Long-term safety of OTX-101 0.09%, a novel nanomicellar formulation of cyclosporine A, and its efficacy in patients with keratoconjunctivitis sicca

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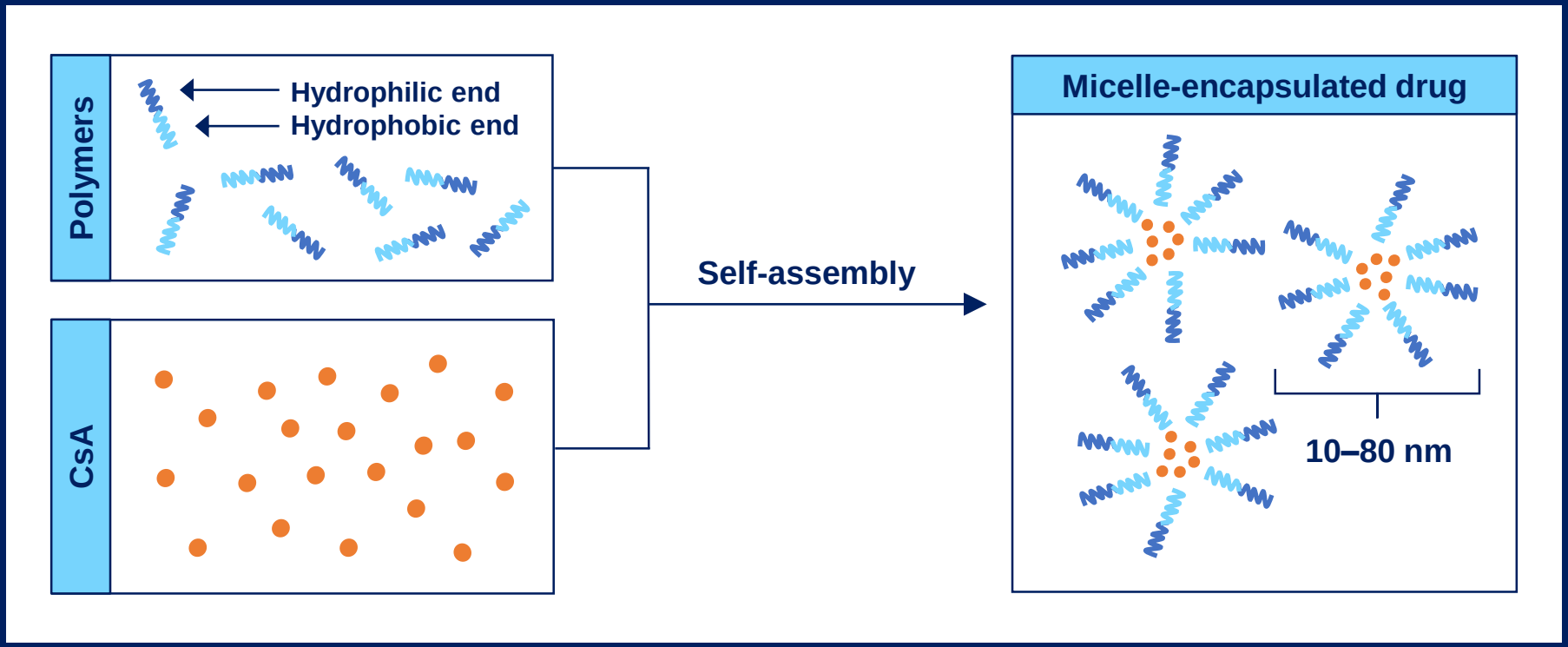
Introduction

- KCS is a multifactorial disease of the ocular surface, characterized by loss of homeostasis of the tear film[1]
- The central mechanism of KCS is evaporative water loss of inadequate aqueous product, both of which lead to hyperosmolarity, inflammation, and damage to the ocular surface, including damage to the cornea and conjunctiva[2]
- OTX-101 (CEQUA™)—a novel, nanomicellar formulation of CsA approved by the FDA to increase tear production in patients with KCS—was designed to deliver high CsA levels to relevant ocular tissues to address the underlying inflammation associated with KCS[3-5]

CsA, cyclosporine A; FDA, US Food and Drug Administration; KCS, keratoconjunctivitis sicca.

OTX-101 Formulation

- The nanomicelle structures in OTX-101 are formed using polymers that entrap the lipophilic molecules within its hydrophobic core, while the hydrophilic (water soluble) domain of the polymers make up the outer shell[6]



CsA, cyclosporine A.

OTX-101

- Both phase 2b/3 and phase 3 clinical trials independently showed OTX-101 0.09% was superior to vehicle in improving tear production and conjunctival and corneal staining in patients with KCS[4,5]
- Conjunctival staining, an objective sign of KCS, correlates with disease severity[7]
- CFS indicates corneal damage associated with KCS; reduced CFS indicates improvements in the corneal surface integrity[8]
- Unanesthetized Schirmer's test estimates stimulated reflex tear flow, and is used to diagnose loss of tear volume, which may be a key pathogenic mechanism in KCS[9]
- Few studies have evaluated the long-term safety of topical ophthalmic CsA[10]

CFS, corneal fluorescein staining; CsA, cyclosporine A; KCS, keratoconjunctivitis sicca.

