

Study Designs and References for CEQUA® (cyclosporine ophthalmic solution) 0.09%

Study design: Phase 2b/3, randomized, multicenter, double-masked, vehicle-controlled, dose-ranging study. The co-primary efficacy endpoints were mean reduction in total conjunctival staining score and mean reduction in global symptom score at Day 84. Conjunctival and corneal staining were assessed at baseline and Days 14, 28, 42, 56, and 84/early discontinuation. Conjunctival staining was assessed in 6 conjunctival zones 1–4 minutes after instilling 1 drop of 1% lissamine green. Corneal staining was evaluated in 5 corneal regions 2–2.5 minutes after instilling 1 drop of 0.5% fluorescein.¹

Study design: CEQUA was studied in two 12-week, randomized, multicenter, double-masked, vehicle-controlled studies. Patients were randomly assigned to treatment and dosed twice a day. Study 1 included 455 patients (152 received CEQUA) and Study 2 included 744 patients (371 received CEQUA). The co-primary endpoints for Study 1 were conjunctival staining and global symptom scores (change from baseline to Day 84). The primary endpoint for Study 2 was percentage of eyes demonstrating an improvement of ≥ 10 mm in Schirmer score after 84 days of treatment. Both studies assessed corneal staining as a secondary endpoint.^{2,3,5}

Staining in each region of the conjunctiva was evaluated using a score ranging from 0 (no staining) to 3 (severe staining). Staining in each region of the cornea was evaluated using a score ranging from 0 (no staining) to 4 (severe staining).^{2,5}

Patients were excluded from the studies if they experienced prior treatment failure with cyclosporine 0.05% or used the therapy within 3 months prior to screening. Use of artificial tears was not allowed during the studies. The mean age was 59 years (range, 18-90 years). Eighty-three percent of patients were female.^{2,5}

Study design: Single arm, Phase 4, 12-week, multicenter study of 124 adults with DED inadequately controlled (ie, still symptomatic and/or exhibiting disease signs) on current Restasis® therapy. The co-primary endpoints were corneal fluorescein staining (CFS) and modified Symptom Assessment in Dry Eye (mSANDE) at Week 12. Patients received 1 drop, 2X daily of CEQUA in each eye. Enrolled patients were selected by their doctors based on: Clinical diagnosis of DED and treatment on Restasis for ≥ 3 months; BCVA of $\geq 20/200$; mSANDE score of ≥ 40 ; total CFS ≥ 6 or CFS in an individual zone ≥ 2 at baseline.^{7,8,9}

Exclusions: Previous history of failure on Restasis; discontinued/switched to a different immunomodulatory; allergic conjunctivitis; stable dose for ≥ 3 months of immunomodulators, antihistamines, cholinergics, antimuscarinics, phenothiazines, retinoids, or any systemic or topical corticosteroids.⁸

References:

1. Schechter BA, Urbietta M, Bacharach J, et al. Effect of OTX-101 on patients with dry eye disease at day 14 of treatment: ocular surface endpoint results from the phase 2b/3 clinical trial. *Clin Ophthalmol*. 2022;16:4145-4151.
2. Goldberg DF, Malhotra RP, Schechter BA, Justice A, Weiss SL, Sheppard JD. A phase 3, randomized, double-masked study of OTX-101 ophthalmic solution 0.09% in the treatment of dry eye disease. *Ophthalmology*. 2019;126(9):1230-1237.
3. CEQUA [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2022.

4. Malhotra R, Devries DK, Luchs J, et al. Effect of OTX-101, a novel nanomicellar formulation of cyclosporine A, on corneal staining in patients with keratoconjunctivitis sicca: A pooled analysis of phase 2b/3 and phase 3 studies. *Cornea*. 2019;38:1259-1265.
5. Tauber J, Schechter BA, Bacharach J, et al. A phase II/III, randomized, double-masked, vehicle-controlled, dose-ranging study of the safety and efficacy of OTX-101 in the treatment of dry eye disease. *Clin Ophthalmol*. 2018;12:1921-1929.
6. Karpecki P, Barghout V, Schenkel B, et al. Real-world treatment patterns of OTX-101 ophthalmic solution, cyclosporine ophthalmic emulsion, and lifitegrast ophthalmic solution in patients with dry eye disease: a retrospective analysis. *BMC Ophthalmol*. 2023;23(1):443.
7. Data on file. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.
8. Effect of CEQUA in Subjects with Dry Eye Disease, ClinicalTrials.gov identifier NCT04357795. Updated Sept 09, 2022. Accessed August 29, 2023.
9. Johnston, J. Effect of OTX-101 0.09% on corneal staining and SANDE scores in patients with dry eye disease uncontrolled on cyclosporine ophthalmic emulsion 0.05%. Abstract presented at American Academy of Optometry 2023; October 12, 2023; New Orleans, LA.
10. White DE, Zhao Y, Ogundele A, et al. Real-world treatment patterns of cyclosporine ophthalmic emulsion and lifitegrast ophthalmic solution among patients with dry eye. *Clin Ophthalmol*. 2019;13:2285-2292.
11. Sheppard J, Bergmann M, Schechter BA, Luchs J, Ogundele A, Karpecki P. Phase 3 efficacy (worse-eye analysis) and long-term safety evaluation of OTX-101 in patients with keratoconjunctivitis sicca. *Clin Ophthalmol*. 2021;15:129-140.
12. US Patent 9,937,225 B2.
13. Cholkar K, Gilger BC, Mitra AK. Topical, aqueous, clear cyclosporine formulation design for anterior and posterior ocular delivery. *Transl Vis Sci Technol*. 2015;4(3):1-16.
14. Mandal A, Bisht R, Rupenthal ID, Mitra AK. Polymeric micelles for ocular drug delivery: from structural frameworks to recent preclinical studies. *J Control Release*. 2017;248:96-116.
15. Cholkar K, Patel A, Vadlapudi AD, Mitra AK. Novel nanomicellar formulation approaches for anterior and posterior segment ocular drug delivery. *Recent Pat Nanomed*. 2012;2(2):82-95.

© 2024 Sun Pharmaceutical Industries, Inc. All rights reserved. CEQUA is a registered trademark of Sun Pharmaceutical Industries Limited. All other trademarks are the property of their respective owners.
PM-US-CQA-1616 08/2024

