Phase 1/2 Trial Evaluating a Novel, Hydrogel-based Cyclosporine Intracanalicular Insert in Subjects with Dry Eye Disease

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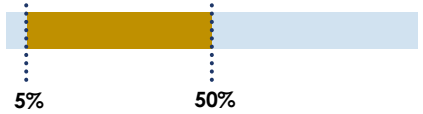
Financial Disclosures

- William C. Christie, Bruce A. Segal, David Evans, and Lee Shettle were investigators in the clinical trial
- Noreen McClain, Nysha Blender, Matthew Cheung, and Michael H. Goldstein are employees of Ocular Therapeutix, Inc.
- This clinical trial was sponsored by Ocular Therapeutix, Inc.

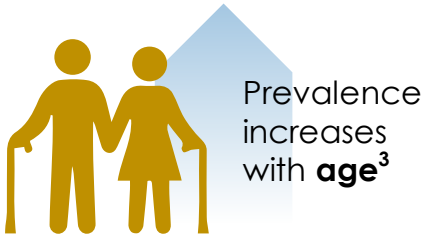
Unmet Needs in Dry Eye Disease Therapy

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]:

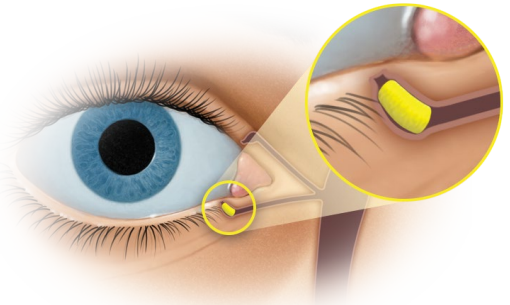
- Take weeks to months for therapeutic effect
- Tolerability issues (i.e., stinging, burning, ocular irritation and dysgeusia)
- Burden of patient administration

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, a Cyclosporine Intracanalicular Insert

A sustained-release, biodegradable, preservative-free cyclosporine insert designed to provide effective therapy for up 12 weeks

- Combines two DED treatment modalities into a single therapy: cyclosporine and punctal occlusion
- Inserted into the canaliculus and slowly releases cyclosporine to the ocular surface
- Contains 0.36 mg of cyclosporine in a polyethylene glycol (PEG) hydrogel rod



Rendering of placement of insert in the canaliculus

Preclinical Pharmacokinetics in Beagle Dogs

- Reduced tear fluid production (typically seen in dry eye disease) did not inhibit transport of cyclosporine from the insert to the tear fluid[1]
- Tear fluid drug levels were maintained above the target concentration required for T-cell immunomodulation for 12 weeks[2]

