Pharmacokinetics of OTX-CSI, a Cyclosporine Intracanalicular Insert, in Surgically Induced Dry Eye Beagle Dogs

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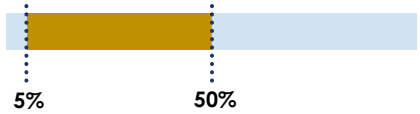
Disclosures

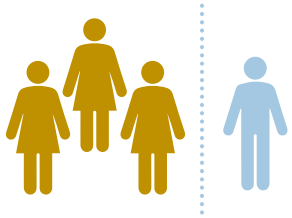
- This study was funded by Ocular Therapeutix, Inc.
- All authors are employees of Ocular Therapeutix, Inc.

Unmet Needs in Dry Eye Disease Therapy

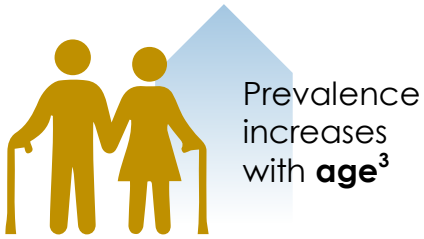
Dry eye disease (DED) is a multifactorial disorder of the tears and ocular surface and represents the most common reason for seeking medical eye care.[1,2]



Prevalence is estimated to be **5**% to **50**% of the global population[2]



Prevalence is 2-3 times higher in the **female** population compared to the male population[3]



Prevalence increases with **age**[3]

Cyclosporine is a potent immunomodulator that acts selectively and locally when administered to the ocular surface.[4,5]

- FDA-approved for treatment of dry eye disease signs and symptoms
- Demonstrated to decrease inflammatory mediators and increase tear fluid secretions

Challenges with existing treatments[6-10]:

- Take weeks to months for therapeutic effect
- Tolerability issues (i.e., stinging, burning, ocular irritation and dysgeusia)
- Burden of patient administration
- Contain preservatives that can lead to corneal toxicity and further aggravate DED

A therapy with a quick onset, long duration, better tolerability profile, that obviates patient administration is needed

References: 1. Craig JP, et al. *Ocul Surf*. 2017 Jul;15(3):276-283. **2.** Stapleton F, et al. *Ocul Surf*. 2017;15(3):334-365. **3.** Dana R, et al. *Am J Ophthalmol*. 2019;202:47-54. **4.** Stevenson W, et al. *Arch Ophthalmol*. 2012;130(1):90-100. **5**. Turner K, et al. *Cornea*. 2000;19(4):492-496. **6.** RESTASIS [prescribing information]. Irvine, CA; Allergan, Inc; 2012. **7.** CEQUA [prescribing information]. Cranbery, NJ; Sun Pharmaceuticals; 2018. **8.** XIIDRA [prescribing information]. Lexington, MA; Shire US Inc.; 2016. **9.** Fraunfelder FT, et al. *J Ophthalmol*. 2012;2012:285851. **10.** Epstein SP, et al. *J Ocul Pharmacol Ther*. 2009;25(2):113-119.

OTX-CSI (Cyclosporine Intracanalicular Insert)

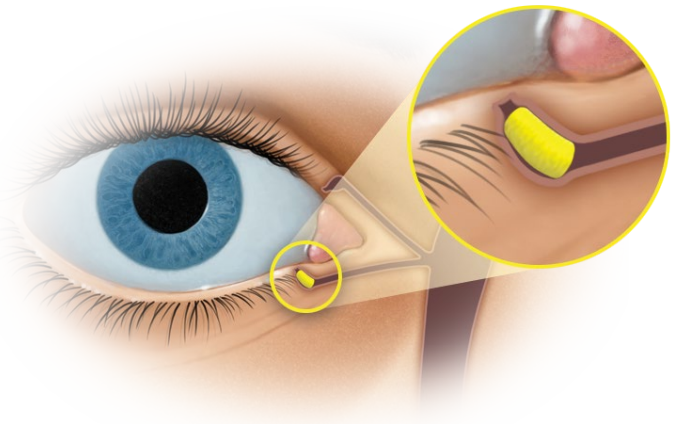
OTX-CSI is a long-acting, preservative-free cyclosporine intracanalicular insert being evaluated for the treatment of DED

