



# **Reproxalap Phase 2b Dry Eye Disease Results**

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September 2018

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# Dry Eye Disease: A Chronic Disease with Inadequate Therapy

## Large Disease Burden

**20**  
million

# of adults in the U.S. estimated to suffer from Dry Eye Disease (DED)



Women are twice as likely to suffer from DED than men

Age 50+

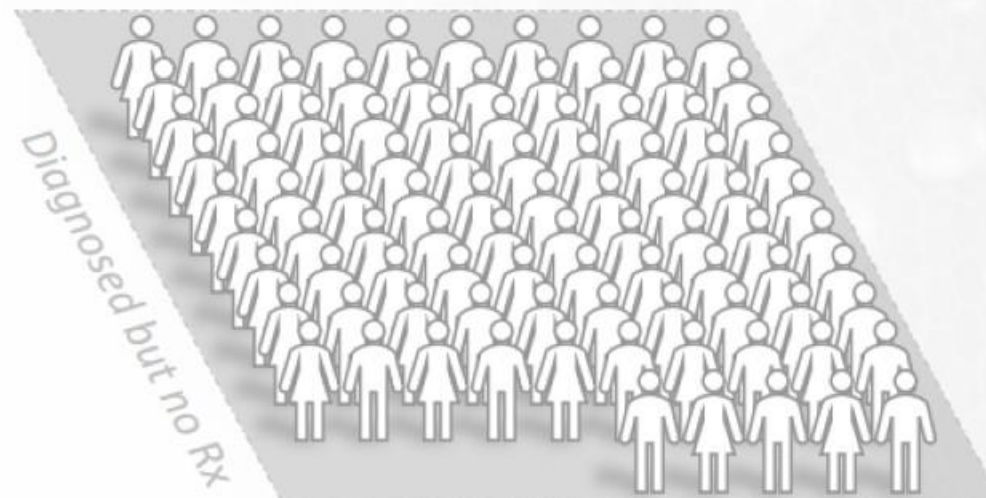
>3x

DED increases with age, with those over age 50 three times more likely to suffer from DED



DED can significantly effect vision-related **quality of life**

## Under-served Patient Population



Only  
**5%**

of diagnosed DED patients utilize current Rx treatments for dry eye disease

Sources: "Dry Eyes" by R. M. Shtein, MD; [www.uptodate.com](http://www.uptodate.com), May 2018; Farrand et al; American Journal of Ophthalmology 90:98, 2017; Aldeyra primary and secondary research and estimates; Clin Ophthalmol. 2009; 3: 405-412; Symphony Rx Data.

# Reproxalap: A Novel Drug Candidate for the Treatment of Dry Eye Disease

## Positive Phase 2b Clinical Trial Results

- **Primary objective achieved:**  
Endpoint selection and sample size powering confirmed for Phase 3 clinical trials
- Reproxalap demonstrated **statistically significant improvements** versus vehicle across multiple symptom and sign measures, consistent with novel and broad mechanism of action
- **Pathway to registration trials confirmed** with ocular dryness symptom score, ocular staining score, and 0.25% reproxalap dose
- **Improvements in symptoms and signs observed as early as two weeks**, consistent with prior reproxalap clinical trial results and supportive of differentiated product profile
- Aldeyra plans to discuss results with regulatory authorities, and expects to **initiate Phase 3 clinical trials in 2019**
- Rigorous clinical data demonstrate the efficacy and safety of reproxalap in **dry eye disease and allergic conjunctivitis**, two medical conditions with considerable overlap

