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Effect of OTX-101, a Novel Nanomicellar Formulation of Cyclosporine A, on Conjunctival Staining in Patients with Keratoconjunctivitis Sicca: A Pooled Analysis of Phase 2b/3 and 3 Clinical Trials

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Abstract

Purpose: Keratoconjunctivitis sicca (KCS), a multifactorial disease, is the most common ocular condition for patients seeking medical treatment and is characterized by ocular burning, stinging, and dryness. This pooled analysis examined the effect of OTX-101 0.09% versus vehicle on the total and individual conjunctival staining in patients with KCS from phase 2b/3 and phase 3 studies.
Methods: In these randomized, multicenter, double-masked, and vehicle-controlled studies, patients received 1 drop of OTX-101 0.09% or vehicle in both eyes twice daily. The time points for the pooled analysis were baseline (day 0) and study days 28, 56, and 84/early discontinuation. Conjunctival staining was graded on a 0- to 3-point scale per zone and averaged over both eyes at each assessment. Pooled safety assessments included adverse event (AE) reporting.
Results: The total mean (standard deviation) conjunctival staining scores at baseline were 5.4 (1.7) for OTX-101 ($n=523$) and 5.5 (1.7) for vehicle ($n=525$). OTX-101 versus vehicle significantly reduced the total conjunctival staining scores ($P=0.0316$, <0.0001, and 0.0002) for days 28, 56, and 84, respectively. The most common treatment-related AE was instillation site pain (21.8% OTX-101 vs. 4.0% vehicle); most AEs were mild in nature.
Conclusions: Treatment with OTX-101 versus vehicle significantly improved the conjunctival staining in KCS as early as 4 weeks, and the improvement was maintained through 12 weeks. OTX-101 was effective and well tolerated for use in KCS.

Keywords: keratoconjunctivitis sicca, dry eye disease, nanomicelles, OTX-101

Introduction

Dry eye disease, or keratoconjunctivitis sicca (KCS), is a multifactorial disease characterized by tear instability and loss of tear film homeostasis.[1] KCS is prevalent in ~16.4 million people in the United States; prevalence outside the United States vary from 5% to 33% depending on the geographical location.[2] Advancing age is a risk factor for KCS and there is a higher prevalence in Asians.[2] The incidence rate for KCS is higher among females and the gender

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difference becomes more pronounced with increasing age.[2] In addition, there is a trend toward increasing prevalence of KCS in the younger population, potentially due to increased digital device usage.[2] KCS is associated with reduced work productivity and significant health care burden and cost.[2]

Based on the causative factors, KCS can be broadly classified into evaporative dry eye and aqueous deficient dry eye, although a mixed type with characteristics of both subtypes is common.[3] Regardless of subtype, KCS is characterized by a vicious cycle where tear hyperosmolarity leads to inflammation and results in ocular surface damage.[3]

Cyclosporine A (CsA) exerts its anti-inflammatory action by blocking T cell activation and the subsequent release of proinflammatory cytokines.[4] Unlike glucocorticoids, CsA also has an antiapoptotic action on the conjunctival goblet cells that are essential for tear production and maintenance of ocular homeostasis.[3,5,6] The disease modifying potential of CsA may reduce the need for further immunomodulatory treatment with glucocorticoids, long-term use of which are associated with undesirable adverse effects such as ocular hypertension and increased risk of infections.[5]

Currently marketed CsA emulsions (eg, Restasis®; Allergan, Irvine, CA) are limited by a low bioavailability in ocular tissues, which may affect the onset of efficacy, and overall patient dissatisfaction.[7–9] The unmet need for faster efficacy and enhanced delivery of CsA into ocular tissues has led to the development of newer formulations.

OTX-101 (CsA 0.09%, CEQUA™; Sun Pharmaceutical Industries, Inc., Cranbury, NJ) is a novel clear aqueous nanomicellar solution recently approved by the Food and Drug Administration (FDA) to increase tear production in patients with KCS.[10] Both phase 2b/3 and phase 3 clinical trials independently showed that OTX-101 0.09% was superior to vehicle in increasing tear production and improving both conjunctival and corneal staining in patients with KCS.[11] This analysis pooled data from both studies to compare the effect of OTX-101 0.09% versus vehicle on conjunctival zone staining in patients with KCS. Conjunctival staining, an objective sign of KCS, correlates with disease severity.[12,13] Staining of the lateral versus medial conjunctival zone may indicate more advanced disease and progression of KCS.[13,14] Therefore, conjunctival staining was analyzed in each zone.