OTX-CSI combines two DED treatment modalities into a single therapy:

- Increases tear production through a sustained release of cyclosporine
- Potentially aids tear conservation through punctal occlusion

Product Attributes

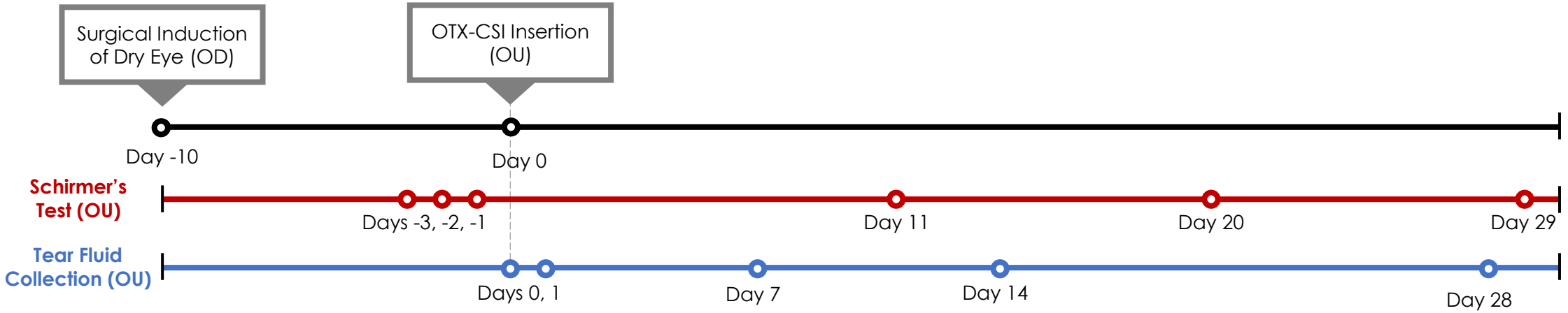
- Contains 0.36 mg cyclosporine in a polyethylene glycol (PEG) hydrogel
- Designed to provide effective therapy for up to 12 weeks with a single insert
- Occludes the punctum
- Preservative-free
- Fully biodegradable
- Conjugated with fluorescein for visualization



Rendering of placement of insert in the canaliculus

Study Objective and Design

- **Objective:** to investigate the pharmacokinetics of cyclosporine drug released from OTX-CSI in a dry eye model following administration in beagle dogs

