CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216675Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW of NDA 216675

Application Type	NDA
Application Number(s)	216675
Priority or Standard	Standard
Submit Date(s)	June 28, 2022
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Division/Office	DO/OND/OSM
Reviewer Name(s)	Shilpa Rose, MD
Review Completion Date	See DAARTS stamp date
Established/Proper Name	perfluorohexyloctane ophthalmic solution
(Proposed) Trade Name	Miebo
Applicant	Bausch & Lomb Incorporated (B&L)
Dosage Form(s)	Topical ophthalmic solution
Applicant Proposed Dosing Regimen(s)	The recommended dose is one drop four times daily into each eye.
Applicant Proposed Indication(s)/Population(s)	For the treatment of the signs and symptoms of Dry Eye Disease (DED) associated with Meibomian Gland Dysfunction (MGD).
Recommendation on Regulatory Action	Recommend Approval
Recommended Indication(s)/Population(s)	Adult patients with dry eye disease

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

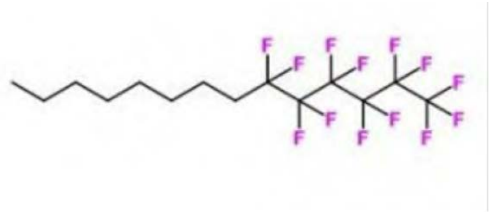
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Miebo (perfluorohexyloctane ophthalmic solution) is a sterile single component drug product. NOV03 consists of 100% perfluorohexyloctane, a linear semifluorinated alkane, which has six perfluorinated and eight hydrogenated carbon atoms. Due to its low surface tension, NOV03 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 decreases evaporation of the aqueous tear film component. NOV03, as a water-free liquid, has no moisture to support bacterial growth. Thus, it can be used in multi-dose units without the need of antimicrobial preservatives.

Chemical structure of NOVO3



1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 216675 for Miebo (perfluorohexyloctane ophthalmic solution) is recommended for approval for the treatment of dry eye disease. Two trials (NVU-003 and BL-904) were submitted to support the approval of Miebo (perfluorohexyloctane ophthalmic solution) dosed in the affected eye four times per day. Both trials were successful in demonstrating efficacy of Miebo (perfluorohexyloctane ophthalmic solution) for the same co-primary efficacy endpoints, change from baseline in total corneal fluorescein staining (tCFS) in the study eye at Day 57, followed by change from baseline in the eye dryness VAS score at Day 57. Additionally, statistically significant treatment group differences were shown between the Miebo (perfluorohexyloctane ophthalmic solution) and saline groups for all four of the key secondary endpoints: eye dryness score at Day 15, tCFS at Day 15 in the study eye, burning/stinging score at Day 57, and cCFS at Day 57 in the study eye.

Approval is recommended for Miebo (perfluorohexyloctane ophthalmic solution) dosed four times a day in the affected for the treatment of dry eye disease.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The adequate and well controlled studies (NVU-003 and BL-904) contained in this submission establish the efficacy of Miebo (perfluorohexyloctane ophthalmic solution) dosed 4 times a day for the treatment of the signs and symptoms of dry eye disease. Both studies met their co-primary endpoints, change from baseline in tCFS at Day 57 and change in baseline in the eye dryness VAS score at Day 57. Both studies also met four key secondary endpoints: eye dryness score at Day 15, tCFS at Day 15 in the study eye, burning/stinging score at Day 57, and cCFS at Day 57 in the study eye. The safety of Miebo was assessed in over 1553 patients dosed bid or qid for 8 weeks. The most common adverse event was blurred vision (3%). The benefit of Miebo dosed four times per day for the treatment of dry eye disease is expected to outweigh the risks associated with its use.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Dry eye disease (DED) is a multi-factorial, age-related, chronic progressive disease of the ocular surface • Chronic DED can cause discomfort, visual impairment, tear film hyperosmolarity, and inflammation • Patients with DED are more susceptible than others to eye infections and damage to the surface of the eye (cornea)	Miebo (perfluorohexyloctane ophthalmic solution) has low surface tension and rapidly spreads cross 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.
Current Treatment Options	• Restasis (cyclosporine ophthalmic emulsion) 0.05% • Xiidra (lifitegrast ophthalmic solution) 0.05% • Cequa (cyclosporine ophthalmic solution 0.09% • (b) (4) (varenicline tartrate inhaler) • OTC Monograph eye drops	Miebo (perfluorohexyloctane ophthalmic solution) would provide an alternate product for the treatment of dry eye disease by preventing the evaporation of the aqueous tear film component.
Benefit	• Demonstrating improvement in both a sign and symptom in dry eye patients provide a clinically relevant benefit in patients with dry eye disease	NVU-003, demonstrated the efficacy for a sign and symptom for the QID dosing of Miebo. BL-904, demonstrated the efficacy for a sign and symptom for the QID dosing of Miebo.
Risk and Risk Management	• The most common adverse event experienced with Miebo (perfluorohexyloctane ophthalmic solution) was blurred vision at a rate of 3.0%.	Treatment with Miebo (perfluorohexyloctane ophthalmic solution) for the treatment of dry eyes has an acceptable risk-benefit profile.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed
	☒	Clinical outcome assessment (COA) data, such as		Sec 6- Study endpoints
		☒	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Dry eye disease (DED) is a common ocular surface disorder with 2 major subtypes: aqueous deficient DED, in which lacrimal secretion is reduced; and evaporative DED,

which results from excessive evaporation of the tear film. Estimates suggest that aqueous deficient dry eye by itself occurs in only 10% to 15% of patients with DED while epidemiological and clinical evidence suggest that the majority of DED is evaporative in nature. Symptoms of DED include irritation, dryness, burning/stinging, and visual disturbances, which may adversely affect patients' quality of life, function, activities of daily living, and work productivity.

2.2. Analysis of Current Treatment Options

Table of Currently Available Treatments for Proposed Indication

Table 1 Approved Drugs for Indications Associated with Dry Eye Disease

Restasis	cyclosporine ophthalmic emulsion, 0.05%	NDA 50-790
Cequa	cyclosporine ophthalmic solution, 0.09%	NDA 210913
Xiidra	lifitegrast ophthalmic solution	NDA 208073
(b) (4)	Varenicline tartrate inhaler	NDA 213978
OTC Monograph	Multiple	21 CFR 349

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Perfluorohexyloctane ophthalmic solution has not been marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

A PreIND meeting was held between the Agency and Novaliq GmbH on July 11, 2016. IND 130558 changed ownership to Bausch and Lomb Incorporated on March 13, 2020. A Pre-NDA meeting was held on December 15, 2021.

3.3. Foreign Regulatory Actions and Marketing History

In Europe, Nova Tears has been classified as a class IIa medical device and received a CE mark in July 2013. The product is currently marketed by Ursapharm in Europe under the name EvoTears.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The following investigators were selected for inspections: David Evan, Bruce Segal, Fred Kurata, David L. Wirta. The OSI Inspection Summary is not yet finalized. Refer to the CDTL for further details.

4.2. Product Quality

The proposed drug product consists of the semifluorinated alkane, perfluorohexyloctane (drug substance) as the single ingredient in the formulation. The drug product contains no additional formulation additives or preservatives.

Table 2 Qualitative and quantitative composition of drug product

Component	Reference to Quality Standard	Function	Quantity per Unit (g/3 mL)
Perfluorohexyloctane	In-house	Active	4.014

Source: 3.2.P.1 Description and Composition of the Drug Product

Table 3 Release and shelf life specifications for drug product

Test	Procedure	Release Criteria	Shelf Life Criteria
Appearance	Visual inspection	Clear, colorless liquid	
Container Description and Appearance	Visual inspection	No physical distortion, discoloration or leaking; translucent (natural) eyedropper bottle with white cap	
Visible Particles	Visual inspection Current USP	Practically free from particles	
Sub-visible Particulate Matter	Current USP	(b) (4) (light obscuration method) NMT (b) (4) particles per container ≥ 10 µm NMT (b) (4) particles per container ≥ 25 µm	
Fill volume [a]	Weighing	NLT 3 mL	Not tested
Weight loss [b]	Weighing	Not tested	NMT (b) (4) wt%
Identification by Infrared Spectrum (IR)	Current USP	Sample spectrum complies with reference spectrum	Not tested
Identification by GC	In house GC-FID method (b) (4)	Retention time complies with reference substance	Not tested
Assay of Perfluorohexyloctane	In house GC-FID method (b) (4)	(b) (4)	
Related Substances/Impurities	In house GC-FID method (b) (4)	Any unspecified impurity: NMT (b) (4) %	
		Total impurities: NMT (b) (4) %	
Sterility	Current USP	Meets USP requirements	

a) This test is performed (b) (4) to ensure fill volume at time of release.
b) This test is performed on stability only.

NMT = Not more than
NLT = Not less than
GC = Gas chromatography
FID = Flame ionization detection USP = United States Pharmacopeia
Source: 3.2.P.5.1 Specifications

Reviewer's Comments: *A specification for visible particles, USP <790> should be included. A specification for subvisible particles is not necessary.*

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Refer to the Pharmacology Toxicology review for details.

4.5. Clinical Pharmacology

Pharmacokinetic (PK) blood samples for perfluorohexyloctane analysis were drawn from the PK population in NVU-002, which was comprised of 79 subjects across treatment groups. The majority (>70%) of samples had blood concentrations below the lower limit of quantitation (<1 ng/mL) and samples with measurable perfluorohexyloctane concentrations were mainly in the low calibration range. Refer to the Clinical Pharmacology review for additional details.

4.6. Devices and Companion Diagnostic Issues

The dispenser of the product is considered a device. The product is regulated as a drug device combination product. CDRH confirmed that the CDRH consult is not necessary on 7/11/2022. The 356h form indicated that it is a combination product (item 24 checked).

