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# A Randomized Clinical Study (SEECASE) to Assess Efficacy, Safety, and Tolerability of NOV03 for Treatment of Dry Eye Disease

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**Purpose:** NOV03 has a unique dual mode of action to address dry eye disease (DED) associated with meibomian gland dysfunction. SEECASE evaluated the efficacy, safety, and tolerability of NOV03 at 2 dosing regimens compared with a saline comparator in patients with DED.

**Methods:** SEECASE was a prospective, multicenter, randomized, double-masked, saline-controlled clinical study. A total of 336 DED patients [tear film breakup time ≤5 seconds, abnormal meibum secretion, total corneal fluorescein staining (tCFS) score of $4 \leq X \leq 11$ (National Eye Institute scale), Schirmer of ≥5 mm] were randomized in a 2:2:1:1 manner to NOV03 4 times daily (QID), NOV03 twice daily (BID), saline BID, and saline QID, respectively. The primary efficacy endpoint was tCFS staining at 8 weeks for both regimens. Secondary endpoints included visual analog scales and the Ocular Surface Disease Index questionnaire for symptom assessment.

**Results:** The study met its primary endpoint, change from baseline of tCFS over control, for both dosing regimens QID and BID ($P < 0.001$ and $P = 0.009$, respectively). NOV03 also showed pronounced improvement in various symptoms. For the Eye Dryness Score, changes from baseline were statistically significant compared with those of the control at week 8 [$P < 0.001$ (QID) and $P = 0.002$ (BID)]. Benefits on tCFS and symptoms started at 2 weeks after start of treatment and were maintained over the study duration. The effects were dosing schedule dependent. NOV03 was well tolerated with instillation site reactions below 3% in both treatment regimes.

**Conclusions:** The SEECASE study demonstrated that NOV03 improves signs and symptoms in patients with highly symptomatic evaporative dry eye disease.

**Key Words:** dry eye disease, keratoconjunctivis sicca, meibomian gland dysfunction, perfluorohexyloctane, clinical trial, clinical study

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Dry eye disease (DED) is one of the most common ocular surface disorders, and meibomian gland dysfunction (MGD) is considered as a key component in the pathogenesis of dry eye.[1] The role of meibomian glands is secretion of lipids that form the outermost layer of the tear film; these lipids spread easily, promoting stability and reducing tear evaporation. MGD is characterized by gland obstruction and quantitative and/or qualitative changes in meibum secretion that contributes to the evaporative loss of the tear film and, thus, leading to evaporative DED.[2]

Epidemiological and clinical evidence suggest that most DED is evaporative in nature.[3] Lemp et al[4] reported ~60% to 80% of DED patients having evaporative DED. For evaporative DED associated with MGD, treatment options are currently limited. The principle goal of all treatments for MGD is to increase the quality and quantity of meibomian expressate. Physical therapies such as eyelid hygiene, warm compresses, intense pulsed light, thermal pulsation system (LipiFlow), or lid expression aim to increase lipid outflow[5] whereas lipid containing artificial tears and emulsions aim to substitute the lipid layer.[6] Substitution of the lipid layer, however, is challenging given its complex structure.[7,8]

NOV03 is an investigational drug in the United States; it is a preservative-free, sterile ophthalmic solution with a unique dual mode of action that affects known abnormalities in the lipid layer and meibomian glands. The sole ingredient of NOV03 is the inert and anhydrous semifluorinated alkane perfluorohexyloctane (F6H8). NOV03 rapidly spreads across the ocular surface because of its low surface/interfacial tension and interacts with the lipophilic part of the tear film, forming a layer at the tear film–air interface. The result of this is prevention of evaporation of the aqueous phase of the

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tears.[9,10] In addition, NOV03 penetrates meibomian glands, where it has been reported to interact with and dissolve the altered, viscous meibum in the glands.[11] In Europe, Australia, and New Zealand, eye drops with an equivalent composition (100% perfluorohexyloctane) are already registered and marketed as medical device (NovaTears; Novaliq GmbH, Heidelberg, Germany/EvoTears; URSAPHARM GmbH, Saarbrücken, Germany). Three postmarket clinical follow-up studies (NT-001, NT-002, NT-003) and 1 interventional, randomized, single-center study (NT-004), all conducted in Europe, evaluated this perfluorohexyloctane containing eye drop (NovaTears; Novaliq GmbH), administered 4 times daily for 4 to 13 weeks. These studies found that NovaTears was both safe and well tolerated and efficacious in treating signs and symptoms and stabilizing the tear film in evaporative DED mainly caused by MGD.[12–14] The clinical study NT-004 further demonstrated that perfluorohexyloctane increases tear film and lipid layer thicknesses compared with a comparator, saline solution.[9] Recently, perfluorohexyloctane was also evaluated as ocular surface treatment after cataract surgery in patients with evaporative dry eye disease, suggesting its suitability in postoperative management.[15]

This report presents the results of the SEECASE study evaluating the efficacy and safety of NOV03 ophthalmic solution compared with saline ophthalmic solution in the treatment of DED associated with MGD. The primary goal of the development program, however, is a DED indication. Consequently, efficacy was primarily assessed using regulatory accepted and standardized DED metrics. There are no such metrics for MGD; all recent MGD trials used DED metrics and a heterogenous mix of nonvalidated MGD endpoints.[16] The primary endpoint of the SEECASE study was change from baseline (CFB) to week 8 in total corneal fluorescein staining (tCFS). Several symptom assessments such as Eye Dryness Score measured using visual analog scale (VAS), VAS for other symptoms such as burning/stinging, itching, blurred vision, and sensitivity to light, and Ocular Surface Disease Index (OSDI) were evaluated to assess the effect of NOV03 on DED symptomatology.

