CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216675Orig1s000

SUMMARY REVIEW

Summary Review of NDA 216675

Cross Discipline Team Leader, Deputy Division Director, Division Director, Office Director Review

Review Completion Date	See DARRTS Stamp Date
From	Rhea Lloyd, MD, William Boyd, MD, Wiley Chambers, MD, Charles Ganley, MD
Subject	Summary Review
BLA #	216675
Applicant	Bausch & Lomb Incorporated
Date of Submission	June 28, 2022
PDUFA Goal Date	June 28, 2023
Proprietary Name	Miebo
Established Name	Perfluorohexyloctane ophthalmic solution
Dosage Form(s)	Topical ophthalmic solution
Original Proposed Indication	Treatment of the signs and symptoms of dry eye disease (DED) associated with Meibomian Gland Dysfunction
Revised Indication	Treatment of the signs and symptoms of dry eye disease (DED)
Dosing Regimen(s)	One drop in each eye four times daily
Regulatory Action	Approval
Indication/Population	Treatment of signs and symptoms of dry eye disease (DED) in patients with DED.

NDA 216675 Review Team Role	Reviewer
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Pharmacology/Toxicology Reviewer	Aling Dong
Statistical Reviewer	Yan Zhou
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OPDP Reviewer	Carrie Newcomer
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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
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 review staff
cCFS	central corneal fluorescein staining
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
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
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	post-marketing commitment
PMR	post-marketing requirement
PP	per protocol
PPI	patient package insert

PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
tCFS	total corneal fluorescein staining
TEAE	treatment emergent adverse event
VAS	visual analog scale

Summary

Miebo (perfluorohexyloctane ophthalmic solution) is a sterile single component drug product. Miebo consists of 100% perfluorohexyloctane, a linear semifluorinated alkane, which has six perfluorinated and eight hydrogenated carbon atoms. When placed topically on the cornea, Miebo spreads across the ocular surface and interacts with the lipophilic part of the tear film forming a layer at the tear film air interface decreasing evaporation of the aqueous tear film component. The action of Miebo is independent of meibomian gland function and therefore the indication has been modified to delete the reference to meibomian gland dysfunction. Two trials (NVU-003 and BL-904) were submitted to support the approval of Miebo dosed in the affected eye four times per day. Both trials successfully demonstrated efficacy on Day 57 for the same co-primary efficacy endpoints, change from baseline in total corneal fluorescein staining (tCFS) and change from baseline in the eye dryness VAS score. Additionally, statistically significant treatment group differences were shown between the Miebo and the saline groups for all four of the secondary endpoints: eye dryness score and tCFS each at Day 15, and burning/stinging score and central corneal fluorescein staining (cCFS) each at Day 57. Reviewers from CMC, Pharmacology/Toxicology, Statistical, Clinical Pharmacology and Labeling have not identified any deficiencies. Manufacturing facility inspections verified that the proposed manufacturing facilities are in compliance with current Good Manufacturing Practices (cGMP). The application will be approved for the use of Miebo (perfluorohexyloctane ophthalmic solution) dosed four times a day in the affected eye(s) for the treatment of DED.

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 DED. Both studies met their co-primary endpoints, change from baseline in tCFS and change in baseline in the eye dryness VAS score at Day 57. Both studies also met all four secondary endpoints: eye dryness score and tCFS at Day 15, burning/stinging score and cCFS at Day 57. The safety of Miebo was assessed in 839 patients dosed bid or qid for 8 weeks in controlled studies and 160 patients treated for one year in an open label extension study. The most common adverse event was blurred vision (3%). The benefit of Miebo dosed four times per day for the treatment of DED is expected to outweigh the risks associated with its use.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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 DED 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 DED	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.

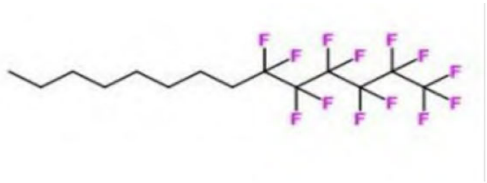
Patient Experience Data

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.			

