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NOV03 for Signs and Symptoms of Dry Eye Disease Associated With Meibomian Gland Dysfunction: The Randomized Phase 3 MOJAVE Study

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• PURPOSE: To evaluate the efficacy and safety of NOV03 (perfluorohexyloctane) ophthalmic drop for the treatment of signs and symptoms of dry eye disease (DED) associated with meibomian gland dysfunction (MGD).

• DESIGN: Randomized, double-masked, controlled trial.

• METHODS: Patients ≥18 years of age with a history of DED and signs of MGD were randomly assigned 1:1 to treatment with NOV03 or hypotonic saline (0.6%) 4 times daily for 8 weeks. The primary sign and symptom endpoints were change from baseline to week 8 in total corneal fluorescein staining (tCFS; National Eye Institute scale) and eye dryness score (0-100 visual analog scale), respectively.

• RESULTS: A total of 620 patients (NOV03, n = 311; saline, n = 309) were randomized and treated. Least-squares (LS) mean change from baseline to week 8 was statistically significantly greater for NOV03 compared with saline for both tCFS (−2.3 vs −1.1; LS mean treatment difference, −1.2 [95% confidence interval −1.7 to −0.8]; $P < .001$) and visual analog scale dryness score (−29.4 vs −19.2; LS mean treatment difference, −10.2 [95% CI −14.4 to −6.1]; $P < .001$), with statistically significant between-group differences observed as early as week 2. The incidence of ocular adverse events was similar for NOV03 (12.9%) and saline (12.3%). There were no serious adverse events and no adverse events leading to treatment discontinuation.

• CONCLUSIONS: In this randomized controlled trial of patients with DED associated with MGD, NOV03 significantly reduced both signs and symptoms of DED compared with hypotonic saline control. NOV03 was well tolerated, with an adverse event profile similar to that of saline. (Am J Ophthalmol 2023;252: 265–274. © 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/))

Dry eye disease (DED) is a highly prevalent ocular surface disorder with symptoms of ocular discomfort, such as dryness, burning, soreness, itchiness, foreign body sensation, and visual disturbance, along with signs of decreased tear film, tear hyperosmolarity, tear film instability, and damage of the ocular surface (as observed on clinical examination).[1–4] DED can negatively impact patients' quality of life, work productivity, and other daily activities.[5]

DED is a multifactorial disease and may be classified as aqueous-deficient, evaporative, or a combination of the two.[3,6] In aqueous-deficient DED, secretions from the lacrimal glands are reduced, whereas evaporative DED, which accounts for the majority of DED cases, results from excessive evaporation of the tear film.[3,6] The primary cause of evaporative DED is meibomian gland dysfunction (MGD); it is estimated that >80% of patients with DED have meibomian gland involvement.[7–9]

Meibomian glands express a lipid-rich secretion (meibum), which forms the outermost lipid layer of the tear film.[10,11] The tear film lipid layer has nonpolar lipids (eg, cholesteryl esters and wax esters) at the air–tear interface and amphiphilic polar lipids (eg, phospholipids, omega-hydroxy fatty acids) adjacent to the aqueous layer.[11,12] In MGD, alterations in meibum quality and/or reduction in meibum secretion can disrupt the tear film lipid layer, resulting in excessive evaporation and tear film instability.[10,13,14] Tear film evaporation causes thinning of the tear film, which leads to desiccation and tear hyperosmolarity,

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as well as apoptosis and inflammation of the ocular surface, contributing to DED signs and symptoms.[13]

Current management of DED associated with MGD includes physical therapies to promote meibum secretion (eg, warm compresses, thermal pulsation, intense pulsed light, mechanical expression), oral nutraceuticals, and over-the-counter lipid-based artificial tears that supplement meibum secretions.[15–17] Prescription ophthalmic medications (eg, cyclosporine, lifitegrast, varenicline) are approved for DED but have seldom been evaluated specifically in patients with DED associated with MGD and do not target the primary cause of evaporative DED.[18–20]

