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NOV03 for Dry Eye Disease Associated with Meibomian Gland Dysfunction

Results of the Randomized Phase 3 GOBI Study

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Purpose: To evaluate the efficacy and safety of NOV03 (perfluorohexyloctane) ophthalmic drop in patients with dry eye disease (DED) associated with meibomian gland dysfunction (MGD).

Design: Eight-week, phase 3, multicenter, randomized, double-masked, saline-controlled study.

Participants: Adults ≥ 18 years with a history of DED for ≥ 6 months, tear film breakup time of ≤ 5 seconds, Schirmer I test (without anesthesia) score ≥ 5 mm, MGD score ≥ 3 (0−15 scale), and total corneal fluorescein staining (tCFS) score ≥ 4 and ≤ 11 (0−15 National Eye Institute [NEI] scale).

Methods: Patients were randomized 1:1 to NOV03 or hypotonic (0.6%) saline 4 times daily.

Main Outcome Measures: The primary sign and symptom end points were change from baseline in tCFS and eye dryness score (0−100 visual analog scale [VAS]) at week 8. Key secondary end points were change from baseline in eye dryness score at week 2, tCFS at week 2, eye burning or stinging score (0−100 VAS) at week 8, and central corneal fluorescein staining (cCFS; 0−3 NEI scale) at week 8.

Results: Of the 599 patients randomized, 597 were treated (NOV03, n = 303; saline, n = 294). At week 8, improvement from baseline was significantly greater ($P < 0.001$) with NOV03 versus saline for tCFS (least square [LS] mean treatment difference, −0.97; 95% confidence interval [CI]: −1.40, −0.55) and VAS dryness score (−7.6; 95% CI: −11.8, −3.4). Improvement from baseline also significantly ($P < 0.01$) favored NOV03 on all key secondary end points: LS mean treatment difference (95% CI) was −4.7 (−8.2, −1.2) for VAS dryness score at week 2, −0.6 (−0.9, −0.2) for tCFS at week 2, −5.5 (−9.5, −1.6) for VAS burning or stinging score at week 8, and −0.2 (−0.4, −0.1) for cCFS at week 8. Most ocular adverse events (AEs) were mild in severity; no serious ocular AEs occurred. One patient discontinued NOV03 because of an AE (eye irritation).

Conclusions: In patients with DED associated with MGD, NOV03 demonstrated statistically significant and clinically meaningful improvements versus hypotonic saline in signs and symptoms of DED and was well tolerated.

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Dry eye disease (DED) is a common ocular surface disorder with 2 major subtypes: aqueous-deficient DED, in which lacrimal secretion is reduced, and evaporative DED, which results from excessive evaporation of the tear film.[1,2] The prevalence rates of these DED subtypes are dissimilar. Estimates suggest that aqueous-deficient DED by itself occurs in only 10% to 15% of patients with DED.[3−5] Indeed, the vast majority of DED cases are evaporative in nature or include an evaporative component,[3−7] and the primary cause of evaporative DED is meibomian gland dysfunction (MGD).[3,8,9] Meibomian gland secretions include numerous lipids (e.g., cholesterol, cholesterol esters, wax esters, phospholipids, free fatty acids), which are the primary component of the outermost layer of the tear film.[9−12] In MGD, reduction in meibum secretion, qualitative changes (e.g., increased viscosity, loss of polar or amphiphilic lipids, lipid conformation changes), or both alter the tear film lipid layer, which contributes to tear film instability and increased evaporative water loss.[10,11,13] Tear film instability associated with MGD leads to tear hyperosmolarity, resulting in apoptosis and inflammation of ocular surface cells, all of which contribute to and perpetuate the vicious cycle of DED.[13,14]

Symptoms of DED include irritation, dryness, burning or stinging, and visual disturbances, which may adversely affect patients' quality of life, function, activities of daily living, and work productivity.[8,15,16] Signs of DED, which are assessed in clinical testing, include decreased tear fluid (Schirmer I test), ocular surface damage (fluorescein staining), tear film instability (tear film breakup time), and conjunctival

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redness.[17] There are a number of traditional therapies used for DED associated with MGD: physical therapies (e.g., gland expression, warm compresses, thermal pulsation, intense pulsed light) aim to increase the quality and quantity of meibomian gland secretions, oral medications (e.g., doxycycline, azithromycin) are intended to reduce inflammation or to lower meibum viscosity, and over-the-counter lipid-based artificial tears attempt to replenish the tear film lipid layer temporarily.[18–20] Prescription ophthalmic formulations with immunomodulatory or anti-inflammatory properties (i.e., cyclosporine, lifitegrast, loteprednol etabonate [0.25%, short-term use only]) or both are approved by the United States Food and Drug Administration (FDA) for the treatment of the signs and symptoms of DED[21] but have not been evaluated systematically in patients with MGD. The most recent FDA-approved prescription therapy for DED, varenicline solution nasal spray, targets tear production.[22,23] Therefore, to date, none of the available prescription ophthalmic pharmacologic treatments for DED are specifically labeled to address the dysfunctional tear film lipid layer or DED associated with MGD.