Objectives

- The objectives of this analysis were:
  - Determine the percent of eyes with a clinically relevant improvement in tear production (defined as an increase of ≥10 mm from baseline in Schirmer's test) in the worse eye in patients with KCS
  - Evaluate the long-term safety of OTX-101 0.09% after 12 months of use in the safety extension phase of the study

KCS, keratoconjunctivitis sicca.

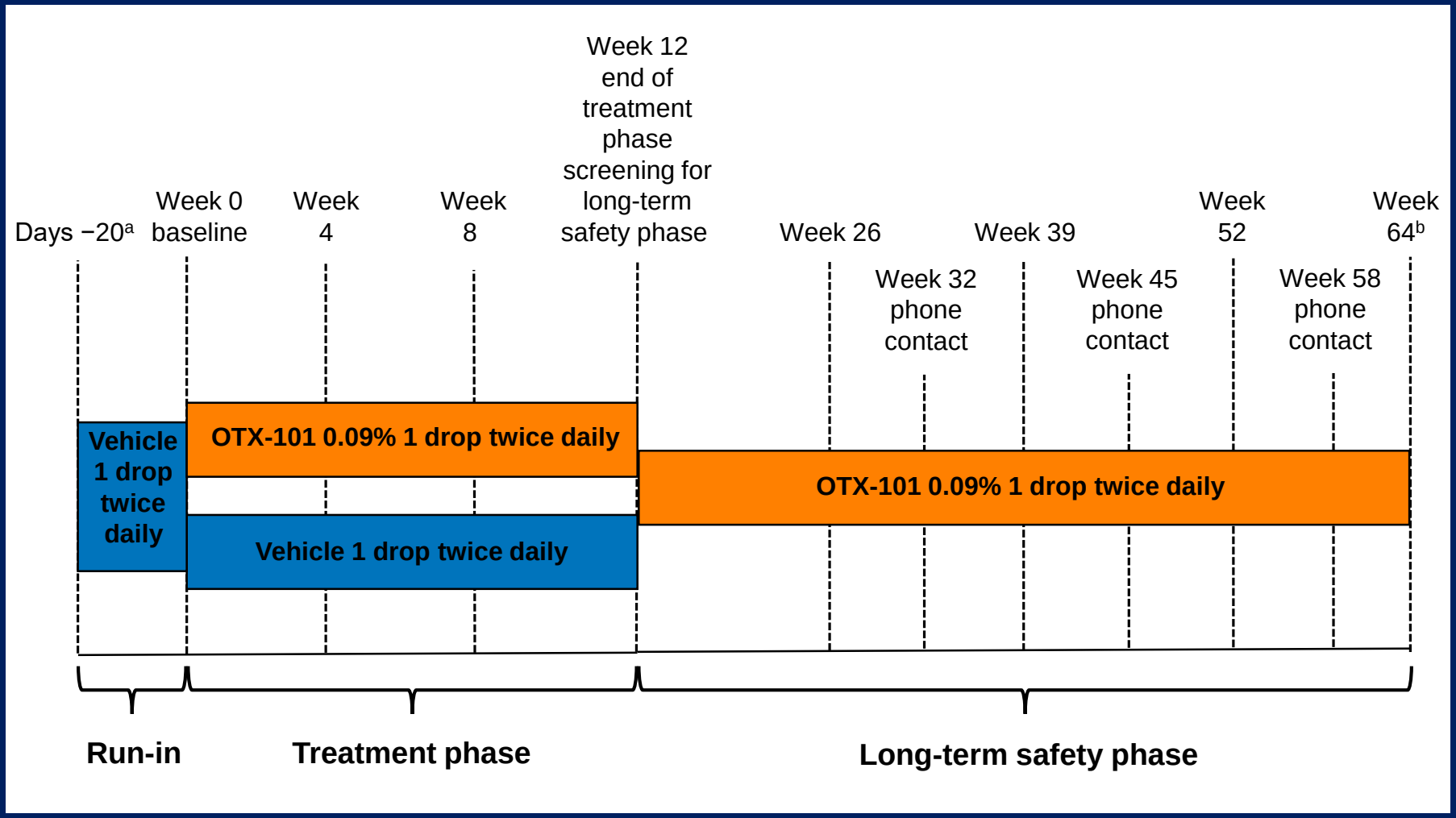
Methods

Study design

- This phase 3, randomized, multicenter study was comprised of 3 phases:
  - Run-in phase: All patients received 1 drop of vehicle per eye twice daily for 14 to 20 days
  - Treatment phase: Patients randomized 1:1 to receive 1 drop of OTX-101 0.09% or vehicle in both eyes twice daily for 12 weeks
  - Long-term safety phase of up to 52 weeks: All patients received 1 drop of OTX-101 0.09% in each eye twice daily for 40 weeks; former vehicle arm had option to participate for an additional 12 weeks, for a total of 52 weeks of therapy

Methods

Study design



[a]Run-in vehicle therapy began 14 to 20 days before baseline.
[b]Former vehicle therapy arm received additional 40 to 52 weeks of OTX-101 therapy.

