, 240±10 min). Any adverse events will be recorded.

Duration:	This trial consists of 2 office visits over a period of approximately 2 weeks.
Controls:	None (single-arm study)
Dosage Instillation:	At Visit 2, a designated clinical staff member or the investigator will instill 1 drop of PFHO into each eye.
Summary of Visit Schedule:	**Visit 1 (Day -14 to Day 0):** Screening / Informed Consent **Visit 2 (Day 1):** Tear film parameters before and after PFHO instillation
Measures Taken to Reduce Bias:	NA
Study Population Characteristics:	
Number of Subjects:	Approximately 50 subjects will be screened in order to enroll approximately 30 subjects
Condition/Disease:	Dry eye disease associated with meibomian gland dysfunction
Inclusion Criteria:	**General/Ocular Inclusion Criteria** 1. Will be at least 18 years of age at the time of consent. 2. Able to provide written voluntary informed consent. 3. Have a subject-reported history of DED in both eyes for at least 6 months prior to Visit 1. 4. Have Tear film break-up time (TFBUT) <10 sec at Visit 1. 5. Have Meibomian Gland Dysfunction (MGD) defined as total MGD score ≥ 3 (secretion of 5 central glands on lower eyelid will be evaluated, each will be scored from 0-3; 0 = normal, 1 = thick/yellow, whitish, particulate 2 = paste; 3 = none/occluded; total score will range from 0-15) at Visit 1. 6. Have a total corneal fluorescein staining score of ≥2 and ≤11 (i.e. sum of inferior, superior, central, nasal, and temporal) according to the National Eye Institute (NEI) scale at Visit 1. 7. Have at least one eye that satisfies all criteria for 4-6 above at Visit 1. 8. Is able to fix his/her gaze for a minute, i.e. can see the fixation target and with no nystagmus 9. Is able and willing to follow instructions, including participation in all trial assessments and visits.
Exclusion Criteria:	**General/Ocular Exclusion Criteria** 1. Have any clinically significant ocular surface slit-lamp findings at Visit 1 and Visit 2 and/or in the opinion of

	the Investigator had any findings that may have interfered 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 that caused incomplete eyelid closure f. abnormal cornea shape (keratoconus) g. corneal epithelial defect or significant confluent staining or filaments h. history of herpetic keratitis. i. has a pterygium in either eye. j. ocular or periocular rosacea that in the judgement of the Investigator interfered with the trial 2. Has used any topical ocular steroids treatments, prescription dry eye therapy including varenicline nasal spray, or topical anti-glaucoma medication within 60 days prior to Visit 1. 3. Have had a LipiFlow procedure within 1 month prior to Visit 2. 4. Have received a permanent punctum plug within 3 months (6 months for dissolvable punctum plugs) prior to Visit 2. Have removed a permanent punctum plug within 1 month prior to Visit 2. 5. Have used any eye drops (prescription or artificial tears) and/or TrueTear™ device (intranasal tear neurostimulator) within 24 hours before Visit 2. 6. Have active ocular allergies or ocular allergies that are expected to be active during the trial period. 7. Have worn contact lenses within 1 month of Visit 1 or anticipate using contact lenses during the trial. 8. Have undergone intraocular surgery or ocular laser surgery within the previous 6 months or had any planned ocular and/or lid surgeries over the trial period. 9. Have an active ocular or systemic infection (bacterial, viral, or fungal), including fever requiring treatment with antibiotics. 10. Is a woman who was pregnant, nursing or planning a pregnancy. 11. Is a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception included: hormonal (oral,

	implantable, injectable, or transdermal contraceptives); mechanical (spermicide in conjunction with a barrier such as a diaphragm or condom); intrauterine device; or surgical sterilization of partner. For non-sexually active females, abstinence could have been 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. 12. Has an uncontrolled systemic disease in the opinion of the Investigator will interfere with the trial. 13. Has a known allergy and/or sensitivity to the investigational drug. 14. Has used any oral medications known to cause ocular drying (e.g., antihistamines, antidepressants, etc.) on a non-stable regimen within 1 month prior to Visit 1 or is expected to be unstable during the trial. 15. Have taken isotretinoin (e.g. Accutane, Myorisan, Claravis, Amnesteem) within 6 months of Visit 1. 16. Has corrected VA worse than or equal to logarithm of the minimum angle of resolution (LogMAR), +0.7 as assessed with Early Treatment Diabetic Retinopathy Study (ETDRS) charts in both eyes at Visit 1. 17. Is currently enrolled in an investigational drug or device study or had used an investigational drug or device within 60 days of Visit 2.
Study Formulations:	**Test Article:** Perfluorohexyloctane
Efficacy Measures and Endpoints:	**<u>Primary Efficacy Measures</u>** • Mucus-aqueous layer thickness (MALT) and thinning rate (MALTR) at baseline and at multiple time points following instillation of PFHO [redacted]
Safety Measures:	• Adverse Events (AEs; reported, elicited and observed)

General Statistics

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

<u>Analysis Populations</u>

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

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

Safety Analysis

The number and percentage of subjects with specific treatment-emergent adverse events (TEAEs) will be summarized for each treatment group. The number of subjects will be tabulated by MedDRA System Organ Class and preferred term within each system organ class.

Primary Efficacy Analyses

The primary comparison in this trial is CFB in MALTR and MALT following a single instillation of PFHO. Change from baseline (post-instillation minus baseline, average of 2 baseline readings) at each post instillation time point will be summarized using continuous summary statistics.

Hypotheses

For each primary endpoint at each post-instillation timepoint, the null hypothesis is that the mean change from baseline is zero. The alternative hypothesis is that the mean change from baseline is not zero.

