## 1.0 TITLE PAGE

# A Phase 3, Multi-Center, Randomized, Double-Masked, Saline-Controlled Trial to Evaluate the Effect of NOV03 (Perfluorohexyloctane) on Signs and Symptoms of Dry Eye Disease Associated with Meibomian Gland Dysfunction (Gobi Study)

## CLINICAL STUDY REPORT

## Study # NVU-003

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| **Investigational Product:** | NOV03 (100% perfluorohexyloctane) |
| **Sponsor representative:** | Jason Vittitow, PhD<br>Bausch & Lomb Incorporated<br>400 Somerset Corporate Boulevard<br>Bridgewater, NJ 08807 |
| **Sponsor:** | Bausch & Lomb Incorporated<br>400 Somerset Corporate Boulevard<br>Bridgewater, NJ 08807 |
| **Phase of Study:** | Phase 3 |
| **Study Design:** | This was an 10-week, 2-arm, randomized (1:1), parallel-group, bilateral, double-masked study conducted in subjects with dry eye disease associated with meibomian gland dysfunction |
| **Dates of the Study:** | Date first subject enrolled: 19 Dec 2019<br>Date last subject exited: 12 Mar 2021 |
| **Date of Report:** | 22 July 2021 |

**Revision Chronology:**

| | |
|---|---|
| Final, Version 1.0 | 22 July 2021 |

This clinical investigation was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and with Good Clinical Practice (GCP), as required by the US Code of Federal Regulations applicable to clinical studies (21 CFR Parts 11, 50, 54, 56 and [312]; 42 USC 282(j); International Council on Harmonization (ICH) Harmonized Tripartite Guideline E6(R2): GCP and E2A: Safety Data Management and applicable local regulations, including the archiving of essential documents.

### CONFIDENTIALITY STATEMENT

## 2.0 SYNOPSIS

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| **Name of Sponsor/Company:** Bausch & Lomb Incorporated | **Individual Study Table Referring to Part of the Dossier** | **(For National Authority Use Only)** |
| **Name of Finished Product:** To be determined | **Volume:** | |
| **Name of Active Ingredient:** NOV03 (100% perfluorohexyloctane) | **Page:** | |

**Title of study:** A Phase 3, Multi-Center, Randomized, Double-Masked, Saline-Controlled Trial to Evaluate the Effect of NOV03 (Perfluorohexyloctane) on Signs and Symptoms of Dry Eye Disease Associated with Meibomian Gland Dysfunction (Gobi Study)

**Investigators:** This study was conducted by 26 sites in the United States.

**Publication (reference):** Not applicable

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| **Studied period:**<br>**Date of first enrollment:** 19 Dec 2019<br>**Date of last completed:** 12 Mar 2021 | **Phase of development:** 3 |

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

The secondary objective was to assess the safety and tolerability of NOV03 versus the saline control in subjects with DED associated with MGD.

Further objectives explored the effect of NOV03 versus the saline control on other efficacy endpoints in the same population.

**Methodology:** This was a Phase 3, multi-center, randomized, double-masked, saline-controlled study conducted in subjects with DED associated with MGD.

The study consisted of 5 visits over a 10-week period: Visit 0 (screening within 14 days before Visit 1 [Day -14 to -1]); Visit 1 (Day 1, baseline/randomization); Visit 2 (Day 15 ± 1 day); Visit 3 (Day 29 ± 2 days); and Visit 4 (Day 57 ± 2 days).

Eligible subjects were assigned to 1 of 2 treatment groups and received NOV03 (100% perfluorohexyloctane) ophthalmic solution QID or saline (0.6% sodium chloride solution) ophthalmic solution QID, starting at Visit 1 and ending at Visit 4. Subjects instilled the investigational product (IP) bilaterally.

In the case that both eyes were eligible for analysis, the worst eye was selected as the study eye, defined as the eye with worse (higher) total corneal staining at Visit 1. If the total corneal staining was the same in both eyes, then the right eye was selected as the study eye.

**Number of subjects (planned and analyzed):** Approximately 560 subjects were planned for enrollment (280 subjects [560 eyes] per treatment group). A total of 599 subjects were randomized, and 597 were treated with IP.

**Number of Subjects Analyzed:**

Full Analysis Set (FAS): 597 subjects
Per-Protocol Set (PPS): 549 subjects
Safety Analysis Set (SAF): 597 subjects

**Diagnosis and main criteria for inclusion:** Subjects had to be least 18 years of age; have a subject-reported history of DED in both eyes for at least 6 months; and have each of following at Visit 0 and Visit 1: tear film break-up time (TFBUT) ≤5 seconds; ocular surface disease index (OSDI) score ≥25; an

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unanesthetized Schirmer's test I score ≥5 mm; total MGD score ≥ 3 (range, 0-15); total corneal fluorescein staining (tCFS) score between 4 and 11 based on the National Eye Institute (NEI) scale. All subjects provided written informed consent.

**Test product, dose, and mode of administration, batch number:** The IP was NOV03 (100% perfluorohexyloctane) ophthalmic solution. Subjects randomized to the NOV03 treatment group instilled 1 drop of NOV03 into each eye QID. Batch numbers for NOV03 were 1934-027 and 1949-027.

**Duration of treatment:** 8 weeks

**Reference therapy, dose and mode of administration, batch number:** The comparator product was saline solution (0.6% sodium chloride solution) preserved with benzalkonium chloride. Subjects randomized to the saline treatment group instilled 1 drop of saline into each eye QID. Batch numbers for the saline control were 1936-007 and 2003-013.

**Criteria for evaluation**:

**Efficacy**: Two primary endpoints were tested using hierarchical fixed sequence testing to maintain an overall 2-sided alpha = 0.05 level:

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

If both primary endpoints demonstrated statistically significant superiority of NOV03 versus saline at the 2-sided alpha = 0.05 level, the following secondary endpoints were tested hierarchically to maintain an overall 2-sided alpha = 0.05:

- Change from baseline of dryness score (VAS) at Day 15.
- Change from baseline in tCFS (NEI scale) at Day 15.
- Change from baseline of VAS burning/stinging at Day 57.
- Change from baseline in central corneal fluorescein staining (cCFS) (NEI scale) at Day 57.

Other pre-specified efficacy endpoints included:

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

Exploratory efficacy endpoints included:

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

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

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

**Statistical methods:**

For categorical variables, summary tabulations of the number and percentage within each category were presented. For continuous variables, the mean, median, standard deviation (SD), minimum and maximum values were presented.

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

The 4 key secondary efficacy endpoints were also tested using hierarchical fixed sequence testing. Inference was to be made only if both primary endpoints and any higher order secondary endpoints were statistically significant at a 2-sided alpha = 0.05, in favor of NOV03.

Endpoints evaluating the proportion of study eyes (or subjects) that met pre-defined criteria were presented and tested between treatment groups using logistic regression analysis, adjusting for baseline score at each measured follow-up visit.

For efficacy assessments performed by eye, study eye and fellow eye were summarized separately.

TEAEs were tabulated; separate summaries were prepared for ocular and non-ocular TEAEs. Ocular TEAEs were summarized at the subject level and by eye. Actual values and changes from baseline were summarized by eye for IOP and VA using summary statistics. Slit-lamp biomicroscopy and dilated fundoscopy findings were summarized by eye using summary statistics and tabulated as the number and percent of subjects with normal/not present and abnormal/present results by treatment group, study visit, and eye. Shifts from baseline indicative of worsening were summarized.

**SUMMARY-CONCLUSIONS:**

In the FAS, mean age of the study population was 60.9 years (range: 19 to 88 years). None of the subjects were <18 years of age; 280 (46.9%) subjects were ≥65 years. The majority of subjects were female (72.5%). The most common race was White (69.7%), followed by Black (18.1%) and Asian (10.4%).

**EFFICACY RESULTS:** Both of the primary endpoints and all 4 key secondary endpoints were met in this study, with NOV03 showing significant improvement over saline in clinically relevant signs and symptoms of DED associated with MGD.

**Fluorescein Corneal Staining**

*Changes from Baseline in tCFS*

In the FAS, mean decreases from baseline in the tCFS score in the study eye (indicating improvement) were observed in both treatment groups on Days 15 (secondary endpoint), 29, and 57 (primary endpoint). Analysis showed statistically significant ($p \leq 0.001$) differences between the NOV03 and saline groups, in

favor of active treatment, at Day 15 and Day 57; a nominally statistically significant difference was also observed on Day 29 (p=0.001).

In the responder analyses, a nominally statistically significant difference was observed between the NOV03 and saline groups, in favor of active treatment, for proportion of subjects who had a ≥3 improvement from baseline in the tCFS score (NEI scale) in the study eye at Day 57 (p<0.001). Subjects in the NOV03 group were nearly twice as likely to achieve a ≥3 improvement in the tCFS score compared to subjects in the saline group (odds ratio [OR] = 1.88).

*Changes from Baseline in CFS in the Central and Inferior Regions*

In the FAS, mean decreases from baseline in the cCFS score in the study eye (indicating improvement) were observed in both treatment groups on Days 15, 29, and 57 (secondary endpoint). Analysis showed a statistically significant (p<0.001) difference between the NOV03 and saline groups, in favor of active treatment, at Day 57; nominally statistically significant differences were also observed on Day 15 and Day 29 (p≤0.006).

Mean decreases from baseline in the inferior CFS score in the study eye (indicating improvement) were observed in both treatment groups on Days 15, 29, and 57. On Days 15 and 57, analysis showed nominally statistically significant (p<0.001) differences between the NOV03 and saline groups, in favor of active treatment; on Day 29, the difference approached significance (p=0.060).

**Subject Assessment of Eye Dryness, Burning/Stinging, and Other Symptoms**

In the FAS, mean decreases from baseline in the eye dryness VAS score (indicating improvement) were observed in both treatment groups on Days 15 (secondary endpoint), 29, and 57 (primary endpoint). At Days 15 and 57, analysis showed statistically significant (p≤0.009) differences between the NOV03 and saline groups, in favor of active treatment.

In the responder analyses, nominally statistically significant differences were observed between the NOV03 and saline groups, in favor of active treatment, for proportion of subjects who had a ≥30% improvement from baseline in the VAS dryness score at Day 15 (p=0.007) and Day 57 (p=0.010). Subjects in the NOV03 group were 59% and 55% more likely to achieve a ≥30% improvement from baseline in the VAS dryness score at Day 15 and Day 57, respectively, compared to subjects in the saline group.

Mean decreases from baseline in the burning/stinging VAS score (indicating improvement) were observed in both treatment groups on Days 15, 29, and 57 (secondary endpoint). Analysis showed nominally statistically significant differences (p≤0.015) between the NOV03 and saline groups in mean change from baseline in the eye burning/stinging VAS score on Days 15 and 57, in favor of active treatment.

Mean decreases from baseline (indicating improvement) were observed for the remaining VAS scores in both treatment groups on Days 15, 29, and 57. Analysis showed nominally statistically significant differences between the NOV03 and saline groups, in favor of active treatment, for most of the ocular symptoms: foreign body sensation (Day 57, p=0.002); itching (Days 15 and 57, p≤0.029); sensitivity to light (Day 15, p=0.011); pain (Days 15 and 57, p≤0.017); awareness of dry eye symptoms (Days 15 and 57, p≤0.040); and frequency of dryness (Days 15 and 57, p≤0.031).

**Other Efficacy Findings**

No appreciable differences were observed between treatment groups in terms of OSDI, total MGD score, the Schirmer's Test I score, and TFBUT.

**SAFETY RESULTS:** NOV03 was safe and well tolerated in this study. Four (0.7%) subjects, 1 (0.3%) in the NOV03 group and 3 (1.0%) in the saline group, had an ocular TEAE that resulted in discontinuation of IP. In the opinion of the Investigator, each event was suspected/related to IP.

None of the ocular TEAEs were serious. Less than 10% of subjects had an ocular TEAE (9.6%, NOV03; 7.5%, saline). Most of the TEAEs were mild in severity; 1 (0.2%) subject had severe eye irritation in both eyes (NOV03). Overall, the most common ocular TEAEs (both groups combined) were blurred vision (1.7%) and instillation site pain (1.0%). Incidences of individual ocular TEAEs were generally similar between treatment groups. The incidence of blurred vision was higher in the NOV03 group (3.0%) than in the saline group (0.3%). Blurred vision was mild, transient in nature, and typically resolved within several minutes post-instillation.

Less than 6% of subjects had a non-ocular TEAE (5.9%, NOV03; 4.1%, saline). Incidences of individual non-ocular TEAEs were low and similar between treatment groups. None of the non-ocular TEAEs were attributed to IP, severe in intensity, or led to discontinuation of IP. One subject had a serious non-ocular TEAE (acute chest pain, saline group).

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None of the BCVA, IOP, slit-lamp examination, or dilated fundoscopy results were indicative of a safety concern for NOV03.

The eyedrop acceptability questionnaire (3 questions) was scored by the subject for the study eye on Day 57 using a VAS ranging from 0 to 10. Higher scores were indicative of better acceptability. Two of the 3 questions (satisfaction with the study eye drop, request for prescription of study drug) showed a nominally statistically significant difference ($p \leq 0.005$) between the NOV03 and saline groups, in favor of active treatment.

The instillation comfort questionnaire (1 question) was scored by the subject for each eye approximately 2 minutes after dosing at Visit 1 using a VAS ranging from 0 to 10. Higher scores were indicative of better comfort. The mean instillation comfort score in the study eye was 7.9 (SD 2.3) in the NOV03 group and 8.3 (SD 2.1) in the saline group. Analysis showed a nominally statistically significant difference ($p=0.016$) between the NOV03 and saline groups, in favor of the control.

**CONCLUSION:**

NOV03 (100% perfluorohexyloctane) demonstrated statistically significant improvement over saline in several clinically relevant signs (tCFS, cCFS, and inferior CFS) and symptoms (VAS scores, including eye dryness and burning/stinging) of DED associated with MGD. Onset of improvement was observed within 2 weeks of first dose (first timepoint measured post-baseline) and remained significant at Day 57. NOV03 was safe and well tolerated. Blurred vision was the only TEAE that occurred in a higher proportion of subjects treated with NOV03 (versus saline); it was mild in severity and transient in nature, typically resolving within minutes of onset. NOV03 is a safe and effective treatment for DED associated with MGD.

**Date of the report:**

Final, Version 1.0, 22 July 2021

# 3.0 TABLE OF CONTENTS

## LIST OF TABLES



## 4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation/Acronym | Term |
|---|---|
| AE | adverse event |
| ANCOVA | analysis of covariance |
| ATC | Anatomical Therapeutic Chemical |
| BCVA | best-corrected visual acuity |
| cCFS | central corneal fluorescein staining |
| CI | confidence interval |
| COVID-19 | Coronavirus Disease 2019 |
| CSR | clinical study report |
| DED | dry eye disease |
| eCRF | electronic case report form |
| ETDRS | Early Treatment Diabetic Retinopathy Study (chart) |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | informed consent form |
| ICH | International Council on Harmonization |
| IOP | intraocular pressure |
| IP | investigational product |
| IRB | Institutional Review Board |
| IRS | interactive randomization system |
| LOCF | last observation carried forward |
| logMAR | logarithm of the minimum angle of resolution |
| LS | least squares |
| MedDRA | Medical Dictionary for Regulatory Activities |

| Abbreviation/Acronym | Term |
|---|---|
| MGD | meibomian gland dysfunction |
| NEI | National Eye Institute |
| OD | right eye |
| OR | odds ratio |
| OS | left eye |
| OSDI | ocular surface disease index |
| OU | both eyes |
| PPS | Per Protocol Set |
| PT | preferred term |
| QID | four times a day |
| SAE | serious adverse event |
| SAF | Safety Analysis Set |
| SD | standard deviation |
| SOC | system organ class |
| tCFS | total corneal fluorescein staining |
| TEAE | treatment-emergent adverse event |
| TFBUT | tear film break-up time |
| US | United States |
| VA | visual acuity |
| VAS | visual analog scale |
| WHO | World Health Organization |

# 5.0 ETHICS

## 5.1 Institutional Review Board

The study protocol and amendment(s), informed consent form (ICF), and other study materials were reviewed and approved by Institutional Review Boards (IRBs) associated with the individual study sites. IRBs were informed of all protocol changes in accordance with the procedures established by the IRBs. Written approval of the study protocol and amendment(s), ICF, and other study materials was provided to each site prior to initiation of the study. Investigators were not to deviate from the study protocol except when necessary for the protection of the subject's health, safety, or welfare.

Refer to Section 16.1.4 for a listing of Principal Investigators and their associated site numbers and Section 16.1.3 for IRB information.

## 5.2 Ethical Conduct of the Study

This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practices (GCPs), as described in the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP; the ethical principles in the Declaration of Helsinki, and applicable local regulations.

