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A Phase 3, Randomized, Double-Masked Study of OTX-101 Ophthalmic Solution 0.09% in the Treatment of Dry Eye Disease

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Purpose: To evaluate the safety and efficacy of OTX-101, a novel aqueous nanomicellar formulation of cyclosporine (0.09%), in the treatment of patients with dry eye disease (DED).

Design: A randomized, multicenter, vehicle-controlled, double-masked, phase 3 clinical trial.

Participants: Adults (18–90 years of age) with a history and clinical diagnosis of DED, a global symptom score of 40 or more (range, 0–100), and a lissamine green conjunctival staining score of 3 or more and 9 or less (range, 0–12) in at least 1 eye.

Methods: Eligible patients entered a run-in period of 14 to 20 days in which all patients administered vehicle twice daily. Patients who remained eligible at the baseline (day 0) visit were randomized in a 1:1 ratio to twice-daily treatment with OTX-101 0.09% or vehicle for 84 days.

Main Outcome Measures: Efficacy assessments included signs (unanesthetized Schirmer tear test, corneal and conjunctival staining) and symptoms (global symptom score) of DED. The primary end point was the proportion of eyes with a clinically meaningful improvement (increase of $\geq$10 mm) in Schirmer test score at day 84. Safety evaluations included adverse events (AEs), visual acuity, and intraocular pressure monitoring, slit-lamp, dilated ophthalmoscopy, and fundus examinations.

Results: A total of 744 patients were randomized and received study medication (371 to OTX-101 0.09% and 373 to vehicle). The primary end point was achieved; a significantly greater percentage of eyes in the OTX-101 0.09% treatment group achieved an increase of 10 mm or more in the Schirmer test score at day 84 (OTX-101 0.09%, 16.6%; vehicle, 9.2%; $P < 0.001$). Significant improvements relative to vehicle also were observed for corneal (days 28, 56, and 84) and conjunctival (days 56 and 84) staining. The global symptom score was reduced from baseline in both treatment groups by approximately 30%; however, no significant separation between groups was observed. The OTX-101 0.09% formulation was well tolerated. Treatment-emergent AEs were primarily mild in intensity.

Conclusions: Clinically and statistically significant improvements in tear production and ocular surface integrity were observed in patients treated with OTX-101 0.09% for DED. *Ophthalmology 2019;126:1230-1237 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Inflammation, which can be initiated by desiccation of the ocular surface and resulting hyperosmolarity of the tear film, is recognized as a contributing factor in the development of dry eye disease (DED). Responses of the immune system lead to the production of inflammatory mediators and can result in disruption of the integrity of the corneal and conjunctival epithelium as well as an increase in the sensitization of corneal nerve endings. An increase in the recruitment and migration of inflammatory cells into ocular surface tissue amplifies the inflammatory response, leading to a chronic cycle of inflammation that is characteristic of DED.[1,2]

Cyclosporine ophthalmic emulsion 0.05% (Restasis; Allergan, Irvine, CA) is indicated to increase tear production in patients with DED.[3] Cyclosporine is an immunomodulatory agent that functions through the inhibition of calcineurin, preventing the activation of T lymphocytes and subsequent release of proinflammatory mediators.[4,5] Topical application of cyclosporine ophthalmic emulsion has been shown to increase tear production and reduce the signs and symptoms of DED, although the exact mechanism of action is not known.[6]

The hydrophobic nature of cyclosporine limits the aqueous solubility in traditional formulations. Nanomicelle formulations solubilize hydrophobic agents by entrapping the drug within the micelle structures, creating a clear aqueous solution.[7] OTX-101 0.09% is a novel, nanomicellar, clear aqueous solution of cyclosporine developed for the treatment of DED (Cequa; Sun Pharmaceutical Industries, Cranbury, NJ). The nanomicellar technology used in OTX-101 0.09% improves the bioavailability and physicochemical stability of the formulation[7] and may result in greater efficacy and tolerability. In nonclinical pharmacokinetic studies, higher levels of cyclosporine were measured in ocular tissue after administration of OTX-101 0.05% as compared with cyclosporine

