OSN New York Retina 2024

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Nasdaq: ALDX

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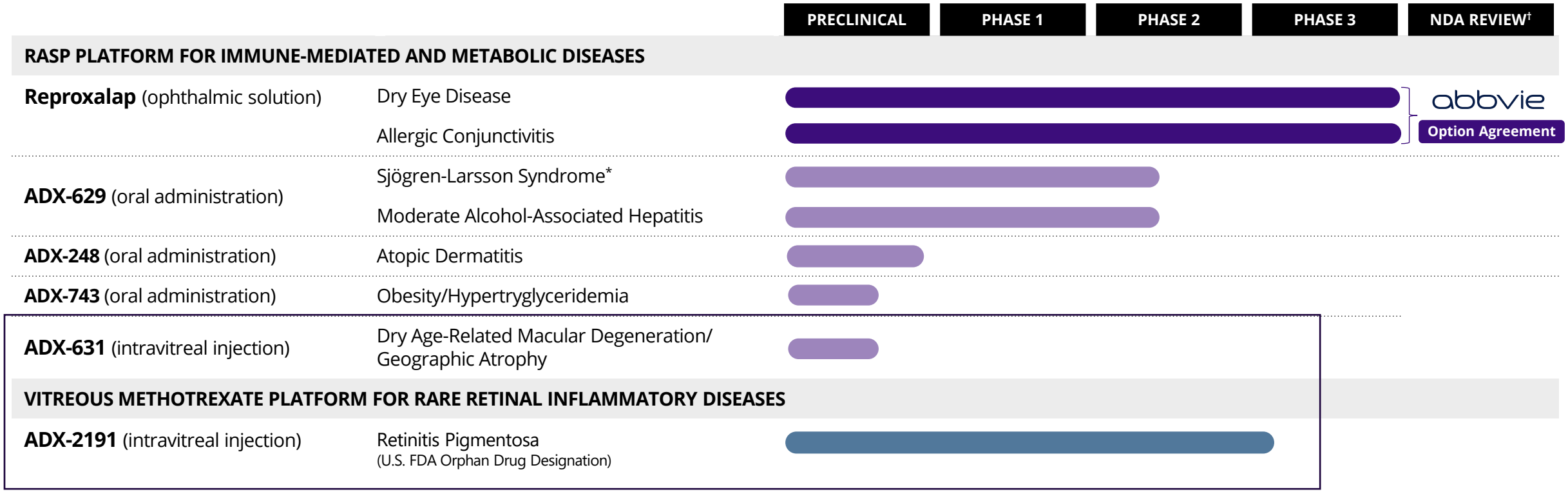
Aldeyra Is a Well-Capitalized Biotechnology Company with a Broad Immunology and Metabolic Pipeline



As of 6/30/2024, cash, cash equivalents, and marketable securities were $120.3M, which Aldeyra believes will be sufficient to fund the Company through 2026.‡

†Regulatory review timelines are flexible and subject to change based on the regulator's workload and other potential review issues. ‡Company guidance as of August 1, 2024; includes continued early and late-stage development of our product candidates in immune-mediated and metabolic diseases. Guidance does not include any potential licensing or product revenue associated with reproxalap. *Investigator sponsored. NDA = New Drug Application

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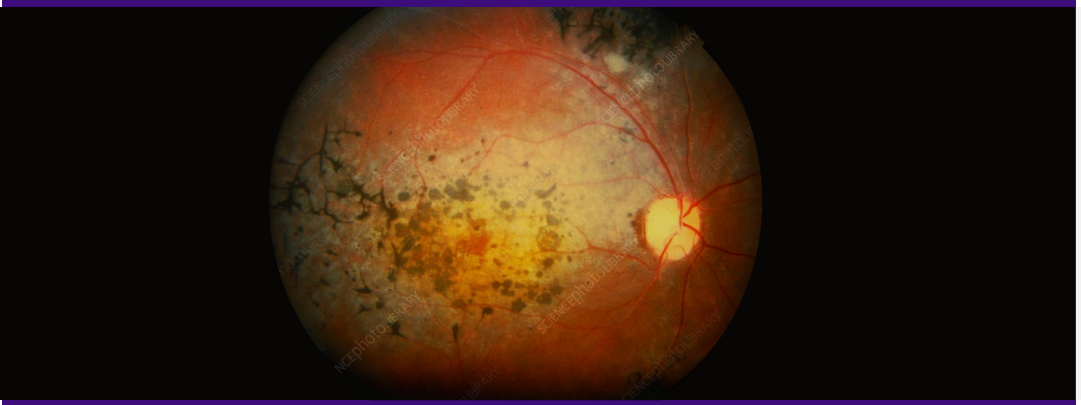
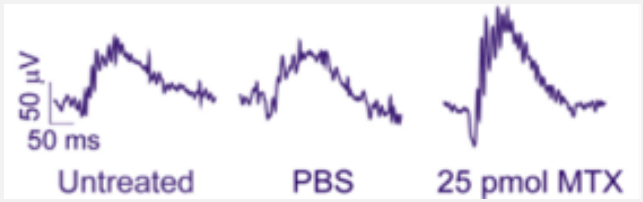
ADX-2191 for the Treatment of Retinitis Pigmentosa