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 4 Listing of Clinical Trials

Study/ Identifier	No. of Centers/ Location	Study Start/ Status/ Total Enrollment/ Enrollment Goal	Design & Control Type	Study Objectives	Dose, Regimen, Duration of Treatment	No. of Subjects by Arm Planned / Entered / Completed	Overall Age (years) range (mean) Percent male/female Percent black/white/other[a]	Primary Efficacy Endpoints
NVU-002	12 centers, US	20 Dec 2017 Completed 336 subjects 300 subjects	Phase 2, multi-center, randomized, double-masked, saline-controlled	Primary: efficacy, safety and tolerability Secondary: compare the effect of NOV03 and saline solution at 2 different dosing regiments on signs and symptoms of DED and evaluate the pharmacokinetics of NOV03 after 57 days of dosing.	NOV03 (100% perfluorohexyloctane) ophthalmic solution, BID or QID for 8 weeks Saline (0.9% NaCl) BID or QID for 8 weeks	NOV03 BID: 75/111/105 NOV03 QID: 75/114/110 Combined Saline (BID or QID): 150/111/108	All subjects: 19-86 (53.6) All subjects: 27.7/72.3 All subjects: 10.1/71.1/18.8	mean change from baseline in the tCFS score at Day 57
NVU-003	26 centers, US	19 Dec 2019 Completed/ 597 subjects/ 560 subjects	Phase 3, multi-center, randomized, double-masked, saline-controlled	Primary: Efficacy Secondary: safety and tolerability	NOV03 (100% perfluorohexyloctane) ophthalmic solution QID for 8 weeks Saline (0.6% NaCl) QID for 8 weeks	280/303/289 280/294/279	All subjects: 19-88 (60.9) All subjects: 27.5/72.5 All subjects: 18.1/69.7/12.2	mean change from baseline in the tCFS score at Day 57 mean change from baseline in the eye dryness VAS score at Day 57

Study/ Identifier	No. of Centers/ Location	Study Start/ Status/ Total Enrollment/ Enrollment Goal	Design & Control Type	Study Objectives	Dose, Regimen, Duration of Treatment	No. of Subjects by Arm Planned / Entered / Completed	Overall Age (years) range (mean) Percent male/female Percent black/white/other[a]	Primary Efficacy Endpoints
BL-904	42 centers, US	18 Nov 2020/ Completed/ 622 subjects[b]/ 560 subjects/	Phase 3, multi-center, randomized, double-masked, saline-controlled	Primary: Efficacy Secondary: safety and tolerability	NOV03 (100% perfluorohexyloctane) ophthalmic solution QID for 8 weeks Saline (0.6% NaCl) QID for 8 weeks	280/311/302 280/309/295	All subjects: 19-88 (53.6) All subjects: 21.3/78.7 All subjects: 6.9/80.5/12.6	mean change from baseline in the tCFS score at Day 57 mean change from baseline in the eye dryness VAS score at Day 57
NVU-004	22 centers, US	24 Sep 2020/ Completed/ 208 subjects/ 250 subjects	Phase 3, multi-center, open-label, single-arm 12-month extension to NVU-003	Primary: safety and tolerability Secondary: efficacy during long term use	NOV03 (100% perfluorohexyloctane) ophthalmic solution QID for 52 weeks	250/208/160	All subjects: 19-88 (61.2) All subjects: 29.8/70.2 All subjects: 20.7/63.9/15.4	Efficacy endpoints were secondary.

Abbreviations: BID = two times a day; DED = dry eye disease; QID = four times a day; tCFS = total corneal fluorescein staining; US = United States; VAS = visual analog scale

[a] Other includes the other racial groups as identified in the case report form for each study.

[b] 620 subjects were randomized and treated and 2 additional subjects were randomized but not treated.

5.2. Review Strategy

Clinical data for Studies NVU003 and BL904 listed in section 5.1 were reviewed to support safety and efficacy.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. NVU-003

Overview and Objective

The primary objective was to assess the efficacy of NOV03 (perfluorohexyloctane) ophthalmic solution at four times a day (QID) dosing regimen in comparison to a saline control for the treatment of the signs and symptoms of dry eye disease (DED) associated with meibomian gland dysfunction (MGD).

The secondary objective was to assess the safety and tolerability of NOV03 versus the saline control in subjects with DED associated with MGD. Further objectives explored the effect of NOV03 versus the saline control on other efficacy endpoints in the same population.

Trial Design

This was a Phase 3, multi-center, randomized, double-masked, saline-controlled study conducted in subjects with DED associated with MGD. The study consisted of 5 visits over a 10-week period: Visit 0 (screening within 14 days before Visit 1[Day -14 to -1]); Visit 1 (Day 1, baseline/randomization); Visit 2 (Day 15 ± 1 day); Visit 3 (Day 29 ± 2 days); and Visit 4 (Day 57 ± 2 days).

Eligible subjects were assigned to 1 of 2 treatment groups and received NOV03 (perfluorohexyloctane ophthalmic solution) QID or saline (0.6% sodium chloride solution) ophthalmic solution QID, starting at Visit 1 and ending at Visit 4. Subjects instilled the investigational product (IP) bilaterally. In the case that both eyes were eligible for analysis, the worst eye was selected as the study eye, defined as the eye with worse (higher) total corneal staining at Visit 1. If the total corneal staining was the same in both eyes, then the right eye was selected as the study eye. Approximately 560 subjects were planned for enrollment (280 subjects [560 eyes] per treatment group). Subjects were randomized to the NOV03 or saline treatment group instilled 1 drop into each eye QID for 8 weeks.

Inclusion Criteria

Each subject had to meet all the following criteria to be eligible for the study:

1. Was at least 18 years of age at the time of consent.
2. Provided written informed consent.
3. Had a subject-reported history of DED in both eyes for at least 6 months prior to Visit 0.
4. Had a TFBUT ≤5 seconds at Visit 0 and Visit 1.
5. Had an OSDI score ≥25 at Visit 0 and Visit 1.
6. Had an unanesthetized Schirmer's test I score ≥5 mm at Visit 0 and Visit 1.
7. Had MGD defined as total MGD score ≥3 at Visit 0 and Visit 1 (secretion of 5 central glands on the lower eyelid was evaluated, and each was scored from 0-3: 0=normal; 1=thick/yellow, whitish, particulate; 2=paste; 3=none/occluded). Total score ranged from 0-15.
8. Had a tCFS score between 4 and 11 (i.e., sum of inferior, superior, central, nasal, and temporal) according to the NEI scale at Visit 0 and Visit 1.
9. Had at least one eye (the same eye) that satisfied all criteria for 4, 6, 7, and 8 above at Visit 0 and Visit 1.
10. Was able and willing to follow instructions, including participation in all trial assessments and visits.

Exclusion Criteria

A subject was excluded from participating in the study if he/she met any of the following:

1. Had been randomized in NVU-002 or BL904.
2. Had any clinically significant ocular surface slit-lamp findings at Visit 0 and Visit 1 and/or in the opinion of the Investigator had any findings that may have interfered with trial parameters, including eye trauma or history of eye trauma or anterior membrane dystrophy.
3. Had a history of Stevens Johnson Syndrome.
4. Had active blepharitis or lid margin inflammation that required any topical antibiotics or topical steroids within last 30 days prior to Visit 0 or would have likely required such treatment during the trial. Any other lid margin therapy such as lid scrubs, lid wipes, warm compresses, systemic antibiotics (such as tetracyclines) and oral supplements for treatment of ocular conditions had to be stable within the last 30 days prior to Visit 1 and was to be maintained throughout the trial.
5. Had had a LipiFlow procedure, intense pulse light procedure or any kind of other procedure affecting meibomian glands within 6 months prior to Visit 1.
6. Had abnormal lid anatomy that caused incomplete eyelid closure, including entropion and ectropion, or floppy lid syndrome that exposed parts of the conjunctiva or impaired the blinking function of the eye.
7. Had received or removed a permanent punctum plug within 3 months (6 months for dissolvable punctum plugs) prior to Visit 1 or was expected to receive a punctum plug or removal of a punctum plug, or had a punctum plug expected to be dissolved during the trial.
8. Had DED secondary to scarring, irradiation, alkali burns, cicatricial pemphigoid, or destruction of conjunctival goblet cells (as with vitamin A deficiency).
9. Had an ocular or periocular malignancy.

10. Had a corneal epithelial defect or had significant confluent staining or filaments anywhere on the cornea.
11. Had a history of herpetic keratitis.
12. Had active ocular allergies or ocular allergies that were expected to be active during the trial period.
13. Was diagnosed with an active ocular or systemic infection (bacterial, viral, or fungal), including fever requiring treatment with antibiotics.
14. Had worn contact lenses within 1 month of Visit 0 or anticipated using contact lenses during the trial.
15. Had used any eye drops and/or TrueTear™ device (intranasal tear neurostimulator) within 24 hours before Visit 1.
16. Had undergone intra-ocular surgery or ocular laser surgery within the previous 6 months or had any planned ocular and/or lid surgeries over the trial period.
17. Was a family member living in the same household as another subject randomized into NVU-003 or BL904, or was a family member living in the same household as a participant in NVU-004 Open-Label Extension.
18. Was a clinical site employee directly involved in the management, administration, or support of this trial or was an immediate family member of the same.
19. Was a woman who was pregnant, nursing or planning a pregnancy.
20. Was unwilling to submit to a urine pregnancy test at Visit 0, Visit 1 and Visit 4 (or early termination visit) if of childbearing potential. Non-childbearing potential was defined as a woman who was permanently sterilized (e.g., had a hysterectomy or bilateral tubal ligation or bilateral oophorectomy) or was post-menopausal (without menses for 12 consecutive months).
21. Was a woman of childbearing potential who was 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 became sexually active during the trial, she had to agree to use adequate birth control as defined above for the remainder of the trial.
22. Had an uncontrolled systemic disease in the opinion of the Investigator.
23. Had a known allergy and/or sensitivity to the investigational drug or saline components.
24. Had active ocular or periocular rosacea that in the judgement of the Investigator interfered with the trial (e.g., clinically relevant lid induration).
25. Had a pterygium in any eye.
26. Was currently enrolled in an investigational drug or device study or had used an investigational drug or device within 60 days of Visit 1.
27. Had used any topical ocular steroids treatments, topical cyclosporine, lifitegrast, serum tears or topical anti-glaucoma medication within 60 days prior to Visit 0.

28. Had 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 0 or was expected to be unstable during the trial.
29. Had 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 0 and Visit 1.
30. Had a condition or be in a situation (including language barrier) which the Investigator felt may put the subject at significant risk, may confound the trial results, or may interfere significantly with the subject's participation in the trial.

