CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216675Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Supplement #:	216-675
Drug Name:	Miebo (perfluorohexyloctane ophthalmic solution), 100%
Indication(s):	Treatment of the signs and symptoms of Dry Eye Disease (DED) associated with Meibomian Gland Dysfunction (MGD)
Applicant:	Bausch & Lomb Incorporated
Date(s):	Date submitted: June 28, 2022 PDUFA date: June 28, 2023
Review Priority:	Standard
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Keywords:	NDA review, clinical studies

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1 EXECUTIVE SUMMARY

Bausch & Lomb Incorporated has developed NOV03 (perfluorohexyloctane, 100%), a sterile ophthalmic solution, and is seeking an indication for treatment of the signs and symptoms of dry eye disease (DED) associated with meibomian gland dysfunction (MGD). To support efficacy, two Phase 3 studies were reviewed, Study NVU-003 and Study BL-904 in subjects with DED associated with MGD. These were randomized (R), multicenter (MC), double-masked (DM), saline-controlled studies.

In both Phase 3 studies, the applicant's primary efficacy endpoints were change from baseline (CFB) in total Corneal Fluorescein Staining (tCFS) (National Eye Institute (NEI) scale) at Day 57 and CFB in Dryness Score (visual analogue scale [VAS] Severity of Dryness) at Day 57. The applicant's key secondary efficacy endpoints were: 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; and change from baseline in central corneal fluorescein staining (cCFS) (NEI scale) at Day 57. 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 associated with MGD.

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, 100%), administered at four times a day (QID), is efficacious for the treatment of the signs and symptoms of Dry Eye Disease (DED) associated with Meibomian Gland Dysfunction (MGD).

2 INTRODUCTION

2.1 Overview

NOV03 (perfluorohexyloctane, 100%) is a sterile ophthalmic solution developed for the treatment of the signs and symptoms of DED associated with MGD. NOV03 was first developed by Novaliq GmbH using patented EyeSol technology. Perfluorohexyloctane was classified as a class IIa (now a class IIb) medical device in Europe in July 2013 under the name NovaTears and marketed as EvoTears since October 2015. NovaTears was subsequently registered in New Zealand and Australia by AFT Pharmaceuticals as a medical device. In 2019, Bausch & Lomb Incorporated acquired an exclusive license for the commercialization and development of NOV03 in the United States (US) and Canada.

The clinical development program of NOV03 has been discussed between the agency and the applicant numerous times under IND 130588. In the EOP2 meeting held on April 10, 2019, the agency stated that an 8-week trial duration with QID treatment was acceptable for the Phase 3 studies. The statistical approach using Hochberg procedure in multiplicity adjustment for the key secondary endpoints was not acceptable, as the Hochberg procedure is not guaranteed to control the overall Type I error rate for more than two endpoints that have unknown correlation structure. In addition, the agency also made comments on the definition of Full Analysis Set (FAS):

- *No, we do not agree with the use of the Hochberg procedure in multiplicity adjustment for the key secondary endpoints. As stated in the FDA draft guidance "Multiple Endpoints in Clinical Trials Guidance for Industry", the Hochberg procedure is not guaranteed to control the overall Type I error rate for more than two endpoints that have unknown correlation structure. Thus, the use of the Hochberg procedure is not recommended unless you can prove that it adequately controls the overall Type I error rate in the setting of your proposed study. Instead, we recommend either the Bonferroni or the Holm procedure.*

- *In addition, the meeting document states that "the primary analysis will use the Full Analysis Set (FAS) with available data per subject". This approach is acceptable only if the proportion of subjects who prematurely discontinue the study prior to Week 8 assessment (due to either lack of efficacy or adverse events) is minimal and balanced between the treatment groups as observed in the completed Phase 2 study. You should encourage the subjects who discontinue study treatment prematurely to stay in the study for all scheduled efficacy and safety assessments.*

The current submission contains one Phase 2, MC, R, DM, saline-controlled study (NVU-002); two Phase 3, MC, R, DM, saline-controlled studies (NVU-003 and BL-904); and one Phase 3, MC, open-label, single-arm, long-term safety extension study in subjects who complete the NVU-003 study (NVU-004). This review focuses on the two Phase 3 studies in subjects with DED associated with MGD (Table 1).

Table 1: Summary of Trials Reviewed

Trial ID	Design†	Treatment/Sample Size	Primary Efficacy Endpoint‡
NVU-003	R, DM, MC, saline-controlled	NOV03: 303 Saline: 294	• Change from baseline in tCFS (NEI scale) at Day 57 • Change from baseline in the dryness score (VAS severity of dryness) at Day 57
BL-904	R, DM, MC, saline-controlled	NOV03: 311 Saline: 309	• Change from baseline in tCFS (NEI scale) at Day 57 • Change from baseline in the dryness score (VAS severity of dryness) at Day 57

Source: Reviewer's analyses.
† R: randomized; DM: double-masked; MC: multi-center;
‡ tCFS: total corneal fluorescein staining;
VAS: visual analog scale;

2.2 Data Sources

The clinical study reports are located at the following location in the CDER electronic document room (EDR): \\CDSESUB1\evsprod\NDA216675\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ded\5351-stud-rep-contr.

The datasets, define files and programs are located in EDR at: \\CDSESUB1\evsprod\NDA216675\0001\m5\datasets. Both SDTM and ADaM Datasets were submitted by the applicant to the CDER EDR in SAS transport format.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The electronic datasets and define files submitted by the applicant were of acceptable quality, and were sufficient for validating study results.

3.2 Evaluation of Efficacy

3.2.1 Study NVU-003

3.2.1.1 Study Design and Endpoints

Study NVU-003 was a Phase 3, MC, R, DM, saline controlled study in subjects with Dry Eye Disease (DED) associated with Meibomian Gland Dysfunction (MGD). 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 DED associated with MGD. The study was conducted at 26 sites in the United States from December 2019 until March 2021.

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 randomized to either receive NOV03 (100% perfluorohexyloctane) or saline (0.6% sodium chloride solution) ophthalmic solution QID. Subjects were dosed over an 8-week period, starting at Visit 1 and ending at Visit 4. Randomization was stratified by clinical site and baseline dryness score (< 70 vs. ≥ 70). 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 worst (higher) total corneal staining at Visit 1. If the total corneal staining was the same in both eyes, then the right eye was selects as the study eye.

There were two primary efficacy endpoints defined in the study:

- Change from baseline in tCFS (NEI scale) at Day 57.
- Change from baseline in the dryness score (VAS severity of dryness) at Day 57.

The applicant's key secondary efficacy endpoints were:

- 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.

Using the NEI/Industry Workshop Scale, CFS scores (5 areas of the cornea) were recorded by the Investigator as Grade 0 (no staining) to Grade 3 (heavy staining). A total score (tCFS) was calculated (maximum of 15). Subjects rated severity of eye dryness and other symptomatology (both eyes simultaneously) using a VAS ranging from 0 (no discomfort) to 100 (maximal discomfort).