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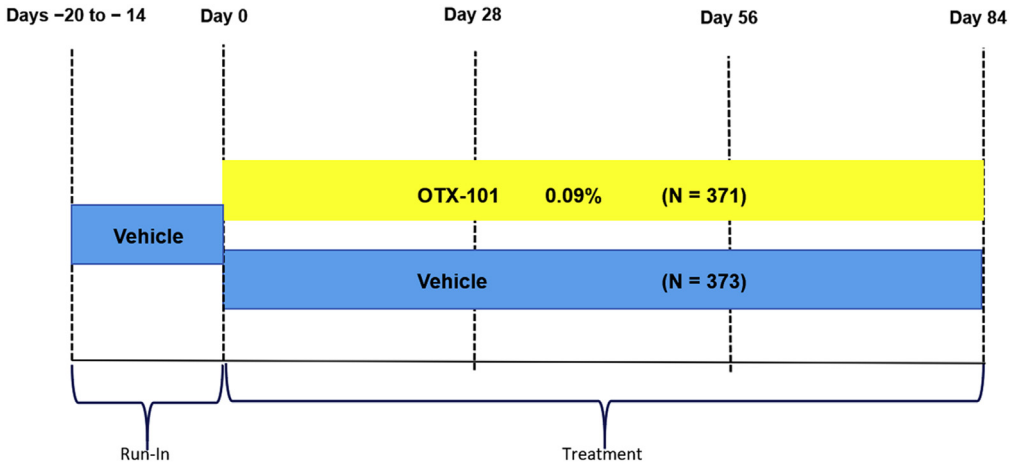

Figure 1. Study schematic.

ophthalmic emulsion 0.05%.[8] The safety and efficacy of OTX-101 initially was evaluated through a phase 2b/3 dose-ranging (0.05% and 0.09%) study.[9] The OTX-101 concentration of 0.09% was selected for continued development.[9] This report presents the results of a phase 3 study evaluating the safety and efficacy of OTX-101 0.09% as compared with vehicle for the treatment of patients with DED.

Methods

This was a phase 3, randomized, multicenter, double-masked, vehicle-controlled study designed to evaluate the safety and efficacy of OTX-101 0.09% for the treatment of DED. Patients were enrolled at 45 sites in the United States. Before initiation of patient enrollment, all study-related documents were reviewed by an institutional review board (Sterling Institutional Review Board, Atlanta, GA). Institutional review board approval was obtained. All patients were required to provide written informed consent before study enrollment and the conduct of any study-related procedures. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was registered through ClinicalTrials.gov (identifier, NCT02688556; https://clinicaltrials.gov/ct2/show/NCT02688556).

Study Patients

To be eligible for study enrollment, patients were required to be 18 years of age or older and to have a self-reported history of DED for a period of at least 6 months, supported by a clinical diagnosis of bilateral DED at the time of screening. At both the screening and baseline visits, patients also were required to have a lissamine green conjunctival staining sum score of 3 or more to 9 or less of a total possible score of 12 in the same eye and a global symptom score (based on symptoms of dryness, irritation, or both) rated by the patient of 40 or more (range, 0−100) on a visual analog scale; a full description of the grading scales is presented next in "Outcome Measures." Corrected Snellen visual acuity of 20/200 or better was required in both eyes. Patients also were required to discontinue the use of any current therapy for DED, including artificial tears or other ocular lubricants, for the duration of the study, beginning at the screening visit.

Patients were excluded from participation in the study if any of the exclusion criteria were met, which included use of cyclosporine ophthalmic emulsion 0.05% within 3 months before screening or a report of a previous treatment failure (lack of efficacy) for topical cyclosporine; a diagnosis of Sjögren's syndrome more than 5 years before the screening visit; a clinical diagnosis or reported history of seasonal or perennial allergic conjunctivitis, or both; any other current active eye disease other than DED that required the use of ophthalmic medication; a history of herpes keratitis; unstable macular disease (change in central visual acuity within 6 months of the screening visit); diagnosis of chronic uveitis or other chronic or potentially recurrent ophthalmic disease; history of a corneal transplant; history of refractive surgery within 6 months of the screening visit or postoperative refractive surgery symptoms of ocular dryness that had not resolved at the screening visit; cataract surgery within 3 months of the screening visit; nonlaser glaucoma surgery at any time and laser glaucoma procedures within 3 months of screening; the presence of punctal plugs or a history of permanent punctal occlusion; lagophthalmos or other clinically significant eyelid irregularity; presence of pterygium or conjunctivochalasis; an unwillingness to discontinue contact lens wear during the study; patients who had a preplanned elective surgery scheduled during the study period; patients with positive human immunodeficiency virus results; patients who were unwilling or considered unable to report symptoms or medical history information reliably; patients with a known hypersensitivity to the study medication or any components of the study medication; history or presence of general systemic conditions or serious or severe ocular conditions that the investigator determined may confound the study or increase the risk to the patient; and women who were pregnant or breastfeeding. Patients also were considered ineligible for study participation if the following medications were used within 7 days before screening or throughout the study period: cholinergics, antimuscarinics, antihistamines, tricyclic antidepressants, phenothiazines, retinoids, and systemic corticosteroids. Immunomodulator medications and omega-3 fatty acid supplements were permitted if the patient's dose was stable for 3 months before screening and was not expected to change during the study period. No other ophthalmic medications or over-the-counter products, including artificial tears, were permitted during the study period.