# Phase 2b Dry Eye Disease Clinical Trial Design

## January – July 2018

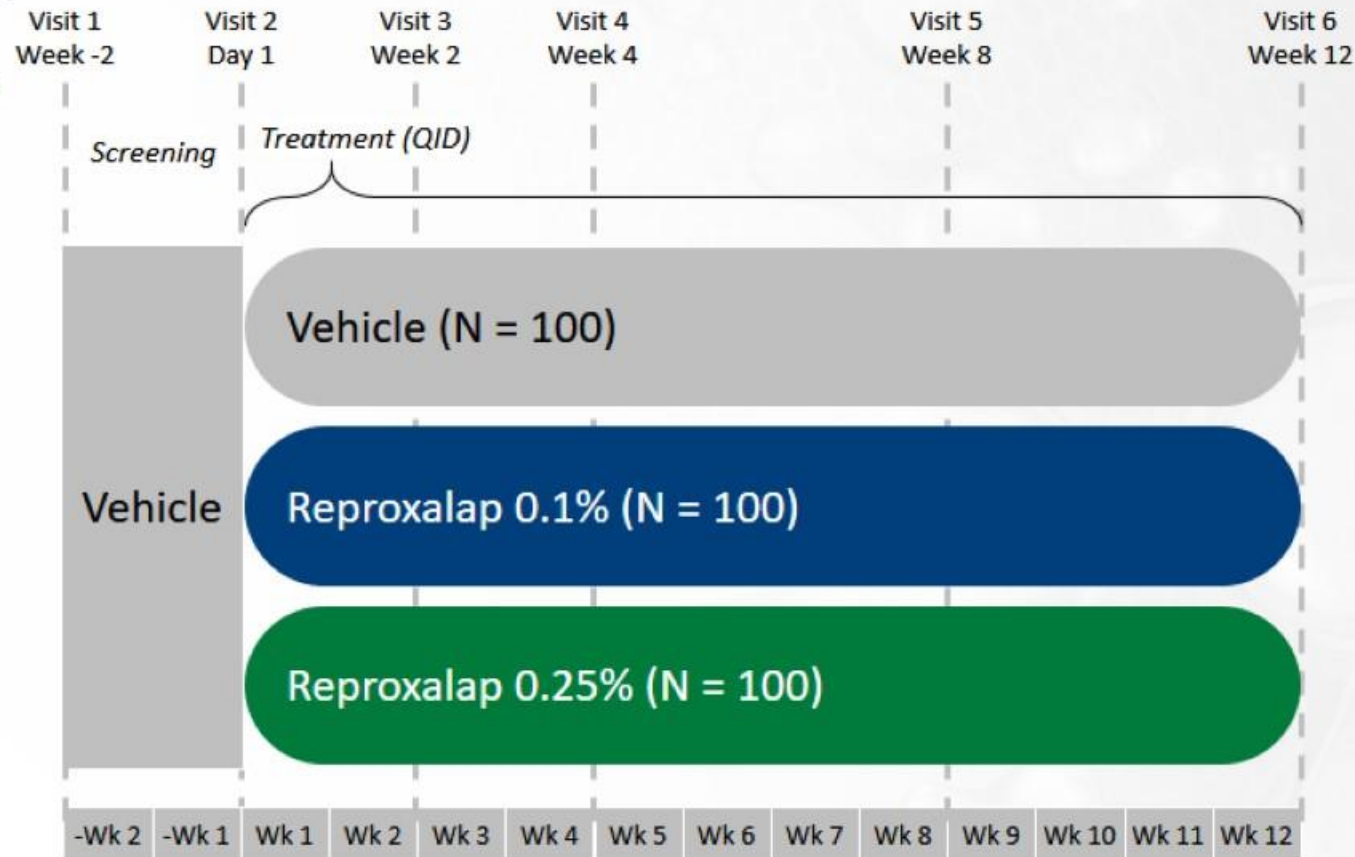
- **Primary objective:**
  - Evaluate efficacy of reproxalap ophthalmic solutions vs. baseline and vehicle to **confirm endpoint selection and sample size for Phase 3 clinical trials**
- **Inclusion/exclusion highlights:**
  - History of dry eye disease for at least 6 months
  - Moderate to severe dry eye disease
    - $\geq 2$  on OD & 4-Symptom Questionnaire (in at least one symptom score)
    - Schirmer's Test  $\leq 10$  mm and  $\geq 1$  mm
    - Tear Film Break-Up Time  $\leq 5$  sec
    - $\geq 2$  staining score in at least one corneal region, and  $\geq 4$  in sum corneal
    - $\geq 2$  staining score in sum conjunctival
  - Demonstrate Controlled Adverse Environment (CAE) response