Methods

Study population

- **Key inclusion criteria:**
  - Age of 18 years or older
  - A self-reported history of ≥6 months of KCS
  - Clinical diagnosis of bilateral KCS
  - Total conjunctival staining sum score of 3–9 out of a possible score of 12, excluding the superior zones, in the same eye
  - Global symptom assessment in dry eye score ≥40 out of a possible 100, both at screening and baseline visits
  - Snellen VA ≥20/200 in each eye
  - Willingness to discontinue any current dry eye treatment
  - For enrollment in the long-term safety extension, successful completion of the treatment phase and corrected Snellen VA >20/200 in each eye at week 12 were further required

KCS, keratoconjunctivis sicca; VA, visual acuity.

Methods

Study population

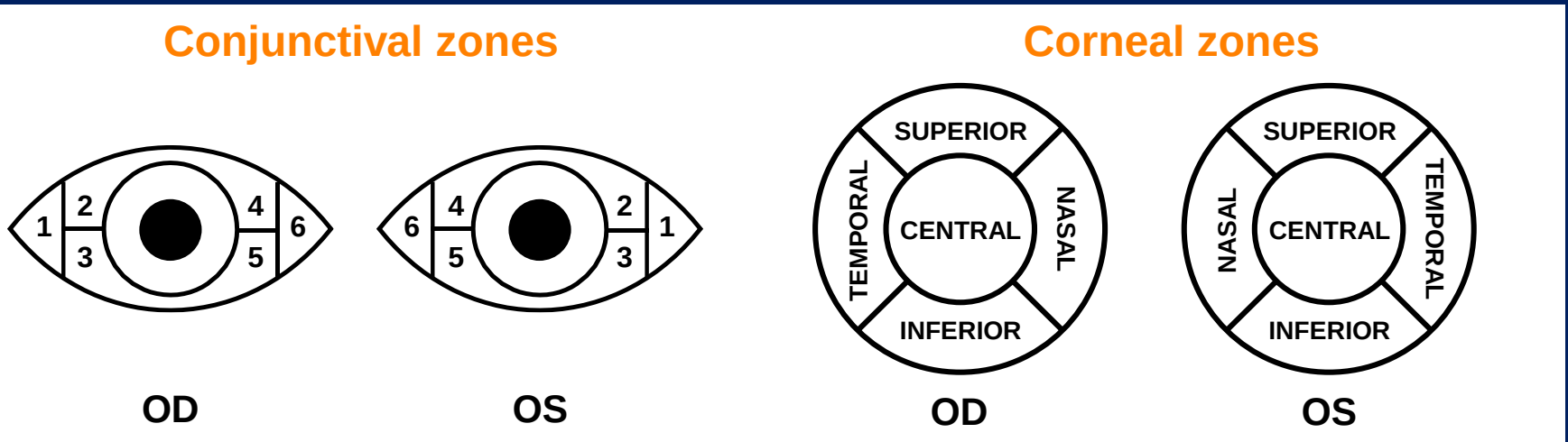
- **Key exclusion criteria:**
  - Use of cyclosporine ophthalmic emulsion 0.05% within 3 months before screening
  - Previous treatment failure with cyclosporine ophthalmic emulsion 0.05%
  - Diagnosis of Sjögren's disease >5 years before screening
  - Corneal refractive surgery within 6 months of screening
  - Key exclusion criteria for the long-term safety extension further included:
    - An AE that had not resolved by week 12 of the treatment phase
    - Use of any topical cyclosporine preparation (excluding OTX-101) or prescription topical ophthalmic medications other than unpreserved artificial tears after the week 12 visit of the treatment phase

AE, adverse event.

Methods

Assessments

- An unanesthetized Schirmer's test was performed at baseline and week 12 (or early discontinuation) of the treatment phase
  - A test strip was placed in both eyes at the same time and remained in place for 5 minutes
  - Strips were removed after 5 minutes and the amount of wetting was recorded in millimeters
- Conjunctival and corneal staining were performed at screening, baseline, and weeks 4, 8, and 12 (or early discontinuation) of the treatment phase



OD, right eye; OS, left eye.

