



June 2019

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JEFFERIES 2019 HEALTHCARE CONFERENCE

Innovating Transformative Therapies

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Our Mission

Developing Next-Generation Medicines to Improve the Lives of Patients with Immune-Mediated Diseases

~7%

Of Western Society

Suffer from some form of **immune-mediated disease**, and **incidence is increasing**

Unmet Needs

Disease control elusive despite existing therapies, and thus **novel approaches are needed**

Source: Lerner, Jeremias, and Matthias, International Journal of Celiac Disease, vol. 3, no. 4 (2015): 151-155;

Shurin and Smolkin, Advances in Experimental Medicines and Biology 601:3-12, 2007; Kuek et al, Postgraduate Medical Journal 83(978): 251-260, 2007.

Deep and Innovative Pipeline Focused on Immune-Mediated Diseases

Disease Area	Compound	[Mechanism]	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Next Anticipated Milestone
Ocular Diseases	Reproxalap	[RASP]	Dry Eye Disease	✓ ✓				
			Allergic Conjunctivitis	✓ ✓ ✓				
			Noninfectious Anterior Uveitis	✓				Phase 3 results H2 2019
	ADX-2191	[DHFR]	Proliferative Vitreoretinopathy					Phase 3-Part 1 initiation H2 2019
	ADX-103	[RASP]	Retinal Disease					Phase 1/2 initiation 2020
	Undisclosed		Ocular Inflammation	Research Collaboration (undisclosed)				
Systemic Diseases	Reproxalap	[RASP]	Sjögren-Larsson Syndrome	✓				Phase 3-Part 1 completion H2 2019
	ADX-1612	[ECHP]	PTLD					Phase 2 initiation 2019
			Mesothelioma	✓				Phase 2 initiation 2019
			Ovarian Cancer	Investigator-Sponsored Trial				
	ADX-629	[RASP]	Autoimmune Disease					Phase 1 initiation H2 2019
	ADX-1615	[ECHP]	Autoimmune Disease / Cancer					
	Undisclosed	[RASP]	Systemic Inflammatory Disease	Research Collaboration				

Our Lead Programs May Offer Potential Benefits Over Standard of Care

Late Stage Programs

Ocular Diseases

	Current Standard of Care	Pricing Benchmarks [†]	Drug Candidate and Dev. Stage	Potential Competitive Advantages [†]
Dry Eye Disease	Xiidra®, Restasis®	\$500-550 per month (dry eye disease pricing)	Reproxalap: Phase 3	Rapid onset, broad activity, reduction in itch
Allergic Conjunctivitis	Antihistamines		Reproxalap: Phase 3	Non-drying, durable activity; Responder superiority vs. vehicle
Noninfectious Anterior Uveitis	Corticosteroids	\$1,500 per regimen (to treat one flare)	Reproxalap: Phase 3	No expected risk of glaucoma or other corticosteroid toxicities
Proliferative Vitreoretinopathy	None (repeat surgeries)	\$30,000 per course (avg. cost of surgeries)	ADX-2191: Phase 3	Clinically demonstrated activity; Currently no FDA- or EMA-approved therapy

Systemic Diseases

Sjögren–Larsson Syndrome	None (manage symptoms)	\$200,000 - \$400,000 per year	Reproxalap: Phase 3	Clinically demonstrated activity; Currently no FDA- or EMA-approved therapy
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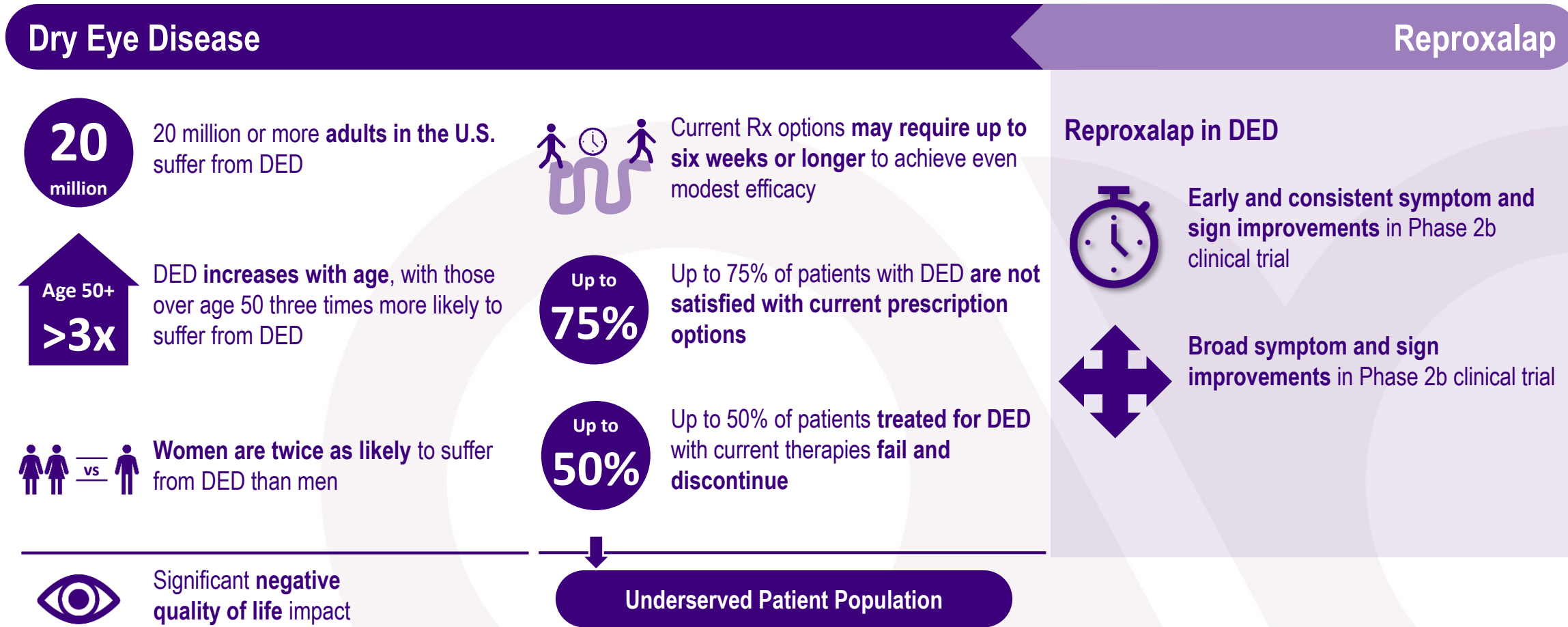
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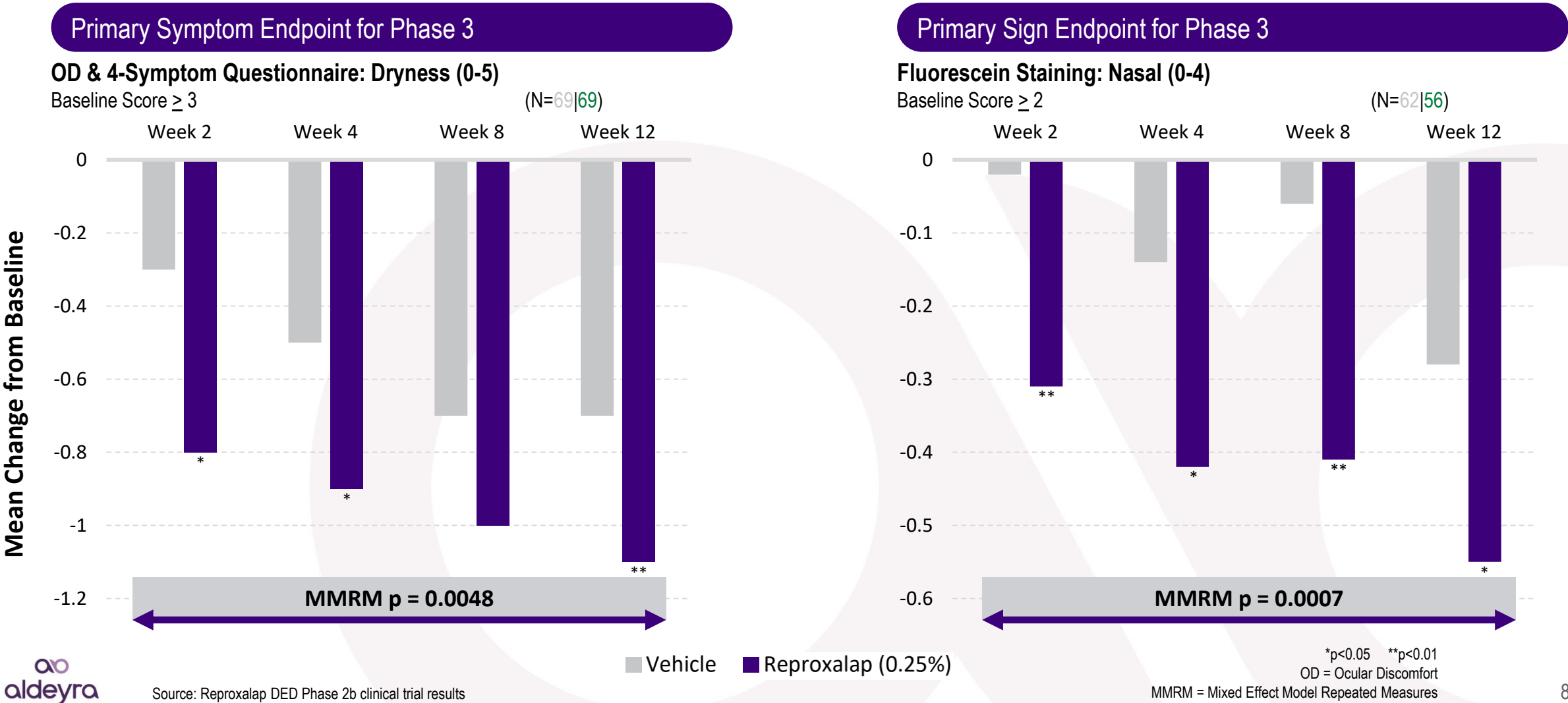
- **DRY EYE DISEASE**
- ALLERGIC CONJUNCTIVITIS
- NONINFECTIOUS ANTERIOR UVEITIS
- PROLIFERATIVE VITREORETINOPATHY