NOV03 (MIEBO [perfluorohexyloctane ophthalmic solution]; Bausch + Lomb), a novel topical drug therapy recently approved by the US Food and Drug Administration (FDA) for treatment of the signs and symptoms of DED, is a single-entity, water-free, preservative-free, ophthalmic drop consisting of perfluorohexyloctane (an anhydrous semifluorinated alkane). Because of the chemical structure of perfluorohexyloctane, NOV03 has amphiphilic properties,[21] and due to its low surface tension, NOV03 spreads rapidly across the ocular surface.[22,23] NOV03 also causes minimal visual disturbances upon administration, compared with gel- or ointment-based therapies, because it has a refractive index similar to that of water.[22] NOV03 is thought to prevent evaporation of the tear film by forming a layer on the ocular surface (air–fluid interface) and thereby acting as a potential functional enhancement for the deficient tear film lipid layer.[21,24] After a single ocular instillation in rabbits, NOV03 was detected in tears through 6 hours and in meibomian glands through 24 hours, with undetectable systemic absorption.[25]

The efficacy and safety of NOV03 were demonstrated in a phase 2 randomized controlled trial (SEECASE)[26] and a phase 3 randomized controlled trial (GOBI),[27] both in patients with DED associated with MGD. In SEECASE, NOV03, administered 2 or 4 times daily, showed a significantly greater reduction in the signs and symptoms of DED compared with the isotonic saline (0.9%) control and also had a favorable safety and tolerability profile.[26] In GOBI, the first of 2 phase 3 trials, NOV03 dosed 4 times daily also demonstrated statistically significant reductions in both the primary signs and symptoms of DED (total corneal fluorescein staining [tCFS] and eye dryness, assessed on a visual analog scale [VAS]) relative to hypotonic saline (0.6%).[27] This report presents the results of a second, similarly designed phase 3 trial, MOJAVE, which evaluated the efficacy and safety of NOV03 in adults with DED associated with MGD.

METHODS

• **STUDY DESIGN:** MOJAVE was a phase 3, multicenter, randomized, double-masked, saline-controlled, 8-week trial (ClinicalTrials.gov identifier NCT04567329), similar in design to the GOBI study. MOJAVE was conducted at 42 sites in the United States between November 2020 and August 2021. The study consisted of 5 visits: screening, baseline (day 1), and 3 follow-up visits at weeks 2, 4, and 8 (Figure 1). Eligible patients were randomized via an interactive system in a 1:1 ratio to receive either NOV03 or hypotonic saline solution (0.6% sodium chloride, preserved with 0.01% benzalkonium chloride [BAK]). Randomization was stratified by investigational site and by the patients' baseline eye dryness score, as measured on a VAS (<70 vs ≥70). Patients were instructed to instill 1 drop of study medication into each eye 4 times daily for 8 weeks; both patients and investigators were masked to treatment assignment.

The study was conducted in accordance with the Good Clinical Practice guideline of the International Conference on Harmonisation and the tenets of the Declaration of Helsinki. The study protocol was approved by Sterling Institutional Review Board (Atlanta, Georgia, USA). All patients provided written informed consent before initiation of any study-related procedures.

• **PATIENTS:** Inclusion and exclusion criteria were consistent with those used in the GOBI study.[27] Briefly, patients ≥18 years of age with a self-reported history of DED in both eyes for ≥6 months were eligible for the study if they met the following key inclusion criteria in ≥1 eye (the same eye) at screening and at randomization: tear film break-up time ≤5 seconds, unanesthetized Schirmer's tear test I ≥5 mm, total MGD score ≥3, tCFS score ≥4 and ≤11, and Ocular Surface Disease Index (OSDI) score ≥25. For the MGD score, 5 central meibomian glands on the lower eyelid were assessed, each scored from 0-3 (0 = normal; 1 = thick/yellow, whitish, particulate; 2 = paste; 3 = absent/occluded); the total score ranged from 0-15. If both eyes met the inclusion criteria, the eye with the higher (ie, worse) tCFS score at baseline was designated as the study eye.