Methods

Assessments

- For conjunctival staining, 1 drop (10 µL) of 1% lissamine green was instilled in each eye and, after 1 to 4 minutes, staining was measured under low to moderate intensity white light using a slit lamp
  - Six zones of the conjunctiva were scored on a 0- to 3-point scale (0 = no punctate stain in zone, 3 = densely concentrated micropunctate stain spots)
  - Zones were designated as 1 = lateral, 2 and 4 = superior, 3 and 5 = inferior, and 6 = medial
  - For the total conjunctival staining score, the scores for each eye (excluding superior zones 2 and 4) were summed for a total possible score of 0 to 12

Methods

Assessments

- For CFS, 1 drop (10 µL) of 0.5% fluorescein solution into the conjunctival cul-de-sac followed by adequate blinking
  - Five zones of the cornea were graded on a 0- to 4-point scale (0.5-point increments; 0 = no staining/clear and 4 = severe diffuse micropunctate staining)
- Worse eye was defined as the eye with the lower baseline Schirmer's score. If both eyes had the same score, the right eye was chosen

CFS, corneal fluorescein staining.

Methods

Safety assessments

- The primary endpoint was long-term safety of OTX-101 0.09% during the open-label extension phase as assessed by:
  - Corrected Snellen VA and SLE measured at treatment phase baseline and weeks 12, 26, 39, 52, and 64/early discontinuation
  - IOP measured at treatment phase screening and weeks 12, 26, 39, 52, and 64/early discontinuation
  - Ophthalmoscopy/dilated fundoscopy performed at treatment phase screening, and weeks 12, 52, and 64/early discontinuation
  - AEs monitored throughout the study at visits and via phone call between visits

AE, adverse event; IOP, intraocular pressure; SLE, slit-lamp examination; VA, visual acuity.

Methods

Statistical analysis

- Continuous variables were summarized with descriptive statistics (n, mean, median, SD, minimum, and maximum) while categorical variables were summarized with counts and percentages
- Expanded National Eye Institute scale was used for corneal scoring
- Missing Schirmer's test results at week 12 were imputed from baseline measures
- Comparisons of patients with Schirmer's score increase ≥10 mm used SAS® PROC GENMOD procedure, with eyes within patient as repeated measures and treatment as a fixed effect using an unstructured covariance structure
- Comparisons of patients with complete central corneal clearing used SAS® PROC GENMOD procedure, with visits and eyes within patients as repeated measures and treatment as a fixed effect using an unstructured covariance structure
- Comparisons of mean change from baseline used a restricted maximum likelihood repeated measures mixed model on change from baseline values, with baseline as a covariate and visit and its interaction with treatment group as repeated measures, using an unstructured covariance structure

SD, standard deviation.

Results

Patient demographics

- The study enrolled 745 patients—372 randomized to OTX-101 0.09% and 373 randomized to vehicle
  - One patient randomized to OTX-101 0.09% withdrew consent before receiving any study medication and was not included in the efficacy analyses
  - Overall, 93.3% of patients randomized to OTX-101 0.09% and 96.8% of patients randomized to vehicle completed the treatment phase
- A total of 258 patients—129 from each prior treatment group—continued to the long-term safety phase; 86.0% from the prior OTX-101 0.09% group and 61.2% from the prior vehicle group completed the study
  - Major reasons for discontinuation (n [%] of patients in prior OTX-101 vs prior vehicle group) included AEs (8 [6.2%] vs 14 [10.9%]), patient's decision (4 [3.1%] vs 12 [9.3%]), and administrative error and sponsor's decision to end study treatment (0 vs 11 [8.5%] for each reason)
- Mean (SD) age was 59.0 (14.4) years for patients in the treatment phase and 60.0 (14.9) years for patients continuing to the long-term safety phase

AE, adverse event; SD, standard deviation.

Results

Patient demographics

	Treatment phase		Long-term safety phase	
	OTX-101 n = 371	Vehicle n = 373	OTX-101[a] n = 129	Vehicle[a] n = 129
Age, years, mean (SD)	58.4 (14.1)	59.5 (14.7)	58.4 (15.5)	61.5 (14.2)
Sex				
Female	315 (84.9)	311 (83.4)	109 (84.5)	107 (82.9)
Ethnicity				
Hispanic or Latino	57 (15.4)	54 (14.5)	18 (14.0)	8 (6.2)
Not Hispanic or Latino	314 (84.6)	319 (85.5)	111 (86.0)	121 (93.8)
Race				
White	310 (83.6)	305 (81.8)	111 (86.0)	110 (85.3)
American Indian[b]	1 (0.3)	0	1 (0.8)	0
Hawaiian or Other Pacific Islander	0	1 (0.3)	0	1 (0.8)
Black or African American	41 (11.1)	45 (12.1)	3 (2.3)	3 (2.3)
Asian	11 (3.0)	12 (3.2)	3 (2.3)	3 (2.3)
Other	8 (2.2)	10 (2.7)	2 (1.6)	2 (1.6)

[a]During the treatment phase, patients self-administered 1 drop in each eye twice daily of OTX-101 0.09% or vehicle. All patients self-administered 1 drop of OTX-101 0.09% in each eye twice daily during the long-term safety phase. [b]Includes Alaska native in long-term safety phase. Data presented as n (%) unless otherwise indicated.
SD, standard deviation.