## METHODS

### Study Design

This was a phase 2, randomized, multicenter, double-masked, saline-controlled study designed to evaluate the efficacy, safety, and tolerability of NOV03 Ophthalmic Solution at 2 dosing regimens [4 times a day (QID) and twice a day (BID)] in subjects with signs and symptoms of DED. The study was performed at 12 investigational sites in the United States. The study protocol was reviewed and approved by the Alpha Institutional Review Board, San Clemente, CA. All subjects were required to provide written informed consent before study enrollment or the conduct of any study-related procedures. The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization guideline on Good Clinical Practices, the Health Insurance Portability and Accountability Act, and all other applicable regulatory requirements and laws. The study is registered on ClinicalTrials.gov (NCT03333057).

After informed consent was obtained, patients who met all eligibility requirements were randomized to 1 of 4 treatment arms to receive BID or QID treatment with either NOV03 or saline, stratified by investigational site, in a 2:2:1:1 ratio. Randomization was centralized across study centers. An interactive web response system was used for randomization. Investigators, study personnel, patients, and sponsor were all masked to study treatment. NOV03 and saline bottles had identical appearance. Treatment duration of the allocated treatment was 8 weeks. Patients were instructed to instill either BID or QID 1 drop in each eye. Patients presented for a total of 5 study visits: visit 0, screening, within 14 days before randomization; visit 1, at day 1, baseline/randomization visit; visit 2, at week 2/day 15 $\pm$ 1; visit 3, at week 4/day 29 $\pm$ 2; and visit 4, at week 8/day 57 $\pm$ 2, or at study exit (Fig. 1).

### Patients

Adult patients aged $\geq$18 years, with a patient-reported history of DED in both eyes, were enrolled into the study if 1 eye (the same eye) met the following main inclusion criteria at screening and at randomization time: tear film breakup time (TFBUT) $\leq$5 seconds, Schirmer I test $\geq$5 mm, MGD score $\geq$3, total corneal fluorescein staining (tCFS) score of between 4 and 11, and OSDI score $\geq$25. Patients were excluded from participation if any of the following were present: clinically significant slit lamp findings or abnormal lid anatomy at screening including eye trauma, Stevens-Johnson syndrome, active blepharitis or active lid margin inflammation; DED secondary to scarring; ocular or periocular malignancy; intraocular surgery or ocular laser surgery within previous 6 months; active ocular allergies; use of contact lenses within 1 month before screening; LipiFlow procedure within 6 months before inclusion; ongoing ocular or systemic infection; uncontrolled systemic disease or history of herpetic keratitis; and use of topical steroids, topical cyclosporine, lifitegrast, serum tears, or topical anti-glaucoma medication within 60 days before screening.

Eyes were eligible for analysis if they met all inclusion criteria and none of the exclusion criteria. For cases in which both eyes were eligible for analysis, the eye with the highest tCFS score [National Eye Institute (NEI) scale] at baseline was deemed to be the "study eye." If the tCFS score at baseline was the same in both qualifying eyes, then the right eye was selected as the study eye.

### Assessments of Outcome Measures

Signs and symptoms of dry eye, in addition to safety parameters, were assessed at screening, baseline (day 1, predose), and again during the 3 follow-up visits (week 2, day 15 $\pm$ 1; week 4, day 29 $\pm$ 2; and week 8, day 57 $\pm$ 2). The primary efficacy outcome assessment of the study was tCFS, assessed in each eye using the NEI scale, which ranges from 0 to 3 for each of the 5 areas of the cornea. Symptom assessments were performed using VAS ranging from 0 to 100 scale with 0 = no discomfort and 100 = maximal discomfort for

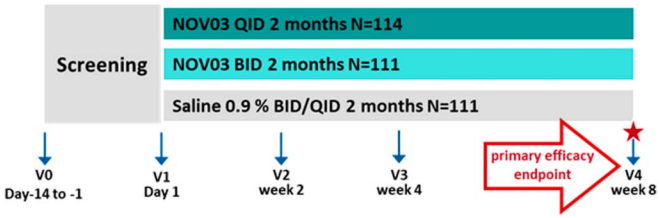


**FIGURE 1.** Study design. Eligible patients entered at visit 1 and were randomized to NOV03 QID, NOV03 BID, saline QID, or saline BID. Primary analysis took place at visit 4 (day 57 = week 8). (The full color version of this figure is available at www.corneajrnl.com.)

the following symptoms: severity of dryness (= Eye Dryness Score), burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, and pain. In addition, frequency of dryness and awareness of dry eye symptoms was assessed using VAS ranging from 0 to 100 scale with 0 = never and 100 = all of the time. In addition, symptoms were assessed using the OSDI questionnaire, a composite endpoint built on 12 questions with total score ranging from 0 to 100, with higher scores representing a worse condition. Further assessments included the following: CFS subregions (NEI scale); conjunctival staining (Oxford scale) by measuring lissamine uptake with scores ranging from 0 to 5 for nasal and temporal regions, with higher scores representing a worse condition; unanesthetized Schirmer I test; TFBUT; and meibomian glands assessment. For the latter, 5 central glands on lower eyelid were evaluated, each was scored from 0 to 3; 0 = normal; 1 = thick/yellow, whitish, particulate; 2 = paste; and 3 = none/occluded; the total MGD score ranged from 0 to 15.