Ocular Disease Area

Dry Eye Disease: Persistently Disturbing Disease with Inadequate Therapy



Dry Eye Disease Symptom and Sign Endpoints Achieved in Phase 2b Clinical Trial



Broad Pattern of Drug Activity Across Dry Eye Disease Symptoms and Signs Supports Differentiated Product Profile

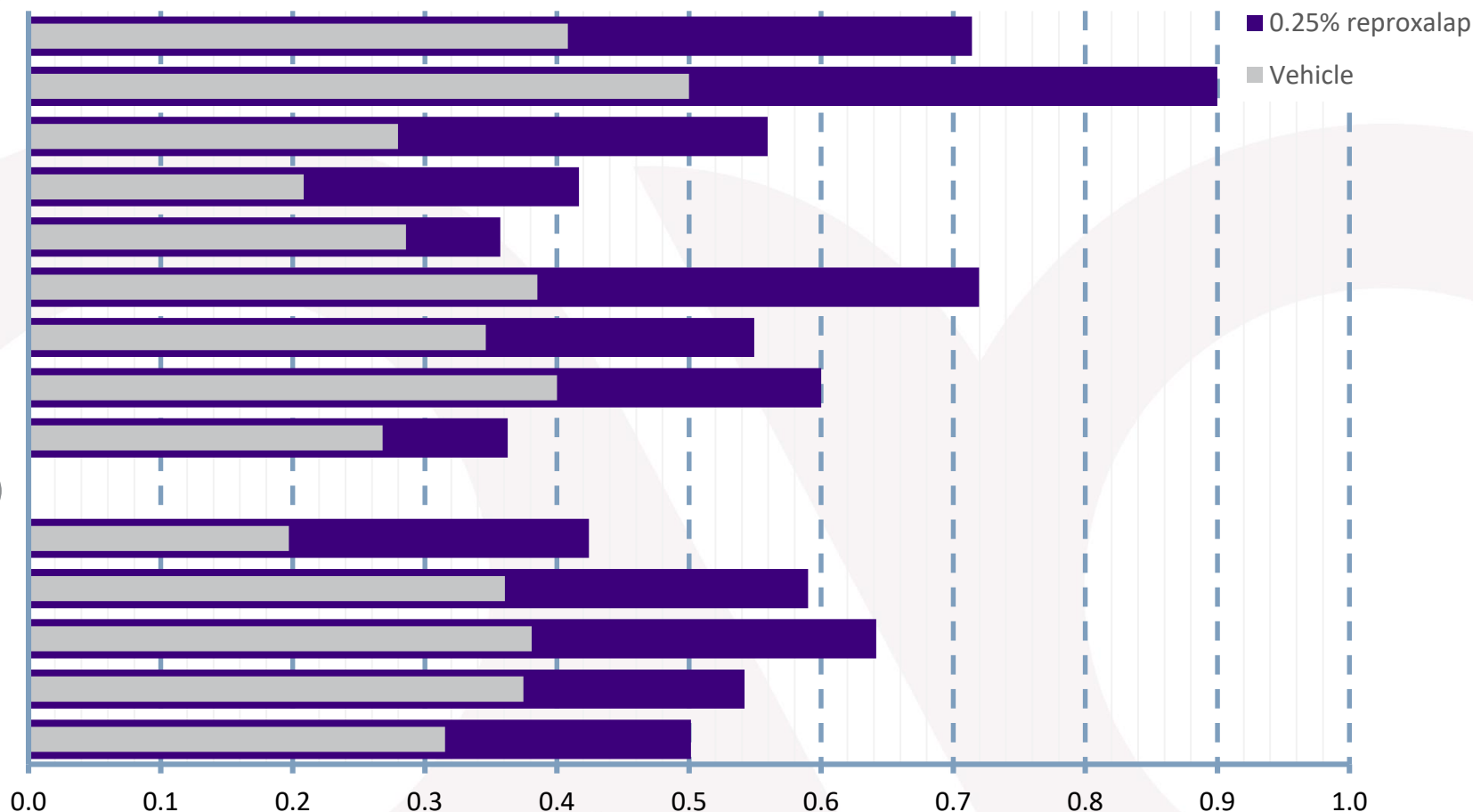
Improvement Effect Size at Week 12

Dry Eye Disease Symptoms

- 4-Symptom: Ocular Discomfort
- 4-Symptom: Dryness
- 4-Symptom: Grittiness
- 4-Symptom: Stinging
- 4-Symptom: Burning
- SANDE: Severity
- SANDE: Frequency
- Ocular Discomfort Scale
- Ocular Surface Disease Index

Dry Eye Disease Signs

- Fluorescein Stain (Nasal)
- Lissamine Green Stain (Nasal)
- Schirmer's Test
- Tear Film Break-Up Time
- Osmolarity



Adaptive Phase 3 Dry Eye Disease Clinical Program

Adaptive Phase 3 Program



Confirm symptom and sign endpoints from Phase 2b trial



Confirm dosing regimen (QID vs. QID to BID taper)



Confirm sample size for subsequent trial

Dry Eye Disease Clinical Program

Initiated April 2019



RENEW
Phase 3 (Part 1)

RENEW
Phase 3 (Part 2)

Confirmatory DED
Phase 3

NDA

Initiated April 2019



Formulation Trial

DED Safety Study

Contingent on funding, regulatory review, and other factors

Adaptive design, co-primary endpoints, and innovative analysis strategy confirmed with FDA at EOP2 Meeting

RENEW Trial Design in Dry Eye Disease

Adaptive Phase 3 (Part 1) Clinical Trial Initiated April 2019

- **Primary objective:**

- Evaluate efficacy of reproxalap ophthalmic solution (0.25%) vs. vehicle to confirm dosing regimen and sample size for Part 2

