July 12, 2022

Top-Line Results from the Dry Eye Disease Chamber Crossover Trial of Reproxalap

NASDAQ: ALDX

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The Dry Eye Disease Crossover Trial Achieved Success for Three Dry Eye Disease Sign Endpoints and Six Secondary Symptom Endpoints

- The ocular redness primary endpoint was achieved (P=0.0004).
- The Schirmer test primary endpoint was achieved (P=0.0005).
- The multiplicity-controlled secondary endpoint of Schirmer test ≥10mm responder analysis was achieved (P=0.0361).
- Secondary endpoints for each assessed symptom (dryness, discomfort, grittiness, burning, stinging, and itching) were achieved.
- All endpoints were assessed over approximately a 24-hour period of dosing, suggesting rapid activity of reproxalap.
- The crossover trial design appeared to reduce the high degree of variability characteristic of dry eye disease clinical trials, at least for a drug with a potentially rapid mechanism of action.

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Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

Aldeyra Intends to Submit Symptom and Three Sign Endpoints to Support Dry Eye Disease NDA Efficacy Requirements†

- Based on previously announced clinical trials, the dry eye disease New Drug Application (NDA) package for 0.25% reproxalap ophthalmic solution is expected to include two clinical trials for each of the following endpoints:
  - Symptoms (ocular dryness symptom score) over 12 weeks,
  - Ocular redness in a dry eye chamber,
  - Schirmer test following a single day of dosing, and
  - Schirmer test ≥10mm responder analysis following a single day of dosing.

†NDA submission requirements depend, in part, on clinical safety results and regulatory feedback. Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

The Crossover Trial Represents a Unique Clinical Paradigm in Dry Eye Disease and Was Designed to Serve as a Pivotal Trial

- The dry eye disease crossover trial was designed to eliminate inter-patient variability by testing all interventions on each patient.
- To our knowledge, an adequate and well-controlled crossover trial has not been previously performed with an investigational drug candidate in dry eye disease patients.
- The dry eye disease crossover clinical trial was intended to support the objective sign results from previously completed clinical trials.
- Because the crossover trial was designed to be adequate and well-controlled, and because the endpoints were multiplicity-controlled, the trial was intended to be submitted as pivotal, assuming success, for one or more of the following objective sign endpoints: ocular redness, Schirmer test, and ≥10mm Schirmer test responder analysis.

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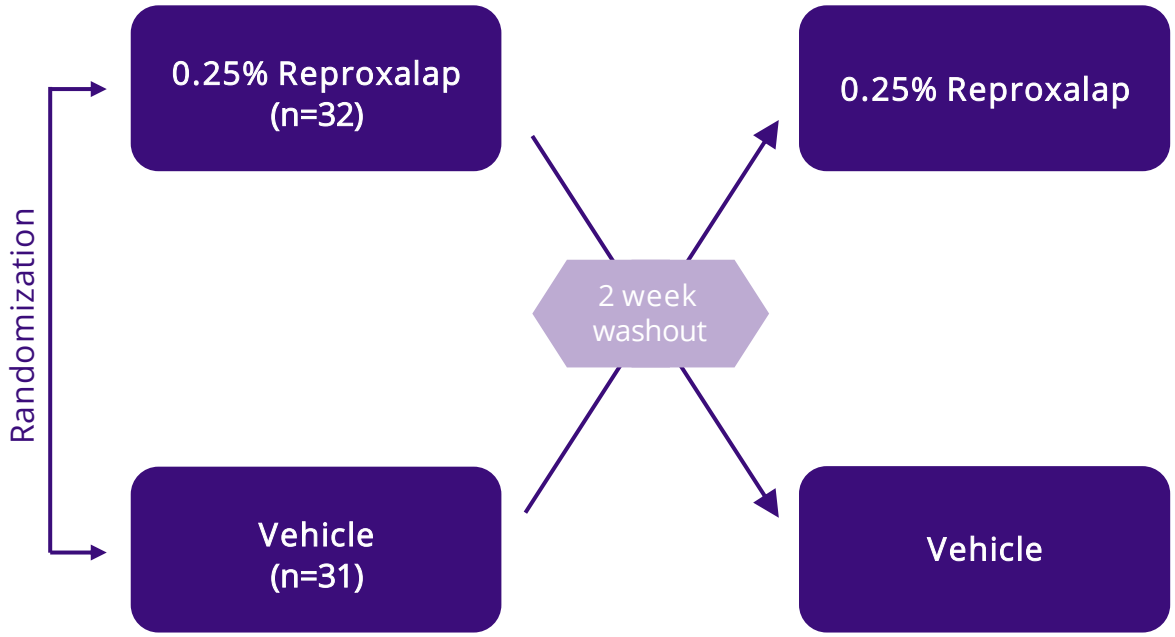
The Crossover Trial Was Designed to Serve as a Pivotal Trial in Support of NDA Submission for Dry Eye Disease