Product Quality

Chemical Structure



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. Perfluorohexyloctane is practically insoluble in water, and the two liquids do not mix. Because perfluorohexyloctane does not mix or contain water, it exhibits no pH, osmolality, or water activity, and is not able to support microbial growth. Therefore, perfluorohexyloctane ophthalmic solution may be used as a preservative-free product itself.

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

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 <71>	Meets USP requiremen	

[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

Facilities

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)		Drug substance synthesis, in-process testing, release testing (all release tests except (b) (4), and microbiological purity), and packaging. || DMF: 0 || 356h Status: Pending CSN	Approve - Based on Previous History
		Alternate drug substance release testing except (b) (4) and microbiological purity. Drug substance stability testing except microbiological purity. Alternate drug product release and stability testing; primary testing facility for assay/purity testing by GC. Finished product release testing on registration batches with the exception of sterility and particulate matter. || DMF: 0 || 356h Status: Pending LCP	Approve - Based on Previous History
		Testing facility for (b) (4) (release) and microbiological purity (release and stability). Particulate matter release testing on registration batches. Particulate matter, sterility and stability testing on registration batches. Microbiological testing for in-use study. || DMF: 0 || 356h Status: Pending LMS LMN LCP	Approve - Based on Previous History
		Drug substance release testing prior to use in the manufacture of the drug product. Drug product manufacturing, packaging, labeling, in- process, release, and stability testing, with the exception of assay/purity testing by GC. Sterility release testing of the drug product registration batches. || DMF: 0 || 356h Status: Pending SLQ	Approve - Based on Previous History
		(b) (4) sterilization (b) (4)). || DMF: 0 || 356h Status: Pending GSP	Approve - Based on Previous History

CMC Recommendations:
Satisfactory information and responses have been submitted to support the drug substance, drug product, quality microbiology and manufacturing process aspects. The product is an NME since it has not been previously approved or marketed in the United States. The product is marketed as a device in Europe on the basis of having received a CE mark. The product is regulated as a drug/device combination product per the Genus decision. The product is packaged in a multi-dose eyedropper and is considered low risk, therefore CDRH confirmed that no CDRH consult is necessary on 7/11/2022. OPMA has issued an overall acceptable recommendation for all the facilities on 9/13/2022. Therefore, NDA 216675 is recommended approval from Product Quality perspective.

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

In a 26-week ocular toxicity study in rabbits, ocular instillation of perfluorohexyloctane ophthalmic solution at the dose of 427.8 mg/day, four times daily bilaterally for up to 26 weeks was well tolerated and did not induce any ocular or systemic signs of toxicity. Miebo is 100% perfluorohexyloctane, (chemical name: $C_{14}H_{17}F_{13}$). It is sometimes referred to as F_6H_8. The systemic no-observed-adverse-effect level (NOAEL) was 427.8 mg/animal/day whereas the ocular NOAEL was 213.92 mg/eye/day. At the proposed clinical dosing regimen, the ocular exposure margin is 3.6X for the maximum recommended human dose (MRHD) (60 mg/eye/day), and the systemic exposure margin is 39X for the MRHD (120 mg/day).

In a 28-day oral toxicity study in rats, once daily oral administration of at doses up to 2000 mg/kg/ for 28 days were well tolerated and did not produce F_6H_8 related toxicity. The NOAEL of F_6H_8 was 2000 mg/kg/day, the highest dose tested in this study.

In an embryofetal developmental (EFD) toxicity study in rats, daily oral administration of F_6H_8 at doses up to 2000 mg/kg/day to pregnant Wistar rats during the period of organogenesis (from GD6 to GD17 inclusive) was well tolerated with no toxicological effects on maternal or embryofetal parameters. Thus, the NOAEL for maternal and embryofetal toxicity was the highest dose tested, 2000 mg/kg/day (human equivalent dose (HED)=19459 mg/day). At the proposed clinical dosing regimen, the systemic exposure margin is 162X for the MRHD (120 mg/day).

