CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	216675
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Submission Date	6/28/2022
PDUFA Goal Date	4/28/2023
Submission Type	New NDA Submission
Brand Name	MIEBO
Generic Name	Perfluorohexyloctane
Dosage Form and Strength	Solution, 100%
Route of Administration	Ophthalmic
Proposed Indication	Treatment of the signs and symptoms of Dry Eye Disease (DED) associated with Meibomian Gland Dysfunction (MGD)
Proposed Dosage Regimen	Instill one drop four times daily (QID) into each eye
Applicant	Bausch & Lomb Incorporated
Associated IND	130558
OCP Review Team	Soo Hyeon Shin, Pharm.D., Ph.D. Ping Ji, Ph.D.
OCP Division	Division of Inflammation and Immune Pharmacology

Table of Contents

1. EXECUTIVE SUMMARY

The Applicant developed an ophthalmic eye drop formulation (referred as NOV03) containing 100% perfluorohexyloctane for the treatment of Dry Eye Disease (DED) associated with meibomian gland dysfunction (MGD). Perfluorohexyloctane is a linear semifluorinated alkane, which has six perfluorinated and eight hydrogenated carbon atoms, and is physically, chemically and physiologically inert. 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 and thus prevents excessive evaporation of the aqueous tear film component.

The clinical development program to support this new 505(b)(1) NDA application includes four clinical studies: one Phase 2 study, multi-center, randomized, double-masked, saline-controlled study (NVU-002), two Phase 3, multi-center, randomized, double-masked, saline-controlled studies (NVU-003 and BL-904) and one Phase 3, multi-center, open-label, single-arm, long-term safety extension study in subjects who complete the NVU-003 study (NVU-004). 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.

1.1 Recommendations

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. The key review issues with specific clinical pharmacology recommendations and comments are summarized below.

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.

Bridge between the to-be-marketed and clinical trial formulations	NOV03 consists of 100% perfluorohexyloctane without any excipients and therefore, no formulation development was conducted and bridging between the to-be-marketed formulation is not warranted.

1.2 Post-Marketing Requirements/Commitments

None

2. CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

The exact mechanism of action of perfluorohexyloctane in the treatment of the signs and symptoms of DED associated with MGD is unknown. By interacting with the lipophilic part of the tear film, perfluorohexyloctane forms a layer on the ocular surface and reduces evaporation of the aqueous tear film component.

Pharmacokinetics

The systemic PK of perfluorohexyloctane in patients with DED following single and repeated BID and QID ocular instillations were evaluated in a phase 2 study (NVU-002). Due to the bioanalytical issues identified during the sample analysis, the system exposure in human could not be quantitatively analyzed. However, the systemic perfluorohexyloctane blood levels following topical ocular administration appear low (Section 4.1.2).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen is to instill one drop of NOV03 QID into each eye.

2.2.2 Therapeutic individualization

The Applicant has not proposed any therapeutic individualization. The available clinical pharmacology information does not warrant a need for therapeutic individualization.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

Labeling recommendations are summarized in Section 1.1 of the review.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

NOV3 is an ophthalmic solution containing 100% perfluorohexyloctane for topical administration. It is a single-ingredient product with no additional formulation additives or preservatives and is provided in a multi-use container closure system. The active ingredient perfluorohexyloctane was classified and registered as medical device in Europe, New Zeland and Australia and is marketed under the names NovaTears® and EvoTears®. Perfluorohexyloctane is a new molecular entity and has no previous approval in the US.

During NOV3's Investigational New Drug (IND) application review, the bioanalysis issues with clinical pharmacology study (NVU-002)'s PK sample analysis were discussed between the Agency and the Applicant. The Agency commented that their clinical PK data cannot be used for labeling purpose unless the samples are re-analyzed with redeveloped bioanalytical method with acceptable in-study bioanalysis results. The Agency also commented that a clinical pharmacology summary is not a requirement in the label if it is not relevant to the safety.

3.2 General Pharmacology and Pharmacokinetic characteristics

General Pharmacology

Perfluorohexyloctane is an inert, anhydrous semifluorinated alkane which has excellent spreading properties due to its low surface/interfacial tension. Although its exact mechanism of action for the treatment of DED associated with MGD is unknown, perfluorohexyloctane is believed to have no known pharmacological mode of action and its activity is due to the physicochemical properties. When topically administered, 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 and preventing evaporation of the aqueous phase of the tear film.

General Pharmacokinetic Characteristics

The biodistribution of perfluorohexyloctane following ocular administration was assessed in animals. Refer to nonclinical review for details. Briefly, following ocular administration in rabbits, 14C-perfluorohexyloctane in the anterior ocular tissues was considerably higher compared to intraocular tissues (vitreous humor, choroid-RPE, and retina). Systemic exposure of 14C-perfluorohexyloctane was low after single dose but was approximately 3 times higher after repeated dose in the twice daily dosing regimen.