Safety assessments included treatment-emergent adverse events (TEAEs) and the following ophthalmic assessments: visual acuity, slit lamp biomicroscopy, intraocular pressure, and dilated fundoscopy. TEAEs were defined as an event that emerges during treatment having been absent pretreatment or worsens relative to the pretreatment state (International Conference on Harmonization E9 guideline). The investigator was responsible for determining the AE severity and relationship to the drug. All AEs were coded using the Medical Dictionary for Regulatory Activities Version 20.1. In addition, blood pressure, heart rate, and safety laboratory tests were performed. Blood samples for determination of perfluorohexyloctane concentration were collected from 77 subjects at selected qualified investigational sites, with the goal of having samples from minimum 20 subjects for each of the active treatment arms.

## Statistical Methods

Sample size was calculated as follows: for the primary sign endpoint, change in total corneal staining, a 0.8-unit difference, and a common SD of 1.9 between the active arm and the combined saline control arm in mean CFB to week 8 was assumed based on findings from earlier studies. Under this assumption, a sample size of 90 subjects/arm (for a total of 300 randomized subjects, assuming 10% dropout rate) was chosen to yield 80% power to detect a significant difference at the 2-sided $\alpha = 0.05$ level.

The intention-to-treat (ITT) population and the safety population included all randomized subjects who received $\geq 1$ dose of investigational product. Analyses conducted using the ITT population were based on treatment assigned, whereas analyses conducted using the safety population were based on treatment received. The efficacy analyses were primarily based on the ITT population. The comparison analysis was conducted using a repeated measures model with treatment, site, visit, and treatment by visit interaction as fixed categorical factors and baseline as a continuous covariate, using an unstructured covariance matrix. The primary evaluation of efficacy of the active arms was conducted against a combined saline group (BID and QID saline arms). Point estimate and corresponding 95% confidence interval (CI) for the treatment difference of both NOV03 treatment groups against the combined saline group are presented. The primary efficacy analysis for the QID and BID NOV03 groups was conducted in a hierarchical manner to control for inflation of type 1 error rate due to multiple hypotheses—the hypothesis testing for the BID arm versus saline was to proceed only if the QID arm versus saline comparison was statistically significant.

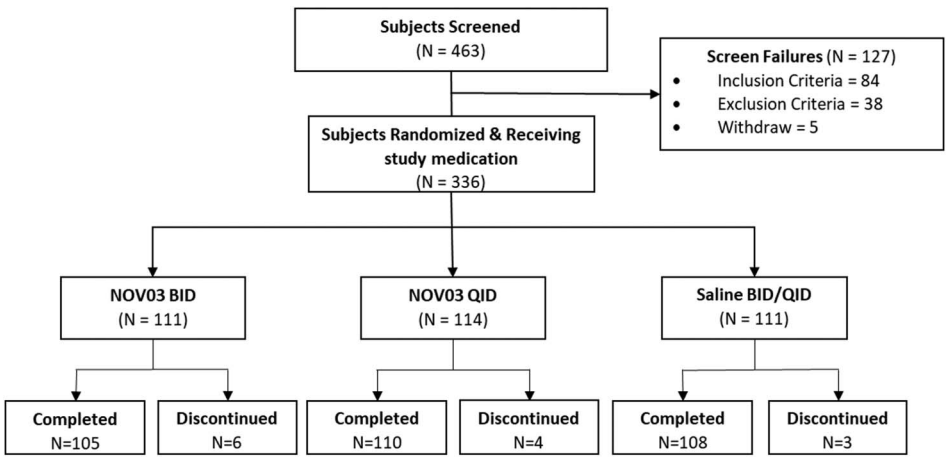


**FIGURE 2.** Patient disposition. In total, 463 patients were screened, and 336 patients were randomized to NOV03 BID (N = 111), NOV03 QID (N = 114), saline BID, or saline QID (N = 111 total). In the NOV03 QID group, 4 patients discontinued, 2 patients withdrew consent, 1 patient was lost to follow-up, and 1 patient discontinued due to pregnancy. In the NOV03 BID group, 6 patients discontinued, 3 patients withdrew consent, 2 patients were noncompliant, and 1 patient discontinued due to an adverse event. In the saline groups, 3 patients discontinued, 2 withdrew consent, and 1 discontinued due to an adverse event.

**TABLE 1.** Demographic and Baseline Clinical Characteristics

| | NOV03 QID (N = 114) | NOV03 BID (N = 111) | Saline QID+BID (N = 111) | Total (N = 336) |
|---|---|---|---|---|
| Age, yrs, mean (min, max) | 53.0 (22, 86) | 54.0 (22, 86) | 53.8 (19, 85) | 53.6 (19, 86) |
| Sex, n (%) | | | | |
| Women | 79 (69.3) | 84 (75.7) | 80 (72.1) | 243 (72.3) |
| Men | 35 (30.7) | 27 (24.3) | 31 (27.9) | 93 (27.7) |
| Baseline efficacy | | | | |
| Mean tCFS (SD) | 7.0 (2.2) | 6.7 (2.1) | 6.7 (2.0) | 6.8 (2.1) |
| Mean total OSDI score (SD) | 55.3 (17.4) | 55.5 (18.6) | 54.0 (16.9) | 55.0 (17.6) |
| Mean Schirmer I test, mm (SD) | 14.6 (8.9) | 15.0 (9.3) | 14.3 (8.8) | 14.6 (9.0) |
| Mean MGD score (SD) | 7.6 (3.5) | 7.3 (3.4) | 8.0 (3.9) | 7.6 (3.6) |
| Mean TFBUT, s (SD) | 3.0 (0.93) | 2.9 (0.91) | 3.0 (0.91) | 3.0 (0.91) |
| Mean VAS Dryness Score (SD) | 68.6 (21.8) | 70.0 (19.6) | 66.8 (21.7) | |
| Artificial tears (stop within 20 d before baseline), n (%) | 51 (45) | 42 (38) | 52 (47) | 145 (43) |
| Ongoing lid scrubs, lid wipes, and warm compresses | 10 | 8 | 1 | 19 |