Results

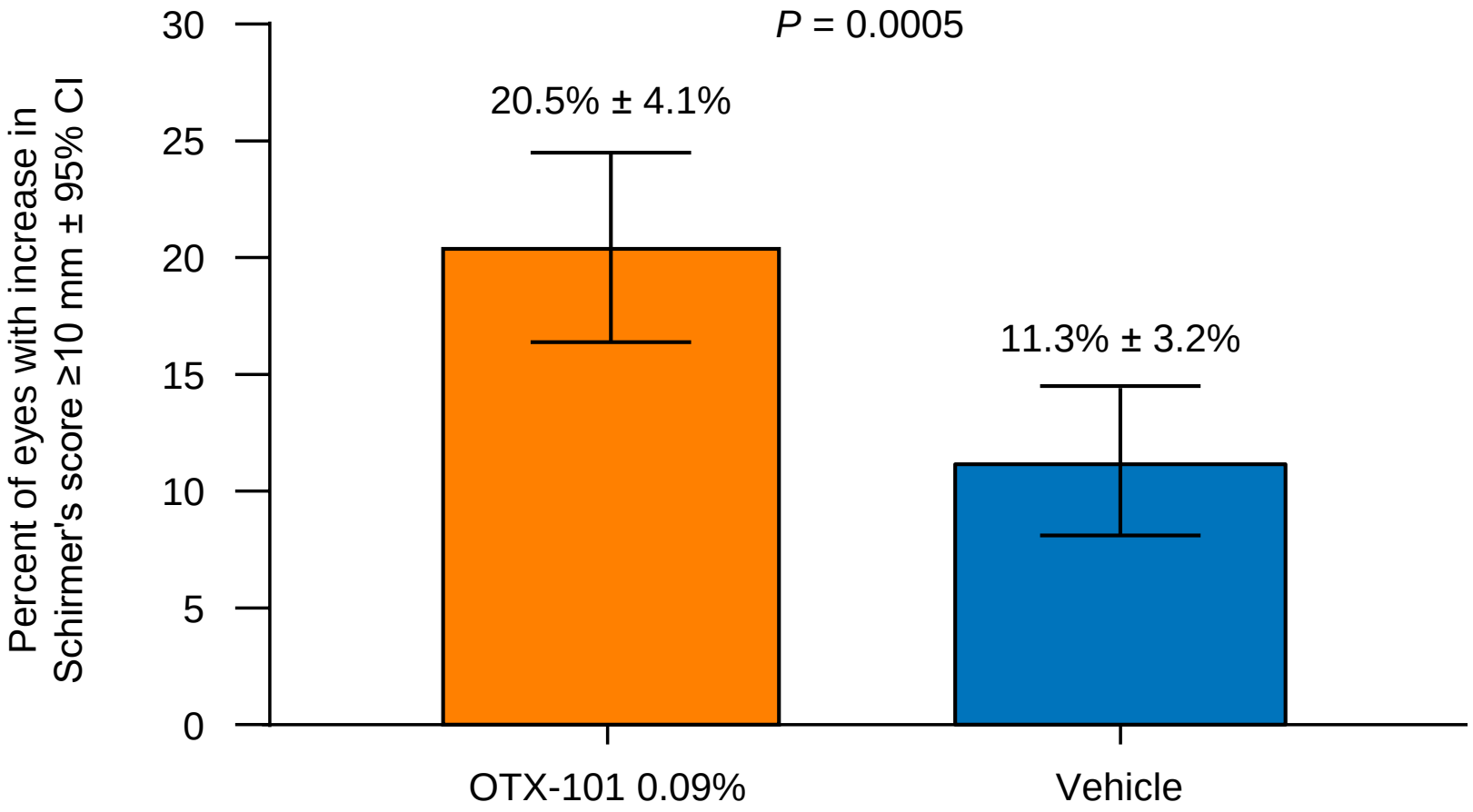
Baseline clinical characteristics

	OTX-101 0.09% n = 371	Vehicle n = 373
Schirmer's score, mean (SD)	9.7 (7.2)	10.2 (7.4)
Conjunctival staining score, mean (SD)		
Total[a]	5.5 (1.9)	5.5 (2.0)
Lateral	1.0 (0.7)	1.0 (0.8)
Inferior lateral	1.5 (0.8)	1.5 (0.7)
Inferior medial	1.6 (0.8)	1.6 (0.8)
Medial	1.5 (0.8)	1.4 (0.7)
Percent of patients with clear central corneas	28.8	28.2

Results are for the intent-to-treat population. Schirmer's scores and conjunctival staining scores describe worse eyes; central corneas describe both eyes per patients. [a]Total excludes superior zones.
SD, standard deviation.