- **Inclusion/exclusion criteria:**

- Same as used for Phase 2b
- Moderate to severe dry eye disease

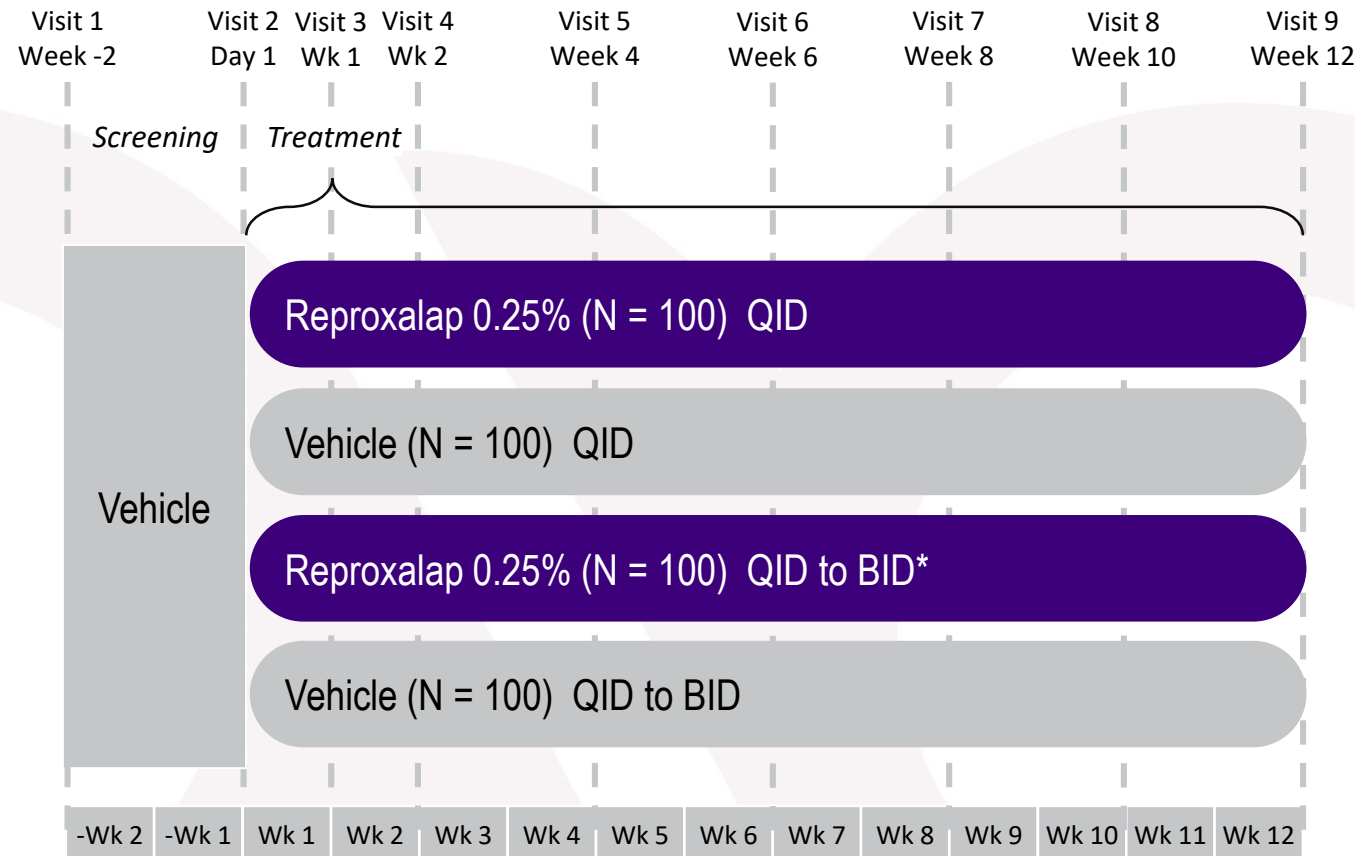
- **Co-primary endpoints:**

- Ocular dryness score (0-100mm VAS) and fluorescein nasal region staining

- **Analysis strategy:**

- Both co-primary endpoints will be assessed using Mixed Model Repeated Measures (MMRM) from week 2 to week 12
- Both co-primary endpoints will be assessed based on separate pre-specified patient populations
 - Ocular dryness score (OD4SS): baseline score of ≥ 3
 - Fluorescein nasal staining: baseline score ≥ 2

Phase 3 Dry Eye Disease Clinical Trial: Part 1



Further information can be found on www.clinicaltrials.gov: Trial #NCT03879863.



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Ocular Disease Area

Allergic Conjunctivitis:

A Common Disease with Unmet Medical Need

Allergic Conjunctivitis

30

million

Up to 30 million of **AC sufferers** in the U.S. **do not respond adequately** to or are **dissatisfied with antihistamines**



Many AC patients make **significant sacrifices** due to lack of drug activity



AC patients experience symptoms throughout **all decades of adult life**

24%

Antihistamines are not effective in an estimated 24% of treated AC patients



AC can result in **acute, intermittent, and chronic** symptoms

2%

~2% of AC patients have severe symptoms and **may be corticosteroid-dependent**



Significant **negative quality of life** impact

Underserved Patient Population

Reproxalap

Reproxalap in AC

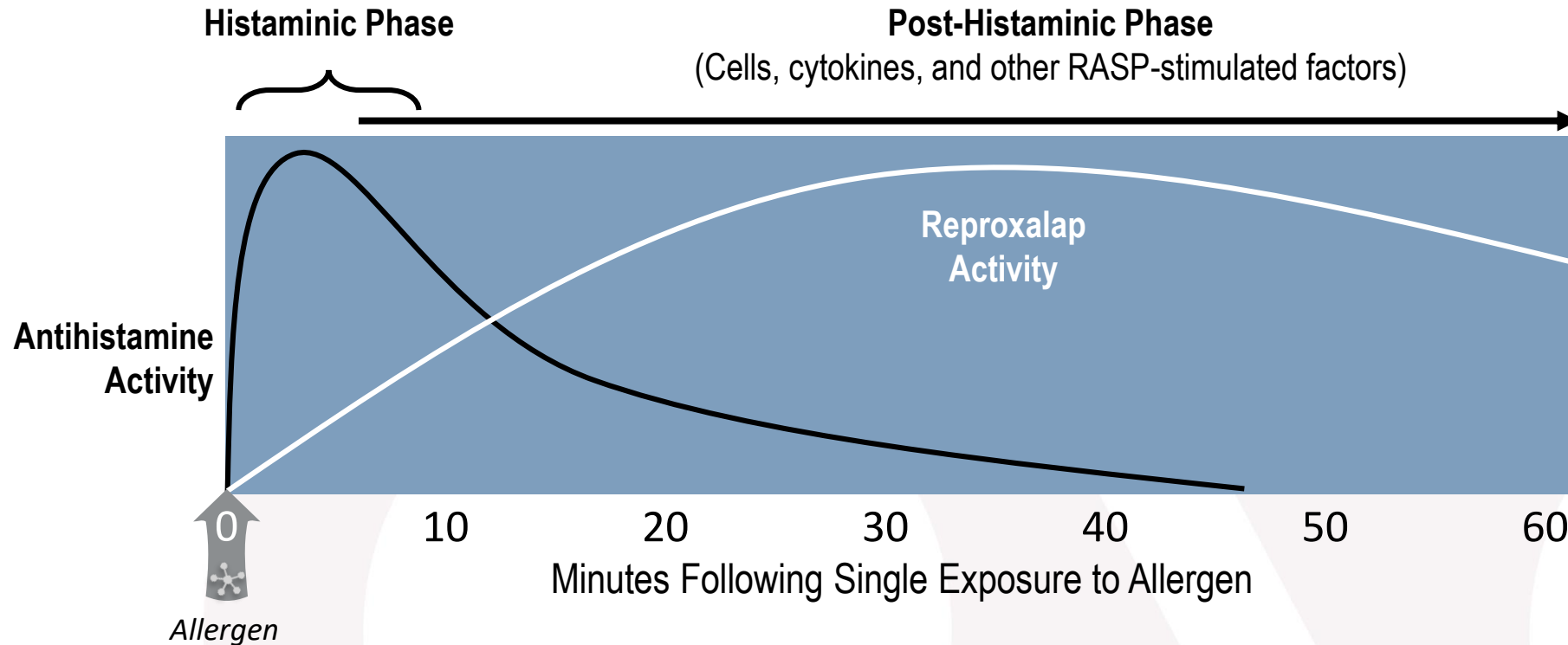


Clinically significant and durable symptom response in Phase 3 clinical trial



Active in post-histaminic allergy, for which no drug is approved

Novel Mechanism of Action has the Potential to Provide Differentiated Activity Versus Antihistamines

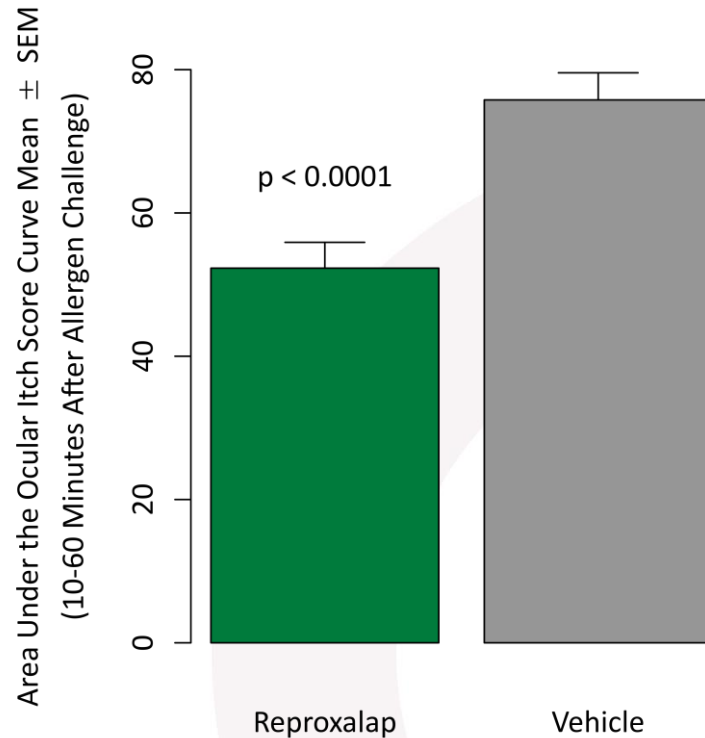


Reproxalap has the potential to be uniquely effective in post-histaminic allergy, which affects all allergic conjunctivitis patients