## 5.3 Subject Information and Consent

Before any study-specific procedures were performed, the Investigator (or designee) provided the subject the ICF and explained the purpose of the study, the associated procedures, and any anticipated effects or adverse reactions. The subject was given sufficient time and opportunity to ask questions regarding any aspect of the study and to decide whether or not to participate in the study.

The Investigator (or designee) explained to the subject that he or she was completely free to refuse to enter the study or to withdraw at any time, without giving a reason. Similarly, the Investigator and Sponsor were free to withdraw the subject at any time for safety or administrative reasons. Other requirements necessary for the protection of the human rights of the subject were also explained according to current ICH GCP guidelines and the World Medical Association Declaration of Helsinki in its revised edition. The content of the ICF adhered to Food and Drug Administration regulations and ICH guidelines and had current IRB approval.

Once the Investigator (or designee) was assured the subject understood the implications of study participation, the subject provided consent to participate in the study by signing and dating the ICF Form and providing Health Insurance Portability and Accountability Act (HIPAA) authorization. The subject was provided a copy of the fully signed ICF and HIPAA authorization form.

A sample ICF used for this study is provided in Section 16.1.3. The identity of the subjects was kept confidential. Each eligible subject was assigned a subject number, which was used on the electronic case report form (eCRF) instead of the subject's name.

# 6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was conducted by Bausch & Lomb Inc. at 26 sites in the United States (US). See Section 16.1.4 for a list of Principal Investigators and their curricula vitae.

Table 6-1 summarizes key parties involved in the conduct, oversight, and reporting of this clinical study. Refer to Section 16.1.4 for the curricula vitae of key study personnel.

**Table 6-1: Study Administrative Structure**

| | |
|---|---|
| **Sponsor:** | Bausch & Lomb Incorporated<br>400 Somerset Corporate Boulevard<br>Bridgewater, NJ 08807<br>USA |
| **Medical Monitor:** | Kenneth Sall, MD<br>PO Box 3623<br>Huntington Beach, CA 92605 |
| **Clinical Affairs:** | Bausch & Lomb Incorporated<br>400 Somerset Corporate Boulevard<br>Bridgewater, NJ 08807 |
| **Clinical Operations:** | Bausch & Lomb Incorporated<br>1400 North Goodman Street.<br>Rochester, NY 14609 |
| **Clinical Trial Supply Management:** | Bausch & Lomb Incorporated<br>1400 North Goodman Street<br>Rochester, New York 14609 |
| **Statistics:** | Bausch & Lomb Incorporated<br>1400 North Goodman Street.<br>Rochester, NY 14609 |
| **Data Management:** | Bausch & Lomb Incorporated<br>1400 North Goodman Street.<br>Rochester, NY 14609 |
| **Contract Research Organization:** | Lexitas Pharma Services<br>313 Foster Street<br>Durham, NC 27701 |

NOTE: Unless otherwise specified, the address for study personnel is the same as the Sponsor's address.

## 7.0 INTRODUCTION

Dry eye disease (DED) is defined by the International Dry Eye Workshop as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (Craig et al, 2017). Symptoms of DED such as feeling of dryness, burning, a sandy/gritty sensation, foreign body sensation, pain or itchiness are quite debilitating. In addition, visual function related symptoms such as fluctuating vision with blinking, blurred vision, and difficulty with reading despite perfect visual acuity (VA) is an important and underestimated aspect of the disease. DED is a serious and chronic disorder that, if left untreated or undertreated, progressively damages the ocular surface and may lead to permanent vision loss due to corneal complications (Lemp et al., 1995). As many as 5% to 35% of subjects visiting ophthalmic clinics report dry eye symptoms, making it one of the most common conditions seen by ophthalmic specialists (McCarty et al. 1998; Lin et al. 2003).

DED can be categorized as either aqueous deficient DED or as evaporative DED. Epidemiological and clinical evidence suggest that the majority of DED cases are evaporative in nature (Craig, et al. 2017). With evaporative DED, the regulation of evaporative loss from the tear film is directly affected through alteration of the lipid layer,

leading to an increase in tear evaporation. The most common cause of evaporative DED is meibomian gland dysfunction (MGD). Meibomian glands secrete lipids which spread across the ocular surface and stabilize the tear film, protecting tears from evaporation. In MGD, chronic disease of these glands leads to blockage of the terminal ducts and/or quantitative/qualitative changes within the glands, altering the tear film and giving rise to symptoms of DED. The meibomian gland is a key component in the etiology of dry eye and contributes to the evaporative status of the tear film (Bron, et al. 2017).

NOV03 is a sterile ophthalmic eye drop formulation being developed for the treatment of the signs and symptoms of DED associated with MGD. It is a single component product consisting of 100% perfluorohexyloctane. Due to its low surface tension, it rapidly spreads across the ocular surface and interacts with the lipophilic part of the tear film forming a layer at the tear film air interface. Such a layer prevents excessive evaporation of the aqueous tear film component. In addition, NOV03 penetrates meibomian glands, where it potentially interacts with and dissolves the altered, viscous meibum secrete in the glands. As a water-free, single component product, it is free of excipients like oils, surfactants, and preservatives.

The active and only ingredient of NOV03, perfluorohexyloctane, is a semi-fluorinated alkane with a well-established tolerability and safety profile. Perfluorohexyloctane, the active ingredient of NOV03, was classified as a class IIa 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. It is not yet approved in the US.

Bausch & Lomb Incorporated is developing NOV03 (perfluorohexyloctane) ophthalmic solution as a treatment of DED associated with MGD. A completed phase 2 trial of NOV03 (NVU-002), conducted in the US, was designed to specifically include a DED population with an MGD component. Safety data in this trial showed an excellent clinical safety and tolerability profile and favorable efficacy in reducing signs and symptoms of disease in subjects with DED associated with MGD. The safety and efficacy profile of NOV03 in the NVU-002 study is supported by post-marketing experience with NovaTears®.

This clinical study report (CSR) was prepared for Study NVU-003, a Phase 3, multi-center, randomized, double-masked, saline-controlled study of NOV03 (perfluorohexyloctane) ophthalmic solution administered four times a day (QID) in subjects with DED associated with MGD.

## 8.0 STUDY OBJECTIVES AND ENDPOINTS

### 8.1 Study Objectives

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

The secondary objective was to assess the safety and tolerability of NOV03 versus the saline control in subjects with DED associated with MGD.

Further objectives explored the effect of NOV03 versus the saline control on other efficacy endpoints in the same population.

## 8.2 Endpoints

Efficacy was based on a panel of assessments related to the signs and symptoms of DED. The 2 primary efficacy endpoints were tested using hierarchical fixed sequence testing:

- Change from baseline in total corneal fluorescein staining (tCFS) score (National Eye Institute [NEI] scale) at Day 57.
- Change from baseline of dryness score (visual analog scale [VAS] severity of dryness) at Day 57.

If both primary endpoints demonstrated statistically significant superiority of NOV03 versus saline at the 2-sided alpha = 0.05 level, the following secondary endpoints were tested hierarchically:

- Change from baseline of dryness score (VAS) at Day 15.
- Change from baseline in tCFS (NEI scale) at Day 15.
- Change from baseline of VAS burning/stinging at Day 57.
- Change from baseline in central corneal fluorescein staining (cCFS) (NEI scale) at Day 57.

Other pre-specified efficacy endpoints included:

- Change from baseline of dryness score (VAS) at Day 29.
- Change from baseline in tCFS at Day 29.
- Change from baseline in CFS central and inferior sub-regions (NEI scale) to each measured post-baseline 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.
- Tear film break-up time (TFBUT) at Day 57.

The safety and tolerability evaluation was based on the occurrence of ocular and non-ocular treatment-emergent adverse events (TEAEs); VA; slit-lamp biomicroscopy; intraocular pressure (IOP); and dilated fundoscopy. Subjects also completed an instillation comfort questionnaire and eyedrop acceptability questionnaire.

# 9.0 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan – Description

This was a Phase 3, multi-center, randomized, double-masked, saline-controlled study conducted in subjects with DED associated with MGD. Approximately 560 subjects (male and female) were planned for enrollment. Subjects had to be least 18 years of age, have a

subject-reported history of DED in both eyes for at least 6 months, and meet all other trial eligibility criteria.

A schematic of the study is presented in the figure below. 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)
- Visit 4 (Day 57 ± 2 days).

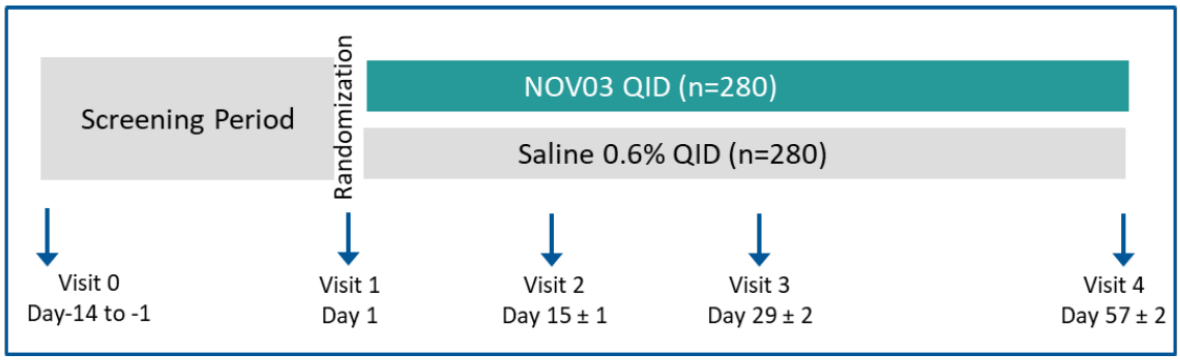
Eligible subjects were randomized in a 1:1 ratio to 1 of 2 treatment groups and administered 1 drop of NOV03 (100% perfluorohexyloctane) QID or 1 drop of saline (0.6% sodium chloride solution) into each eye QID. Subjects were dosed over an 8-week period, starting at Visit 1 and ending at Visit 4. Randomization was stratified by clinical site and by the subject's VAS dryness score at baseline (<70 vs ≥ 70).

In the case that both eyes were eligible for analysis, the worst eye was selected as the study eye, defined as the eye with worse (higher) total corneal staining at Visit 1. If the total corneal staining was the same in both eyes, then the right eye was selected as the study eye.

A schedule of assessments is presented in Section 9.5.1.

No interim analysis was planned or conducted.

See Section 16.1.1 for the protocol and Section 16.1.2 for a sample eCRF used in the study. See Section 9.8 for details of the protocol amendments.




## 9.2 Discussion of Study Design, Including the Choice of Control Groups

The trial was a Phase 3, randomized, double-masked, saline controlled trial designed to demonstrate the efficacy and safety of NOV03 versus a saline control in subjects with signs and symptoms of DED associated with MGD. This target population has responded well to NOV03 based on clinical data from Study NVU-002 and clinical data from NovaTears®, a perfluorohexyloctane product currently marketed outside the US.

The trial was randomized and double-masked to reduce bias. The comparator used in the trial was a sterile saline ophthalmic solution. Vehicle controlled trials are currently the standard for DED trials. However, since NOV03 is a 100% single component product, no vehicle was available for comparison. Therefore, a saline solution, which is commonly used in ophthalmic studies, was selected as the comparator.

Fast onset of efficacy is important for subjects and their compliance to therapies; therefore, early demonstration of efficacy (ie, within a couple of months) is desired. Moreover, DED is a fluctuating condition with recurring dry eye complaints that may be linked to seasonal and/or environmental changes (Van Setten et al., 2016), such that shorter treatment durations may be best suited to demonstrate a true drug effect.

The treatment duration used in this study, 8 weeks, is considered sufficient to evaluate the efficacy and safety of NOV03. The phase 2 clinical trial NVU-002 showed significant efficacy of NOV03 in sign and symptom outcomes at 8 weeks for both BID and QID dosing regimens compared to respective saline controls. In the current study, Week 8 was selected as the primary timepoint for assessment of efficacy; earlier timepoints (eg, Day 15) were also included to further evaluate time to efficacy onset.

See Section 9.4.4 for dose selection of NOV03.

## 9.3 Selection of Study Population

### 9.3.1 Inclusion Criteria

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

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

### 9.3.2 Exclusion Criteria

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

1. Had been randomized in NVU-002 or BL904.
2. Had any clinically significant ocular surface slit-lamp findings at Visit 0 and Visit 1 and/or in the opinion of the Investigator had any findings that may have interfered with trial parameters, including eye trauma or history of eye trauma or anterior membrane dystrophy.
3. Had a history of Stevens Johnson Syndrome.
4. Had active blepharitis or lid margin inflammation that required any topical antibiotics or topical steroids within last 30 days prior to Visit 0 or would have likely required

such treatment during the trial. Any other lid margin therapy such as lid scrubs, lid wipes, warm compresses, systemic antibiotics (such as tetracyclines) and oral supplements for treatment of ocular conditions had to be stable within the last 30 days prior to Visit 1 and was to be maintained throughout the trial.

5. Had had a LipiFlow procedure, intense pulse light procedure or any kind of other procedure affecting meibomian glands within 6 months prior to Visit 1.
6. Had abnormal lid anatomy that caused incomplete eyelid closure, including entropion and ectropion, or floppy lid syndrome that exposed parts of the conjunctiva or impaired the blinking function of the eye.
7. Had received or removed a permanent punctum plug within 3 months (6 months for dissolvable punctum plugs) prior to Visit 1 or was expected to receive a punctum plug or removal of a punctum plug, or had a punctum plug expected to be dissolved during the trial.
8. Had DED secondary to scarring, irradiation, alkali burns, cicatricial pemphigoid, or destruction of conjunctival goblet cells (as with vitamin A deficiency).
9. Had an ocular or periocular malignancy.
10. Had a corneal epithelial defect or had significant confluent staining or filaments anywhere on the cornea.
11. Had a history of herpetic keratitis.
12. Had active ocular allergies or ocular allergies that were expected to be active during the trial period.
13. Was diagnosed with an active ocular or systemic infection (bacterial, viral, or fungal), including fever requiring treatment with antibiotics.
14. Had worn contact lenses within 1 month of Visit 0 or anticipated using contact lenses during the trial.
15. Had used any eye drops and/or TrueTear™ device (intranasal tear neurostimulator) within 24 hours before Visit 1.
16. Had undergone intra-ocular surgery or ocular laser surgery within the previous 6 months or had any planned ocular and/or lid surgeries over the trial period.
17. Was a family member living in the same household as another subject randomized into NVU-003 or BL904, or was a family member living in the same household as a participant in NVU-004 Open-Label Extension.
18. Was a clinical site employee directly involved in the management, administration, or support of this trial or was an immediate family member of the same.
19. Was a woman who was pregnant, nursing or planning a pregnancy.
20. Was unwilling to submit to a urine pregnancy test at Visit 0, Visit 1 and Visit 4 (or early termination visit) if of childbearing potential. Non-childbearing potential was defined as a woman who was permanently sterilized (eg, had a hysterectomy or bilateral tubal ligation or bilateral oophorectomy) or was post-menopausal (without menses for 12 consecutive months).
21. Was a woman of childbearing potential who was not using an acceptable means of birth control; acceptable methods of contraception included: hormonal (oral, implantable, injectable, or transdermal contraceptives); mechanical (spermicide in conjunction with a barrier such as a diaphragm or condom); intrauterine device; or surgical sterilization of partner. For non-sexually active females, abstinence could have been regarded as an adequate method of birth control; however, if the subject became sexually active during the trial, she had to agree to use adequate birth control as defined above for the remainder of the trial.
22. Had an uncontrolled systemic disease in the opinion of the Investigator.

23. Had a known allergy and/or sensitivity to the investigational drug or saline components.
24. Had active ocular or periocular rosacea that in the judgement of the Investigator interfered with the trial (eg, clinically relevant lid induration).
25. Had a pterygium in any eye.
26. Was currently enrolled in an investigational drug or device study or had used an investigational drug or device within 60 days of Visit 1.
27. Had used any topical ocular steroids treatments, topical cyclosporine, lifitegrast, serum tears or topical anti-glaucoma medication within 60 days prior to Visit 0.
28. Had used any oral medications known to cause ocular drying (eg, antihistamines, antidepressants, etc.) on a non-stable regimen within 1 month prior to Visit 0 or was expected to be unstable during the trial.
29. Had corrected VA worse than or equal to logarithm of the minimum angle of resolution (logMAR), +0.7 as assessed with Early Treatment Diabetic Retinopathy Study (ETDRS) charts in both eyes at Visit 0 and Visit 1.
30. Had a condition or be in a situation (including language barrier) which the Investigator felt may put the subject at significant risk, may confound the trial results, or may interfere significantly with the subject's participation in the trial.