Exclusion criteria included clinically significant slit-lamp biomicroscopy findings; active blepharitis; active ocular allergies; ocular or systemic infection; intraocular surgery or ocular laser surgery within the previous 6 months; LipiFlow (Johnson & Johnson Vision Care, Inc), intense pulsed light, or other procedure affecting the meibomian glands within the previous 6 months; use of contact lenses within the previous month; use of topical steroids, topical cyclosporine, lifitegrast, serum tears, or topical intraocular pressure–lowering medication within the previous 60 days; and history of isotretinoin use. Patients were prohibited from wearing contact lenses, undergoing ocular surgery or ocular laser treatment, or using other dry eye treatments, including artificial tears, beginning 1 day before baseline and continuing throughout the treatment period. Physical therapies (eg, lid scrubs, lid wipes), systemic antibiotics, and oral supplements for treatment of ocular conditions were

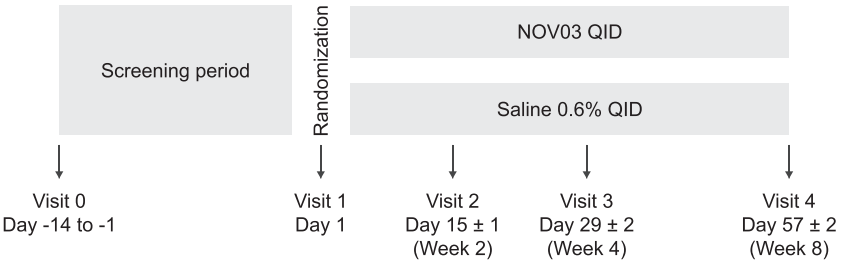

FIGURE 1. Study design. QID = 4 times daily.

permitted, provided use of these treatments had been stable within the 30 days before baseline and was maintained throughout the trial.

• **OUTCOME MEASURES:** Signs and symptoms of dry eye were assessed at screening, baseline (day 1), and 3 follow-up visits: week 2 (day 15 ± 1 day), week 4 (day 29 ± 2 days), and week 8 (day 57 ± 2 days). Efficacy assessments included investigator-rated corneal fluorescein staining and patient-reported symptom severity (eg, eye dryness, burning/stinging). Fluorescein staining of 5 areas of the cornea (inferior, superior, central, nasal, and temporal) was rated by the investigator using the National Eye Institute (NEI) scale from grade 0 (no staining) to grade 3 (heavy staining), and the tCFS score was calculated as the sum of the individual NEI scale scores (maximum total score, 15). Patients rated eye dryness and other symptoms for both eyes at the same time using a VAS ranging from 0 (no discomfort) to 100 (maximal discomfort).

The primary efficacy endpoints were change from baseline at week 8 in tCFS score and VAS eye dryness score. Key secondary efficacy endpoints were change from baseline in VAS dryness score at week 2, tCFS score at week 2, VAS burning/stinging score at week 8, and central corneal fluorescein staining (cCFS) score at week 8. Other endpoints included change from baseline in tCFS at week 4, change from baseline in VAS dryness score at week 4, change from baseline in cCFS at weeks 2 and 4, the proportion of responders for tCFS (defined as an improvement of ≥3 steps on the NEI scale) at week 8, the proportion of responders for eye dryness (defined as ≥30% reduction in VAS score) at week 8, and change from baseline in OSDI score at each postbaseline visit.

Safety assessments included adverse events (AEs), best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure, and dilated fundoscopy. Treatment compliance was determined by reviewing patient dosing diaries and calculated as the total number of doses administered, divided by the total number of doses that should have been administered, multiplied by 100.

• **STATISTICAL METHODS:** The full analysis population included all randomized patients who received ≥1 dose of NOV03 or saline, and the per-protocol population included patients in the full analysis population who did not have significant protocol deviations and completed the study. The primary analysis was conducted on the full analysis population with no imputation of missing data. The 2 primary endpoints (tCFS, VAS dryness score) were evaluated in the full analysis population using hierarchical fixed-sequence testing to control the type 1 error rate, with tCFS tested first. Differences between treatments were evaluated using an analysis of covariance model with terms for baseline value and treatment. If both primary endpoints demonstrated statistical superiority of NOV03 vs saline (2-sided $\alpha = 0.05$), the key secondary endpoints were tested hierarchically in the following order: VAS dryness score at week 2, tCFS score at week 2, VAS burning/stinging score at week 8, cCFS score at week 8. The proportion of study eyes (or patients) that met predefined criteria (≥3-step improvement in tCFS score, ≥30% reduction in VAS dryness score) were compared between treatment groups using logistic regression analysis, adjusting for baseline score at each measured follow-up visit. Odds ratios (ORs) were calculated for NOV03 vs saline. Differences between treatments in OSDI score were evaluated via the primary analytic method (analysis of covariance).