NOV03, a novel, nonaqueous, single-entity, preservative-free, ophthalmic drop consisting of perfluorohexyloctane (an anhydrous, semifluorinated alkane), currently is under review at the FDA in the United States as a topical therapy for DED associated with MGD. NOV03 spreads rapidly across the ocular surface because of its low surface tension; it also causes minimal visual disturbances compared with gel- or ointment-based therapies because its refractive index is similar to that of water.[24,25] After ocular administration in rabbits, NOV03 was detected in tears through 6 hours and in meibomian glands through 24 hours, with minimal systemic exposure.[26] In vitro studies evaluating the effects of NOV03 demonstrated that, when placed over saline, NOV03 reduced the evaporation rate of saline by approximately 80%, suggesting that NOV03 likely forms a layer on the tear film surface to prevent evaporation.[27]

The efficacy and safety of NOV03 were evaluated in a phase 2 randomized controlled trial of patients with DED associated with MGD (SEECASE); results showed significantly greater reduction in the signs and symptoms of DED with NOV03 versus 0.9% saline, with excellent safety and tolerability.[28] The efficacy and safety of NOV03 in the treatment of evaporative DED also are supported by prospective observational studies[29,30] and a small randomized controlled trial[24] of perfluorohexyloctane conducted in Europe. In addition, a prospective, open-label study showed that perfluorohexyloctane was effective in reducing the signs and symptoms of DED in patients with evaporative DED who underwent cataract surgery.[31] This report presents the results of the phase 3 GOBI trial, which evaluated the efficacy and safety of NOV03 in adults with DED associated with MGD.

Methods

Study Design

This was a phase 3, multicenter, randomized, double-masked, saline-controlled trial conducted at 26 investigational sites in the United States between December 2019 and March 2021. Because NOV03 consists of a single chemical entity, a vehicle control group was not an option. Hypotonic saline was selected as the comparator based on input from the FDA. The study was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the tenets of the Declaration of Helsinki. The study protocol was approved by an institutional review board (Sterling Institutional Review Board, Atlanta, Georgia). All patients provided written informed consent before initiation of any study-related procedures. The trial was registered at ClinicalTrials.gov (identifier, NCT04139798).

Patients

Eligible patients were adults ($\geq$ 18 years of age) with a self-reported history of DED in both eyes for $\geq$ 6 months who met all of the following key inclusion criteria in $\geq$ 1 eye at screening and at randomization: tear film break-up time of $\leq$ 5 seconds, ocular surface disease index score of $\geq$ 25, unanesthetized Schirmer I test results of $\geq$ 5 mm, total MGD score of $\geq$ 3, and total corneal fluorescein staining (tCFS) score of $\geq$ 4 and $\leq$ 11 according to the National Eye Institute scale. The MGD score was based on evaluation of secretion of 5 central meibomian glands on the lower eyelid using a Korb Meibomian Gland Evaluator (Tear Science). Each evaluation was scored from 0 to 3 (0 = normal; 1 = thick and yellow, whitish particulate; 2 = paste; 3 = none or occluded), and the total score could range from 0 to 15. If both eyes met the inclusion criteria, the eye with the higher (i.e., worse) tCFS score at baseline was designated as the study eye.

Patients were excluded from participation if they met any of the following criteria: clinically significant slit-lamp findings or abnormal lid anatomic features at screening or baseline including eye trauma, history of Stevens-Johnson syndrome, active blepharitis or active lid margin inflammation that required topical antibiotics or topical steroids; DED secondary to scarring; ocular or periocular malignancy; active ocular allergies; ocular or systemic infection; uncontrolled systemic disease; history of herpetic keratitis; intraocular surgery or ocular laser surgery within the previous 6 months; LipiFlow (Johnson & Johnson Vision Care, Inc), intense pulse light, or other procedure affecting the meibomian glands within the previous 6 months; use of contact lenses within the previous month; or use of topical steroids, topical cyclosporine, lifitegrast, serum tears, or topical glaucoma medication within the previous 60 days. Patients also were excluded if best-corrected visual acuity (BCVA) was 0.7 logarithm of the minimum angle of resolution or worse in both eyes, as assessed with Early Treatment Diabetic Retinopathy Study charts at screening and baseline. Beginning 1 day before baseline and continuing throughout the treatment period, patients were prohibited from wearing contact lenses, undergoing ocular surgery or ocular laser treatment, or using other dry eye treatments, including artificial tears. Physical therapies (e.g., lid scrubs, lid wipes, warm compresses), systemic antibiotics (e.g., tetracyclines), and oral supplements for treatment of ocular conditions were permitted, provided they had been stable within the 30 days before baseline and were maintained throughout the trial.