All secondary sign and symptom endpoints were analyzed using a similar repeated measures model as used for the primary analysis. The incidence of ocular and nonocular TEAEs was summarized descriptively for the 2 active arms and the combined saline arm by system organ class and by preferred term.

# RESULTS

## Subject Disposition

From the 463 patients screened, 336 were enrolled into the study with the first subject enrolled in December 2017 and the last subject evaluated in May 2018. The 336 subjects were randomized into their respective treatment groups as follows: 111 to the NOV03 BID group, 114 to the NOV03 QID group, and 111 to the combined saline group. A total of 127 subjects were screen failures for the following reasons: unmet inclusion criteria (84), met exclusion criteria (38), and withdrawal of consent (5). A total of 105 (95%) subjects in the NOV03 BID group, 110 (96%) in the NOV03 QID group, and 108 (97%) in the saline group completed the study (Fig. 2).

Protocol deviations were classified before database lock and unmasking. Ten major protocol deviations were recorded in 10 subjects and were as follows: failure to follow instructions (2), wrong kit or dosing schedule (3), and use of prohibited concomitant medication (5). No protocol deviations affected enrolment, and all subjects were treated as randomized. The subjects with major protocol deviations were excluded from the per-protocol population for analysis.

## Baseline Characteristics

The distribution of age, sex, and baseline disease characteristics between all treatment groups was well balanced (Table 1). The mean age across all treatment groups was 53.6 years (range 19–86), and of the 336 patients, 243 (72.3%) were women. The mean (SD) tCFS score at baseline was 7.0 (2.2) in the NOV03 QID, 6.7 (2.1) in the NOV03 BID group, and 6.7 (2.0) in the saline group. The mean (SD) of the Dryness Score at baseline was 68.6 (21.8) and 70.0 (19.6) in the NOV03 QID and BID groups, respectively, and 66.8 (21.7) in the saline group. Other than DED and MGD, the most common (>10%) occurrences in ocular medical history were cataract (40.5%), pinguecula (14.3%), presbyopia (11.9%), and myopia (10.1%). Within nonocular medical history, the most common (>10%) occurrences were hypertension (31.8%), menopause (33.6%), hysterectomy (14.6%), hypercholesterolemia (18.2%), hypothyroidism (13.1%), and gastroesophageal reflux disease (10.4%). Artificial tears within the last 20 days before visit 1 were used by 45% patients in the NOV03 QID group, 38% in the NOV03 BID group, and 47% in the saline groups.

## Efficacy

### Primary Sign Endpoint

The tCFS decreased in both NOV03 groups, with a higher degree than in the combined saline group throughout the study. The mean CFB (95% CI) in tCFS at week 8 was −2.11 (−2.59 to −1.63) in the NOV03 QID group, −1.78 (−2.27 to −1.30) in the NOV03 BID group, and −0.93 (−1.41 to −0.45) in the combined saline group. The difference (Δ) was highly statistically significant for CFB in both NOV03 groups compared with control at week 8 (NOV03 QID: Δ −1.18; 95% CI, −1.81 to −0.55, $P < 0.001$; NOV03 BID: Δ −0.85; 95% CI, −1.49 to −0.22, $P = 0.009$), thereby the trial met its prespecified superiority in the primary endpoint. Moreover, the difference in tCFS was statistically significant through all earlier visits, showing that the treatment effect started already at week 2 (Fig. 3). The QID regimen consistently showed larger decreases than the BID regimen. The comparison of the saline QID versus saline BID groups showed that they were not different from each other; therefore, it was justified to make the comparisons of NOV03 treatments against the combined saline group. The sensitivity analysis on the per-protocol population, fellow eyes, and all qualifying eyes showed consistent results on the tCFS outcomes.

### Secondary Symptom and Signs Endpoints

The mean CFB (95% CI) in Dryness Score at week 8 was −31.57 (−36.81 to −26.33) in the NOV03 QID group, −30.43