OD = Ocular Discomfort

QID = four times daily

Source: Reproxalap DED Phase 2b clinical trial protocol

### Phase 2b Dry Eye Disease Clinical Trial

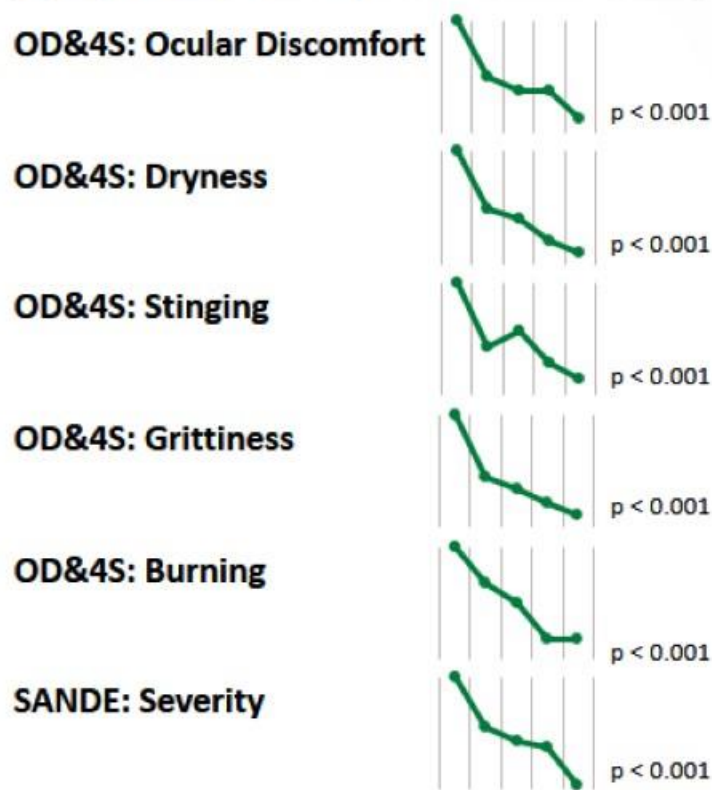


# Reproxalap's Broad Activity Across Dry Eye Symptoms and Signs Consistent with Previous Clinical Trials

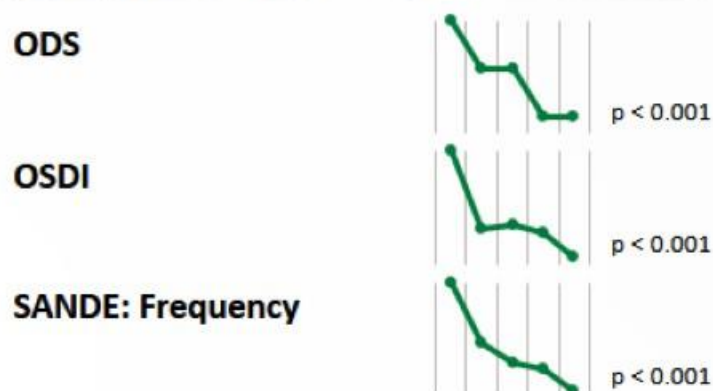
0.25% Reproxalap Change From Baseline (N=100)