Treatments

Eligible patients were randomized in a 1:1 ratio via an interactive system to receive either NOV03 or hypotonic saline solution (0.6% sodium chloride, preserved with 0.01% benzalkonium chloride; Fig 1). Randomization was stratified by clinical site and by baseline eye dryness score measured on a visual analog scale (VAS; $<$ 70 vs. $\geq$ 70). Randomization schedules were created by an unmasked statistician not otherwise involved in the trial. Study medication was provided in identical containers such that patients and investigators were masked to treatment assignment. Patients

were instructed to instill 1 drop of study medication into each eye 4 times daily for 8 weeks. Treatment compliance was assessed using patient dosing diaries. Compliance was calculated as the total number of doses administered divided by the total number of doses that should have been administered multiplied by 100.

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), week 4 (day 29 ± 2), and week 8 (day 57 ± 2). Efficacy assessments included investigator-rated corneal fluorescein staining and patient-reported symptom severity (e.g., eye dryness, burning or 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 scale from grade 0 (no staining) to grade 3 (heavy staining); the tCFS score was the sum of the individual scores (maximum of 15). Patients rated eye dryness and other symptoms, considering both eyes together, using a VAS ranging from 0 (no discomfort) to 100 (maximal discomfort).

The primary efficacy end points were change from baseline at week 8 in tCFS score and VAS eye dryness score. Key secondary efficacy end points were change from baseline in VAS dryness score at week 2, tCFS score at week 2, VAS burning or stinging score at week 8, and central corneal fluorescein (cCFS) staining score at week 8. Additional end points 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 $\geq$ 3 steps on the National Eye Institute scale) at week 8, and the proportion of responders for eye dryness (defined as $\geq$ 30% reduction in VAS score) at week 8. Safety assessments included adverse events (AEs), BCVA, slit-lamp biomicroscopy, intraocular pressure, and dilated funduscopy.

Statistical Methods

Sample size was calculated based on the following assumptions: for the primary ocular sign, 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 of 2.8 units; for the primary ocular symptom, change in VAS dryness score, a −10-unit difference between treatment groups (NOV03 minus saline) in mean change from baseline at week 8, and a common standard deviation of 28 units. These assumptions were informed by results from the prior phase 2 study of NOV03.[28] Under both assumptions, a sample size of 250 per treatment group (for a total of approximately 280 randomized patients per group, assuming 10% discontinuation rate) was chosen to yield > 90% power to detect a significant difference at the 2-sided α value of 0.05.

The primary analysis was conducted on the full analysis set (FAS), which included all patients who were assigned randomly to a treatment group (NOV03 or saline) and received study medication, with no imputation of missing data. To control the type I error rate, the 2 primary end points (tCFS, VAS dryness score) were evaluated in the FAS using hierarchical fixed sequence testing, 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 end points demonstrated statistical superiority of NOV03 versus saline (2-sided $\alpha = 0.05$), then the key secondary end points were tested hierarchically in the following order: VAS dryness score at week 2, tCFS score at week 2, VAS burning or stinging score at week 8, and cCFS score at week 8. The proportion of study eyes (or patients) that met predefined criteria (e.g., $\geq$ 3-step improvement in tCFS score, $\geq$ 30% reduction in VAS dryness score) was compared between treatment groups using logistic regression analysis adjusting for baseline score at each measured follow-up visit, and odds ratios were calculated for NOV03 versus saline.

The per-protocol population included patients in the FAS who did not have significant protocol deviations and who completed the study. A sensitivity analysis evaluated NOV03 versus saline on the primary end points in the per-protocol population using the primary analytic method (analysis of covariance), with no imputation of missing data. Additional sensitivity analysis included comparison of treatment groups on the primary end points in the FAS using 2-sample *t* tests (equal variance assumed), Wilcoxon rank-sum tests, and mixed-effect repeated measures analysis.

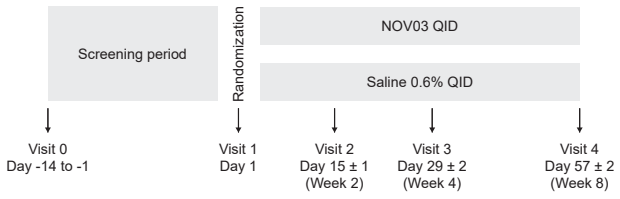

Figure 1. Diagram showing study design. QID = 4 times daily.

Results

Patients

A total of 599 patients were randomized, and 597 patients were treated (NOV03, n = 303; saline, n = 294; Fig 2). Of these, 289 patients in the NOV03 group (95.4%) and 279 patients in the control group (94.9%) completed the study. Demographic and baseline disease characteristics were well balanced between the treatment groups (Table 1). Other than DED, common occurrences ($\geq$ 10% of patients) in ocular medical history were cataract, intraocular lens implantation (13.9%), vitreous detachment, and blepharitis. For nonocular medical history, the most common occurrences ($\geq$ 20% of patients) were hypertension, postmenopause, and hypercholesterolemia.

On the basis of dosing recorded in the dosing diaries, patient compliance with dosing was high and similar between treatment groups, with 99.3% of patients in the NOV03 group and 99.0% of patients in the saline group considered compliant (defined as 80%–120% of expected doses administered).