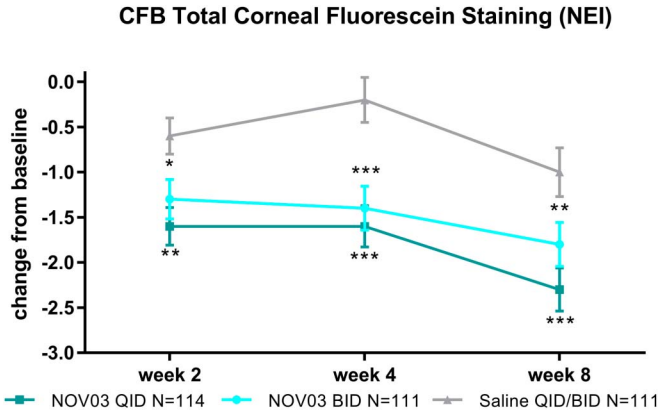


**FIGURE 3.** Mean CFB (±SEM) for tCFS over the treatment period for study eye in the intent-to-treat population. High statistically significant difference for CFB in tCFS for both NOV03 QID and BID groups versus saline at week 8 ($P$= 0.009 for BID and $P \leq 0.001$ for QID) and for all other tested timepoints (weeks 2 and 4) in a repeated measure model. Two-sided $P$ values shown are as follows:*$P \leq 0.05$; **$P \leq 0.01$; and ***$P \leq 0.001$. The NEI scale divides the cornea into 5 regions. The total score is the sum of all regions (0–3 per region, total score of 15 indicates maximum staining). (The full color version of this figure is available at www.corneajrnl.com.)

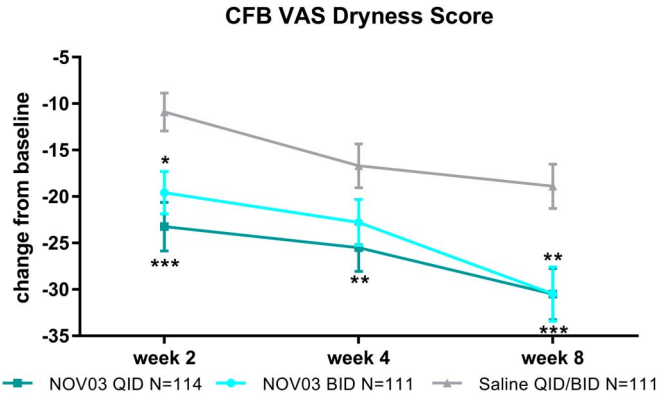


**FIGURE 4.** Mean CFB (±SEM) for VAS Dryness Score over the treatment period in the intent-to-treat population. High statistically significant difference for CFB in VAS Dryness Score for both NOV03 QID and BID groups versus saline at week 8 ($P$ = 0.002 for BID and $P \leq 0.001$ for QID) and for all other tested timepoints (weeks 2 and 4) in the NOV03 QID group in a repeated measure model. Two-sided $P$ values shown are as follows: *$P \leq 0.05$; **$P \leq 0.01$; and ***$P \leq 0.001$. The VAS grading scale ranges from 0 to 100. (The full color version of this figure is available at www.corneajrnl.com.)

(−35.75 to −25.11) in the NOV03 BID group, and −19.73 (−24.99 to −14.48) in the combined saline group. This improvement from baseline in mean Eye Dryness Score was statistically significantly greater in the NOV03 QID and BID groups than that in the control group (week 8: NOV03 QID − control: Δ −11.84; 95% CI, −18.7 to −5.0; $P < 0.001$. NOV03 BID − control: Δ −10.7; 95% CI, −17.6 to −3.8; $P$= 0.002; Fig. 4). The symptom relief started as early as 2 weeks after NOV03 administration and was dose schedule dependent, favoring the QID schedule over the BID schedule. For the QID group, statistical significance over control was demonstrated throughout the study (Fig. 4). A similar pattern was observed for most symptom endpoints with statistical significance for several timepoints (Table 2). Onset of effect occurred at week 2, and the strongest effect was seen in the NOV03 QID group. At week 8, the following symptoms endpoints were statistically significant in the NOV03 QID group versus control: frequency of dryness (Δ −12.87; 95% CI, −20.28 to −5.45; $P < 0.001$), awareness of symptoms (Δ −13.06; 95% CI, −20.50 to −5.62; $P < 0.001$), burning stinging (Δ −10.65; 95% CI, −16.72 to −4.58; $P < 0.001$), sensitivity to light (Δ −8.13; 95% CI, −15.36 to −0.90; $P = 0.028$), and pain (Δ −7.83; 95% CI, −13.31 to −2.36; $P = 0.005$).

In line with the primary outcome parameter (tCFS), more pronounced improvements were observed with NOV03 treatment in most of the CFS subregions outcomes (Table 3). The central area of the cornea seemed to benefit most in both treatments, NOV03 QID and BID; the difference (Δ) to the combined saline group was statistically significant for both treatments at all timepoints (week 8: NOV03 QID − control: Δ −0.29; 95% CI, −0.48 to −0.10; $P = 0.003$; NOV03 BID − control: Δ −0.22; 95% CI, −0.41 to −0.03; $P$= 0.025). The temporal, nasal, and inferior regions also showed consistently pronounced improvements versus the combined saline group and reached statistical significance at several timepoints as well (Table 3). Results were similar for the fellow eye. Other signs of DED improved over the course of the study without clear differences between treatments.

## Subgroup Analysis

Ad hoc subgroup analyses were performed for tCFS and VAS Dryness Score with following subgroups: baseline MGD score <7 and ≥7 and baseline Schirmer I test values <10 and ≥10. The effect on tCFS was more pronounced in subjects with baseline MGD score ≥7 (week 8: NOV03 QID − control Δ −1.43; 95% CI, −2.31 to −0.54; $P \leq 0.01$) and Schirmer I test ≥10 (week 8: NOV03 QID − control Δ −1.28; 95% CI, −2.16 to −0.40; $P \leq 0.01$), favoring NOV03 QID over saline. The same pattern was seen for CFB in Dryness Score for subjects with baseline MGD score ≥7 (week 8: NOV03 QID − control Δ −13.39; 95% CI, −22.72 to −4.07; $P \leq 0.01$) and Schirmer I test ≥10 (week 8: NOV03 QID − control Δ −19.96; 95% CI, −28.28 to −11.09; $P \leq 0.001$) (Fig. 5).