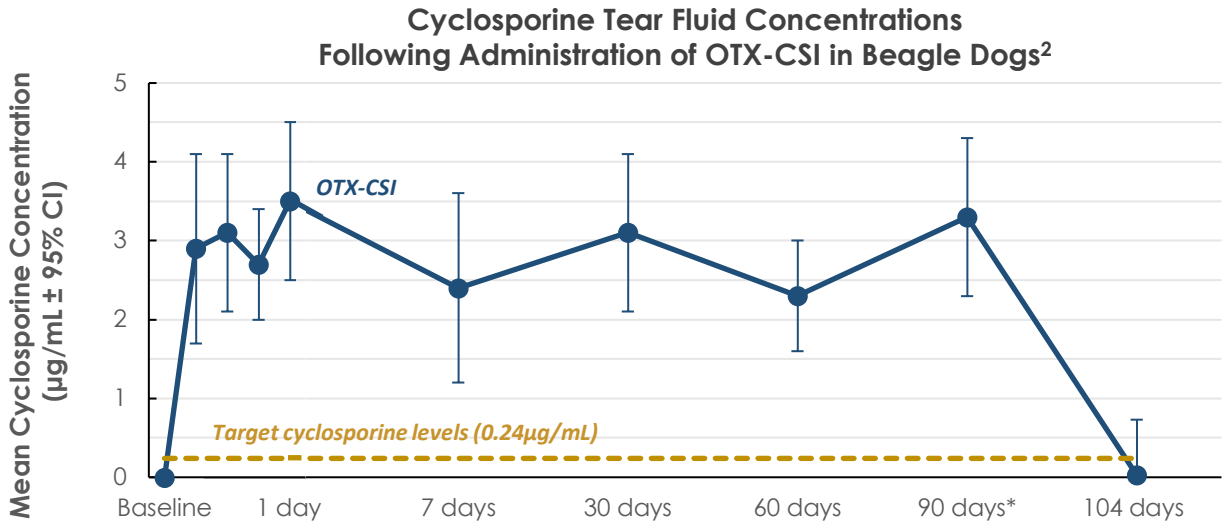
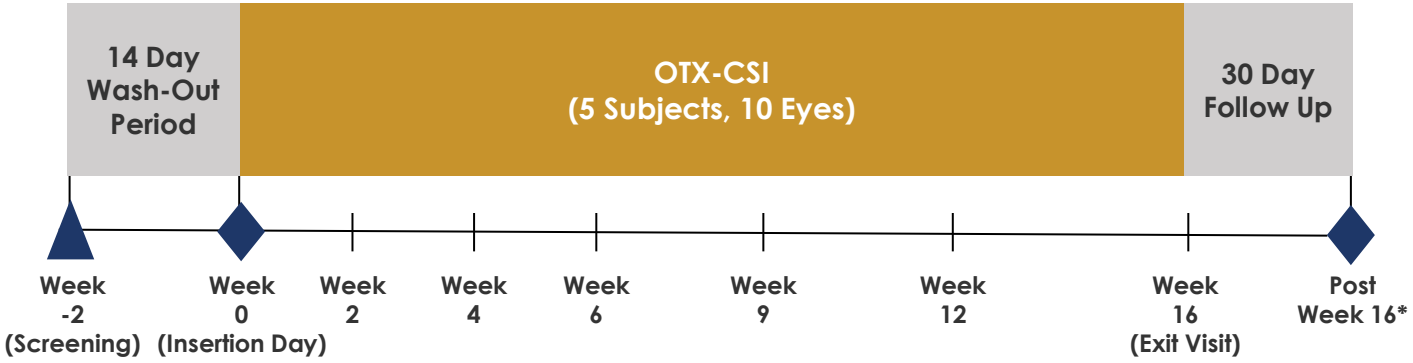


Image courtesy of Ocular Therapeutix, Inc.

References: 1. Vanslette A, Blizzard CD, Driscoll A, et al. Pharmacokinetics of OTX-CSI, a cyclosporine intracanalicular insert, in surgically induced dry eye beagle dogs . Presented at the Association for Research in Vision and Ophthalmology Annual Meeting. Virtual. May 2021. 2. Vanslette A, Haberman P, Blizzard C, et al. Evaluating Safety and Pharmacokinetics of OTX-CSI, a Sustained Cyclosporine Releasing Intracanalicular Insert in Beagles. Presented at the Association for Research in Vision and Ophthalmology Annual Meeting. Virtual. May 2020.

Clinical Study Design and Baseline Demographics

A Phase 1, Open-label Study in Subjects with DED



*Subject remains in study until insert is no longer visible and no evidence of biological activity

Key Inclusion Criteria

- DED in both eyes for ≥ 6 months
- VAS eye dryness severity score ≥30 in the study eye
- Total Corneal Fluorescein Staining Score (NEI scale) ≥6 and <15
- Schirmer score (unanesthetized) >0mm and ≤10mm at 5 minutes

Endpoints

- Safety (adverse events collection)
- Schirmer's Test (without anesthesia) at Week 12
- Eye Dryness Score Severity and Frequency
- Total Corneal Fluorescein Staining (NEI scale)
- Ocular Surface Disease Index (OSDI)