Methods

Study design

This study reports the pooled analysis of phase 2b/3 (NCT02254265) and phase 3 (NCT02688556) trials, the study design, and methods of which are published[11] and briefly described here. The studies were both 12-week randomized multicenter double-masked vehicle-controlled studies. Patients were enrolled from a total of 29 centers for phase 2b/3 and from 45 centers for phase 3 studies, all in the United States. Before the study initiation, all study-related documents were submitted to a central institutional review board for approval. The studies were conducted in accordance with the guidelines of Declaration of Helsinki, the International Council for Harmonization, and all applicable U.S. federal regulatory requirements.[11]

Time points and treatments. All enrolled patients entered a run-in period before randomization in both studies during which the patients received 1 drop of vehicle per eye, twice daily (Supplementary Fig. S1). In phase 2b/3, the run-in period was 14 to 17 days and the patients were randomized 1:1:1 to OTX-101 0.05%, 0.09%, or vehicle. Study visits were at baseline (day 0) and on days 14, 28, 42, 56, and 84 (or at early discontinuation).

In the phase 3 study, the run-in period was 14 to 20 days and the patients were randomized 1:1 to OTX-101 0.09% or vehicle. Visit days were at baseline and on days 28, 56, and 84 (or at early discontinuation). The vehicle was identical to OTX-101, except for the omission of the active component (CsA). During the treatment period, patients self-administered 1 drop of treatment from a new unit dose vial to both eyes twice daily for a total of 84 days, and the accountability was assessed at each study visit by the monitor. Artificial tears or combination therapy was not allowed by any patients in either study.

All study personnel and patients were blinded to the randomization assignments during the treatment phase of the studies. The current analysis only reports the pooled data from the FDA-approved dose of 0.09% versus vehicle from the common study time points of phase 2b/3 and phase 3 studies (baseline; days 28, 56, and 84; or early discontinuation).

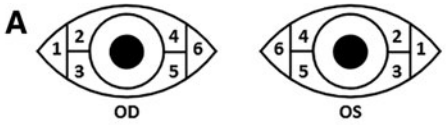
Patient selection. Both studies had identical eligibility criteria that were published previously.[11] The key inclusion criteria for both studies were adults ≥18 years of age with a patient-reported history and clinical diagnosis of bilateral KCS for at least 6 months; total conjunctival staining score of ≥3 to ≤9 out of a possible score of 12 (excluding the superior zones) in the same eye at both screening and baseline; and willingness to discontinue any current dry eye therapy during the study, beginning from the run-in period. Key exclusion criteria were use of CsA ophthalmic emulsion 0.05% within 3 months before screening or a history of treatment failure to CsA ophthalmic emulsion 0.05%, diagnosis of Sjögren's disease >5 years before screening, and presence of concurrent ocular diseases or select prior ocular procedures.

Total conjunctival staining

Conjunctival staining was performed at baseline and on days 28, 56, and 84 (or early discontinuation) before treatment using 1 drop (10 μL) of 1% lissamine green staining dye solution by pipette. The staining was evaluated 1 to 4 min after instillation under low-to-moderate intensity white light from the slit lamp. The individual 6 conjunctival zones were evaluated and graded on a 0-to-3-point scale (Fig. 1). For the analysis, zones 2 and 4 were combined as the superior zone and zones 3 and 5 were combined as the inferior zone.

Additional assessments

Other assessments included corneal fluorescein staining and grading and Symptom Assessment iN Dry Eye to assess frequency and severity of dryness and/or irritation; assessments were performed on days 0, 28, 56, and 84 (or early discontinuation); unanesthetized Schirmer's test to assess tear production was performed on days 0 and 84.



B

Grade	Description
0	No punctate stain in zone
1	Scattered micropunctate stain spots
2	Moderately concentrated micropunctate stain spots
3	Densely concentrated micropunctate stain spots

FIG. 1. **(A)** Schematic of the eye with individual conjunctival zones indicated and **(B)** grading of conjunctival staining. Medial, zone 6; lateral, zone 1; inferior, zones 3+5; superior, zones 2+4; total, medial+lateral+inferior zones. OD, right eye; OS, left eye.