In an EFD toxicity study in rabbits, following daily oral administration of F_6H_8 at doses of 0 (saline), 250, 500 and 1000 mg/kg/day to pregnant female NZW rabbits during the period of organogenesis (from GD6 to GD19 inclusive), there were abortions in all treated groups (6, 3 and 3 females in the 250, 500 and 1000 mg/kg/day groups, respectively), compared with no abortion in the control group.

- During the dosing period, dose-depended reduced mean body weight (BW) gain was noted in all treated groups (as -28%, -53% and -93% in the low, mid and high dose group, respectively). Reduced food consumption was also noted at a dose-related trend. There were higher incidences of reduced fecal output, soft feces and/or absent urine in all groups during the dosing period compared with the control group, which was consistent with the reduced food consumption. Thus, a NOAEL for maternal toxicity could not be established in rabbits.
- Consistent with the maternal toxicity, mean fetal weight was reduced in all treated groups compared with the concurrent control group and the Testing Facility's historical control data (HCD). Note, there was no increase in embryofetal death nor test article-related delay in skeletal ossification in any treated groups.
- There were 1 (1), 7 (5) and 6 (5) fetuses (litters) with fetal malformations (external, visceral and/or skeletal) in the low, mid and high dose treatment groups as compared with 1 (1) in the control group. Although the findings were within the range of Testing Facility's HCD (when verified individually), considering the significant increased incidences of these findings (when taken together) in the mid and high dose groups compared with the concurrent control group,

this reviewer agrees with the Applicant on that "*based on the maternal systemic exposure saturation, the developmental NOAEL can be more conservatively established at 250 mg/kg/day for safety margin calculations*".

- As such, the fetal NOAEL was the low dose, 250 mg/kg/day (HED= 4865 mg/day). At the proposed clinical dosing regimen, the systemic exposure margin is 41X for the MRHD (120 mg/day).

Systemic Exposure Margins Per the Pivotal Toxicity Studies

Clinical Exposure Margins (Based on Dose)			
Species/Type of Study	NOAEL (mg/kg/day or mg/day)	HED (mg/day)	Exposure Margins (Based on a MRHD of 120 mg/day
Rabbit/26-week ocular	427.8 (mg/day)	4625*	38.54X
Rat/ EFD	2000 (mg/kg/day)	19459	162X
Rabbit/ EFD	250 (mg/kg/day) (for fetal)	4865	40.54X

NOAEL = no-observed-adverse-effect level; MRHD = maximum recommended human dose; HED = human equivalent dose (based on body surface area) * Calculated based on 1.8 kg body weight for rabbits

Ocular Exposure Margins Per the Pivotal Toxicity Studies

Species/Type of Study	NOAEL (mg/eye/day)	Exposure Margins (Based on a MRHD of 60 mg/eye/day)
Rabbit/26-week ocular	213.9	3.6X

NOAEL = no-observed-adverse-effect level; MRHD = maximum recommended human dose

As such, P/T has no objection to the approval of Perfluorohexyloctane Ophthalmic Solution . In addition, minor format and language changes were made in Sections 8.1, 8.2, 12.1, and 13 of the Applicant-proposed labeling text to adhere to PLLR guidance and to provide consistency of language across paragraphs of the labeling.

Clinical Pharmacology

The primary clinical pharmacology data comes from NVU-002, which evaluated systemic concentrations of perfluorohexyloctane following single and repeated dose administrations in patients with DED. The Office of Clinical Pharmacology has reviewed clinical pharmacology data submitted for NDA 216675 and recommends approval of this NDA from a clinical pharmacology perspective.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Pivotal evidence of effectiveness of perfluorohexyloctane in patients with DED associated with MGD comes from three phase 3 clinical studies (NVU-003, NVU-004, and BL-904) in which NOV03 was administered four times a day (QID). Refer to the clinical/statistical review for the risk/benefit assessment of perfluorohexyloctane in treatment of DED associated with MGD.
General dosing instructions	The proposed dosing regimen is to instill one drop of NOV03 QID into each eye. This dosing regimen is supported by a phase 2 study (NVU-002) which compared two dosing frequencies, BID and QID, and three phase 3 clinical studies (NVU-003, NVU-004, and BL-904) which evaluated the proposed dosing regimen.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments based on any intrinsic or extrinsic factors are recommended.
Labeling	The proposed Clinical Pharmacology relevant information in Section 12.3 appears acceptable. There may be edits provided to the USPI that are not captured in this document but will be finalized as the labeling discussions are held internally and with the Applicant regarding this NDA.