Study Protocol

Patients were required to attend a total of 5 study visits, including screening (day −20 to day −14), baseline (day 0), and 3 follow-up visits on days 28, 56, and 84 for safety and efficacy evaluations

(Fig 1). During the screening visit, written informed consent was collected, and patients were evaluated for suitability according to the inclusion and exclusion criteria. Demographic information and medical, ocular, and concomitant medication histories also were collected. Ophthalmic examinations were performed, and patient-reported symptom assessments were obtained. After the evaluations, eligible patients entered an open-label vehicle run-in or initiation period (14−20 days). Patients administered the first drop of vehicle in each eye at the screening visit and were instructed to instill 1 drop into each eye twice daily throughout the run-in period.

Patients returned to the clinic for the baseline visit (day 0) for confirmation of eligibility based on the same set of inclusion and exclusion criteria and objective and subjective assessments used at the screening visit. Eligible patients were randomized to study medication at the baseline visit. The clinical sites used an Interactive Web Response System (Medidata Solutions, New York, NY) to assign kit numbers to patients. The assigned kit number was recorded for each patient. Study medication was randomized in a 1:1 ratio to either OTX-101 0.09% or vehicle. A randomized block design was used to maintain balance between the treatment groups, but the randomization was not stratified within the investigation sites. The block size was 4 (2 times the number of treatment groups); this information was not disclosed to site personnel or personnel involved in the data management. OTX-101 0.09% is a preservative-free aqueous nanomicellar formulation of cyclosporine (0.09%) provided in unit-dose vials. The vehicle formulation was identical to the OTX-101 0.09% formulation except for the omission of the cyclosporine and was provided in unit-dose vials that were identical in appearance to those containing active drug. Patients self-administered study drug at the baseline visit and were instructed to instill their assigned study medication for 84 days (12 weeks) twice daily approximately 12 hours apart. A new vial was provided for each dose, and patients were instructed to instill 1 full drop in each eye. Patients, investigators, other clinical site staff, and monitoring personnel remained masked to patient's randomized treatment assignment throughout the study.

Outcome Measures

Schirmer tests (unanesthetized) were performed at the baseline and final (day 84) visits. Other efficacy end points were assessed at screening, baseline, and each follow-up visit; these included corneal fluorescein staining, conjunctival lissamine staining, and the frequency and severity of dryness, irritation, or both using a modified Symptom Assessment iN Dry Eye (SANDE) questionnaire.[10]

The unanesthetized Schirmer test was performed by placing a strip in each eye and recording the length of the strip that was wetted in millimeters after 5 minutes. Lissamine green staining was conducted by instilling 1 drop of 1% lissamine green. Conjunctival staining was evaluated 1 to 4 minutes after instillation of the lissamine green stain, which was evaluated based on assessment of 6 regions of the conjunctiva (temporal, nasal, 2 inferior regions, and 2 superior regions) on a 0-to-3 scale (0 = no punctate staining, 3 = densely concentrated micropunctate staining) for each region. The total lissamine green staining score was calculated for each patient by adding the scores of the individual regions, excluding the 2 superior regions (range, 0−12).[11] Corneal fluorescein staining was evaluated 2 to 2.5 minutes after the instillation of 1 drop of 0.5% fluorescein with a yellow barrier filter. Corneal fluorescein staining was assessed for each of the 5 regions of the cornea (central, superior, inferior, nasal, and temporal) on a 0-to-4 scale (0 = no punctate staining, 4 = severe diffuse or coalescent macropunctate staining) for each region in 0.5 increments. The score for each region was summed for a total corneal staining score (range, 0−20).[11]

A modified version of the SANDE questionnaire was used to measure patient-reported symptoms.[10] Patients were asked to report both the frequency and severity of their ocular dryness and irritation symptoms ("Please indicate how often, over the past week, your eyes felt dry and/or irritated"; "Please indicate how severe, on average, you felt your symptoms of dryness and/or irritation were over the past week") on a visual analog scale of 0 to 100 (0 = rarely, 100 = all the time, and 0 = very mild, 100 = very severe, respectively). A global symptom score was calculated based on a prespecified method as the square root of the frequency score multiplied by the severity score.

The primary efficacy end point for the study was the proportion of eyes in which a clinically meaningful improvement (increase of $\geq$10 mm) from baseline was observed at day 84 in the Schirmer test scores. Key secondary efficacy end points included the mean change from baseline in Schirmer test scores, total conjunctival staining, central corneal staining, complete clearing of central corneal staining, clearing of temporal conjunctival staining, and global SANDE symptom scores. All signs were evaluated and analyzed bilaterally using statistical methods that accounted for within-patient correlation.