A sensitivity analysis evaluated NOV03 vs saline on the primary endpoints in the per-protocol population via the primary analytic method, with no imputation of missing data. Additional sensitivity analyses included comparison of treatment groups on the primary endpoints in the full analysis population, using 2-sample *t* tests (equal variance assumed), Wilcoxon rank-sum tests, and mixed-effect repeated measures analysis.

Sample size estimates were based on the following assumptions, which were predicated on the results of the phase 2 study of NOV03 (SEECASE)[26]: for the primary endpoint of ocular sign (ie, change in tCFS score), a −1.0 unit difference between treatment groups (NOV03 minus saline) in mean change from baseline at week 8 and a common standard deviation (SD) of 2.8 units; for the primary endpoint of ocular symptom (ie, change in VAS dryness score), a −10 unit difference between treatment groups (NOV03 minus saline) in mean change from baseline at

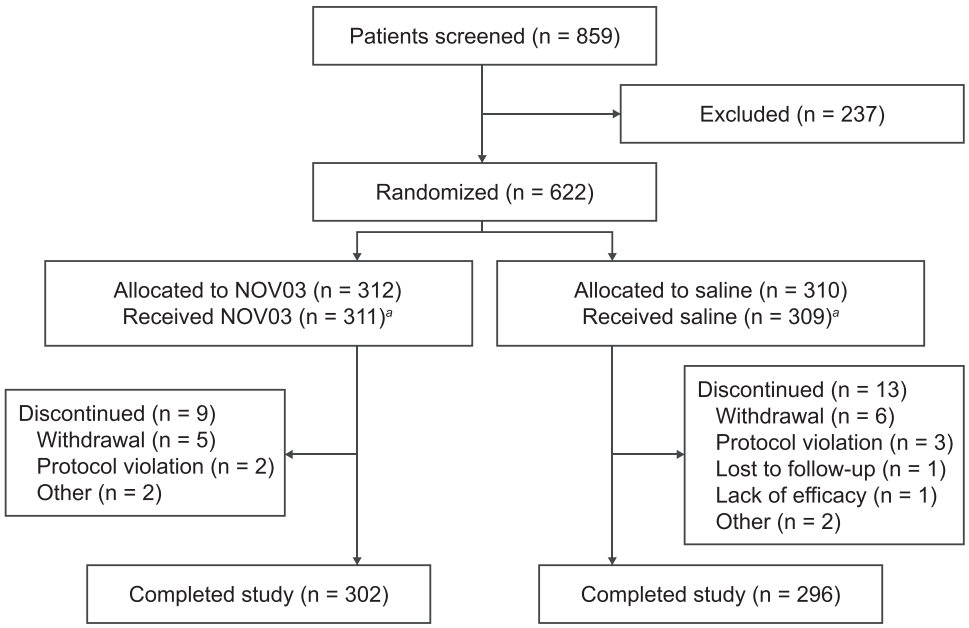

FIGURE 2. Patient disposition. [a]Two patients (1 per group) were randomized but did not receive study medication: 1 patient (NOV03) was randomized in error because of a data entry error, and 1 patient (saline) was randomized incorrectly using the record for another patient.

week 8, and a common SD of 28 units. Under these assumptions, a sample size of 250 patients per treatment group (for a total of ~280 randomized patients per group, assuming 10% discontinuation rate) was chosen to yield >90% power to detect a significant difference at the 2-sided $\alpha = 0.05$ level.

RESULTS

• **PATIENTS:** The full analysis population included 620 patients: 311 in the NOV03 group and 309 in the control group (Figure 2). A total of 302 (97.1%) and 296 (95.8%) patients completed the study in the NOV03 and control groups, respectively. The distribution of demographic and baseline disease characteristics was well balanced between the treatment groups, with no appreciable differences observed between treatment groups (Table 1). The most common (≥10% for all patients) ocular medical history occurrences other than DED with MGD were cataracts and vitreous detachment. For nonocular medical history, the most common (≥20% of patients) occurrence was hypertension.

Patient-reported dosing diaries indicated that most patients were compliant with dosing (defined as 80%-120% of expected doses administered): the compliance rate was 98.4% for patients in both the NOV03 and saline groups. Twenty-eight patients (9.0%) in the NOV03 group and 23 patients (7.4%) in the saline group were excluded from the per-protocol population due to major protocol deviations (eg, use of prohibited medications, investigational product deviations, study visit schedule deviations). Study visit schedule deviation (4.0% of patients overall) was the most common major protocol deviation.