Clinical Efficacy

NVU-003 Study Results

Demographics	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 (%)		
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)
Study Eye, n (%)		
Right Eye	183 (60.4)	170 (57.8)
Left Eye	120 (39.6)	124 (42.2)

Review Comments: *The treatment groups were considered balanced and representative of patients with dry eye disease. Meibomian gland dysfunction is a subset of dry eye disease. The inclusion/exclusion criteria mentions an aspect of meibomian gland function, but does not distinguish these patients from other dry eye patients.*

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

Change from Baseline	NOV03	Saline
tCFS (Study Eye)	N=289	N=279
Baseline (SD)	6.7 (1.8)	6.7 (1.9)
Mean (SD)	-2.0 (2.6)	-1.0 (2.7)
Median	-2.0	-1.0
Min, max	-10; 7	-9; 7
LS mean	-2.02	-1.05
NOV03 – Saline (95% CI)	-1.0 (-1.4, -0.6)	
p-value	<0.001	
Dryness Score (VAS)	N=289	N=279
Baseline (SD)	66.5 (19.1)	66.8 (18.7)
Mean (SD)	-27.4 (27.9)	-19.7 (26.7)
Median	-29.0	-18.0
Min, max	-90; 50	-96; 66
LS mean	-27.3	-19.7
NOV03 – Saline (95% CI)	-7.6 (-11.8, -3.4)	
p-value	<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

Review Comments: *The primary endpoints demonstrated successful treatment.*

Secondary Efficacy Endpoints (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

Review Comments: *The secondary endpoints demonstrated successful treatment.*

BL-904 Study Results

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 (%)		
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)
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

Review Comments: *The treatment groups were considered balanced and representative of patients with dry eye disease. Meibomian gland dysfunction is a subset of dry eye disease. The inclusion/exclusion criteria mentions an aspect of meibomian gland function, but does not distinguish these patients from other dry eye patients.*

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

Change from Baseline	NOV03	Saline
tCFS (Study Eye)	N=302	N=296
Baseline	7.0 (2.0)	7.1 (2.1)
Mean (SD)	-2.3 (2.8)	-1.1 (2.9)
Median	-2.5	-1.0
Min, max	-11, 7	-11, 7
LS mean	-2.3	-1.1
NOV03 – Saline (95% CI)	-1.21 (-1.66, -0.76)	
p-value	<0.001	
Dryness Score (VAS)	N=302	N=296
Baseline	64.7 (19.5)	64.3 (19.8)
Mean (SD)	-29.5 (28.6)	-19.0 (27.2)
Median	-30.5	-18.5
Min, max	-90, 53	-100, 90
LS mean	-29.4	-19.2
NOV03 – Saline (95% CI)	-10.2 (-14.3, -6.1)	
p-value	<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

Review Comments: *The primary endpoints demonstrated successful treatment.*

Secondary Endpoints

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

Review Comments: *The secondary endpoints demonstrated successful treatment.*

Safety

Safety Database

Study Medication Exposure and Compliance Analysis Set: Safety Analysis Set in Controlled Trials

	NOV03 BID (N=111)		NOV03 QID [a] (N=728)		All NOV03 [a] (N=839)		Saline (N=714)	
Randomized, n (%)	111	(100)	728	(100.0)	839	(100.0)	714	(100.0)
Phase 2	111	(100)	114	(16)	225	(27)	111	(15)
Phase 3	0		614	(84)	614	(73)	603	(85)
Dosed, n (%)	111	(100)	728	(100)	839	(100)	714	(100)
Completed Study Drug, n (%)	105	(95)	702*	(96.4)	807*	(96)	683	(96)
Prematurely Discontinued Study Drug, n (%)	6	(5)	24	(3)	30	(4)	31	(4)
Reason for Discontinuation Adverse Event [c] of Study Drug, N (%) [b]	0		1	(0.2)	1	(0.2)	3	(0.5)
Protocol Violation	0		3	(0.5)	3	(0.5)	3	(0.5)
Administrative Reason	0		0		0		1	(0.2)
Lack of Efficacy	0		0		0		1	(0.2)
Subject Choice	0		12	(2)	12	(2)	9	(1.5)
Other	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.