Figure 1 Study Scheme

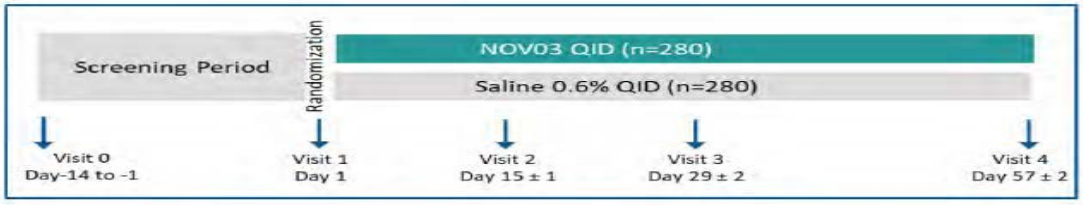


Table 5 Schedule of Visits and Parameters

Procedure	Visit 0 Within 14 d before Visit 1 (Day -14 to -1)	Visit 1 Day 1	Visit 2 Day 15 ± 1	Visit 3 Day 29 ± 2	Visit 4 /(ET) Day 57 ± 2
Informed Consent / HIPAA	X				
Demographics	X				
Medical/Surgical History	X				
Previous/Concomitant Medication	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X			
Urine Pregnancy Test	X	X			X
Dryness Score (VAS severity of dryness)*		X	X	X	X
VAS*		X	X	X	X
OSDI*	X	X	X	X	X
Eyedrop Acceptability Questionnaire*					X
Visual Acuity (ETDRS)	X	X	X	X	X
Slit-Lamp Biomicroscopy	X	X	X	X	X
TFBUT*	X	X			X
Corneal Fluorescein Staining (NEI scale)*	X	X	X	X	X
Meibomian Gland Assessment (MGD score)*	X	X			X
Schirmer's Test I (without anesthesia)*	X	X			X
Intraocular Pressure	X				X
Dilated Fundoscopy	X				X
Randomization (via IRS)		X			
In-office instillation of randomized IP		X			
Instillation Comfort Questionnaire		X			
Adverse Event Query	X	X	X	X	X
Dosing Diary Dispensation and/or Review		X	X	X	X
Dispensation of trial medication		X	X	X	
Collection of trial medication			X	X	X
Trial Exit					X

Abbreviations: ETDRS = Early Treatment Diabetic Retinopathy Study; HIPAA = Health Information Portability and Accountability Act; IP = investigational product; IRS = interactive randomization system; MGD = meibomian gland dysfunction; NEI = National Eye Institute; OSDI = Ocular Surface Disease Index; TFBUT = Tear Film Break Up Time; ET = Early Termination; VAS: burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, frequency of dryness, and awareness of dry eye symptoms
*NOTE: Assessments were conducted in the order depicted above.

Study Endpoints

Co-Primary Efficacy Endpoints were tested using hierarchical fixed sequence testing to maintain an overall 2-sided alpha = 0.05 level:
- Change from baseline in total corneal fluorescein staining score (tCFS) (NEI scale) at Day 57.
- Change from baseline in the dryness score (visual analog scale [VAS] severity of dryness) at Day 57.

If both co-primary endpoints demonstrated statistically significant superiority of NOV03 versus saline at the 2-sided alpha = 0.05 level, the following secondary endpoints were tested hierarchically to maintain an overall 2-sided alpha = 0.05:
- Change from baseline of dryness score (VAS) at Day 15.
- Change from baseline in tCFS (NEI scale) at Day 15.
- Change from baseline of VAS burning/stinging at Day 57.
- Change from baseline in central corneal fluorescein staining (cCFS) (NEI scale) at Day 57.

Other pre-specified efficacy endpoints included:
- Change from baseline of dryness score (VAS) at Day 29.
- Change from baseline in tCFS at Day 29.
- Change from baseline in CFS central and inferior sub-regions (NEI scale) to each measured postbaseline visit.
- Proportion of tCFS responders (≥3 improvement based on NEI scale) at Day 57.
- Proportion of dryness score responders (≥30 % improvement from baseline) at Day 57.
- Change from baseline in VAS burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, frequency of dryness, and awareness of dry eye symptoms at each measured post-baseline visit.
- Change from baseline in OSDI at each measured post-baseline visit.

Exploratory efficacy endpoints included:

- MGD score at Day 57.
- Schirmer's Test I (without anesthesia) at Day 57.
- TFBUT at Day 57.

Safety: The safety evaluation was based on the occurrence of ocular and non-ocular treatment-emergent adverse events (TEAEs); best-corrected visual acuity (BCVA); slit-lamp biomicroscopy; intraocular pressure (IOP); and dilated fundoscopy.

Other Assessments: Subjects took 2 questionnaires during the study: instillation comfort questionnaire and eyedrop acceptability questionnaire.

Statistical Analysis Plan

The primary comparison in this trial was between the NOV03 and saline groups at Day 57. The primary efficacy endpoints were tested using hierarchical fixed sequence testing and summarized descriptively and analyzed separately using an analysis of covariance (ANCOVA) model with terms for baseline value and treatment. Least squares (LS) means for each treatment group and for the difference between treatment groups were presented from each model, together with 2-sided p-values (used for primary inference) and 95% confidence intervals (CIs).

The key secondary efficacy endpoints were also tested using hierarchical fixed sequence testing. Inference was to be made only if both primary endpoints and any higher order secondary endpoints were statistically significant at a 2-sided alpha = 0.05, in favor of NOV03. Endpoints evaluating the proportion of study eyes (or subjects) that met pre-defined criteria were presented and tested between treatment groups using logistic regression analysis, adjusting for baseline score at each measured follow-up visit. For efficacy assessments performed by eye, study eye and fellow eye were summarized separately. TEAEs were tabulated; separate summaries were prepared for ocular and non-ocular TEAEs. Ocular TEAEs were summarized at the subject level and by eye. Actual values and changes from baseline were summarized by eye for IOP and VA using summary statistics. Slit-lamp biomicroscopy and dilated fundoscopy findings were summarized by eye using summary statistics and tabulated as the number and percent of subjects with normal/not present and abnormal/present results by treatment group, study visit, and eye. Shifts from baseline indicative of worsening were summarized.

Protocol Amendments

Significant Changes in the Conduct of the Study
The original protocol, dated 10 Oct 2019, was amended 3 times: Amendment 1 (03 Dec2019); Amendment 2 (16 Mar 2020); and Amendment 3 (27 Aug 2020).

- Protocol Amendment 1: The number of secondary endpoints was reduced; therefore, a new category “other pre-specified endpoints” was introduced. This modification led to some adaptions in the statistical section. The wording of several exclusion criteria and examination procedures was specified to provide better clarity.
- Protocol Amendment 2 introduced Bausch & Lomb, Incorporated as the new Sponsor.
- Protocol Amendment 3: The amendment excluded subjects randomized in NVU-002 or BL904.

6.1.1. NVU-003 Study Results

6.1.2. Compliance with Good Clinical Practices

This study was conducted per the principles of Good Clinical Practices (GCP).

Table 6 Patient Disposition (All Randomized)

	NOV03	Saline	All Subjects
No. Subjects Randomized	304	295	599
No. Subjects Randomized and Dosed: N	303	294	597
No. Subjects Completed IP: n (%)	290 (95.7)	280 (95.2)	570 (95.5)
No. Subjects Discontinued IP: n (%)	12 (4.0)	14 (4.8)	26 (4.4)
Subject Choice	6 (2.0)	4 (1.4)	10 (1.7)
Other	4 (1.3)	6 (2.0)	10 (1.7)
Adverse Event	1 (0.3)	3 (1.0)	4 (0.7)
Administrative Reason	0 (0.0)	1 (0.3)	1 (0.2)
Protocol Violation	1 (0.3)	0 (0.0)	1 (0.2)
No. Subjects with Missing IP Completion Status: n (%)	1 (0.3)	0	1 (0.2)
No. Subjects Completed Study: n (%)	289 (95.4)	279 (94.9)	568 (95.1)
No. Subjects Discontinued Study: n (%)	14 (4.6)	15 (5.1)	29 (4.9)
Withdrawal by Subject	6 (2.0)	5 (1.7)	11 (1.8)
Lost to Follow up	2 (0.7)	5 (1.7)	7 (1.2)
Other	4 (1.3)	2 (0.7)	6 (1.0)
Adverse Event	1 (0.3)	3 (1.0)	4 (0.7)
Protocol Violation	1 (0.3)	0 (0.0)	1 (0.2)

Abbreviations: IP = investigational product
Source: Table 14.1.1.1, Table 14.1.2.1, Table 14.1.2.2

Table 7 Analysis Sets (All Randomized)

Data Set/Reason for Exclusion	NOV03 (N=304) n (%)	Saline (N=295) n (%)
FAS & SAF	303 (99.7)	294 (99.7)
Did not receive at least 1 dose of IP	1 (0.3)	1 (0.3)
PPS	279 (91.8)	270 (91.5)
Subject did not complete the study	14 (4.6)	15 (5.1)
Study visit schedule deviations	5 (1.6)	8 (2.7)
Use of prohibited concomitant medications	3 (1.0)	2 (0.7)
Inclusion and exclusion criteria	2 (0.7)	1 (0.3)
IP deviation/compliance	1 (0.3)	2 (0.7)
Subject was not in the FAS	1 (0.3)	1 (0.3)
Missed/delayed/not per protocol procedures	1 (0.3)	0 (0.0)
Study medication compliance <80%	0 (0.0)	1 (0.3)
Subject non-compliance with instructions	1 (0.3)	0 (0.0)

Abbreviations: FAS = Full Analysis Set; IP = investigational product; PPS = Per Protocol Set; SAF = Safety Set
Note: Subjects may have been excluded from the PPS for >1 reason. Source: Table 14.1.2.1, Table 14.1.2.2

Protocol Violations/Deviations

A total of 24 (4.0%) subjects, 12 (4.0%) in the NOV03 group and 12 (4.1%) in the saline group, had at least 1 major protocol deviation during the study. The most common types of major protocol deviations were related to study visit/schedule deviations (13 events [5, NOV03; 8, saline]) and use of prohibited concomitant medications (5 events [3, NOV03; 2, saline]).

Demographic Characteristics

In the FAS, mean age of the study population was 61 years (range: 19 to 88 years). None of the subjects were <18 years of age; 280 (47%) subjects were ≥65 years. The majority of subjects were female (72%). The majority of subjects had their right eye designated as the study eye (59%).