Design	Randomized, double-masked, crossover, vehicle-controlled, single-center
Dosing	0.25% reproxalap or vehicle, two-week washout Day 1: four doses Day 2: one dose before 90-minute dry eye chamber, one dose 45 minutes after chamber entry
Size	63 patients
Primary Endpoints[†]	• Schirmer test on Day 1 (pre/post fourth dose) • Ocular redness in dry eye disease chamber
Secondary Endpoints	• Schirmer test ≥10mm responder analysis • Dry eye disease symptoms

Treatment Visits

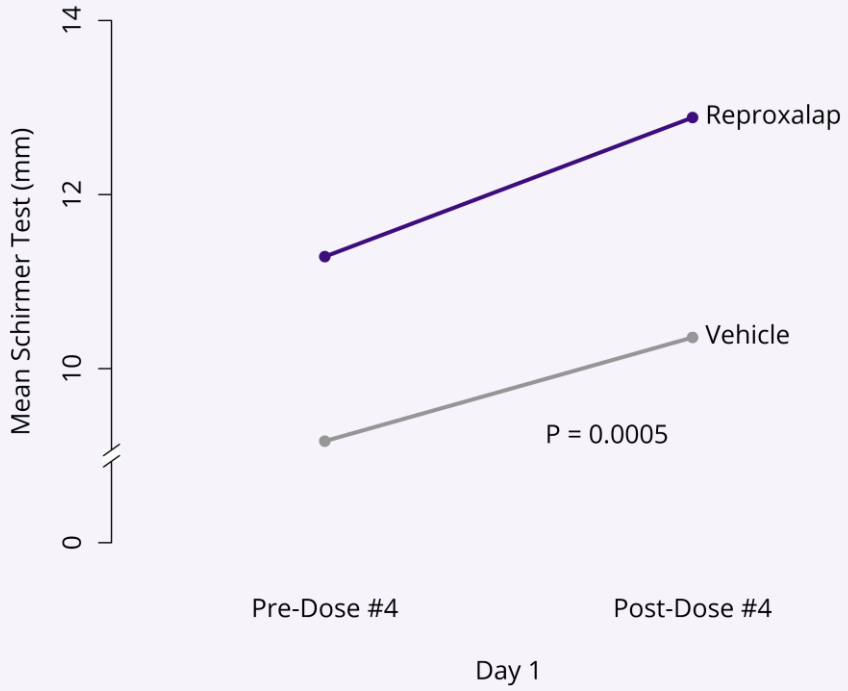
Each treatment visit represents Day 1 (pre-chamber) and Day 2 (chamber) visits.



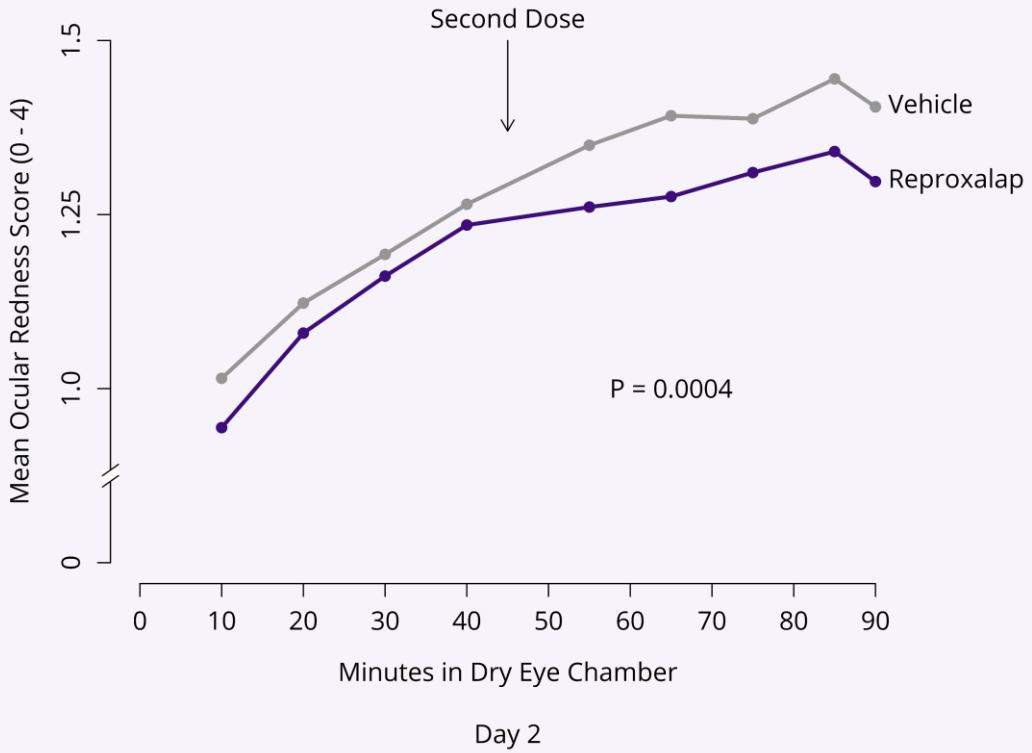
[†] The Hochberg procedure was used to control for multiplicity. Unused alpha from the Hochberg procedure was passed to a fixed sequence of secondaries, the first of which was the Schirmer responder analysis. Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