Safety. Snellen visual acuity (VA) and slit-lamp examination were done at baseline and on days 28, 56, and 84 (or early discontinuation). Intraocular pressure (IOP) measurements and fundus examination were performed at screening and on day 84. All adverse events (AEs) were monitored spontaneously throughout the study, from time of informed consent until the last study visit. The incidence of AEs was summarized and classified according to the Medical Dictionary for Regulatory Activities version 19.0.

Statistical analysis

Efficacy analyses included all the randomized patients in the intent-to-treat population from phase 2b/3 and phase 3 studies, and the safety population included all patients who received at least 1 dose of either OTX-101 0.09% or vehicle. The data for this secondary analysis were pooled at the common time points (baseline and study days 28, 56, and 84) from both eyes of all patients. Summary statistics (*n*, mean, median, minimum, and maximum) were prepared for the continuous variables describing observed values and arithmetic changes from baseline on a by-patient basis.

Only the eye zones with nonzero conjunctival scores at baseline were included for the calculation of percentage change from baseline. The total single eye score was calculated by first averaging the scores of the inferior zones 3 and 5 before summing with the medial and lateral single zone scores. Zones 2 and 4 (superior) were excluded at screening and for data analysis to reduce variability between the treatment groups.

Test statistics of conjunctival scores were from a restricted maximum likelihood repeated measures mixed model on change from baseline values with baseline as a covariate (and visit when applicable) and its interaction with treatment group as repeated measures on observations from both eyes using an unstructured covariance structure. *P* values for the differences in mean changes from baseline between the treatments were calculated using an analysis of covariance.

Results

Patient disposition and demographics

This pooled analysis included 523 patients in the OTX-101 0.09% arm and 525 patients in the vehicle arm, of whom 93.1% and 96.2% completed the study, respectively (Fig. 2 and Table 1). The mean age [standard deviation (SD)] of the enrolled patients was 58.6 years (14.2) for OTX-101 0.09% and 59.5 years (14.4) for vehicle (Table 2). The majority of patients were female (83.6% in OTX-101 0.09% and 82.1% in vehicle group).

Effect of OTX-101 on conjunctival staining

The total mean (SD) conjunctival staining scores at baseline were similar for the 2 treatment groups: 5.4 (1.9) for OTX-101 0.09% and 5.5 (1.9) for vehicle. On day 84, the total mean (SD) conjunctival staining score for both eyes was 3.9 (2.3) for OTX-101 vs 4.5 (2.5) for vehicle (Table 3).

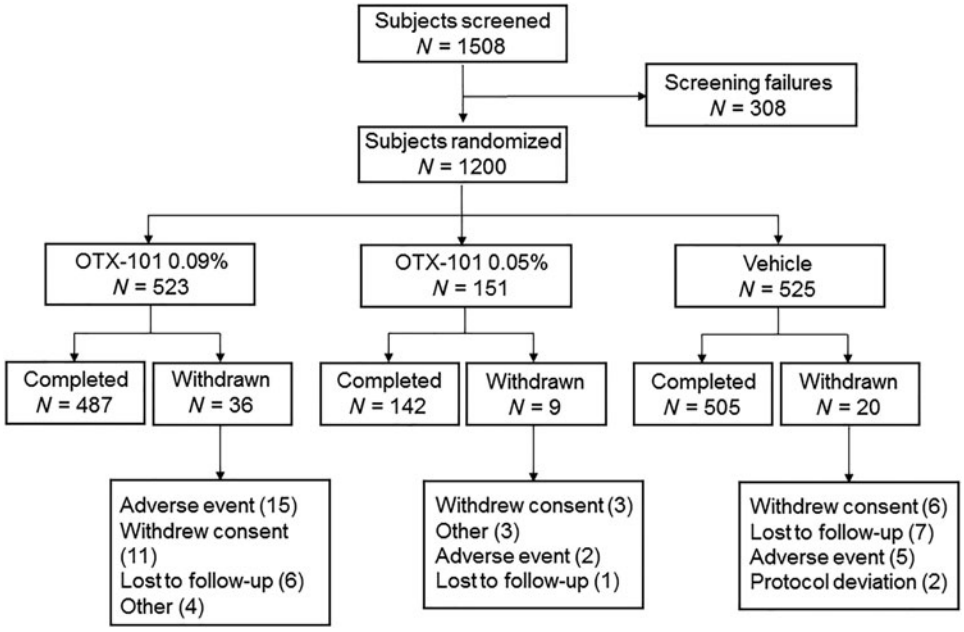


FIG. 2. Patient disposition. Patients who received OTX-101 0.05% only in the phase 2b/3 study are not included in the present pooled analysis.