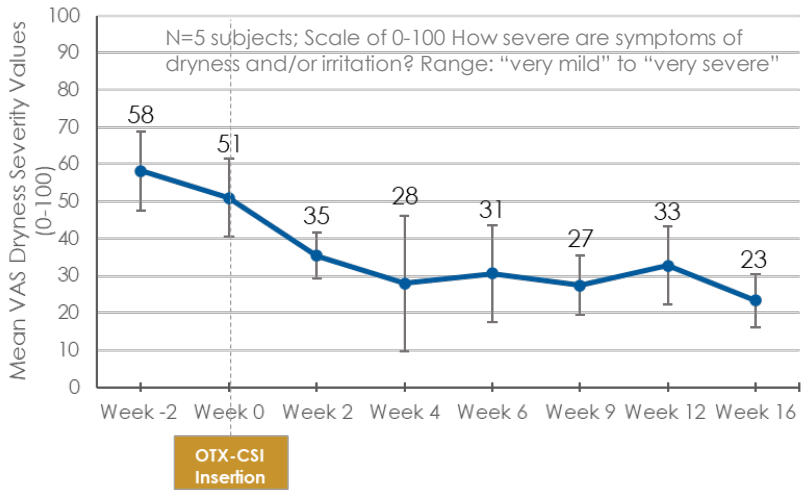
Baseline Demographics and Measurements

	All Subjects (N=5 subjects)
Age, mean (range)	73.0 (63-82)
Female, n (%)	5 (100%)
Race, n (%)	
White	5 (100%)
Mean Schirmer's Test Score without anesthesia (SD, mm)	4.2 (2.3)
Mean Total Corneal Fluorescein Staining Score (SD, NEI scale)	6.7 (0.5)
Mean Eye Dryness Severity Score (SD, 0-100 scale)	51 (10.6)
Mean Eye Dryness Frequency Score (SD, 0-100 scale)	51 (14.4)
Mean Ocular Surface Disease Index (SD, 0-100 scale)	45.7 (17.8)

Phase 1 Trial Results

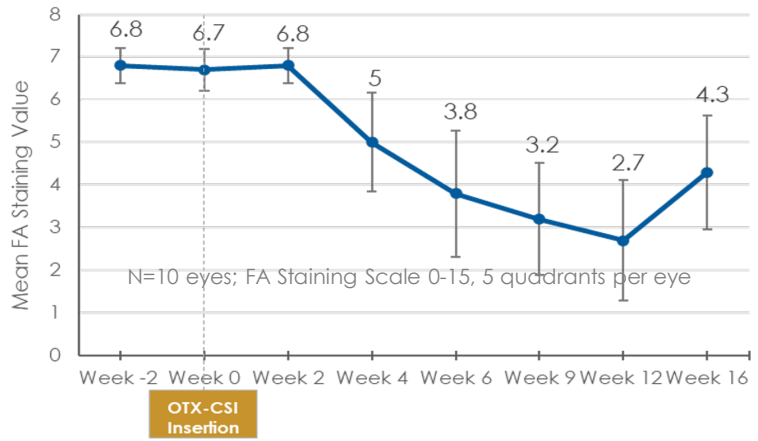
SUBJECTS REPORTED IMPROVEMENT IN DRYNESS SEVERITY ON A SCALE OF 0-100 (VERY MILD TO VERY SEVERE) OVER 16 WEEKS