In the Dry Eye Disease Crossover Trial, Both Primary Endpoints Were Statistically Significant in Favor of Reproxalap over Vehicle

Tear Production
(Higher scores favor reproxalap.)



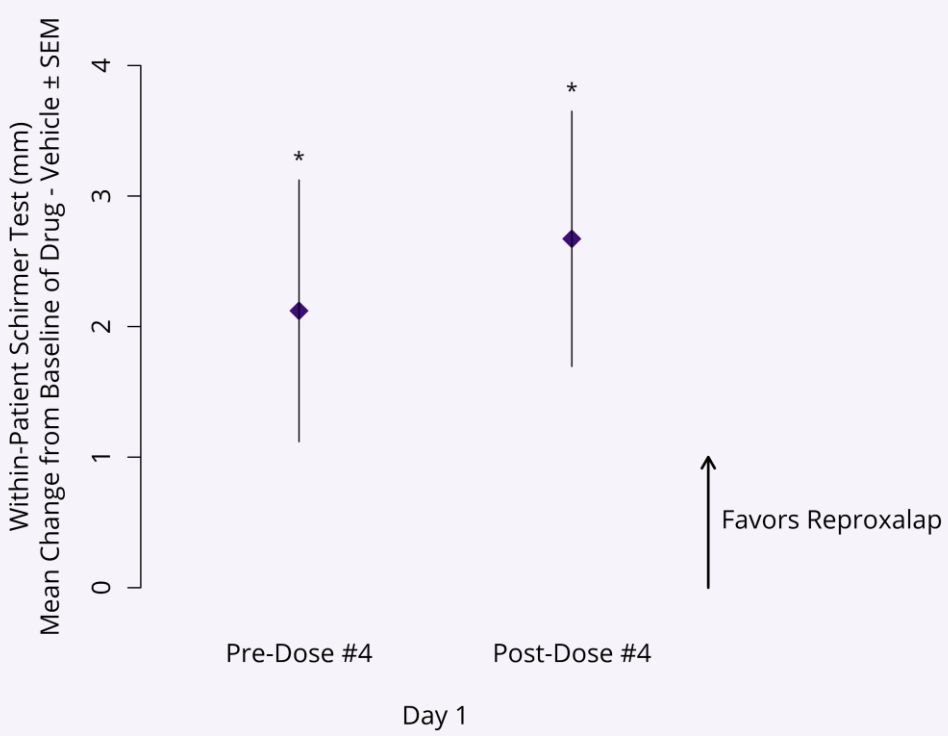
Ocular Redness
(Lower scores favor reproxalap.)