ADX-2191 Has the Potential to be the First Approved Drug for Retinitis Pigmentosa

Retinitis pigmentosa affects more than 1 million people worldwide. Rhodopsin misfolding mutations account for approximately one-third of cases.



- By facilitating degradation of mutated rhodopsin (via lysosomal clearance), methotrexate may represent a potential treatment for retinitis pigmentosa patients with rhodopsin misfolding mutations.
- ADX-2191 (methotrexate injection, USP) is a concentrated, high-density, non-compounded formulation of methotrexate designed to meet the unique requirements of intravitreal administration.
- **U.S. FDA Orphan Drug Designation** was received in August 2021.



Preclinical electroretinographic evidence in a P23H rhodopsin mutation mouse model of retinitis pigmentosa **suggests that methotrexate improves retinal function.**

ADX-2191 (methotrexate injection, USP) for intravitreal administration is an investigational drug candidate. Sources: Aldeyra internal estimates; FASEB J. 2020 Aug;34(8):10146-10167. PBS = phosphate-buffered saline; MTX = methotrexate.

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ADX-2191: Phase 1/2 Trial Design in Retinitis Pigmentosa (RHO)

Design

Single-center, dose-ranging, open-label clinical trial of ADX-2191 (400µg methotrexate in 0.05mL) in patients with retinitis pigmentosa

Inclusion Highlights

Diagnosis of retinitis pigmentosa due to rhodopsin gene mutations, including P23H