### 9.3.3 Removal of Subjects from Therapy or Assessment

Subjects were free to discontinue their participation in the trial at any time without providing a reason.

Subjects had to be discontinued from the trial for any of the following reasons:

- Occurrence of pregnancy.
- Subject withdrew consent.
- An emergency unblinding of IP occurred.

Subjects had to be discontinued from treatment (but may remain in the trial for follow up assessments) for any of the following reasons:

- If at any time during the trial, the Investigator determined that a subject's safety had been compromised.
- Subject met a clinically relevant exclusion criterion that could affect the subject's safety.
- If discontinuation was considered necessary by the Investigator and/or Sponsor.
- Subject had an AE that presented an unacceptable consequence or risk to the subject in the judgment of the Investigator, Sponsor, or the medical monitor; or was intolerable to the subject.

In case of premature withdrawal from the trial, the appropriate eCRF was completed by the Investigator, stating the reason for discontinuation. Prior to discontinuing a subject, every effort was made to contact the subject, schedule a final study visit, obtain as much follow-up data as possible, and to retrieve all study materials.

Subjects withdrawn from the trial after the start of dosing were not replaced.

## 9.4 Treatments

### 9.4.1 Treatments Administered

At Visit 1, eligible subjects were randomized in a 1:1 ratio to 1 of 2 treatment groups and instilled 1 drop of NOV03 (100% perfluorohexyloctane) QID or 1 drop of saline (0.6% sodium chloride solution) QID into each eye. Subjects were dosed over an 8-week period, starting at Visit 1 and ending at Visit 4.

Subjects were instructed on application of IP; the first dose of IP was administered in the clinic at Visit 1.

### 9.4.2 Identity of Investigational Product

NOV03 drug product was a thin, clear, preservative-free ophthalmic solution drop (Table 9-1). Saline eye drops preserved with benzalkonium chloride were provided as the control.

Batch numbers for NOV03 were 1934-027 and 1949-027. Batch numbers for the saline control were 1936-007 and 2003-013.

**Table 9-1: Investigational Product**

| | Active Investigational Product | Control Investigational Product |
|---|---|---|
| Product code | NOV03 | Saline solution |
| Chemical name | Perfluorohexyloctane | Sodium chloride solution (0.6 %) |
| Molecular formula | $C_{14}H_{17}F_{13}$ | NaCl |
| Dosage form | 3 mL ophthalmic solution | 3 mL ophthalmic solution |
| Unit dose | 11 µL drop size; 100% perfluorohexyloctane | 35-40 µL drop size |
| Route of administration | Topical ocular administration | Topical ocular administration |
| Physical description | Colorless and clear ophthalmic solution | Colorless and clear ophthalmic solution |
| Excipients | None | 0.01% benzalkonium chloride w/v |
| Manufacturer | Alliance Medical Products, Inc. | Alliance Medical Products, Inc. |

IP was labelled according to legal requirements and packaged in individual subject kits, each containing 2 bottles of NOV03 or saline solution.

At the sites, IP was stored in a secure area accessible only to the Investigator or pharmacist and his/her designees. IP was stored at room temperature under temperature-monitored conditions and was not refrigerated.

Subjects were instructed to store IP at room temperature and not use any bottle that had been opened for > 30 days.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

At the end of Visit 1, eligible subjects received a randomly-assigned kit of IP using an interactive randomization system (IRS). Randomization was stratified by investigational site and by the subject's VAS dryness score at baseline (<70 vs ≥ 70).

The randomization schedules were created by an unmasked statistician not otherwise involved in the trial. Refer to Section 16.1.7 for the randomization list used in the study.

### 9.4.4 Selection of Doses in the Study

The NOV03 QID dosing regimen evaluated in this trial was based on the results from the phase 2 NVU-002 trial. The QID regimen showed more pronounced reductions in tCFS and symptom scores as measured by OSDI and VAS. This was confirmed by responder analyses on signs (tCFS) as well as symptoms (dryness score) that underlined the relevance of these observed changes.

Based on the safety and tolerability profile observed for both treatment regimens (BID and QID) in NVU-002 and the consistent trend for better efficacy with NOV03 QID in both signs and symptoms, the QID dose regimen was selected in the current trial.

### 9.4.5 Masking/Unmasking

Identical packaging and labelling of the investigational drug product and control maintained the double-masked nature of the trial. The Investigator/site staff and Bausch & Lomb, Incorporated personnel or designee(s) involved in the conduct of the trial were masked to the IP.

Due to physicochemical differences between NOV03 and saline, there was a dedicated, unmasked dosing coordinator at each site who was responsible for the handling of all IP-related activities (eg, IP handling/administration, dispensation, and accountability; review of dosing diaries; performing the study questionnaires; and handling all discussions with study subjects related to IP). The dosing coordinator did not participate in any other trial procedures.

Subjects were instructed to administer IP out of the sight of the Investigator or site staff, other than the dedicated dosing coordinator. Subjects were instructed to not to show or discuss the properties of the assigned IP to the Investigator or site staff other than the dedicated dosing coordinator, unless instructed to do so.

Unmasking was allowed in the event of a medical emergency. Over the course of the study, no unmasking was necessary.

### 9.4.6 Prior and Concomitant Therapy

The use of any concurrent medication, prescription or over-the-counter, was recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken. Concurrent or previous medications were recorded for 60 days prior to Visit 0. Any physical therapies, or surgeries were documented for 6 months prior to Visit 0.

Therapy considered necessary for the subject's welfare that did not interfere with the evaluation of the study medication was allowed at the discretion of the Investigator and in consultation with the medical monitor. Whenever possible, medication dosages were to remain constant throughout the study duration.

Physical therapies such as lid scrubs, lid wipes, warm compresses, systemic antibiotics (such as tetracyclines) and oral supplements for treatment of ocular conditions had to be stable within the last 30 days prior to Visit 1 and maintained throughout the trial. Changes in those therapies or initiation of such therapies were recorded on the subject's source document and corresponding eCRF.

Medications and treatments listed in the exclusion criteria were not allowed (see Section 9.3.2). All medications and treatments not allowed prior to study entry were also not

allowed during the trial. In particular, the following were not to be used within 24 hours prior to Visit 1 or throughout the study: wearing of contact lenses, ocular surgery/ocular laser treatment of any kind, other dry eye treatments such as artificial tears, gels, or ointments or TrueTear™ device (Intranasal Tear Neurostimulator).

Other specific prohibitions included:

- Topical ocular steroid treatments, topical cyclosporine, lifitegrast, serum tears or topical anti-glaucoma medication within 60 days prior to Visit 0 or during the trial.
- Oral medications known to cause ocular drying (eg, antihistamines, antidepressants, etc.) on a non-stable regimen within 1 month prior to Visit 0 or expected to be unstable during the trial. Amitriptyline (eg, Elavil) was only allowed as sleep aid and was not to be used within 24 hours prior to any visit.

Subjects were asked to refrain from dangerous sport activities and challenging climates for 24 hours prior to their visits. Subjects were also asked to refrain from swimming in a chlorinated pool for 12 hours prior to their visits.

#### 9.4.7 Treatment Compliance

Subjects recorded dosing in a dosing diary, which was reviewed by a dedicated dosing coordinator. At Visits 2, 3 and 4, all (used/unused) IP bottles were collected from subjects for drug accountability purposes.

## 9.5 Efficacy and Safety Variables

#### 9.5.1 Efficacy and Safety Assessments and Flow Chart

The schedule of assessments, including timing for all efficacy and safety evaluations, is provided in Table 9-2. Additional visits could have been scheduled, as necessary, to ensure the safety and well-being of subjects.

**Table 9-2: Schedule of Visits and Parameters**

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

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

#### 9.5.1.1 Efficacy Variables

The efficacy evaluation was based on the following (see Appendix 3 of the protocol [Section 16.1.1] for details):

- tCFS and cCFS scores (NEI scale) (0-15 scale)
- Subject-reported VAS scores for severity of eye dryness and burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, frequency of dryness, and awareness of dry eye symptoms.
- OSDI questionnaire
- MGD scores

- Unanesthetized Schirmer's test scores
- TFBUT.

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).

The OSDI questionnaire was completed by the subject, who answered 12 questions using a 5-point scale (0 to 4). The scores were tallied by the Investigator, who used the total score to calculate the subject's OSDI score; OSDI scores ranged from 0 to 100, with higher scores representing greater disability.

The Meibomian Gland Evaluator stick (Korb MGE®-Stick) with standardized force application was used for the MGD assessment. The secretion of 5 central glands on the lower eyelid was evaluated by the Investigator for each eye. Each of the glands was scored from 0-3: 0 = normal; 1 = thick/yellow, whitish, particulate; 2 = paste; and 3 = none/occluded. The total MGD score ranged from 0-15 for each eyelid.

The Schirmer's test was conducted on unanesthetized eyes. A Schirmer's test strip was placed in the lower temporal lid margin of each eye and was used to measure the amount tear production. After 5 minutes, the strip was removed and the length of the moistened area was recorded (mm) for each eye.

With the aid of a slit-lamp, the examiner monitored integrity of the tear film, noting the time it took to form micelles from the time the eye was opened. TFBUT was measured in seconds using a stopwatch, first for the right eye then the left eye. Two measurements were taken and entered into eCRF. However, if the 2 measurements were > 2 seconds apart and were each <10 seconds, a third measurement was taken and the two closest of the three were averaged.

#### 9.5.1.2 Safety Variables

The safety and tolerability evaluation was based on the occurrence of ocular and non-ocular TEAEs; VA; slit-lamp biomicroscopy; IOP; and dilated fundoscopy. Subjects also completed an instillation comfort questionnaire and eyedrop acceptability questionnaire.

##### 9.5.1.2.1 Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event was considered drug-related. An AE could therefore have been any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease occurring after the subject signature of the ICF without any judgment on causality.

Worsening of DED was considered an AE only if the dry eye status of the subject exceeded their previous experiences with the condition. A clinically significant VA worsening (defined as an increase of 0.22 or greater in logMAR score) from screening (Visit 0) was to be recorded as an AE.

A serious AE (SAE) was any AE that:

- Resulted in death.

- Was life-threatening.
- Required inpatient hospitalization or prolonged inpatient hospitalization.
- Resulted in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Was a congenital anomaly/birth defect.
- Was a medically important event (ie, one that may have jeopardized the subject or may have required medical or surgical intervention to prevent one or more of the other outcomes listed above).

AEs were monitored throughout the study and were recorded on the eCRF with the date and time of onset, date and time of resolution, severity, seriousness, causality (relationship to use of IP), treatment required, and outcome.

The severity of each AE was categorized by the Investigator as mild, moderate, or severe. Relationship to use of IP was reported by the Investigator as suspected or not suspected.

#### 9.5.1.2.2 Ocular Safety Evaluations

LogMAR VA was assessed using an ETDRS-like chart. VA testing was performed with best correction. To provide standardized and well-controlled assessments of VA, the same conditions were used throughout the study.

IOP measurements were performed using contact tonometry according to the Investigator's standard procedure. IOP was recorded in mmHg.

Slit-lamp biomicroscopy (including an external eye exam) was used to evaluate status of the lids, cornea, conjunctiva, anterior chamber, iris, and lens. The Investigator rated the findings as normal or abnormal (not clinically significant or clinically significant).

Dilated fundoscopy included assessment of the vitreous, retina, macula, choroid, and optic nerve. The Investigator rated the findings as normal or abnormal.

### 9.5.1.3 Patient-reported Questionnaires

Subjects took 2 questionnaires during the study: instillation comfort questionnaire and eyedrop acceptability questionnaire. The questionnaires were administered to the subject by a dedicated, unmasked dosing coordinator at each site (see Section 9.4.5). Subjects used a VAS ranging from 0 to 10 to describe the degree of comfort with instillation of eye drops; higher scores represented greater comfort. Using the same VAS, subjects answered 3 questions related to acceptability of the eye drops.

## 9.5.2 Appropriateness of Measurements

The measurements used in the assessment of efficacy and safety in this study are generally accepted standard methods in ophthalmology trials and recognized as reliable, accurate, and relevant.

### 9.5.3 Primary Efficacy Variables

tCFS (NEI scale) and the VAS dryness score were selected as the primary endpoints in the study. tCFS is a measure of signs associated with DED, whereas the VAS dryness score is a measure of symptomatology.

Corneal staining is an accepted clinical endpoint in DED and a highly relevant marker in this disease, as stained areas represent punctate disruption and damage of the corneal epithelium (Pflugfelder and de Pavia, 2017). Reduction of corneal staining reflects corneal surface healing and thus is highly representative of treatment success.

In DED trials, common symptoms such as dryness, frequency of dryness, blurred vision are frequently graded using the VAS (Novack et al., 2017). Questionnaires using VAS to assess symptoms in DED are generally considered validated symptom questionnaires in DED.

The two primary endpoints, tCFS and VAS dryness score, were tested in hierarchical order with total CFS being tested first. Data from the NVU-002 study indicated tCFS is a stronger endpoint to assess efficacy.

### 9.5.4 Drug Concentration Measurements

Not applicable in this study.

## 9.6 Data Quality Assurance

Representatives or affiliates of Bausch + Lomb contacted/visited the Investigator and site staff prior to the start of the trial to review the procedures to be followed in conducting the study, as well as the correct methods for recording data, and to confirm the readiness of the facility to conduct the clinical trial. Meetings (in person or via telephone) for Investigators and relevant study site personnel were held, at which the detailed conduct of the study was explained and discussed.

Clinical research associates monitored the study conduct to ensure adherence to the protocol and GCP/ICH guidelines and to ensure that all study-related records were complete and had been transcribed accurately from source documents.

Study data were collected and managed as outlined in the study Data Management Plan.

Two clinical site audits were performed of high enrolling sites to ensure compliance with GCP guidelines. There were no significant findings that affected the data or any analyses.

Due to the Coronavirus Disease 2019 (COVID-19) pandemic, a remote monitoring/source data verification process was developed and implemented in the study's Monitoring Plan.

## 9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

### 9.7.1 Statistical Analysis and Analytical Plans

The final version of the statistical analysis plan was finalized on 10 Jul 2020. See Section 16.1.9 for detailed documentation of the statistical methods.

All descriptive statistical analyses were performed using SAS statistical software (Version 9.4), unless otherwise noted.

For categorical variables, summary tabulations of the number and percentage within each category were presented. For continuous variables, the mean, median, standard deviation (SD), minimum and maximum values were presented.

By-subject listings were prepared for most analyses.

#### 9.7.1.1 Study Populations

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

The Per Protocol Set (PPS) included subjects in the FAS who did not have significant protocol deviations and who completed the study. Inclusion in the PPS was determined programmatically from eCRF data and a masked Sponsor review of protocol deviations reported. Protocol deviations resulting in exclusion from the PPS were assessed prior to database lock and unmasking. The PPS was analyzed using observed data only for efficacy variables. Subjects in the PPS were analyzed as treated. PPS analyses were performed to support the FAS analysis of efficacy (sensitivity analyses).

The Safety Analysis Set (SAF) included all randomized subjects who have received at least one dose of the IP. The Safety Set was used for all safety assessments. Subjects in the SAF were analyzed as treated.

#### 9.7.1.2 Protocol Deviations

Protocol deviations were collected in the eCRF. Major protocol deviations that could potentially affect the efficacy were assessed and identified prior to database lock and unmasking. Subjects with major protocol deviations were not included in the PPS.

#### 9.7.1.3 Subject Disposition, Demographics, and Baseline Characteristics

Tabular summaries of disposition were prepared for each data set. Demographic and baseline characteristics, including baseline ocular assessments, medical and surgical histories, and concomitant medications and therapies were summarized by treatmentgroup and all groups combined in FAS, PPS, and SAF.

Medical history, including ocular medical history, was coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.1 or higher. Concomitant medications were coded to the Anatomical Therapeutic Chemical (ATC) classification levels 1-4 and preferred terms (PTs) using the World Health Organization Drug Dictionary (WHODrug B3 Global Sept 2019).

#### 9.7.1.4 Efficacy Analyses

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

Additional robustness analyses included repeating the primary analysis on the PPS; the FAS imputing missing data using last observation carried forward (LOCF); and the FAS

imputing missing data using Markov Chain Monte Carlo multiple imputation methodology under different assumptions of missingness (at random and not at random) each using 30 imputed values.

The key 4 secondary efficacy endpoints were also tested using hierarchical fixed sequence testing and summarized descriptively and analyzed. Inference was to be made on these endpoints, at a 2-sided alpha = 0.05, only if both primary endpoints and any higher order secondary endpoints were statistically significant at a 2-sided alpha = 0.05, in favor of NOV03.