Table 1. Patient Disposition of the Pooled Population

	OTX-101 0.09%, N = *523*	*Vehicle*, N = *525*
Patient completed	487 (93.1)	505 (96.2)
Reasons for withdrawal		
Adverse event	15 (2.9)	5 (1.0)
Withdrawal of consent	11 (2.1)	6 (1.1)
Lost to follow-up	6 (1.1)	7 (1.3)
Other	4 (0.8)	2 (0.4)

Data presented as *n* (%) of patients. Phase 2b/3 study evaluated OTX-101 0.05% and 0.09%; OTX-101 0.05% was not included for the pooled analysis.

Treatment with OTX-101 0.09% significantly reduced total conjunctival staining scores at all time points compared with vehicle ($P = 0.0316$, <0.0001, and 0.0002 for days 28, 56, and 84, respectively) (Fig. 3A). Similarly, OTX-101 0.09% significantly reduced the conjunctival staining scores at all time points compared with vehicle in the inferior and superior zones (Fig. 3D, E) and on days 56 and 84 in the lateral zone (Fig. 3C). For the medial zone, the scores between the groups were similar at all time points (Fig. 3B).

Other assessments

There were significantly more eyes with a clinically relevant improvement (defined as ≥10 mm increase from baseline) in Schirmer's test score on day 84 with OTX-101 0.09% than vehicle in both studies. Treatment with OTX-101 0.09% versus vehicle significantly decreased corneal staining from baseline. Global symptom scores (SD) were similar for both treatment groups at baseline [62.9 (15.4) vs. 62.0 (15.6) for OTX-101 and vehicle, respectively] and had a similar percentage change from baseline (SD) on day 84, –29.0 (39.0) vs. –30.4 (39.5) for OTX-101 and vehicle, respectively.

Table 2. Demographic and Baseline Clinical Characteristics of the Pooled Population

	OTX-101 0.09%, N = *523*	*Vehicle*, N = *525*
Age, years, mean (SD)	58.6 (14.2)	59.5 (14.4)
Sex		
Male	86 (16.4)	94 (17.9)
Female	437 (83.6)	431 (82.1)
Ethnicity		
Hispanic or Latino	86 (16.4)	84 (16.0)
Not Hispanic or Latino	437 (83.6)	441 (84.0)
Race		
White	436 (83.4)	425 (81.0)
American Indian or Alaskan Native	1 (0.2)	0
Native Hawaiian or other Pacific Islander	0	3 (0.6)
Black or African American	54 (10.3)	65 (12.4)
Asian	18 (3.4)	15 (2.9)
Other	14 (2.7)	17 (3.2)

Data presented as *n* (%) of patients unless indicated.
SD, standard deviation.

Table 3. Mean Conjunctival Staining Score (SD) in Both Eyes at Baseline and on Day 84

	OTX-101 0.09%, N = *523*	*Vehicle*, N = *525*
Total conjunctival score		
Baseline	5.4 (1.7)	5.5 (1.7)
Day 84	3.9 (2.3)	4.5 (2.5)
Medial zone		
Baseline	1.4 (0.7)	1.4 (0.6)
Day 84	1.0 (0.8)	1.1 (0.8)
Lateral zone		
Baseline	0.9 (0.6)	1.0 (0.7)
Day 84	0.6 (0.7)	0.8 (0.7)
Superior zone		
Baseline	1.0 (0.6)	1.1 (0.6)
Day 84	0.7 (0.6)	0.9 (0.7)
Inferior zone		
Baseline	1.5 (0.6)	1.6 (0.6)
Day 84	1.1 (0.7)	1.3 (0.7)

SD, standard deviation.

Safety. In the pooled analysis, most treatment-emergent AEs (TEAEs) were mild or moderate in nature and resolved without treatment. The most frequently reported TEAE was instillation site pain: 21.8% in OTX-101 0.09% group vs. 4.0% in vehicle group followed by conjunctival hyperemia (5.7% and 3.6%, respectively).