Methods

Each primary endpoint will be summarized by post-instillation timepoint using continuous summary statistics for the FAS. Paired t-tests will be used to test the statistical hypotheses. Each null hypothesis will be rejected if the corresponding two-sided p-value is less than 0.05.

Sample Size Calculations

A sample size of 30 subjects will have 80% power to detect a difference in means of 0.529 times the standard deviation of the paired differences, using a paired t-test with a 5% two-sided significance level.

Summary of Known and Potential Risks and Benefits to Human Subjects

Refer to MIEBO Prescribing Information (Appendix 3).

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LIST OF ABBREVIATIONS

AE	adverse event
BCVA	best-corrected visual acuity
CFB	Change from baseline
CFS	Corneal Fluorescein Staining
CRF	case report form
DED	Dry Eye Disease
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
FAS	Full Analysis Set
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
IBI	Inter-Blink-Interval
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IP	investigational product
IRB	institutional review board
ITT	intent to treat
LBUT	Lipid Break Up Time
LLT	Lipid Layer Thickness
LMU	Lipid Map Uniformity
MALT	Muco-Aqueous Layer Thickness
MALTR	rate of change of the MALT value
MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian Gland Dysfunction
NEI	National Eye Institute
NOV03	Development name for perfluorohexyloctane (MIEBO)
OD	right eye
OS	left eye
OU	both eyes
OSDI©	Ocular Surface Disease Index
PP	per protocol
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	statistical analysis plan

SD	standard deviation
SDC	Statistics and Data Corporation
SOP	standard operating procedure
TEAEs	Treatment-emergent Adverse Events
TFBUT	Tear Film Break-up Time
VA	Visual Acuity

1 INTRODUCTION

Dry eye disease (DED) is a common ocular condition with approx. 18 million currently diagnosed with the disease in the US, and with many more people remaining undiagnosed (Farrand, et al. 2017; MarketScope 2020). Typical clinical signs of DED include decreased tear fluid, tear film instability, and ocular surface damage with associated symptoms of dryness, grittiness, burning, stinging, light sensitivity, and blurred vision (Bartlett, et al. 2015; Craig, et al. 2017). Previously, DED was characterized into 2 main types, aqueous deficient (in which lacrimal secretion is reduced) or evaporative (in which evaporation of aqueous from the tear film is excessive) (Bron, et al. 2017; Craig, et al. 2017). It is now recognized that DED is on a continuum and that the most common cause of the disease is excessive evaporation due to conditions such as meibomian gland dysfunction (MGD), a reduced blink rate (for example due to long-term use of digital displays), certain drugs, contact lens use, and some eyelid disorders (Craig, et al. 2017). The most common cause of evaporative DED is MGD, which is present in approx. 9 out of 10 patients with the disease (Lemp, et al. 2012; Rabensteiner, et al. 2018; Badian, et al. 2021). MGD results in thinning of the tear film lipid layer leading to excessive evaporation of the underlying aqueous layer and associated tear film instability, hyperosmolarity, desiccation stress, and loss of mucin-producing goblet cells, which all cascade into a continuing cycle of inflammation and ocular surface damage (Baudouin, et al. 2016; Craig, et al. 2017).

Current prescription DED therapies are aimed at reducing inflammation or increasing tear secretion but are not directly targeted at the main root cause of DED, namely excessive evaporation. Perfluorohexyloctane ophthalmic solution (PFHO; trade name MIEBO™; development name NOV03) is an FDA approved, water-free, non-steroidal, preservative-free eye drop indicated for treatment of the signs and symptoms of DED. PFHO belongs to a unique class of compounds known as semifluorinated alkanes which have low surface tension and amphiphilic properties due to a lipophobic/aerophilic fluorinated segment and a lipophilic hydrocarbon segment (Meinert and Roy 2000). PFHO is thought to act as a functional replacement for the lipid layer by spreading rapidly over the ocular surface to form a long-lasting, anti-evaporative barrier (Agarwal, et al. 2018; Krosser 2018; Borchman 2022). Therefore, PFHO may prevent excessive evaporation of the aqueous component of the tear film in patients with evaporative DED, thus reducing the signs and symptoms of DED as has been consistently demonstrated in both a Phase 2 study and 2 Phase 3 clinical studies (Tauber, et al. 2021; Sheppard 2022; Tauber, et al. 2022).

To date, the effect of PFHO on inhibiting evaporation *in vivo* has not been demonstrated and there is limited available information regarding how PFHO modulates the lipid and aqueous tear film layers; in addition, demonstration of inhibition of evaporation by PFHO is currently limited to *in vitro* data. The Tear Film Imager (AdOM, Advanced Optical Technologies Ltd, Lod, Israel) combines spectrometry and imaging to quantitatively assess changes in the tear lipid and aqueous layers with nanometer resolution. There are 6 tear film parameters which are measured simultaneously with the TFI:

1. MALT: the average Muco-Aqueous Layer Thickness in nanometer resolution
2. MALTR: the rate of change of the MALT value in nm/sec, as measured in the steady state phase of a representative blink
3. LLT: the average Lipid Layer Thickness in nanometer resolution
4. LBUT: the Lipid Break Up Time (in sec) which strongly correlates to tear breakup time
5. IBI: the average Inter-Blink-Interval (in sec).
6. LMU: the average Lipid Map Uniformity measured on the Lipid map taken about 1 second after the blink which allows quantitation of the spatial variation of lipid across the cornea.