Endpoints evaluating the proportion of study eyes (or subjects) that met pre-defined criteria were presented and tested between treatment groups using logistic regression analysis, adjusting for baseline score at each measured follow-up visit.

Two-sample t-tests (equal variance assumed), Wilcoxon rank sum tests and mixed-effect repeated measures analysis comparing treatment groups were performed as sensitivity analyses.

For assessments performed by eye, study eye and fellow eye were summarized separately.

#### 9.7.1.5 Safety Analyses

##### 9.7.1.5.1 Exposure and Compliance

Exposure to study drug was summarized in days. Exposure was calculated as (last dose date – first dose date + 1). Duration of exposure (days) was summarized using descriptive statistics by treatment group and all groups combined in the SAF. Duration of exposure was also presented categorically (< 15 days; 15-<29 days; 29-<57 days; ≥57 days).

Compliance was summarized using descriptive statistics by treatment group and all groups combined in the SAF. Compliance was also presented categorically (< 50%; 50-<80%; 80-<90; 90-100%; >100%-120%; >120%).

##### 9.7.1.5.2 Adverse Events

AEs were coded using MedDRA, version 22.1 or higher. A TEAE was defined as any AE that occurred or worsened after the firstdose of IP.

Tables and listings present data at the system organ class (SOC) and PT level.

Tabular summaries of TEAEs were prepared for TEAEs by SOC; TEAEs by SOC and PT; most common TEAEs by SOC and PT; TEAEs at rates of 1%, 2%, 3%, 4%, and 5% in at least one treatment group; TEAEs by SOC, PT and maximal severity; TEAEs by SOC, PT, and strongest relationship to study drug; TEAEs by SOC, PT, maximal severity, and strongest relationship; serious TEAEs by SOC and PT; and TEAEs leading to premature discontinuation of treatment by SOC and PT. An overview table was also prepared.

Separate summaries were prepared for ocular and non-ocular TEAEs; ocular TEAEs were summarized at the subject level and by eye.

##### 9.7.1.5.3 Ocular Safety

Actual values and changes from baseline were summarized for IOP and VA using summary statistics; results were presented by treatment group and visit for each eye. VA was expressed in logMAR. The calculated logMAR was automatically generated by the EDC as base logMAR + (number of total letters missed × 0.02).

Slit-lamp biomicroscopy and external eye exam findings were summarized descriptively, including the number and percent of subjects with normal/not present and abnormal/present results at baseline and each study visit by treatment group and eye. Shifts from baseline indicative of worsening were also summarized. Worsening was defined as a shift from normal to abnormal not clinically significant, normal to abnormal clinically significant, and abnormal not clinically significant to abnormal clinically significant.

Dilated fundoscopy findings were summarized descriptively, including the number and percent of subjects with normal and abnormal results for the vitreous, retina, macula, choroid and optic nerve. Results were presented by visit, treatment group and eye. Shifts from baseline indicative of worsening were also summarized, as described above.

#### 9.7.1.5.4 Comfort and Acceptability Questionnaires

In addition to the efficacy and safety endpoints above, results of the comfort and acceptability questionnaires were evaluated by study visit and treatment group. Results were summarized and analyzed in a manner similar to that used for the pre-specified efficacy endpoints.

### 9.7.1.6 Interim Analysis

An interim analysis was not planned for this study.

## 9.7.2 Determination of Sample Size

The statistical hypotheses for the primary endpoint of change from baseline in corneal fluorescein staining (NEI scale) total score at Day 57 were as follows:

- $H_{01}$: The difference, between study eyes treated with NOV03 and study eyes treated with saline, in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 57 = 0.
- $H_{A1}$: The difference, between study eyes treated with NOV03 and study eyes treated with saline, in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 57 ≠ 0, with superiority claimed if the difference was less than 0 (NOV03 minus saline).

The statistical hypotheses for the hierarchical primary endpoint of change from baseline in the VAS dryness score at Day 57 were as follows:

- $H_{02}$: The difference, between subjects treated with NOV03 and subjects treated with saline, in the mean change from baseline in the VAS dryness score at Day 57= 0.
- $H_{A2}$: The difference, between subjects treated with NOV03 and subjects treated with saline, in the mean change from baseline in the VAS dryness score at Day 57 ≠ 0, with superiority claimed if the difference was less than 0 (NOV03 minus saline).

Two hundred fifty (250) subjects (study eyes) per treatment group yields 97.9% power to reject $H_{01}$ in favor of $H_{A1}$ and conclude superiority of NOV03 over saline in the mean change from baseline tCFS score at Day 57, assuming a true difference (NOV03 minus saline) of -1.0, a common SD of 2.8, and a 2-sided alpha = 0.05. Two hundred fifty (250) subjects per treatment group yields 97.9% power to reject $H_{02}$ in favor of $H_{A2}$ and conclude superiority of NOV03 over saline in the mean change from baseline in the VAS dryness score at Day 57, assuming a true difference (NOV03 minus saline) of -10, a common SD

of 28, and a 2-sided alpha = 0.05. Accounting for an assumed 10% subject discontinuation rate, approximately 560 subjects (280 subject each arm) were to be randomly assigned to study treatment such that approximately 250 evaluable subjects per arm completed the trial.

Therefore, assuming independence between tCFS score and the VAS dryness score, 250 FAS subjects per treatment group at Day 57 was expected to yield 95.8% power to reject both H01 and H02. A positive correlation between these two endpoints would increase the overall power.

## 9.8 Changes in the Conduct of the Study or Planned Analyses

### 9.8.1 Changes in the Conduct of the Study

The original protocol, dated 10 Oct 2019, was amended 3 times: Amendment 1 (03 Dec 2019); Amendment 2 (16 Mar 2020); and Amendment 3 (27 Aug 2020).

Protocol Amendment 1 introduced a new role of a dedicated dosing coordinator to minimize bias due to different physicochemical properties between NOV03 and saline. Furthermore, it was decided to reduce the number of secondary endpoints; therefore, a new category “other pre-specified endpoints” was introduced. This modification led to some adaptions in the statistical section. Lastly, the wording of several exclusion criteria and examination procedures was specified to provide better clarity.

Protocol Amendment 2 introduced Bausch & Lomb, Incorporated as the new Sponsor.

Protocol Amendment 3 clarified several items in the previously amended protocol. The amendment also excluded subjects randomized in NVU-002 or BL904.

Refer to Section 16.1.1 for Summary of Changes for the amendments.

### 9.8.2 Changes in the Planned Analyses

Not applicable.

# 10.0 STUDY SUBJECTS

## 10.1 Disposition of Subjects

By-subject listings of disposition are presented in Listing 16.2.1 and Listing 16.3.2.

Overall, 825 subjects were screened for the study, of whom 226 were screen failures (Table 14.1.1.1).

A total of 597 subjects were randomized into the study across 26 sites in the US and received NOV03 (N=303) or saline (N=294) (Table 10-1, Table 14.1.2.1). Two additional subjects (1 per group) were randomized but did not receive IP (Table 14.1.2.2).

Most (95.5%) of the 597 treated subjects completed the dosing regimen; 26 (4.4%) subjects prematurely discontinued IP (4.0%, NOV03; 4.8%, saline) (Table 10-1). The most common reasons for discontinuation of IP were subject withdrawal and reasons classified as Other (10 [1.7%] subjects each). For reasons classified as Other, the majority (6/10) were due to loss to follow-up or COVID (Listing 16.3.2). 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 (see Section 12.3.1.3 for details).

Overall, 568 (95.1%) subjects completed the study (Table 10-1), and 29 (4.9%) prematurely discontinued (4.6%, NOV03; 5.1%, saline). The most common reasons for

discontinuation of the study were subject withdrawal (11 [1.8%] subjects), loss to follow-up (7 [1.2%] subjects) and reasons classified as Other (6 [1.0%] subjects). The same 4 subjects who discontinued IP due to an AE also discontinued the study due to an AE (Listing 16.3.2).

**Table 10-1: Disposition (All Randomized)**

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

Abbreviations: IP = investigational product

Source: Table 14.1.1.1, Table 14.1.2.1, Table 14.1.2.2

## 10.2 Protocol Deviations

A total of 24 (4.0%) subjects, 12 (4.0%) in the NOV03 group and 12 (4.1%) in the saline group, had at least 1 major protocol deviation during the study (Table 14.1.3). The most common types of major protocol deviations were related to study visit/schedule deviations (13 events [5, NOV03; 8, saline]) and use of prohibited concomitant medications (5 events [3, NOV03; 2, saline]).

A by-subject listing of protocol deviations is presented in Listing 16.2.2.3.

# 11.0 EFFICACY EVALUATION

## 11.1 Data Sets Analyzed

A total of 597 subjects (303, NOV03; 294, saline) were included in the FAS and SAF (Table 11-1).

A total of 549 subjects (279, NOV03; 270, saline) were included in the PPS (Table 11-1); 50 subjects were excluded from the PPS (Listing 16.2.3.1). The most common reasons for exclusion were due to the subject not completing the study (29 [4.8%] subjects), study visit/schedule deviations (13 [2.2%] subjects), and use of prohibited concomitant medications (5 [0.8%] subjects) (Table 11-1).

**Table 11-1: Analysis Sets (All Randomized)**

| Data Set/Reason for Exclusion | NOV03 (N=304) n (%) | Saline (N=295) n (%) | All Subjects (N=599) n (%) |
|---|---|---|---|
| FAS | 303 (99.7) | 294 (99.7) | 597 (99.7) |
| Did not receive at least 1 dose of IP | 1 (0.3) | 1 (0.3) | 2 (0.3) |
| SAF | 303 (99.7) | 294 (99.7) | 597 (99.7) |
| Did not receive at least 1 dose of IP | 1 (0.3) | 1 (0.3) | 2 (0.3) |
| PPS | 279 (91.8) | 270 (91.5) | 549 (91.7) |
| Subject did not complete the study | 14 (4.6) | 15 (5.1) | 29 (4.8) |
| Study visit schedule deviations | 5 (1.6) | 8 (2.7) | 13 (2.2) |
| Use of prohibited concomitant medications | 3 (1.0) | 2 (0.7) | 5 (0.8) |
| Inclusion and exclusion criteria | 2 (0.7) | 1 (0.3) | 3 (0.5) |
| IP deviation/compliance | 1 (0.3) | 2 (0.7) | 3 (0.5) |
| Subject was not in the FAS | 1 (0.3) | 1 (0.3) | 2 (0.3) |
| Missed/delayed/not per protocol procedures | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Study medication compliance <80% | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| Subject non-compliance with instructions | 1 (0.3) | 0 (0.0) | 1 (0.2) |

Abbreviations: FAS = Full Analysis Set; IP = investigational product; PPS = Per Protocol Set; SAF = Safety Set

Note: Subjects may have been excluded from the PPS for >1 reason.
Source: Table 14.1.2.1, Table 14.1.2.2

## 11.2 Demographic and Other Baseline Characteristics

### 11.2.1 Demographics

In the FAS, mean age of the study population was 60.9 years (range: 19 to 88 years) (Table 11-2). None of the subjects were <18 years of age; 280 (46.9%) subjects were ≥65 years. The majority of subjects were female (72.5%). The most common race was White (69.7%), followed by Black (18.1%) and Asian (10.4%). The majority of subjects had their right eye designated as the study eye (59.1%).

No appreciable differences were observed between the NOV03 and saline groups in the demographic characteristics (Table 11-2).

Demographic results in the PPS (Table 14.1.4.2) were consistent with the FAS findings.

A by-subject listing of demographics is presented in Listing 16.2.4.1.

**Table 11-2: Demographics (FAS)**

| | 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

Source: Table 14.1.4.1

### 11.2.2 Baseline Ocular Characteristics

See Section 9.5.1.1 for scoring and measurement of the baseline ocular characteristics.

In the FAS, mean tCFS in the study eye was 6.7 (SD 1.8) (Table 11-3). The mean VAS dryness and burning/stinging scores were 66.7 (SD 18.9) and 52.6 (SD 26.63), respectively. The mean total MGD score, TFBUT, and Schirmer's Test I in the study eye were 7.5 (SD 3.1), 3.2 sec (SD 0.8 sec), and 11.9 mm (SD 8.0 mm), respectively. The mean OSDI score was 54.2 (SD 17.3), and mean best-corrected VA (BCVA) (study eye) was 0.080 logMAR (SD 0.143 logMAR). With the exception of the lens, most subjects had normal slit lamp findings in the study eye at baseline. For lens, 43.7% of subjects had a normal finding at baseline, 52.4% had an abnormal but not clinically significant finding, and 3.9% had a clinically significant abnormality (Table 14.1.5.1).

No appreciable differences were observed between the NOV03 and saline groups in baseline ocular characteristics (Table 11-3).

Baseline ocular characteristics observed in the PPS (Table 14.1.5.2) were consistent with the FAS findings.

By-subject listings of baseline ocular characteristics are presented in Listing 16.2.6.1, Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4, Listing 16.2.6.5, Listing 16.2.6.6, and Listing 16.2.6.7.

**Table 11-3: Baseline Ocular Characteristics (FAS)**

| | 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

Source: Table 14.1.5.1

### 11.2.3 Medical History

In the FAS, all subjects had an ocular medical history (either eye) (Table 14.1.6.3). The most common SOC was Eye Disorders (100.0%), followed by Surgical and Medical Procedures (14.7%). The most common PTs were dry eye (100.0%), cataract (37.2%), intraocular lens implant (13.9%), cataract nuclear (13.7%), and vitreous detachment

(13.6%). Summaries of ocular medical history specifically for the study eye and fellow eye are presented in Table 14.1.6.1 and Table 14.1.6.2, respectively; results were similar between eyes.

Most (84.8%) subjects in the FAS had a non-ocular medical history (Table 14.1.6.4). The most common SOCs were Social Circumstances (44.6%), Vascular Disorders (43.7%), Metabolism and Nutrition Disorders (37.7%), and Musculoskeletal and Connective Tissue Disorders (28.0%). The most common PTs were hypertension (42.5%), postmenopause (42.5%), and hypercholesterolemia (25.8%).

No appreciable differences were observed between the NOV03 and saline groups in ocular and non-ocular medical histories (Table 14.1.6.3, Table 14.1.6.4).

By-subject listings of ocular medical and surgical histories are presented in Listing 16.2.4.2 and Listing 16.2.4.3, respectively. By-subject listings of non-ocular medical and surgical histories are presented in Listing 16.2.4.4 and Listing 16.2.4.5, respectively.

### 11.2.4 Concomitant Medications

In the FAS, 276 (46.2%) subjects took at least 1 ocular concomitant medication (either eye) during the study (Table 14.1.7.3). The most common ocular concomitant medications were artificial tears (19.8%), macrogel 400/propylene glycol (7.0%), and carmellose sodium (6.5%). Summaries of concomitant medication use specifically in the study eye and fellow eye are presented in Table 14.1.7.1 and Table 14.1.7.2, respectively; results were similar between eyes.

A total of 474 (79.4%) subjects in the FAS took at least 1 non-ocular concomitant medication during the study (Table 14.1.7.4). The most common classes of non-ocular medications were lipid-modifying agents, plain (30.3%), vitamin A and D, including combination of the two (17.3%), antithrombotic agents (16.9%), and drugs for peptic ulcer and gastroesophageal reflux disease (16.8%).

No appreciable differences were observed between the NOV03 and saline groups in ocular and non-ocular concomitant medications (Table 14.1.7.3, Table 14.1.7.4).

By-subject listings of ocular medications, ocular therapies, non-ocular medications, and non-ocular therapies are presented in Listing 16.2.9.5, Listing 16.2.9.6, Listing 16.2.9.7, and Listing 16.2.9.8, respectively.

## 11.3 Measurements of Treatment Compliance

In the SAF, most of the subjects in each treatment group were at least 90% compliant with use of IP; 74.9% of subjects were 90-100% compliant with use of IP and 22.8% were >100-120% complaint (Table 14.1.8). Compliance was comparable between the 2 treatment groups.

A by-subject listing of dosing compliance is presented in Listing 16.2.5.1. Subjects who were at least 80% compliant with IP are flagged in Listing 16.2.1.

## 11.4 Efficacy Results and Tabulations of Individual Subject Data

### 11.4.1 Analysis of Efficacy

#### 11.4.1.1 Hierarchical Analyses

##### 11.4.1.1.1 Primary Endpoints

The 2 primary efficacy endpoints were tested using hierarchical fixed sequence testing at $\alpha = 0.05$: change from baseline in tCFS in the study eye at Day 57, followed by change from baseline in the eye dryness VAS score at Day 57.

Both of the primary endpoints were met in this study (Table 11-4).

In the FAS, 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 11-4). Analysis showed a statistically significant difference ($p<0.001$) between the NOV03 and saline groups in mean change from baseline in tCFS on Day 57, in favor of active treatment.