Table 8 Demographics (FAS)

	NOV03 (N=303)	Saline (N=294)
Age (Years)		
Mean (SD)	60.3 (14.23)	61.6 (13.57)
Median	63.0	64.0
Min, Max	20, 87	19, 88
Age Categories, n (%)		
<18 years	0 (0.0)	0 (0.0)
≥18 to <65 years	169 (55.8)	148 (50.3)
≥65 years	134 (44.2)	146 (49.7)
Gender, n (%)		
Male	84 (27.7)	80 (27.2)
Female	219 (72.3)	214 (72.8)
Race, n (%)		
White	212 (70.0)	204 (69.4)
Black	53 (17.5)	55 (18.7)
Asian	34 (11.2)	28 (9.5)
Other	2 (0.7)	4 (1.4)
Multiple	1 (0.3)	1 (0.3)
American Indian or Alaska Native	1 (0.3)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.3)
Unknown	0 (0.0)	1 (0.3)
Ethnicity, n (%)		
Hispanic or Latino	43 (14.2)	51 (17.3)
Not Hispanic or Latino	260 (85.8)	243 (82.7)
Study Eye, n (%)		
OD	183 (60.4)	170 (57.8)
OS	120 (39.6)	124 (42.2)

Abbreviations: FAS = Full Analysis Set; OD = right eye; OS = left eye; SD = standard deviation Source: Table 14.1.4.1

Reviewer's Comment: *No appreciable differences were observed between the NOV03 and saline groups in the demographic characteristics.*

Table 9 Baseline Ocular Characteristics (FAS)	NOV03 (N=303)	Saline (N=294)
tCFS, Study Eye		
Mean (SD)	6.7 (1.8)	6.7 (1.9)
Median	7.0	6.0
Min, Max	4, 11	4, 11
VAS Dryness Score		
Mean (SD)	66.5 (19.1)	66.8 (18.7)
Median	70.0	70.0
Min, Max	3, 100	0, 100
VAS Burning/Stinging Score		
Mean (SD)	53.0 (26.73)	52.1 (26.55)
Median	57.0	57.0
Min, Max	0, 100	0, 100
Total MGD Score, Study Eye		
Mean (SD)	7.4 (3.06)	7.7 (3.16)
Median	7.0	7.0
Min, Max	3, 15	3, 15
Average TFBUT, Study Eye (sec)		
Mean (SD)	3.193 (0.838)	3.265 (0.831)
Median	3.130	3.150
Min, Max	1.34, 5.01	1.00, 5.00
Unanesthetized Schirmer's Test I, Study Eye (mm)		
Mean (SD)	12.0 (8.30)	11.7 (7.60)
Median	9.0	8.0
Min, Max	5, 35	5, 35
OSDI Score		
Mean (SD)	53.92 (17.55)	54.40 (16.98)
Median	52.10	54.20
Min, Max	25.0, 100.0	25.0, 97.9
BCVA (logMAR)		
Mean (SD)	0.073 (0.142)	0.086 (0.143)
Median	0.040	0.090
Min, Max	-0.26; 0.62	-0.30; 0.54

Abbreviations: BCVA=best-corrected visual acuity; FAS=Full Analysis Set; logMAR=logarithm of the minimum angle of resolution; MGD=meibomian gland assessment; OSDI=ocular surface disease index; SD=standard deviation; tCFS=total fluorescein corneal staining; TFBUT=tear film break-up time; VAS=visual analog scale. Source: Table 14.1.5.1

Reviewer's Comment: *Baseline ocular characteristics were similar across treatment groups.*

Efficacy Results – Primary Endpoint

The primary efficacy endpoints were tested using hierarchical fixed sequence testing at α=0.05: change from baseline in total corneal fluorescein staining (tCFS) in the study eye at Day 57, followed by change from baseline in the eye dryness VAS score at Day 57.

Table 10 Primary Endpoints: Change from Baseline in tCFS in the Study Eye and Eye Dryness Score (VAS) at Day 57 (FAS and PPS)

	FAS		PPS	
Change from Baseline	NOV03	Saline	NOV03	Saline
tCFS (Study Eye)	N=289	N=279	N=279	N=270
Baseline (SD)	6.7 (1.8)	6.7 (1.9)	6.8 (1.8)	6.6 (1.9)
Mean (SD)	-2.0 (2.6)	-1.0 (2.7)	-2.1 (2.5)	-1.0 (2.7)
Median	-2.0	-1.0	-2.0	-1.0
Min, max	-10; 7	-9; 7	-10; 7	-9; 7
LS mean	-2.02	-1.05	-2.03	-1.03
NOV03 – Saline (95% CI)	-1.0 (-1.4, -0.6)		-1.0 (-1.4, -0.6)	
p-value	<0.001		<0.001	
Dryness Score (VAS)	N=289	N=279	N=279	N=270
Baseline (SD)	66.5 (19.1)	66.8 (18.7)	66.8 (19.1)	66.5 (18.6)
Mean (SD)	-27.4 (27.9)	-19.7 (26.7)	-26.9 (27.9)	-19.6 (26.6)
Median	-29.0	-18.0	-27.0	-17.5
Min, max	-90; 50	-96; 66	-90; 50	-96; 66
LS mean	-27.3	-19.7	-26.8	-19.7
NOV03 – Saline (95% CI)	-7.6 (-11.8, -3.4)		-7.10 (-11.4, -2.8)	
p-value	<0.001		0.001	

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; FAS=Full Analysis Set; LS=least squares; PPS=Per Protocol Set; SD=standard deviation; tCFS=total corneal fluorescein staining; VAS=visual analog scale
Note: LS Mean, Diff, 95% CI, and p-value are from an ANCOVA model with terms for baseline value and treatment.
Source: Table 14.2.1.1, Table 14.2.1.2

Reviewer Comments: Both of the primary endpoints were met in this study. Change from baseline in total corneal fluorescein(tCFS) and change from baseline in the eye dryness VAS score at Day 57 are statistically significant favoring drug product.

Data Quality and Integrity
This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

Table 11 Change from Baseline in Secondary Efficacy Endpoints (FAS)

	FAS	
Change from Baseline	NOV03	Saline
Dryness Score (VAS) at Day 15	N=297	N=289
Baseline	66.5 (19.1)	66.8 (18.7)
Mean (SD)	-18.0 (24.0)	-13.4 (23.3)
Median	-17.0	-10.0
Min, max	-90; 91	-96; 64
LS mean	-18.0	-13.3
NOV03 – Saline (95% CI)	-4.7 (-8.2, -1.2)	
p-value	0.009	
tCFS (Study Eye) at Day 15	N=296	N=288
Baseline	6.7 (1.8)	6.7 (1.9)
Mean (SD)	-1.7 (2.1)	-1.1 (2.2)
Median	-2.0	-1.0
Min, max	-7; 6	-8; 6
LS mean	-1.7	-1.1
NOV03 – Saline (95% CI)	-0.6 (-0.9, -0.2)	
p-value	0.001	
Burning/Stinging Score (VAS) at Day 57	N=289	N=278
Baseline	53.0 (26.73)	52.1 (26.55)
Mean (SD)	-23.6 (29.8)	-18.0 (25.3)
Median	-21.0	-15.0
Min, max	-99; 79	-84; 79
LS mean	-23.5	-18.01
NOV03 – Saline (95% CI)	-5.52 (-9.46, -1.59)	
p-value	0.006	
cCFS (Study Eye) at Day 57	n=289	N=279
Baseline	1.07	1.09
Mean (SD)	-0.4 (0.8)	-0.1 (0.9)
Median	0.0	0.0
Min, max	-3; 2	-3; 3
LS mean	-0.4	-0.1
NOV03 – Saline (95% CI)	-0.2 (-0.4, -0.1)	
p-value	<0.001	

Abbreviations: ANCOVA=analysis of covariance; cCFS=central corneal fluorescein staining; CI=confidence interval; FAS=Full Analysis Set; LS=least squares; SD=standard deviation; tCFS=total corneal fluorescein staining; VAS=visual analog scale. Note: LS Mean, Diff, 95% CI, and p-value are from an ANCOVA model with terms for baseline value and treatment. Source: Table 14.2.4.1

Reviewer Comments: Analysis showed a statistically significant difference between the NOV03 and saline groups for all secondary endpoints.

6.2. BL-904

Overview and Objective -Same as NVU-003
Trial Design –Same as NVU-003
Schedule of Visits and Parameters – Same as NVU-003
Study Endpoints – Same as NVU-003
Safety Evaluations – Same as NVU-003
Statistical Analysis Plan – Same as NVU-003

BL-904 Study Results

Table 12 Patient Disposition (FAS)

	NOV03 n (%)	Saline n (%)
No. Subjects Randomized: n (%)	311 (100.0)	309 (100.0)
No. Subjects Completed IP: n (%)	302 (97.1)	295 (95.5)
No. Subjects Discontinued IP: n (%)	9 (2.9)	14 (4.5)
Subject Choice	6 (1.9)	5 (1.6)
Other	1 (0.3)	5 (1.6)
Protocol Violation	2 (0.6)	3 (1.0)
Lack of Efficacy	0 (0.0)	1 (0.3)
Adverse Event	0 (0.0)	0 (0.0)
Administrative Reason	0 (0.0)	0 (0.0)
No. Subjects Completed Study: n (%)	302 (97.1)	296 (95.8)
No. Subjects Discontinued Study: n (%)	9 (2.9)	13 (4.2)
Withdrawal by Subject	5 (1.6)	6 (1.9)
Protocol Violation	2 (0.6)	3 (1.0)
Other	2 (0.6)	2 (0.6)
Lost to Follow Up	0 (0.0)	1 (0.3)
Lack of Efficacy	0 (0.0)	1 (0.3)
Adverse Event	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)

Abbreviations: IP = investigational product
Source: Table 14.1.1.1, Table 14.1.2.1, Table 14.1.2.2

Table 13 Analysis Sets (All Randomized)

Data Set / Reason for Exclusion	NOV03 (N=312) n (%)	Saline (N=310) n (%)
FAS and SAF	311* (99.7)	309 (99.7)
Did not receive at least 1 dose of IP	1 (0.3)	1 (0.3)
PPS	278 (89.1)	278 (89.7)
Study Visit Schedule Deviations	13 (4.2)	12 (3.9)
Patient Did Not Complete the Study	9 (2.9)	13 (4.2)
Investigational Product Deviation / Compliance	9 (2.9)	5 (1.6)
Study Medication Compliance <80%	5 (1.6)	5 (1.6)
Use of Prohibited Concomitant Medications	3 (1.0)	4 (1.3)
Missed / Delayed / Not Per Protocol Procedures	3 (1.0)	2 (0.6)
Per Protocol Set (PPS) Inclusion and Exclusion Criteria	2 (0.6)	2 (0.6)
Other	2 (0.6)	1 (0.3)
Patient is Not in Full Analysis Set (FAS)	1 (0.3)	1 (0.3)
Informed Consent Procedures	1 (0.3)	0 (0.0)
Subject Non-compliance with Instructions	1 (0.3)	0 (0.0)

Abbreviations: FAS = Full Analysis Set; IP = investigational product; PPS = Per Protocol Set; SAF = Safety Set
* Subject (b) (6), who was incorrectly treated with both NOV03 and saline during the study, is reported in the NOV03 group. Note: Subjects may have been excluded from the PPS for >1 reason. Source: Table 14.1.2.1, Table 14.1.2.2

Protocol Violations/Deviation

A total of 51 (8%) subjects, 28 (9%) in the NOV03 group and 23 (7%) in the saline group, had at least 1 major protocol deviation during the study. The most common types of major protocol deviations were related to study visit/schedule deviations (25 events [13, NOV03; 12, saline]) and IP deviation/compliance (13 events [8, NOV03;5, saline]).