Baseline | Wk 2 | Wk 4 | Wk 8 | Wk 12

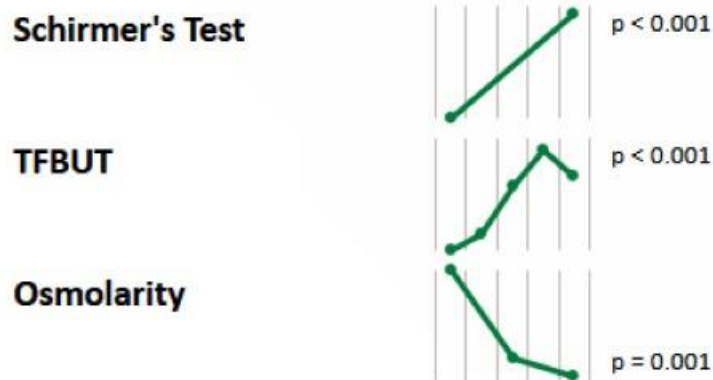
## Symptom Severity Measures



## Symptom Frequency Measures

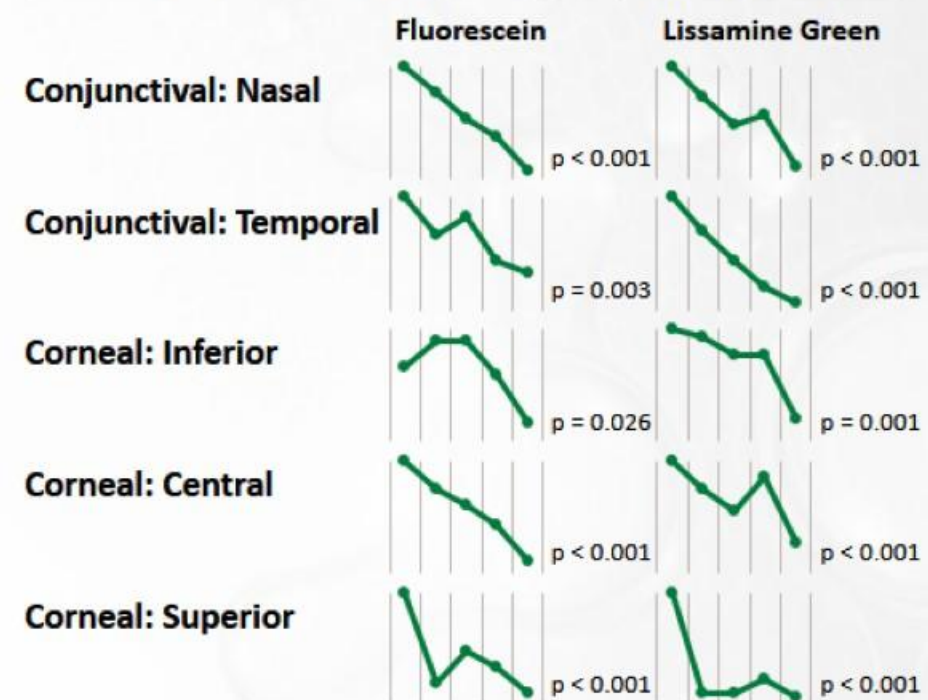


## Tear Quantity and Quality Signs



ITT Population with Observed Data Only

## Ocular Surface Damage Signs (Stains)



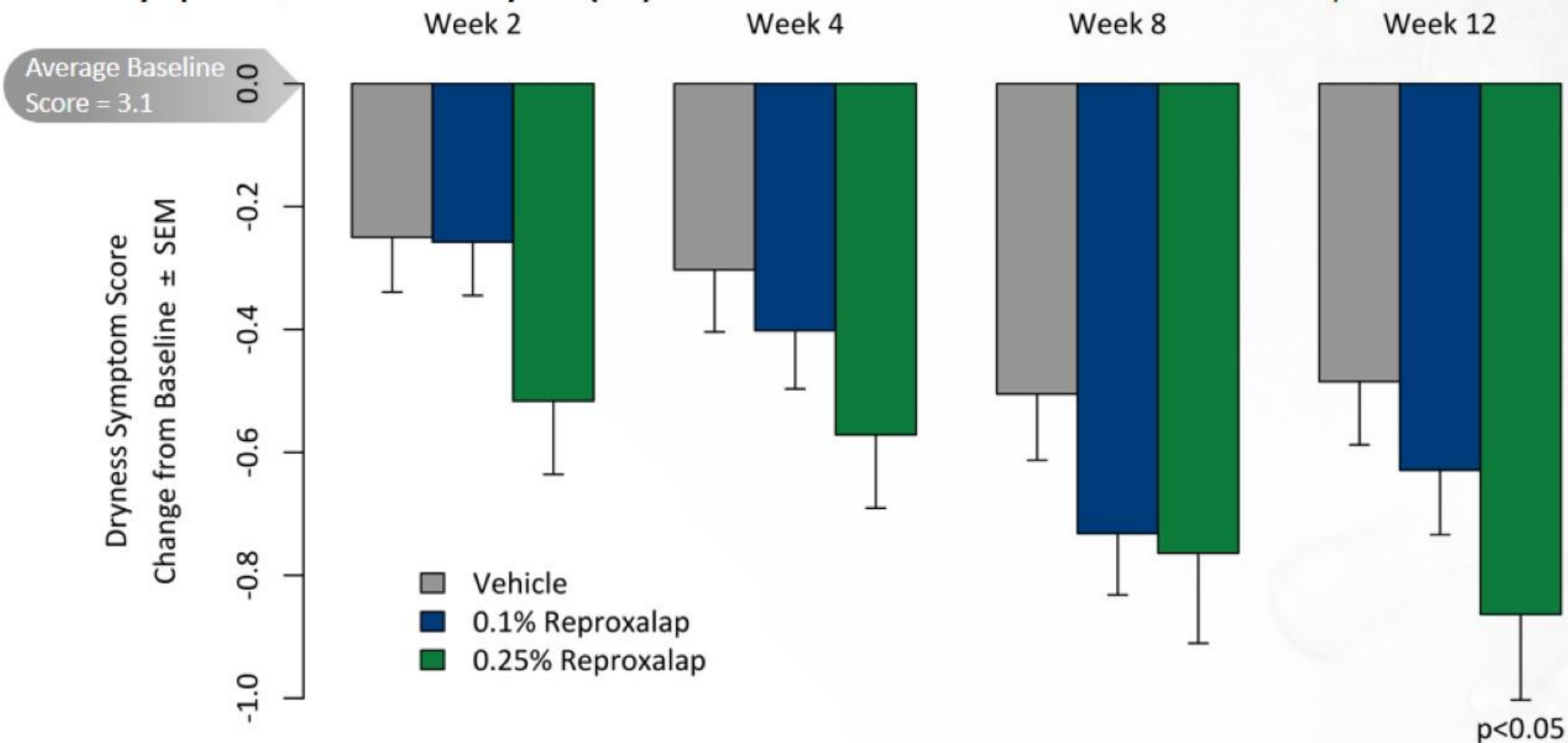
OD&4S = Ocular Discomfort & 4 Symptom  
 ODS = Ocular Discomfort Scale  
 OSDI = Ocular Surface Disease Index  
 SANDE = Symptom Assessment in Dry Eye  
 TFBUT = Tear Film Break-Up Time