In the FAS, 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 in both treatment groups (Table 11-4). Analysis showed a statistically significant difference ($p<0.001$) between the NOV03 and saline groups, in favor of active treatment.

For both of the primary endpoints, results observed in the PPS (Table 11-4) and the FAS sensitivity analysis (Table 14.2.3) were consistent with the main FAS findings.

Additional results are presented for tCFS and the eye dryness VAS score in Section 11.4.1.2 and Section 11.4.1.3, respectively.

**Table 11-4: Primary Endpoints: Change from Baseline in tCFS in the Study Eye and Eye Dryness Score (VAS) at Day 57 (FAS and PPS)**

| | FAS | | PPS | |
|---|---|---|---|---|
| **Change from Baseline** | **NOV03** | **Saline** | **NOV03** | **Saline** |
| **tCFS (Study Eye)** | | | | |
| n (missing) | 289 (0) | 279 (0) | 279 (0) | 270 (0) |
| Mean (SD) | -2.0 (2.6) | -1.0 (2.7) | -2.1 (2.5) | -1.0 (2.7) |
| Median | -2.0 | -1.0 | -2.0 | -1.0 |
| Min, max | -10; 7 | -9; 7 | -10; 7 | -9; 7 |
| LS mean | -2.02 | -1.05 | -2.03 | -1.03 |
| NOV03 – Saline (95% CI) | **-0.97 (-1.40, -0.55)** | | **-1.00 (-1.43, -0.57)** | |
| p-value | **<0.001** | | **<0.001** | |
| **Dryness Score (VAS)** | | | | |
| n (missing) | 289 (3) | 279 (1) | 279 (0) | 270 (0) |
| Mean (SD) | -27.4 (27.9) | -19.7 (26.7) | -26.9 (27.9) | -19.6 (26.6) |
| Median | -29.0 | -18.0 | -27.0 | -17.5 |
| Min, max | -90; 50 | -96; 66 | -90; 50 | -96; 66 |
| LS mean | -27.32 | -19.71 | -26.82 | -19.72 |
| NOV03 – Saline (95% CI) | **-7.61 (-11.82, -3.40)** | | **-7.10 (-11.37, -2.82)** | |
| p-value | **<0.001** | | **0.001** | |

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

#### 11.4.1.1.2 Key Secondary Endpoints

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

- eye dryness score at Day 15,
- tCFS at Day 15 in the study eye,
- burning/stinging score at Day 57,
- cCFS at Day 57 in the study eye.

For each of the key secondary endpoints, mean decreases from baseline were observed in both treatment groups, indicating improvement from baseline. Analysis showed a statistically significant difference between the NOV03 and saline groups in mean changes from baseline in eye dryness score at Day 15 (p=0.009), tCFS at Day 15 (p=0.001), burning/stinging score at Day 57 (p=0.006), and cCFS at Day 57 (p<0.001), in favor of active treatment (Table 11-5).

**Table 11-5: Change from Baseline in Key Secondary Efficacy Endpoints (FAS)**

| | FAS | |
|---|---|---|
| **Change from Baseline** | **NOV03** | **Saline** |
| **Dryness Score (VAS) at Day 15** | | |
| n (missing) | 297 (1) | 289 (1) |
| Mean (SD) | -18.0 (24.0) | -13.4 (23.3) |
| Median | -17.0 | -10.0 |
| Min, max | -90; 91 | -96; 64 |
| LS mean | -18.04 | -13.32 |
| NOV03 – Saline (95% CI) | **-4.72 (-8.25, -1.20)** | |
| p-value | **0.009** | |
| **tCFS (Study Eye) at Day 15** | | |
| n (missing) | 296 (0) | 288 (0) |
| Mean (SD) | -1.7 (2.1) | -1.1 (2.2) |
| Median | -2.0 | -1.0 |
| Min, max | -7; 6 | -8; 6 |
| LS mean | -1.69 | -1.11 |
| NOV03 – Saline (95% CI) | **-0.58 (-0.93, -0.23)** | |
| p-value | **0.001** | |
| **Burning/Stinging Score (VAS) at Day 57** | | |
| n (missing) | 289 (0) | 278 (1) |
| Mean (SD) | -23.6 (29.8) | -18.0 (25.3) |
| Median | -21.0 | -15.0 |
| Min, max | -99; 79 | -84; 79 |
| LS mean | -23.53 | -18.01 |
| NOV03 – Saline (95% CI) | **-5.52 (-9.46, -1.59)** | |
| p-value | **0.006** | |
| **cCFS (Study Eye) at Day 57** | | |
| n (missing) | 289 (0) | 279 (0) |
| Mean (SD) | -0.4 (0.8) | -0.1 (0.9) |
| Median | 0.0 | 0.0 |
| Min, max | -3; 2 | -3; 3 |
| LS mean | -0.36 | -0.12 |
| NOV03 – Saline (95% CI) | **-0.24 (-0.36, -0.11)** | |
| 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

### 11.4.1.2 Corneal Fluorescein Staining

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).

### tCFS: Mean Change from Baseline

In the FAS, mean tCFS in the study eye was 6.7 (SD 1.8) in the NOV03 group and 6.7 (SD 1.9) in the saline group at baseline and ranged from 4 to 11 in both groups (Table 14.2.6.1). Mean decreases from baseline in the tCFS score (indicating improvement) were observed in both treatment groups on Days 15, 29, and 57.

Analysis showed statistically significant ($p \leq 0.001$) differences between the NOV03 and saline groups, in favor of active treatment, at Day 15 and Day 57 (Table 11-6); a nominally statistically significant difference was also observed on Day 29 ($p=0.001$).

Similar results were observed in the fellow eye, although the treatment difference was numerically more pronounced in the study eye (Table 11-6).

Results observed in the FAS sensitivity analyses (Table 14.2.6.3 [study eye]; Table 14.2.6.4 [fellow eye]) were consistent with the main FAS findings.

**Table 11-6: Change from Baseline in tCFS by Study Visit and Eye (FAS)**

| | Study Eye | | Fellow Eye | |
|---|---|---|---|---|
| **Change from Baseline** | **NOV03** | **Saline** | **NOV03** | **Saline** |
| **Day 15** | | | | |
| n (missing) | 296 (0) | 288 (0) | 296 (0) | 288 (0) |
| Mean (SD) | -1.7 (2.1) | -1.1 (2.2) | -1.1 (2.1) | -0.7 (2.2) |
| Median | -2.0 | -1.0 | -1.0 | -1.0 |
| Min, max | -7; 6 | -8; 6 | -7; 5 | -8; 6 |
| LS mean | -1.69 | -1.11 | -1.06 | -0.69 |
| NOV03 – Saline (95% CI) | **-0.58 (-0.93, -0.23)** | | **-0.37 (-0.71, -0.04)** | |
| p-value | **0.001** | | **0.030** | |
| **Day 29** | | | | |
| n (missing) | 297 (0) | 285 (0) | 297 (0) | 285 (0) |
| Mean (SD) | -2.1 (2.3) | -1.5 (2.4) | -1.4 (2.4) | -0.9 (2.3) |
| Median | -2.0 | -1.0 | -2.0 | -1.0 |
| Min, max | -10; 7 | -9; 5 | -9; 8 | -9; 8 |
| LS mean | -2.13 | -1.52 | -1.39 | -0.91 |
| NOV03 – Saline (95% CI) | **-0.61 (-0.98, -0.24)** | | **-0.47 (-0.85, -0.10)** | |
| p-value | **0.001** | | **0.014** | |
| **Day 57** | | | | |
| n (missing) | 289 (0) | 279 (0) | 289 (0) | 279 (0) |
| Mean (SD) | -2.0 (2.6) | -1.0 (2.7) | -1.4 (2.5) | -0.6 (2.6) |
| Median | -2.0 | -1.0 | -1.0 | -1.0 |
| Min, max | -10; 7 | -9; 7 | -9; 10 | -7; 8 |
| LS mean | -2.02 | -1.05 | -1.39 | -0.63 |
| NOV03 – Saline (95% CI) | **-0.97 (-1.40, -0.55)** | | **-0.76 (-1.16, -0.35)** | |
| p-value | **<0.001** | | **<0.001** | |

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; FAS = Full Analysis Set; LS = least squares; SD = standard deviation; tCFS = total corneal fluorescein staining
Note: LS Mean, Diff, 95% CI, and p-value are from an ANCOVA model with terms for baseline value and treatment.
Source: Table 14.2.6.1, Table 14.2.6.2

### tCFS: Proportion of Responders

In the FAS, the proportion of subjects who had a 3-step improvement in the tCFS score in the study eye was higher in the NOV03 group than in the saline group at Day 15, 29, and 57 (Table 11-7). Nominally statistically significant differences, in favor of active treatment, were observed at each timepoint: Day 15 (odds ratio [OR] of 1.52, p=0.028); Day 29 (OR of 1.66, p=0.004); and Day 57 (OR of 1.88, p<0.001). A similar trend was observed in the fellow eye, although treatment differences were more pronounced in the study eye, and the difference between treatment groups was not significant for the fellow eye on Day 57.

Results observed in the FAS sensitivity analyses (Table 14.2.9.3 [study eye]; Table 14.2.9.4 [fellow eye]) were consistent with the main FAS findings, except that the difference between treatment groups did not reach significance in the fellow eye on Day 15 (p=0.058) or Day 57 (p=0.091).

**Table 11-7: Proportion of tCFS Responders by Study Visit and Eye (FAS)**

| | Study Eye | | Fellow Eye | |
|---|---|---|---|---|
| | **NOV03 (N=303)** | **Saline (N=294)** | **NOV03 (N=303)** | **Saline (N=294)** |
| **Day 15** | | | | |
| n (%) of responders | 94 (31.8) | 68 (23.6) | 69 (23.3) | 49 (17.0) |
| Proportion diff [a] | 0.082 | | 0.063 | |
| Odds ratio [b] (95% CI) | 1.52 (1.05, 2.21) | | 1.54 (1.01, 2.34) | |
| p-value | **0.028** | | **0.046** | |
| **Day 29** | | | | |
| n (%) of responders | 133 (44.8) | 94 (33.0) | 91 (30.6) | 61 (21.4) |
| Proportion diff [a] | 0.118 | | 0.092 | |
| Odds ratio [b] (95% CI) | 1.66 (1.18, 2.34) | | 1.66 (1.13, 2.43) | |
| p-value | **0.004** | | **0.010** | |
| **Day 57** | | | | |
| n (%) of responders | 119 (41.2) | 76 (27.2) | 91 (31.5) | 70 (25.1) |
| Proportion diff [a] | 0.140 | | 0.064 | |
| Odds ratio [b] (95% CI) | 1.88 (1.31, 2.71) | | 1.39 (0.95, 2.02) | |
| p-value | **<0.001** | | 0.092 | |

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; NEI=National Eye Institute; tCFS = total corneal fluorescein staining

[a] NOV03 – saline.

[b] NOV03 versus saline.

Note: tCFS responders are defined as eyes with a ≥3 improvement from baseline (based on NEI scale).

Note: Odds ratio (NOV03 vs. saline), 95% CI, and p-value are from a logistic regression adjusting for baseline tCFS score at each measured follow-up visit.

Source: Table 14.2.9.1, Table 14.2.9.2

### cCFS: Mean Change from Baseline

In the FAS, mean cCFS in the study eye was 1.1 (SD 0.8) in both treatment groups at baseline and ranged from 0 to 3 (Table 14.2.7.1). Mean decreases from baseline in the cCFS score (indicating improvement) were observed in both treatment groups on Days 15, 29, and 57. Analysis showed a statistically significant ($p<0.001$) difference between the NOV03 and saline groups, in favor of active treatment, at Day 57 (Table 11-8); nominally statistically significant differences were also observed on Day 15 and Day 29 ($p\leq0.006$).

Similar results were observed in the fellow eye, although treatment differences were more pronounced in the study eye at each timepoint, and the difference between treatment groups was not significant in the fellow eye at Day 15. (Table 11-8).

Results observed in the FAS sensitivity analyses (Table 14.2.7.3 [study eye]; Table 14.2.7.4 [fellow eye]) were generally consistent with the main FAS findings.

**Table 11-8: Change from Baseline in cCFS by Study Visit and Eye (FAS)**

| | Study Eye | | Fellow Eye | |
|---|---|---|---|---|
| **Change from Baseline** | **NOV03** | **Saline** | **NOV03** | **Saline** |
| **Day 15** | | | | |
| n (missing) | 296 (0) | 288 (0) | 296 (0) | 288 (0) |
| Mean (SD) | -0.3 (0.8) | -0.2 (0.9) | -0.1 (0.8) | -0.1 (0.8) |
| Median | 0.0 | 0.0 | 0.0 | 0.0 |
| Min, max | -2; 3 | -2; 3 | -3; 2 | -2; 2 |
| LS mean | -0.31 | -0.15 | -0.17 | -0.12 |
| NOV03 – Saline (95% CI) | **-0.16 (-0.28, -0.05)** | | -0.05 (-0.16, 0.07) | |
| p-value | **0.006** | | 0.424 | |
| **Day 29** | | | | |
| n (missing) | 297 (0) | 285 (0) | 297 (0) | 285 (0) |
| Mean (SD) | -0.4 (0.8) | -0.2 (0.9) | -0.2 (0.8) | -0.1 (0.9) |
| Median | 0.0 | 0.0 | 0.0 | 0.0 |
| Min, max | -3; 2 | -3; 2 | -3; 2 | -3; 3 |
| LS mean | -0.45 | -0.22 | -0.24 | -0.12 |
| NOV03 – Saline (95% CI) | **-0.23 (-0.34, -0.11)** | | **-0.13 (-0.24, -0.01)** | |
| p-value | **<0.001** | | **0.033** | |
| **Day 57** | | | | |
| n (missing) | 289 (0) | 279 (0) | 289 (0) | 279 (0) |
| Mean (SD) | -0.4 (0.8) | -0.1 (0.9) | -0.2 (0.8) | -0.1 (0.9) |
| Median | 0.0 | 0.0 | 0.0 | 0.0 |
| Min, max | -3; 2 | -3; 3 | -3; 2 | -3; 3 |
| LS mean | -0.36 | -0.12 | -0.22 | -0.07 |
| NOV03 – Saline (95% CI) | **-0.24 (-0.36, -0.11)** | | **-0.14 (-0.27, -0.02)** | |
| p-value | **<0.001** | | **0.023** | |

Abbreviations: ANCOVA = analysis of covariance; cCFS = central corneal fluorescein staining; CI = confidence interval; FAS = Full Analysis Set; LS = least squares; SD = standard deviation
Note: LS Mean, Diff, 95% CI, and p-value are from an ANCOVA model with terms for baseline value and treatment.
Source: Table 14.2.7.1, Table 14.2.7.2

### cCFS: Proportion of Subjects by Grade

Table 11-9 summarizes the proportion of study and fellow eyes that had a cCFS grade of 0 (none), 1 (mild), 2 (moderate) or 3 (severe) by study visit and treatment group. Regardless of eye or treatment group, approximately 50-55% of eyes were Grade 1 at baseline. Improvement in cCFS was observed post-baseline, as evidenced by a higher proportion of eyes with Grade 0 post-baseline versus at baseline.