Dosing Regimen

Cohort A (n = 4):
Monthly injections of ADX-2191 for three months

Cohort B (n = 4):
Twice-monthly injections of ADX-2191 for three months

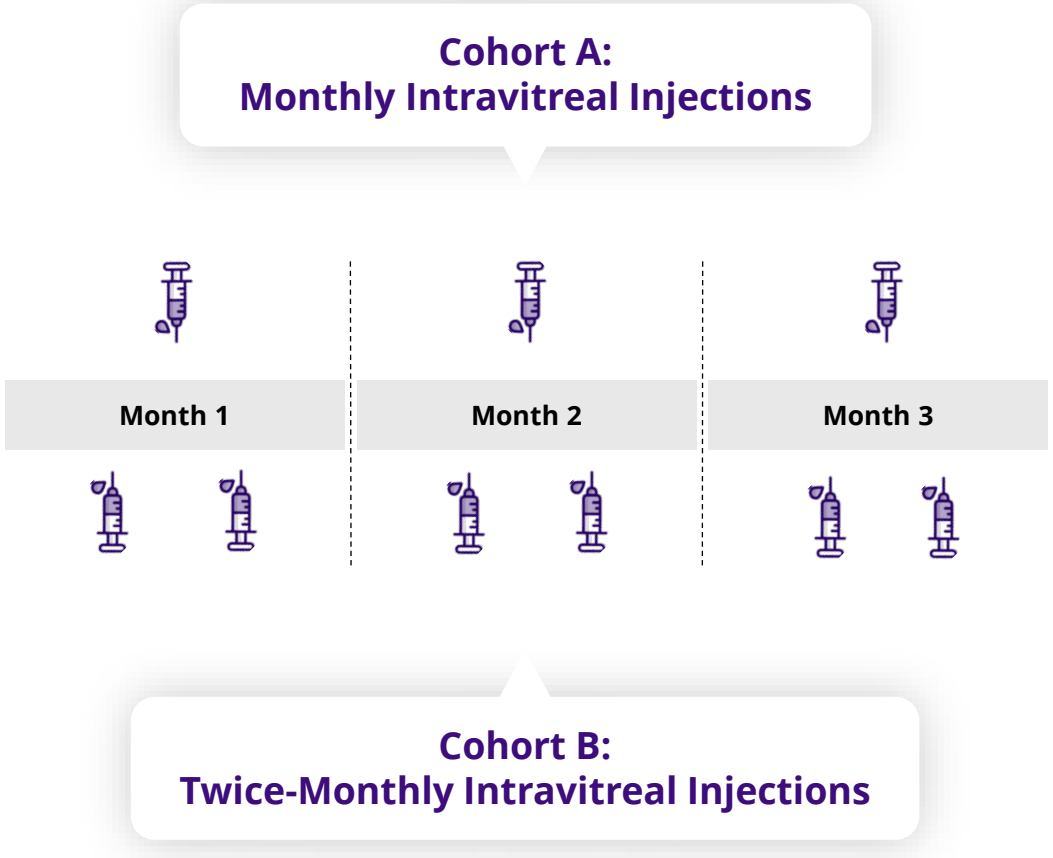
Primary Endpoint

Safety and tolerability

Secondary Endpoints

1. Best corrected and low-light visual acuity
2. Macular retinal sensitivity as assessed by MAIA perimetry
3. Dark-adapted flash analyzed by ERG
4. Peripheral retinal sensitivity as assessed by Dark Adapted Chromatic perimetry
5. Retinal morphology as assessed by OCT

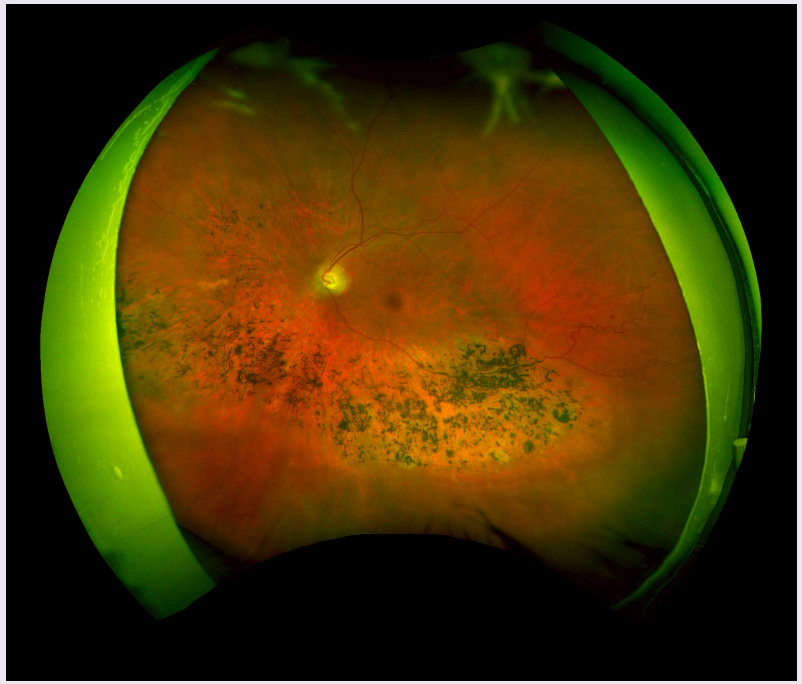
Acuity, perimetry, and OCT assessments were performed monthly for four months from initiation of therapy. ERG was performed at baseline and at 90 days from initiation of therapy.



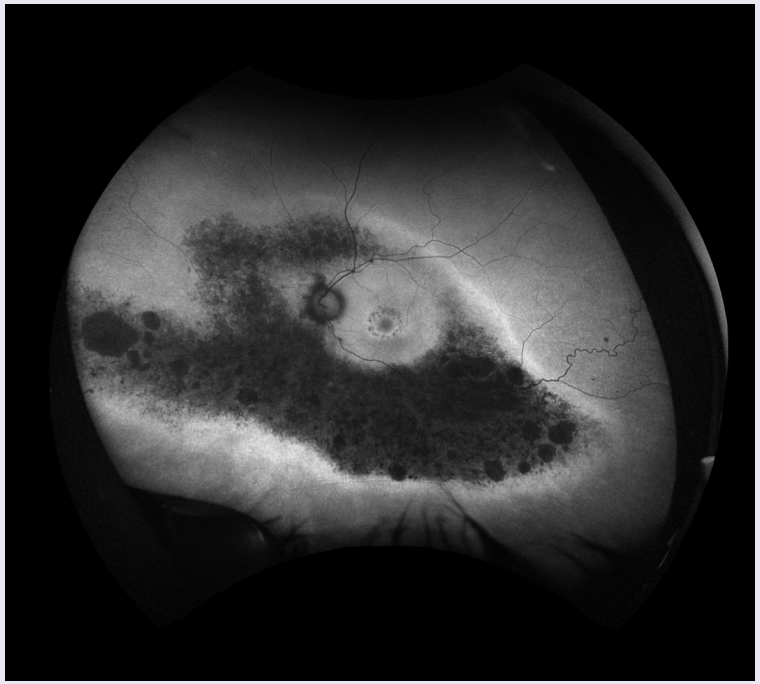
ADX-2191 (methotrexate injection, USP) for intravitreal administration is an investigational drug candidate. **MAIA** = Macular Integrity Assessment; **ERG** = full field electroretinography; **DAC** = dark-adapted chromatic; **OCT** = optical coherence tomography.