Reproxalap Showed Greater and More Durable Clinical Responses vs. Vehicle Group in ALLEVIATE Phase 3 Clinical Trial

Primary Endpoint

Area Under the Curve: Ocular Itch Score (0-4) 10 to 60 Minutes After Allergen Challenge

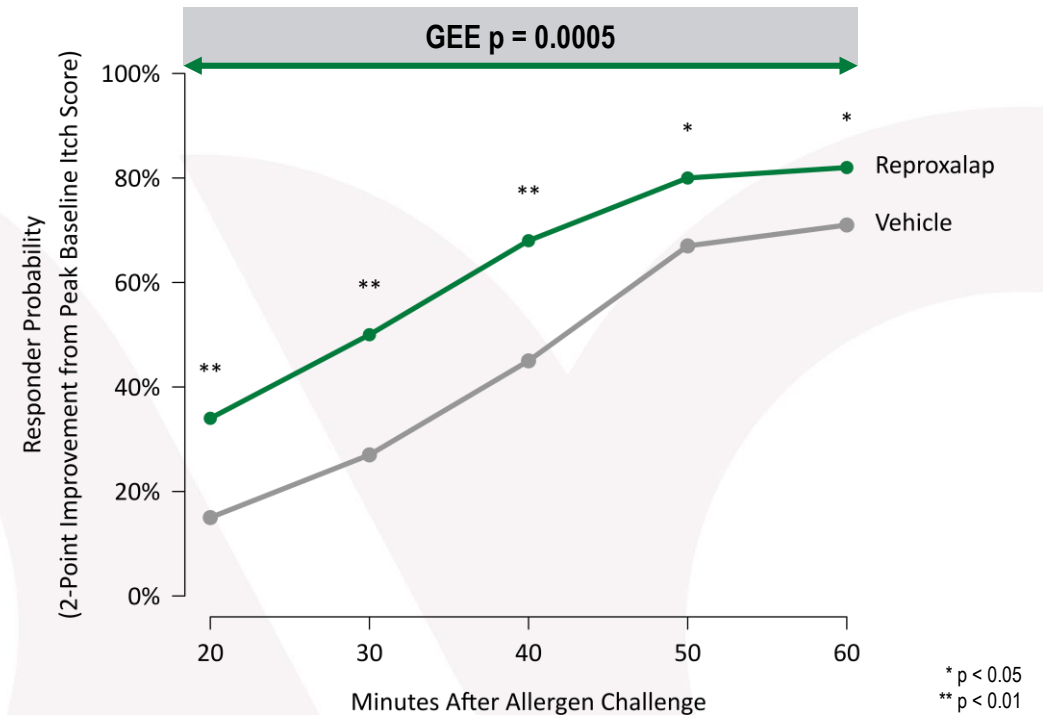


Improvement in itch score over one hour after allergen exposure statistically greater for reproxalap vs. vehicle

SEM = Standard error of the mean

Key Secondary Endpoint

Probability of Two-Point Response: Ocular Itch Score (0-4)

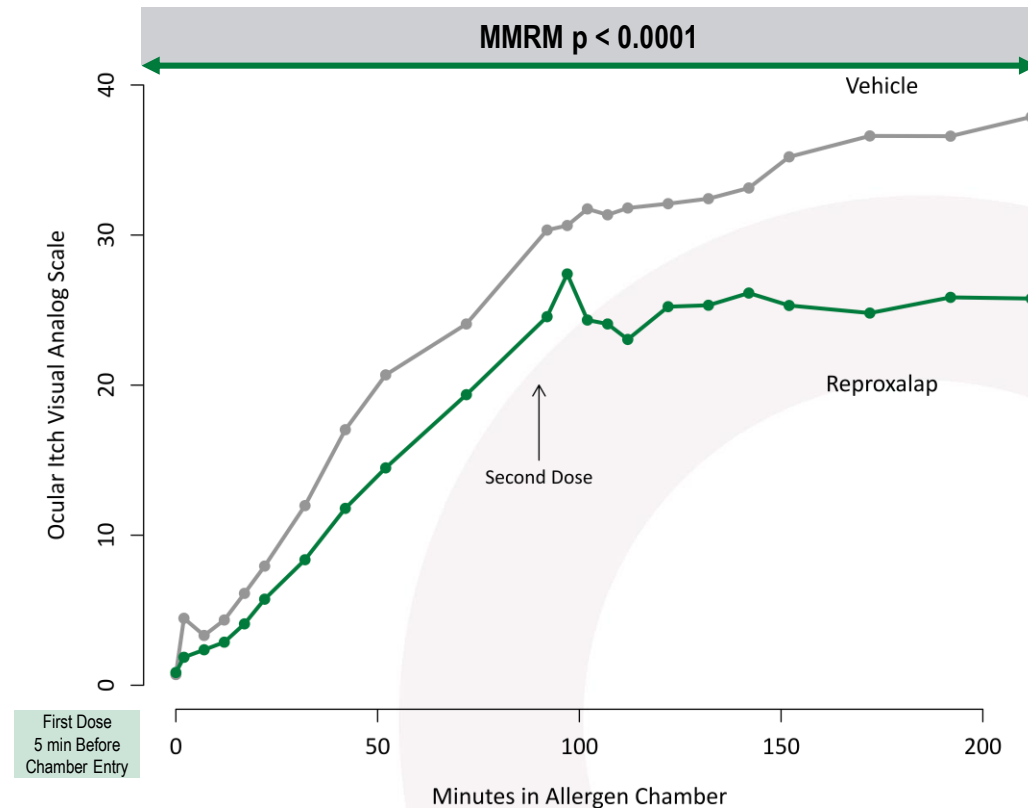


Clinically significant response rate of reproxalap statistically higher than that of vehicle

GEE = Generalized estimating equation analysis

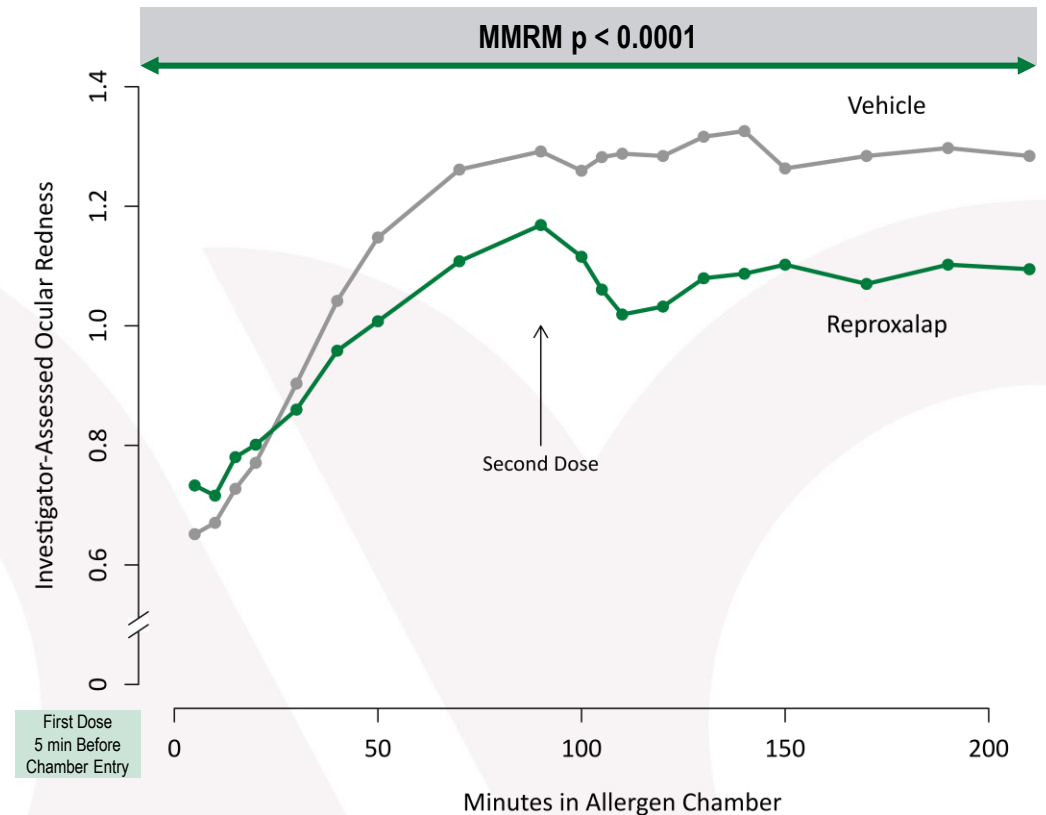
Reproxalap Showed Greater and More Durable Clinical Responses vs. Vehicle in Allergen Chamber Clinical Trial