Safety evaluations included the collection of all adverse events (AEs), monitoring of corrected Snellen visual acuity and intraocular pressure, a routine slit-lamp examination, and a dilated ophthalmoscopy and fundus examination.

Statistical Methods

The study population sample size of 350 patients in each group was calculated to provide 95% power to detect a true 10% difference in the proportion of eyes with an increase of 10 mm or more in Schirmer tear test scores from baseline to day 84 using a chi-square test (α = 0.05, 2-tailed). The intention-to-treat population, which included all randomized patients, was used in all analyses of efficacy. The safety population included all patients who received at least 1 dose of study medication.

Test statistics were based on a restricted maximum likelihood repeated measures mixed model on change from baseline values with baseline as a covariate, treatment group as a fixed factor, and observations from both eyes as repeated measures using an unstructured covariance structure. Analysis of the mean change from baseline was based on the adjusted estimate of the difference between groups at each postbaseline visit obtained through a restricted maximum likelihood repeated measures mixed model on change from baseline values with baseline as a covariate, treatment group as a fixed factor, and observations from both eyes as repeated measures using an unstructured covariance structure. Comparisons of binary response measures were calculated using observations from both eyes as repeated measures with treatment as a fixed effect using an unstructured correlation matrix. In the event of missing data, the analysis was conducted using the baseline carried forward for continuous measures and failure imputed for binary responder measures if only one postbaseline data point was available. A closed testing procedure was used with respect to secondary end points to control the type I error rate. The secondary end points were ordered in a prespecified hierarchy: mean change from baseline in total conjunctival staining score at day 84, mean change from baseline in Schirmer test results at day 84, mean change from baseline in central corneal staining at day 84, complete clearing of central corneal staining at day 84, and mean change from baseline in SANDE global symptom score at

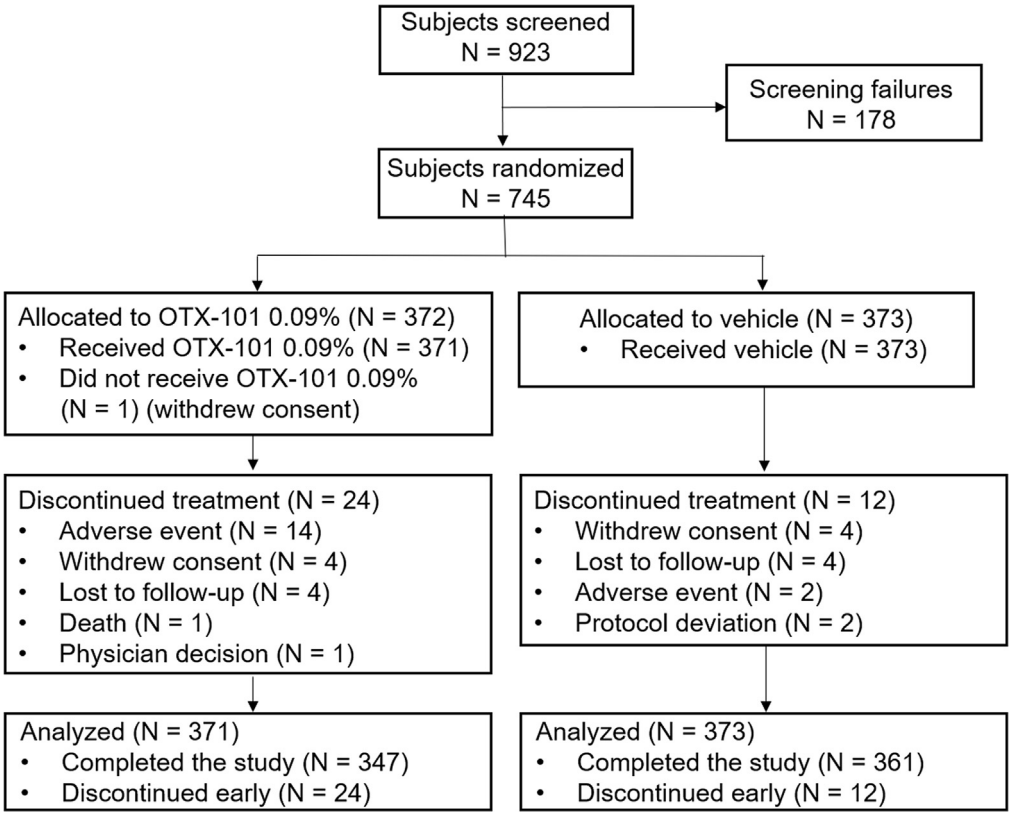

Figure 2. Flowchart showing patient disposition throughout the study. One patient was randomized to the OTX-101 0.09% group but withdrew consent before receiving study medication.

day 84. For a claim of statistical significance, the null hypothesis being tested and all higher-ordered null hypotheses had to be rejected. Each hypothesis in the hierarchy was tested within the treatment regimen against vehicle at a significance level of 0.05. A 2-sided significance level of 0.05 was used for the analysis.