p values subject to change based on quality control analysis  
 Source: Reproxalap DED Phase 2b clinical trial results

# Proposed Co-Primary Endpoint: Reproxalap Improved Ocular Dryness vs. Vehicle

OD & 4-Symptom Questionnaire: Dryness (0-5)

ITT Population with Observed Data Only



p values subject to change based on quality control analysis  
Source: Reproxalap DED Phase 2b clinical trial results

OD = Ocular Discomfort

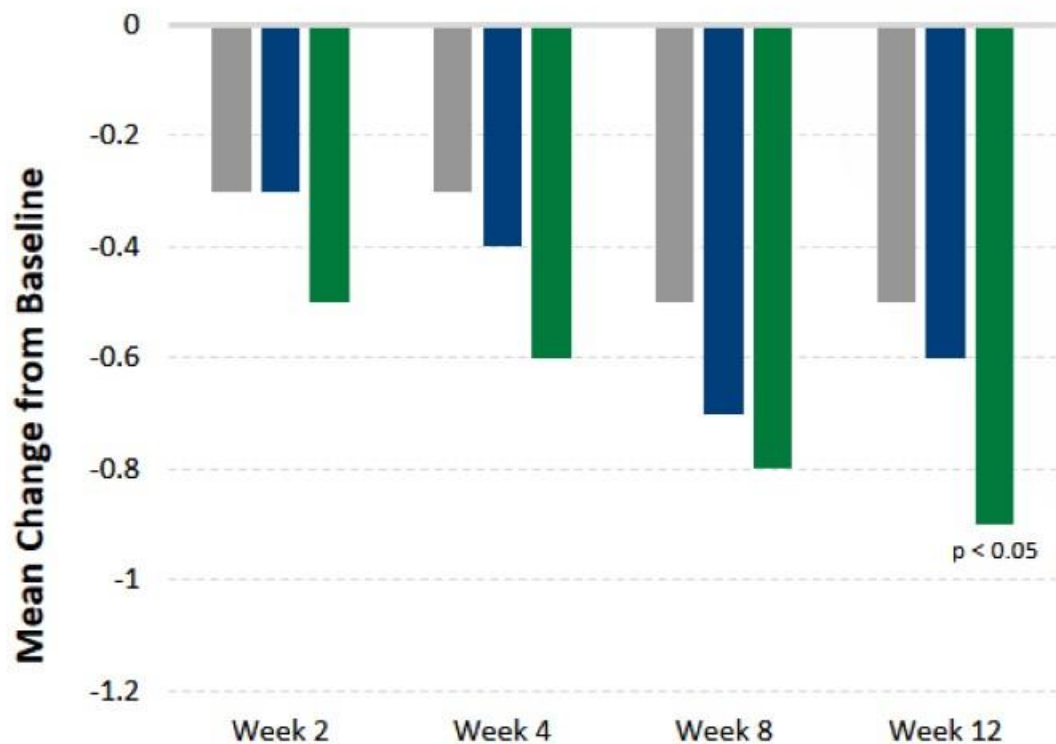
# Drug Potency Supported by Ocular Dryness Improvement vs. Vehicle in Higher Baseline Patients