Several studies have been published which evaluated tear film parameters with the TFI. Cohen et al used the TFI to demonstrate that the distribution of lipid in eyes with DED is nonuniform and has more variance over the corneal surface as compared to normal eyes and hypothesized that this nonuniformity may be the cause of increased evaporation of the aqueous tear film layer in DED (Cohen, et al. 2020). In addition, the parameters of MALT and LBUT have been shown to be significantly thinner and shorter, respectively, in patients with DED vs controls (Segev, et al. 2020). Data from a recent study has also demonstrated correlation of specific tear film parameters with certain DED symptoms and/or signs (Arita, et al. 2022). Lastly, unpublished pilot data suggests that PFHO may decrease the MALTR and thus the rate of evaporation in a subject with evaporative DED.

2 STUDY OBJECTIVES

The primary objective is to test the hypotheses (twelve) that the effects of a single instillation of PFHO in the study eye on the thickness and evaporation rate of the mucus-aqueous layer of the tear film at six time points between 5 minutes and 4-hours (5±1 min, 15±2 min, 30±2 min, 60±5 min, 120±10 min, 240±10 min) after instillation are nominally statistically significant in adults with established currently untreated bilateral dry eye disease associated with meibomian gland dysfunction who are not recent users of contact lenses or any medication that could affect ocular dryness.

[redacted]

3 CLINICAL HYPOTHESES

It is hypothesized that PFHO will increase MALT and decrease MALTR in a population of subjects with dry eye disease associated with MGD.

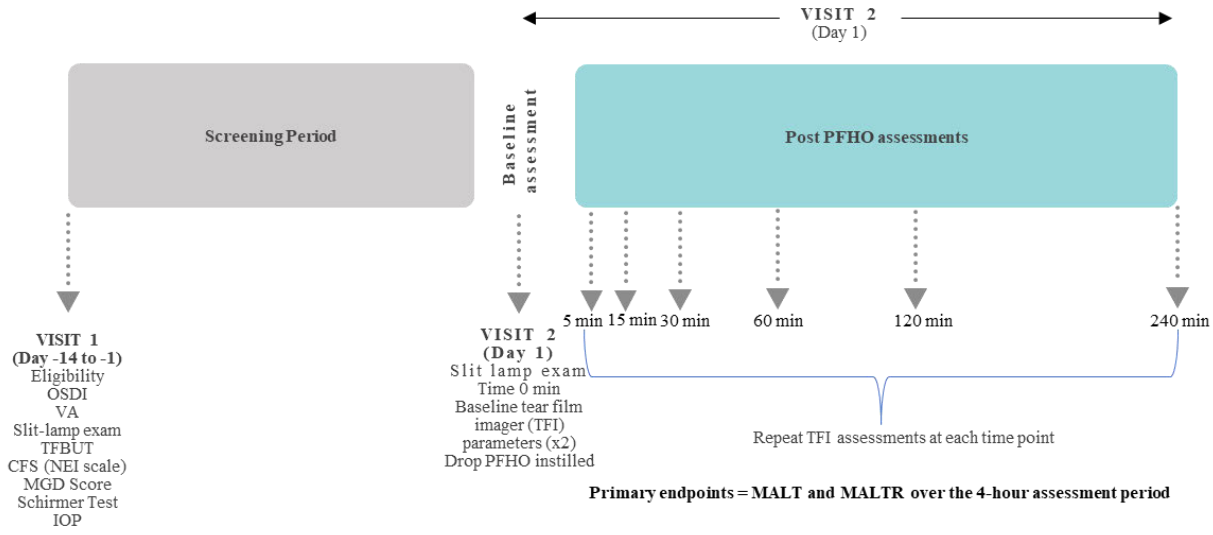
4 OVERALL STUDY DESIGN

This is a pilot, open label, single arm study.

The study will consist of 2 study visits: a Screening Visit to verify subjects are eligible to participate and an Assessment study visit to evaluate tear film parameters at baseline and over approx. 4 hours following a single instillation of PFHO (Figure 1).

At Visit 1, the subjects will complete the informed consent process followed by a screening visit to determine the presence of dry eye and associated MGD, which will include slit-lamp exam, visual acuity (VA), IOP, MGD assessment, Schirmer test, TBUT, CFS, OSDI. At Visit 2, a slit lamp examination will be performed. After 20 min, a baseline examination will be conducted by performing a Tear Film Imager assessment in the study eye (tear film parameters measured twice 20-40 min apart; study eye = worst CFS eye at baseline). The study eye drop will then be applied to both eyes. Tear film imager assessments will then be performed in the study eye at multiple time points up to 4 hours post-instillation as shown in Figure 1.

Figure 1: Study Design Schematic



5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Approximately 50 subjects will be screened in order to enroll approximately 30 subjects.

5.2 Study Population Characteristics

Subjects of at least 18 years of age of either sex and any race, with a diagnosis of dry eye disease, who meet all of the inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

General/Ocular Inclusion Criteria

1. Will be at least 18 years of age at the time of consent.
2. Able to provide written voluntary informed consent.
3. Have a subject-reported history of DED in both eyes for at least 6 months prior to Visit 1.
4. Have Tear film break-up time (TFBUT) <10 sec at Visit 1.
5. Have Meibomian Gland Dysfunction (MGD) defined as total MGD score ≥ 3 (secretion of 5 central glands on lower eyelid will be evaluated, each will be scored from 0-3; 0 = normal, 1 = thick/yellow, whitish, particulate 2 = paste; 3 = none/occluded; total score will range from 0-15) at Visit 1.
6. Have a total corneal fluorescein staining score of ≥2 and ≤11 (i.e. sum of inferior, superior, central, nasal, and temporal) according to the National Eye Institute (NEI) scale at Visit 1.
7. Have at least one eye that satisfies all criteria for 4-6 above at Visit 1.
8. Is able to fix his/her gaze for a minute, i.e. can see the fixation target and with no nystagmus
9. Is able and willing to follow instructions, including participation in all trial assessments and visits.