Illustrative Images from an Enrolled Patient in the Phase 1/2 Retinitis Pigmentosa Trial

Color Fundus Photograph

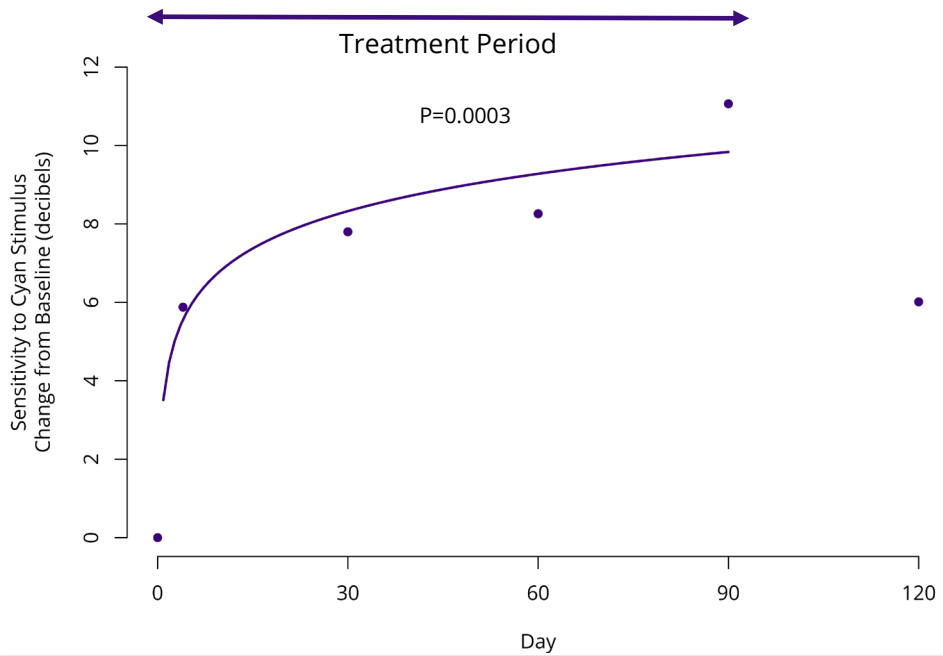


Autofluorescence Photograph

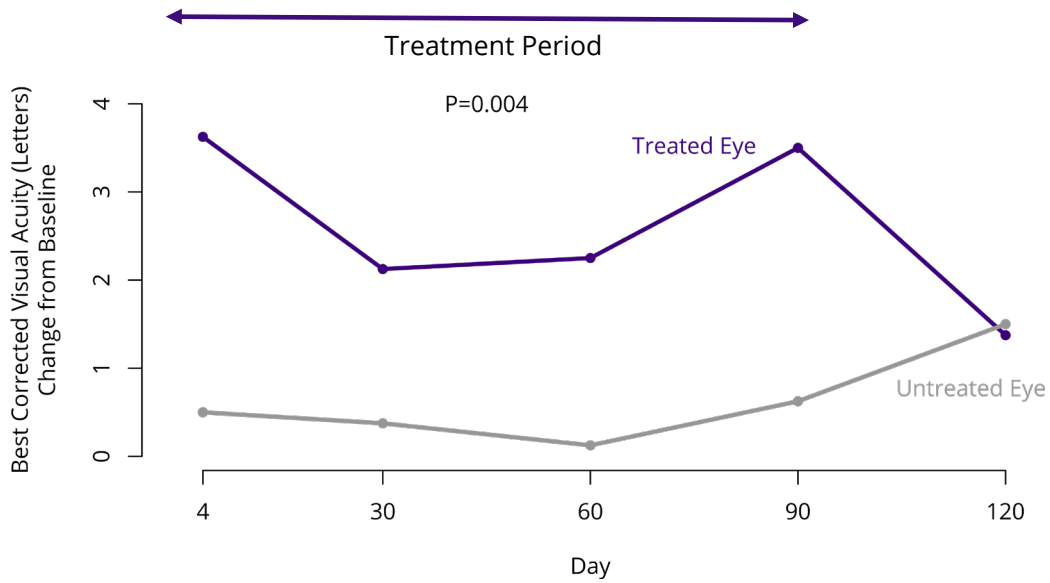


In the Phase 1/2 Retinitis Pigmentosa Clinical Trial of ADX-2191, Rod Sensitivity and Visual Acuity Improved from Baseline