## Safety

Eighty-eight of the 336 randomized patients (26.2%) reported 189 TEAEs during the study period. The number of patients reporting at least 1 TEAE was similar between the treatment groups (NOV03 QID: 24.6%; NOV03 BID 24.3%; control: 29.7%). The number of patients reporting at least 1 ocular TEAE was 11.4% in the NOV03 QID, 4.5% in the NOV03 BID, and 11.7% in the control group. Blurred vision in the NOV03 QID group, eye irritation in the NOV03 BID group, and eye pain in the saline group were the only terms

**TABLE 2.** Change From Baseline in VAS Scores (0–100) and OSDI

| | NOV03 QID–Saline* | NOV03 BID–Saline* |
|---|---|---|
| | Point Estimate of Mean Difference (95% CI); *P* | Point Estimate of Mean Difference (95% CI); *P* |
| Dryness Score | | |
| Week 2 | −11.8 (−17.6 to −6.0); <0.001 | −7.3 (−13.2 to −1.5); 0.015 |
| Week 4 | −9.1 (−1.91 to −0.65); 0.005 | −5.3 (−11.6 to 1.07); 0.103 |
| Week 8 | −11.8 (−18.7 to −5.0); <0.001 | −10.7 (−17.6 to −3.8); 0.002 |
| Frequency of dryness | | |
| Week 2 | −10.6 (−17.0 to −4.2); 0.001 | −3.9 (−10.3 to 2.6); 0.237 |
| Week 4 | −8.8 (−15.4 to −2.2); 0.009 | −4.2 (−10.8 to 2.4); 0.216 |
| Week 8 | −12.9 (−20.3 to −5.5); <0.001 | −11.6 (−19.1 to −4.1); 0.002 |
| Awareness of eye symptoms | | |
| Week 2 | −11.0 (−17.5 to −4.6); <0.001 | −5.1 (−11.5 to 1.4); 0.124 |
| Week 4 | −11.4 (−18.2 to −4.6); 0.001 | −7.1 (−13.9 to −0.3); 0.040 |
| Week 8 | −13.1 (−20.5 to −5.6); <0.001 | −12.6 (−20.1 to −5.1); 0.001 |
| Sticky feeling | | |
| Week 2 | −9.7 (−15.2 to −4.1); <0.001 | −6.0 (−11.6 to −0.4); 0.035 |
| Week 4 | −3.3 (−9.0 to 2.4); 0.259 | −0.7 (−6.5 to 5.0); 0.805 |
| Week 8 | −3.6 (−9.7 to 2.5); 0.246 | −3.0 (−9.2 to 3.2); 0.338 |
| Burning/stinging | | |
| Week 2 | −8.00 (−14.1 to −1.8); 0.011 | −6.7 (−12.9 to −0.5); 0.034 |
| Week 4 | −5.6 (−12.1 to 0.9); 0.092 | −1.0 (−7.5 to 5.6); 0.771 |
| Week 8 | −10.7 (−16.7 to −4.6); <0.001 | −6.4 (−12.6 to −0.3); 0.04 |
| Foreign body sensation | | |
| Week 2 | −6.6 (−12.6 to −0.7); 0.029 | −6.2 (−12.2 to 0.3); 0.041 |
| Week 4 | −8.3 (−14.4 to −2.3); 0.007 | −2.3 (−8.4 to 3.8); 0.453 |
| Week 8 | −4.0 (−10.2 to 2.3); 0.213 | −3.0 (−9.3 to 3.3); 0.345 |
| Itching | | |
| Week 2 | −8.7 (−14.7 to −2.8); 0.004 | −6.9 (−12.9 to −0.9); 0.025 |
| Week 4 | −7.4 (−13.7 to −1.1); 0.022 | −3.0 (−9.3 to 3.3); 0.353 |
| Week 8 | −5.1 (−11.1 to 1.0); 0.103 | −4.3 (−10.4 to 1.8); 0.168 |
| Blurred vision | | |
| Week 2 | −2.6 (−9.0 to 3.8); 0.423 | −2.3 (−8.8 to 4.1); 0.479 |
| Week 4 | −3.6 (−10.4 to 3.2); 0.294 | −1.9 (−8.7 to 5.0); 0.592 |
| Week 8 | −3.7 (−10.8 to 3.3); 0.301 | −3.4 (−10.5 to 3.8); 0.352 |
| Pain | | |
| Week 2 | −3.6 (−9.7 to 2.5); 0.246 | −0.3 (−6.5 to 5.8); 0.916 |
| Week 4 | −0.4 (−5.8 to 4.9); 0.872 | 1.3 (−4.1 to 6.7); 0.634 |
| Week 8 | −7.8 (−13.3 to −2.4); 0.005 | −4.4 (−10.0 to 1.1); 0.116 |
| Sensitivity to light | | |
| Week 2 | −3.6 (−9.8 to 2.6); 0.250 | −4.4 (−10.6 to 1.8); 0.167 |
| Week 4 | −1.7 (−8.5 to 5.2); 0.634 | −2.3 (−9.2 to 4.6); 0.511 |
| Week 8 | −8.1 (−15.4 to −0.9); 0.028 | −6.6 (−13.9 to 0.74); 0.078 |
| OSDI | | |
| Week 2 | −4.2 (−8.32 to −0.04); 0.048 | −1.8 (−5.91 to 2.42); 0.410 |
| Week 4 | −4.7 (−9.37 to −0.10); 0.045 | −1.2 (−5.86 to 3.45); 0.610 |
| Week 8 | −4.3 (−9.24 to 0.62); 0.087 | −3.0 (−7.98 to 1.97); 0.235 |