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 ocular surface disease index (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.

3.2.1.2 Statistical Methodologies

The primary analysis was performed on the Full Analysis Set (FAS) which included all randomized subjects who received at least one dose of IP. Subjects in the FAS were analyzed as randomized.

The primary comparisons in the study were between NOV03 versus saline at Day 57 in the FAS. The applicant's defined the primary estimand of interest as the following:

- Endpoint:
  - CFB in tCFS in the study eye at Day 57
  - CFB of Dryness Score (VAS) at Day 57

- Intercurrent event (IE):
  - Discontinuation of study medications is ignored. [treatment policy strategy]
  - Non-optimal compliance is ignored. [treatment policy strategy]
  - Withdrawal due to any reason. Missing data not imputed. [hypothetical strategy if overall study discontinuation rate is <5%]

- Population-level summary:
  - Difference in the mean CFB in tCFS in the study eye at Day 57 between NOV03 and saline
  - Difference in the mean CFB of Dryness Score (VAS) at Day 57 between NOV03 and saline

The applicant analyzed each of the primary efficacy endpoints using an analysis of covariance (ANCOVA) model with terms for baseline value and treatment. Least squares (LS) mean for each treatment group and for the difference between treatment groups were presented from each model, together with two-sided p-values (used for primary inference) and 95% confidence intervals (CIs). 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. An information request (IR) was sent out on September 08, 2022, to request the applicant to perform the analyses by incorporating these two stratification factors into the ANCOVA model. On October 14, 2022, the applicant submitted the response which included the updated analysis results for both primary and secondary efficacy endpoints. The reviewer's analyses included these two stratification factors.

Two primary endpoints were tested using hierarchical fixed sequence (in the order specified in section 3.2.1.1) testing to maintain an overall two-sided alpha = 0.05 level. If both primary endpoints demonstrated statistically significant superiority of NOV03 versus saline at the two-sided alpha = 0.05 level, the secondary endpoints were tested hierarchically (in the order specified in section 3.2.1.1) to maintain an overall two-sided alpha = 0.05.

The applicant stated that there was no imputation to missing values as the study had an overall study discontinuation rate less than 5%. The primary analysis was completed on the FAS using the available data per subject. The reviewer conducted the analyses using available data without any imputation. In addition, the reviewer performed the sensitivity analyses 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.

The applicant conducted the sample size calculation by assuming a true difference (NOV03 minus saline) of -1.0 in the mean tCFS score at Day 57, a common standard deviation of 2.8, and a two-sided alpha = 0.05. Two hundred fifty (250) subjects (study eyes) per treatment group yields 97.9% power to show superiority of NOV03 over saline. Assuming a true difference (NOV03 minus saline) of -10 in the mean Dryness Score (VAS) at Day 57, a common standard deviation of 28, and a two-sided alpha = 0.05, 250 subjects per treatment group yields 97.9% power to show superiority of NOV03 over saline. Accounting for an assumed 10% subject discontinuation rate, approximately 560 subjects (280 subject each arm) will be randomly assigned to trial treatment such that approximately 250 evaluable participants per arm complete the trial. Therefore, assuming independence between tCFS score and Dryness Score (VAS), 250 FAS subjects per treatment group at Day 57 yields 97.9%* 97.9%= 95.8% power to show superiority of NOV03 over saline. A positive correlation between these two endpoints would increase the overall power.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition of all randomized subjects is shown in Table 2. The FAS population included a total of 597 subjects and 570 subjects (95.5%) completed the dosing regimen. Twenty six (4.4%) subjects prematurely discontinued IP (4.0%, NOV03; 4.8%, saline) and 1 subject (0.2%) had missing IP completion status. The most common reasons for discontinuation of IP were subject withdrawal and reasons classified as Other. For reasons classified as Other, the majority were due to loss to follow-up (0.8%). Four (0.7%) subjects, 1 (0.3%) in the NOV03 group and 3 (1.0%) in the saline group, discontinued IP due to an AE.

Overall, 568 (95.1%) subjects completed the study and 29 (4.9%) prematurely discontinued the study (4.6%, NOV03; 5.1%, saline). The most common reasons for discontinuation of the study were subject withdrawal (1.8%), loss to follow-up (1.2%) and reasons classified as Other (1.0%). The same 4 subjects who discontinued IP due to an AE also discontinued the study due to an AE.

The demographic and other background characteristics for all subjects in the FAS population are presented in the appendix (Table 10 and Table 11). The majority of subjects (72.5%) were female, white (69.7%) and the mean age was 60.9 years (range:19 to 88 years). Two hundred eighty (46.9%) subjects were ≥ 65 years and 59.1% of subjects had their right eye designated as the study eye. In the FAS, mean tCFS in the study eye was 6.7 (SD 1.8). The mean VAS dryness and burning/stinging scores were 66.7 (SD 18.9) and 52.6 (SD 26.6), respectively. The demographic and baseline ocular characteristics were comparable between the two treatment groups.

Table 2: Subject Disposition in Study NVU-003 – All Randomized

	NOV03	Saline	All Subjects
Subjects Randomized	304	295	599
Subjects Randomized and Dosed	303	294	597
Subjects Completed IP: n (%)	290 (95.7)	280 (95.2)	570 (95.5)
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)
Other: Lost to follow up	1 (0.3)	4 (1.4)	5 (0.8)
Other: Patient was an early termination due to covid 19	2 (0.7)	0 (0.0)	2 (0.3)
Other: Patient withdrew consent	0 (0.0)	1 (0.3)	1 (0.2)
Other: Randomization error	1 (0.3)	1 (0.3)	2 (0.3)
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)
Subjects with Missing IP Completion Status: n (%)	1 (0.3)	0 (0.0)	1 (0.2)
Subjects Completed Study: n (%)	289 (95.4)	279 (94.9)	568 (95.1)
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)
Other: Family member had covid 19	1 (0.3)	0 (0.0)	1 (0.2)
Other: Patient was an early termination due to covid 19	2 (0.7)	0 (0.0)	2 (0.3)
Other: Randomization error	1 (0.3)	1 (0.3)	2 (0.3)
Other: Sponsor request subject to be an early termination due to missed visits and having insufficient supply of IP	0	1	1
Adverse Event	1 (0.3)	3 (1.0)	4 (0.7)
Protocol Violation	1 (0.3)	0 (0.0)	1 (0.2)

IP: investigational product

Source: Reviewer's analyses; Clinical Study Report Table 14.1.1.1, Table 14.1.2.1, Table 14.1.2.2

3.2.1.4 Results and Conclusions

The primary efficacy objective of the study was to assess the efficacy of NOV03 in comparison to a saline control for the treatment of the signs and symptoms of DED associated with MGD. The primary estimand of interest to address the primary efficacy objective of the study was the difference in the mean tCFS in the study eye at Day 57 between NOV03 and saline, and the difference in the mean Dryness Score at Day 57 between NOV03 and saline in all randomized subjects regardless of occurrence of IEs (see details in Section 3.2.1.2).