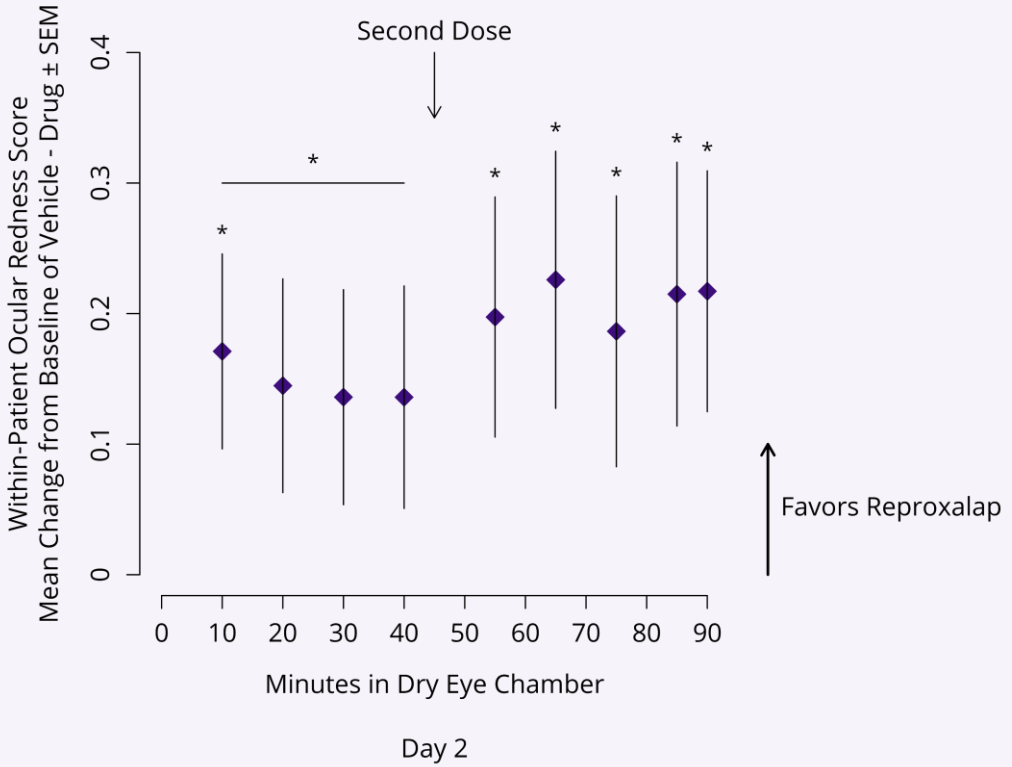
P values derived from mixed effect model of repeated measures of change from baseline. **Source**: Dry eye disease crossover clinical trial results on file. Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

In the Dry Eye Disease Crossover Trial, Within-Patient Clinical Relevance Assessments Demonstrated Reproxalap Superiority

Tear Production



Ocular Redness



*P < 0.05. **SEM** = standard error of the mean. **mm** = millimeter. **Source**: Dry eye disease crossover clinical trial results on file. Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

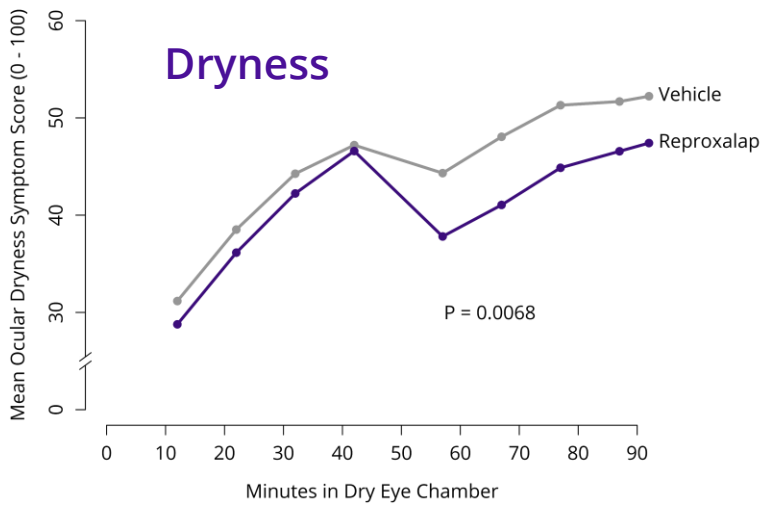
In the Dry Eye Disease Crossover Trial, the Multiplicity-Controlled Schirmer Test ≥10mm Responder Secondary Endpoint Was Achieved