Mean Absolute Values

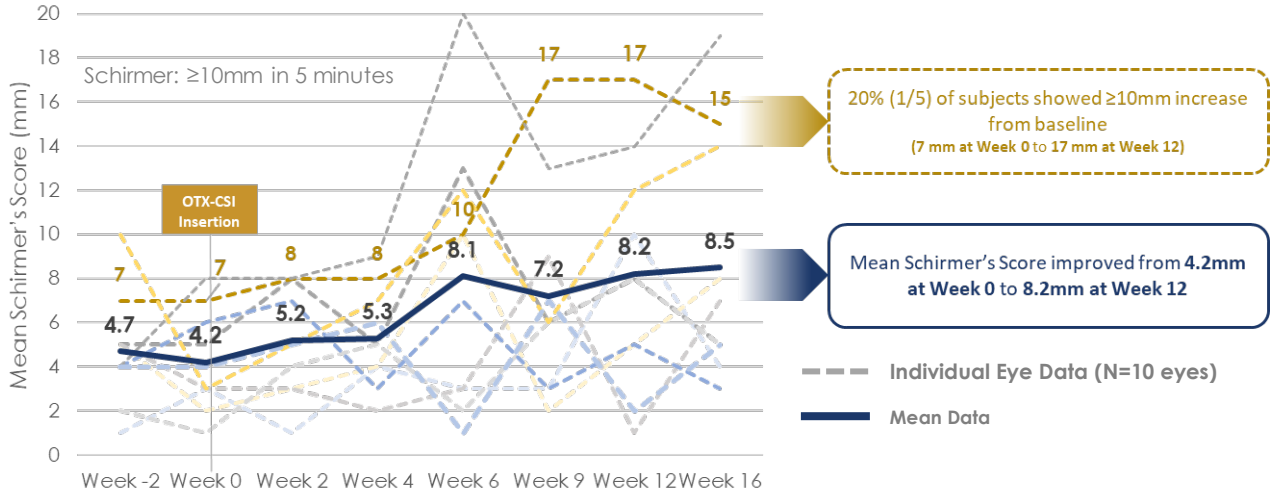


IMPROVED TOTAL CORNEAL FLUORESCEIN STAINING VALUES WEEK 4 TO 16 COMPARED TO BASELINE

Mean Absolute Values



SUBJECTS SHOWED AN IMPROVEMENT IN MEAN SCHIRMER TEST SCORES FROM WEEK 0 TO WEEK 16



OTX-CSI WAS GENERALLY OBSERVED TO HAVE A FAVORABLE SAFETY PROFILE & WAS WELL TOLERATED

No AEs of stinging, burning, irritation, tearing, or blurred vision were reported over the 16-week period

Phase 2 Study Objective and Design

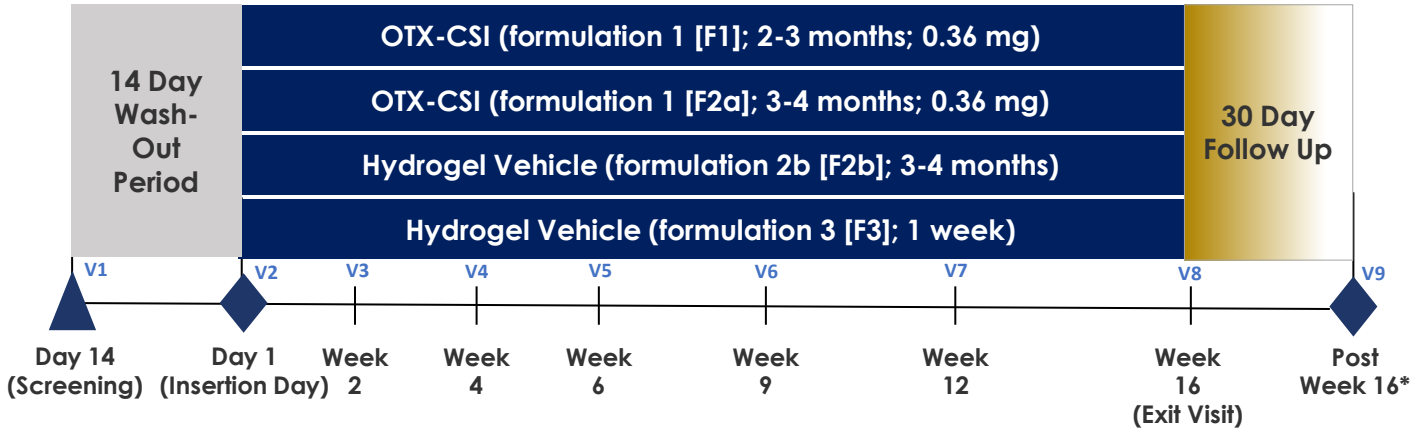
OBJECTIVE: EVALUATING THE SAFETY, TOLERABILITY, AND EFFICACY OF OTX-CSI FOR THE TREATMENT OF SUBJECTS WITH DRY EYE DISEASE

Design

- Prospective, Randomized, Double-Masked, Vehicle-controlled study
- Key Inclusion criteria:
  - DED diagnosis in both eyes for ≥6 months
  - VAS eye dryness severity score ≥30

Endpoints

- Schirmer Test (without anesthesia) at Week 12
- Total Corneal Fluorescein Staining (tCFS) using NEI scale
- Eye Dryness Score (visual analogue scale [VAS])
- Adverse Events (Ocular and Non-ocular)
- Presence of OTX-CSI or HV insert at all post-baseline visits



*Subject remains in study until insert is no longer visible and no evidence of biological activity