The incidence of AEs was summarized and classified according the Medical Dictionary for Regulatory Activities system (version 19.0) to the levels of system organ class and primary preferred term. Adverse events were classified by severity and relationship to the study medication.

Table 1. Demographic Characteristics

Parameter	OTX-101 0.09% (n = 371)	Vehicle (n = 373)	Overall (n = 744)
Age (yrs)			
Mean (SD)	58.4 (14.10)	59.5 (14.68)	59.0 (14.40)
Minimum–maximum	18–89	20–90	18–90
Gender, no. (%)			
Female	315 (84.9)	311 (83.4)	626 (84.1)
Male	56 (15.1)	62 (16.6)	118 (15.9)
Race, no. (%)			
White	310 (83.6)	305 (81.8)	615 (82.7)
Black	41 (11.1)	45 (12.1)	86 (11.6)
Asian	11 (3.0)	12 (3.2)	23 (3.1)
Other	9 (2.4)	11 (3.0)	20 (2.7)
Ethnicity, no. (%)			
Not Hispanic/Latino	314 (84.6)	319 (85.5)	633 (85.1)
Hispanic/Latino	57 (15.4)	54 (14.5)	111 (14.9)

SD = standard deviation.
Intention-to-treat population. No significant differences were observed between groups.

Results

A total of 923 patients were evaluated at the screening visit; 744 patients met the eligibility criteria, were randomized, and received either OTX-101 0.09% or vehicle. Patients were recruited between February 2016 and November 2016. One patient was randomized to the OTX-101 0.09% group but withdrew consent before receiving study medication. Thirty-six patients (4.8%) discontinued from the study, and 708 patients (95.2%) completed all study visits. The disposition of patients throughout the study is presented in Figure 2. The demographic information, including age, gender, race, and ethnicity, is presented in Table 1. The

Table 2. Percentage of Eyes with an Increase from Baseline of 10 mm or More in Schirmer Test Scores

Parameter	OTX-101 0.09% (n = 371)	Vehicle (n = 373)	Treatment Difference
% of eyes	16.6	9.2	7.3*
95% CL	13.4,19.7	6.8,11.7	3.3,11.3

CL = confidence limits; – = not available.
Intent-to-treat population.
*P value <0.001.

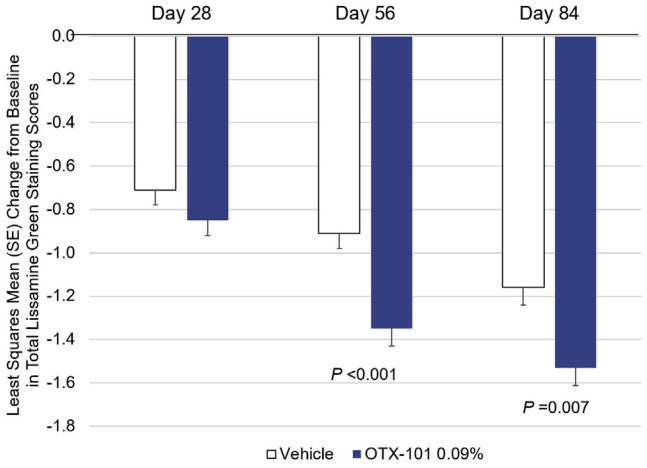

Figure 3. Bar graph showing the least squares mean changes from baseline in total conjunctival lissamine green staining scores presented by study visit for the vehicle group (unshaded bars) and OTX-101 0.09% (blue shading). Statistically significant differences between groups were observed at day 56 ($P < 0.001$) and day 84 ($P = 0.007$). SE = standard error.

demographic characteristics were similar between the 2 treatment groups; most patients in the study population were women (84.1%), were white (82.7%), and identified as neither Hispanic nor Latino (85.1%).

Efficacy Evaluation

Primary End Point. Schirmer test scores at baseline were similar between groups, with a mean±standard deviation score of 11.9±7.8 mm for the OTX-101 0.09% group and 12.1±7.7 mm for the vehicle group. A higher percentage of eyes of patients in the OTX-101 0.09% group (16.6%) experienced a clinically meaningful improvement in Schirmer 2 tear test results (≥10 mm) from baseline to day 84 as compared with the vehicle group (9.2%). The treatment difference between groups was statistically significant (95% confidence interval, 3.3%−11.3%; $P < 0.001$), achieving the study primary end point. The percentage of eyes in which a clinically meaningful improvement in Schirmer 2 tear test results on day 84 was observed is presented in Table 2.