There were 289 (95.4%) subjects from the NOV03 treatment group and 279 (94.9%) subjects from the saline group having observed primary endpoints: change from baseline in tCFS in the study eye at Day 57 and change from baseline in the eye dryness VAS score at Day 57. Using the observed data, mean changes from baseline in tCFS in the study eye on Day 57 were -2.0 in the NOV03 group and -1.0 in the saline group, indicating improvement from baseline in both treatment groups (Table 3). The applicant analyzed the two primary efficacy endpoints 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 the primary efficacy endpoints were not adjusted for the stratification factors. An IR was sent out on September 08, 2022, to request the applicant to perform the analyses by incorporating these two stratification factors into the ANCOVA model. On October 14, 2022, the applicant submitted the response which included the updated analysis results for the primary efficacy endpoints. The reviewer's analyses included these two stratification factors. Analysis results in Table 3 showed that NOV03 had statistically significant improvement over saline in tCFS in the study eye ($p < 0.0001$). In addition, using the observed data, mean changes from baseline in the eye dryness VAS score on Day 57 were -27.4 in the NOV03 group and -19.7 in the saline group, indicating improvement from baseline in both treatment groups (Table 3). Analysis results from the ANCOVA model (incorporating two stratification factors) showed that NOV03 had statistically significant improvement over saline in the eye dryness VAS score ($p = 0.0007$).

Table 3: Primary Endpoints: Change from Baseline in tCFS in the Study Eye and Eye Dryness Score (VAS) at Day 57 (FAS)

	tCFS (Study Eye)		**Dryness Score (VAS)**	
Change from Baseline	**NOV03** (n=303)	**Saline** (n=294)	**NOV03** (n=303)	**Saline** (n=294)
Using Available Data				
N	289	279	289	279
Mean (SD)	-2.0 (2.6)	-1.0 (2.7)	-27.4 (27.9)	-19.7 (26.7)
Median (Min, Max)	-2.0 (-10, 7)	-1.0 (-9, 7)	-29.0 (-90, 50)	-18.0 (-96, 66)
LS mean	-2.22	-1.28	-27.75	-20.31
NOV03 – Saline (95% CI)	**-0.95 (-1.35, -0.54)**		**-7.44 (-11.74, -3.13)**	
p-value	**< 0.0001**		**0.0007**	
LOCF				
N	303	294	303	294
Mean (SD)	-2.0 (2.5)	-1.0 (2.7)	-26.5 (27.8)	-19.6 (26.6)
Median (Min, Max)	-2.0 (-10, 7)	-1.0 (-9, 7)	-26.0 (-90, 50)	-17.0 (-96, 66)
LS mean	-2.22	-1.26	-27.04	-20.26
NOV03 – Saline (95% CI)	**-0.95 (-1.34, -0.56)**		**-6.78 (-10.96, -2.60)**	
p-value	**< 0.0001**		**0.0015**	
BOCF				
N	303	294	303	294
Mean (SD)	-1.9 (2.5)	-1.0 (2.7)	-26.2 (27.8)	-19.3 (26.6)
Median (Min, Max)	-2.0 (-10, 7)	-1.0 (-9, 7)	-25.0 (-90, 50)	-15.0 (-96, 66)
LS mean	-2.14	-1.21	-27.49	-20.06
NOV03 – Saline (95% CI)	**-0.93 (-1.32, -0.54)**		**-6.69 (-10.89, -2.50)**	
p-value	**< 0.0001**		**0.0018**	

CI: confidence interval; LS: least square; SD: standard deviation; tCFS: total corneal fluorescein staining; VAS: visual analog scale;
LOCF: last observation carried forward; BOCF: baseline observation carried forward.
Note: LS mean, Diff, 95% CI and p-value are from an ANCOVA model with terms for baseline value, treatment, study site and baseline Dryness score (<70 vs. ≥70). For dryness score, baseline value was not included in the ANCOVA model.
Source: Reviewer's analyses.

To assess the robustness of the primary efficacy analysis results with respect to the handling of missing and intercurrent data, sensitivity analyses were conducted where missing data were imputed using LOCF and BOCF approaches. As shown in Table 3, 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. Although the LOCF and BOCF 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 and they would not make a big impact on the primary efficacy analyses.

Since statistical significance was achieved between the NOV03 and saline treatment group for the primary efficacy endpoints, the 4 key secondary endpoints were tested hierarchically at $\alpha = 0.05$:

- 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.

Table 4: Change from Baseline in Key Secondary Efficacy Endpoints (FAS)

Change from Baseline	**NOV03** (n=303)	**Saline** (n=294)
Dryness Score (VAS) at Day 15		
N	297	289
Mean (SD)	-18.0 (24.0)	-13.4 (23.3)
Median (Min, Max)	-17.0 (-90, 91)	-10.0 (-96, 64)
LS mean	-18.46	-13.89
NOV03 – Saline (95% CI)	**-4.57 (-8.15, -0.99)**	
p-value	**0.0125**	
tCFS (Study Eye) at Day 15		
N	296	288
Mean (SD)	-1.7 (2.1)	-1.1 (2.2)
Median (Min, Max)	-2.0 (-7, 6)	-1.0 (-8, 6)
LS mean	-1.68	-1.10
NOV03 – Saline (95% CI)	**-0.58 (-0.91, -0.26)**	
p-value	**0.0005**	
Burning/Stinging Score (VAS) at Day 57		
N	289	278
Mean (SD)	-23.6 (29.8)	-18.0 (25.3)
Median (Min, Max)	-21.0 (-99, 79)	-15.0 (-84, 79)
LS mean	-23.92	-18.31
NOV03 – Saline (95% CI)	**-5.61 (-9.53, -1.69)**	
p-value	**0.0051**	
cCFS (Study Eye) at Day 57		
N	289	279
Mean (SD)	-0.4 (0.8)	-0.1 (0.9)
Median (Min, Max)	0.0 (-3, 2)	0.0 (-3, 3)
LS mean	-0.38	-0.14
NOV03 – Saline (95% CI)	**-0.24 (-0.36, -0.12)**	
p-value	**< 0.0001**	

CI: confidence interval; LS: least square; 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, treatment, study site and baseline Dryness score (<70 vs. ≥70). For dryness score, baseline value was not included in the ANCOVA model.
Source: Reviewer's analyses using available data.