• **EFFICACY:**

Primary endpoints

Patients treated with NOV03 experienced significantly greater reduction from baseline at week 8 in both tCFS score and VAS dryness score vs patients who received the saline control treatment (Figure 3), thereby meeting both primary efficacy endpoints. The least-squares (LS) mean treatment difference for change from baseline to week 8 in tCFS score was −1.2 (95% confidence interval [CI] −1.7 to −0.8; $P < .001$). The LS mean treatment difference for change from baseline to week 8 in VAS dryness score was −10.2 (95% CI −14.4 to −6.1; $P < .001$). For both primary endpoints, results from the sensitivity analyses of the per-protocol population (same analytic method as the primary analysis) and the full analysis population (2-sample *t* tests, Wilcoxon rank-sum tests, mixed-effect repeated measures analysis) were consistent with the main findings.

Key secondary endpoints

For all key secondary endpoints, mean improvement from baseline was significantly greater for NOV03 vs saline con-

TABLE 1. Demographic and Baseline Clinical Characteristics

Characteristic	NOV03, n = 311	Saline, n = 309
Mean (range) age (y)	53.3 (19-85)	53.8 (20-88)
≥65 y, n (%)	101 (32.5)	96 (31.1)
Female, n (%)	250 (80.4)	238 (77.0)
Race, n (%)		
White	244 (78.5)	255 (82.5)
Asian	36 (11.6)	27 (8.7)
Black	23 (7.4)	20 (6.5)
Multiple/other	8 (2.5)	7 (2.3)
Baseline ocular characteristics		
tCFS score (NEI), study eye, mean (SD)	7.0 (2.0)	7.1 (2.1)
Eye dryness score (VAS), mean (SD)	64.7 (19.5)	64.3 (19.8)
Eye burning/stinging score (VAS), mean (SD)	50.1 (25.8)	48.4 (26.2)
Total MGD score, study eye, mean (SD)	7.9 (3.5)	8.1 (3.5)
TFBUT, study eye, sec, mean (SD)	3.2 (0.9)	3.1 (0.9)
Unanesthetized Schirmer's test I, study eye, mm, mean (SD)	12.7 (7.5)	12.8 (7.9)
OSDI score, mean (SD)	55.2 (17.4)	55.8 (17.2)
BCVA (logMAR), study eye, mean (SD)	0.07 (0.1)	0.07 (0.1)

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; MGD = meibomian gland dysfunction; NEI = National Eye Institute; OSDI = ocular surface disease index; SD = standard deviation; tCFS = total corneal fluorescein staining; TFBUT = tear film break-up time; VAS = visual analog scale.

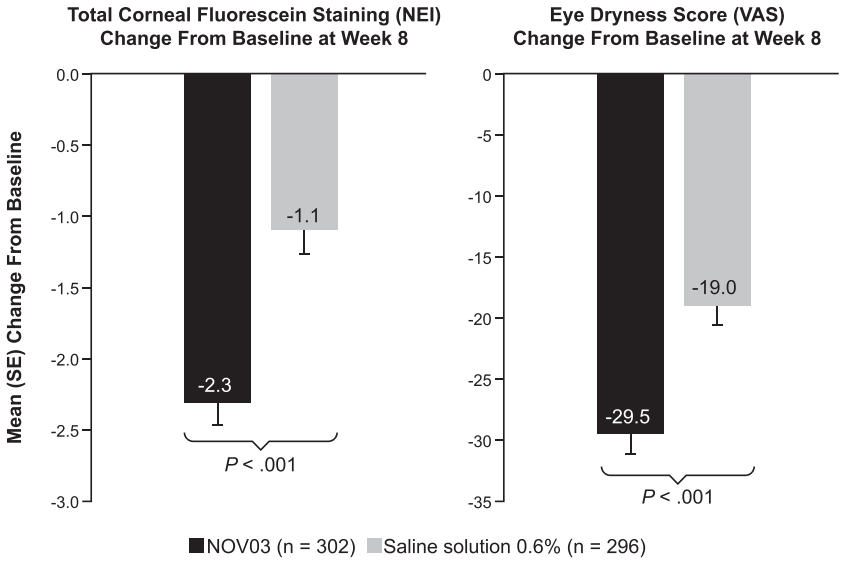

FIGURE 3. Mean change from baseline at week 8 for the primary efficacy outcomes: total corneal fluorescein staining score (NEI) and eye dryness score (VAS). NEI = National Eye Institute scale; SE = standard error; VAS = visual analog scale.