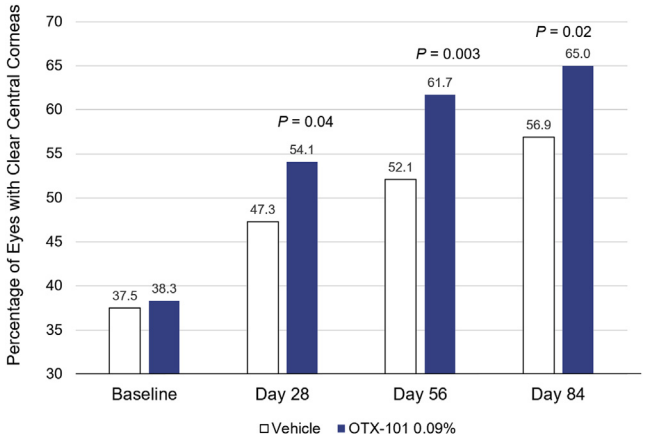

Figure 4. Bar graph showing the percentage of eyes with complete clearing (score = 0) of central corneal fluorescein staining presented by study visit for the vehicle group (unshaded bars) and OTX-101 0.09% group (blue shading). Statistically significant differences between groups were observed at day 28 ($P = 0.04$), day 56 ($P = 0.003$), and day 84 ($P = 0.02$).

Table 3. Incidence of Ocular Treatment-Emergent Adverse Events

Systems Organ Class and Preferred Term	OTX-101 0.09% (n = 372)	Vehicle (n = 372)
Eye disorders		
Conjunctival hyperemia	30 (8.1)	19 (5.1)
Blepharitis	5 (1.3)	0
Eye irritation	3 (0.8)	5 (1.3)
Eye pruritus	1 (0.3)	5 (1.3)
Foreign body sensation in eyes	1 (0.3)	5 (1.3)
General disorders and administration site conditions		
Instillation site pain	90 (24.2)	16 (4.3)
Instillation site lacrimation	4 (1.1)	0
Instillation site reaction	4 (1.1)	2 (0.5)

Secondary End Points. Mean total conjunctival staining scores at baseline were 5.4±1.7 and 5.5±1.8 for the OTX-101 0.09% and vehicle groups, respectively. A significantly greater improvement (decrease) in total conjunctival staining was observed in the OTX-101 0.09% treatment group by day 56 and at day 84 as compared with the vehicle group. Mean changes from baseline in total conjunctival lissamine green staining scores are presented by study visit in Figure 3.

Mean total corneal staining scores at baseline were 4.1±2.4 for the OTX-101 0.09% group and 4.3±2.7 for the vehicle group. Improvements in total corneal staining were observed for both treatment groups at each postbaseline visit. The change from baseline in total corneal staining scores for patients in the OTX-101 0.09% treatment group were −0.8±1.9 (day 28), −1.3±1.9 (day 56), and −1.4±2.0 (day 84) as compared with −0.6±1.8 (day 28), −0.9±2.0 (day 56), and −1.2±2.2 (day 84) for patients in the vehicle group. Significantly greater reductions in total corneal fluorescein staining occurred in the OTX-101 0.09% treatment group at each postbaseline visit as compared with the vehicle group ($P < 0.01$ for each postbaseline visit [days 28, 56, and 84]). Similar results were obtained for fluorescein staining of the central region of the cornea.

Complete clearing of central corneal staining, or a staining score of 0, also was evaluated as a secondary end point. The 2 groups were comparable with respect to the proportion of clear central corneas at baseline: 284 eyes (38.3%) in the OTX-101 0.09% group and 280 eyes (37.5%) in the vehicle group. Both treatment groups showed improvement at each postbaseline visit, but statistically significantly larger increases in the proportion of eyes with clear central corneas were observed in patients in the OTX-101 0.09% treatment group as compared with the vehicle group. The proportions of eyes with clear central corneas are presented by study visit in Figure 4.

Patient-Reported Symptoms

Patient-reported symptom scores were reduced after treatment in both groups. Mean values for the global symptom scores, based on the modified SANDE questionnaire, were similar at baseline for the OTX-101 0.09% (63.1±15.7) and vehicle (62.2±16.1) groups. The mean changes from baseline in the global symptom score by day 84 were −18.8 for the OTX-101 0.09% group and −19.1 for the vehicle group; there were no statistically significant differences in the change from baseline in the global symptom score at any of the posttreatment visits.