**Table 11-9: cCFS - Proportion of Subjects by Grade, Study Visit, and Eye (FAS)**

| | Study Eye | | Fellow Eye | |
|---|---|---|---|---|
| | NOV03 n (%) | Saline n (%) | NOV03 n (%) | Saline n (%) |
| **Baseline** | | | | |
| N (missing) | 303 (0) | 294 (0) | 303 (0) | 294 (0) |
| Grade 0 | 62 (20.5) | 65 (22.1) | 94 (31.0) | 80 (27.2) |
| Grade 1 | 169 (55.8) | 150 (51.0) | 159 (52.5) | 156 (53.1) |
| Grade 2 | 59 (19.5) | 65 (22.1) | 44 (14.5) | 47 (16.0) |
| Grade 3 | 13 (4.3) | 14 (4.8) | 6 (2.0) | 11 (3.7) |
| **Day 15** | | | | |
| N (missing) | 296 (0) | 288 (0) | 296 (0) | 288 (0) |
| Grade 0 | 124 (41.9) | 92 (31.9) | 127 (42.9) | 117 (40.6) |
| Grade 1 | 128 (43.2) | 134 (46.5) | 130 (43.9) | 117 (40.6) |
| Grade 2 | 34 (11.5) | 48 (16.7) | 32 (10.8) | 44 (15.3) |
| Grade 3 | 10 (3.4) | 14 (4.9) | 7 (2.4) | 10 (3.5) |
| **Day 29** | | | | |
| N (missing) | 297 (0) | 285 (0) | 297 (0) | 285 (0) |
| Grade 0 | 153 (51.5) | 109 (38.2) | 144 (48.5) | 118 (41.4) |
| Grade 1 | 108 (36.4) | 118 (41.4) | 119 (40.1) | 117 (41.1) |
| Grade 2 | 31 (10.4) | 47 (16.5) | 28 (9.4) | 36 (12.6) |
| Grade 3 | 5 (1.7) | 11 (3.9) | 6 (2.0) | 14 (4.9) |
| **Day 57** | | | | |
| N (missing) | 289 (0) | 279 (0) | 289 (0) | 279 (0) |
| Grade 0 | 134 (46.4) | 92 (33.0) | 139 (48.1) | 106 (38.0) |
| Grade 1 | 110 (38.1) | 119 (42.7) | 110 (38.1) | 125 (44.8) |
| Grade 2 | 38 (13.1) | 55 (19.7) | 33 (11.4) | 33 (11.8) |
| Grade 3 | 7 (2.4) | 13 (4.7) | 7 (2.4) | 15 (5.4) |

Abbreviations: cCFS = central corneal fluorescein staining; FAS = Full Analysis Set
Note: cCFS was rated by grade: Grade 0 (none), Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe).
Source: Table 14.2.8.1, Table 14.2.8.2

### CFS (Inferior Region): Mean Change from Baseline

In the FAS, mean CFS in the inferior sub-region of the study eye was 1.9 (SD 0.7) in both treatment groups at baseline and ranged from 0 to 3 (Table 14.2.7.5). Mean decreases from baseline in the inferior sub-region CFS score (indicating improvement) were observed in both treatment groups on Days 15, 29, and 57. On Days 15 and 57, analysis showed nominally statistically significant ($p<0.001$) differences between the NOV03 and saline groups, in favor of active treatment; on Day 29, the difference approached significance ($p=0.060$) (Table 11-10).

Similar results were observed in the fellow eye, although the difference between treatment groups was nominally significant in the fellow eye at Day 29 (Table 11-10).

Results observed in the FAS sensitivity analyses (Table 14.2.7.7 [study eye]; Table 14.2.7.8 [fellow eye]) were consistent with the main FAS findings.

**Table 11-10: Change from Baseline in CFS in the Inferior Sub-Region by Study Visit and Eye (FAS)**

| | Study Eye | | Fellow Eye | |
|---|---|---|---|---|
| **Change from Baseline** | **NOV03** | **Saline** | **NOV03** | **Saline** |
| **Day 15** | | | | |
| n (missing) | 296 (0) | 288 (0) | 296 (0) | 288 (0) |
| Mean (SD) | -0.4 (0.8) | -0.2 (0.8) | -0.3 (0.8) | -0.1 (0.8) |
| Median | 0.0 | 0.0 | 0.0 | 0.0 |
| Min, max | -2; 2 | -3; 2 | -2; 2 | -3; 2 |
| LS mean | -0.38 | -0.17 | -0.27 | -0.10 |
| NOV03 – Saline (95% CI) | **-0.21 (-0.33, -0.09)** | | **-0.17 (-0.28, -0.05)** | |
| p-value | **<0.001** | | **0.004** | |
| **Day 29** | | | | |
| n (missing) | 297 (0) | 285 (0) | 297 (0) | 285 (0) |
| Mean (SD) | -0.4 (0.9) | -0.3 (0.9) | -0.3 (0.9) | -0.1 (0.8) |
| Median | 0.0 | 0.0 | 0.0 | 0.0 |
| Min, max | -3; 2 | -3; 2 | -3; 2 | -3; 2 |
| LS mean | -0.42 | -0.30 | -0.34 | -0.15 |
| NOV03 – Saline (95% CI) | -0.12 (-0.24, 0.01) | | **-0.19 (-0.31, -0.06)** | |
| p-value | 0.060 | | **0.003** | |
| **Day 57** | | | | |
| n (missing) | 289 (0) | 279 (0) | 289 (0) | 279 (0) |
| Mean (SD) | -0.4 (0.9) | -0.2 (0.9) | -0.4 (0.9) | -0.1 (0.8) |
| Median | 0.0 | 0.0 | 0.0 | 0.0 |
| Min, max | -3; 2 | -3; 2 | -3; 2 | -2; 2 |
| LS mean | -0.44 | -0.18 | -0.36 | -0.12 |
| NOV03 – Saline (95% CI) | **-0.26 (-0.39, -0.13)** | | **-0.24 (-0.36, -0.11)** | |
| p-value | **<0.001** | | **<0.001** | |

Abbreviations: ANCOVA = analysis of covariance; CFS= corneal fluorescein staining; CI = confidence interval; FAS = Full Analysis Set; LS = least squares; SD = standard deviation
Note: LS Mean, Diff, 95% CI, and p-value are from an ANCOVA model with terms for baseline value and treatment.
Source: Table 14.2.7.5, Table 14.2.7.6

### CFS of the Inferior Sub-Region: Proportion of Subjects by Grade

As with cCFS, improvement in CFS in the inferior sub-region was observed post-baseline, as evidenced by a higher proportion of eyes with Grade 0 post-baseline versus at baseline (Table 11-11).

**Table 11-11: CFS in the Inferior Sub-Region - Proportion of Subjects by Grade, Study Visit, and Eye (FAS)**

| | Study Eye | | Fellow Eye | |
|---|---|---|---|---|
| | **NOV03 n (%)** | **Saline n (%)** | **NOV03 n (%)** | **Saline n (%)** |
| **Baseline** | | | | |
| N (missing) | 303 (0) | 294 (0) | 303 (0) | 294 (0) |
| Grade 0 | 1 (0.3) | 1 (0.3) | 1 (0.3) | 4 (1.4) |
| Grade 1 | 93 (30.7) | 88 (29.9) | 123 (40.6) | 114 (38.8) |
| Grade 2 | 146 (48.2) | 151 (51.4) | 128 (42.2) | 128 (43.5) |
| Grade 3 | 63 (20.8) | 54 (18.4) | 51 (16.8) | 48 (16.3) |
| **Day 15** | | | | |
| N (missing) | 296 (0) | 288 (0) | 296 (0) | 288 (0) |
| Grade 0 | 16 (5.4) | 15 (5.2) | 16 (5.4) | 18 (6.3) |
| Grade 1 | 148 (50.0) | 107 (37.2) | 147 (49.7) | 115 (39.9) |
| Grade 2 | 98 (33.1) | 112 (38.9) | 105 (35.5) | 104 (36.1) |
| Grade 3 | 34 (11.5) | 54 (18.8) | 28 (9.5) | 51 (17.7) |
| **Day 29** | | | | |
| N (missing) | 297 (0) | 285 (0) | 297 (0) | 285 (0) |
| Grade 0 | 22 (7.4) | 20 (7.0) | 26 (8.8) | 13 (4.6) |
| Grade 1 | 147 (49.5) | 121 (42.5) | 155 (52.2) | 135 (47.4) |
| Grade 2 | 95 (32.0) | 103 (36.1) | 83 (27.9) | 93 (32.6) |
| Grade 3 | 33 (11.1) | 41 (14.4) | 33 (11.1) | 44 (15.4) |
| **Day 57** | | | | |
| N (missing) | 289 (0) | 279 (0) | 289 (0) | 279 (0) |
| Grade 0 | 28 (9.7) | 17 (6.1) | 33 (11.4) | 15 (5.4) |
| Grade 1 | 136 (47.1) | 110 (39.4) | 147 (50.9) | 124 (44.4) |
| Grade 2 | 93 (32.2) | 94 (33.7) | 71 (24.6) | 93 (33.3) |
| Grade 3 | 32 (11.1) | 58 (20.8) | 38 (13.1) | 47 (16.8) |

Abbreviations: CFS=corneal fluorescein staining; FAS = Full Analysis Set
Note: CFS in the inferior sub-region was rated by grade: Grade 0 (none), Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe).
Source: Table 14.2.8.1, Table 14.2.8.2

### 11.4.1.3 Eye Dryness VAS Score

Subjects rated severity of eye dryness and other symptomatology (both eyes simultaneously) using a VAS ranging from 0 (no discomfort) to 100 (maximal discomfort).

### Mean Change from Baseline

In the FAS, the mean eye dryness VAS score was 66.5 (SD 19.1) in the NOV03 group and 66.8 (SD 18.7) in the saline group at baseline (Table 14.2.5.1). Mean decreases from baseline in the eye dryness VAS score (indicating improvement) were observed in both treatment groups on Days 15, 29, and 57. At Days 15 and 57, analysis showed statistically significant ($p \leq 0.009$) differences between the NOV03 and saline groups, in favor of active treatment (Table 11-12).

Results observed in the FAS sensitivity analyses (Table 14.2.5.2) were consistent with the main FAS findings.

**Table 11-12: Change from Baseline in the Eye Dryness VAS Score by Study Visit (FAS)**

| Change from Baseline | NOV03 | Saline |
|---|---|---|
| **Day 15** | | |
| n (missing) | 297 (1) | 289 (1) |
| Mean (SD) | -18.0 (24.0) | -13.4 (23.3) |
| Median | -17.0 | -10.0 |
| Min, max | -90; 91 | -96; 64 |
| LS mean | -18.04 | -13.32 |
| NOV03 – Saline (95% CI) | **-4.72 (-8.25, -1.20)** | |
| p-value | **0.009** | |
| **Day 29** | | |
| n (missing) | 297 (0) | 285 (1) |
| Mean (SD) | -20.9 (25.1) | -18.1 (24.9) |
| Median | -17.0 | -15.0 |
| Min, max | -94; 39 | -85; 48 |
| LS mean | -20.92 | -18.15 |
| NOV03 – Saline (95% CI) | -2.77 (-6.57, 1.02) | |
| p-value | 0.152 | |
| **Day 57** | | |
| n (missing) | 289 (3) | 279 (1) |
| Mean (SD) | -27.4 (27.9) | -19.7 (26.7) |
| Median | -29.0 | -18.0 |
| Min, max | -90; 50 | -96; 66 |
| LS mean | -27.32 | -19.71 |
| NOV03 – Saline (95% CI) | **-7.61 (-11.82, -3.40)** | |
| p-value | **<0.001** | |

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; FAS = Full Analysis Set; LS = least squares; SD = standard deviation; 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 14.2.5.1

### Proportion of Responders

In the FAS, the proportion of subjects who had a ≥30% improvement from baseline in the VAS dryness score was numerically higher in the NOV03 group than in the saline group

at Day 15, 29, and 57 (Table 11-13). Nominally statistically significant differences, in favor of active treatment, were observed at Day 15 (OR of 1.59, p=0.007) and Day 57 (OR of 1.55, p=0.010).

Results observed in the FAS sensitivity analyses (Table 14.2.10.2) were consistent with the main FAS findings.

**Table 11-13: Proportion of Responders for the Eye Dryness VAS Score by Study Visit (FAS)**

| | NOV03 (N=303) | Saline (N=294) |
|---|---|---|
| **Day 15** | | |
| n (%) of responders | 134 (45.1) | 99 (34.3) |
| Proportion diff [a] | 0.108 | |
| Odds ratio [b] (95% CI) | 1.59 (1.13, 2.22) | |
| p-value | **0.007** | |
| **Day 29** | | |
| n (%) of responders | 134 (45.1) | 122 (42.8) |
| Proportion diff [a] | 0.023 | |
| Odds ratio [b] (95% CI) | 1.10 (0.79, 1.53) | |
| p-value | 0.574 | |
| **Day 57** | | |
| n (%) of responders | 166 (57.4) | 130 (46.6) |
| Proportion diff [a] | 0.108 | |
| Odds ratio [b] (95% CI) | 1.55 (1.11, 2.16) | |
| p-value | **0.010** | |

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; VAS = visual analog scale
[a] NOV03 – saline.
[b] NOV03 versus saline.
Note: Responders are defined as subjects with a ≥30% improvement from baseline in the VAS dryness score.
Note: Odds ratio (NOV03 vs. saline), 95% CI, and p-value are from a logistic regression adjusting for baseline VAS dryness score at each measured follow-up visit.
Source: Table 14.2.10.1

### 11.4.1.4 Other VAS Scores

Table 14.2.11.1 summarizes mean changes from baseline in the 9 VAS scores for ocular symptoms due to ocular dryness by treatment group and study visit: sticky feeling, burning/stinging, foreign body sensation, itching, blurred vision, sensitivity to light, pain, awareness of dry eye symptoms, and frequency of dryness. Lower scores were indicative of better status.

In the FAS, mean decreases from baseline (indicating improvement) were observed for each VAS score in both treatment groups throughout the study. Mean decreases from baseline were generally greater in the NOV03 group than in the saline group.

Analysis showed nominally statistically significant differences between the NOV03 and saline groups, in favor of active treatment, for most of the ocular symptoms. These included burning/stinging (Day 15 [p=0.015], Day 57 [0.006]); foreign body sensation (Day 57 [p=0.002]); itching (Day 15 [p=0.029], Day 57 [0.019]); sensitivity to light (Day 15

[p=0.011]); pain (Day 15 [p=0.017], Day 57 [0.015]); awareness of dry eye symptoms (Day 15 [p=0.040], Day 57 [0.002]); and frequency of dryness (Day 15 [p=0.003], Day 57 [0.031]).

Results observed in the FAS sensitivity analyses (Table 14.2.11.2) were generally consistent with the main FAS findings.

#### 11.4.1.5 OSDI

The OSDI ranged from 0 to 100, with lower scores indicative of less disability (see Section 9.5.1.1 for details).

In the FAS, the mean OSDI score at baseline was 53.92 (SD 17.55) in the NOV03 group and 54.40 (SD 16.98) in the saline group (Table 14.2.12.1). Mean decreases from baseline in the OSDI score (indicating improvement) were observed in both treatment groups on Days 15 (-16.64, NOV03; -14.54, saline), 29 (-18.14, NOV03; -16.05, saline), and 57 (-21.08, NOV03; -18.85, saline). Analysis did not show any significant differences between the NOV03 and saline groups.

Results observed in the FAS sensitivity analyses (Table 14.2.12.2) were consistent with the main FAS findings.

Table 14.2.13 presents the proportion of subjects who responded to the 12 individual OSDI items of the questionnaire by response category (none, some, half, most, or all of the time), study visit, and treatment group. Positive shifts from baseline in responses to “none of the time” (indicating improvement) were consistent with the mean change from baseline findings.

#### 11.4.1.6 Total MGD Score

Secretion of 5 central glands on the lower eyelid was evaluated by the Investigator for each eye. Each of the glands was scored from 0-3: 0 = normal; 1 = thick/yellow, whitish, particulate; 2 = paste; and 3 = none/occluded. The total MGD score ranged from 0-15, with lower scores indicative of better status.

In the FAS, the mean total MGD score in the study eye at baseline was 7.4 (SD 3.1) in the NOV03 group and 7.7 (SD 3.2) in the saline group (Table 14.2.14.1). On Day 57, mean decreases from baseline in the total MGD score (indicating improvement) were observed in both treatment groups (-0.5, NOV03; -0.7, saline). Analysis did not show a significant difference between the NOV03 and saline groups. Similar results were observed in the fellow eye (Table 14.2.14.2).

Table 14.2.15.1 and Table 14.2.15.2 present categorical grading of the 5 individual central glands in the study eye and fellow eye, respectively, by response category (Grade 0 to Grade 3), study visit, and treatment group. Positive shifts from baseline in responses to Grade 0 (indicating improvement) were consistent with the mean change from baseline findings.

#### 11.4.1.7 Schirmer’s Test I (Without Anesthesia)

The Schirmer’s Test I measures tear production, with lower scores indicative of less production.

In the FAS, the mean Schirmer’s Test I score in the study eye at baseline was 12.0 mm (SD 8.3 mm) in the NOV03 group and 11.7 mm (SD 7.6 mm) in the saline group (Table 14.2.16.1). On Day 57, small mean decreases from baseline in the Schirmer’s Test

I score were observed in both treatment groups (-0.7 mm in each group). Analysis did not show a significant difference between the NOV03 and saline groups.

In the fellow eye, the mean Schirmer's Test I score at baseline was 11.7 mm (SD 9.0 mm) in the NOV03 group and 10.8 mm (SD 7.8 mm) in the saline group (Table 14.2.16.2). On Day 57, a small mean decrease from baseline in the mean Schirmer's Test I score was observed in the NOV03 group (-0.1 mm) and a mean increase was observed in the saline group (0.6 mm). Analysis did not show a significant difference between the NOV03 and saline groups.

#### 11.4.1.8 TFBUT

With the aid of a slit-lamp, the examiner monitored integrity of the tear film, noting the time it took to form micelles from the time the eye was opened. Two measurements were taken, with the average of these two measurements used for analysis.