Dark-Adapted Sensitivity to Cyan Stimuli



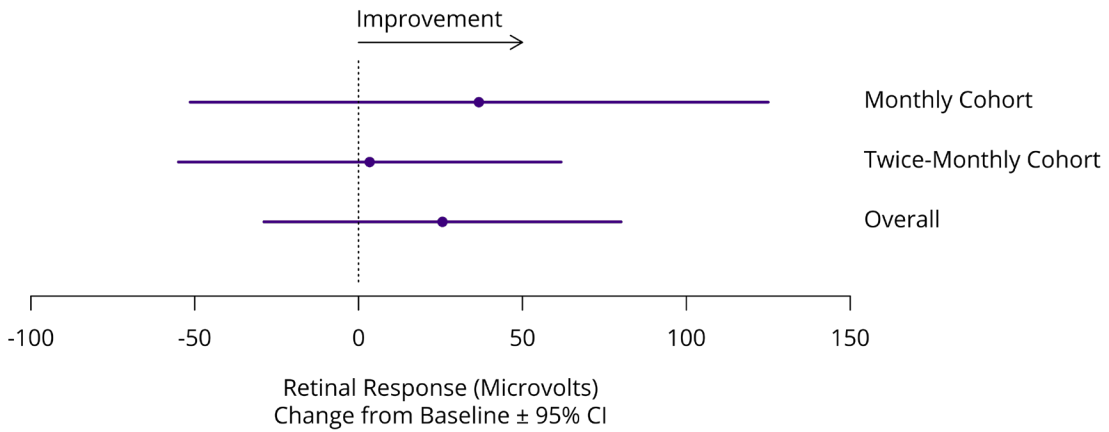
Best Corrected Visual Acuity



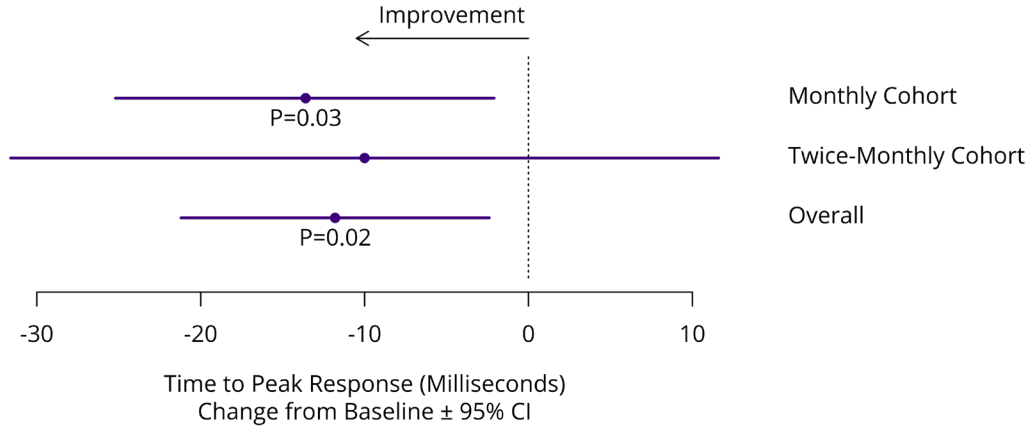
ADX-2191 (methotrexate injection, USP) for intravitreal administration is an investigational drug candidate. Phase 2 clinical trial was performed in eight retinitis pigmentosa patients with rhodopsin misfolding mutations: four patients received monthly injections for three months; four patients received twice-monthly injections for three months. Dark adapted chromatic perimetry used to assess sensitivity to green light stimuli. Data derived from mixed model for repeated measures with baseline and day as factors. Retinal sensitivity assessed where baseline values were >0 and ≤15 decibels. P value relative to 0 (no change from baseline). **DAC** = dark-adapted chromatic; **CI** = confidence interval.

In the Phase 1/2 Retinitis Pigmentosa Clinical Trial of ADX-2191, Full Field ERG Improved from Baseline

Strength of Response



Time to Response



ADX-2191 (methotrexate injection, USP) for intravitreal administration is an investigational drug candidate. B-wave response and implicit time following dim flash under scotopic conditions were assessed. Data derived from mixed model for repeated measures with baseline and dose (if applicable) as factors. **CI** = confidence interval; **ERG** = full field electroretinography.

Planned Phase 2/3 Clinical Trial of ADX-2191 in Retinitis Pigmentosa

Design	Randomized, double-masked, clinical trial
Dosing	40 µg vs. 400 µg administered monthly for 12 months
Size	30 retinitis pigmentosa patients with rhodopsin mutations, randomized 1:1
Primary Endpoint	Rod-mediated, peripheral vision sensitivity (dB) under dark-adapted conditions
Other Endpoints	Best-corrected and Low-light visual acuity, safety

Clinical trial initiation expected in H2 2024†

†The timing of clinical trials depends, in part, on the availability of clinical research facilities and staffing, the ability to recruit patients, and the number of patients in the trial.