Safety Assessments

A total of 744 patients were included in the safety population. There were 626 AEs reported by 242 patients during the study period: 423 AEs from 151 patients (40.6%) in the OTX-101 0.09% group and 203 AEs from 91 patients (24.5%) in the vehicle group. Most of the AEs were mild in severity: 111 patients (29.8%) in the OTX-101 0.09% group and 74 patients (19.9%) in the vehicle group experienced a mild AE as the highest-severity AE, and 34 patients (9.1%) in the OTX-101 0.09% group and 15 patients (4.0%) in the vehicle group reported a moderate AE as the highest-severity AE. The most commonly reported ocular AE in the OTX-101 0.09% group was instillation site pain (OTX-101 0.09%, 90 patients [24.2%]; vehicle, 16 patients [4.3%]). Events coded to this Medical Dictionary for Regulatory Activities term typically were described as "mild stinging and/or burning for several minutes following each instillation." Most of these events in both treatment groups were mild in severity (OTX-101 0.09%, 77 patients [20.7%]; vehicle, 16 patients [4.3%]). Few patients permanently discontinued study drug because of instillation site pain (OTX-101 0.09%, 9 patients [2.4%]; vehicle, 0 patients). A summary of the most common ocular treatment-emergent AEs (TEAEs) is presented in Table 3.

Nonocular AEs reported during the study by 1% or more of patients were headache (6 patients [1.6%] in the OTX-101 0.09% group; 2 patients [0.5%] in the vehicle group), sinusitis (4 patients [1.1%] in the OTX-101 0.09% group; 5 patients [1.3%] in the vehicle group), and urinary tract infection (4 patients [1.1%] in the OTX-101 0.09% group; 2 patients [0.5%] in the vehicle group). There were 8 serious AEs (SAEs) that occurred during the treatment phase of the study. None of the SAEs encountered during the study were ocular in nature or were considered to be related to study treatment. Six patients (1.6%) in the OTX-101 0.09% group experienced SAEs, including pneumonia, subdural hematoma, spinal column stenosis, nephrolithiasis, malignant lung neoplasm, and 1 death (unknown cause). Two patients (0.5%) in the vehicle group experienced SAEs, including a perforated ulcer and spinal osteoarthritis.

A total of 13 patients (3.5%) in the OTX-101 0.09% treatment group and 2 patients (0.5%) in the vehicle group reported TEAEs that were considered related to the study drug and that resulted in withdrawal of study medication. The most common TEAE that led to study medication withdrawal was mild to moderate instillation site pain.

No clinically significant changes in visual acuity were observed in either of the treatment groups throughout the study. Clinically significant slit-lamp examination findings were noted for 6 patients (1.6%) in the OTX-101 0.09% group and 1 patient (0.3%) in the vehicle group. Conjunctival hyperemia (bilateral or unilateral) was the primary finding observed during the slit-lamp examination and was recorded as a TEAE. No abnormal increases or decreases in intraocular pressure were noted. One patient in each treatment group was noted to demonstrate an abnormality associated with the macula, optic nerve, or both during the dilated funduscopy examination; both events were considered unrelated to the study medication.

Discussion

OTX-101 0.09% is a clear aqueous nanomicellar formulation of cyclosporine that may prove to be a useful addition to the armamentarium of agents for the treatment of DED. The technology used in the OTX-101 0.09% formulation allows for a stable solution with more than a 10-fold increase in the aqueous solubility of cyclosporine. The currently marketed topical ophthalmic formulation of cyclosporine in the United States is a turbid oil-in-water emulsion that requires shaking before instillation.[3] The OTX-101 0.09% formulation was chosen for continued development based on the findings of the previously conducted phase 2b/3 study evaluating 2 concentrations of OTX-101 (0.05% and 0.09%) relative to its vehicle for the treatment of patients with DED, anticipating a clinical benefit from a higher dosing concentration.[9]

This phase 3, randomized, multicenter, double-masked, vehicle-controlled study evaluated the safety and efficacy of OTX-101 0.09% administered twice daily in the treatment of patients with DED. The study design was based on the earlier phase 2b/3 dose-ranging study.[8] The primary efficacy end point, increased tear production, was achieved in this study. A significantly higher proportion of eyes in the OTX-101 0.09% group demonstrated a clinically meaningful improvement in the Schirmer tear test scores (≥10-mm increase from baseline) at day 84 (Table 2). Notably, significant improvement was seen within 12 weeks of treatment initiation with OTX-101 0.09%. Moreover, this result was obtained in a study population of patients with DED that was not restricted to only those assumed to be aqueous deficient (mean Schirmer scores were 11.9 mm for the OTX-101 group and 12.1 mm for the vehicle group at baseline).