Major protocol deviations were recorded for 12 patients in each treatment group, who were excluded from the per protocol population. The most common major protocol deviations were related to study visit or schedule deviations (2.2% of patients overall) and use of prohibited medications with the potential of altering signs or symptoms of DED (0.8% of patients overall).

Efficacy

Primary End Points. At week 8, NOV03-treated patients experienced significantly greater improvement from baseline in both tCFS score and VAS dryness score versus patients who received saline (Fig 3), meeting both primary efficacy end points. For change from baseline to week 8 in tCFS score, the least square (LS) mean treatment difference was −0.97 (95% confidence interval [CI]: −1.40, −0.55; $P < 0.001$). For change from baseline to week 8 in VAS dryness score, the LS mean treatment difference was −7.6 (95% CI: −11.8, −3.4; $P < 0.001$).

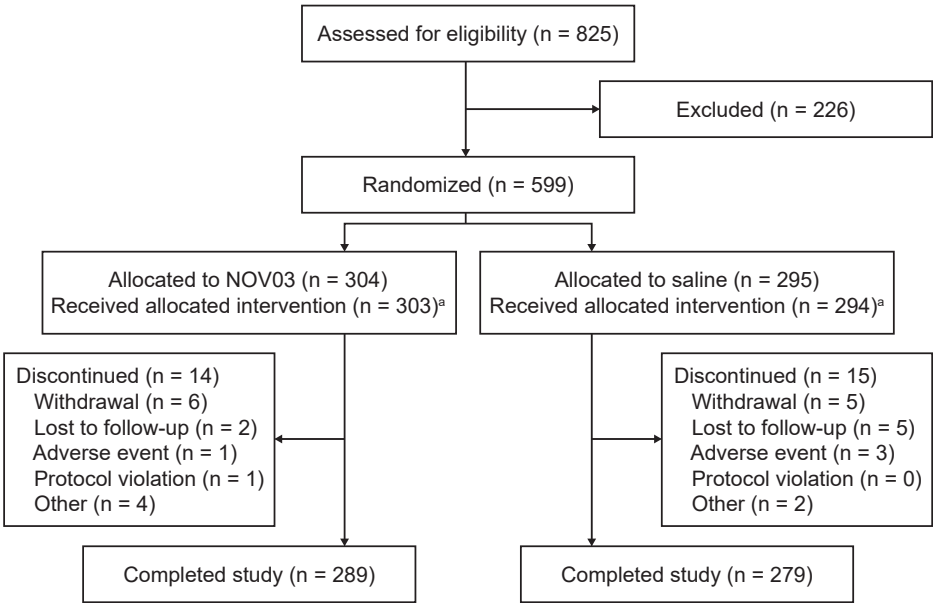

Figure 2. Flow diagram showing patient disposition. [a]Full analysis set.

For both primary end points, results observed in the sensitivity analyses based on the per-protocol population (same analytic method as the primary analysis) and the FAS (2-sample *t* tests, Wilcoxon rank-sum tests, mixed-effect repeated measures analysis) were consistent with the main findings.

Key Secondary End Points. Because NOV03 was statistically superior to saline for both primary end points, the 4 key secondary end points were tested hierarchically; mean improvement from baseline was significantly greater for NOV03 versus saline for all key secondary end points (Fig 4). The LS mean treatment difference was −4.7 (95% CI: −8.2, −1.2) for change from baseline in VAS dryness score at week 2 ($P = 0.009$), −0.6 (95% CI: −0.9, −0.2) for change from baseline in tCFS score (study eye) at week 2 ($P = 0.001$), −5.5 (95% CI: −9.5, −1.6) for change from baseline in VAS burning or stinging score at week 8 ($P = 0.006$), and −0.2 (95% CI: −0.4, −0.1) for change from baseline in cCFS score (study eye) at week 8 ($P < 0.001$).

Table 1. Demographic and Baseline Clinical Characteristics

Characteristic	NOV03 (n = 303)	Saline (n = 294)
Age, yrs		
Mean (range)	60.3 (20–87)	61.6 (19–88)
≥ 65 years	134 (44.2)	146 (49.7)
Female sex	219 (72.3)	214 (72.8)
Race		
Asian	34 (11.2)	28 (9.5)
Black	53 (17.5)	55 (18.7)
White	212 (70.0)	204 (69.4)
Other	3 (1.0)	7 (2.4)
Baseline ocular characteristics		
tCFS score, study eye	6.7 ± 1.8	6.7 ± 1.9
Eye dryness VAS score	66.5 ± 19.1	66.8 ± 18.7
Eye burning or stinging VAS score	53.0 ± 26.7	52.1 ± 26.6
Total MGD score	7.4 ± 3.1	7.7 ± 3.2
TFBUT in the study eye, seconds	3.2 ± 0.8	3.3 ± 0.8
Unanesthetized Schirmer I test in the study eye, mm	12.0 ± 8.3	11.7 ± 7.6
OSDI score	53.9 ± 17.6	54.4 ± 17.0
BCVA (logMAR)	0.07 ± 0.1	0.09 ± 0.1

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; MGD = meibomian gland dysfunction; OSDI = ocular surface disease index; tCFS = total corneal fluorescein staining; TFBUT = tear film breakup time; VAS = visual analog scale.
Data are presented as no. (%) or mean ± standard deviation, unless otherwise indicated.