trol groups (Figure 4). For change from baseline in tCFS score (study eye) at week 2, the LS mean treatment difference was −0.6 (95% CI −1.0 to −0.2; $P = .001$). The LS mean treatment difference was −7.8 (95% CI −11.3 to −4.3; $P < .001$) for change from baseline in VAS dryness score at week 2. The LS mean treatment difference was −7.3 (95% CI −11.3 to −3.4; $P < .001$) for change from baseline in VAS burning/stinging score at week 8. For change from baseline in cCFS score (study eye) at week 8, the LS mean treatment difference was −0.3 (95% CI −0.5 to −0.2; $P < .001$). For all key secondary endpoints, results observed in the sensitivity analyses confirmed the results from the primary analysis.

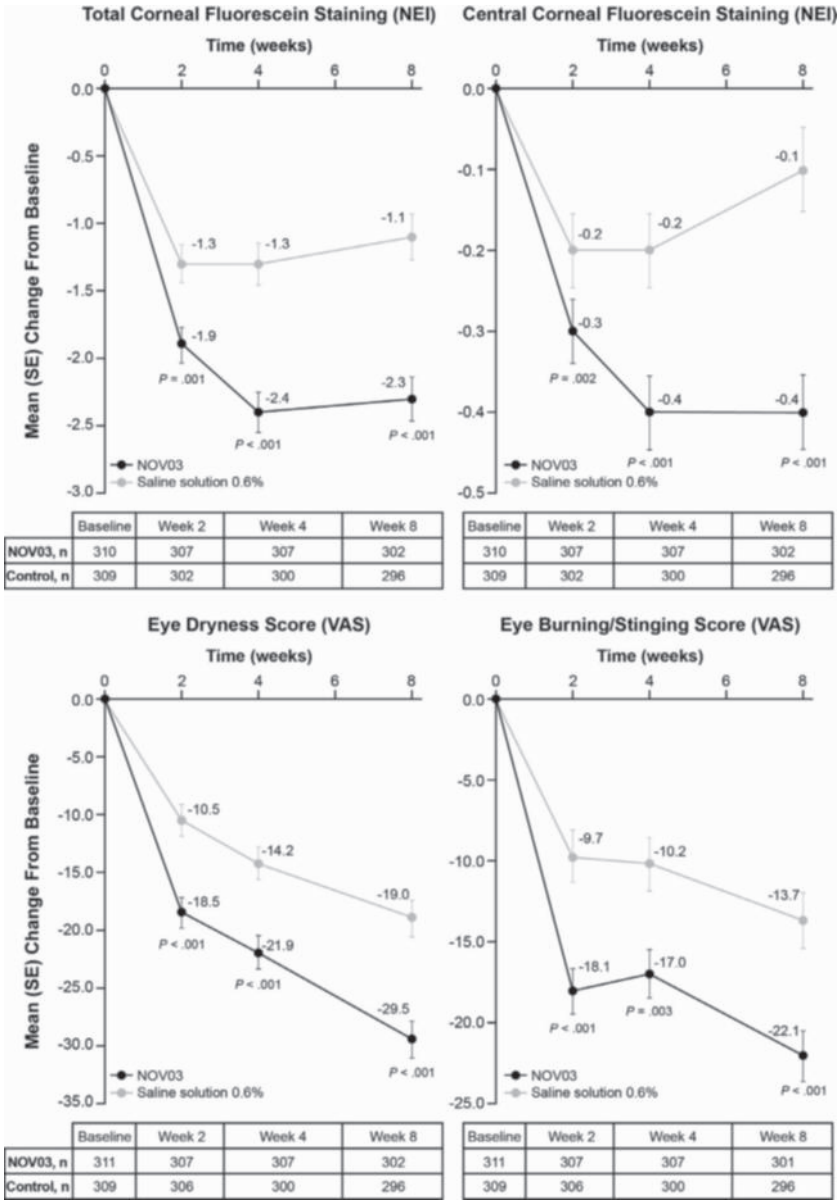

FIGURE 4. Mean change from baseline for secondary efficacy endpoints. NEI = National Eye Institute scale; SE = standard error; VAS = visual analog scale.