Additional Uncontrolled Drug Studies and Device Studies

Study Number (Summary)	Design & Control Type	Dose, Regimen, Duration of Treatment	No. of Subjects by Arm Planned / Entered / Completed
NVU-004	Phase 3, multi-center, open-label, single-arm 12-month extension to NVU-003	NOV03, QID for 52 weeks	250/208/160
NT-001	European Device Study, uncontrolled, post-market follow-up study (treatment survey)	NOV03, 3-4 drops daily for 6 weeks	30/30/29

NT-002	European Device Study, uncontrolled, post-market clinical follow-up study	NOV03, 3-4 drops daily for 7 weeks	90/72/61
NT-003	European Device Study, uncontrolled, post-market clinical follow-up study	NOV03, one drop 3-4 times daily for 12 weeks	30/25/23
NT-004	Randomized, single-center, single-masked, parallel group study	NovaTears or Hydrabak 0.9%, one drop, 4-6 times daily for 30 days	48 subjects (24 per group). 2 subjects in NovaTears discontinued.

Abbreviations: BID, 2 times a day; NOV03/NovaTears, perfluorohexyloctane ophthalmic solution; QID, 4 times a day.

NT-001, NT-002, NT-003, and NT-004 were conducted overseas, predominately Germany or Austria where the product is classified as a Class IIb medical device.

Review Comments: *Adverse event reports from studies NVU-004, NT-001, NT-002, NT-003 and NT-004 were consistent with reports from controlled clinical trials and raised no additional safety concerns.*

Deaths

No deaths occurred in any of the clinical trials.

Serious Adverse Events

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).

Treatment Emergent Adverse Events and Adverse Reactions

Ocular Adverse Events	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)

Ocular Adverse Events	NOV03 BID N=111 n (%)	NOV03 QID N=728 n (%)	Saline N=714 n (%)
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)
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)

Non-ocular Adverse Events occurring in >1 Subject

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)
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)

Post-marketing as a Device in Europe

Perfluorohexyloctane, the active ingredient of NOV03, was classified as a class IIa medical device in Europe in July 2013 (recently reclassified as class IIb) under the name NovaTears® and marketed as EvoTears® since October 2015. NovaTears® was subsequently registered in New Zealand and Australia.

A post-marketing analysis conducted by Novaliq between 2015 and 2022 shows no evidence of new side effects or a (significant) increase in the number of already known side effects in patients treated with NovaTears or EvoTears. A total of 478 non-serious events were reported, the most common of which were eye irritation, ocular hyperemia, and eye pruritus. One subject (51 year old male) had 5 serious events reported as: corneal opacity, corneal edema, ocular irritation, ocular hyperemia, and eye pain. The events occurred after instillation of EvoTears for 1 week after corneal transplantation. The events resolved after a second corneal transplantation. With limited information, there is no clear evidence supporting a causal role of EvoTears for these serious events. Two SAEs were reported in a Phase 3 study (SHR8058-301) conducted by Jiangsu Hengrui Pharmaceuticals Co., Ltd. ("Hengrui Pharma") in the People's Republic of China using SHR8058 eye drops (perfluorohexyloctane ophthalmic solution) in subjects with DED associated with MGD. These events were tendon rupture (active treatment) and vertigo (saline control).

Advisory Committee Meeting

There were no issues that were thought to benefit from a discussion at an Advisory Committee Meeting. No Advisory Committee Meeting was held for this supplemental application.

Pediatrics

The applicant requested a full product specific waiver for all pediatric age groups (i.e., birth to < 18 years) for the treatment of dry eye disease on the grounds that studies would be impossible or highly impractical due to the very limited number of pediatric patients. The Agency agrees.