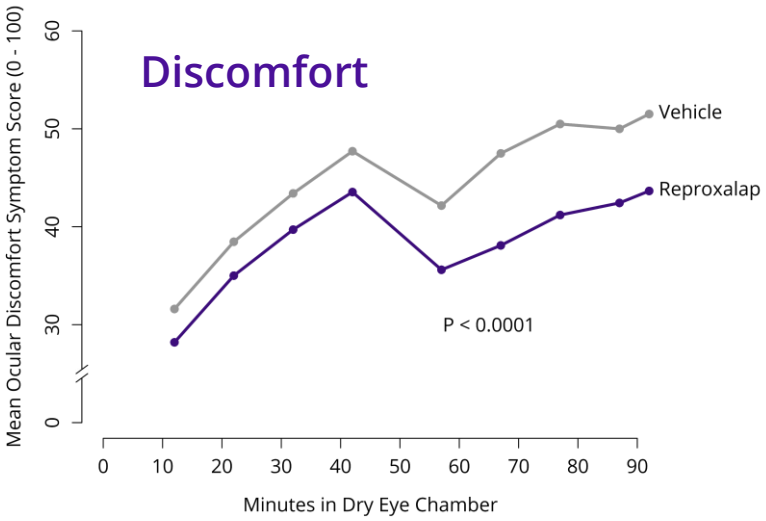
Schirmer Test Responder Analysis

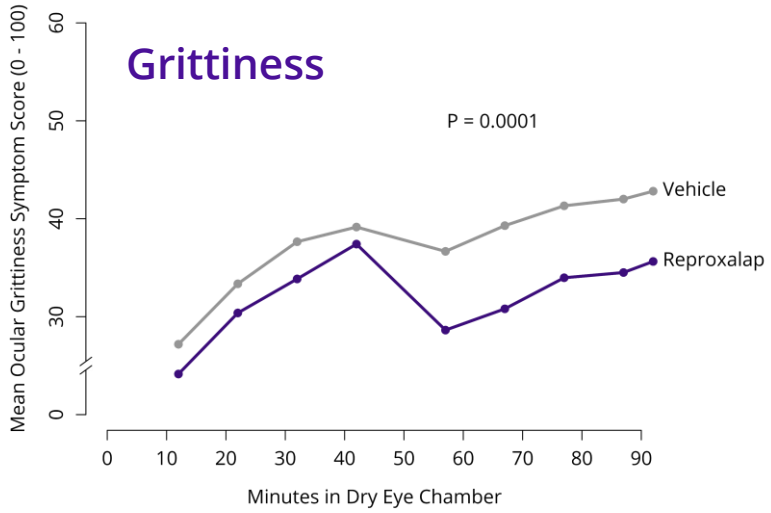
	Reproxalap	Vehicle
≥10 mm tear production post-Dose #4 on Day 1	48%	41%
Odds ratio (95% confidence interval)†	1.551 (1.029, 2.338)	
P value versus vehicle†	0.0361	

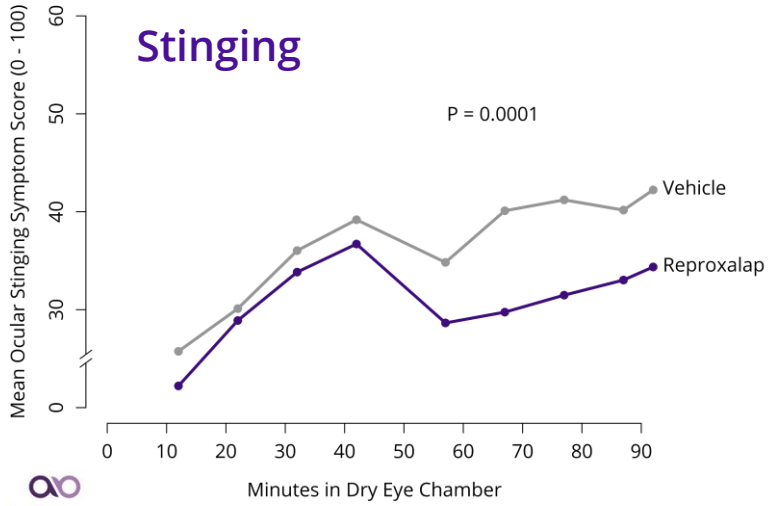
† Generalized estimating equation analysis of Schirmer test score ≥10mm pre- and post-Dose #4 on Day 1. **Source**: Dry eye disease crossover clinical trial results on file. Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