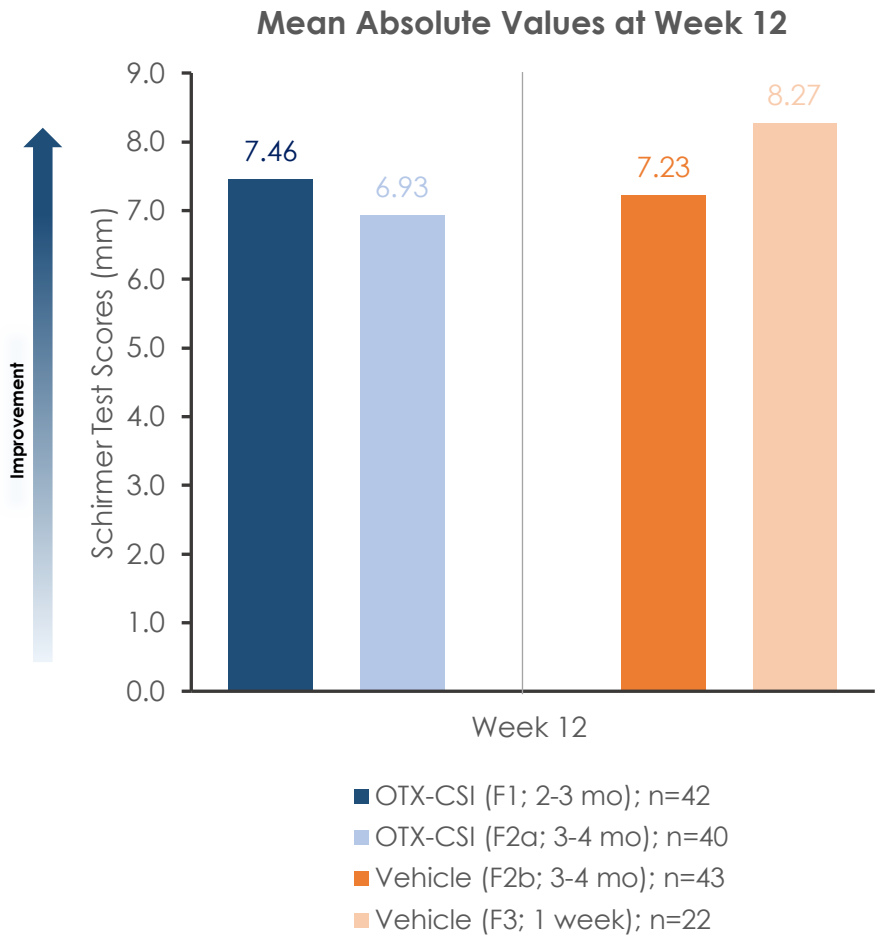
Study to Evaluate the Safety, Tolerability, and Efficacy of OTX-CSI in Subjects With Dry Eye Disease. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04362670. Accessed October 16, 2020.