OD & 4-Symptom Questionnaire: Dryness (0-5)

Total Population (N=100 | 100 | 100)

ITT Population with Observed Data Only

Total Population Average Baseline Score = 3.1

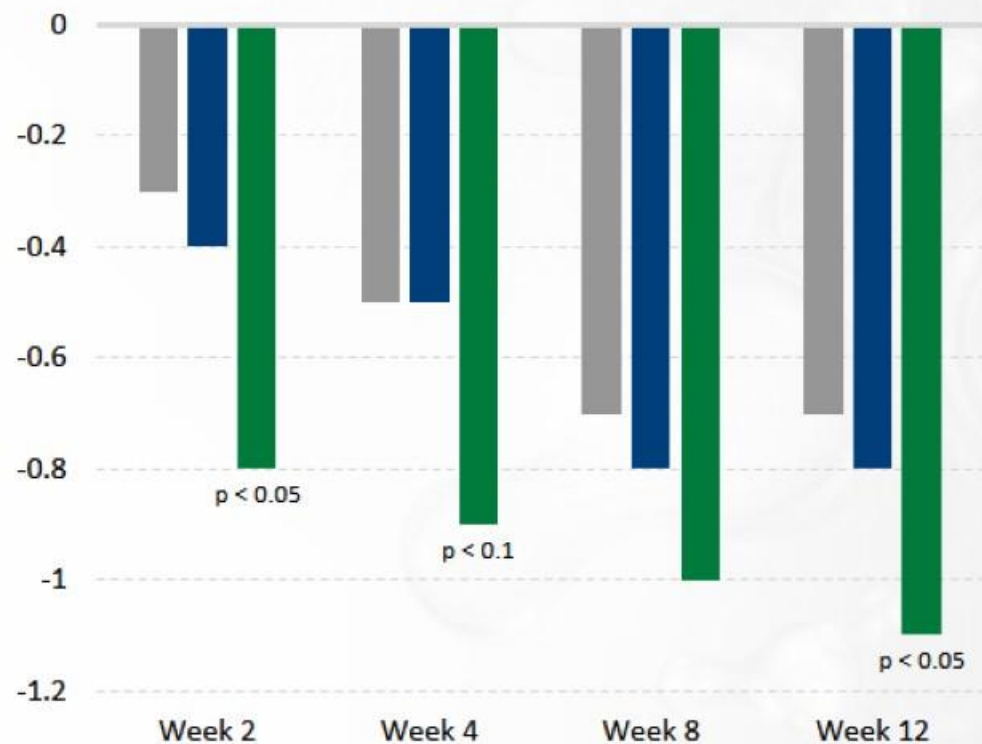


VS.