Table 14 Demographic Characteristics

	NOV03 (N=311)	Saline (N=309)
Age (Years)		
Mean (SD)	53.3 (17.38)	53.8 (16.26)
Median	55.0	56.0
Min, Max	19, 85	20, 88
Age Categories, n (%)		
<18 years	0 (0.0)	0 (0.0)
≥18 to <65 years	210 (67.5)	213 (68.9)
≥65 years	101 (32.5)	96 (31.1)
Gender, n (%)		
Male	61 (19.6)	71 (23.0)

	NOV03 (N=311)	Saline (N=309)
Female	250 (80.4)	238 (77.0)
Race, n (%)		
White	244 (78.5)	255 (82.5)
Asian	36 (11.6)	27 (8.7)
Black	23 (7.4)	20 (6.5)
Native Hawaiian or Other Pacific Islander	3 (1.0)	2 (0.6)
Multiple	2 (0.6)	3 (1.0)
Other	1 (0.3)	2 (0.6)
American Indian or Alaska Native	2 (0.6)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)
Ethnicity, n (%)		
Hispanic or Latino	63 (20.3)	65 (21.0)
Not Hispanic or Latino	248 (79.7)	244 (79.0)
Study Eye, n (%)		
n (missing)	310 (1)	309 (0)
OD	168 (54.0)	182 (58.9)
OS	142 (45.7)	127 (41.1)

Abbreviations: FAS = Full Analysis Set; OD = right eye; OS = left eye; SD = standard deviation Notes: A database entry error in the birthdate of Subject (b) (6) did not affect the subject's age classification. Subject (b) (6) with missing study eye information was not included in the eye-level analysis. Source: Table 14.1.4.1

Reviewer's Comment: *Demographic characteristics were balanced between treatment groups.*

Table 15 Baseline Ocular Characteristics

	NOV03 (N=311)	Saline (N=309)
tCFS, Study Eye*		
Mean (SD)	7.0 (2.0)	7.1 (2.1)
Median	7.0	7.0
Min, Max	4, 11	4, 11
VAS Dryness Score		
Mean (SD)	64.7 (19.5)	64.3 (19.8)
Median	70.0	69.0
Min, Max	0, 100	10, 100
VAS Burning/Stinging Score		
Mean (SD)	50.1 (25.83)	48.4 (26.19)
Median	51.0	50.0
Min, Max	0, 100	0, 100

Total MGD Score, Study Eye*		
Mean (SD)	7.9 (3.45)	8.1 (3.47)
Median	7.0	7.0
Min, Max	3, 15	3, 15
Average TFBUT, Study Eye (seconds)		
Mean (SD)	3.165 (0.921)	3.144 (0.922)
Median	3.145	3.050
Min, Max	0.95, 5.00	0.75, 5.00
Unanesthetized Schirmer's Test I, Study Eye (mm)*		
Mean (SD)	12.7 (7.54)	12.8 (7.93)
Median	10.0	10.0
Min, Max	5, 35	5, 35
OSDI Score		
Mean (SD)	55.16 (17.44)	55.80 (17.21)
Median	54.50	55.00
Min, Max	25.0, 95.8	25.0, 100.0
Calculated BCVA (LogMAR), Study Eye*		
Mean (SD)	0.072 (0.141)	0.067 (0.134)
Median	0.040	0.040
Min, Max	-0.30, 0.54	-0.28, 0.60

Abbreviations: BCVA = best corrected visual acuity; FAS = Full Analysis Set; LogMAR = logarithm of the minimum angle of resolution; MGD = meibomian gland dysfunction; OSDI = ocular surface disease index; SD = standard deviation; tCFS = total corneal fluorescein staining; TFBUT = tear film break-up time; VAS = visual analog scale

Note: Subject (b) (6) with missing study eye information was not included in the eye-level analysis.

* NOV03 n = 310 and All Subjects n = 619. Otherwise, n = N in the column heading. Source: Table 14.1.5.1

Reviewer's Comment: *Baseline ocular characteristics were balanced between treatment groups.*

Efficacy Results – Primary Endpoint

The primary efficacy endpoints were tested using hierarchical fixed sequence testing at α=0.05: change from baseline in tCFS in the study eye at Day 57, followed by change from baseline in the eye dryness VAS score at Day 57.

A total of 556 subjects (278, NOV03; 278, saline) were included in the PPS; 64 subjects in the FAS were excluded from the PPS (Listing 16.2.3.1). The most common reasons for exclusion were study visit/schedule deviations (25 [4.0%] subjects), noncompletion of the study (22 [3.5%] subjects), and IP deviation (14 [2.3%] subjects).

Table 16 Primary Endpoints: Change from Baseline in tCFS in the Study Eye and Eye Dryness Score (VAS) at Day 57 (FAS and PPS)

	FAS		PPS	
Change from Baseline	NOV03	Saline	NOV03	Saline
tCFS (Study Eye)	N=302	N=296	N=278	N=278
Baseline	7.0 (2.0)	7.1 (2.1)	7.1 (2.0)	7.1 (2.2)
Mean (SD)	-2.3 (2.8)	-1.1 (2.9)	-2.4 (2.8)	-1.1 (2.8)
Median	-2.5	-1.0	-3.0	-1.0
Min, max	-11, 7	-11, 7	-11, 7	-8, 7
LS mean	-2.3	-1.1	-2.4	-1.1
NOV03 – Saline (95% CI)	-1.21 (-1.66, -0.76)		-1.27 (-1.72, -0.81)	
p-value	<0.001		<0.001	
Dryness Score (VAS)	N=302	N=296	N=278	N=278
Baseline	64.7 (19.5)	64.3 (19.8)	64.7 (19.5)	64.2 (20.1)
Mean (SD)	-29.5 (28.6)	-19.0 (27.2)	-29.2 (28.6)	-19.1 (27.5)
Median	-30.5	-18.5	-30.5	-19.0
Min, max	-90, 53	-100, 90	-90, 53	-100, 90
LS mean	-29.4	-19.2	-29.1	-19.2
NOV03 – Saline (95% CI)	-10.2 (-14.3, -6.1)		-9.9 (-14.2, -5.6)	
p-value	<0.001		<0.001	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; FAS = Full Analysis Set; LS = least squares; PPS = Per Protocol Set; SD = standard deviation; tCFS = total corneal fluorescein staining; VAS = Visual Analog Scale
Note: Subject (b) (6) with missing study eye information was not included in the eye-level analysis. tCFS is of the study eye. tCFS and Dryness Score (VAS) tested using hierarchical fixed sequence. Least squares mean, NOV03 – Saline Difference, 95% CI, and p-value are from an ANCOVA model with terms for baseline value and treatment. Because the discontinuation rate was <5%, there was no need to conduct the planned MCMC robustness analysis (Table 14.2.2).
Source: Table 14.2.1.1, Table 14.2.1.2

Reviewer Comments: Both of the primary endpoints were met in this study. Change from baseline in total corneal fluorescein staining (tCFS) and change from baseline in the eye dryness VAS score at Day 57 are statistically significant favoring drug product.

Data Quality and Integrity

This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results - Table 17 Change from Baseline in Key Secondary Efficacy Endpoints (FAS)

	FAS	
Change from Baseline	NOV03	Saline
Dryness Score (VAS) at Day 15	307	306
Baseline	64.7 (19.5)	64.3 (19.8)
Mean (SD)	-18.5 (23.6)	-10.5 (23.9)
Median	-19.0	-9.0
Min, max	-88, 70	-90, 60
LS mean	-18.39	-10.61
NOV03 – Saline (95% CI)	-7.8 (-11.3, -4.3)	
p-value	<0.001	
tCFS (Study Eye) at Day 15	307	302
Baseline	7.0 (2.0)	7.1 (2.1)
Mean (SD)	-1.9 (2.3)	-1.3 (2.4)
Median	-2.0	-1.0
Min, max	-9, 7	-9, 7
LS mean	-1.9	-1.3
NOV03 – Saline (95% CI)	-0.60 (-1.0, -0.2)	
p-value	0.001	
Burning/Stinging Score (VAS) at Day 57	301	296
Baseline	50.1 (25.83)	48.4 (26.19)
Mean (SD)	-22.1 (27.5)	-13.7 (29.9)
Median	-20.0	-10.0
Min, max	-95, 60	-100, 89
LS mean	-21.5	-14.2
NOV03 – Saline (95% CI)	-7.31 (-11.3, -3.3)	
p-value	<0.001	
cCFS (Study Eye) at Day 57	302	296
Baseline	1.1	1.2
Median	0.0	0.0
Min, max	-3, 3	-3, 2
LS mean	-0.4	-0.1
NOV03 – Saline (95% CI)	-0.3 (-0.5, -0.2)	
p-value	<0.001	

Abbreviations: ANCOVA=analysis of covariance; cCFS=central corneal fluorescein staining; CI=confidence interval; FAS=Full Analysis Set; LS=least squares; SD=standard deviation; tCFS=total corneal fluorescein staining; VAS=visual analog scale. Note: Subject (b) (6) with missing study eye information was not included in the eye-level analysis. tCFS and cCFS are of the study eye. Endpoints are tested using hierarchical fixed sequence as they appear sequentially above. LS Mean, Diff, 95% CI, and p-value are from an ANCOVA model with terms for baseline value and treatment. Source: Table 14.2.4.1

Reviewer Comments: Analysis showed a statistically significant difference between the NOV03 and saline groups for all key secondary endpoints.

7. Integrated Review of Effectiveness

Two trials (NVU-003 and BL-904) studied the same endpoints and demonstrated efficacy for both an objective sign and a subjective symptom.