Since very few subjects (< 5%) didn't complete the study and they would not make a big impact on the efficacy analyses which had been shown on the analyses of the primary efficacy endpoints, the observed data were utilized to analyze each of the key secondary endpoints and the analysis results were displayed in Table 4. Mean decreases from baseline were observed in both treatment groups, indicating improvement from baseline. Similar to the primary efficacy endpoints, the applicant analyzed the key secondary efficacy endpoints using an ANCOVA model with terms for baseline value and treatment, without an adjustment for the randomization stratification factors. An IR was sent out on September 08, 2022, and the applicant submitted the response which included the updated analysis results for the key secondary efficacy endpoints on October 14, 2022. The reviewer's analyses included the stratification factors and analysis results in Table 4 showed a statistically significant difference between the NOV03 and saline groups in mean changes from baseline in eye dryness score at Day 15 ($p = 0.0125$), tCFS at Day 15 ($p = 0.0005$), burning/stinging score at Day 57 ($p = 0.0051$), and cCFS at Day 57 ($p < 0.0001$), in favor of active treatment NOV03.

3.2.2 Study BL-904

3.2.2.1 Study Design and Endpoints

Study BL-904 was a Phase 3, MC, R, DM, saline controlled study in subjects with DED associated with MGD. The study was conducted at 42 sites in the United States from November 2020 until August 2021. Study BL-904 had a similar design to Study NVU-003.

The primary objective was to assess the efficacy of NOV03 (perfluorohexyloctane) ophthalmic solution at a QID dosing regimen in comparison to a saline control for the treatment of the signs and symptoms of DED associated with MGD. The primary and key secondary efficacy endpoints were same as those in Study NVU-003.

3.2.2.2 Statistical Methodologies

The statistical methods utilized to analyze the efficacy endpoints in Study BL-904 are same as the methods used in Study NVU-003.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition of all randomized subjects is shown in Table 5. The FAS population included a total of 620 subjects and 597 subjects (96.3%) completed the dosing regimen. Twenty three (3.7%) subjects prematurely discontinued IP (2.9%, NOV03; 4.5%, saline). The most common reasons for discontinuation of IP were subject choice and reasons classified as Other. For reasons classified as Other, half were due to subject moving. No subjects in either the NOV03 group or the saline group discontinued IP due to an AE.

Overall, 598 (96.5%) subjects completed the study and 22 (3.5%) prematurely discontinued the study (2.9%, NOV03; 4.2%, saline). The most common reasons for discontinuation of the study were subject withdrawal (1.8%), protocol violation (0.8%) and reasons classified as Other (0.6%).

Twenty-three subjects prematurely discontinued IP and 22 subjects prematurely discontinued the study. Twenty subjects discontinued both IP and the study. Three subjects (subjects (b) (6)) discontinued IP dosing post–Visit 3 but completed the study, returning for Visit 4 assessments. Two subjects (subjects (b) (6)) completed IP dosing but discontinued the study. This accounts for the 1-subject difference in premature discontinuation of study but completed IP vs. premature discontinuation of IP but completed study.

The demographic and other background characteristics for all subjects in the FAS population are presented in the appendix (Table 12 and Table 13). The majority of subjects (78.7%) were female, white (80.5%) and the mean age was 53.6 years (range:19 to 88 years). One hundred ninety seven (31.8%) subjects were ≥ 65 years and 56.5% of subjects had their right eye designated as the study eye. In the FAS, mean tCFS in the study eye was 7.0 (SD 2.0). The mean VAS dryness and burning/stinging scores were 64.5 (SD 19.7) and 49.3 (SD 26.0), respectively. The demographic and baseline ocular characteristics were comparable between the two treatment groups.

Table 5: Subject Disposition in Study BL-904 – All Randomized

	NOV03	Saline	All Subjects
Subjects Randomized	311	309	620
Subjects Completed IP: n (%)	302 (97.1)	295 (95.5)	597 (96.3)
Subjects Discontinued IP: n (%)	9 (2.9)	14 (4.5)	23 (3.7)
Subject Choice	6 (1.9)	5 (1.6)	11 (1.8)
Other	1 (0.3)	5 (1.6)	6 (1.0)
Other: Subject was in California and run out of drops	0 (0.0)	1 (0.3)	1 (0.2)
Other: Subject leaving the country for elective surgery	0 (0.0)	1 (0.3)	1 (0.2)
Other: Subject moved	1 (0.3)	2 (0.6)	3 (0.6)
Other: Subject did not received IP at Visit 3	0 (0.0)	1 (0.3)	1 (0.2)
Adverse Event	0 (0.0)	0 (0.0)	0 (0.0)
Lack of Efficacy	0 (0.0)	1 (0.3)	1 (0.2)
Protocol Violation	2 (0.6)	3 (1.0)	5 (0.8)
Subjects Completed Study: n (%)	302 (97.1)	296 (95.8)	598 (96.5)
Subjects Discontinued Study: n (%)	9 (2.9)	13 (4.2)	22 (3.5)
Withdrawal by Subject	5 (1.6)	6 (1.9)	11 (1.8)
Lost to Follow up	0 (0.0)	1 (0.3)	1 (0.2)
Other	2 (0.6)	2 (0.6)	4 (0.6)
Other: Due to subject personal schedule	1 (0.3)	0 (0.0)	1 (0.2)
Other: Subject leaving the country for elective surgery	0 (0.0)	1 (0.3)	1 (0.2)
Other: Subject moved	1 (0.3)	1 (0.3)	2 (0.3)
Lack of Efficacy	0 (0.0)	1 (0.3)	1 (0.2)
Adverse Event	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Violation	2 (0.6)	3 (1.0)	5 (0.8)

IP: investigational product
Source: Reviewer's analyses; Clinical Study Report Table 14.1.1.1, Table 14.1.2.1, Table 14.1.2.2

3.2.2.4 Results and Conclusions

The primary efficacy objective of the study was to assess the efficacy of NOV03 in comparison to a saline control for the treatment of the signs and symptoms of DED associated with MGD.

Similar to Study NVU-003, the primary estimand of interest to address the primary efficacy objective of the study was the difference in the mean tCFS in the study eye at Day 57 between NOV03 and saline, and the difference in the mean Dryness Score at Day 57 between NOV03 and saline in all randomized subjects regardless of occurrence of IEs (see details in Section 3.2.1.2).

There were 302 (97.1%) subjects from the NOV03 treatment group and 296 (95.8%) subjects from the saline group having observed primary endpoints: change from baseline in tCFS in the study eye at Day 57 and change from baseline in the eye dryness VAS score at Day 57. Using the observed data, mean changes from baseline in tCFS in the study eye on Day 57 were -2.3 in the NOV03 group and -1.1 in the saline group, indicating improvement from baseline in both treatment groups (Table 6). Similar to Study NVU-003, the applicant analyzed the two primary efficacy endpoints using an ANCOVA model with terms for baseline value and treatment, without including the two stratification factors: clinical site and dryness score (< 70 vs. ≥ 70) (VAS) at baseline. Following the IR sent out on September 08, 2022, the applicant updated analysis results for the primary efficacy endpoints. The reviewer's analyses included these two stratification factors. Analysis results in Table 6 showed that NOV03 had statistically significant improvement over saline in tCFS in the study eye ($p < 0.0001$). In addition, using the observed data, mean changes from baseline in the eye dryness VAS score on Day 57 were -29.5 in the NOV03 group and -19.0 in the saline group, indicating improvement from baseline in both treatment groups (Table 6). Analysis results from the ANCOVA model (incorporating two stratification factors) showed that NOV03 had statistically significant improvement over saline in the eye dryness VAS score ($p < 0.0001$).