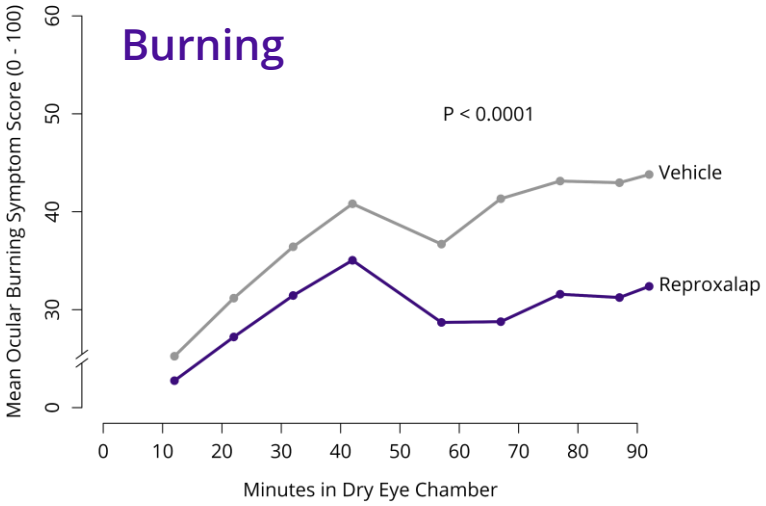
In the Dry Eye Disease Crossover Trial, Secondary Endpoints for All Assessed Symptoms Were Achieved

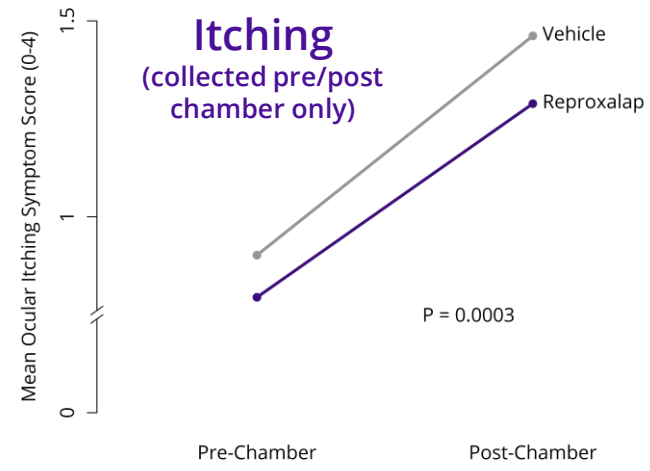












P values derived from mixed effect model of repeated measures of change from baseline. **Source**: Dry eye disease crossover clinical trial results on file. Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

The Dry Eye Disease Crossover Trial Met Each of the Sign Endpoints Intended to be Submitted to Support a Potential NDA

- The results suggest that a crossover design may reduce the high degree of variability characteristic of dry eye disease clinical trials.
- The primary endpoints of ocular redness and Schirmer test were achieved.
- The Schirmer test ≥10mm responder analysis, which was also achieved, correlates with symptomatic improvement[†], consistent with the achievement of secondary endpoints for each of the assessed symptoms (dryness, discomfort, grittiness, stinging, burning, and itching).
- Consistent with prior trials, no clinically significant safety signals were observed.
- A pre-NDA (New Drug Application) meeting has been scheduled for third quarter of 2022.
- Clinical data submitted to the NDA[‡] is expected to encompass acute (single-day dosing, dry eye chamber) and chronic (12-week) assessments, as well as parallel-group and crossover clinical designs, offering what is expected to be unparalleled analysis of rapid and sustained activity across a combination of challenge and field-based assessments.

[†]Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol. 2000;118(5):615-21. [‡]NDA submission requirements depend, in part, on clinical safety results and regulatory feedback. The NDA submission is expected to include a combination of prespecified, post-hoc, primary, secondary, multiplicity-controlled, and nominal p-value endpoints. Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

Reproxalap May Have the Potential to Address Significant Unmet Needs in Dry Eye Disease

- Over the past ~12 months, Aldeyra has met with 40 MDs and 25 ODs, attended 8 conferences, and published 1 abstract[†] and 6 peer-reviewed manuscripts.[‡]
- In conjunction with ClearView Healthcare Partners, Aldeyra has completed target product profile testing with 40 eyecare professionals and 20 dry eye disease patients.
  - With lifitegrast and cyclosporine, ~60%-70% of patients discontinue treatment with median time to discontinuation of ~1 month and ~3 months, respectively.[*]
  - Among healthcare providers, the target product profile of rapid onset of action and improvement in dryness symptoms was viewed as highly favorable. [§]
  - Among dry eye disease patients, the target product profile of reduction in symptoms and redness was viewed as highly favorable.[§]
- Pending FDA feedback, reproxalap, if approved, has the potential to be the first drug label to include clinical data for multiple objective signs of dry eye disease.