Other Secondary End Points. Consistent with the results for the primary and key secondary end points, improvements on most other secondary end points were significantly greater with NOV03 versus saline. The proportion of tCFS responders (≥ 3-step improvement in tCFS score) at week 8 was significantly greater in the NOV03 group (41.2%) than in the control group (27.2%), with an odds ratio of 1.88 (95% CI: 1.3, 2.7; $P < 0.001$). Similarly, the proportion of eye dryness responders (≥ 30% reduction in VAS dryness score) at week 8 was significantly greater in the NOV03 group (57.4%) than in the control group (46.6%), with an odds ratio of 1.55 (95% CI: 1.1, 2.2; $P = 0.010$). The LS mean change from baseline in VAS dryness score at week 4 was numerically greater in the NOV03 group (−20.9) than in the control group (−18.2), but the difference was not statistically significant ($P = 0.152$). In addition to week 8 (primary end point) and week 2 (key secondary end point), LS mean change from baseline in tCFS score at week 4 was significantly more improved in the NOV03 group (−2.13) than in the control group (−1.52; $P < 0.001$). In addition to week 8 (key secondary end point), LS mean change from baseline in cCFS score was significantly greater for NOV03 versus control at week 2 (−0.31 vs. −0.15; $P = 0.006$) and week 4 (−0.45 vs. −0.22; $P < 0.001$).

Safety

Ocular AEs were experienced by 9.6% of patients in the NOV03 group and 7.5% of patients in the saline group; ocular AEs were considered by the investigator to be related to study medication in 6.3% and 3.1% of patients, respectively (Table 2). No serious ocular AEs occurred. Most ocular AEs were mild or moderate in

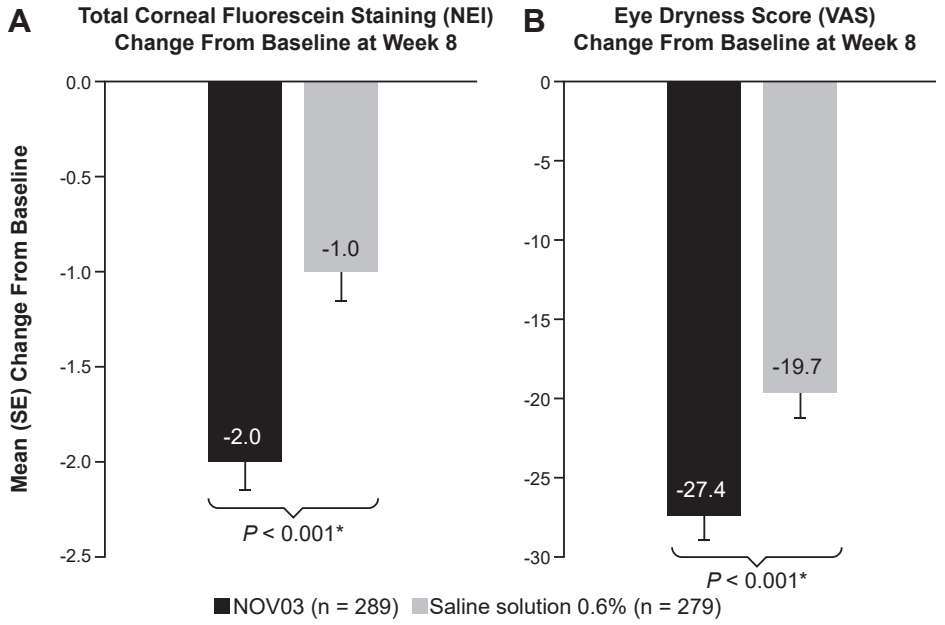

Figure 3. Bar graphs showing the mean change from baseline at week 8 for the primary efficacy outcomes: (**A**) total corneal fluorescein staining on the National Eye Institute (NEI) scale (5 regions, score of 0–3 per region, maximum total score of 15) and (**B**) eye dryness score on a visual analog scale (VAS) ranging from 0 to 100. *P value from analysis of least square mean treatment difference. SE = standard error.

severity; 1 patient receiving NOV03 experienced a severe AE of eye irritation. Ocular AEs led to treatment discontinuation in 1 patient in the NOV03 group (eye irritation) and 3 patients in the saline group (conjunctivitis, dry eye, punctate keratitis). The most common (incidence ≥ 1%) ocular AEs in the NOV03 group were blurred vision (mostly mild and transient), instillation site pain, and eye discharge (Table 2). No clinically meaningful changes were observed in BCVA, slit-lamp examination findings, intraocular pressure, or dilated funduscopy examination results.

Nonocular AEs were experienced by 9.6% of patients in the NOV03 group and 7.5% of patients in the saline group; none of these AEs were attributed to study medication. No severe nonocular AEs occurred, and no nonocular AEs led to study discontinuation. One patient in the saline group experienced a serious nonocular AE (acute chest pain).