Ocular Itch Score (0-100) During 3.5 Hours of Allergen Exposure



Statistically significant reduction in ocular itch vs. vehicle for more than three hours of exposure to allergen

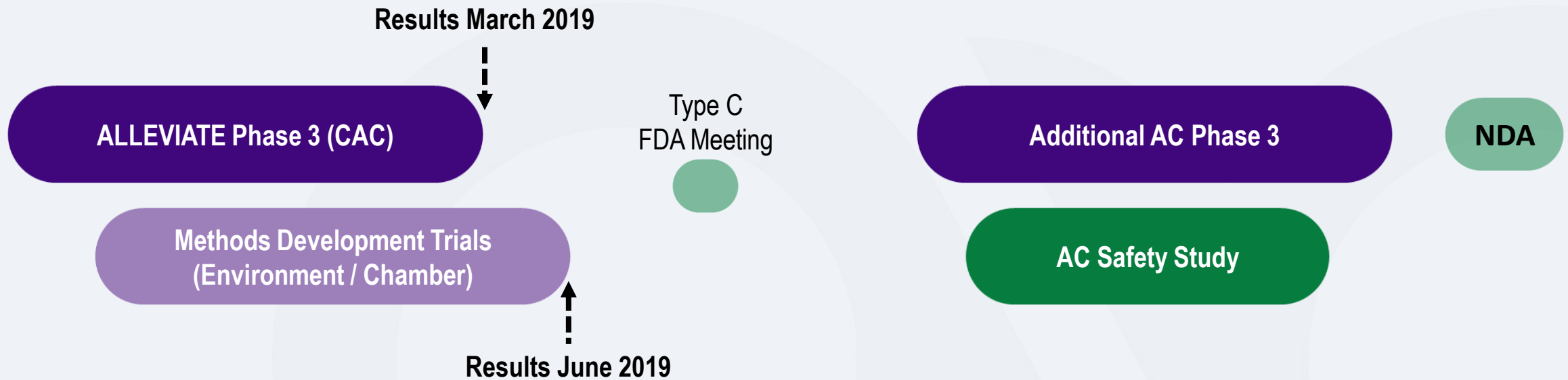
Ocular Redness Score (0-4) During 3.5 Hours of Allergen Exposure



Statistically significant reduction in ocular redness vs. vehicle for more than three hours of exposure to allergen

Allergic Conjunctivitis Phase 3 Clinical Program Design Elements

Allergic Conjunctivitis Clinical Program





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- DRY EYE DISEASE
- ALLERGIC CONJUNCTIVITIS
- NONINFECTIOUS ANTERIOR UVEITIS
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Ocular Disease Area

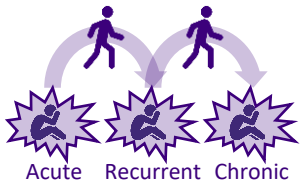
Noninfectious anterior uveitis: A Serious Inflammatory Disease With Inadequate Current Therapy

Noninfectious Anterior Uveitis

Reproxalap

260K
annually

Noninfectious anterior uveitis (NAU) is **the most common form of uveitis**, with an estimated 260,000 U.S. patients per year



~50% of NAU patients have **recurrent or chronic conditions** requiring multiple interventions per year



Corticosteroids are currently SOC and **require monitoring due to serious toxicities**

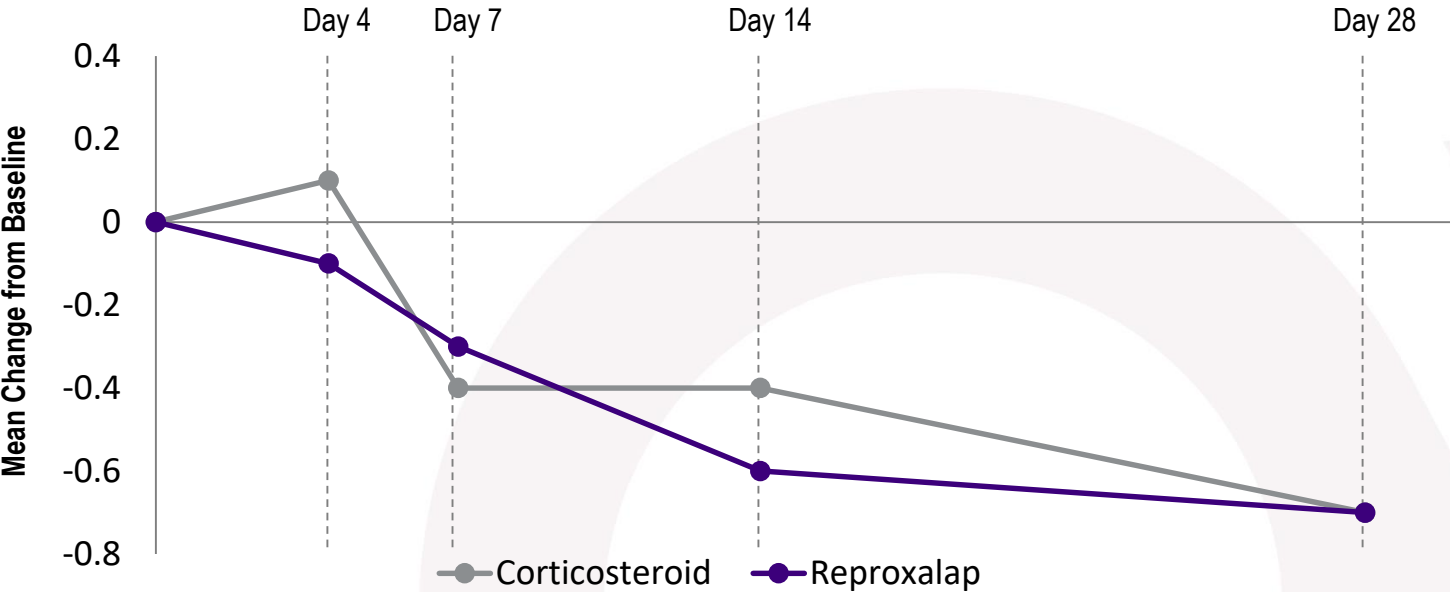
Prolonged usage may lead to **glaucoma, cataracts, corneal ulceration**, and other serious side effects

Reproxalap

- A **novel and differentiated** approach to treat NAU
- **Reduced anterior chamber cell count** in a Phase 2 clinical trial, and was **statistically non-inferior to corticosteroid treatment**
- **Safety and tolerability without intraocular pressure increase** in a Phase 2 clinical trial
- SOLACE Phase 3 clinical trial **results expected H2 2019**

Reproxalap Reduced Inflammation in Noninfectious Anterior Uveitis Phase 2 Clinical Trial

Change from Baseline in Anterior Chamber Inflammatory Cell Grade
ITT Population with Last Observation Carried Forward



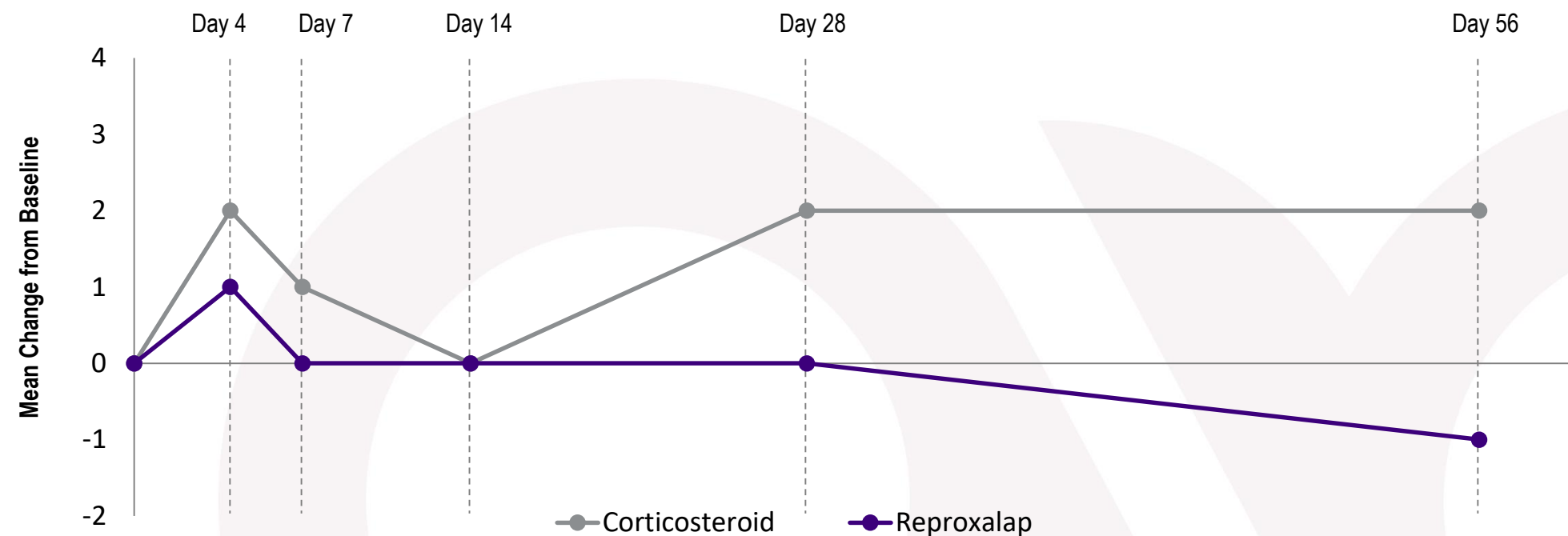
Proportion Cured (Grade 0 = no inflammatory cells observed)	
Week 4 Grade 0	Percent of Subjects
Reproxalap	53% (8/15)
Corticosteroid	38% (5/13)