5.4 Exclusion Criteria

General/Ocular Exclusion Criteria

1. Have any clinically significant ocular surface slit-lamp findings at Visit 1 and Visit 2 and/or in the opinion of the Investigator had any findings that may have interfered 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 that caused incomplete eyelid closure
    f. corneal epithelial defect or significant confluent staining or filaments
    g. abnormal cornea shape (keratoconus)
    h. history of herpetic keratitis.
    i. has a pterygium in either eye.
    j. ocular or periocular rosacea that in the judgement of the Investigator interfered with the trial
2. Has used any topical ocular steroids treatments, prescription dry eye therapy including varenicline nasal spray, or topical anti-glaucoma medication within 60 days prior to Visit 1.
3. Have had a LipiFlow procedure within 1 month prior to Visit 2.
4. Have received a permanent punctum plug within 3 months (6 months for dissolvable punctum plugs) prior to Visit 2. Have removed a permanent punctum plug within 1 month prior to Visit 2.
5. Have used any eye drops (prescription or artificial tears) and/or TrueTear™ device (intranasal tear neurostimulator) within 24 hours before Visit 2.
6. Have active ocular allergies or ocular allergies that are expected to be active during the trial period.
7. Have worn contact lenses within 1 month of Visit 1 or anticipate using contact lenses during the trial.
8. Have undergone intraocular surgery or ocular laser surgery within the previous 6 months or had any planned ocular and/or lid surgeries over the trial period.
9. Have an active ocular or systemic infection (bacterial, viral, or fungal), including fever requiring treatment with antibiotics.
10. Is a woman who was pregnant, nursing or planning a pregnancy.
11. Is a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception included: hormonal (oral, implantable, injectable, or transdermal contraceptives); mechanical (spermicide in conjunction with a barrier such as a diaphragm or condom); intrauterine device; or surgical sterilization of partner. For non-sexually active females, abstinence could have been 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.
12. Has an uncontrolled systemic disease in the opinion of the Investigator will interfere with the trial.
13. Has a known allergy and/or sensitivity to the investigational drug or saline components.
14. Has used 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.
15. Have taken isotretinoin (e.g. Accutane, Myorisan, Claravis, Amnesteem) within 6 months of Visit 1
16. Has corrected VA worse than or equal to logarithm of the minimum angle of resolution (LogMAR), +0.7 as assessed with Early Treatment Diabetic Retinopathy Study (ETDRS) charts in both eyes at Visit 1.

17. Is currently enrolled in an investigational drug or device study or had used an investigational drug or device within 60 days of Visit 2.

5.5 Withdrawal Criteria (if applicable)

Subjects may voluntarily withdraw from the study at any time.

Additionally, subjects may be discontinued for safety reasons as determined by the investigator (see Section 8.6.2).

6 STUDY PARAMETERS

6.1 Efficacy Measures and Endpoints

6.1.1 Primary Efficacy Measure(s) and Endpoints

- Change from baseline in mucus-aqueous layer thickness (MALT) and thinning rate (MALTR) for study eyes at 5±1 min, 15±2 min, 30±2 min, 60±5 min, 120±10 min, and 240±10 min following instillation of NOV03

6.1.2 [redacted]

6.2 Safety Measures

- Adverse Events (AEs; reported, elicited and observed)

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Study Treatment

PFHO drug product is a thin, clear, preservative-free ophthalmic drop (see Table 1). PFHO must be stored in a secure area accessible only to the investigator or pharmacist and his/her designees. PFHO must be stored **at room temperature** under temperature- monitored conditions and must not be refrigerated.

Table 1 Active Investigational Product

	Investigational Product
Product code:	NOV03 (MIEBO™)
Chemical name:	Perfluorohexyloctane (PFHO)
Molecular formula:	$C_{14}H_{17}F_{13}$
Dosage form:	3 mL ophthalmic solution
Unit dose:	11 µL drop size; 100% perfluorohexyloctane
Route of administration:	Topical ocular administration
Physical description:	Colorless and clear ophthalmic solution
Excipients:	None
Manufacturer:	[redacted]

7.1.2 Instructions for Use and Administration

- At Visit 2, a designated clinical staff member will instill 1 drop of the investigational product into each eye:

7.2 Other Study Supplies

- Questionnaires, Urine Pregnancy Tests, sterile cotton-tipped swab (for MGD assessment), Schirmer's test strips, sodium fluorescein.

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in sections 5.2, 5.3, and 5.4 will be considered for entry into this study.

8.1.2 Informed Consent

Following identification of a potential subject, the Investigator (or designee) will explain the purpose of the study, procedures, risks/benefits, and subject responsibilities to the potential subject. The subject's willingness and ability to meet the follow-up requirements of the study will be determined. If the subject chooses to participate in the investigation, written informed consent will be obtained. The subject and the person obtaining written consent will sign and date the IRB-approved ICF, at which point the subject is considered part of the study population. The original signed document will be retained in the subject records, and a copy will be provided to the subject. In addition, the applicable privacy regulation requirements must be met.