Results

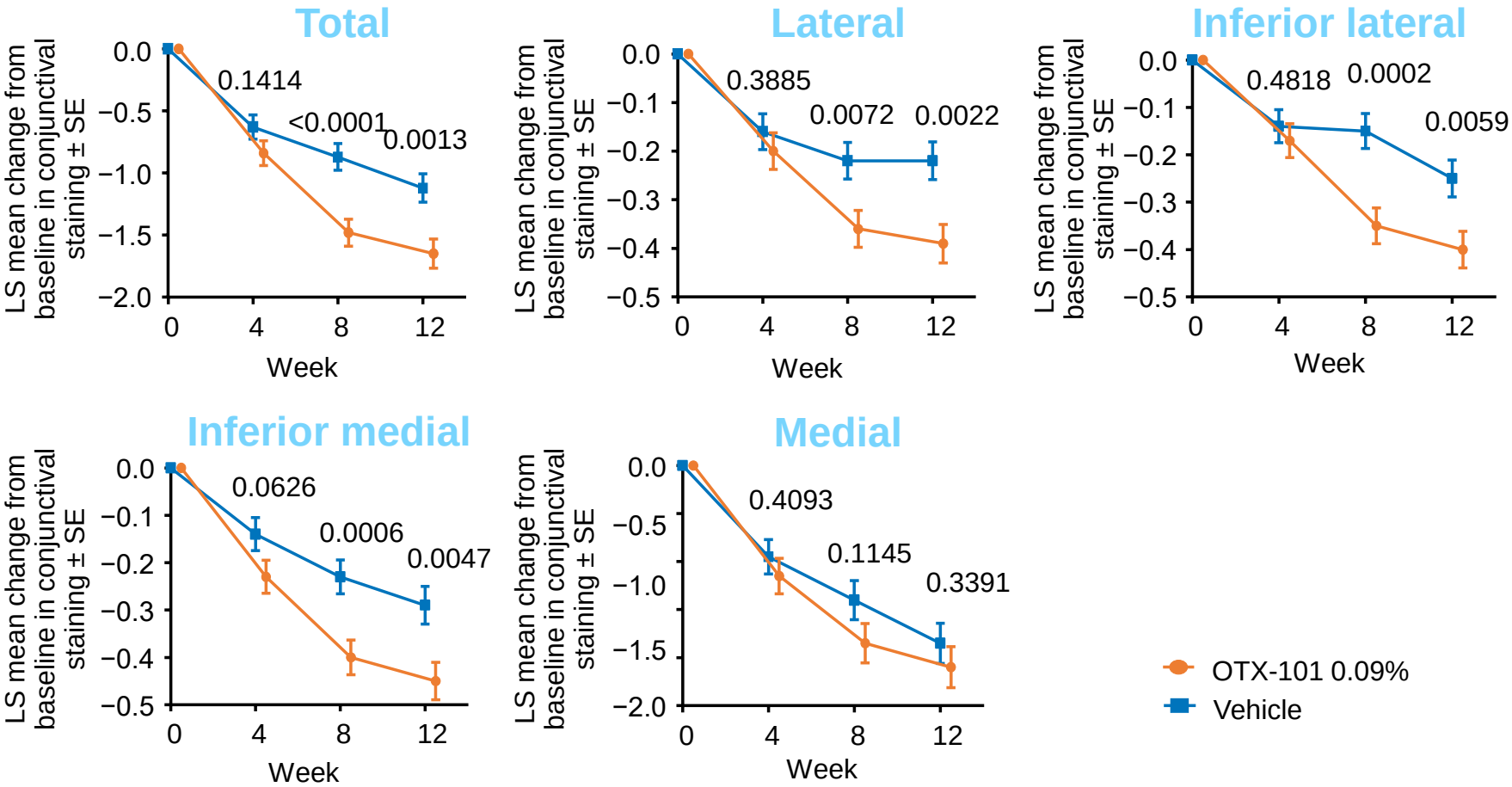
Percent of eyes with an increase of ≥10 mm at baseline



CI, confidence interval.