Biostatistics

Two primary efficacy endpoints were tested using hierarchical fixed sequence testing to maintain an overall two-sided alpha = 0.05 level. If both primary efficacy endpoints demonstrated statistically significant superiority of NOV03 versus saline at the two-sided alpha = 0.05 level, the key secondary efficacy endpoints were tested hierarchically to maintain an overall two-sided alpha = 0.05.

The applicant analyzed each of the primary efficacy endpoints using an analysis of covariance (ANCOVA) model with terms for baseline value and treatment. The four key secondary efficacy endpoints were also analyzed separately using an ANCOVA model with terms for baseline value and treatment. In the study, subject randomization was stratified by clinical site and dryness score (< 70 vs. ≥ 70) (VAS) at baseline. However, the applicant's analyses for both primary and secondary efficacy endpoints were not adjusted for the stratification factors. Following an information request (IR), the applicant reanalyzed the

primary and key secondary efficacy endpoints by incorporating the two stratification factors into the ANCOVA model. Both the applicant's updated analysis results and the reviewer's analysis results which included the two stratification factors indicated that NOV03 showed statistically significant improvement over saline in clinically relevant signs and symptoms of DED.

As both of Phase 3 studies had an overall study discontinuation rate less than 5%, the applicant did not do any imputation to missing values. Besides conducting the analyses using available data without any imputation, the reviewer performed the sensitivity analyses for the primary efficacy endpoints where missing data were imputed using the last observation carried forward (LOCF) and baseline observation carried forward (BOCF) method. Although these methods are single imputation methods which are not recommended by the National Academy of Science (NAS) report on missing data, this was not a concern as very few subjects (< 5%) didn't complete the study. Sensitivity analysis results were consistent with the primary efficacy analysis results, leading to the same conclusion that NOV03 had statistically significant improvement over saline in tCFS in the study eye and eye dryness VAS score.

Based on the review of the two Phase 3 studies submitted, there is sufficient evidence that the proposed study drug, NOV03 (perfluorohexyloctane), administered at four times a day (QID), is efficacious for the treatment of the signs and symptoms of DED.

Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Was a list of clinical investigators provided?	Yes ☒	No ☐
Total number of investigators identified: 107		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
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: 0 Significant payments of other sorts: 19 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☒	No ☐

Is a description of the steps taken to minimize potential bias provided?	Yes ☒	No ☐
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason?	Yes ☐	No ☐

Study Integrity

The following investigators were selected for inspections: David Evan, Bruce Segal, Fred Kurata, David L. Wirta. Inspection of the 4 clinical sites have been completed and classification are as follow: David Evans: NAI (final), Bruce Segal: NAI (final), David Wirta: NAI (preliminary), Fred Kurata: VAI (preliminary). No significant concerns have been raised by these clinical inspections.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized their review on 12/14/2022. The proposed prescribing information (PI) container label, carton labeling, professional sample container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Bausch & Lomb Incorporated.

Table 1. Identified Issues and Recommendations for Division of Ophthalmology (DO)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION	DO ACTION
1.	We note that the placeholder, "TRADENAME" is included throughout the PI.	The proposed proprietary name, Miebo, was found conditionally acceptable on August 30, 2022[1]. The proprietary name, "Miebo," should be used throughout the PI.	Replace the placeholder, "TRADENAME," with the conditionally acceptable proprietary name, "Miebo."	Agree. Trademark placeholder has been replaced with "Miebo."
2.	As currently presented, we note throughout the PI, container label and carton labeling (b) (4)	We confirmed with our Office of Pharmaceutical Quality colleagues (b) (4)	We recommend revising (b) (4)	Disagree (b) (4)

[1] Chan, I. Proprietary Name Request Conditionally Acceptable for Miebo. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 AUG 30. NDA 216675.