Similar to Study NVU-003, to assess the robustness of the primary efficacy analysis results with respect to the handling of missing and intercurrent data, sensitivity analyses were conducted where missing data were imputed using LOCF and BOCF approaches. As shown in Table 6, 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. Although the LOCF and BOCF are single imputation methods which are not recommended by the NAS report on missing data, this was not a concern as very few subjects (< 5%) didn't complete the study and they would not make a big impact on the primary efficacy analyses.

Since statistical significance was achieved between the NOV03 and saline treatment group for the primary efficacy endpoints, the 4 key secondary endpoints were tested hierarchically at $\alpha = 0.05$:

- 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.

Table 6: Primary Endpoints: Change from Baseline in tCFS in the Study Eye and Eye Dryness Score (VAS) at Day 57 (FAS)

	tCFS (Study Eye)		Dryness Score (VAS)	
Change from Baseline	**NOV03** (n=311)	**Saline** (n=309)	**NOV03** (n=311)	**Saline** (n=309)
Using Available Data				
N	302	296	302	296
Mean (SD)	-2.3 (2.8)	-1.1 (2.9)	-29.5 (28.6)	-19.0 (27.2)
Median (Min, Max)	-2.5 (-11, 7)	-1.0 (-11, 7)	-30.5 (-90, 53)	-18.5 (-100, 90)
LS mean	-2.80	-1.52	-29.54	-19.56
NOV03 – Saline (95% CI)	**-1.28 (-1.69, -0.87)**		**-9.98 (-14.25, -5.72)**	
p-value	**< 0.0001**		**< 0.0001**	
LOCF				
N	311	309	311	309
Mean (SD)	-2.2 (2.9)	-1.1 (2.8)	-29.1 (28.5)	-18.6 (27.3)
Median (Min, Max)	-2.0 (-11, 7)	-1.0 (-11, 7)	-30.0 (-90, 53)	-16.0 (-100, 90)
LS mean	-2.57	-1.38	-30.01	-19.90
NOV03 – Saline (95% CI)	**-1.19 (-1.59, -0.79)**		**-10.11 (-14.27, -5.95)**	
p-value	**< 0.0001**		**< 0.0001**	
BOCF				
N	311	309	311	309
Mean (SD)	-2.2 (2.9)	-1.1 (2.8)	-29.0 (28.5)	-18.4 (27.1)
Median (Min, Max)	-2.0 (-11, 7)	-1.0 (-11, 7)	-30.0 (-90, 53)	-16.0 (-100, 90)
LS mean	-2.57	-1.36	-29.87	-19.70
NOV03 – Saline (95% CI)	**-1.21 (-1.61, -0.80)**		**-10.16 (-14.31, -6.01)**	
p-value	**< 0.0001**		**< 0.0001**	

CI: confidence interval; LS: least square; SD: standard deviation; tCFS: total corneal fluorescein staining; VAS: visual analog scale;
LOCF: last observation carried forward; BOCF: baseline observation carried forward.
Note: LS mean, Diff, 95% CI and p-value are from an ANCOVA model with terms for baseline value, treatment, study site and baseline Dryness score (<70 vs. ≥70). For dryness score, baseline value was not included in the ANCOVA model.
Source: Reviewer's analyses.

Similar to Study NVU-003, as very few subjects (< 5%) didn't complete the study and they would not make a big impact on the efficacy analyses which had been shown on the analyses of the primary efficacy endpoints, the observed data were utilized to analyze each of the key secondary endpoints and the analysis results were displayed in Table 7. Mean decreases from baseline were observed in both treatment groups, indicating improvement from baseline. Similar to Study NVU-003, the applicant analyzed the key secondary efficacy endpoints using an ANCOVA model with terms for baseline value and treatment, without an adjustment for the randomization stratification factors. An IR was sent out on September 08, 2022, and the applicant submitted the response which included the updated analysis results for the key secondary efficacy endpoints on October 14, 2022. The reviewer's analyses included the stratification factors and analysis results in Table 7 showed a statistically significant difference between the NOV03 and saline groups in mean changes from baseline in eye dryness score at Day 15 ($p < 0.0001$), tCFS at Day 15 ($p = 0.0002$), burning/stinging score at Day 57 ($p = 0.0002$), and cCFS at Day 57 ($p < 0.0001$), in favor of active treatment NOV03.

Table 7: Change from Baseline in Key Secondary Efficacy Endpoints (FAS)

Change from Baseline	NOV03 (n=311)	Saline (n=309)
Dryness Score (VAS) at Day 15		
N	307	306
Mean (SD)	-18.5 (23.6)	-10.5 (23.9)
Median (Min, Max)	-19.0 (-88, 70)	-9.0 (-90, 60)
LS mean	-19.05	-11.69
NOV03 – Saline (95% CI)	**-7.36 (-10.90, -3.83)**	
p-value	**< 0.0001**	
tCFS (Study Eye) at Day 15		
N	307	302
Mean (SD)	-1.9 (2.3)	-1.3 (2.4)
Median (Min, Max)	-2.0 (-9, 7)	-1.0 (-9, 7)
LS mean	-2.20	-1.54
NOV03 – Saline (95% CI)	**-0.65 (-0.99, -0.31)**	
p-value	**0.0002**	
Burning/Stinging Score (VAS) at Day 57		
N	301	296
Mean (SD)	-22.1 (27.5)	-13.7 (29.9)
Median (Min, Max)	-20.0 (-95, 60)	-10.0 (-100, 89)
LS mean	-25.66	-18.37
NOV03 – Saline (95% CI)	**-7.29 (-11.11, -3.47)**	
p-value	**0.0002**	
cCFS (Study Eye) at Day 57		
N	302	296
Mean (SD)	-0.4 (0.8)	-0.1 (0.9)
Median (Min, Max)	0.0 (-3, 3)	0.0 (-3, 2)
LS mean	-0.62	-0.27
NOV03 – Saline (95% CI)	**-0.35 (-0.46, -0.23)**	
p-value	**< 0.0001**	

CI: confidence interval; LS: least square; 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, treatment, study site and baseline Dryness score (<70 vs. ≥70). For dryness score, baseline value was not included in the ANCOVA model.
Source: Reviewer's analyses using available data.