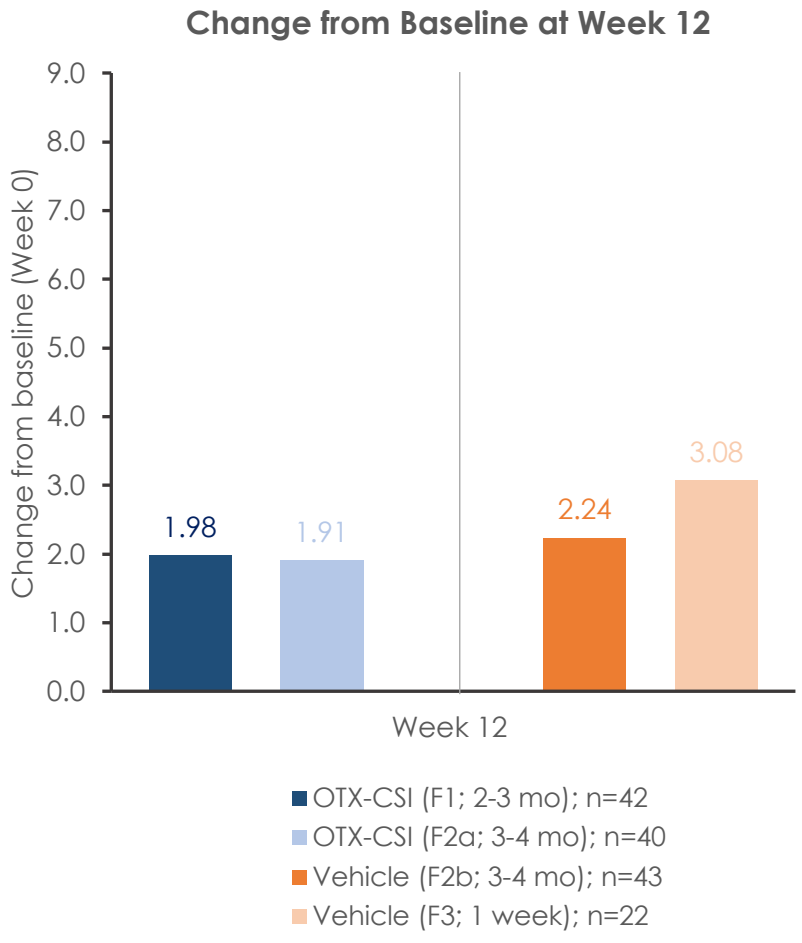
Demographics and Baseline measurements

	OTX-CSI (F1; 2-3 months)	OTX-CSI (F2a; 3-4 months)	Vehicle (F2b; 3-4 months)	Vehicle (F3; 1 week)
Modified Intent to Treat (mITT)	**42**	**40**	**43**	**22**
Age, mean	67.9	68	65.5	65.2
Female, %	69	62.5	90.7	77.3
Race, %				
White	85.7	82.5	79.1	81.8
Mean Schirmer Test Score without anesthesia (mm)	6.07	4.75	4.65	5.23
Mean Total Corneal Fluorescein Staining Score (0-15 NEI scale)	7.2	7.2	7.1	7.7
Mean Eye Dryness Severity Score (0-100 scale)	67.8	72.4	73.4	75.4
Mean Eye Dryness Frequency Score (0-100 scale)	71	75.3	71.8	79.5

Primary Efficacy Endpoint: Schirmer Test at Week 12

No separation of effect observed between active drug & control groups (both formulations)

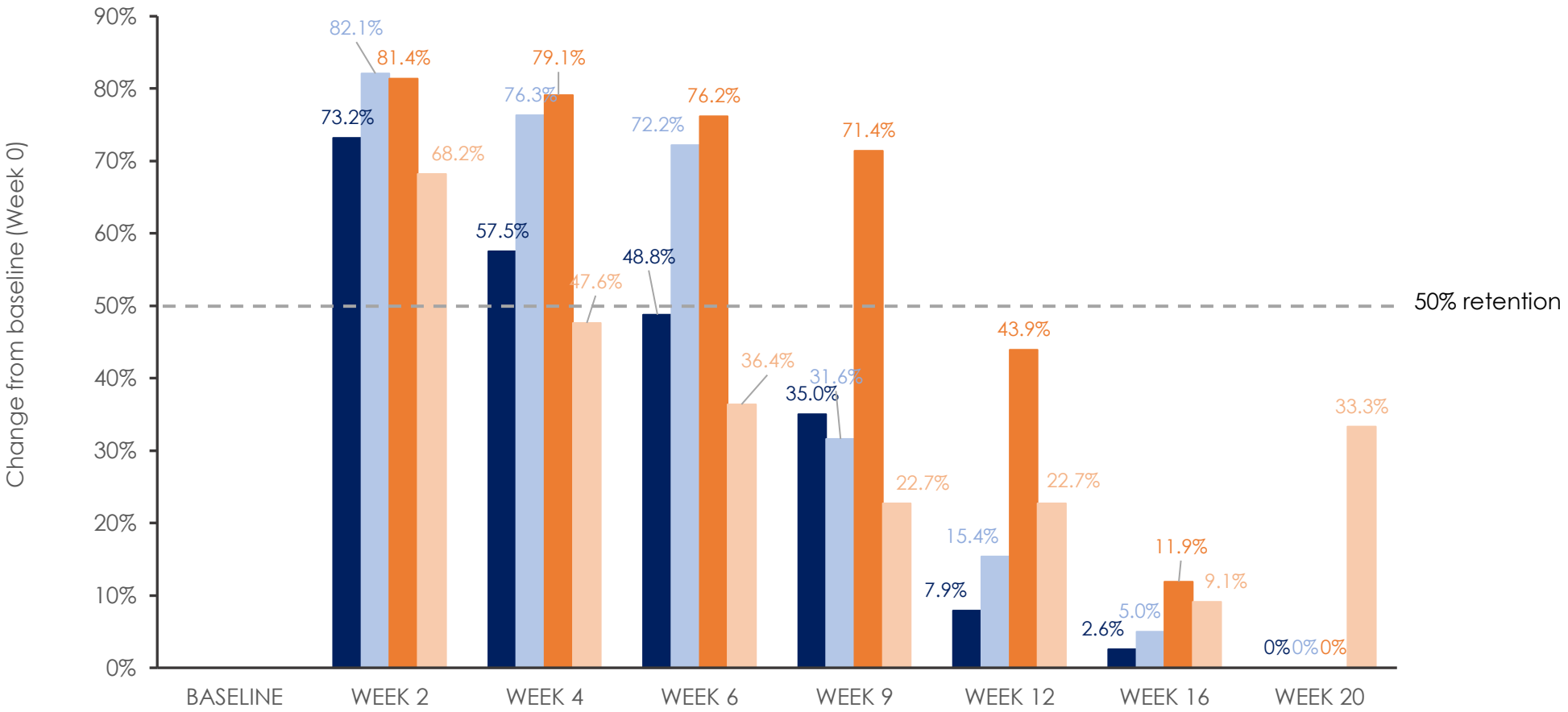




Modified Intent to Treat Population (N=148); Least Squares Means for change from baseline