8. Review of Safety

8.1. Safety Review Approach

The safety data from Studies NVU-002, NVU-003, and BL-904 were reviewed to evaluate the safety of Miebo (perfluorohexyloctane solution). Study NVU-004 was an open-label safety extension of NVU-003 was not pooled with the other studies for analysis.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 18 Study Medication Exposure and Compliance Analysis Set: Safety Analysis Set

	NOV03 BID (N=111)		NOV03 QID [a] (N=728)		All NOV03 [a] (N=839)		Saline (N=714)	
Randomized, n (%)	111	(100.0)	728	(100.0)	839	(100.0)	714	(100.0)
Phase 2	111	(100.0)	114	(15.7)	225	(26.8)	111	(15.5)
Phase 3	0	(0)	614	(84.3)	614	(73.2)	603	(84.5)
Dosed, n (%)	111	(100.0)	728	(100.0)	839	(100.0)	714	(100.0)
Completed Study Drug, n (%)	105	(94.6)	702*	(96.4)	807*	(96.2)	683	(95.7)
Prematurely Discontinued Study Drug, n (%)	6	(5.4)	24	(3.3)	30	(3.6)	31	(4.3)
Reason for Discontinuation Adverse Event [c] of Study Drug, N (%) [b]	0	(0)	1	(0.2)	1	(0.2)	3	(0.5)
Protocol Violation	0	(0)	3	(0.5)	3	(0.5)	3	(0.5)
Administrative Reason	0	(0)	0	(0)	0	(0)	1	(0.2)
Lack of Efficacy	0	(0)	0	(0)	0	(0)	1	(0.2)
Subject Choice	0	(0)	12	(2.0)	12	(2.0)	9	(1.5)
Other	0	(0)	5	(0.8)	5	(0.8)	11	(1.8)

Note: Percentages are based on the number of subjects randomized except as noted for Reason for Discontinuation of Study Drug.
* Subjects NVU-002 (b) (6) and NVU-003 (b) (6) had missing treatment completion information.
[a] Subject BL-904 (b) (6) who was incorrectly treated with both NOV03 QID and Saline during the study is reported in the NOV03 QID group.
[b] Reason for Discontinuation of Study Drug is not available for NVU-002. Percentages are based on the number of subjects randomized in the Phase 3 studies.
[c] Adverse events noted on the AE CRF as leading to discontinuation of study treatment in NVU-002 are not included in the disposition summary but are included in the AE summary tables.
Reference: NVU-002 Table 14.1.1.1, NVU-003 Table 14.1.1.3, BL-904 Table 14.1.1.3.

Mean duration of exposure to IP was 55.7 days (range: 1 day to 76 days); mean duration of exposure was similar among treatment groups: 55.3 days, 55.9 days, and 55.5 days in the NOV03 BID, NOV03 QID, and saline groups, respectively.

8.2.2. Relevant characteristics of the safety population:

Table 19 Demographic Characteristics – Pooled Studies

	NOV03 BID N=111	NOV03 QID N=728	Saline N=714
Age (Years)			
Mean (SD)	54.0 (14.91)	56.2 (16.55)	57.0 (15.62)
Median	57.0	59.0	60.0
Min, Max	22; 86	19; 87	19; 88
Age Categories, n (%)			
<18 years	0	0	0
≥18 to <65 years	82 (73.9)	456 (62.6)	437 (61.2)
≥65 years	29 (26.1)	272 (37.4)	277 (38.8)
Sex, n (%)			
Male	27 (24.3)	180 (24.7)	182 (25.5)
Female	84 (75.7)	548 (75.3)	532 (74.5)
Race, n (%)			
White	78 (70.3)	536 (73.6)	540 (75.6)
Black	13 (11.7)	89 (12.2)	83 (11.6)
Asian	20 (18.0)	88 (12.1)	76 (10.6)
Other	0	3 (0.4)	6 (0.8)
Native Hawaiian or Other Pacific Islander	0	5 (0.7)	3 (0.4)
Multiple	0	3 (0.4)	4 (0.6)
American Indian or Alaska Native	0	4 (0.5)	1 (0.1)
Unknown	0	0	1 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	26 (23.4)	136 (18.7)	137 (19.2)
Not Hispanic or Latino	85 (76.6)	592 (81.3)	577 (80.8)
Study Eye, n (%)			
n (missing)	111 (0)	727 (1)	714 (0)
OD	59 (53.2)	416 (57.1)	423 (59.2)
OS	52 (46.8)	311 (42.7)	291 (40.8)

Abbreviations: BID = two times a day; OD = right eye; OS = left eye; QID = four times a day; SD = standard deviation
Note: Subject (b) (6), who was incorrectly treated with both NOV03 QID and saline during the BL-904 study, is reported in the NOV03 QID group.
Note: Subject (b) (6) (NOV03 QID) did not have a study eye defined and therefore is not included in the eye- level summaries. Source: ISS Table 1.2.1

8.2.3. Adequacy of the safety database:

The overall exposure to perfluorohexyloctane ophthalmic solution and size of the database and the clinical evaluations conducted during development were adequate to assess the safety profile of this drug product.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Routine Clinical Tests

None of the clinical laboratory results in NVU-002 (hematology, clinical chemistry) were indicative of a safety concern for NOV03. There were no clinically significant changes from baseline in any laboratory parameter. The most common laboratory-related adverse events were increased blood lactate dehydrogenase (2 subjects NOV03 QID; 2 subjects NOV03 BID) increased blood triglycerides (2 subjects NOV03 QID; 2 subjects NOV03 BID), and increased blood uric acid (1 subject NOV03 QID; 2 subjects NOV03 BID; 1 subject saline)

The routine clinical testing required to evaluate the safety concerns associated with the treatment of ophthalmic conditions (i.e., biomicroscopy, fundoscopy, visual acuity, etc.) were adequately addressed in the design and conduct of the trials There were no clinically relevant changes from baseline in visual acuity, slit-lamp biomicroscopy, intraocular pressure, dilated fundoscopy.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in any of the pooled clinical trials during the treatment period.

8.4.2. Serious Adverse Events

No ocular serious adverse events occurred in the trials. Five (0.3%) subjects (1 NOV03 BID, 3 NOV03 QID, 1 saline) experienced a serious, non- ocular adverse events in the pooled studies: chest pain (1 NOV03 BID, 1 saline), diverticulum (1 NOV03 QID), endometrial adenocarcinoma (1 NOV03 QID), and spontaneous abortion (1 NOV03 QID).

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Of the 1553 subjects randomized into the pooled studies, 64 (4.1%) subjects did not complete the studies. The most common reasons for premature withdrawal were subject withdrawal (29 subjects) and reason classified as "Other" (10 subjects). Six (0.4%) subjects had a TEAE that led to withdrawal from the study; 2 other subjects (both in NVU-002, NOV03 BID) were counted as having discontinued IP due to a TEAE but were withdrawn from the study due to a protocol violation.

8.4.4. Treatment Emergent Adverse Events

Overall, 268 (17.3%) subjects had at least 1 adverse event during the pooled studies. Eighty-five (5.5%) subjects had at least 1 adverse event considered to be related/suspected to use of perfluorohexyloctane. Most of the TEAEs were mild or moderate in severity.

Table 20 Overview of Ocular Adverse Events (Subject Level) – Pooled Studies

Subjects With	NOV03 BID N=111 n (%)	NOV03 QID N=728 n (%)	Saline N=714 n (%)
At Least 1 TEAE	5 (4.5)	82 (11.3)	73 (10.2)
Mild	4 (3.6)	73 (10.0)	67 (9.4)
Moderate	1 (0.9)	8 (1.1)	5 (0.7)
Severe	0	1 (0.1)	1 (0.1)
At Least 1 Drug-related TEAE	2 (1.8)	44 (6.0)	35 (4.9)
At Least 1 SAE	0	0	0
A TEAE that led to Drug Withdrawal	0	1 (0.1)	4 (0.6)
A TEAE that led to Study Withdrawal	0	1 (0.1)	4 (0.6)

Abbreviations: BID = two times a day; eCRF = electronic case report form; IP = investigational product; QID = four times a day; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Note: ISS Table 2.1.4.1 shows that 5 subjects had a TEAE that led to premature discontinuation of IP, whereas 4 subjects had action taken with IP in response to a TEAE reported as "IP withdrawn." This discrepancy (5 vs 4) is due to Subject (b) (6) (NVU-003 study) who had action taken with IP due to a TEAE reported as "dose not changed" even though a "yes" response was recorded in the eCRF for the question regarding whether the TEAE resulted in treatment discontinuation or not. Source: ISS Table 2.1.4.1

Table 21 Ocular Adverse Events Occurring in >1 Subject – Pooled Studies

Preferred Term	NOV03 BID N=111 n (%)	NOV03 QID N=728 n (%)	Saline N=714 n (%)
Vision blurred	0	22 (3.0)	10 (1.4)
Ocular hyperemia	0	8 (1.1)	1 (0.1)
Conjunctival hyperemia	0	5 (0.7)	6 (0.8)
Eye pruritus	0	5 (0.7)	6 (0.8)
Eye discharge	0	5 (0.7)	4 (0.6)
Instillation site pain	1 (0.9)	5 (0.7)	3 (0.4)
Blepharitis	0	5 (0.7)	1 (0.1)
Eye irritation	3 (2.7)	4 (0.5)	3 (0.4)
Conjunctival papillae	0	4 (0.5)	5 (0.7)
Foreign body sensation in eyes	2 (1.8)	4 (0.5)	1 (0.1)
Hordeolum	0	4 (0.5)	3 (0.4)
Lacrimation increased	1 (0.9)	4 (0.5)	0
Eye pain	0	2 (0.3)	7 (1.0)
Conjunctival hemorrhage	0	2 (0.3)	4 (0.6)
Corneal abrasion	0	2 (0.3)	2 (0.3)
Swelling of eyelid	0	2 (0.3)	2 (0.3)
Conjunctivitis	0	2 (0.3)	1 (0.1)
Ophthalmological examination abnormal	0	2 (0.3)	1 (0.1)
Trichiasis	0	2 (0.3)	1 (0.1)
Erythema of eyelid	0	2 (0.3)	0
Instillation site irritation	0	1 (0.1)	3 (0.4)
Vitreous detachment	0	1 (0.1)	2 (0.3)
Chalazion	0	1 (0.1)	1 (0.1)

Preferred Term	NOV03 BID N=111 n (%)	NOV03 QID N=728 n (%)	Saline N=714 n (%)
Conjunctivitis allergic	0	1 (0.1)	1 (0.1)
Corneal epithelial microcysts	0	1 (0.1)	1 (0.1)
Eyelid margin crusting	0	1 (0.1)	1 (0.1)
Eyelid oedema	1 (0.9)	1 (0.1)	0
Eyelid pain	0	1 (0.1)	1 (0.1)
Photophobia	0	1 (0.1)	1 (0.1)
Vitreous floaters	0	1 (0.1)	1 (0.1)
Hyperemia	0	0	3 (0.4)
Ocular discomfort	1 (0.9)	0	2 (0.3)
Punctate keratitis	0	0	3 (0.4)
Dry eye	0	0	2 (0.3)