The blood-plasma concentration ratios were approximately 0.8. No protein biding studies were conducted.

In vitro, perfluorohexyloctane was not metabolized by liver microsomes.

Following oral administration of 14C-perfluorohexyloctane in rats, low systemic absorption was observed, and the majority of the radioactivity was excreted unabsorbed in feces (up to 70%). Less than 0.1% and 0.04% of radioactivity were recovered in urine bile, respectively.

Drug Interactions

No drug interaction studies were conducted.

3.2 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The clinical pharmacology information in this NDA does not provide pivotal or supportive evidence of effectiveness of perflurohexyloctane. Since perfluorohexyloctane is administered as eye drop and the site of action is local (the eye), the systematic exposure is not expected to affect treatment effect by mechanism.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen of one drop QID into each eye is appropriate for treatment of the signs and symptoms of DED associated with MGD. The safety and efficacy of perflurohexyloctane at the proposed dosing regimen was assessed in four well-controlled studies (NVU-002, NVU-003, NVU-004, and BL-904). Refer to clinical and statistical review for detailed assessment and review for the safety and effectiveness of perflurohexylocatane. The available clinical pharmacology information submitted in this NDA is limited to data collected from a phase 2 study (NVU-002), which evaluated two dosing frequencies, BID and QID. As NOV03 is consisted of 100% perfluorohexyloctane, dose-exploration in this NDA was limited to evaluating dosing frequencies. While there were bioanalytical issues for the PK sample analysis, the limited data show that the systemic exposure following administration of NOV03 appear low and thus support the systemic safety of perfluorohexyloctane.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

An alternate dosing regimen is not needed for any of the subpopulations. For the proposed drug product, the intended site of drug delivery and action is local (the eye); therefore, the extent of systemic exposure based on differences among subpopulations is not likely to influence the proposed drug product's efficacy.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The drug product is given via topical ocular route; therefore, the issue of a food-drug interaction is not relevant.

No clinical DDI studies were conducted because the in vitro study results and evaluations of the absorption, distribution, metabolism, and excretion properties of perfluorohexyloctane indicate that perfluorohexyloctane has a low potential for mediating a DDI with coadministered agents via CYP or drug transporter pathways.

4. Appendix

4.1. Clinical Pharmacology Study, Study NVU-002

Title: Study NVU-002 was a phase 2, multi-center, randomized, double-masked, saline-controlled study to evaluate the effect of NOV03 at two different dosing regimens on signs and symptoms of DED. The treatment period was 57 days (8 weeks).

Objectives: The primary objective was to evaluate the efficacy, safety, and tolerability of NOV03 at two different dosing regimens compared to saline solution in subjects with DED. The secondary objectives were: 1) to compare the effect of NOV03 and saline solution at two different dosing regimens on signs and symptoms of DED and 2) to evaluate the PK of NOV03.

Trial Design:

Dosing Regimen: Study subjects were instructed to self-administer NOV03 or saline solution, one drop per each eye to both eyes, BID or QID, according to the randomization scheme.

Study Subjects: A total of 336 adult subjects were enrolled in the study, with 111 subjects in the NOV03 BID treatment group, 114 subjects in the NOV03 QID treatment group and 111 subjects in the combined (BID and QID) saline treatment group. A total of 323 (96%) subjects completed the study.

The PK subgroup included a total of 79 subjects, with 30 subjects in the NOV03 BID group, 23 subjects in the NOV03 QID group and 26 subjects in the saline group.

PK Sampling: The PK samples were collected from a subset of subjects at pre-dose and at 0.5, 1, 2, and 4 hours after a single ocular instillation on Day 1, and prior to the second daily dose. An additional single blood sample was collected at the end of the study (Visit 4, Day 57) or early termination. The PK samples were analyzed using a validated GC-MS/MS method for quantification of perfluorohexyloctane concentrations in blood.

PK Results: The perfluorohexyloctane concentrations after a single ocular installation on Day 1 is summarized in Table 1. Only 25% (36 out of 119 samples) and 24% (22 out of 92 samples) of post-dose samples in the NOV03 BID and QID groups, respectively, had quantifiable perfluorohexyloctane concentrations above the lower limit of quantitation (LLOQ). The data indicate that the perfluorohexyloctane systemic exposure after single instillation is low in general.

The perfluorohexyloctane concentrations from on Day 57 is summarized in Table 2. Most of samples collected on Day 57 had quantifiable perfluorohexyloctane concentrations.