Reproxalap was statistically non-inferior to corticosteroid in a noninfectious anterior uveitis Phase 2 clinical trial

Reproxalap Did Not Increase Intraocular Pressure in Noninfectious Anterior Uveitis Phase 2 Clinical Trial

Change from Baseline in Intraocular Pressure (mmHg)

Safety Population



Increase in intraocular pressure, which may lead to glaucoma, is a major corticosteroid toxicity that is not apparent with reproxalap

SOLACE Trial Design in Noninfectious Anterior Uveitis

Phase 3 Clinical Trial Initiated April 2017

- **Primary objective:**

- Evaluate efficacy of reproxalap ophthalmic solution (0.5%) on anterior chamber cell count (ACC) vs. vehicle

- **Inclusion highlights:**

- Acute endogenous NAU with onset of symptoms within the previous 2 weeks
- 6-50 ACC in the study eye
- Intraocular pressure <21

- **Dosing regimen:**

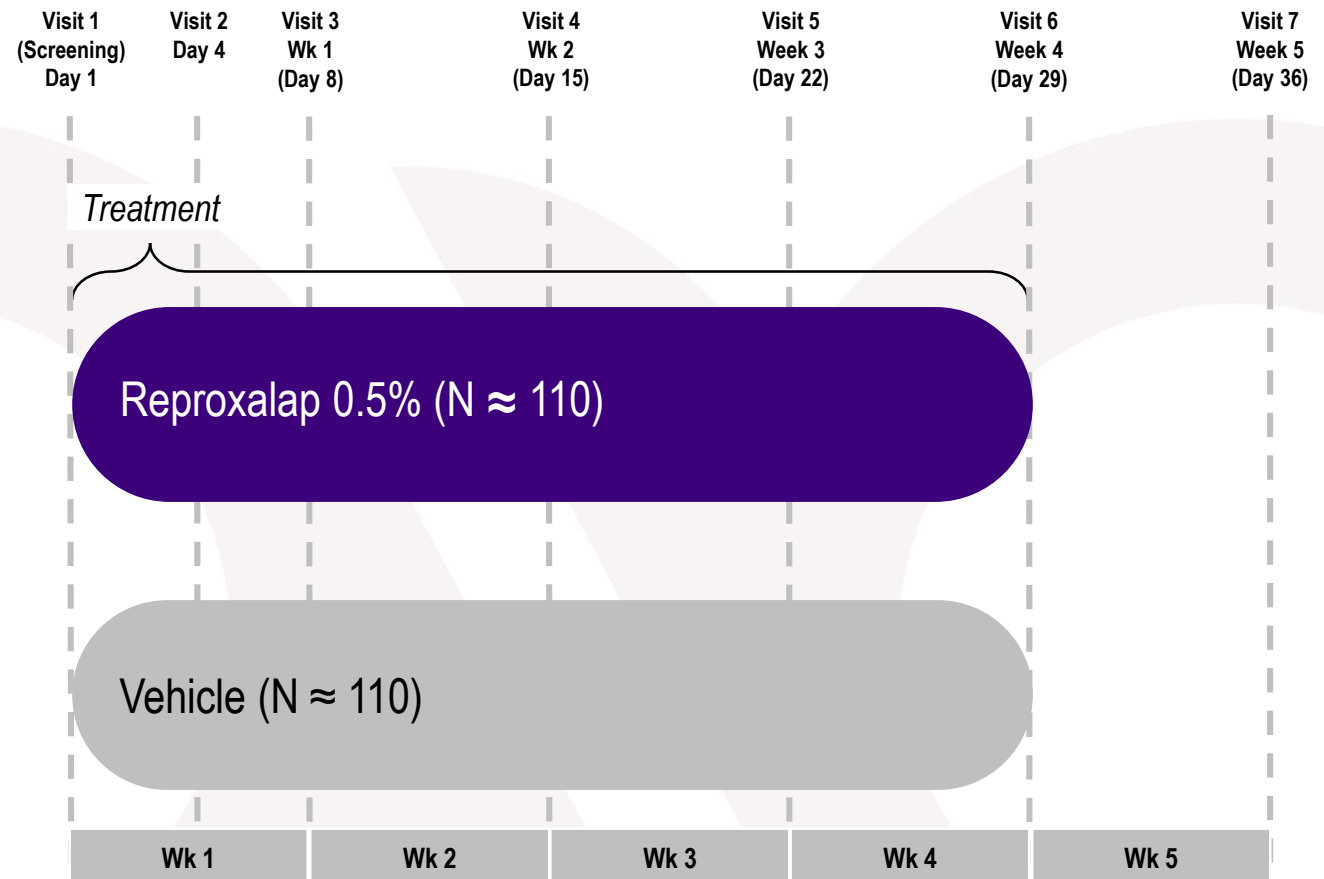
- Week 1 8x/day
- Week 2 6x/day
- Weeks 3-4 4x/day
- Week 5 None

- **Endpoints:**

- Time-to-cure (zero inflammatory cells in anterior chamber) without rescue

- **Results expected to be announced H2 2019**

Phase 3 Noninfectious Anterior Uveitis Trial





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Ocular Disease Area

Proliferative vitreoretinopathy:

A Rare Sight-Threatening Retinal Disease With No Approved Therapies

Proliferative vitreoretinopathy

ADX-2191

4,000
U.S.

PVR is a **rare disease**, with ~4,000 patients per year in the U.S. and nearly twice as many in Europe and Japan



Left untreated, retinal detachment due to PVR can **progress to permanent blindness**



No FDA- or EMA-approved therapy



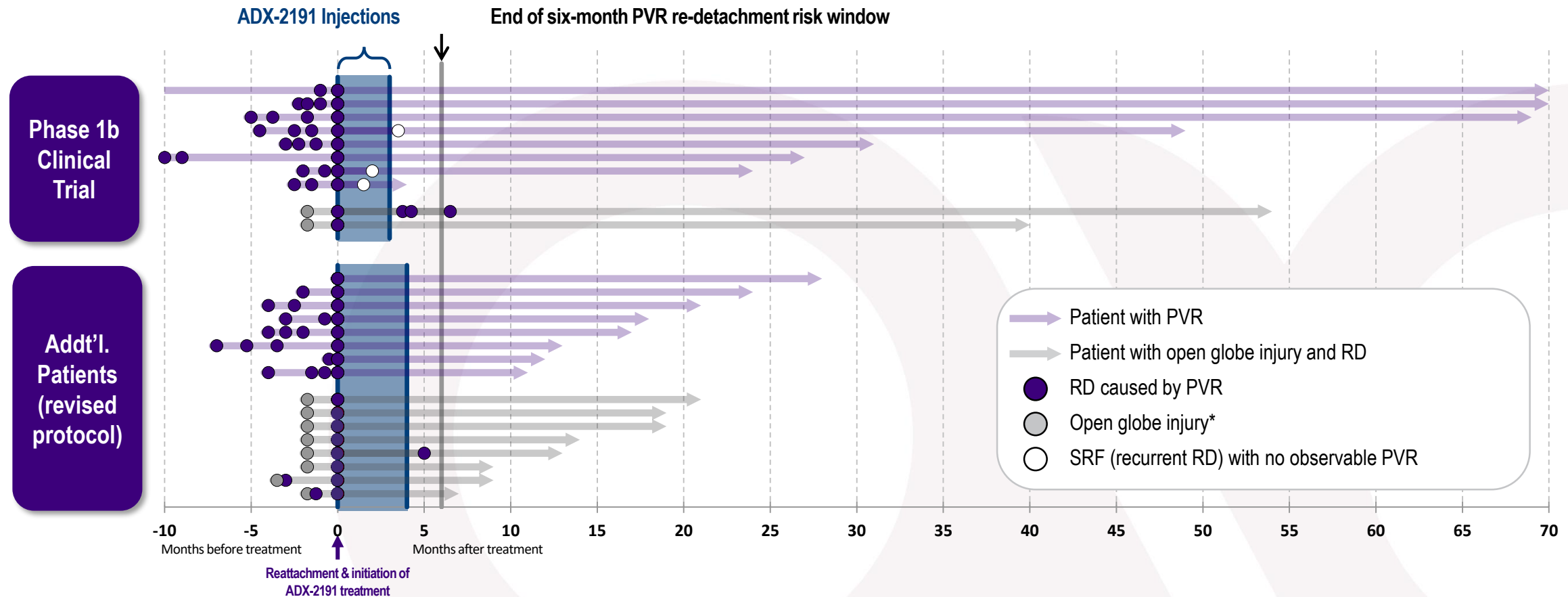
Repeat surgery and subsequent **vision loss** currently the only possible course of action