8.1.3 Washout Intervals

Subjects will adhere to the following medication washout intervals during the period indicated **prior to Visit 1 or 2 as indicated** and will refrain from using these medications during the study:

24 Hours

Artificial tears, topical ocular prescription eye drops, True Tear device, lid scrubs, lid wipes, warm compresses within 24 hours of Visit 2 (Assessments)

1 Month

- contact lenses within 30 days of Visit 1 (Screening)
- oral medications known to cause ocular drying (e.g. antihistamines, antidepressants etc) on a non-stable regimen with 30 days of Visit 1 (Screening)
- Lipiflow within 30 days of Visit 2 (Assessment)
- Removed a punctal plug within 30 days on Visit 1 (Screening)

2 Months

- Topical steroids, cyclosporine, lifitegrast, serum tears, glaucoma medication within 60 days of Visit 1 (Screening)

3 Months

- Received a permanent punctum plug within 90 days of Visit 2 (Assessment)

6 Months

- Received or removed a dissolvable punctum plug within 6 months of Visit 2 (Assessment)
- Have taken isotretinoin (e.g. Accutane, Myorisan, Claravis, Amnesteem) within 6 months of Visit 1 (Assessment)

8.1.4 Procedures for Final Study Entry

Subjects must meet all of the inclusion criteria and none of the exclusion criteria in order to be enrolled in the study.

8.2 Concurrent Therapies

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding case report form (CRF) along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or medical device study is not permitted.

8.2.1 Prohibited Medications/Treatments

Refer to Section 8.1.3 for a complete list

8.3 Examination Procedures

8.3.1 Procedures to be Performed at Each Study Visit

Refer to Appendix 2 for details on the ocular assessments.

8.3.1.1 VISIT 1 (Day -14 to Day -1): Screening/ Informed Consent/ Eligibility

- *Informed Consent/HIPAA:* Prior to any changes in a subject's medical treatment and/or study visit procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent and sign a HIPAA form.

  In the event that a subject has a medical condition, medication/contact lens washout, or needs to speak with the Investigator prior to Visit 1, the subject will be given an informed consent form. Medical/medication history, demographics, and inclusion/exclusion review may be performed at the time of informed consent signing prior to Visit 1, but must be confirmed at Visit 1.

- *Demographic data and medical/medication/ocular and non-ocular history:* Collect and record all demographic data, medical history, any medications, and any underlying condition(s). Current underlying conditions, including those that began within the last 30 days, which may have been resolved before screening must be recorded. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within 60 days prior to Visit 1.

- *Review of Inclusion/Exclusion Criteria:* A review of protocol inclusion and exclusion criteria will be confirmed for each subject.

- *Urine Pregnancy Test (for females of childbearing potential):* Females of childbearing potential must have a negative urine pregnancy test to continue in the study and must agree to use an acceptable method of contraception throughout participation in the study.
- *Ocular Surface Disease Index (OSDI©) questionnaire*
- *Visual acuity (ETDRS)*
- *Slit-Lamp biomicroscopy*
- *Tear Film Break-up Time (TFBUT)*
- *Fluorescein staining (NEI scale)*
- *Meibomian gland assessment (MGD score) (wait 5 min prior to start of Schirmer`s test)*
- *Schirmer's test I (without anesthesia)*
- *Intraocular pressure*
- *Adverse Event Query*
- *Schedule Visit 2:* Qualifying subjects will be scheduled to return to the office for Visit 2.

8.3.1.2 VISIT 2 (Day 1)

- *Update of Medical/Medication History*
- *Slit-Lamp biomicroscopy (wait ~20 min prior to TFI baseline measurements)*

- *Baseline Tear Film Imager assessments (2 measurements made 20-40 min apart)*
- *Instillation of study drug*
- *Post-instillation Tear Film Imager assessments (at 5, 15, 30, 60, 120 and 240 min following PFHO instillation)*
- *Adverse Event Query*
- *Study Exit*

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

If a subject is discontinued at a scheduled study visit, the remaining assessments should be captured on the Unscheduled Visit/Early Exit Visit pages of the Source Document and corresponding CRF.

8.4.2 Unscheduled Visits

For Unscheduled Visits, the reason for the visit should be clearly documented on the appropriate CRF, including findings from all evaluations that are completed.

These visits may be performed to ensure subject safety. All information gathered at unscheduled visits should be recorded on the Unscheduled Visit/ Early Exit Visit pages of the Source Document and corresponding CRF.

8.5 Compliance with Protocol

Subjects who are inappropriately enrolled may be discontinued from the study. The reason for such discontinuation will be recorded as “protocol violation” in the source document and on the appropriate page in the CRF.

Site staff will review concomitant medication use at each visit. Any new medication (or) changes in existing concomitant medication use will be recorded in the source document and on the Concomitant medication CRF.

8.6 Subject Disposition

8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the study.

8.6.2 Discontinued Subjects

Subjects may be discontinued prior to their completion of the study due to:

- subject request/withdrawal
- AEs
- protocol violations

- administrative reasons (e.g., inability to continue, lost to follow up)
- sponsor termination of study
- other

Note: In addition, any subject may be discontinued for any sound medical reason.

Notification of a subject discontinuation and the reason for discontinuation will be made to the sponsor and will be clearly documented on the CRF.

8.7 Study Termination

The study may be stopped at any time by the investigator or the sponsor with appropriate notification.

8.8 Study Duration

This trial consists of 2 office visits over a period of approximately 2 weeks.

8.9 Monitoring and Quality Assurance

Audits of clinical research activities in accordance with the Bausch + Lomb's internal Standard Operating Procedures (SOPs) to evaluate compliance with the principles of GCP may take place. A regulatory authority may also 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 Bausch + Lomb immediately that this request has been made.