Other secondary endpoints

Significant improvement in other secondary endpoints was seen with NOV03 vs saline, consistent with the results for the primary and secondary endpoints. A significantly greater proportion of patients in the NOV03 group were tCFS responders (≥3-step improvement in tCFS score) at week 8 (50.0%) compared with the control group (30.7%), with an OR of 2.35 (95% CI 1.7 to 3.3; $P < .001$). The proportion of eye dryness responders (≥30% reduction in VAS dryness score) at week 8 was significantly greater in the NOV03 group (65.6%) compared with the control group (45.3%), with an OR of 2.30 (95% CI 1.7 to 3.2; $P < .001$). The LS mean change from baseline in tCFS score at week 4 was significantly more improved in the NOV03 group (−2.4) compared with the control group (−1.3; $P < .001$). For cCFS score, the LS mean change from baseline was significantly greater in the NOV03 group compared with the control group at week 2 (−0.35 vs −0.19; $P = .002$) and week 4 (−0.44 vs −0.20; $P < .001$). LS mean change from baseline in VAS dryness score at week 4 was significantly greater for NOV03 (−21.8) vs control (−14.3; $P < .001$). Finally, LS mean decreases from baseline in OSDI score (indicating improvement) were greater for NOV03 vs control at week 2 (NOV03, −15.78; saline, −11.85), week 4

TABLE 2. Summary of Ocular Adverse Events

Parameter, n (%)	NOV03, n = 311	Saline, n = 309
Patients with ≥1 ocular AE[a]	40 (12.9)	38 (12.3)
Mild	36 (11.6)	36 (11.7)
Moderate	4 (1.3)	1 (0.3)
Severe	0 (0)	1 (0.3)
Drug-related ocular AE[b]	20 (6.4)	21 (6.8)
Serious ocular AE	0 (0)	0 (0)
Ocular AE leading to discontinuation	0 (0)	0 (0)
Most common ocular AEs[c]		
Blepharitis	5 (1.6)	1 (0.3)
Conjunctival hyperemia	4 (1.3)	6 (1.9)
Conjunctival papillae	4 (1.3)	5 (1.6)
Ocular hyperemia	4 (1.3)	1 (0.3)
Blurred vision	4 (1.3)	1 (0.3)
Visual acuity reduction	3 (1.0)	3 (1.0)
Hordeolum	3 (1.0)	2 (0.6)
Eye pruritus	2 (0.6)	3 (1.0)
Eye discharge	1 (0.3)	4 (1.3)
Eye pain	1 (0.3)	4 (1.3)

AE = adverse event.
[a] Patients instilled drops in both eyes; values represent n (%) of patients with an AE in either eye.
[b] Considered by the investigator as suspected/related to study medication.
[c] Incidence ≥1% in either treatment group.

(NOV03, −18.66; saline, −13.68), and week 8 (NOV03, −23.34; saline, −15.92; $P \leq .002$ for all timepoints).

- **SAFETY:**

Ocular AEs and other ocular safety assessments

Ocular AEs were experienced by 12.9% of patients in the NOV03 group and 12.3% of patients in the saline group (Table 2). Most ocular AEs were mild or moderate in severity; however, 1 patient receiving saline had a severe AE of eye irritation. Ocular AEs were considered by the investigator as related to study medication in 6.4% of the patients in the NOV03 group and 6.8% in the saline group. There were no serious ocular AEs, and no patient in either the NOV03 group or the saline group had an ocular AE that led to treatment discontinuation or withdrawal from the study. The most common (incidence ≥1%) ocular AEs in the NOV03 group were blepharitis, conjunctival hyperemia, conjunctival papillae, ocular hyperemia, blurred vision, hordeolum (stye), and visual acuity reduction (Table 2). No clinically meaningful safety concerns were observed in best-corrected visual acuity, slit-lamp examination, intraocular pressure, or dilated fundoscopy examination.