3.3 Evaluation of Safety

The safety database included all subjects in one Phase 2 (NVU-002), two Phase 3 (NVU-003, BL-904) and one Phase 3 long-term safety extension study (NVU-004). There was one death in the NOV03 group and none in the saline group. The event was considered unrelated to the study drug. The most common adverse events in the study eye (occurring at an incidence of ⩾ 1% in any treatment group) in the pooled studies were vision blurred, eye pain, ocular hyperemia, eye irritation, foreign body sensation in eyes. Of these, vision blurred (1.9%), and ocular hyperemia (1.0%) were observed at an incidence of ⩾ 1% in all NOV03 treatment group. In the long-term extension study NVU-004, the most common ocular treatment emergent adverse events (TEAEs) in ⩾ 1% of subjects were vitreous detachment (1.9%) and allergic conjunctivitis, increased lacrimation, and blurred vision (1.4% each).

In the pooled studies, 1 (0.1%) subject on NOV03 QID had an ocular adverse event, eye irritation, that led to discontinuation of IP and withdrawal from the study. In the long-term extension study NVU-004, 5 (2.4%) subjects had mild ocular adverse events: chalazion, dry eye, increased lacrimation, blurred vision, and increased intraocular pressure (1 subject each) that led to discontinuation of IP.

Additionally, non-ocular adverse events were reported in low numbers of subjects, and all but one were considered unrelated to treatment. In the Phase 2 study NVU-002, the events of pain in extremity, burning sensation, and muscle spasms, all of which occurred in the same subject, were considered by the investigator to be possibly related/suspected to NOV03 BID. The systemic absorption of NOV03 is low or minimal, and none of the laboratory results (hematology, clinical chemistry) were indicative of a safety concern for NOV03. None of the ocular adverse events were serious in any of studies.

The safety results demonstrate that NOV03 administered QID are safe and well-tolerated in adults with DED associated with MGD.

However, none of the trials that evaluated NOV03 were powered to specifically determine safety risk. The reader is referred to Dr. Shipa Rose's review for detailed information regarding the adverse event profile.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In Study NVU-003 and Study BL-904, the applicant stated that examination of subgroups on the efficacy was not applicable. However, in the clinical overview, they conducted subgroup analyses on age, race, sex, and baseline eye dryness score for both primary efficacy endpoints using the pooled phase 3 studies. On September 08, 2022, an IR was sent out to request a clarification why subgroup analysis was not conducted on each of the Phase 3 studies, but on the pooled Phase 3 studies. The applicant responded with the following:

> *Pooled analyses have greater power to gain insight into the nature of a drug's effectiveness in demographic subpopulations, provide a clearer understanding of responses across different populations, and are more likely to support meaningful conclusions than are analyses of individual studies. Consequently, Bausch & Lomb examined the effects of subgroups using the pooled datasets instead of using the individual studies.*

For each of the Phase 3 studies, the reviewer performed subgroup analyses on the primary efficacy endpoints for age (≥18 to <65 years vs. ≥ 65 years), race (White vs. Black, Asian and Others), sex (Female vs. Male) and baseline eye dryness score ([VAS] < 70 vs. ≥ 70).

4.1 Age, Sex, Race and Baseline Eye Dryness Score

Study NVU-003

In the subgroup analyses, the reviewer utilized the same ANCOVA model as in the primary analyses with additional terms for each demographic variable and its interaction with treatment.

There was no statistically significant interaction between the treatment and any of age, gender, race and baseline eye dryness score.

Results of the subgroup analyses are presented in Table 8, where observed values were utilized to calculate mean and least square mean difference (with 95% confidence interval) between two treatment groups. For both primary endpoints, the 95% confidence interval for all patient subgroups (Age groups: ⩾18 to <65 years vs. ⩾ 65 years; Race: White vs. Black, Asian and Others; Sex: Female vs. Male; Baseline eye dryness score [VAS] < 70 vs. ⩾ 70) entirely favored NOV03 except for: eye dryness score in the male subgroup, eye dryness score in the Black, Asian and Others subgroup, eye dryness score in the subgroup with baseline eye dryness score less than 70, and tCFS in the male subgroup.

Table 8: Subgroup Analyses for Study NVU-003

	tCFS (Study Eye)					Dryness Score (VAS)				
Change from Baseline	**NOV03** (n=289)		**Saline** (n=279)		**NOV03-Saline**	**NOV03** (n=289)		**Saline** (n=279)		**NOV03-Saline**
	N (%)	Mean (SD)	N (%)	Mean (SD)	LSMD 95% CI	N (%)	Mean (SD)	N (%)	Mean (SD)	LSMD 95% CI
Sex										
Male	77 (27%)	-2.2 (2.2)	77 (28%)	-1.4 (2.2)	-0.5 (-1.3, 0.2)	77 (26%)	-21.1 (23.6)	77 (28%)	-19.9 (23.3)	-0.6 (-8.5, 7.3)
Female	212 (73%)	-2.0 (2.7)	202 (72%)	-0.9 (2.9)	-1.1 (-1.6, -0.6)	212 (74%)	-29.6 (29.0)	202 (72%)	-19.6 (28.0)	-9.6 (-14.9, -4.2)
Age										
< 65	160 (55%)	-2.3 (2.4)	141 (51%)	-1.0 (2.9)	-1.2 (-1.8, -0.6)	160 (55%)	-28.2 (27.8)	141 (51%)	-17.5 (24.7)	-9.7 (-15.8, -3.7)
≥ 65	129 (45%)	-1.7 (2.7)	138 (49%)	-1.0 (2.5)	-0.8 (-1.4, -0.2)	129 (45%)	-26.3 (28.1)	138 (49%)	-21.9 (28.5)	-7.4 (-14.0, -0.7)
Race										
White	202 (70%)	-2.1 (2.5)	194 (70%)	-1.1 (2.7)	-1.0 (-1.4, -0.5)	202 (70%)	-29.4 (26.8)	194 (70%)	-20.6 (27.7)	-8.7 (-14.0, -3.5)
Black, Asian and Others	87 (30%)	-1.8 (2.6)	85 (30%)	-0.8 (2.7)	-1.2 (-2.0, -0.4)	87 (30%)	-22.5 (29.9)	85 (30%)	-17.5 (24.3)	-2.3 (-10.2, 5.7)
Baseline eye dryness score										
< 70	128 (44%)	-1.7 (2.6)	127 (46%)	-1.1 (2.6)	-0.6 (-1.2, -0.0)	128 (44%)	-16.1 (24.8)	127 (46%)	-13.4 (24.9)	-3.4 (-9.3, 2.6)
≥ 70	161 (56%)	-2.3 (2.5)	152 (54%)	-1.0 (2.8)	-1.3 (-1.8, -0.7)	161 (56%)	-36.3 (27.0)	152 (54%)	-24.9 (27.1)	-11.0 (-17.0, -5.1)

CI: confidence interval; LSMD: least square mean difference; SD: standard deviation; tCFS: total corneal fluorescein staining; VAS: visual analog scale;
Source: Reviewer's analyses using available data.