Discussion

GOBI was the first phase 3 study to evaluate the efficacy and safety of NOV03. This multicenter, randomized, double-masked, saline-controlled trial enrolled patients with DED associated with MGD. The study met both the primary sign end point (change in tCFS) and the primary symptom end point (change in patient-reported eye dryness). For both end points, change from baseline at week 8 was significantly greater with NOV03 versus hypotonic saline. NOV03 also was superior to hypotonic saline for all 4 key secondary end points: rapid onset of effect to reduce tCFS and eye dryness occurred as early as week 2 (the first assessment after initiating treatment), as well as improvement in an additional sign (cCFS) and an additional symptom (eye burning or stinging) at week 8. In all, NOV03 demonstrated statistically significant and clinically meaningful improvements in the signs and symptoms of DED associated with MGD. There are currently no FDA-approved, prescription pharmacologic treatments for DED associated with MGD, and the results of this study suggest that NOV03 may potentially fulfill this unmet need.

Demonstration of consistent treatment benefits for both signs and symptoms of DED in 1 trial has been challenging and rarely has been shown, likely because of variability of clinical end points.[17] Notably, the GOBI study demonstrated a consistent treatment effect on signs and symptoms over a number of time points, replicating results from a previous phase 2 trial (SEECASE) that found significantly greater improvements with NOV03 relative to an isotonic saline comparator (0.9%).[28] The GOBI study had the added rigor of using hypotonic saline (0.6%) as the control treatment; hypotonic solutions can reduce tear film hyperosmolarity, which usually accompanies DED, and have been shown to be effective in treatment of DED.[32] These consistent results for sign and symptom end points across studies suggest that NOV03 may be a highly effective treatment for DED associated with MGD.

The tear film lipid layer plays an important role in the cause and treatment of DED.[33] Lipids are a complex group of molecules in terms of both structure and function.[34] The tear film lipid layer includes an outer layer of nonpolar lipids and an inner layer of polar or amphiphilic lipids, which are derived primarily from meibomian gland secretions.[12,34] Meibomian gland dysfunction alters the tear film lipid layer and contributes to tear film instability.[11,13,35] Although the precise mechanism of action is not known currently, NOV03 is thought to spread over the ocular surface to form a long-lasting, antievaporative barrier, thereby preventing evaporation of the aqueous component