*For mean treatment difference in CFB.

reported by more than 2% of subjects (2.6%–2.7%). Most TEAEs reported in the study were of mild to moderate intensity (Table 4). Two patients withdrew from study treatment due to a TEAE: 1 occurred in the NOV03 BID and 1 in the control group (Fig. 2). No deaths were reported in the study. Four serious TEAEs were reported during the study by patients in the NOV03 groups; all were nonocular, and none was considered related to study treatment. Across all treatment groups, no significant changes were observed by slit lamp biomicroscopy or dilated fundoscopy. Mean visual acuity and mean intraocular pressure remained unchanged throughout the study.

No clinically significant change in the safety laboratory values or vital signs were observed. The pharmacokinetics

**TABLE 3.** Change From Baseline in Corneal Fluorescein Staining: Total and Subregions

| | NOV03 QID–Saline* | NOV03 BID–Saline* |
|---|---|---|
| | **Point Estimate of Mean Difference (95% CI); *P*** | **Point Estimate of Mean Difference (95% CI); *P*** |
| tCFS | | |
| Week 2 | −0.86 (−1.39 to −0.32); 0.002 | −0.65 (−1.19 to −0.11); 0.018 |
| Week 4 | −1.28 (−1.91 to −0.65); <0.001 | −1.29 (−1.93 to −0.66); <0.001 |
| Week 8 | −1.18 (−1.81 to −0.55); <0.001 | −0.85 (−1.49 to −0.22); 0.009 |
| Central | | |
| Week 2 | −0.27 (−0.45 to −0.08); 0.004 | −0.24 (−0.42 to −0.06); 0.010 |
| Week 4 | −0.29 (−0.49 to −0.08); 0.006 | −0.33 (−0.53 to −0.13); 0.002 |
| Week 8 | −0.29 (−0.48 to −0.10); 0.003 | −0.22 (−0.41 to −0.03); 0.025 |
| Temporal | | |
| Week 2 | −0.11 (−0.27 to 0.06); 0.197 | −0.11 (−0.27 to 0.05); 0.192 |
| Week 4 | −0.38 (−0.56 to −0.19); <0.001 | −0.30 (−0.49 to −0.11); 0.002 |
| Week 8 | −0.29 (−0.47 to −0.11); 0.001 | −0.20 (−0.38 to −0.02); 0.028 |
| Inferior | | |
| Week 2 | −0.15 (−0.33 to 0.03); 0.098 | −0.12 (−0.31 to 0.06); 0.181 |
| Week 4 | −0.24 (−0.44 to −0.04); 0.020 | −0.19 (−0.40 to 0.01); 0.064 |
| Week 8 | −0.27 (−0.46 to −0.08); 0.006 | −0.13 (−0.33 to 0.06); 0.179 |

*For mean treatment difference in CFB.

analysis in this study showed that most (>70%) blood samples did not have a measurable perfluorohexyloctane concentration, and the remaining concentrations were in the very low calibration range, just above the limit of quantification (1 ng/mL).

## DISCUSSION

This is the first multicenter, double-masked, and controlled study to evaluate the efficacy of NOV03 (perfluorohexyloctane) at 2 dosing regimens versus control in subjects with DED. As intended by the selection criteria, the study population reflects a predominantly evaporative, highly symptomatic DED population with presence of MGD and characterized by high Schirmer I test scores and low TFBUT. For this patient population, treatment options are currently limited; they include physical therapies such as eyelid hygiene, intense pulsed light, thermal pulsation, or lid expression, whereas the currently approved DED drug therapies have not been systematically tested in these patients.[16–19]

The study met its primary objective of demonstrating superior improvements in tCFS at 8 weeks compared with the saline control for both BID and QID dosing regimens with high statistical significance. NOV03 showed clinically meaningful and consistent improvements in a variety of symptoms. The effects on the Dryness Score and other symptoms measured by VAS, for example, burning/stinging, awareness of DED symptoms, and frequency of dryness, were highly statistically significant for the QID group over the control. Benefits in both signs and symptoms were dosing schedule dependent, favoring the QID schedule over the BID schedule. The treatment effects were observed already at the first visit after treatment initiation (week 2) and were maintained throughout the study duration.

These findings are noteworthy, given that, in DED, it has been challenging to show benefit in both signs and symptoms in 1 study. There are several reasons for this finding, including limited correlation between dry eye signs and symptoms, high and/or variable placebo treatment responses and limited validated patient outcome instruments for dry eye symptoms.[20–23] Recently, it has been shown that Dryness Score (VAS 0–100 for eye dryness) might be the best tool to capture patients' response to treatment, given that this is the symptom frequently scored highest at baseline, and it has the lowest variability, reasons for which it was also successfully used for DED drug approval (lifitegrast).[17,20] Our study showed a statistically significant and dose-dependent NOV03 treatment effect on this symptom outcome measure. In comparison with many other trials, NOV03 showed the same dose-dependent pattern on a number of other symptoms outcome measures. To our knowledge, the consistency of outcomes shown with NOV03 treatment, particularly the homogenous results over all timepoints for several of both symptom and sign endpoints and dose response, has not been shown before in a randomized and controlled trial. Consequently, the study provides clinically meaningful evidence that use of NOV03 can reduce signs and symptoms of DED as early as week 2 when administered BID or QID over an 8-week treatment period.