Nonocular AEs

Nonocular AEs were experienced by 7.1% of patients in the NOV03 group and 5.2% of the saline group; none of these AEs led to treatment discontinuation or withdrawal from the study. No nonocular AEs were attributed to NOV03 treatment, and no patients experienced a serious nonocular AE.

DISCUSSION

MOJAVE, which had a design nearly identical to that of the GOBI study,[27] was the second phase 3 trial to evaluate the safety and efficacy of NOV03. This multicenter, randomized, double-masked, hypotonic saline–controlled trial enrolled patients with DED associated with MGD, a major subtype of DED. Consistent with the GOBI study results,[27] NOV03 achieved statistical superiority compared with hypotonic saline for both of the primary endpoints (tCFS and VAS dryness score at week 8) and all 4 of the key secondary endpoints. Furthermore, NOV03 demonstrated benefits vs hypotonic saline in both DED signs (tCFS and cCFS) and symptoms (VAS dryness and burning/stinging) at all 3 follow-up visits (weeks 2, 4, and 8) in this study. As hypotonic solutions have been shown to be effective in the treatment of DED,[28–30] using a hypotonic saline control treatment added rigor to these phase 3 studies.

NOV03, administered 4 times daily for 8 weeks, has shown consistent improvements in both signs and symptoms of DED in 3 randomized, double-masked, saline-controlled trials in patients with DED associated with

MGD: 2 phase 3 studies (GOBI and the current study, MOJAVE) and 1 phase 2 study (SEECASE).[26,27] These findings are noteworthy, given that demonstration of consistent treatment benefits for both signs and symptoms of DED in repeated clinical studies has not been shown to date for other approved prescription DED therapies. NOV03 also demonstrated a sizeable magnitude of effect for these endpoints in the phase 3 studies.[27] After 8 weeks of treatment, >60% of the patients in the NOV03 group in this study showed a clinically meaningful improvement in patient-reported eye dryness symptom (≥30% reduction in VAS dryness score) and 50% of the patients showed a clinically meaningful improvement in tCFS score (≥3-step improvement), reflecting corneal surface healing. These consistent and robust benefits, observed across 3 studies, suggest that NOV03 may be a highly effective treatment for DED associated with MGD.

In this study, NOV03 was safe and well tolerated, confirming the findings from the GOBI and SEECASE studies, with a safety profile similar to that of hypotonic saline control.[26,27] There were no serious ocular or nonocular AEs reported in patients treated with NOV03 in this study; furthermore, all AEs in the NOV03 group were mild or moderate in intensity and none led to treatment discontinuation. The safety profile of NOV03 is advantageous, considering that several other approved prescription DED treatments have tolerability issues leading to treatment discontinuations.[31]

Although the mechanism(s) by which NOV03 improves signs and symptoms of DED associated with MGD have not been fully elucidated, these positive clinical effects are thought to be due to the formation of a long-lasting barrier that prevents evaporation of the underlying aqueous layer of the tear film.[22,23,25] Consistent with this mechanism of action, NOV03 reduced the evaporation rate of saline by ~80% in an in vitro study that evaluated the evaporation rate for physiological saline alone vs saline covered by NOV03.[24] NOV03 may also act to enhance tear film spreading and reduce friction during blinking. Notably, the clinical finding of significant improvement in tCFS as early as week 2 in this study, as well as the previous phase 3 and phase 2 studies, suggests that NOV03's mechanism of action facilitates rapid corneal healing. Limitations of the current study, similar to those of the GOBI study, include the exclusion of patients with severe DED (tCFS >11), the relatively short treatment period of 8 weeks, and the first assessment not being made earlier than at 2 weeks, precluding a precise determination of the onset of action.[27] To maintain study masking through use of the same dropper bottle for both NOV03 and hypotonic saline control, BAK (0.01%) was required to preserve the latter. However, based on the low BAK concentration used and the short treatment duration, the authors do not consider the use of BAK in the control arm to be a significant confounder. Finally, longer-term evaluation of treatment with NOV03 in patients with DED associated with MGD is warranted; in fact, a 12-month, open-label safety study of NOV03 (KALAHARI) was recently completed.

In conclusion, in this phase 3 study of patients with DED associated with MGD, NOV03 demonstrated statistically significant improvements in signs and symptoms of DED compared with the saline control, thereby confirming findings from the previous phase 3 GOBI study. NOV03 was well tolerated in this patient population.

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