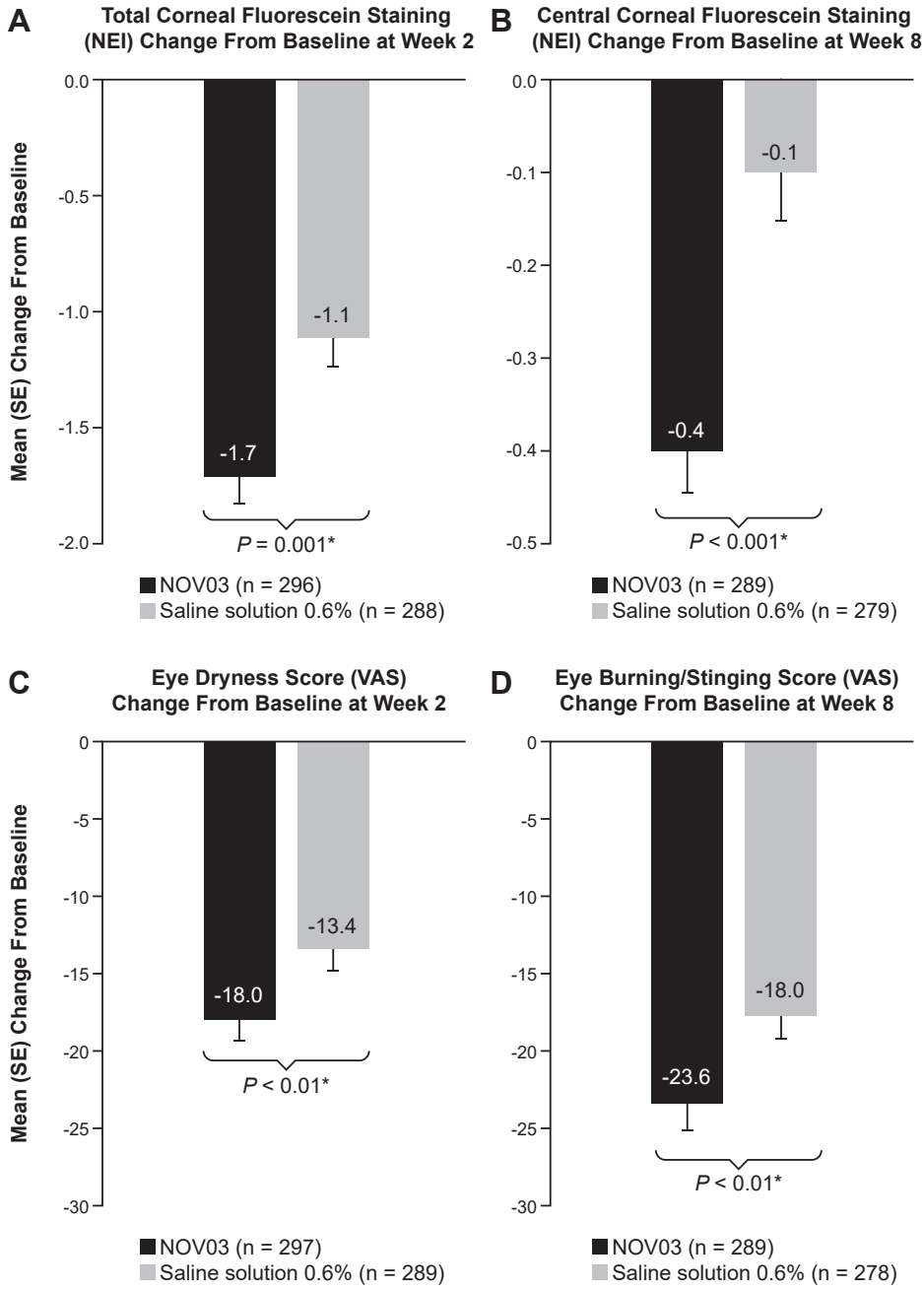

Figure 4. Bar graphs showing the mean change from baseline for key secondary efficacy end points: (**A**, **B**) total and central corneal fluorescein staining on the National Eye Institute (NEI) scale (5 regions, score of 0–3 per region, maximum total score of 15) at week 2 and week 8, respectively, and (**C**, **D**) eye dryness scores and eye burning or stinging scores on a visual analog scale (VAS) ranging from 0 to 100. *P value from analysis of least square mean treatment difference. SE = standard error.

of the tear film, which reduces the signs and symptoms of DED.[24,25] It also may act to reduce friction during blinking. In animal studies, administration of NOV03 produced improvement in the quality of the tear film lipid layer.[25] In animal studies, NOV03 also has been shown to penetrate meibomian glands,[26] although the implications of this finding as yet are unclear. The current study included patients with a range of MGD severity at baseline (mean MGD score, 7.5; range, 3–15), and thus it is expected that, even for patients with little to no functional production of meibum from the glands (for whom mechanical expression of glands cannot restore meibum to the tear film), NOV03 could improve the signs and symptoms of DED. Additional research into the mechanism of action of NOV03 is ongoing.

In this study, NOV03 administered 4 times daily for 8 weeks generally was safe and well tolerated. Only 1 AE was considered to be severe in intensity (eye irritation), and

Table 2. Summary of Ocular AEs

Parameter	NOV03 (n = 303)	Saline (n = 294)
Patients with ≥ 1 ocular AE*	29 (9.6)	22 (7.5)
Mild	25 (8.3)	18 (6.1)
Moderate	3 (1.0)	4 (1.4)
Severe	1 (0.3)	0 (0.0)
Drug-related ocular AE†	19 (6.3)	9 (3.1)
Serious ocular AE	0 (0.0)	0 (0.0)
Ocular AE leading to discontinuation	1 (0.3)	3 (1.0)
Most common ocular AEs‡		
Vision blurred	9 (3.0)	1 (0.3)
Instillation site pain	3 (1.0)	3 (1.0)
Conjunctival hemorrhage	1 (0.3)	4 (1.4)
Eye discharge	3 (1.0)	0 (0.0)
Punctate keratitis	0 (0.0)	3 (1.0)

AE = adverse event.
Data are presented as no. (%) of patients with an AE in either eye.
*Patients instilled drops in both eyes.
†Considered by the investigator as suspected or related to study medication.
‡Incidence of ≥ 1% in either treatment group.

this was the only AE leading to discontinuation of NOV03. No serious AEs were reported in the NOV03 group. The most common ocular AE was blurred vision, which occurred in 3.0% of patients using NOV03. It was mild in severity and transient in nature, typically resolving within minutes of onset. NOV03 drops are preservative free, which may improve tolerability in patients with DED, as supported by the low rate of instillation site reactions observed in this study. By contrast, preservatives may exacerbate the signs and symptoms of DED.[36]

Study limitations include the relatively short treatment period (8 weeks) and the exclusion of patients with severe dry eye (tCFS score, > 11). The hypotonic saline drop used by control patients was preserved with benzalkonium chloride, whereas the NOV03 drop was not; thus, outcomes in control patients may have been confounded somewhat by effects of that preservative. It was not possible to control for the unique physicochemical properties of NOV03. Although both NOV03 and saline are clear, colorless drops, the NOV03 drop is considerably smaller, with a much lower surface tension. Therefore, one cannot rule out the possibility that some patients may have been aware of being assigned a distinctive treatment, as opposed to saline, despite being masked. However, the choice of hypotonic saline as a control is a study strength, given hypotonic solutions have shown efficacy in the treatment of DED.[37,38] Assessments at the slit lamp were performed by the investigators at each site without further validation by an independent assessor. Because DED is a chronic condition, longer-term evaluation of treatment is needed; a recently completed 12-month, open-label safety study of NOV03 will provide additional information regarding long-term use.