Abbreviations: BID = two times a day; PT = preferred term; QID = four times a day
Note: Subject (b) (6), who was incorrectly treated with both NOV03 QID and saline during the BL-904 study, is reported in the NOV03 QID group.
Note: PTs are listed in order of descending incidence in the All Subjects Column and then alphabetically with PTs of like incidence. Source: ISS Table 2.3.4.1

Reviewer's Comment: *The most common ocular adverse events occurring in ≥ 1% of subjects were vision blurred, eye irritation, foreign body sensation, instillation site pain, lacrimation increased and ocular hyperemia.*

Table 22 Non-ocular Adverse Events Occurring in >1 Subject – Pooled Studies

Preferred Term	NOV03 BID N=111 n (%)	NOV03 QID N=728 n (%)	Saline N=714 n (%)
Headache	2 (1.8)	8 (1.1)	10 (1.4)
Pain	0	6 (0.8)	1 (0.1)
Nasopharyngitis	0	5 (0.7)	2 (0.3)
Sinusitis	1 (0.9)	5 (0.7)	0
Pyrexia	0	4 (0.5)	3 (0.4)
Upper respiratory tract infection	3 (2.7)	3 (0.4)	3 (0.4)
Chills	0	3 (0.4)	2 (0.3)
Coronavirus infection	0	3 (0.4)	2 (0.3)
Urinary tract infection	3 (2.7)	2 (0.3)	5 (0.7)
Blood lactate dehydrogenase increased	2 (1.8)	2 (0.3)	0
Blood triglycerides increased	2 (1.8)	2 (0.3)	0
Alanine aminotransferase increased	0	2 (0.3)	0
Cough	0	2 (0.3)	0
Intervertebral disc protrusion	0	2 (0.3)	0
Nausea	0	2 (0.3)	0
Blood uric acid increased	2 (1.8)	1 (0.1)	1 (0.1)
Covid-19	0	1 (0.1)	2 (0.3)
Fall	1 (0.9)	1 (0.1)	1 (0.1)

Preferred Term	NOV03 BID N=111 n (%)	NOV03 QID N=728 n (%)	Saline N=714 n (%)
High density lipoprotein increased	0	1 (0.1)	2 (0.3)
Pneumonia	0	1 (0.1)	2 (0.3)
Arthritis	0	1 (0.1)	1 (0.1)
Back pain	0	1 (0.1)	1 (0.1)
Blood cholesterol increased	0	1 (0.1)	1 (0.1)
Blood urea increased	1 (0.9)	1 (0.1)	0
Gamma-glutamyltransferase increased	0	1 (0.1)	1 (0.1)
Hematocrit decreased	0	1 (0.1)	1 (0.1)
Low density lipoprotein increased	0	1 (0.1)	1 (0.1)
Pain in extremity	1 (0.9)	1 (0.1)	0
Sinus headache	0	1 (0.1)	1 (0.1)
Arthralgia	3 (2.7)	0	2 (0.3)
Gastroesophageal reflux disease	2 (1.8)	0	1 (0.1)
Anxiety	0	0	2 (0.3)
Chest pain	1 (0.9)	0	1 (0.1)
Influenza	2 (1.8)	0	0
Seasonal allergy	0	0	2 (0.3)

Abbreviations: BID = two times a day; PT = preferred term; QID = four times a day
Note: Subject (b) (6), who was incorrectly treated with both NOV03 QID and saline during the BL-904 study, is reported in the NOV03 QID group.
Note: PTs are listed in order of descending incidence in the All Subjects Column and then alphabetically with PTs of like incidence.
Source: ISS Table 2.3.5

Reviewer's Comment: *The most common non-ocular adverse events occurring in ≥ 2% of subjects were upper respiratory infection (3.1%), urinary tract infection (3.0%), headache (2.9%), arthralgia (2.7%), increased lactic dehydrogenase (2.1%) and increased triglycerides (2.1%).*

8.4.5. Vital Signs

Vital signs were not assessed during this development program.

8.4.6. Electrocardiograms (ECGs)

Electrocardiograms were not assessed during this development program.

8.5. Safety in the Postmarket Setting

8.5.1. Safety Concerns Identified Through Postmarket Experience

The product is currently marketed by Ursapharm in Europe under the name EvoTears. There are no known safety concerns identified.

8.6. Integrated Assessment of Safety

The safety of Miebo (perfluorohexyloctane ophthalmic solution) 100% was assessed in over 1553 patients dosed bid or qid for 8 weeks. The most common adverse event was blurred vision (3%). The benefit of Miebo (perfluorohexyloctane ophthalmic solution) 100% dosed four times per day for the treatment of dry eye disease outweigh the risks associated with its use.

Evaluation of the effect of Meibo on corneal endothelium was not performed. It is recommended that a post marketing commitment to evaluate the effect of the product on the corneal endothelium in at least 100 patients at 12 months be requested.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not held for the NDA. There were no issues that were felt to benefit from discussion at an Advisory Committee Meeting

10.Labeling Recommendations

10.1. Prescription Drug Labeling

See Appendix 13.4 for recommended edits to the draft labeling.

11.Risk Evaluation and Mitigation Strategies (REMS)

There are no recommended Risk Evaluation or Mitigation strategies for this NDA.

12.Postmarketing Requirements and Commitments

Evaluation of the effect of Meibo on corneal endothelium was not performed. It is recommended that a post marketing commitment to evaluate the effect of the product on the corneal endothelium in at least 100 patients at 12 months be requested.

13.Appendices

13.1. References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by the applicant in this application for this indication.

13.2. Financial Disclosure

Covered Clinical Study (NVU-002, NVU-003, BL-904 and NVU-004)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 107		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. List of Investigators

NVU-003 List and Description of Investigators

*Principle Investigator changed from Steven Rauchman,MD to Robert John Smyth-Medina, MD.
** One subject was randomized, but not treated.

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
101	David L. Wirta, MD Eye Research Foundation 520 Superior Avenue, Suite 235 Newport Beach, CA 92663	(b) (6)	**Total:** # 60 NOV03 QID: # 32 Saline QID: # 28
102	Robert John Smyth-Medina, MD* North Valley Eye Medical Group 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345		**Total:** # 17 NOV03 QID: # 8 Saline QID: # 9
103	Damien Goldberg, MD Wolstan & Goldberg Eye Associates 23600 Telo Avenue, Suite 100 Torrance, CA 90505		**Total:** # 16 NOV03 QID: # 8 Saline QID: # 8

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
104	Kyle Rhodes, MD Lake Travis Eye and Laser Center/Revolution Research 3503 Wild Cherry Drive, Bldg. 3 Lakeway, TX 78738	(b) (6)	**Total: # 37** NOV03 QID: # 19 Saline QID: # 18
105	Joseph L. Meyer, MD Round Rock Eye Consultants/Revolution Research 1880 Round Rock Avenue, Suite 100 Round Rock, TX 78681		**Total: # 7** NOV03 QID: # 4 Saline QID: # 3
106	Philip Lee Shettle, DO Shettle Eye Research, Inc. 13113 66th Street N. Largo, FL 33773		**Total: # 19** NOV03 QID: # 10 Saline QID: # 9
107	David G. Evans, OD Total Eye Care, PA 6060 Primacy Parkway, Suite 200 Memphis, TN 38119		**Total: # 60** NOV03 QID: # 30 Saline QID: # 30
108	Mitchell A. Jackson, MD Jackson Eye, SC 300 N. Milwaukee Avenue, Suite L Lake Villa, IL 60046		**Total: # 20** NOV03 QID: # 10 Saline QID: # 10
109	Gary W. Jerkins, MD Advancing Vision Research, LLC 515 Stonecrest Parkway, Suite 210 Smyrna, TN 37167		**Total: # 13** NOV03 QID: # 6 Saline QID: # 7

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
110	Sherif El-Harazi, MD Global Research Management, Inc. 1510 S. Central Avenue, Suite 300 Glendale, CA 91204	(b) (6)	**Total: # 41**** NOV03 QID: # 19 Saline QID: # 21
111	Gregg J. Berdy, MD Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131		**Total: # 17** NOV03 QID: # 8 Saline QID: # 9
112	Kathleen Kelley, OD Price Vision Group & Cornea Research Foundation of America 9002 N. Meridian Street, Suite 100 Indianapolis, IN 46260		**Total: # 9** NOV03 QID: # 6 Saline QID: # 3
113	Joseph Tauber, MD Tauber Eye Center 4400 Broadway, Suite 202 Kansas City, MO 64111		**Total: # 16** NOV03 QID: # 7 Saline QID: # 9
114	Carol Aune, OD Oculus Research, Inc. at EyeCare Center 4170 Fayetteville Road Raleigh, NC 27603		**Total: # 49**** NOV03 QID: # 25 Saline QID: # 23

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
115	Jerry L. Robben, OD Bowden Eye & Associates 7205 Bonneval Road Jacksonville, FL 32256	(b) (6)	**Total: # 25** NOV03 QID: #12 Saline QID: # 13
116	Joseph Martel, MD Martel Eye Medical Group 11216 Trinity River Drive Rancho Cordova, CA 95670		**Total: # 22** NOV03 QID: # 11 Saline QID: # 11
117	Bernard R. Perez, MD, FACS International Research Center 4506 Wishart Place Tampa, FL 33603		**Total: # 6** NOV03 QID: # 3 Saline QID: # 3
118	Edward R. Rashid, MD R and R Eye Research, LLC 5430 Fredericksburg Road, Suite 100, 102, 120 San Antonio, TX 78229		**Total: # 10** NOV03 QID: # 5 Saline QID: # 5
119	Edward Holland, MD Cincinnati Eye Institute 580 South Loop Road Suite 200 Edgewood, KY 41017		**Total: # 5** NOV03 QID: # 3 Saline QID: # 2

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
120	Louis Alpern, MD Louis M. Alpern, MD, MPH, PA 4171 North Mesa Street, Bldg. D, Suite 100 El Paso, TX 79902	(b) (6)	**Total: # 16** NOV03 QID: # 8 Saline QID: # 8
121	Theodore Pasquali, MD SoCal Eye Physicians and Associates 3300 E. South Street Suites 100, 105 Long Beach, CA 90805		**Total: # 21** NOV03 QID: # 11 Saline QID: # 10
122	Daniel V. Zimmer, MD, FACS Scott & Christie and Associates, PC 105 Brandt Drive, Suite 201, 202, 204 Cranberry Township, PA 16066		**Total: # 26** NOV03 QID: # 13 Saline QID: # 13
123	Johnathon Eric Downing, MD Premiere Practice Management, LLC 23441 Madison Street, Suite 120 Torrance, CA 90505		**Total: # 60** NOV03 QID: # 31 Saline QID: # 29
126	Jack Greiner, OD, DO, PhD Clinical Eye Research of Boston, LLC 955 Main Street, Suite 307 Winchester, MA 01890		**Total: # 6** NOV03 QID: # 2 Saline QID: # 4

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
127	Matthew D. Paul, MD Connecticut Eye Consultants, P.C. 69 Sand Pit Road, Suite 101, 102, 200, 203 Danbury, CT 06810	(b) (6)	**Total:** # 16 NOV03 QID: # 9 Saline QID: # 7
129	Stephen E. Smith, MD Eye Associates of Fort Meyers 4225 Evans Avenue Fort Meyers, FL 33901		**Total:** # 5 NOV03 QID: # 3 Saline QID: # 2

BL-904 List and Description of Investigators

* Investigator Principle changed from James Boyce, MD to Norman Liu, MD.
** One subject was randomized, but not treated.