Table 1. Perfluorohexyloctane Blood Concentrations (ng/mL) with NOV03 After a Single Ocular Installation on Day 1

Sampling Timepoints	BID (N=30)	QID (N=23)	Saline (QID + BID) (N=26)
Pre-Dose			
n	30	21	25
Mean (SD)	0.174 (0.6947)	0.000 (0.0000)	0.000 (0.0000)
Median (Min, Max)	0.000 (0.00, 3.40)	0.000 (0.00, 0.00)	0.000 (0.00, 0.00)
Nquant	2	0	0
0.5 Hour			
n	30	23	26
Mean (SD)	0.733 (1.2069)	0.263 (0.6037)	0.380 (1.3562)
Median (Min, Max)	0.000 (0.00, 5.75)	0.000 (0.00, 1.86)	0.000 (0.00, 6.60)
Nquant	12	4	3
1 Hour			
n	29	23	26
Mean (SD)	2.524 (12.0192)	0.241 (0.6729)	0.235 (0.8942)
Median (Min, Max)	0.000 (0.00, 64.90)	0.000 (0.00, 2.58)	0.000 (0.00, 4.23)
Nquant	6	3	2
2 Hours			
n	30	23	26
Mean (SD)	0.347 (1.0024)	0.379 (1.0006)	0.379 (1.9337)
Median (Min, Max)	0.000 (0.00, 4.56)	0.000 (0.00, 4.59)	0.000 (0.00, 9.86)
Nquant	4	5	1
4 Hours			
n	30	23	26
Mean (SD)	1.217 (1.6680)	0.805 (1.0846)	0.208 (0.7923)
Median (Min, Max)	0.000 (0.00, 6.42)	0.000 (0.00, 3.43)	0.000 (0.00, 3.75)
Nquant	14	10	2

SD=Standard deviation ; Min= Minimum; Max=Maximum; Nquant=Number of subjects with quantifiable observation (above LLOQ, 1 ng/mL)

Source: Module 2.7.2, Table 2.7.2.2-1

Table 2. Perfluorohexyloctane Blood Concentrations (ng/mL) with NOV03 on Day 57

Day 57	BID (N=30)	QID (N=23)	Saline (QID + BID) (N=26)
n	30	21	26
Mean (SD)	8.536 (8.8735)	8.192 (8.2367)	7.119 (8.9426)
Median (Min, Max)	3.660 (1.27, 28.10)	4.010 (0.00, 25.50)	2.890 (0.00, 27.90)
Nquant	30	19	22

Min= Minimum; Max=Maximum; Nquant=Number of subjects with quantifiable observation (above LLOQ, 1 ng/mL); SD=Standard deviation

Source: Module 2.7.2, Table 2.7.2.2-2

Reviewer's comment: As shown in Table 1 *and* Table 2*, samples from pre-dose timepoint and the saline treatment groups had detectable perfluorohexyloctane concentrations, which were not expected. Specifically, 2 pre-dose samples and 8 samples in the saline control group collected on Day 1 and the majority (22 out of 26; 85%) of samples in the saline control group collected on Day 57 had perfluorohexyloctane concentrations. The PK results, in addition to other issues observed from bioanalysis described in Section 3.4, indicate that there were issues during bioanalysis of these samples and therefore the PK data obtained from this study cannot be used for the quantitative PK characterization of NOV03. It is noted that the bioanalysis issues were more pronounced with samples obtained from Day 57 than from Day 1. While the results should be interpreted carefully knowing the bioanalysis issues, it appears that systemic exposure of perfluorohexyloctane following a single dose of NOV03 is low, which is also in line with the nonclinical findings in rabbits.*

The issues with the bioanalysis were previously discussed with the Applicant at the Pre-NDA meeting on 12/15/2021. The Agency commented that the PK data from this study cannot be used for labeling purpose, and to include PK data in the labeling, the samples should be re-analyzed with a new bioanalytical method and with acceptable bioanalysis results. The Agency also commented that a clinical pharmacology summary is not a requirement in the label for NDA if it is not relevant to the safety concerns. The Applicant did not re-analyze the samples, and provided the data from the original bioanalysis in this NDA submission.

In general, drugs administered by topical ocular route are not expected to result in high systemic exposure. Given that perfluorohexyloctane physiologically and chemically inert and that the systemic exposure following single and repeated doses of radiolabeled perfluorohexyloctane was low in rabbits were low, it is reasonable to assume that PK of perfluorohexyloctane is likely not relevant to the safety concerns. Thus, the lack of reanalyzed PK samples in this submission does not pose an approvability issue of this NDA.

4.2 Summary of Bioanalytical Method Validation and Performance

The PK samples obtained from NVU-002 were analyzed suing a validated GC-MS/MS method for determination of perfluorohexyloctane concentrations in human blood.