A summary of TEAEs that occurred in ≥1% of patients is shown in Table 4. There were no clinically significant changes from baseline in VA and IOP measurements. Fundus examination revealed 1 clinically significant shift from baseline in 1 patient (0.2%) from each treatment arm. Very few patients discontinued the study due to AEs (2.9% in OTX-101 0.09% and 1.0% in vehicle group, Table 1). There were no serious TEAEs that were considered related to treatment. There was 1 death under OTX-101 0.09% arm in phase 3 trial but it was not considered related to the treatment.

Discussion

In this pooled analysis of phases 2b/3 and 3 studies, OTX-101 0.09% significantly decreased conjunctival staining compared with vehicle at 4 weeks and each subsequent planned assessment through 12 weeks. Both trials separately and pooled showed that OTX-101 0.09% was superior to vehicle in improving the clinical signs of KCS with acceptable safety and tolerability.[11] The improvement in both conjunctival and corneal staining occurred at 28 days and continued through the end of the study after treatment with OTX-101.[9] The early onset of effect seen with this CsA formulation (OTX-101 0.09%) could potentially help improve patient compliance.[15]

Clearing of conjunctival staining correlates with the improvement of ocular surface integrity and the underlying inflammation.[8,14] Therefore, the decreased staining noted with OTX-101 0.09% treatment vs vehicle suggests the effective release of CsA from nanomicelles, and it reaching local therapeutic levels in ocular tissue. A significant