Retention Rate (Insert Presence Visualization)

Lower than anticipated retention rates observed in the active drug groups (both formulations)



* Week 20 visit was 30 days follow up after the exit visit at Week 16
Analysis population: Modified Intent to Treat Population (N=148)

Safety: Treatment Emergent Adverse Events

	OTX-CSI (n=42) F1; 2-3 mo	OTX-CSI (n=41) F2a; 3-4 mo	OTX-CSI TOTAL (N=83)	Vehicle (n=43) F2b; 3-4 mo	Vehicle (n=22) F3; 1 week	Total (N=148)
Subjects with at least 1 TEAE	16	15	31	5	1	37
%	38.1%	36.6%	37.3%	11.6%	4.5%	245%
Subjects with at least 1 Ocular TEAE	13	11	24	3	1	28
%	31%	26.8%	28.9%	7%	4.5%	18.9%
Subjects with at least 1 non-ocular TEAE	3	6	9	2	0	11
%	7.1%	14.6%	10.8%	4.7%	0.0%	7.4%
SAE's	1	2	3	0	0	3
Ocular SAE's	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
Severity of AE's						
Mild AE's	7	6	13	5	1	19
Moderate AE's	9	8	17	0	0	17
Severe AE's	0	1	1	0	0	1
TEAEs leading to insert removal	1	0	1	0	0	1
TEAES leading to withdrawal	0	0	0	0	0	0

Modified Intent to Treat Population (N=148)

Ocular Treatment Emergent Adverse Events

Most common ocular adverse event was ocular pruritis seen in <16% of subjects

	OTX-CSI (n=42) F1; 2-3 mo	OTX-CSI (n=41) F2a; 3-4 mo	OTX-CSI TOTAL (N=83)	Vehicle (n=43) F2b; 3-4 mo	Vehicle (n=22) F3; 1 week	Total (N=148)
Subjects with any Ocular TEAEs	13	11	24	3	1	28
%	30.95%	26.83%	28.92%	6.98%	4.55%	18.92%
MOST COMMON OCULAR AEs						
Eye Pruritus	8	5	13*	1		14
%	19.05%	12.20%	15.66%*	2.33%		9.46%
OCULAR AEs OF INTEREST						
Dacryocanaliculitis	2	1	3			3
%	4.76%	2.44%	3.61%			2.03%
Eye irritation		1	1			1
%		2.44%	1.20%			0.68%
Eye Pain		1	1			1
%		2.44%	1.20%			0.68%
FB Sensation				1		1
%				2.33%		0.68%
Lacrimation Increase		2	2	1		3
%		4.88%	2.41%	2.33%		2.03%

- No Ocular Serious Adverse Events
- No Ocular Severe Adverse Events

Modified Intent to Treat Population (N=148)

***All reported at one site**

Conclusions

Phase II Study Evaluating Safety and Efficacy of OTX-CSI in Subjects with DED

- At Week 12, there was very little separation noted between the active drug groups and control groups for the primary endpoint of increased tear product measured by Schirmer test score
- Overall, the OTX-CSI insert was generally safe and well tolerated.
  - More subjects experienced adverse events (AEs) in the active treatment groups (35.35%) vs the vehicle treated groups (9.23%)
  - AEs of stinging, burning, irritation were very low (under 3%)
  - Most frequent AE was eye pruritis which was seen in 15% of subjects (13 subjects all at one site)
  - Dacryocanaliculitis rate was 4% in OTX-CSI group (0% in vehicle)
  - Epiphora was 2%
- Retention much lower than expected at all timepoints for the OTX-CSI and longer acting hydrogel formulation
  - Conversely, retention higher than expected in rapidly degrading hydrogel insert (1 week)

NEXT STEPS: Full dataset is being analyzed further to determine subsequent steps