Results

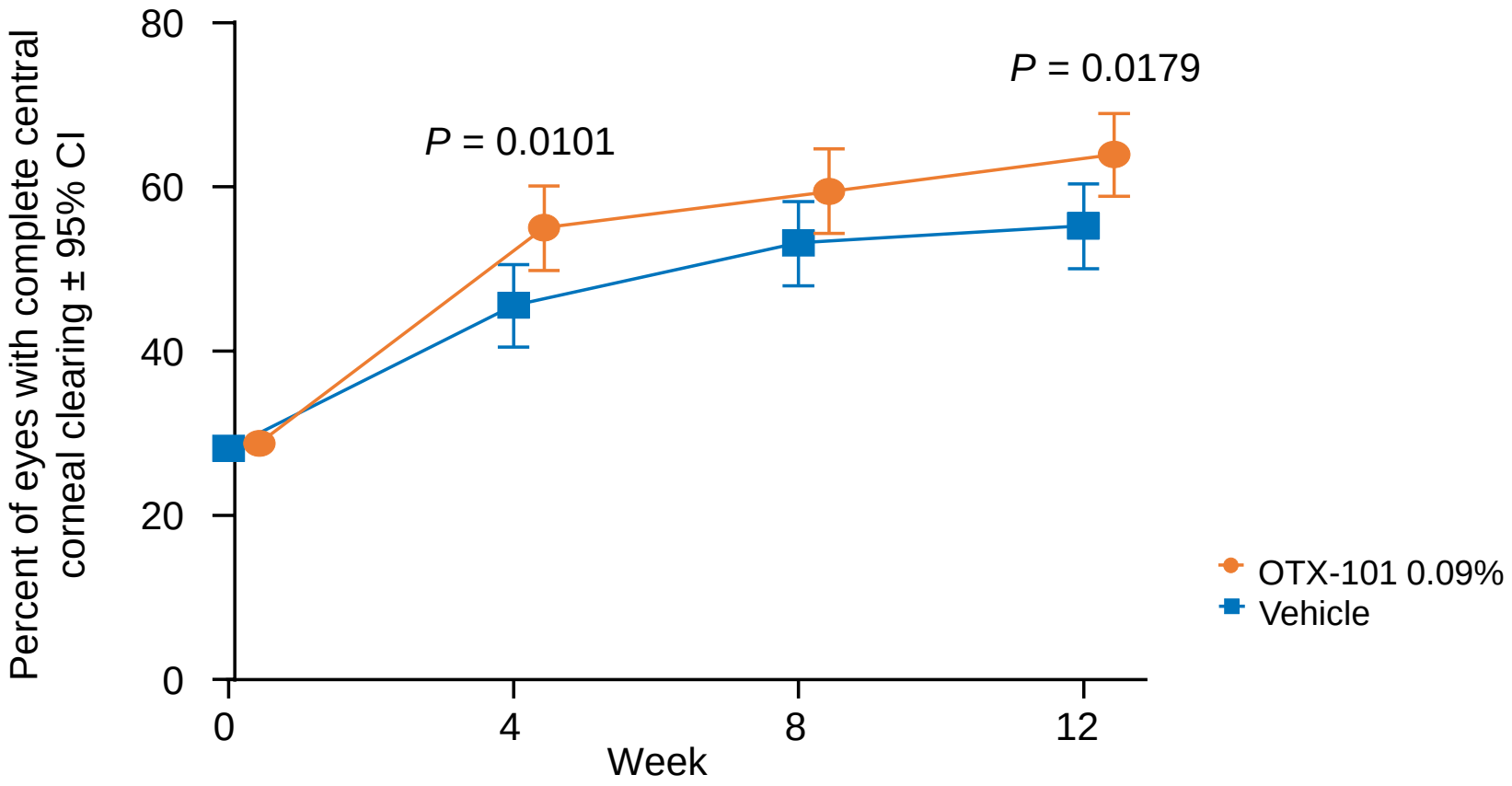
Least squares mean change from baseline in conjunctival staining



LS, least squares; SE, standard error.

Results

Percent of eyes with complete clearing of central cornea



CI, confidence interval.

Results

Efficacy assessment

- Baseline mean (SD) Schirmer's scores in the worse eye were 9.7 (7.2) and 10.2 (7.4) mm for the OTX-101 0.09% and vehicle groups, respectively
- Mean (SD) change from baseline in Schirmer's scores at week 12 was significantly higher in the OTX-101 0.09% group (4.0 [7.8] mm) vs the vehicle group (2.2 [6.8] mm, *P* = 0.0017)
- Mean (SD) total conjunctival staining scores in the worse eye at baseline were 5.50 (1.92) and 5.53 (1.96) for the OTX-101 0.09% and vehicle groups, respectively
- At weeks 8 and 12, OTX-101 0.09% significantly improved total conjunctival staining scores vs vehicle, as well as scores for the lateral, inferior lateral, and inferior medial zones
- There were no significant differences between OTX-101 0.09% and vehicle in least squares mean change from baseline in the medial zone
- At baseline, the percent of subjects with both eyes with complete central corneal clearing was 28.8% for the OTX-101 group and 28.2% for the vehicle group
- The percent of eyes with clear central corneas was significantly higher in the OTX-101 0.09% vs vehicle group at weeks 4 and 12

SD, standard deviation.

Safety

Summary of treatment-emergent adverse events during long-term safety phase

	Prior OTX-101 0.09%[a] n = 129	Prior vehicle[a] n = 129	Overall N = 258
Total AEs reported: n (%) patients	209:68 (52.7)	238:81 (62.8)	447:149 (57.8)
Patients reporting			
0 AEs	61 (47.3)	48 (37.2)	109 (42.2)
1 AE	13 (10.1)	12 (9.3)	25 (9.7)
>1 AE	55 (42.6)	69 (53.5)	124 (48.1)
Maximum intensity			
Mild	41 (31.8)	57 (44.2)	98 (38.0)
Moderate	24 (18.6)	22 (17.1)	46 (17.8)
Severe	3 (2.3)	2 (1.6)	5 (1.9)
Relationship to study drug			
Not suspected	45 (34.9)	32 (24.8)	77 (29.8)
Suspected	23 (17.8)	49 (38.0)	72 (27.9)
AEs leading to discontinuation	9 (7.0)	16 (12.4)	25 (9.7)
AEs leading to treatment interruption	5 (3.9)	5 (3.9)	10 (3.9)
SAEs	4 (3.1)	4 (3.1)	8 (3.1)

[a]During the treatment phase, patients self-administered 1 drop in each eye twice daily of OTX-101 0.09% or vehicle. All patients self-administered 1 drop of OTX-101 0.09% in each eye twice daily during the long-term safety phase. Data presented for the safety population as n (%) patients.
AE, adverse event; SAE, serious AE.