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
201	Mark Bergmann, MD Apex Eye 6507 Harrison Ave Suite E Cincinnati, OH 45247	(b) (6)	**Total: # 4** NOV03 QID: # 2 Saline QID: # 2
202	Norman Liu, MD* Orange County Ophthalmology Medical Group 12665 Garden Grove Blvd, Suite 401 Garden Grove, CA 92843		**Total: # 31** NOV03 QID: # 16 Saline QID: # 15
203	Jeannine Eunice Camacho, OD Kozlovsky Delay & Winter Eye Consultants, LLC 2929 Mossrock, Suite 104 San Antonio, TX 78230		**Total: # 16** NOV03 QID: # 8 Saline QID: # 8

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
204	Jennifer Lee Kim, MD Clayton Eye Clinical Research, LLC 1000 Corporate Center Drive, Suite 100, 120 Morrow, GA 30260	(b) (6)	**Total: # 16** NOV03 QID: # 8 Saline QID: # 8
206	Robert H. Gross, MD Cornea and Cataract Consultants of Arizona 3815 E. Bell Road, Suite 2500 Phoenix, AZ 85032		**Total: # 18** NOV03 QID: # 9 Saline QID: # 9
207	Mohammad Ali Haider, DO Senior Health Services 2932 Breckenridge Lane, Suite 5 Louisville, KY 40220		**Total: # 16** NOV03 QID: # 8 Saline QID: # 8
208	Paul James Hartman, MD Rochester Ophthalmological Group, PC 2100 South Clinton Avenue Rochester, NY 14618		**Total: # 17** NOV03 QID: # 8 Saline QID: # 9
209	Jennifer Harthan, OD Illinois Eye Institute 3241 South Michigan Ave Chicago, IL 60616		**Total: # 12** NOV03 QID: # 6 Saline QID: # 6

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
210	Jeffrey Schultz, OD Asheville Eye Associates, PLLC 8 Medical Park Drive Asheville, NC 28803	(b) (6)	**Total: # 17** NOV03 QID: # 10 Saline QID: # 7
211	Bruce Arthur Segal, MD, PA Bruce Segal, MD, PA 5258 Linton Blvd, #302-301A Delray Beach, FL 33484		**Total: # 40**[++] NOV03 QID: # 19 Saline QID: # 20
212	Nancy E. Stephens, OD Advanced Laser Vision & Surgical Institute 11550 Fuqua St., Suite 215 Houston, TX 77034		**Total: # 27** NOV03 QID: # 13 Saline QID: # 14
213	Michael Sheety, MD Sierra Clinical Trials Research Organization 2010 E. First Street, Suite 160 Santa Ana, CA 92705		**Total: # 20** NOV03 QID: # 9 Saline QID: # 11
214	James Harmon Peace, MD United Medical Research Institute 431-433 North Prairie Ave Inglewood, CA 90301		**Total: # 4** NOV03 QID: # 2 Saline QID: # 2

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
215	Melissa Morrison Toyos, MD West Tennessee Eyecare dba Toyos Clinic 2204 Crestmoor Road Nashville, TN 37215	(b) (6)	**Total: # 16** NOV03 QID: # 7 Saline QID: # 9
216	Marc Alan Abrams, MD Abrams Eye Center 2322 E. 22nd St., Suite 102 Cleveland, OH 44115		**Total: # 16** NOV03 QID: # 9 Saline QID: # 7
217	Michael S. Korenfeld, MD Comprehensive Eye Care, Ltd 901 East 3rd Street Washington, MO 63090		**Total: # 14** NOV03 QID: # 7 Saline QID: # 7
218	Maria Rosselson, MD Chicago Cornea Consultants 1585 N. Barrington Road, Suite 502 Hoffman Estates, IL 60169		**Total: # 0** NOV03 QID: # 0 Saline QID: # 0
219	Vincent A. Restivo, Jr., MD Hill Country Eye Center 11901 West Parmer Lane, Suite 400 Cedar Park, TX 78613		**Total: # 4** NOV03 QID: # 2 Saline QID: # 2

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
220	John D. Sheppard, MD, M.M.Sc Virginia Eye Consultants 241 Corporate Blvd Norfolk, VA 23502	(b) (6)	**Total: # 2** NOV03 QID: # 1 Saline QID: # 1
221	Robert C. Sorenson, MD Inland Eye Specialists 3953 West Stetson Avenue Hemet, CA 92545		**Total: # 0** NOV03 QID: # 0 Saline QID: # 0
222	Da-Thuy Van, DO San Antonio Eye Center, PA 511 Dallas Street San Antonio, TX 78215		**Total: # 21** NOV03 QID: # 10 Saline QID: # 11
223	Alice Epitropoulos, MD Ophthalmic Surgeons & Consultants of Ohio 262 Neil Avenue, Suite 430 Columbus, OH 43215		**Total: # 5** NOV03 QID: # 3 Saline QID: # 2

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel	No. of Subjects Randomized
224	Joseph Gira, MD Ophthalmology Consultants 12990 Manchester Rd., Suite 201 St. Louis, MO 63131	(b) (6)	**Total: # 16** NOV03 QID: # 9 Saline QID: # 7
225	James A. Fox, MD Icon Eye Care 1000 Wellington Ave. Grand Junction, CO 81501		**Total: # 23** NOV03 QID: # 12 Saline QID: # 11
226	Ryan Gene Miller, OD LoBue Laser and Eye Medical Center 40700 California Oaks Rd., Suite 106 Murrieta, CA 92562		**Total: # 34** NOV03 QID: # 18 Saline QID: # 16
227	Laura M. Periman, MD Periman Eye Institute 320 West Galer Street, Suite 201 Seattle, WA 98119		**Total: # 2** NOV03 QID: # 1 Saline QID: # 1
228	Eugene E. Protzko, MD Seidenberg Protzko Eye Associates 2023 Pulaski Hwy Havre de Grace, MD 21078		**Total: # 44** NOV03 QID: # 22 Saline QID: # 22
229	Navin H. Tekwani, MD Tekwani Vision Center 9911 Kennerly Road, Suite A St. Louis, MO 63128		**Total: # 2** NOV03 QID: # 0 Saline QID: # 2

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel (b) (6)	No. of Subjects Randomized
230	Jason E. Stahl, MD Durrie Vision 8300 College Blvd., Suite 201 Overland Park, KS 66210		**Total: # 15** NOV03 QID: # 8 Saline QID: # 7
231	Ahmad M. Fahmy, OD, FAAO, Dipl. ABO Minnesota Eye Consultants 9801 Dupont Ave S., Suite 200 Bloomington, MN 55431		**Total: # 6** NOV03 QID: # 4 Saline QID: # 2
232	Anna Fakadej, MD Carolina Eye Associates 2170 Midland Rd Southern Pines, NC 28387		**Total: # 2** NOV03 QID: # 0 Saline QID: # 2
233	Michael E. Tepedino, MD Wake Forest Health Network Ophthalmology - Oak Hollow 1565 N. University Parkway High Point, NC 27262		**Total: # 3** NOV03 QID: # 1 Saline QID: # 2
234	Jay Rubin, MD Eye Clinics of South Texas 999 E. Basse Road, Suite 128-B San Antonio, TX 78209		**Total: # 13** NOV03 QID: # 7 Saline QID: # 6
235	Yen Dang Nieman, MD Keystone Research 5717 Balcones Drive Austin, TX 78731		**Total: # 1** NOV03 QID: # 0 Saline QID: # 1
236	Michael Khanh Le Tran, MD Michael K. Tran, M.D., Inc 15355 Brookhurst St., Suite 104 Westminster, CA 92683		**Total: # 12** NOV03 QID: # 6 Saline QID: # 6

Site Number	Principle Investigator and Site Address	Sub-investigators and Additional Personnel (b) (6)	No. of Subjects Randomized
237	Edward John Meier, MD Apex Eye Clinical Research 6150 Radio Way Mason, OH 45040		**Total: # 9** NOV03 QID: # 4 Saline QID: # 5
238	Jason Bacharach, MD North Bay Eye Associates, Inc. 104 Lynch Creek Way, Suite 12 Petaluma, CA 94954		**Total: # 1** NOV03 QID: # 1 Saline QID: # 0
239	Armin Vishteh, MD Velvet Clinical Research 2211 W Magnolia Blvd, Suite 211 Burbank, CA 91506		**Total: # 8^^** NOV03 QID: # 3 Saline QID: # 4
240	Stephen M. Montaquila, OD, FAAO West Bay Eye Associates 222 Jefferson Blvd Warwick, RI 02888		**Total: # 16** NOV03 QID: # 9 Saline QID: # 7
241	Gregory Katz, MD Huron Ophthalmology 5477 West Clark Rd. Ypsilanti, MI 48197		**Total: # 16** NOV03 QID: #7 Saline QID: #9
243	Kavita Surti, MD Premiere Practice Management, LLC 475 W. Badillo St. Covina, CA 91723		**Total: # 13** NOV03 QID: # 6 Saline QID: # 7
244	Fred Kurata, MD Premiere Practice Management, LLC 420 E. 3rd Street, Suite 603 Los Angeles, CA 90013		**Total: # 70** NOV03 QID: # 36 Saline QID: # 34

13.4. Labeling Recommendations

NDA 216675 is recommended for approval with the draft labeling revisions found in this review. This is draft labeling. Refer to the CDTL review for final labeling.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHILPA D ROSE
04/13/2023 03:14:38 PM

RHEA A LLOYD
04/13/2023 03:36:59 PM