9 ADVERSE EVENTS

9.1 Definition of Adverse Event (AE)

An adverse event is any untoward medical occurrence in a subject participating in a clinical study, which does not necessarily have a causal relationship with the study product/procedure. Therefore, an adverse event includes:

- Any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease onset, that occurs at any time between the signing of the ICF and study exit, without any judgement about causality (i.e., whether or not it is considered to be related to the study product)
- Exacerbation, worsening, or progression of a pre-existing illness, including an increase in severity, frequency, and/or duration of a pre-existing episodic event or condition
- Events occurring from drug overdose (accidental or intentional), drug abuse or misuse, drug hypersensitivity, drug extravasation, drug interactions, drug dependency, events occurring from drug withdrawal and medication errors
- A condition detected or diagnosed after study product administration even though it may have been present prior to the start of the study

A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the first dose of study drug, or that worsened following administration of study drug.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) as event terms; the condition that led to the procedure is the AE if it meets the definition of an AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery; and social and/or convenience admissions).

Symptoms associated with disease, which are consistent with the subject's usual clinical course; unless the subject experiences worsening of their symptom(s) or the symptom(s) meet the criteria for an SAE.

9.1.1 Assessment of Severity of Adverse Events

The severity of an AE will be graded as follows:

Mild	Awareness of a sign or symptom but is easily tolerated, requires no treatment, and does not interfere with subject's daily activities
Moderate	Low level of concern to the subject and may interfere with daily activities but can be relieved by simple therapeutic care.
Severe	Interrupts the subject's daily activity and requires systemic therapy or other treatment

9.1.2 Assessment of Causality of Adverse Events

The relationship of an AE to the study product will be assessed using the following guidelines, based upon available information:

Related	There is at least a reasonable possibility that the AE/SAE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.
Not Related	There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists.

Rationale MUST be provided for any "not related" assessment and is recommended for "related" assessments.

9.2 **Serious Adverse Events**

An AE is considered "serious" if it meets at least one of the following criteria. The event:

- Results in death

- Is life threatening (places the subject at immediate risk of death)

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization NOTE: The term "hospitalization" refers to admission to a hospital as an in-patient for more than 24 hours. Therefore, an adverse event would meet the SAE criterion of "requires hospitalization" only if the event necessitated admission to a health care facility for longer than 24 hours. Elective hospitalization for an intervention that was already planned before inclusion of the subject in the study, hospitalization solely for the purpose of diagnostic tests (even if related to an AE), hospital admission for social circumstances, and admission to a day-care facility may not constitute sufficient grounds to be considered an SAE.

  Cases in which subjects are retained in the emergency room for more than 24 hours but not admitted for medical care should be evaluated individually, because the criterion "otherwise medically significant" may apply (see below).

- Results in persistent or significant disability/incapacity

  NOTE: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance (e.g., uncomplicated headache, influenza, or sprained ankle) that may transiently interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect

- Is considered otherwise medically significant, as determined by the PI or medically qualified sub-investigator

  NOTE: The term "medically significant" refers to important medical events that may not immediately be life threatening or result in death or hospitalization, but, based upon appropriate medical judgment, they jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the definition of an SAE.

  Examples of such medically significant events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Spontaneous abortion, elective abortion and ectopic pregnancy will be considered SAEs and must be reported to the sponsor within 24 hours of awareness of the event.

Subjects will be withdrawn from the study if an SAE is identified and thought to be related to the study drug.

The investigator is responsible for the reporting of all SAEs.

Within 24 hours following the investigator's knowledge of an SAE, the investigator must:

- Report the SAE to the sponsor/designee.

  All SAEs occurring between screening and 30 days after the last administered dose of study drug (inclusive) must be reported to the sponsor/designee, independent of the circumstance or suspected cause, and regardless of the relationship to the study drug or protocol, within 24 hours from the time the event was reported to the investigator. For events occurring beyond the 30-day period after the last application of study drug, or for any timeframe greater than 30 days deemed medically

significant, only SAEs considered related to the study drug should be reported promptly to the sponsor.

If the subject dies during participation in the study or during recognized follow-up period, and if cause of death is not available within the 24-hour reporting period, "death" must be reported as an SAE term to meet the timelines. Cause of death must be actively queried and submitted as a follow-up report.

- Fax or email a completed Serious Adverse Event Report to the following designees:

  Sponsor Contact:
  Email: drugsafety@bausch.com
  cc: clinicalsafety@bausch.com
  Fax: +1-585-510-5552

  Include copies of all confirmatory examinations carried out and the dates on which these examinations were performed. 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 trial (i.e., subject number) are clearly visible on every page/copy of source document provided to the sponsor. For laboratory results, include the laboratory normal ranges.

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

Within 48 hours following the investigator's knowledge of an SAE, the investigator must:

- Enter the information related to the SAE in the appropriate sections of the CRF.
- Send notification of the SAE to the monitoring team after investigator approval of the CRF

All further data updates should be recorded in the CRF within one working day of knowledge of this additional information. Send notification of the updated SAE information to the monitoring team after investigator approval of the CRF.

Additional documentation (e.g., laboratory data, concomitant medication, subject status, etc.), should be sent by fax or e-mail to the monitoring team within one working day of knowledge of this information. 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 trial (i.e., subject number) are clearly visible on every page/copy of source document that is provided to the monitoring team. For laboratory results, include the laboratory normal ranges.