The method validation and bioanalysis performance are summarized in Table 3 and Table 4, respectively.

Table 3. Validation Summary of a Bioanalytical Method for the Quantification of Perfluorohexyloctane in EDTA Human

Method ID	519170
Study Report	514490 (full validation) and 514492 (long-term stability)
Study Title	Validation of a Bioanalytical method for the Quantification of Perfluorohexyloctane (F6H8) in EDTA Human; Long Term Stability of Perfluorohexyloctane (F6H8) in EDTA Human Blood
Analyte	Perfluorohexyloctane
Internal Standard (IS)	Perfluorohexyloctane-[^{13}C3]
Matrix	Human Blood Human
Assay Range	1.00 - 200 ng/mL
Accuracy	QC-LLOQ (1.00 ng/mL): 80-120% QC-low (3.00 ng/mL): 85-115% QC-middle (15.0 ng/mL): 85-115% QC-high (150 ng/mL): 85-115%
Precision	QC-LLOQ (1.00 ng/mL): $\leq$ 20% QC-low (3.00 ng/mL): $\leq$ 15% QC-middle (15.0 ng/mL): $\leq$ 15% QC-high (150 ng/mL): $\leq$ 15%
Matrix effect	Precision $\leq$ 15%: passed
Selectivity	Ten individual sources of matrix were tested and there were no interfering components at the retention time of the analyte and internal standard. The analytical method was found to be selective for the analyte in human blood at concentration levels $\geq$ 1.00 ng/mL.
Bench-top/process stability	Stock solutions of perfluorohexyloctane in acetone at 1 mg/mL were stable for 6 hours at room temperature. Human blood samples were stable when stored at room temperature for at least 9 hours, but not stable for 26 hours. Processed samples were stable for 44 hours at room temperature
Freeze-Thaw stability	3 freeze/thaw cycles
Long-term storage	At least 210 days in the ultra-low freezer ($\leq$ -75°C)

Table 4. Bioanalysis Performance Summary

Bioanalytical Report	No. 20135590; Determination of Perfluorohexyloctane (F6H8) in EDTA Human Blood Samples of the Clinical Study NVU-002)
Method ID	519170
Assay passing rate	Eight of 10 runs were accepted (80%). 44 % of the samples analyzed for incurred sample reanalysis (ISR) was within ±20%.
Standard curve performance	• Cumulative bias range: -12 to 11% (with excluding 2 unacceptable data) • Cumulative precision: NA
QC performance	Cumulative bias range: -19 to 14%
Incurred sample reanalysis	Incurred sample re-analysis was performed in a total of 46 (9.7%) samples (8 samples from Day 1 and 38 samples from Day 57).
Study sample analysis/stability	The first samples were collected on 15 Jan 2018. Analysis was started on 18 May 2018, and the bioanalytical was completed on 27 July 2018. The maximum storage time for low and high QC samples was 210 days. All study samples were analyzed within the proven stability period of 210 days.

The data reported in the validation report of the GC-MS/MS method met the guidelines specified in the FDA guidance on the bioanalytical method validation, and all samples were analysed within the established stability window. However, several issues were observed from the bioanalysis of the clinical phase 2 study NVU-002 samples, as listed below:

1. Detectable concentrations of perfluorohexyloctane were found in pre-dose samples and samples from the placebo groups.
2. Lower internal standard (IS) response was observed in some study samples, especially from samples obtained at Day 57, compared to those in calibration standards and quality control (QC) samples. A majority of the samples from Day 57 were below 50% of the mean IS response of the calibration standards and QCs. Differences in IS response were also observed between study sites with samples from study stie 012 being affected the most.
3. Only 44% of the samples analyzed for incurred sample reanalysis (ISR) were within 20% of the originally reported result, when the FDA guidance's criterion is for at least 67% of the ISR samples to be within 20% of the original result. The passing rate among samples from Day 1 and Day 57 were 75% (6 out of 8 samples) and 40% (15 out of 38 samples), respectively.

Per the Applicant, an investigation to identify the root cause(s) of the issues were conducted but no root causes were found.

<u>Reviewer's comment:</u> The mean (±SD) concentration of Day 1 samples that passed the acceptance criterion for ISR (i.e., the %difference between the concentrations obtained from the initial analysis and the reanalysis are within 20%) was 3.68 (0.55) from 6 samples. The mean (±SD) concentration of Day 57 samples that passed the acceptance criterion for ISR was 11.73 (9.37) from 15 samples. While these mean values should be interpretated with caution due to small number of samples and the fact that only samples with concentrations above LLOQ from the initial analysis were selected for ISR, the values suggest that systemic exposure following ocular administration of NOV3 is low, especially following a single dose on Day 1.

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