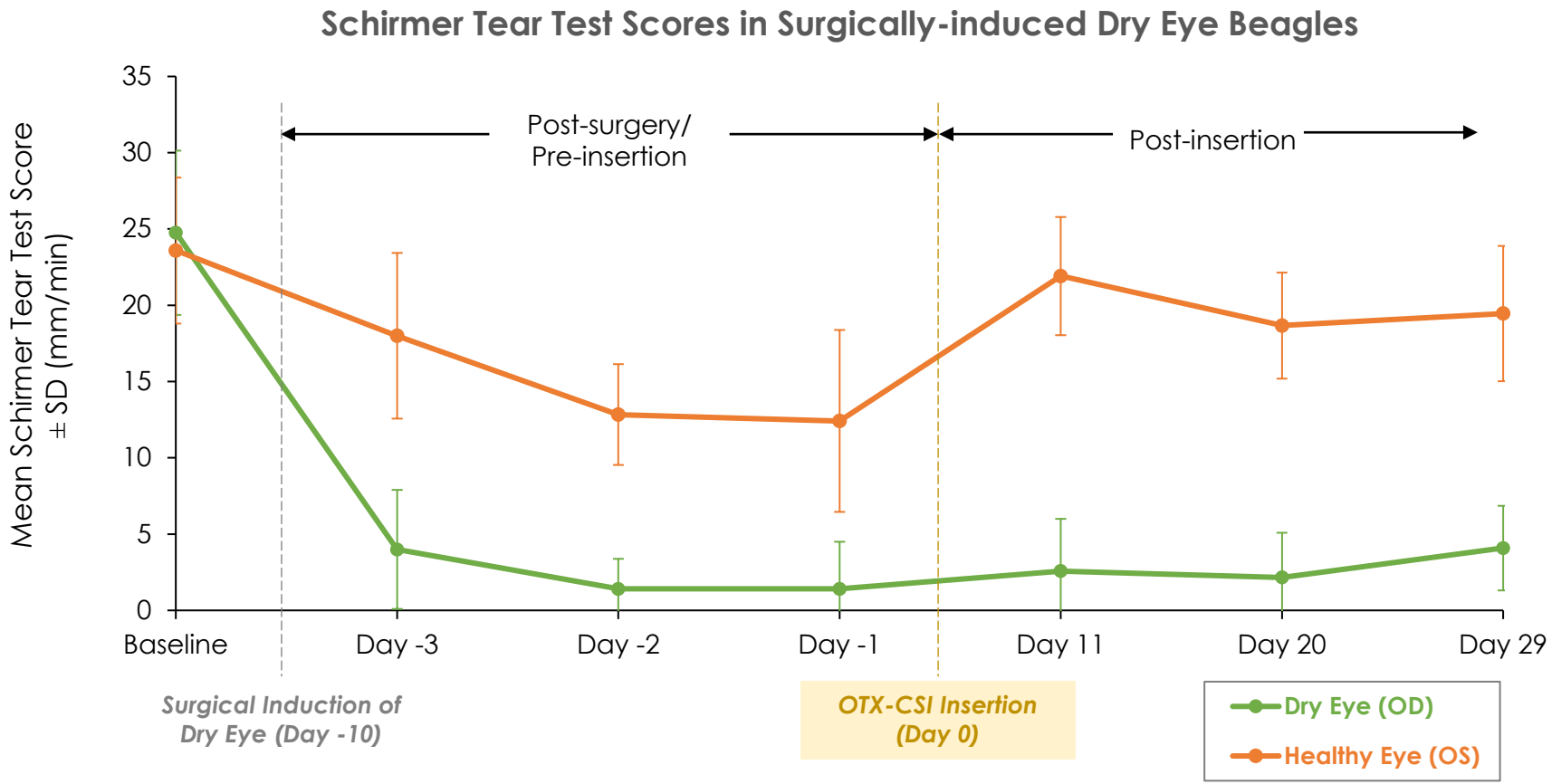


Techniques

- Dry eye was surgically-induced in the right eye (OD) of 12 beagle dogs by removal of lacrimal glands while the left eye (OS) was untreated
- Tear fluid samples were collected from both eyes (OU) using 10 mm Schirmer test strips and analyzed for cyclosporine concentrations by liquid chromatography with tandem mass spectrometry