The selection of the primary end point in this study, a 10-mm or more increase from baseline in Schirmer test scores, was chosen based on the established approval pathway for topical application of cyclosporine in the treatment of patients with DED.[3] In a summary analysis of the registration studies evaluating the efficacy of topical cyclosporine ophthalmic emulsion, 15% of patients treated with topical cyclosporine experienced a 10-mm increase in Schirmer scores after 6 months as compared with 5% of patients assigned to vehicle.[3] In addition to the selection of Schirmer score as the basis for the primary efficacy end point, additional clinical signs and symptoms of DED were evaluated to provide a more thorough data set on the profile of OTX-101 in the treatment of DED. Future studies may provide further insight into the effect of OTX-101 treatment on inflammatory markers that have been identified as elevated in patients with DED, such as cytokine or human leukocyte antigen—DR isotype expression levels.[12]

Improvements in clinical signs were observed as early as day 28 in the present study. These results may be the result of the higher ocular tissue concentrations of cyclosporine produced by this novel nanomicellar formulation relative to the currently marketed emulsion.[8] Mean improvements from baseline in total corneal staining and total conjunctival staining were greater for patients treated with OTX-101 0.09% than vehicle at each follow-up visit after initiation of treatment. Statistical significance was achieved at the first postbaseline visit (day 28) for total corneal staining and the second postbaseline visit (day 56) for total conjunctival staining. Significantly greater improvements in central corneal staining, including clearing of staining, also were observed by day 28 in patients treated with OTX-101 0.09%. These results suggest that improvements in the integrity of the ocular surface occur soon after initiating therapy with OTX-101 0.09%. A component of the decrease in conjunctival staining may be attributable to the regression of the mean resulting from the requirement of a minimum

threshold of 3 or more (of 12) in the total lissamine green staining score at screening and baseline.

Both treatment groups demonstrated an approximate 30% mean decrease from baseline in modified SANDE scores; however, no difference in treatment effect was observed. This result is not unexpected, given the well-established discordant relationship between the signs and symptoms of DED and the complex causes of the condition.[13] The large mean improvement from baseline in both groups may be attributable partially to the regression to the mean effect arising from the requirement of a minimum threshold of 40 or more in the SANDE score. Topical artificial tear formulations often are used as the standard of care in the treatment of DED. Artificial tear use was not permitted during the study. Lubrication of the ocular surface can alleviate symptoms; as such, the lubricating effect of the polymeric vehicle also may have contributed to the improvement in symptoms.

Overall, OTX-101 0.09% generally was well tolerated and has an acceptable safety profile. Most ocular AEs were mild in severity and did not require additional treatment. The most common ocular AE in both treatment groups was mild stinging or burning after instillation of the study medication, coded as "instillation site pain" (24.2% in the OTX-101 0.09% group and 4.3% in the vehicle group). No abnormal changes in visual acuity or intraocular pressure were observed, and no ocular SAEs were reported during the study. Patient discontinuation associated with AEs was low in the present study, with 2.4% of patients in the OTX-101 0.09% treatment group discontinuing study drug because of ocular AEs.

Potential limitations of this study include the selection criteria for enrollment of the study population, including minimum or maximum characteristics, or both, for conjunctival staining as a clinical sign of DED and the frequency and severity of symptoms of dryness or discomfort related to DED. Also, patients were treated and evaluated for only 84 days (12 weeks). Further head-to-head clinical trials comparing OTX-101 0.09% with cyclosporine ophthalmic emulsion 0.05% will be required to establish if the faster onset of efficacy suggested by these data can be proven clinically. One other potential limitation of the study is based on the use of cyclosporine ophthalmic emulsion 0.05% within 3 months before screening or a report of a previous treatment failure (lack of efficacy) on topical cyclosporine as an exclusion criteria; however, the report of prior use of cyclosporine was low in randomized patients (5 patients in the OTX-101 group and 1 patient randomized to the vehicle group), reducing the potential impact on the study findings.

Clinically and statistically significant improvements in the signs of DED were observed in patients treated with OTX-101 0.09%, including tear production as assessed by the Schirmer test and the integrity of the ocular surface as evaluated by corneal and conjunctival staining. Differentiation between the OTX-101 0.09% and vehicle groups in the improvements for multiple clinical signs occurred within 28 days of OTX-101 0.09% treatment initiation. The clinical improvement demonstrated in this study supports the continued development of OTX-101 as a treatment for DED.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
AE = adverse event; **DED** = dry eye disease; **ITT** = intention-to-treat; **SANDE** = Symptom Assessment iN Dry Eye; **SAE** = serious adverse event; **SE** = standard error; **TEAE** = treatment-emergent adverse event.

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