A potential explanation of the positive clinical effects observed is the unique mode of action tackling both the lipid layer structure and the meibomian gland function. NOV03 forms a thin layer with the hydrophobic part of the lipid layer of the tear film. This "strengthened" lipid layer is responsible for inhibiting the evaporation of tears. In addition, NOV03 has the potential to penetrate the

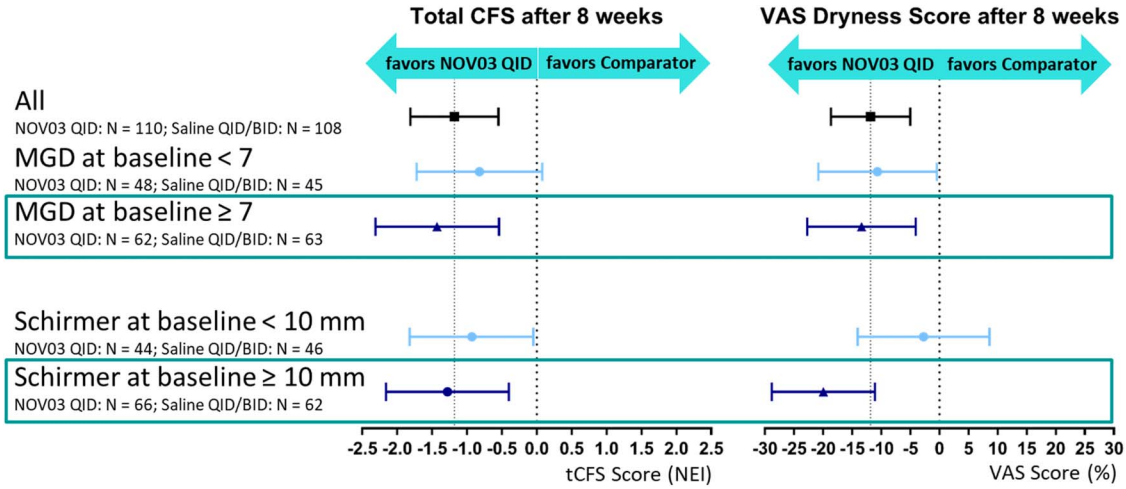


**FIGURE 5.** The tCFS and VAS Dryness Score subgroup analysis. Analyses of the subgroups defined by higher degree of MGD involvement at baseline (MGD score ≥7) and higher Schirmer I test ≥10, showed that NOV03 QID treatment had a larger treatment effect in these subgroups. (The full color version of this figure is available at www.corneajrnl.com.)

meibomian glands and possibly liquefy the lipid containing meibum. This aspect of the mode of action of NOV03 in the observed efficacy is supported by the subgroup analysis of the current trial data, showing that patients with higher Schirmer I test values and higher MGD scores at baseline, for example, predominantly evaporative DED with presence of MGD in this study, benefitted most from the NOV03 treatment.

The safety and tolerability of NOV03 was excellent, with a very low rate of instillation site reaction and irritation: NOV03 QID: 2.6%; NOV03 BID 0.9%; saline: 1.8%, compared with published rates with current therapies for DED, which are approximately 15.0% for both lifitegrast solution[24] and cyclosporine containing emulsion.[18] An improved tolerability profile versus currently available therapies is important for the clinical management of DED in practice, considering that up to 60% of patients stop their therapy within 12 months.[25]

One limitation is the short treatment duration. The restriction toward patients with predominantly evaporative DED associated with MGD might be seen as another limitation because study results are arguably not generalizable to all forms of DED. On the other hand, NOV03's mode of action and previous data indicate that the patients investigated in this study benefit most from the treatment with NOV03, and hence, the treatment could address a considerable unmet clinical need in DED.

In conclusion, this phase 2 study has demonstrated the therapeutic ability of NOV03 to reduce signs and symptoms of DED, thereby showing the potential of its novel mode of action to address the clinical management of patients with DED associated with MGD. A phase 3 development program is underway.

**TABLE 4.** Treatment-Emergent Adverse Events

| Ocular and Nonocular Adverse Events | NOV03 QID, n (%) | NOV03 BID, n (%) | Saline BID + QID, n (%) |
|---|---|---|---|
| No. of TEAEs | 62 | 60 | 67 |
| No. of subjects with at least 1 TEAE | 27 (23.7) | 27 (24.3) | 32 (28.8) |
| No. of treatment-emergent serious adverse events | 3 (2.6) | 1 (0.9) | 0 |
| No. of subjects discontinued treatment due to an adverse event | 0 | 3 (2.7) | 1 (0.9) |
| Ocular adverse events* | | | |
| No. of TEAEs | 22 | 21 | 18 |
| No of subjects with at least 1 TEAE | 13 (11.4) | 5 (4.5) | 13 (11.7) |
| Ocular adverse events* that occurred in more than 2% of subjects | | | |
| Eye irritation | 1 (0.9) | 3 (2.7) | 0 |
| Eye pain | 1 (0.9) | 1 (0.9) | 3 (2.7) |
| Vision blurred | 3 (2.6) | 0 | 1 (0.9) |

*Assessment relates to both eyes.

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