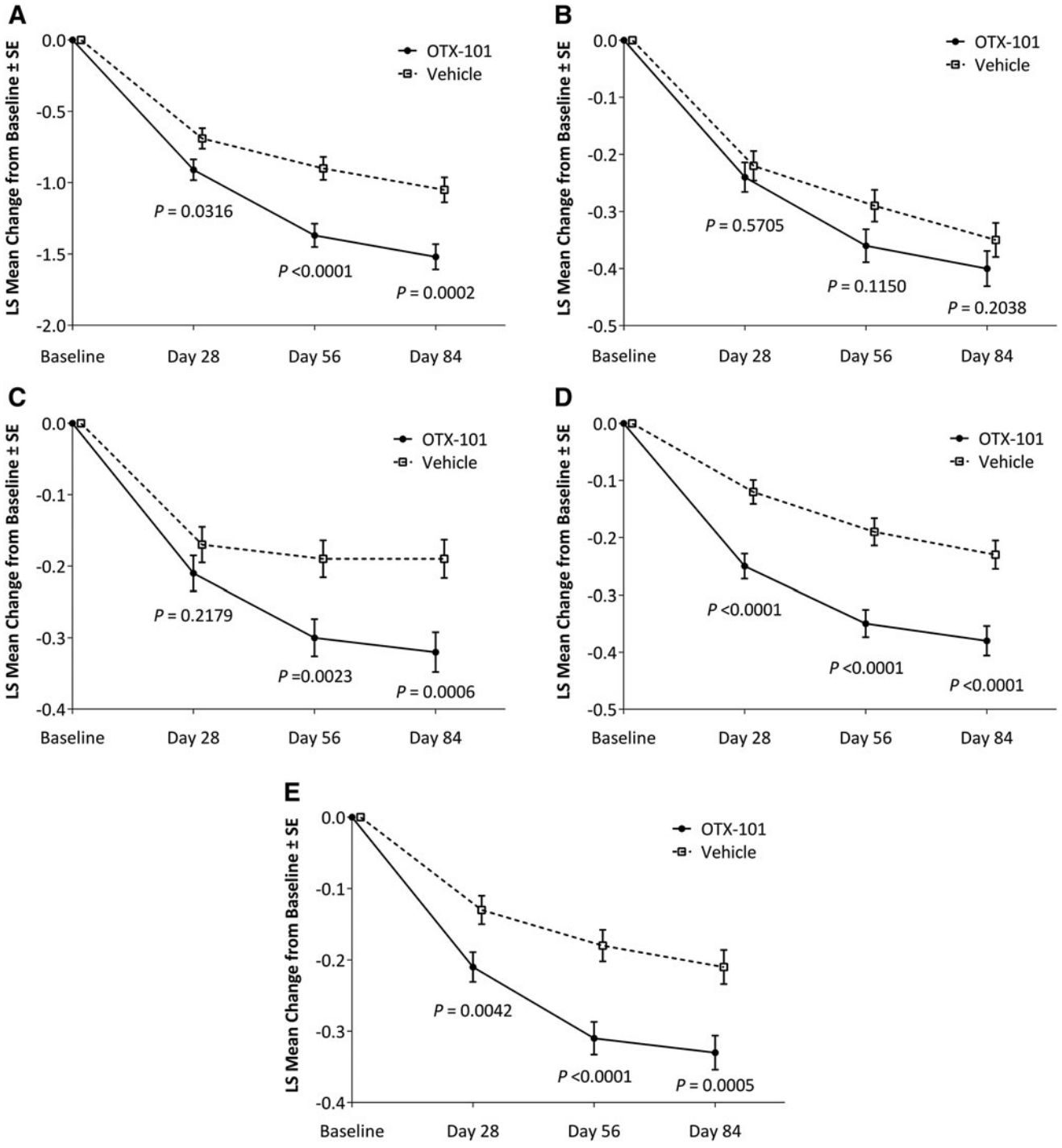


FIG. 3. Least squares mean change from baseline in conjunctival staining in the pooled population treated with OTX-101 0.09% versus vehicle on days 28, 56, and 84 for **(A)** total (medial, lateral, and inferior), **(B)** medial, **(C)** lateral, **(D)** inferior, and **(E)** superior conjunctival zones. LS, least squares; SE, standard error.

decrease from baseline of conjunctival staining was seen in all individual zones except the medial zone. However, it should be noted that the medial zone had the lowest conjunctival staining score at baseline compared with other zones. In addition, the medial zone staining is often associated with mild KCS or with nonspecific staining seen in asymptomatic patients.[13]

Both studies enrolled patients with baseline total conjunctival staining score of ≥3 to ≤9 out of 12. This could be a potential limitation as the analysis may not represent patients with very mild or very severe conjunctival damage. The exclusion of patients with Sjögren's disease precludes the generalization of the results to the severe forms of KCS, as these patients tend to have a strong correlation with severe clinical signs such as lateral conjunctival staining.[16] Although the study duration of 84 days is considered relatively short, significant efficacy was achieved throughout the study period; this suggests the possibility of continued improvement, provided use of OTX-101 0.09% is extended.

Table 4. Summary of Common (≥1%) Ocular and Nonocular Treatment-Emergent Adverse Events in the Pooled Safety Population

	OTX-101 0.09%, N = *524*	*Vehicle,* N = *524*
Eye disorders		
Conjunctival hyperemia	30 (5.7)	19 (3.6)
Eye irritation	6 (1.1)	6 (1.1)
Blepharitis	5 (1.0)	0
Eye pruritus	2 (0.4)	8 (1.5)
Foreign body sensation in eyes	2 (0.4)	5 (1.0)
Vitreous floaters	2 (0.4)	5 (1.0)
Instillation site conditions		
Pain	114 (21.8)	21 (4.0)
Nonocular events		
Headache	8 (1.5)	2 (0.4)
Urinary tract infection	6 (1.1)	4 (0.8)
Bronchitis	5 (1.0)	3 (0.6)
Sinusitis	4 (0.8)	5 (1.0)
Upper respiratory tract infection	4 (0.8)	5 (1.0)
Nasopharyngitis	1 (0.2)	5 (1.0)

Data presented as *n* (%) of patients. *N* is number of patients in the safety population.

Most of TEAEs were mild or moderate in nature, with the occurrence of instillation site reactions comparable with that experienced with the marketed emulsion formulations.[17,18] Most of the complaints of instillation site pain were transient and rated mild in intensity. A long-term safety extension study after OTX-101 use for up to 1 year showed similar incidences of instillation site pain as seen in the treatment phase of the phase 3 study.

This secondary analysis of phase 2b/3 and 3 trials showed that OTX-101 0.09% is superior to vehicle in decreasing the conjunctival staining in patients with KCS at and after 4 weeks of therapy. Overall, these results support OTX-101 0.09% as an effective and well-tolerated treatment in the management of KCS.

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Author Disclosure Statement

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Supplementary Material

Supplementary Figure S1

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