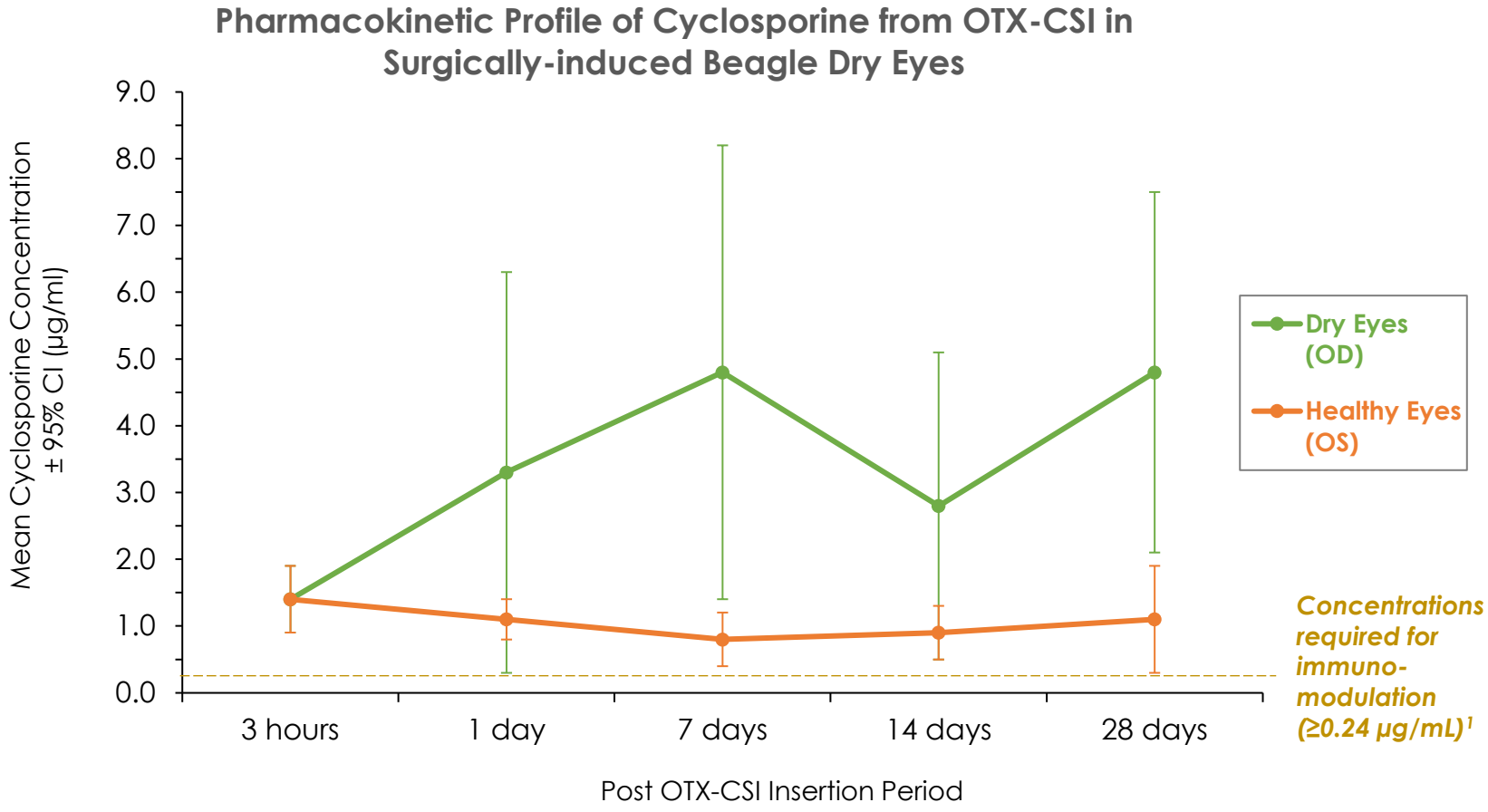
Surgically Induced Dry Eye Model

Mean Schirmer tear test score was higher in healthy eyes than dry eyes at all post-baseline timepoints indicating **successful induction of dry eye.**



Cyclosporine Pharmacokinetic Profile in Beagle Tear Fluid

- **Cyclosporine levels in tear fluid delivered by OTX-CSI were above concentrations required for immunomodulation**
- Tear fluid cyclosporine concentrations were higher in dry eyes likely due to less dilution of cyclosporine on the ocular surface from the reduced tear fluid production



References: 1. Tang-Liu DD, Acheampong A. Ocular pharmacokinetics and safety of ciclosporin, a novel topical treatment for dry eye. *Clin Pharmacokinet*. 2005;44(3):247-61.

Conclusions

- Existing DED treatments have limitations and drawbacks, mainly tolerability issues and a slow onset of action
- OTX-CSI is a novel, hydrogel-based, resorbable, preservative-free, 0.36 mg cyclosporine intracanalicular insert designed to address limitations of current therapies
- In this study, **OTX-CSI successfully released cyclosporine into the tear fluid of surgically-induced dry eyes of beagle dogs**
  - Mean cyclosporine concentrations in dry eyes were greater than or equal to mean concentrations in healthy eyes
  - **The reduction in tear fluid production (typically seen in dry eye subjects) does not appear to inhibit transport of cyclosporine from the insert into the tear fluid in beagle dry eyes**
- **Cyclosporine levels in tear fluid delivered by OTX-CSI were above concentrations required for immunomodulation (≥ 0.24 µg/mL)[1]**
- OTX-CSI is currently being evaluated for the treatment of DED in a Phase 2, randomized, double-masked, vehicle-controlled, multicenter clinical trial

References: 1. Tang-Liu DD, Acheampong A. Ocular pharmacokinetics and safety of ciclosporin, a novel topical treatment for dry eye. *Clin Pharmacokinet*. 2005;44(3):247-61.