Conclusions

This phase 3 study of patients with DED associated with MGD provides statistically significant and clinically meaningful evidence of the reduction of signs and symptoms of DED during 8 weeks of treatment with NOV03. NOV03 was well tolerated in this population.

Footnotes and Disclosures

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[5] Bausch + Lomb, Bridgewater, New Jersey.

*Members of the GOBI Study Group appear in the Appendix (www.aaojournal.org).

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s):

J.T.: Investigator − Alcon, Aramis Biosciences, Bausch + Lomb, Claris Bio, Novaliq, Novartis, Oyster Point Pharma, Sylentis, Tarsus, Tear Solutions, Trefoil Therapeutics, Visus Therapeutics

G.J.B.: Investigator − Aerie, Alcon, Allakos, Allergan/AbbVie, Bausch + Lomb, Claris Bio, Dompe, Kala, Novaliq, Sight Sciences, Tarsus, Tear Film Innovations, Tear Solutions; Consultant − Aerie, Alcon, Allergan/AbbVie, Bausch + Lomb, Dompe, Kala, Novartis, Sight Sciences, Sun, Tarsus, Tear Solutions; Lecturer − Alcon, Allergan/AbbVie, Bausch + Lomb, Dompe, Kala, Novartis, Sight Sciences, Sun, Tarsus

D.L.W.: Grant support − Bausch + Lomb, Novaliq

S.K.: Employee − Novaliq

J.L.V.: Employee − Bausch + Lomb

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HUMAN SUBJECTS: Human subjects were included in this study. The study was conducted in accordance with the Good Clinical Practice guideline of the International Council for Harmonisation and the tenets of the Declaration of Helsinki. The study protocol was approved by an institutional review board (Sterling Institutional Review Board, Atlanta, Georgia). All patients provided written informed consent before initiation of any study-related procedures.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Krösser, Vittitow

Analysis and interpretation: Tauber, Berdy, Wirta, Krösser, Vittitow

Data collection: Tauber, Berdy, Wirta

Obtained funding: N/A

Overall responsibility: Tauber, Berdy, Wirta, Krösser, Vittitow

Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best-corrected visual acuity; **cCFS** = central corneal fluorescein staining; **CI** = confidence interval; **DED** = dry eye disease; **FAS** = full analysis set; **FDA** = United States Food and Drug Administration; **LS** = least square; **MGD** = meibomian gland dysfunction; **tCFS** = total corneal fluorescein staining; **VAS** = visual analog scale.

Keywords:
Clinical trial, Dry eye disease, Meibomian gland dysfunction, NOV03, Perfluorohexyloctane.

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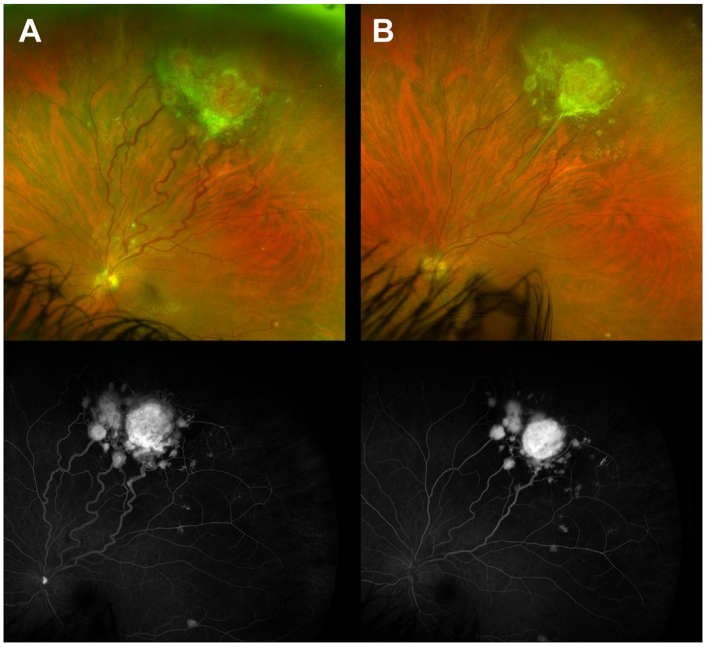
Pictures & Perspectives



Systemic Treatment Reduces Von-Hippel-Lindau–Associated Retinal Capillary Hemangioblastoma

A 24-year-old man with Von-Hippel-Lindau syndrome and central nervous system (CNS) hemangioblastomas was found to have multiple leaking retinal capillary hemangioblastomas in the superotemporal periphery of the left eye (**A**). Systemic treatment was initiated with Belzutifan, a hypoxia-inducible factor-2α inhibitor. There was marked improvement in the engorgement and tortuosity of the feeding arterioles and draining veins, and a reduction in the number and size of the retinal capillary and CNS hemangioblastomas after 6 months of treatment (**B**) (Magnified version of Fig **A**-**B** is available online at www.aaojournal.org).

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Footnotes and Disclosures

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