In the FAS, the mean TFBUT in the study eye at baseline was 3.2 seconds (SD 0.8 seconds) in the NOV03 group and 3.3 seconds (SD 0.8 seconds) in the saline group (Table 14.2.17.1). On Day 57, mean increases from baseline in the TFBUT were observed in both treatment groups (0.9, NOV03; 0.7, saline). Analysis did not show a significant difference between the NOV03 and saline groups. Similar results were observed in the fellow eye (Table 14.2.17.2).

### 11.4.2 Statistical/Analytical Issues

Refer to Section 16.1.9 for documentation of the statistical methods. Noteworthy items of the analysis are summarized here in detail.

#### 11.4.2.1 Analysis Visits

Nominal study visits (eCRF) were used for the analysis.

#### 11.4.2.2 Adjustments for Covariates

The primary endpoints were change from baseline in tCFS at Day 57 and change from baseline in VAS dryness score at Day 57. The two primary endpoints were analyzed separately using an ANCOVA model with baseline measurement as a numeric covariate and treatment as the main effect.

Subject randomization was stratified by clinical site and dryness score <70 vs ≥ 70 (VAS) at baseline (Visit 1). The analyses were not adjusted for the stratification factors.

Secondary endpoints analyzed using ANCOVA were adjusted for baseline values when available.

#### 11.4.2.3 Handling of Dropouts and Missing Data

Because the overall study discontinuation rates was <5%, the primary analysis was completed on the FAS using the available data per subject. Missing data for other endpoints will be left as missing.

All missing dates for medications or events that occur after randomization will be queried for a date. If no date is obtained, the following imputation rules will apply:

- For start dates, missing months and days will be imputed as "01", provided this occurs on or after the date of first study drug self-administration. Otherwise, the

date or month (as appropriate) of the first self-administration of study drug will be used.

- For stop dates, missing months will be imputed as "12" and missing days will be imputed as the last day of the month. If this creates a date after discontinuation/completion, the date of discontinuation/completion will be used.

The imputed dates will only be used to classify events, medications, or therapy as treatment emergent or concomitant. Imputed dates will only be used in the table analyses. Listings will display the available date data.

Whether the adverse event occurred after the first dose of study drug, relationship, and severity should not be missing and will be queried for value. If missing data is present, the AE date will be imputed as detailed above, will be assumed to be related to study drug, and will be assumed to be severe.

#### 11.4.2.4 Interim Analyses and Data Monitoring

No formal interim analyses were planned or conducted. No data monitoring board was used in this study.

#### 11.4.2.5 Multicenter Studies

Overall, 597 subjects were randomized into the study across 26 sites. No formal by-site analyses were conducted.

#### 11.4.2.6 Multiple Comparison/Multiplicity

To control for inflation of type 1 error rate due to multiple hypotheses, the analysis of the two primary endpoints was conducted in a hierarchical manner. If both primary endpoints demonstrated statistically significant superiority of NOV03 versus saline at the 2-sided alpha = 0.05 level, the following secondary endpoints were tested hierarchically to maintain an overall 2-sided alpha = 0.05.

- Change from baseline in dryness score (VAS) at Day 15.
- Change from baseline in tCFS (NEI scale) in the study eye at Day 15.
- Change from baseline in VAS burning/stinging at Day 57.
- Change from baseline in cCFS (NEI scale) in the study eye at Day 57.

The 2 primary and 4 key secondary endpoints all met statistical significance at $\alpha = 0.05$ using the hierarchical testing scheme.

#### 11.4.2.7 Use of an "Efficacy Subset" of Subjects

The primary analysis was repeated in the PPS with observed data only as sensitivity analysis. Subjects in the PPS were analyzed as treated.

#### 11.4.2.8 Active-Control Studies Intended to Show Equivalence

Not applicable.

#### 11.4.2.9 Examination of Subgroups

Not applicable.

### 11.4.3 Tabulation of Individual Response Data

By-subject listings of efficacy results are presented in Listing 16.2.6.1 (CFS), Listing 16.2.6.2 (dryness VAS), Listing 16.2.6.3 (ocular symptoms VAS), Listing 16.2.6.4 (OSDI), Listing 16.2.6.5 (MGD), Listing 16.2.6.6 (Schirmer`s Test I), Listing 16.2.6.7 (TFBUT), Listing 16.2.6.8 (instillation questionnaire), and Listing 16.2.6.9 (acceptability questionnaire).

### 11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Not applicable.

### 11.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable.

### 11.4.6 By-Subject Displays

Not applicable.

### 11.4.7 Efficacy Conclusions

This section of the report focuses on results observed in the FAS. Results observed in the PPS and sensitivity analyses were generally consistent with the FAS results.

Both of the primary endpoints and all 4 key secondary endpoints were met in this study, with NOV03 showing significant improvement over saline in clinically relevant signs and symptoms of DED associated with MGD:

Primary

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

Secondary

- 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 cCFS (NEI scale) at Day 57.

#### 11.4.7.1 Fluorescein Corneal Staining

*Changes from Baseline in tCFS*

In the FAS, mean decreases from baseline in the tCFS score in the study eye (indicating improvement) were observed in both treatment groups on Days 15 (secondary endpoint), 29, and 57 (primary endpoint). Analysis showed statistically significant ($p \leq 0.001$) differences between the NOV03 and saline groups, in favor of active treatment, at Day 15 and Day 57; a nominally statistically significant difference was also observed on Day 29 ($p=0.001$).

In the responder analyses, a nominally statistically significant difference was observed between the NOV03 and saline groups, in favor of active treatment, for proportion of subjects who had a ≥3 improvement from baseline in the tCFS score (NEI scale) in the study eye at Day 57 ($p<0.001$). Subjects in the NOV03 group were nearly twice as likely

to achieve a ≥3 improvement in the tCFS score compared to subjects in the saline group (OR = 1.88).

*Changes from Baseline in CFS in the Central and Inferior Regions*

In the FAS, mean decreases from baseline in the cCFS score in the study eye (indicating improvement) were observed in both treatment groups on Days 15, 29, and 57 (secondary endpoint). Analysis showed a statistically significant ($p<0.001$) difference between the NOV03 and saline groups, in favor of active treatment, at Day 57; nominally statistically significant differences were also observed on Day 15 and Day 29 ($p\leq0.006$).

Mean decreases from baseline in the inferior CFS score in the study eye (indicating improvement) were observed in both treatment groups on Days 15, 29, and 57. On Days 15 and 57, analysis showed nominally statistically significant ($p<0.001$) differences between the NOV03 and saline groups, in favor of active treatment; on Day 29, the difference approached significance ($p=0.060$).

#### 11.4.7.2 Subject Assessment of Eye Dryness, Burning/Stinging, and Other Symptoms

In the FAS, mean decreases from baseline in the eye dryness VAS score (indicating improvement) were observed in both treatment groups on Days 15 (secondary endpoint), 29, and 57 (primary endpoint). At Days 15 and 57, analysis showed statistically significant ($p\leq0.009$) differences between the NOV03 and saline groups, in favor of active treatment.

In the responder analyses, nominally statistically significant differences were observed between the NOV03 and saline groups, in favor of active treatment, for proportion of subjects who had a ≥30% improvement from baseline in the VAS dryness score at Day 15 ($p=0.007$) and Day 57 ($p=0.010$). Subjects in the NOV03 group were 59% and 55% more likely to achieve a ≥30% improvement from baseline in the VAS dryness score at Day 15 and Day 57, respectively, compared to subjects in the saline group.

Mean decreases from baseline in the burning/stinging VAS score (indicating improvement) were observed in both treatment groups on Days 15, 29, and 57 (secondary endpoint). Analysis showed nominally statistically significant differences ($p\leq0.015$) between the NOV03 and saline groups in mean change from baseline in the eye burning/stinging VAS score on Days 15 and 57, in favor of active treatment.

Mean decreases from baseline (indicating improvement) were observed for the remaining VAS scores in both treatment groups on Days 15, 29, and 57. Analysis showed nominally statistically significant differences between the NOV03 and saline groups, in favor of active treatment, for most of the ocular symptoms: foreign body sensation (Day 57, $p=0.002$); itching (Days 15 and 57, $p\leq0.029$); sensitivity to light (Day 15, $p=0.011$); pain (Days 15 and 57, $p\leq0.017$); awareness of dry eye symptoms (Days 15 and 57, $p\leq0.040$); and frequency of dryness (Days 15 and 57, $p\leq0.031$).

#### 11.4.7.3 Other Efficacy Findings

No appreciable differences were observed between treatment groups in terms of OSDI, total MGD score, the Schirmer's Test I score, and TFBUT.

# 12.0 SAFETY EVALUATION

## 12.1 Extent of Exposure

In the SAF, 8 (1.3%) subjects received IP for <15 days, 12 (2.0%) received IP for 15 to <29 days, 198 (33.2%) received IP for 29 to <57 days, and 379 (63.5%) received IP for ≥57 days (Table 14.1.8). Duration of exposure was similar between treatment groups.

A by-subject listing of exposure is presented in Listing 16.2.5.1.

## 12.2 Adverse Events (AEs)

Subjects instilled IP into both eyes. Therefore, in this CSR, the AE discussion focuses on all treated eyes (ie, subject level data presentations). Results for the study eye and fellow eye were analyzed separately and discussed as appropriate.

### 12.2.1 Brief Summary of Adverse Events

No deaths were reported in the study (Table 12-1).

*Ocular TEAEs*

Overall, 51 (8.5%) subjects, 29 (9.6%) in the NOV03 group and 22 (7.5%) in the saline group, had at least 1 ocular TEAE (either eye, subject level) (Table 12-1). Twenty-eight (4.7%) subjects had at least 1 ocular TEAE attributed to use of IP (6.3%, NOV03; 3.1%, saline). Most of the TEAEs were mild in severity; 1 (0.2%) subject had a severe ocular TEAE (OU [both eyes] eye irritation, NOV03 group) (Table 14.3.4.1, Table 14.3.4.2, Listing 16.2.7.1).

None of the ocular TEAEs were serious. Four (0.7%) subjects, 1 (0.3%) in the NOV03 group and 3 (1.0%) in the saline group, had an ocular TEAE that led to discontinuation of IP and withdrawal from the study (Table 12-1). These events were allergic conjunctivitis (OU, saline), dry eye (OU, saline), eye irritation (OU, NOV03), and punctate keratitis (OS [left eye], saline) (Table 14.3.8.1, Table 14.3.8.2, Listing 16.2.7.2).

Ocular TEAE profiles were similar between treatment groups at the subject level and between the study and fellow eyes at the eye level (Table 12-1).

*Non-ocular TEAEs*

Overall, 30 (5.0%) subjects, 18 (5.9%) in the NOV03 group and 12 (4.1%) in the saline group, had at least 1 non-ocular TEAE (Table 12-1). None of the events were attributed to IP, severe in intensity, or led to discontinuation of IP or withdrawal from the study. One subject had a serious non-ocular TEAE (acute chest pain, saline group); see Section 12.3.1.2 for details.

Non-ocular TEAE profiles were similar between treatment groups (Table 12-1).

**Table 12-1: Overview of Treatment-emergent Adverse Events (SAF)**

| | NOV03 N=303 n (%) | Saline N=294 n (%) | Combined N=597 n (%) |
|---|---|---|---|
| **Ocular TEAEs (Study or Fellow Eye)** | | | |
| Subjects with at Least 1 TEAE | 29 (9.6) | 22 (7.5) | 51 (8.5) |
| Mild | 25 (8.3) | 18 (6.1) | 43 (7.2) |
| Moderate | 3 (1.0) | 4 (1.4) | 7 (1.2) |
| Severe | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Subjects with at Least 1 Drug-related TEAE | 19 (6.3) | 9 (3.1) | 28 (4.7) |
| Subjects with at Least 1 SAE | 0 | 0 | 0 |
| Subjects with a TEAE that led to Drug Withdrawal | 1 (0.3) | 3 (1.0) | 4 (0.7) |
| Subjects with a TEAE that led to Study Withdrawal | 1 (0.3) | 3 (1.0) | 4 (0.7) |
| **Ocular TEAEs (Study Eye)** | | | |
| Subjects with at Least 1 TEAE | 25 (8.3) | 15 (5.1) | 40 (6.7) |
| Mild | 21 (6.9) | 12 (4.1) | 33 (5.5) |
| Moderate | 3 (1.0) | 3 (1.0) | 6 (1.0) |
| Severe | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Subjects with at Least 1 Drug-related TEAE | 18 (5.9) | 8 (2.7) | 26 (4.4) |
| Subjects with a TEAE that led to Drug Withdrawal | 1 (0.3) | 2 (0.7) | 3 (0.5) |
| Subjects with a TEAE that led to Study Withdrawal | 1 (0.3) | 2 (0.7) | 3 (0.5) |
| **Ocular TEAEs (Fellow Eye)** | | | |
| Subjects with at Least 1 TEAE | 25 (8.3) | 18 (6.1) | 43 (7.2) |
| Mild | 22 (7.3) | 14 (4.8) | 36 (6.0) |
| Moderate | 2 (0.7) | 4 (1.4) | 6 (1.0) |
| Severe | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Subjects with at Least 1 Drug-related TEAE | 16 (5.3) | 9 (3.1) | 25 (4.2) |
| Subjects with a TEAE that led to Drug Withdrawal | 1 (0.3) | 3 (1.0) | 4 (0.7) |
| Subjects with a TEAE that led to Study Withdrawal | 1 (0.3) | 3 (1.0) | 4 (0.7) |
| **Non-Ocular TEAEs** | | | |
| Subjects with at Least 1 TEAE | 18 (5.9) | 12 (4.1) | 30 (5.0) |
| Mild | 11 (3.6) | 5 (1.7) | 16 (2.7) |
| Moderate | 7 (2.3) | 7 (2.4) | 14 (2.3) |
| Severe | 0 | 0 | 0 |
| Subjects with at Least 1 Drug-related TEAE | 0 | 0 | 0 |
| Subjects with at Least 1 SAE | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| Subjects with a TEAE that led to Drug Withdrawal | 0 | 0 | 0 |
| Subjects with a TEAE that led to Study Withdrawal | 0 | 0 | 0 |

Abbreviations: SAE = serious adverse event; SAF = Safety Analysis Set; TEAE = treatment-emergent adverse event
Source: Table 14.3.1.1, Table 14.3.1.2, Table 14.3.1.3, Table 14.3.1.4

### 12.2.2 Display of Adverse Events

The following displays are provided for ocular TEAEs: overview (Table 14.3.1.1 [study eye], Table 14.3.1.2 [fellow eye], Table 14.3.1.3 [either eye]); ocular TEAEs by SOC (Table 14.3.2.1, Table 14.3.2.2, Table 14.3.2.3); ocular TEAEs by SOC and PT

(Table 14.3.3.1, Table 14.3.3.2, Table 14.3.3.3); ocular TEAEs by SOC and PT and severity (Table 14.3.4.1, Table 14.3.4.2, Table 14.3.4.3); ocular TEAEs by SOC and PT and relationship to study drug (Table 14.3.5.1, Table 14.3.5.2, Table 14.3.5.3); ocular TEAEs by SOC, PT, severity and relationship to study drug (Table 14.3.6.1, Table 14.3.6.2, Table 14.3.6.3); ocular TEAEs at PT rates of 1%, 2%, 3%, 4%, and 5% in at least one treatment group (Table 14.3.9.1, Table 14.3.9.2, Table 14.3.9.3).

Non-ocular TEAEs are presented in Table 14.3.1.4 (overview), Table 14.3.2.4 (TEAEs by SOC), Table 14.3.3.4 (TEAEs by SOC and PT), Table 14.3.4.4 (TEAEs by SOC and PT and severity), Table 14.3.5.4 (TEAEs by SOC and PT and relationship to study drug), and Table 14.3.6.4 (TEAEs by SOC, PT, severity and relationship to study drug). Table 14.3.9.4 summarizes non-ocular TEAEs by SOC and PT occurring at PT rates of 1%, 2%, 3%, 4%, and 5% in at least one treatment group.

### 12.2.3 Analysis of Adverse Events

*Ocular TEAEs*

In the SAF, the most common ocular SOCs (subject level) were Eye Disorders (42 [7.0%] subjects), General Disorders and Administration Site Conditions (8 [1.3%] subjects), and Infections and infestations (3 [0.5%] subjects) (Table 14.3.2.3).

TEAEs that occurred in at least 1.0% of subjects in at least one treatment group are presented in Table 12-2 (subject level). Overall, the most common ocular TEAEs (both groups combined) were blurred vision (1.7%) and instillation site pain (1.0%).