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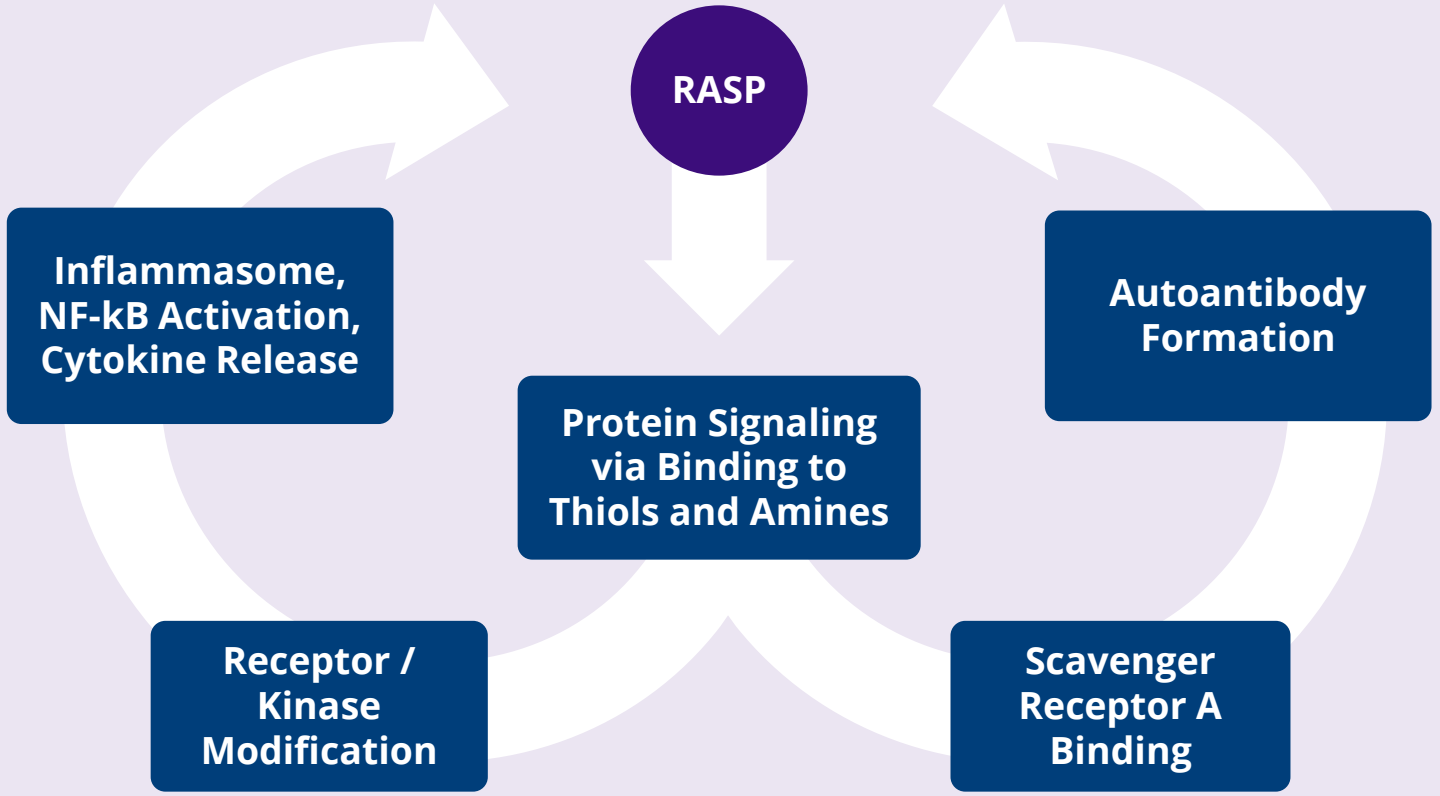
RASP Modulation for the Treatment of Dry AMD and Associated Diseases

RASP Induce Inflammation via Multiple Mechanisms

- Aldehydes **covalently bind** thiol (Michael addition) and amine (Schiff base) residues on proteins.
- Direct protein binding leads to **conformational and functional** changes in proteins, which in turn initiate a pro-inflammatory signaling cascade.



RASP = reactive aldehyde species

In the Retina, Free Retinaldehyde Mediates Inflammation and Aggregate Formation

Published in final edited form as:
Ophthalmology. 2019 June ; 126(6): 866–867. doi:10.1016/j.ophtha.2018.12.024.