[†]Holland EJ, Cavanagh B, Machatha ST, et al. The Novel RASP Modulator Reproxalap Rapidly Improves Signs and Symptoms of Dry Eye Disease: The TRANQUILITY Run-In Cohort. Paper session presented at: Ocular Surface Disease III. ASCRS;2022 Apr 23; Washington, D.C. [‡]Cavanagh B, Gomes PJ, Starr CE, et al. Ophthalmol Ther. 2022;11(4):1449-61. Clark D, Karpecki P, Salapatek AM, et al. Clin Ophthalmol. 2022;16:15-23. McMullin D, Clark D, Cavanagh B, et al. Clin Ophthalmol. 2021;15:3889-3900. Clark D, Sheppard J, Brady TC. J Ocul Pharmacol Ther. 2021;37(4):193-99. Clark D, Cavanagh B, Shields AL, et al. Am J Ophthalmol. 2021;230:60-7. Clark D, Tauber J, Sheppard J, Brady TC. Early Onset and Broad Activity of Reproxalap in a Randomized, Double-Masked, Vehicle-Controlled Phase 2b Trial in Dry Eye Disease. Am J Ophthalmol. 2021 Jun;226:22-31. [§]ClearView analysis of market research conducted Q4 2021 – Q1 2022. [*]White DE, Zhao Y, Ogundele A, Fulcher N, Acs A, Moore-Schiltz L, Karpecki PM. Real-World Treatment Patterns Of Cyclosporine Ophthalmic Emulsion And Lifitegrast Ophthalmic Solution Among Patients With Dry Eye. Clin Ophthalmol. 2019 Nov 22;13:2285-2292.Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

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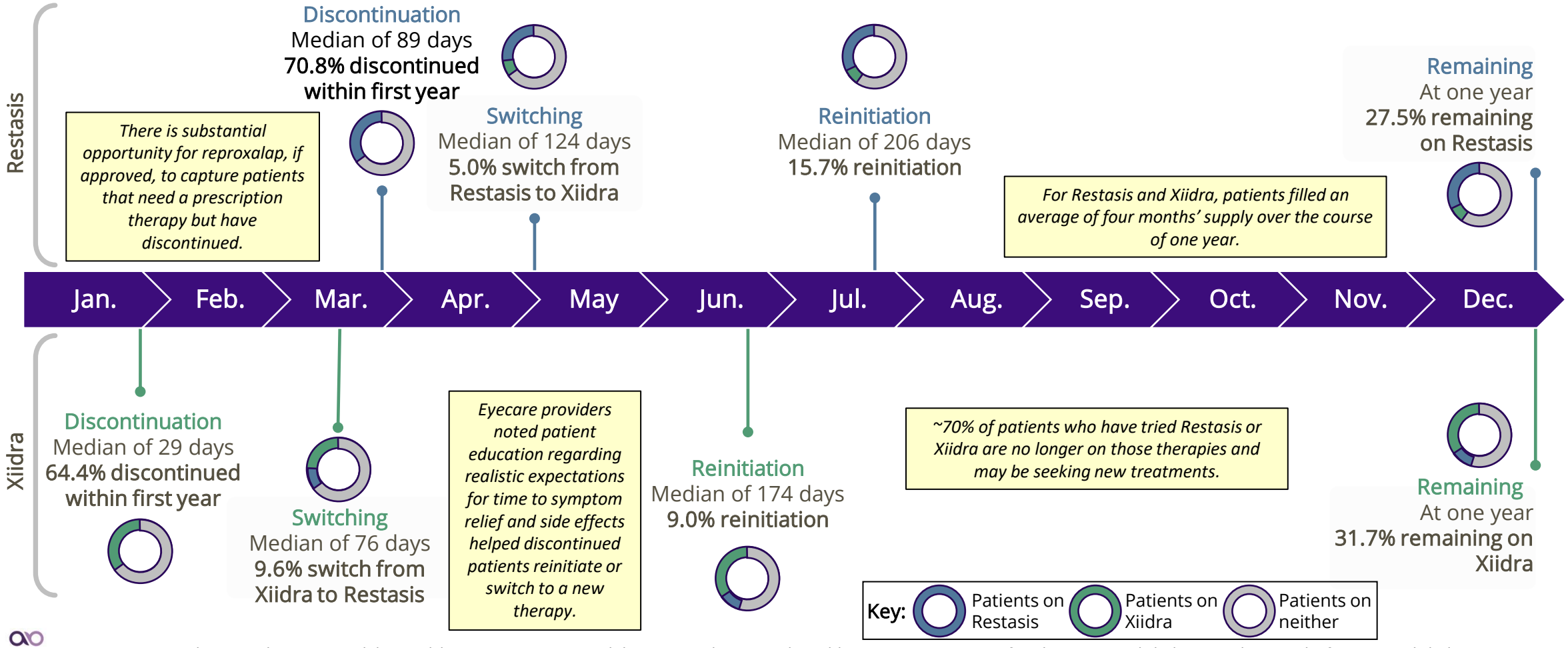
With Currently Available Dry Eye Disease Therapies, Discontinuation and Switching Rates are Early and Prevalent for Most Patients