Study BL-904

Similar to Study NVU-003, the reviewer utilized the same ANCOVA model as in the primary analyses with additional terms for each demographic variable and its interaction with treatment. There was no statistically significant interaction between the treatment and any of age, gender, race and baseline eye dryness score.

Results of the subgroup analyses are presented in Table 9, where observed values were utilized to calculate mean and least square mean difference (with 95% confidence interval) between two

treatment groups. For both primary endpoints, the 95% confidence interval for all patient subgroups (Age groups: ⩾18 to <65 years vs. ⩾ 65 years; Race: White vs. Black, Asian and Others; Sex: Female vs. Male; Baseline eye dryness score [VAS] < 70 vs. ⩾ 70) entirely favored NOV03 except for: eye dryness score in the Black, Asian and Others subgroup, and tCFS in the male subgroup.

Table 9: Subgroup Analyses for Study BL-904

	tCFS (Study Eye)					Dryness Score (VAS)				
Change from Baseline	**NOV03** (n=302)		**Saline** (n=296)		**NOV03-Saline**	**NOV03** (n=302)		**Saline** (n=296)		**NOV03-Saline**
	N (%)	Mean (SD)	N (%)	Mean (SD)	LSMD 95% CI	N (%)	Mean (SD)	N (%)	Mean (SD)	LSMD 95% CI
Sex										
Male	59 (20%)	-2.3 (2.8)	70 (24%)	-1.3 (2.3)	-0.7 (-1.6, 0.2)	59 (20%)	-32.4 (25.0)	70 (24%)	-21.5 (25.4)	-13.9 (-24.2, -3.7)
Female	243 (80%)	-2.3 (2.8)	226 (76%)	-1.1 (3.1)	-1.5 (-2.0, -1.0)	243 (80%)	-28.8 (29.4)	226 (76%)	-18.2 (27.8)	-9.4 (-14.3, -4.4)
Age										
< 65	204 (68%)	-2.6 (2.7)	205 (69%)	-1.2 (2.9)	-1.5 (-2.0, -1.1)	204 (68%)	-30.5 (27.1)	205 (69%)	-18.7 (27.9)	-10.7 (-15.8, -5.6)
≥ 65	98 (32%)	-1.8 (3.0)	91 (31%)	-1.0 (3.0)	-1.0 (-1.9, -0.2)	98 (32%)	-27.7 (31.5)	91 (31%)	-19.7 (25.7)	-8.6 (-16.8, -0.4)
Race										
White	236 (78%)	-2.3 (2.9)	245 (83%)	-1.1 (3.0)	-1.2 (-1.7, -0.8)	236 (78%)	-29.1 (28.6)	245 (83%)	-18.7 (27.8)	-10.7 (-15.6, -5.8)
Black, Asian and Others	66 (22%)	-2.6 (2.4)	51 (17%)	-1.1 (2.6)	-1.5 (-2.3, -0.6)	66 (22%)	-31.2 (28.5)	51 (17%)	-20.1 (24.6)	-8.2 (-17.8, 1.4)
Baseline eye dryness score										
< 70	147 (49%)	-2.1 (3.1)	156 (53%)	-1.2 (3.1)	-1.2 (-1.8, -0.5)	147 (49%)	-20.3 (26.5)	156 (53%)	-11.4 (25.1)	-8.4, (-13.9, -2.9)
≥ 70	155 (51%)	-2.5 (2.5)	140 (47%)	-1.1 (2.7)	-1.4 (-1.9, -0.8)	155 (51%)	-38.3 (27.8)	140 (47%)	-27.5 (27.1)	-11.1 (-17.3, -4.9)

CI: confidence interval; LSMD: least square mean difference; SD: standard deviation; tCFS: total corneal fluorescein staining; VAS: visual analog scale;
Source: Reviewer's analyses using available data.

4.2 Other Special/Subgroup Populations

No other subgroup analyses were performed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In the two Phase 3 studies, 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. Under the request of an IR, the applicant re-evaluated the primary and 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 there was a statistically significant treatment effect noted in favor of NOV03.

Given the overall study discontinuation rate less than 5% in the two Phase 3 studies, the applicant did not do any imputation to missing values. The reviewer conducted the analyses using available data without any imputation. In addition, the reviewer performed the sensitivity analyses where missing data were imputed using the LOCF and BOCF method. Although these methods are single imputation methods which are not recommended by the NAS report on missing data, this was not a concern as very few subjects (< 5%) didn't complete the study which would not make an impact on the efficacy analyses.

5.2 Collective Evidence

For the Phase 3 studies (NVU-003 and BL-904), the efficacy of NOV03 (perfluorohexyloctane, 100%) was evaluated by the change from baseline in the tCFS (NEI scale) at Day 57 and the change from baseline in the dryness score (VAS severity of dryness) at Day 57. The NOV03 group had a statistically significant greater decreases from baseline in the tCFS and dryness score at Day 57 compared to the saline group. The NOV03 group also had a statistically greater reduction from baseline in the dryness score at Day 15, tCFS at Day 15, VAS burning/stinging at Day 57 and cCFS at Day 57 compared with the saline group.

5.3 Conclusions and Recommendations

Based on the analyses of the primary and key secondary efficacy endpoints in the two Phase 3 studies reviewed, there was substantial evidence that NOV03 (perfluorohexyloctane, 100%) administered four times a day improves clinically relevant signs and symptoms of Dry Eye Disease associated with Meibomian Gland Dysfunction. Therefore, we recommend an approval to perfluorohexyloctane ophthalmic solution (100%) from a statistical perspective.

5.4 Labeling Recommendations

For Section 14, we recommend updating the analysis results for the primary and key secondary efficacy endpoints where the two stratification factors are included in the ANCOVA model.