Rod-mediated dark adaptation as a suitable outcome for early and intermediate age-related macular degeneration

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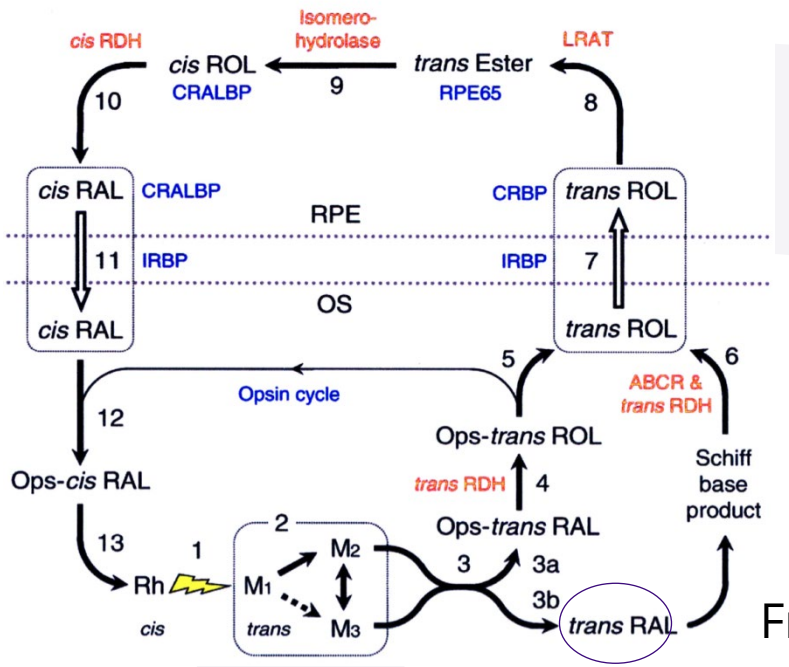


Adapted from: *Prog Retin Eye Res.* 23:307, 2004.

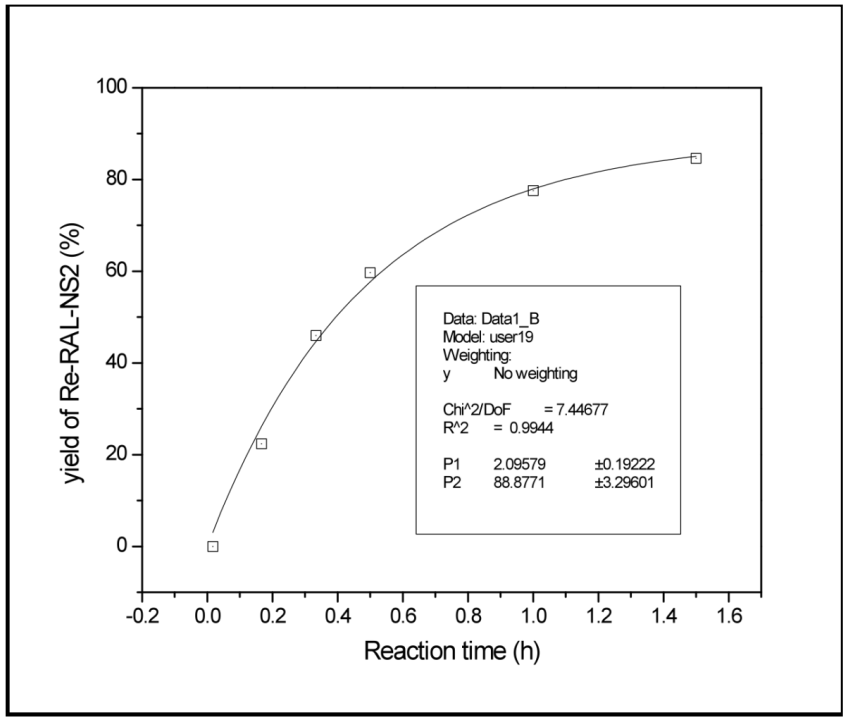
Free *trans* RAL (aldehyde)