After the EOS visit, the investigator does not need to actively monitor subjects for new SAEs. However, if the investigator becomes aware of a new or previously unreported serious adverse event within 30 days after the last investigational drug instillation, the event should be reported to the sponsor/designee within 24 hours of learning of the event. If the investigator becomes aware of a new or previously unreported SAE after 30 days from the last investigational drug instillation, only SAEs considered related to the study drug should be reported to the sponsor within 24 hours of the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial SAE Report Form cases for the purposes of expedited reporting.

9.2.1 Expedited Serious Adverse Events

Any suspected unexpected serious adverse event considered related to the study drug may warrant expedited reporting. In addition, any unexpected SAE related to a subject's participation in the study (or related to the conduct of the study), regardless of whether or not the study drug was administered, will be evaluated by Global Pharmacovigilance and Risk Management to determine if expedited reporting is required. For example, an unexpected, severe SAE that could be associated with the study procedures and could modify the study conduct requires expedited reporting.

Each expedited safety report will routinely include a brief cover memorandum, the completed MedWatch Form FDA 3500A, a clinical analysis of the event with any similar events that have occurred with the product, and any additional pertinent information recommended by the study medical monitor. Once the report is compiled, the study center's investigator must submit the expedited safety report to the local IRB/IEC within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available. The principal investigator must retain a complete copy of each expedited safety report as it was submitted to the IRB/IEC. It is important that the principal investigator review these expedited reports, as they contain safety information that may be relevant to each of the participating subjects.

9.2.2 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. Abstinence is allowed as a birth control method. 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 informed consent form, 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 informed consent form to enroll in the study. During the study, all subjects should be instructed to contact the investigator immediately if they suspect that they or their partners might be pregnant (e.g., missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to treatment, the study drug 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 drug. If pregnancy is suspected while the subject is receiving study treatment, the study drug must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued, and the subject and neonate will be followed until 30 days after the pregnancy comes to term. 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 subject is withdrawn from the study and is found to be pregnant within 30 days of withdrawal, the subject and neonate will be followed until 30 days after the pregnancy comes to term.

All confirmed pregnancies must be immediately reported to the sponsor/designee and medical monitor on a Pregnancy Report form within 24 hours of the investigator's awareness of the pregnancy. If a pregnancy is associated with an SAE, an SAE report form should also be submitted to the sponsor/designee and medical monitor within 24 hours of the investigator's awareness. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Completed SAE Report Forms and completed Pregnancy Report Forms should be transmitted to the sponsor/designee and the medical monitor using the contact information provided in Section 9.2 above.

If/when the investigator becomes aware of any new information regarding a pregnancy, the sponsor/designee and medical monitor should be notified of these updates as soon as the new information becomes available. Updates should be documented on a Pregnancy Report Form and sent by fax or email using the contact information provided above. The report should be marked as a follow-up report" and should include the updated status of the pregnancy. The original Pregnancy Report Form is not to be altered.

9.3 General Guidelines for Reporting Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the course of the study. Throughout the study, efforts will be made by the investigator to remain alert to possible AEs. The period of observation for collection of AEs extends from the time the subject gives informed consent until the last study visit or discontinuation from the study. The first concern will always be the safety of the subject, and appropriate medical intervention will be made.

The AEs should be documented as a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject at each study visit. Each AE which appears to be independent of any prior event will be reported separately.

All AEs occurring after the subject signs the informed consent through the last study visit must be reported, regardless of whether or not the AEs are considered drug-related. All AEs, whether in response to a query, observed by the study site personnel, or reported spontaneously by the subject, will be recorded. Any AEs deemed related to treatment reported or observed at the final study/treatment visit will be followed until stabilization or resolution (or up to 30 days after final study visit).

At each visit during the study, the subject will be assessed for the occurrence of new and ongoing AEs. Tolerability signs and symptoms that result in the subject's requiring a concomitant therapy, interruption of treatment, or discontinuation from the study will be reported as an AE. The following data will be collected on all AEs and recorded on the appropriate CRF:

- Event name (diagnosis preferred, if unknown, record the signs/symptoms)
- Onset date and end date
- Maximum intensity (severity)
- Seriousness
- Action taken regarding study drug
- Corrective treatment/therapy, if given
- Outcome

- Resolution

The investigator will also provide an assessment of the causal relationship to the study drug (for pre-treatment AEs, causality is "not related"). Rationale MUST be provided for any "not related" assessment and is recommended for "related" assessments.

All AEs must be reported regardless of whether the AEs are considered drug-related.

In order to ensure the safety of the subjects, the investigator should take appropriate measures to follow all subjects with adverse events until clinical recovery is complete, progression has been stabilized, the subject is lost to follow-up, or until death. This may result in the need for observations to continue beyond the last planned protocol specified visit, and additional investigations may be requested by the monitoring team.

If a subject requires further follow-up of ongoing AEs upon discontinuation or completion of the study, the Investigator should schedule post-study follow-up visits, as necessary.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs (or SAEs, if applicable) only if at least one of the following apply:

- the result is clinically significant
- the subject is symptomatic
- the subject requires either corrective treatment or consultation
- the lab result, vital sign, or ECG abnormality leads to study drug discontinuation or dose modification
- the event fulfills a criterion for an SAE

In addition, the investigator's assessment of causality will be recorded.

Vital sign abnormalities are to be recorded as AEs (or SAEs, if applicable) only if they are clinically significant (for example: are symptomatic, requiring corrective treatment, leading to discontinuation or fulfilling a seriousness criterion).

10 STATISTICS

10.1 Assessment of Efficacy

Efficacy evaluations will be completed using the Full Analysis Set.