6 Appendix

6.1 Demographic and Baseline Characteristics

Table 10: Demographic Characteristics of Study NVU-003

Source: Clinical Study Report Section 11.2.1

	NOV03 (N=303)	Saline (N=294)	All Subjects (N=597)
Age (Years)			
Mean (SD)	60.3 (14.23)	61.6 (13.57)	60.9 (13.91)
Median	63.0	64.0	63.0
Min, Max	20, 87	19, 88	19, 88
Age Categories, n (%)			
<18 years	0 (0.0)	0 (0.0)	0 (0.0)
≥18 to <65 years	169 (55.8)	148 (50.3)	317 (53.1)
≥65 years	134 (44.2)	146 (49.7)	280 (46.9)
Sex, n (%)			
Male	84 (27.7)	80 (27.2)	164 (27.5)
Female	219 (72.3)	214 (72.8)	433 (72.5)
Race, n (%)			
White	212 (70.0)	204 (69.4)	416 (69.7)
Black	53 (17.5)	55 (18.7)	108 (18.1)
Asian	34 (11.2)	28 (9.5)	62 (10.4)
Other	2 (0.7)	4 (1.4)	6 (1.0)
Multiple	1 (0.3)	1 (0.3)	2 (0.3)
American Indian or Alaska Native	1 (0.3)	0 (0.0)	1 (0.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.3)	1 (0.2)
Unknown	0 (0.0)	1 (0.3)	1 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	43 (14.2)	51 (17.3)	94 (15.7)
Not Hispanic or Latino	260 (85.8)	243 (82.7)	503 (84.3)
Study Eye, n (%)			
OD	183 (60.4)	170 (57.8)	353 (59.1)
OS	120 (39.6)	124 (42.2)	244 (40.9)

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

Table 11: Baseline Ocular Characteristics of Study NVU-003

Source: Clinical Study Report Section 11.2.2

	NOV03 (N=303)	Saline (N=294)	All Subjects (N=597)
tCFS, Study Eye			
Mean (SD)	6.7 (1.8)	6.7 (1.9)	6.7 (1.8)
Median	7.0	6.0	6.0
Min, Max	4, 11	4, 11	4, 11
VAS Dryness Score			
Mean (SD)	66.5 (19.1)	66.8 (18.7)	66.7 (18.9)
Median	70.0	70.0	70.0
Min, Max	3, 100	0, 100	0, 100
VAS Burning/Stinging Score			
Mean (SD)	53.0 (26.73)	52.1 (26.55)	52.6 (26.63)
Median	57.0	57.0	57.0
Min, Max	0, 100	0, 100	0, 100
Total MGD Score, Study Eye			
Mean (SD)	7.4 (3.06)	7.7 (3.16)	7.5 (3.11)
Median	7.0	7.0	7.0
Min, Max	3, 15	3, 15	3, 15
Average TFBUT, Study Eye (sec)			
Mean (SD)	3.193 (0.838)	3.265 (0.831)	3.229 (0.835)
Median	3.130	3.150	3.140
Min, Max	1.34, 5.01	1.00, 5.00	1.00, 5.01
Unanesthetized Schirmer's Test I, Study Eye (mm)			
Mean (SD)	12.0 (8.30)	11.7 (7.60)	11.9 (7.96)
Median	9.0	8.0	9.0
Min, Max	5, 35	5, 35	5, 35
OSDI Score			
Mean (SD)	53.92 (17.55)	54.40 (16.98)	54.16 (17.26)
Median	52.10	54.20	52.50
Min, Max	25.0, 100.0	25.0, 97.9	25.0, 100.0
BCVA (logMAR)			
Mean (SD)	0.073 (0.142)	0.086 (0.143)	0.080 (0.143)
Median	0.040	0.090	0.060
Min, Max	-0.26; 0.62	-0.30; 0.54	-0.30; 0.62

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

Table 12: Demographic Characteristics of Study BL-904

Source: Clinical Study Report Section 11.2.1

	NOV03 (N=311)	Saline (N=309)	All Subjects (N=620)
Age (Years)			
Mean (SD)	53.3 (17.38)	53.8 (16.26)	53.6 (16.82)
Median	55.0	56.0	56.0
Min, Max	19, 85	20, 88	19, 88
Age Categories, n (%)			
<18 years	0 (0.0)	0 (0.0)	0 (0.0)
≥18 to <65 years	210 (67.5)	213 (68.9)	423 (68.2)
≥65 years	101 (32.5)	96 (31.1)	197 (31.8)
Sex, n (%)			
Male	61 (19.6)	71 (23.0)	132 (21.3)
Female	250 (80.4)	238 (77.0)	488 (78.7)
Race, n (%)			
White	244 (78.5)	255 (82.5)	499 (80.5)
Asian	36 (11.6)	27 (8.7)	63 (10.2)
Black	23 (7.4)	20 (6.5)	43 (6.9)
Native Hawaiian or Other Pacific Islander	3 (1.0)	2 (0.6)	5 (0.8)
Multiple	2 (0.6)	3 (1.0)	5 (0.8)
Other	1 (0.3)	2 (0.6)	3 (0.5)
American Indian or Alaska Native	2 (0.6)	0 (0.0)	2 (0.3)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)			
Hispanic or Latino	63 (20.3)	65 (21.0)	128 (20.6)
Not Hispanic or Latino	248 (79.7)	244 (79.0)	492 (79.4)
Study Eye, n (%)			
n (missing)	310 (1)	309 (0)	619 (1)
OD	168 (54.0)	182 (58.9)	350 (56.5)
OS	142 (45.7)	127 (41.1)	269 (43.4)

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.

Table 13: Baseline Ocular Characteristics of Study BL-904

Source: Clinical Study Report Section 11.2.2

	NOV03 (N=311)	Saline (N=309)	All Subjects (N=620)
tCFS, Study Eye*			
Mean (SD)	7.0 (2.0)	7.1 (2.1)	7.0 (2.0)
Median	7.0	7.0	7.0
Min, Max	4, 11	4, 11	4, 11
VAS Dryness Score			
Mean (SD)	64.7 (19.5)	64.3 (19.8)	64.5 (19.7)
Median	70.0	69.0	69.0
Min, Max	0, 100	10, 100	0, 100
VAS Burning/Stinging Score			
Mean (SD)	50.1 (25.83)	48.4 (26.19)	49.3 (26.00)
Median	51.0	50.0	50.5
Min, Max	0, 100	0, 100	0, 100
Total MGD Score, Study Eye*			
Mean (SD)	7.9 (3.45)	8.1 (3.47)	8.0 (3.46)
Median	7.0	7.0	7.0
Min, Max	3, 15	3, 15	3, 15
Average TFBUT, Study Eye (seconds)			
Mean (SD)	3.165 (0.921)	3.144 (0.922)	3.155 (0.920)
Median	3.145	3.050	3.110
Min, Max	0.95, 5.00	0.75, 5.00	0.75, 5.00
Unanesthetized Schirmer's Test I, Study Eye (mm)*			
Mean (SD)	12.7 (7.54)	12.8 (7.93)	12.7 (7.73)
Median	10.0	10.0	10.0
Min, Max	5, 35	5, 35	5, 35
OSDI Score			
Mean (SD)	55.16 (17.44)	55.80 (17.21)	55.48 (17.32)
Median	54.50	55.00	55.00
Min, Max	25.0, 95.8	25.0, 100.0	25.0, 100.0
Calculated BCVA (LogMAR), Study Eye*			
Mean (SD)	0.072 (0.141)	0.067 (0.134)	0.069 (0.138)
Median	0.040	0.040	0.040
Min, Max	-0.30, 0.54	-0.28, 0.60	-0.30, 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.

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