- Direct toxicity
- A2E
- Other toxic byproducts

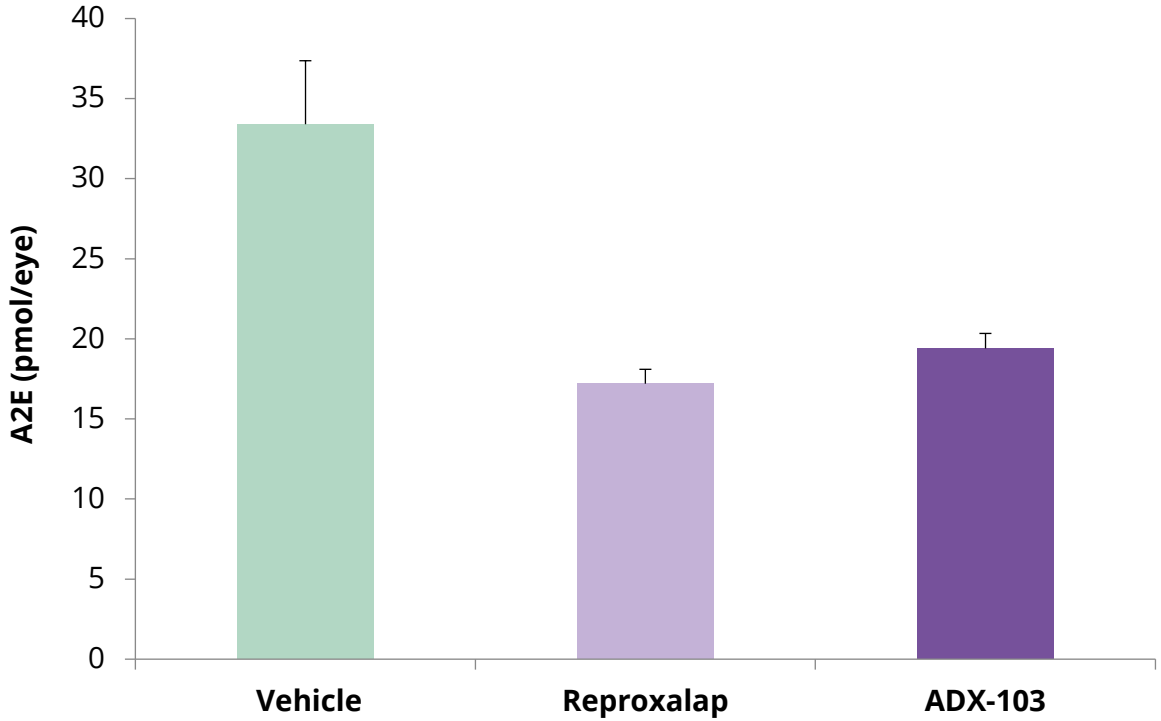
→ Inflammation, retinal aggregates → Dark adaptation & Scotopic Visual deficits

RASP Modulators Rapidly Bind Retinaldehyde and Reduce Levels of Toxic Metabolite A2E in abcr -/- Mice

Representative Binding Time course of RASP Modulator to Retinaldehyde



Retinal A2E Levels in abcr -/- Mice following 56 Days of Intraperitoneal RASP Modulator Treatment



Data Presented at ARVO 2018

RASP Modulation Could Represent a New Approach for the Treatment of Dry Age-Related Macular Degeneration

- Retinaldehyde is associated with inflammation and binds other molecules to form retinal aggregates.
- RASP modulators that sequester retinaldehyde could treat retinal diseases by reducing inflammation and the accumulation of retinal aggregates.
- The association with retinaldehyde and deficits in scotopic vision allows for the assessment of novel visual function endpoints in clinical trials of RASP modulators.

Clinical and Regulatory Milestones

2024

- [x] **Allergic Conjunctivitis (Reproxalap)**
  Positive Phase 3 INVIGORATE 2 trial top-line results announced
- [x] **Dry Eye Disease (Reproxalap)**
  Positive Phase 3 dry eye chamber clinical trial top-line results announced
- [x] **Dry Eye Disease (Reproxalap)**
  NDA resubmitted†
- [ ] **Moderate Alcohol-Associated Hepatitis (ADX-629)**
  Open-label Phase 2 clinical trial top-line results expected H2 2024‡
- [ ] **Atopic Dermatitis (ADX-248)**
  Phase 1 clinical trial initiation expected in H2 2024‡
- [ ] **Retinitis Pigmentosa (ADX-2191)**
  Phase 2/3 clinical trial initiation expected in H2 2024‡

2025

- [ ] **Dry Age-Related Macular Degeneration/Geographic Atrophy (ADX-631)**
  Investigational New Drug application expected to be submitted in H1 2025
- [ ] **Sjögren-Larsson Syndrome (ADX-629)**
  Phase 2 clinical trial pediatric cohort top-line results expected 2025
- [ ] **Obesity/Hypertryglyceridemia (ADX-743)**
  Investigational New Drug application expected to be submitted in 2025

†Regulatory review and discussion timelines are flexible and subject to change based on the regulator's workload and other potential review issues. ‡The timing of clinical trials depends, in part, on the availability of clinical research facilities and staffing, the ability to recruit patients, and the number of patients in the trial. *Investigator sponsored.

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