Illustrative Patient Experience with Restasis® and Xiidra® in Year One



Sources: White DE, Zhao Y, Ogundele A, Fulcher N, Acs A, Moore-Schiltz L, Karpecki PM. Real-World Treatment Patterns Of Cyclosporine Ophthalmic Emulsion And Lifitegrast Ophthalmic Solution Among Patients With Dry Eye. Clin Ophthalmol. 2019 Nov 22;13:2285-2292. Eyecare provider Interviews; ClearView analysis of market research conducted Q4 2021 – Q1 2022.

Surveyed Eyecare Providers Viewed Reproxalap's Potential Benefits Highly Favorably

Key Healthcare Provider Feedback

- Rapid onset of action is differentiated from existing options and likely to improve compliance.
- Ocular dryness and related symptoms are the key metrics for activity in dry eye disease.
- Redness improvement may allow for reduction in number of therapies used (e.g., not needing vasoconstrictors).

Key Drivers of Eyecare Provider Enthusiasm

Strength of Value Proposition

Onset of Action

Enthusiasm: Low – High

- Rapid impact on dryness may improve patient compliance
- 90-minute redness reduction is valuable for a subset of patients

"Significant dryness improvement in 8 days is impressive and highly valuable." – MO Ophtho.

Dryness

Enthusiasm: Low – High

- Considered an important measure of efficacy as dryness is a common driver of patient discomfort

"Getting the patient comfortable by reducing dryness is what's most important." – SO Ophtho.

Redness

Enthusiasm: Low – High

- 15 – 30% of DED patients report redness as a driving concern

"I have some patients who complain about redness, and this could help with compliance for them." – HP Optom.

Source: Eyecare provider Interviews (n=40); ClearView analysis of market research conducted Q4 2021 – Q1 2022. Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

Patient Research Indicates Value for a Dry Eye Disease Therapy that May Reduce Symptomatic Burden and Ocular Redness

Efficacy Feedback (Patients)

Dryness

Importance 

- Patients noted ocular dryness as one of their top complaints amongst symptoms of dry eye disease.
  - Reproxalap's targeting of dryness was **viewed highly favorably** as this symptom impacts daily activities and leads to a lower quality of life.
- Overall, **patients placed a greater value on dryness** than redness.

"The eye dryness is so terrible it really does affect my daily life. I love that this drug is going after dryness." – Severe Patient

"I definitely care about my dryness being resolved first before anything else." – Mild Patient

"I don't think I would take a drug if it didn't help my dryness because that's my biggest problem." – Moderate Patient

Redness

Importance 

- Redness was mainly viewed as **"a nice-to-have not a need-to-have."**
- Some patients expressed redness as a top complaint and **viewed the redness endpoint as highly valuable.**

"I hate when my eyes are red. This sounds amazing because it can help my dry eye and resolve my redness!" – Moderate Patient

"My eyes never really get red, so I don't care very much about the redness endpoint." – Moderate Patient

"My eyes get red sometimes. Its annoying so I guess the fact that this targets redness too is a bonus." – Severe Patient

Key: *Low Importance*  *High Importance* 

Source: Patient Interviews (n=40); ClearView analysis of market research conducted Q4 2021 – Q1 2022. Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials

Pending FDA Feedback, Reproxalap Has the Potential to Be the First Dry Eye Disease Drug Approved Based on Multiple Objective Signs

Drug	Indication Excerpt from Label	Clinical Data in Label
Restasis®	Increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca	Schirmer test ≥10 mm responder analysis
Tyrvaya®	Treatment of the signs and symptoms of dry eye disease	Schirmer test ≥10 mm responder analysis, mean change in Schirmer test score
Cequa®	Increase tear production in patients with keratoconjunctivitis sicca (dry eye)	Schirmer test ≥10 mm responder analysis
Eysuvis®	Short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease	Ocular discomfort severity score, conjunctival hyperemia score
Xiidra®	Treatment of the signs and symptoms of dry eye disease	Eye dryness score, inferior fluorescein staining score

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