Safety

Treatment-emergent adverse events in ≥2% of patients during long-term safety phase

	Prior OTX-101 0.09%[a] n = 129	Prior vehicle[a] n = 129	Overall N = 258
Ocular			
Eye disorders			
Conjunctival hyperemia	12 (9.3)	14 (10.9)	26 (10.1)
Punctate keratitis	12 (9.3)	4 (3.1)	16 (6.2)
Blepharitis	3 (2.3)	4 (3.1)	7 (2.7)
Vitreous detachment	5 (3.9)	2 (1.6)	7 (2.7)
Posterior capsule opacification	5 (3.9)	1 (0.8)	6 (2.3)
General disorders and administration site conditions			
Instillation site pain	17 (13.2)	42 (32.6)	59 (22.9)
Non-ocular			
Infections and infestations			
Bronchitis	2 (1.6)	4 (3.1)	6 (2.3)

[a]During the treatment phase, patients self-administered 1 drop in each eye twice daily of OTX-101 0.09% or vehicle. All patients self-administered 1 drop of OTX-101 0.09% in each eye twice daily during the long-term safety phase. Data presented for the safety population as n (%) patients.

Results

Safety

- Median (SD) duration of exposure to OTX-101 0.09% during the long-term safety phase was 9.47 (2.40) months for the prior OTX-101 0.09% group, 9.53 (3.24) months for the prior vehicle group, and 9.50 (2.86) months overall
- Observed mean IOP values at baseline and all post-baseline time points were within normal limits for both eyes
- Snellen VA assessments did not exhibit any clinically significant changes or trends
- Three patients in the prior vehicle group found to have clinically significant mild conjunctival hyperemia upon SLE; conjunctival hyperemia was considered treatment related but did not result in interruption or permanent withdrawal of study treatment
- All abnormal clinically significant findings from dilated fundoscopy were mild, not considered treatment related, and did not require any action regarding changes in study medication
- The most common AE was instillation site pain, occurring in 59 (22.9%) patients; 17 patients (13.2%) vs 42 (32.6%) in the prior OTX-101 0.09% and vehicle group, respectively
  - Instillation site pain was mostly mild; 1 (0.8%) patient in the prior vehicle group had severe instillation site pain and this was the only severe AE suspected to be related to study drug

AE, adverse event; IOP, intraocular pressure; SD, standard deviation; SLE, slit-lamp examination; VA, visual acuity.

Conclusions

- Treatment with OTX-101 0.09% significantly improved objective signs of KCS as demonstrated by:
  - Clinically meaningful improvement of tear production at week 12 compared to baseline
  - Improvement in total, lateral, inferior lateral, and inferior medial conjunctival staining scores compared to vehicle first observed at week 8 and sustained through week 12
  - Higher percent of patients with clear central corneas relative to vehicle
- OTX-101 0.09% appeared well-tolerated in patients with KCS during a 1-year long-term safety extension phase
- Results presented here support the safety of long-term use of OTX-101 0.09% for the treatment of KCS

KCS, keratoconjunctivitis sicca.

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Disclosures

- JL receives personal fees from Alcon; Allergan; Bausch + Lomb; Shire; TearLab; and Sun Pharmaceutical Industries, Inc; and other fees from Calhoun Vision, CLXO, Insightful Solutions, and Trefoil Therapeutics.
- BS receives fees from Johnson & Johnson; Shire; Valeant; and Sun Pharmaceutical Industries, Inc.
- JS reports personal fees from Allergan; Alcon/Novartis; Avedro; Bausch + Lomb; Clementia Pharma; Ocular Therapeutix; Science Based Health; Senju; Shire; Sun Pharmaceuticals Industries, Inc.; TearLab; TearScience; Topcon; and TopiVert; and other fees from Alcon/Novartis, Kala Pharmaceuticals, Novaliq, Noveome, Ocular Therapeutix, Shire, and TearLab.
- AO is an employee of Sun Pharmaceutical Industries, Inc.
- CD is a contracted statistical consultant to Sun Pharma Advanced Research Company, Ltd.
- MB receives fees from ICON Clinical Research, InSite Vision, Kala Pharmaceuticals, Oculos Clinical Research, RevitaLid, and Shire.
- PK receives fees from Aerie, Akorn, Alcon, Allergan, Avellino Labs, Bausch + Lomb, Beaver Visitec, Bio-Tissue, BlephEx, Bruder, Cambium, DGH Technology, EyeBrain/Neurolens, and EyeGate Pharma.