ADX-2191

- A **novel approach and potential therapeutic breakthrough** in PVR treatment
- **Granted U.S. orphan designation** for the prevention of PVR
- **Tolerability and reattachment success** during study period **demonstrated in Phase 1b** open-label investigator sponsored clinical trial
- Adaptive Phase 3 clinical trial **expected to initiate H2 2019**

ADX-2191 Reduced Recurrent Retinal Detachment in Investigator Sponsored Phase 1b Clinical Trial and in Additional In-Practice Use

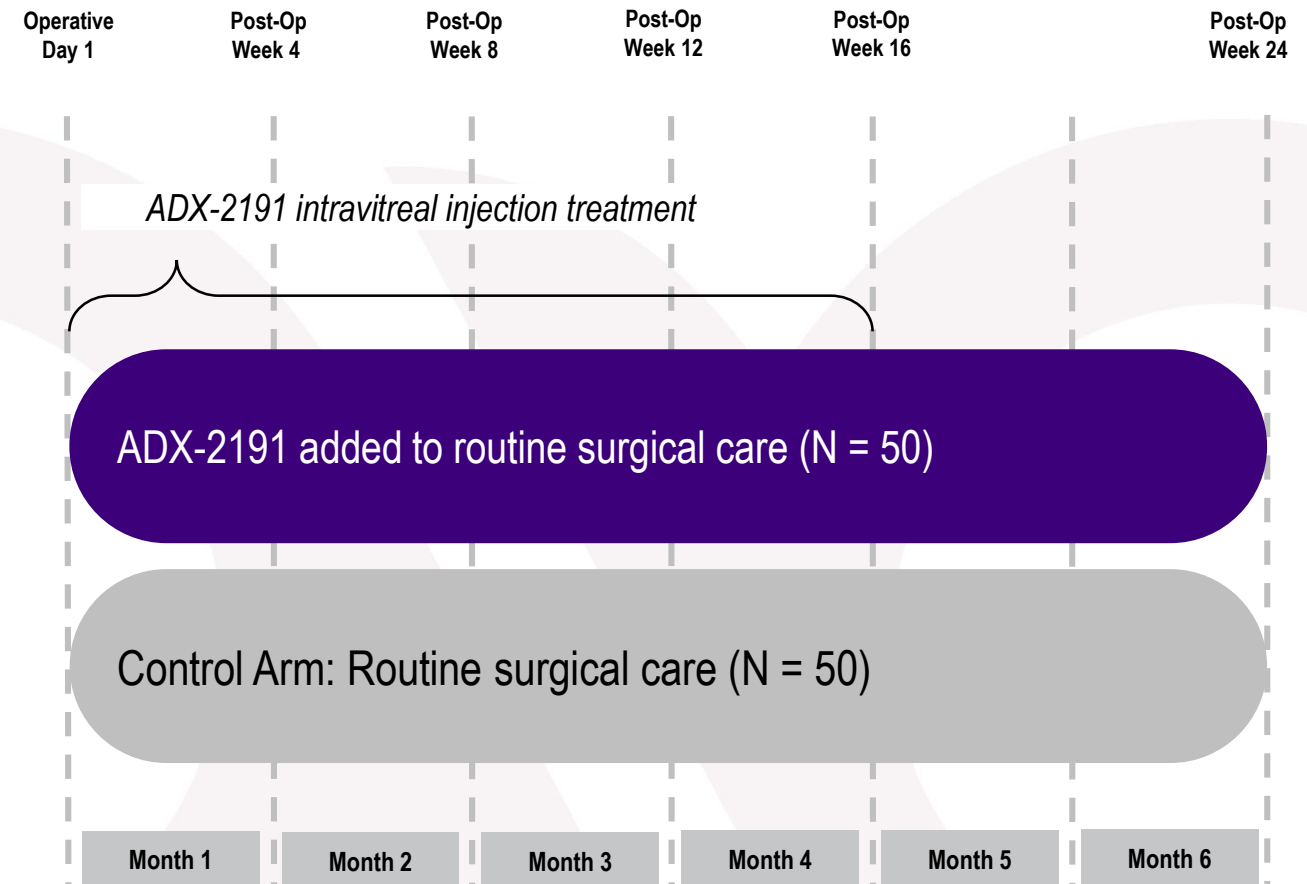
Retinal Detachments Over Time by Patient



ADX-2191: Adaptive Phase 3 (Part 1) Proliferative Vitreoretinopathy Clinical Trial Design*

- **Primary objective:**
 - Evaluate efficacy of intravitreal ADX-2191 injections for prevention of recurrent retinal detachment due to proliferative vitreoretinopathy (PVR)
- **Design:**
 - Multi-center, non-masked, randomized, controlled, two- part, adaptive Phase 3 clinical trial
- **Inclusion highlights:**
 - Recurrent retinal detachment due to PVR, or
 - Retinal detachment associated with open-globe trauma
- **Dosing regimen:**
 - At surgery, weekly (x8), and then every other week (x4) intravitreal ADX-2191 injections
- **Endpoint:**
 - Retinal re-detachments due to PVR requiring re-operation within 6 months:
 1. OCT demonstrating fovea-off retinal detachment
 2. Photographic documentation retinal detachment

Adaptive Phase 3 PVR Clinical Trial Design: Part 1





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SJÖGREN-LARSSON SYNDROME

Systemic Disease Area

Sjögren-Larsson Syndrome:

A Rare RASP-Mediated Disease with No Approved Therapy

Sjögren-Larsson Syndrome

1,000
U.S.

SLS is a **rare disease caused by an enzyme mutation** (Fatty Aldehyde Dehydrogenase), with ~1,000 SLS patients in the U.S. and a greater number in Europe



Severe symptoms significantly impacts **SLS patient and caregiver quality of life**



No FDA- or EMA-approved therapy



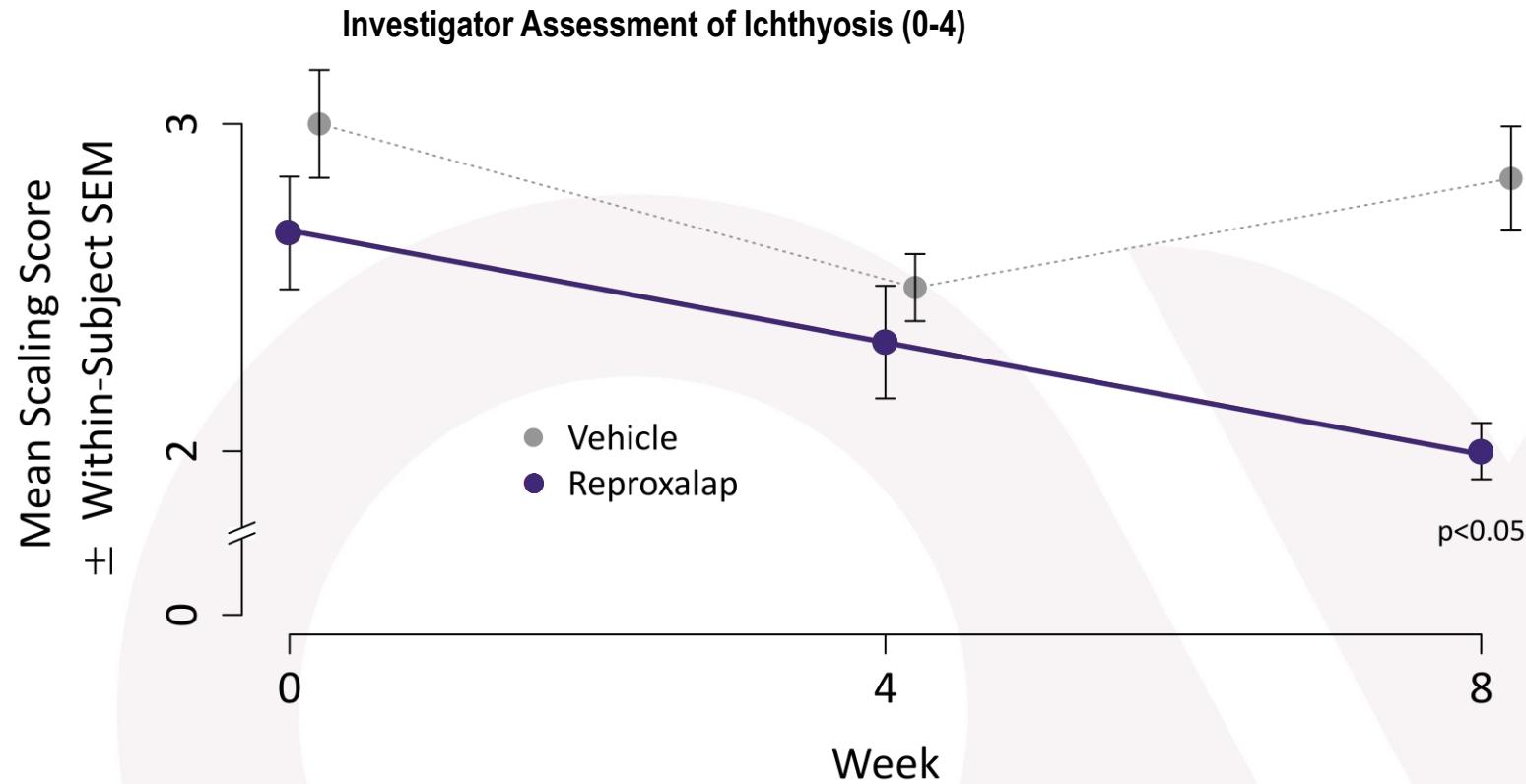
Nonstop disease burden prevents normal patient/caregiver life, with hours devoted to managing painful scaling, monitoring, & care