Incidences of individual ocular TEAEs were generally similar between treatment groups (Table 14.3.3.3). The incidence of blurred vision was higher in the NOV03 group (3.0%) than in the saline group (0.3%). Blurred vision was transient in nature and typically resolved within 5-10 minutes post-instillation (Listing 16.2.7.1).

Most of the ocular TEAEs were mild in severity; 1 (0.2%) subject (NOV03 group) had a severe TEAE of eye irritation (OU) (Table 14.3.4.1, Table 14.3.4.2, Listing 16.2.7.1). All cases of blurred vision were mild.

**Table 12-2: Ocular Treatment-emergent Adverse Events Occurring in at Least 1.0% of Subjects in at Least One Treatment Group (SAF)**

| | NOV03 N=303 n (%) | Saline N=294 n (%) | Combined N=597 n (%) |
|---|---|---|---|
| Vision blurred | 9 (3.0) | 1 (0.3) | 10 (1.7) |
| Instillation site pain | 3 (1.0) | 3 (1.0) | 6 (1.0) |
| Conjunctival haemorrhage | 1 (0.3) | 4 (1.4) | 5 (0.8) |
| Eye discharge | 3 (1.0) | 0 (0.0) | 3 (0.5) |
| Punctate keratitis | 0 (0.0) | 3 (1.0) | 3 (0.5) |

Abbreviations: SAF = Safety Analysis Set
Source: Table 14.3.9.3

For TEAEs related to IP, the most common SOCs were Eye Disorders (20 [3.4%] subjects), and General Disorders and Administration Site Conditions (8 [1.3%] subjects) (Table 14.3.5.3). The most common IP-related TEAEs were blurred vision (10 [1.7%] subjects) and instillation site pain (6 [1.0%] subjects).

*Non-ocular TEAEs*

In the SAF, the most common non-ocular SOCs were Infections and infestations (14 [2.3%] subjects) and Musculoskeletal and Connective Tissue Disorders, (5 [0.8%] subjects) (Table 14.3.2.4). Non-ocular TEAEs that occurred in >1 subject (either group) were corona virus infection (5 [0.8%] subjects), nasopharyngitis (3 [0.5%] subjects), sinusitis (3 [0.5%] subjects), headache (3 [0.5%] subjects), and intervertebral disc protrusion (2 [0.3%] subjects) (Table 14.3.3.4). Incidences of individual non-ocular TEAEs were low and similar between treatment groups.

All of the non-ocular TEAEs were mild or moderate in severity (Table 14.3.4.4).

12.2.4 Listing of Adverse Events by Subject

All AEs are presented by subject in Listing 16.2.7.1.

## 12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The following displays are provided for serious TEAEs: Table 14.3.7.1 (ocular, study eye); Table 14.3.7.2 (ocular, fellow eye); Table 14.3.7.3 (ocular, subject level); and Table 14.3.7.4 (non-ocular). Likewise, the following displays are provided for TEAEs that resulted in discontinuation of IP: Table 14.3.8.1 (ocular, study eye); Table 14.3.8.2 (ocular, fellow eye); Table 14.3.8.3 (ocular, subject level); and Table 14.3.8.4 (non-ocular).

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1 Deaths

No deaths were reported in this study (Listing 16.2.7.4).

12.3.1.2 Other Serious Adverse Events

One subject experienced an SAE during the study (Listing 16.2.7.3). Subject 106-005 (saline group) experienced a single episode of moderate chest pain, resulting in hospitalization. IP was temporarily interrupted. The event resolved the same day as onset. In the opinion of the Investigator, the chest pain was not suspected/not related to IP.

12.3.1.3 Other Significant Adverse Events

Four (0.7%) subjects, 1 (0.3%) in the NOV03 group and 3 (1.0%) in the saline group, experienced a TEAE that resulted in discontinuation of IP (Listing 16.2.7.2). All of the discontinuation events were ocular in nature: severe eye irritation (NOV03, OU), mild dry eye (saline, OU), moderate punctate keratitis (saline, OS), and moderate allergic conjunctivitis (saline, OU). In the opinion of the Investigator, all of these events were suspected/related to IP.

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

See Section 14.3.3.

#### 12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

None of the subjects died or experienced an ocular SAE. Four (0.7%) subjects, 1 (0.3%) in the NOV03 group and 3 (1.0%) in the saline group, experienced a TEAE that resulted in discontinuation of IP; each event was ocular in nature and suspected/related to IP.

### 12.4 Clinical Laboratory Evaluation

Not applicable.

### 12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

#### 12.5.1 Best-Corrected Visual Acuity

Table 14.4.1.1 and Table 14.4.1.2 summarize baseline values and changes from baseline for BCVA in the study eye and fellow eye, respectively.

In the SAF, mean BCVA values at baseline in the study eye were 0.073 (SD 0.142) logMAR in the NOV03 group and 0.086 (SD 0.143) logMAR in the saline group (Table 14.4.1.1). Mean changes from baseline in BCVA at Days 15, 29, and 57 were minimal and comparable between treatment groups. Similar results were observed in the fellow eye (Table 14.4.1.2).

#### 12.5.2 Intraocular Pressure

Table 14.4.6.1 and Table 14.4.6.2 summarize baseline values and changes from baseline for IOP in the study eye and fellow eye, respectively.

In the SAF, mean IOP values at baseline in the study eye were 15.2 (SD 2.6) mmHg in the NOV03 group and 15.3 (SD 2.7) mmHg in the saline group (Table 14.4.6.1). Mean change from baseline in IOP at Day 57 was minimal and comparable between treatment groups. Similar results were observed in the fellow eye (Table 14.4.6.2).

#### 12.5.3 Slit-Lamp Examination

At baseline, most subjects had normal or abnormal, not clinically significant slit-lamp examination results in the study eye (Table 14.4.2.1). Overall, 23 (3.9%) subjects had a clinically significant abnormality in the lens (3.6%, NOV03; 4.1%, saline), 10 (1.7%) had a clinically significant abnormality in the cornea (1.7%, each group), 6 (1.0%) had a clinically significant abnormality in the conjunctiva (1.0%, each group); and 1 subject each (both NOV03) had a clinically significant abnormality in the eyelid and iris.

Overall, very few subjects (≤0.7%) had a worsening shift in a slit-lamp examination result in the study eye from baseline to any given post-baseline visit (Table 14.4.3.1).

Similar results were observed in the fellow eye (Table 14.4.2.2, Table 14.4.3.2).

#### 12.5.4 Dilated Fundoscopy

At baseline, most subjects had normal or abnormal, not clinically significant dilated fundoscopy results in the study eye (Table 14.4.4.1). Overall, 3 (0.5%) subjects had a clinically significant abnormality in the vitreous (0.3%, NOV03; 0.7%, saline), 1 (0.2%) had a clinically significant abnormality in the macula (saline), and 1 (0.2%) had a clinically significant abnormality in the optic nerve (saline).

Overall, very few subjects (≤0.2%) had a worsening shift in a dilated fundoscopy result in the study eye from baseline to any given post-baseline visit (Table 14.4.5.1).

Similar results were observed in the fellow eye (Table 14.4.4.2, Table 14.4.5.2).

### 12.5.5 Eyedrop Acceptability and Instillation Comfort

**Eyedrop Acceptability**

The eyedrop acceptability questionnaire (3 questions) was scored by the subject for the study eye on Day 57 using a VAS ranging from 0 to 10. Higher scores were indicative of better acceptability.

For the question related to satisfaction with the study eye drop, the mean score in the study eye was 7.4 (SD 2.6) in the NOV03 group and 6.7 (SD 3.1) in the saline group (Table 14.2.19). Analysis showed a nominally statistically significant difference (p=0.005) between the NOV03 and saline groups, in favor of active treatment.

For the question related to ease of administering the study eye drop, the mean score in the study eye was 8.7 (SD 2.1) in the NOV03 group and 9.0 (SD 1.6) in the saline group (Table 14.2.19). Analysis showed a nominally statistically significant difference (p=0.041) between the NOV03 and saline groups, in favor of the control.

For the question related to whether the subject would ask for a prescription of study drug, the mean score in the study eye was 7.4 (SD 3.0) in the NOV03 group and 6.6 (SD 3.5) in the saline group (Table 14.2.19). Analysis showed a nominally statistically significant difference (p=0.003) between the NOV03 and saline groups, in favor of active treatment.

**Instillation Comfort**

The instillation comfort questionnaire (1 question) was scored by the subject for each eye approximately 2 minutes after initial dosing at Visit 1 using a VAS ranging from 0 to 10. Higher scores were indicative of better comfort.

In the FAS, the mean instillation comfort score in the study eye was 7.9 (SD 2.3) in the NOV03 group and 8.3 (SD 2.1) in the saline group (Table 14.2.18). Analysis showed a nominally statistically significant difference (p=0.016) between the NOV03 and saline groups, in favor of the control.

## 12.6 Safety Conclusions

The results of this study indicate that NOV03 is safe and well tolerated in subjects with DED associated with MGD. Four (0.7%) subjects, 1 (0.3%) in the NOV03 group and 3 (1.0%) in the saline group, had an ocular TEAE that resulted in discontinuation of IP. In the opinion of the Investigator, each event was suspected/related to IP.

None of the ocular TEAEs were serious. Less than 10% of subjects had an ocular TEAE (9.6%, NOV03; 7.5%, saline). Most of the TEAEs were mild in severity; 1 (0.2%) subject had severe eye irritation in both eyes (NOV03). Overall, the most common ocular TEAEs (both groups combined) were blurred vision (1.7%) and instillation site pain (1.0%). Incidences of individual ocular TEAEs were generally similar between treatment groups. The incidence of blurred vision was higher in the NOV03 group (3.0%) than in the saline

group (0.3%). Blurred vision was transient in nature and typically resolved within several minutes post-instillation.

Less than 6% of subjects had a non-ocular TEAE (5.9%, NOV03; 4.1%, saline). Incidences of individual non-ocular TEAEs were low and similar between treatment groups. None of the non-ocular TEAEs were attributed to IP, severe in intensity, or led to discontinuation of IP. One subject had a serious non-ocular TEAE (acute chest pain, saline group).

None of the BCVA, IOP, slit-lamp examination, or dilated fundoscopy results were indicative of a safety concern for NOV03.

The eyedrop acceptability questionnaire (3 questions) was scored by the subject for the study eye on Day 57 using a VAS ranging from 0 to 10. Higher scores were indicative of better acceptability. Two of the 3 questions (satisfaction with the study eye drop, request for prescription of study drug) showed a nominally statistically significant difference ($p \leq 0.005$) between the NOV03 and saline groups, in favor of active treatment.

The instillation comfort questionnaire (1 question) was scored by the subject for each eye approximately 2 minutes after dosing at Visit 1 using a VAS ranging from 0 to 10. Higher scores were indicative of better comfort. The mean instillation comfort score in the study eye was 7.9 (SD 2.3) in the NOV03 group and 8.3 (SD 2.1) in the saline group. Analysis showed a nominally statistically significant difference ($p=0.016$) between the NOV03 and saline groups, in favor of the control.

## 13.0 DISCUSSION AND OVERALL CONCLUSIONS

This Phase 3, multi-center, randomized, double-masked, saline-controlled study evaluated the efficacy and safety of NOV03 (perfluorohexyloctane) ophthalmic solution in subjects with DED associated with MGD. Eligible subjects were assigned to 1 of 2 treatment groups and instilled 1 drop of NOV03 (100% perfluorohexyloctane) ophthalmic solution QID or 1 drop of saline (0.6% sodium chloride solution) ophthalmic solution QID into each eye for 8 weeks. In the case both eyes were eligible at study entry, the worst eye was selected as the study eye, defined as the eye with worse (higher) total corneal staining at Visit 1. If the total corneal staining was the same in both eyes, then the right eye was selected as the study eye.

### 13.1 Efficacy Findings

The study had 2 primary efficacy endpoints: mean change from baseline in tCFS (NEI scale) in the study eye at Day 57 and the VAS dryness score at Day 57. tCFS is a measure of signs associated with DED, whereas the VAS dryness score is a measure of symptomatology. Corneal staining is an accepted clinical endpoint in DED and a highly relevant marker in this disease (Pflugfelder and de Pavia, 2017). Reduction of corneal staining reflects corneal surface healing and treatment success. Questionnaires using VAS are often used in ophthalmic trials in subjects with DED to assess ocular symptoms.

The two primary endpoints of the study were tested in hierarchical order. Data from the NVU-002 study indicated that tCFS is a stronger measure of efficacy; therefore, it was tested first. Four key secondary efficacy endpoints tested were also tested in hierarchical order after the primary endpoints: mean change from baseline in tCFS in the study eye at Day 15, VAS dryness score at Day 15, VAS burning/stinging score at Day 57, and cCFS in the study eye at Day 57.

Both of the primary endpoints and all 4 key secondary endpoints were met in this study, with NOV03 showing statistically significant improvement over saline in clinically relevant signs and symptoms of DED associated with MGD.

Analysis of tCFS showed statistically significant ($p \leq 0.001$) differences between the NOV03 and saline groups, in favor of active treatment, at Day 15 (the first time point measured) and Day 57; a nominally statistically significant difference was also observed on Day 29 ($p=0.001$). Subjects in the NOV03 group were nearly twice as likely to achieve a ≥3 improvement in the tCFS score (NEI scale) at Day 57 compared to subjects in the saline group (OR = 1.88, $p<0.001$).

Improvements in the eye dryness VAS score were observed throughout the study and were statistically significant on Days 15 and 57, in favor of active treatment ($p \leq 0.009$). Subjects in the NOV03 group were 59% and 55% more likely to achieve a ≥30% improvement from baseline in the VAS dryness score at Day 15 ($p=0.007$) and Day 57 ($p=0.010$), respectively, compared to subjects in the saline group.

Results for cCFS and inferior CFS (study eye) typically mirrored those observed for tCFS, showing significant improvement from baseline in the central and inferior region of the cornea relative to saline. Further, results for the burning/stinging VAS score mirrored those for the eye dryness VAS score. Significant improvements from baseline relative to saline were also observed for most of the remaining VAS scores at Day 57, including foreign body sensation, itching, pain, awareness of dry eye symptoms, and frequency of dryness.

### 13.2 Safety Findings

The results of this study indicate that NOV03 is safe and well tolerated in subjects with DED associated with MGD. The proportion of subjects who discontinued IP due to an ocular TEAE was low in each treatment group (≤1.0%). None of the subjects had a serious ocular TEAE; 1 subject (saline) had a serious non-ocular TEAE (acute chest pain). Less than 10% of subjects had an ocular TEAE (9.6%, NOV03; 7.5%, saline), and most were mild in severity. The most common ocular TEAEs (both groups combined) were blurred vision (1.7%) and instillation site pain (1.0%). Blurred vision was the only TEAE with an incidence that was notably higher in subjects treated with NOV03 (3.0% versus 0.3%). Blurred vision was mild, transient in nature, and typically resolved within several minutes post-instillation. None of the BCVA, IOP, slit-lamp examination, or dilated fundoscopy results were indicative of a safety concern for NOV03.

Two of the 3 questions on the eyedrop acceptability questionnaire scored by the subject for the study eye on Day 57 (satisfaction with the study eye drop, request for prescription of study drug) showed a nominally statistically significant difference ($p \leq 0.005$) between the NOV03 and saline groups, in favor of active treatment.

### 13.3 Conclusion

In conclusion, NOV03 (100% perfluorohexyloctane) demonstrated statistically significant improvement over saline in several clinically relevant signs (tCFS, cCFS, and inferior CFS) and symptoms (VAS scores, including eye dryness and burning/stinging) of DED associated with MGD. Onset of improvement was typically within 2 weeks of first dose (first timepoint measured post-baseline) and remained significant at Day 57. NOV03 was safe and well tolerated. Blurred vision was the only TEAE that occurred in a higher proportion of subjects treated with NOV03 (versus saline); it was mild in severity and

transient in nature, typically resolving within minutes of onset. NOV03 is a safe and effective treatment for DED associated with MGD.

# 14.0 TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

## 14.1 Demographic Data

The demographic data tables, figures, and graphs referred to but not included in the text begin on the following page.

## 14.2 Efficacy Data

The efficacy data tables, figures, and graphs referred to but not included in the text begin on the following page.

## 14.3 Safety Data

The safety data tables, figures, and graphs referred to but not included in the text begin on the following page.

### 14.3.1 Displays of Adverse Events

### 14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

Refer to Listing 16.2.7.4, Listing 16.2.7.3, and Listing 16.2.7.2 for listings of deaths, other SAEs, and TEAEs leading to study discontinuation, respectively.

### 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Narratives for deaths, SAEs, and discontinuations due to a TEAE begin on the following page.

### 14.3.4 Abnormal Laboratory Value Listing (each subject)

## 15.0 REFERENCE LIST

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# 16.0 APPENDICES