Table 1. Identified Issues and Recommendations for Division of Ophthalmology (DO)				
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION	DO ACTION
	(b) (4)	(b) (4) .	"Miebo (perfluorohexyloctane ophthalmic solution), (b) (4)	(b) (4)
Full Prescribing Information – Section 3 Dosage Forms and Strengths				
1.	As currently presented the appropriate information to facilitate identification of the dosage form is not included.	A description of identifying characteristic can be used to help identify the product and is required by 21 CFR 201.57(c)(4)(ii).	Include the description of identifying characteristic of the dosage form, such as color and clarity in accordance with 21 CFR 201.57(c)(4(ii). Similar to what is stated in *Section 11, Description*, "Clear and colorless liquid."	Disagree. Clear and colorless liquid is not an identifying characteristic.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling				
	As currently presented the appropriate information to facilitate identification of the dosage form is not included.	A description of identifying characteristic can be used to help identify the product and is required by 21 CFR 201.57(c)(17)(iii).	Include the description of identifying characteristic of the dosage form, such as color and clarity in accordance with 21 CFR 201.57(c)(17)(iii). Similar to what is stated in *Section 11, Description*, "Clear and colorless liquid."	Disagree. Clear and colorless liquid is not an identifying characteristic.

Table 2. Identified Issues and Recommendations for Bausch & Lomb Incorporated (entire table to be conveyed to Applicant)				
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION	DO ACTION
Container Labels and Carton Labeling				
1.	As currently presented, we note on the container label and carton labeling	(b) (4)	We recommend revising (b) (4)	Disagree. (b) (4)

Table 2. Identified Issues and Recommendations for Bausch & Lomb Incorporated (entire table to be conveyed to Applicant)				
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION	DO ACTION
	(b) (4)		"Miebo (perfluorohexyloctane ophthalmic solution), (b) (4)	(b) (4)
2.	The format for expiration date is not defined.	A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.	Agree.
3.	As currently presented, the terminology "(b) (4) " is inconsistent with the	The recommended dosage statement terminology should be	To ensure consistency with the Prescribing Information, we recommend revising the dosage statement, (b) (4) " to read	Agree

Table 2. Identified Issues and Recommendations for Bausch & Lomb Incorporated (entire table to be conveyed to Applicant)				
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION	DO ACTION
	terminology used in the Prescribing Information Dosage and Administration section.	consistent across the labeling to mitigate risk of confusion.	"Dosage: See Prescribing Information."	
Carton Labeling				
	As currently presented, the proposed carton labeling and professional sample carton labeling denote an "Area for Lot, Exp. and Serialization." However, the intended location of the machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) is not provided.	The Drug Supply Chain Security Act (DSCSA) requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: *Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (July 2021).[2] If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.	Agree.

[2] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Post-marking Risk Management

Post-marketing Requirements

While clinical signs of corneal endothelial cell dysfunction or death have not been observed with the use of perfluorohexyloctane ophthalmic solution, the health of prolonged exposure has not been fully investigated. Therefore, the Review Team considers that the investigations required under section 505(b) of the Federal Food, Drug, and Cosmetic Act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. A concurrently controlled, randomized, 12-month clinical study in which perfluorohexyloctane ophthalmic solution is dosed as monotherapy and corneal endothelial cell counts are compared to a concurrent control without perfluorohexyloctane ophthalmic solution is being required to be conducted and submitted.

PMR # 4447-1

PMR Description
Conduct a randomized, controlled trial to evaluate the corneal endothelial health of eyes treated with perfluorohexyloctane ophthalmic solution by monitoring the number/density of corneal endothelial cells using specular microscopy at baseline and over a period of at least one year in at least 100 patients receiving perfluorohexyloctane ophthalmic solution.

PMR Schedule Milestones
Draft Protocol Submission: 7/2023
Final Protocol Submission: 9/2023
Trial Completion: 6/2026
Final Report Submission: 9/2026

There are no additional recommended post marketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

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

16. Regulatory Action

The application will be approved with the labeling described in this review.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
05/18/2023 10:15:07 AM

RHEA A LLOYD
05/18/2023 10:17:04 AM

WILEY A CHAMBERS
05/18/2023 10:21:21 AM

CHARLES J GANLEY
05/18/2023 10:23:56 AM