Reproxalap

Reproxalap

- A **novel approach and potential lifelong therapy** to replace missing enzymatic activity in SLS
- **Granted U.S. orphan designation** for the treatment of congenital ichthyosis (primary symptom of SLS)
- **Significantly reduced SLS ichthyosis** in a randomized, vehicle-controlled Phase 2 clinical trial
- RESET Part 1 Phase 3 clinical trial **completion expected H2 2019**

Reproxalap Demonstrated Clinically Relevant and Consistent Activity in Phase 2 Clinical Trial



Over two months of treatment, ichthyosis improved consistently from moderate to mild disease

RESET Trial Design in Sjögren-Larsson Syndrome

Phase 3 Part 1 Clinical Trial Initiated July 2018

- **Primary objective:**

- Evaluate efficacy of reproxalap topical dermal cream (1%) for the treatment of SLS associated ichthyosis

- **Inclusion/exclusion highlights:**

- Genetically confirmed diagnosis of SLS and at least 3 years of age or older
- Active ichthyosis grade ≥ 2 on the VIIS scaling score
- No systemic or topical retinoids or other topical medications with in the past 30 days prior to baseline visit 1

- **Dosing regimen:**

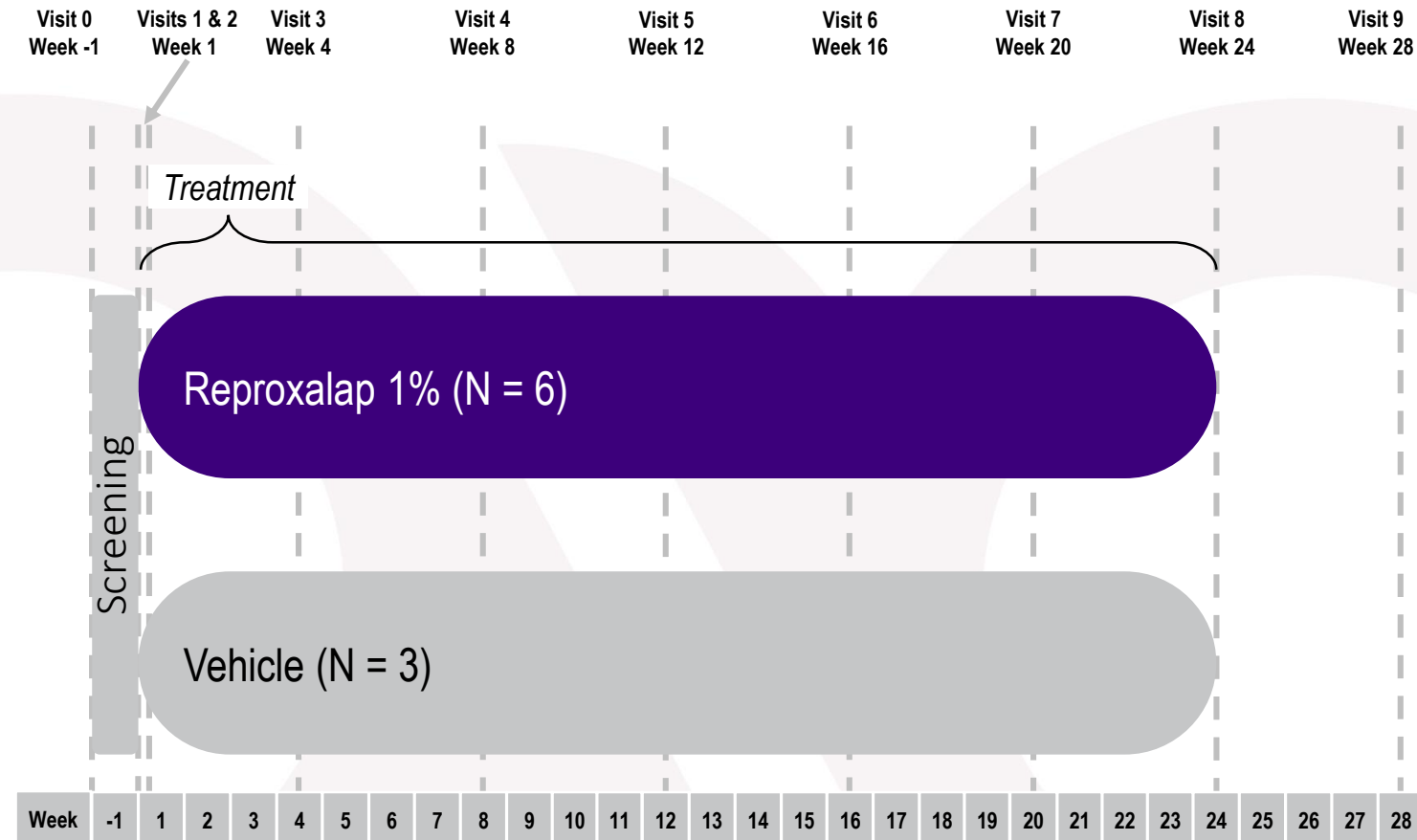
- Weeks 1-12: 20% of Body Surface Area (BSA)
- Weeks 13-20: 40-45% of BSA
- Weeks 21-24: 90% of BSA

- **Endpoints:**

- Baseline ichthyosis change in drug-treated subjects
- Safety / tolerability

- **Completion expected H2 2019**

Phase 3 SLS-Ichthyosis Study: Part 1





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Building The Future

Our Value Proposition



Experienced Management Team and Board of Directors

Management Team

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President, CEO, & Director

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Chief Financial Officer

David Clark, M.D.
Chief Medical Officer

David McMullin, M.B.A.
Chief Commercial Officer

Stephen Machatha, Ph.D.
SVP Technical Operations



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CEO Aclaris Therapeutics

Todd Brady, M.D., Ph.D.

CEO Aldeyra Therapeutics






1. Acquired by Xanthus/Antisoma
2. Acquired by Schwarz/UCB
3. Acquired by Alexion
4. Acquired by Takeda

5. Acquired by Ligand
6. Acquired by Merck
7. Acquired by Alexion
8. Acquired by Genzyme





Expected Development Milestones:^{*}

Novel Approaches to Address Immune-Mediated Disease

Ocular Diseases: Anticipated Milestones

-  Positive reproxalap **ALLEVIATE Phase 3 clinical trial results March 2019**
-  Reproxalap dry eye disease **RENEW Phase 3 clinical trial program initiation April 2019**
-  Reproxalap noninfectious anterior uveitis **SOLACE Phase 3 clinical trial results H2 2019**
-  ADX-2191 Proliferative Vitreoretinopathy **Phase 3 clinical program initiation H2 2019**
-  **Remaining clinical requirements** for potential allergic conjunctivitis NDA to be **confirmed H2 2019**

Systemic Diseases: Anticipated Milestones

-  Reproxalap Sjögren-Larsson Syndrome **RESET Phase 3-Part 1 clinical trial completion H2 2019**
-  ADX-629 **Phase 1 clinical trial initiation H2 2019** followed by NASH and/or IBD Phase 2a
-  ADX-1612 post-transplant lymphoproliferative disorder **Phase 2 clinical trial initiation 2019**
-  ADX-1612 mesothelioma **Phase 2 clinical trial initiation 2019**



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