10.1.1 Primary Efficacy

For each primary endpoint at each post-instillation timepoint, the null hypothesis (H_0) is that the mean change from baseline (δ) is zero. The alternative hypothesis is that the mean change from baseline is not zero.

$$HH_0: \delta\delta = 0$$

$$HH_1: \delta\delta \neq 0$$

MALT and MALTR will be summarized using continuous summary statistics by time point (baseline, 5 minutes, 15 minutes, 30 minutes, 1-, 2-, and 4 hours). Change from baseline (post-instillation minus baseline) at each post instillation time point will be summarized using continuous summary statistics. Paired t-tests will be used to test the statistical hypotheses.

10.1.2 Secondary Efficacy

This section is not applicable because there are no secondary efficacy endpoints.

10.1.3 Exploratory Efficacy

The exploratory endpoints will be analyzed in the same manner as the primary efficacy endpoints.

10.1.4 Statistical Hypothesis Testing and Control of Multiplicity

Due to clinical considerations, the 36 statistical tests will not be adjusted for multiplicity. The p-values and any conclusions of statistical significance will be considered nominal.

10.1.5 General Considerations

Quantitative variables will be summarized descriptively using the number of subjects (n), mean, median, standard deviation, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

All efficacy analyses will use a two-sided alpha = 0.05 test unless otherwise stated and corresponding 2-sided 95% confidence intervals (CIs) will be presented as applicable.

For efficacy and non-ocular safety analyses, the unit of analysis will be the subject. In the cases where assessments are recorded for each eye, the study eye and fellow eye will be summarized separately and a mean across all eyes will also be calculated.

Adverse events will also be summarized at the subject level; if an AE occurs in either or both eyes, the subject will be counted as having the AE. For other ocular safety analyses the unit of analysis will be the eye, with summaries showing results for the study eye and the fellow eye separately.

10.2 Assessment of Safety

The following safety variables will be recorded:

- Adverse Events (AEs; reported, elicited and observed)

10.2.1 Adverse Events

Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of treatment-emergent adverse events (TEAEs) will be summarized at the subject level by system organ class and preferred term for all TEAEs, treatment related TEAEs, and serious TEAEs. An AE is treatment emergent if it occurs or worsens after the first dose of study medication. Similar summaries will be presented for all TEAEs by maximal severity. Separate summaries will be performed for ocular and non-ocular AEs.

10.2.2 Concomitant Medications

All previous concomitant medications will be classified based on terminology from the WHO Drug Dictionary. Previous therapies and concomitant medications data will be presented in data listings.

10.3 Subject Disposition

Subject disposition will be presented in terms of the numbers and percentages of subjects who completed the study and discontinued from the study.

The number and percentage of subjects who prematurely discontinue from the study and the reasons for study discontinuation will be summarized.

10.4 Demographics and Baseline Characteristics

Subject demographics including age, sex, ethnicity, race, and baseline characteristics will be summarized using the appropriate descriptive statistics.

10.5 Protocol Deviations

All protocol deviations will be reported to the sponsor and recorded throughout the study. A tabulation of protocol deviations (including categorizations of major and minor) will be presented.

Important protocol deviations leading to exclusion from the Per-Protocol Population will include the following.

- Ineligibility
- Missing primary endpoint data at any time point at Visit 1
- Use of any prohibited medication potentially affecting the primary endpoint at Visit 1

10.6 Compliance

Compliance will not be evaluated in this study since the site will administer the drop.

10.7 Interim Analyses

There are no interim analyses planned for this study.

10.8 Additional Statistical Considerations

10.8.1 Analysis Population

- *Full Analysis Set (FAS):* The FAS will consist of all subjects who are instilled with study drug.
- *Per Protocol Set (PP Set):* The PP Set will consist of FAS subjects with no protocol deviations expected to affect the evaluability of efficacy.

10.8.2 Sample Size Determination

A sample size of 30 subjects will have 80% power to detect a difference in means of 0.529 times the standard deviation of the paired differences, using a paired t-test with a 5% two-sided significance level.

10.8.3 Multiplicity Issues

The probability of at least one type 1 error will be approximately 79% under the universal null hypothesis if the 36 endpoints are independent.

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonisation (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of IP in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent/assent forms must be approved for use by the sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by B+L prior to submission to the governing IRB/IEC and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

11.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 CFR Part 56.103). The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB/IEC approved version of the informed consent form will be used.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data is in accordance with local, state, and federal laws and regulations.

Anonymized TFI measurement data will be analyzed by AdOM.

Monitors, auditors and other authorized representatives of the sponsor, the IRB/IEC approving this study, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the IP may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's study subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and EKGs. The investigator's copy of the CRFs serves as the investigator's record of a subject's study-related data.

11.4.1 Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all IP, and copies of CRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

11.5.1 Labeling/Packaging

The investigational materials will be packaged and labeled in a manner consistent with the study design. They will be labelled according to the local regulatory requirements

11.5.2 Storage of Investigational Product

The IP must be stored in a secure area accessible only to the investigator and his/her designees. The IP will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol.

11.5.3 Accountability of Investigational Product

The IP is to only be prescribed by the principal investigator or his/her named sub-investigator(s), and is to only be used in accordance with this protocol. The IP must only be distributed to subjects properly qualified under this protocol to receive IP.

The investigator must keep an accurate accounting of the IP received from the sponsor on the Product Accountability Log.

11.5.4 Return or Disposal of Investigational Product

All IP will be returned to the sponsor at the end of the study.

11.6 Recording of Data on Source Documents and Case Reports Forms (CRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's CRF, source document, and all study-related material. All study data should also be attributable,

legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

11.7 Handling of Biological Specimens

Not Applicable.

11.8 [redacted]

[redacted]

[redacted]

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