Above Median Baseline Population (N=79 | 69 | 69)

ITT Population with Observed Data Only

Above Median Population Average Baseline Score = 3.6



p values subject to change based on quality control analysis  
Source: Reproxalap DED Phase 2b clinical trial results

■ Vehicle ■ Reproxalap (0.1%) ■ Reproxalap (0.25%)

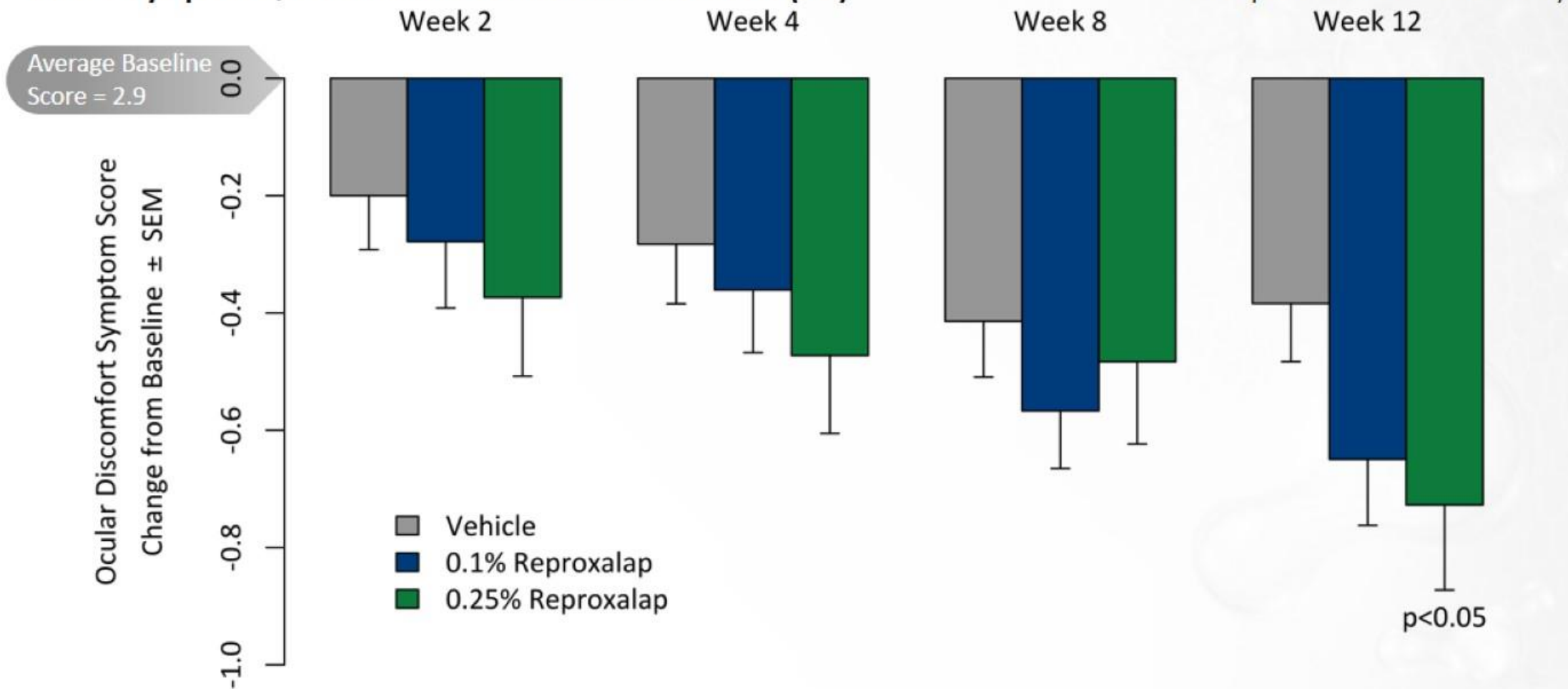
OD = Ocular Discomfort



# Ocular Discomfort Symptom Results Support Observed Improvement in Ocular Dryness Score

OD & 4-Symptom Questionnaire: Overall Ocular Discomfort (0-5)

ITT Population with Observed Data Only



p values subject to change based on quality control analysis  
Source: Reproxalap DED Phase 2b clinical trial results

OD = Ocular Discomfort

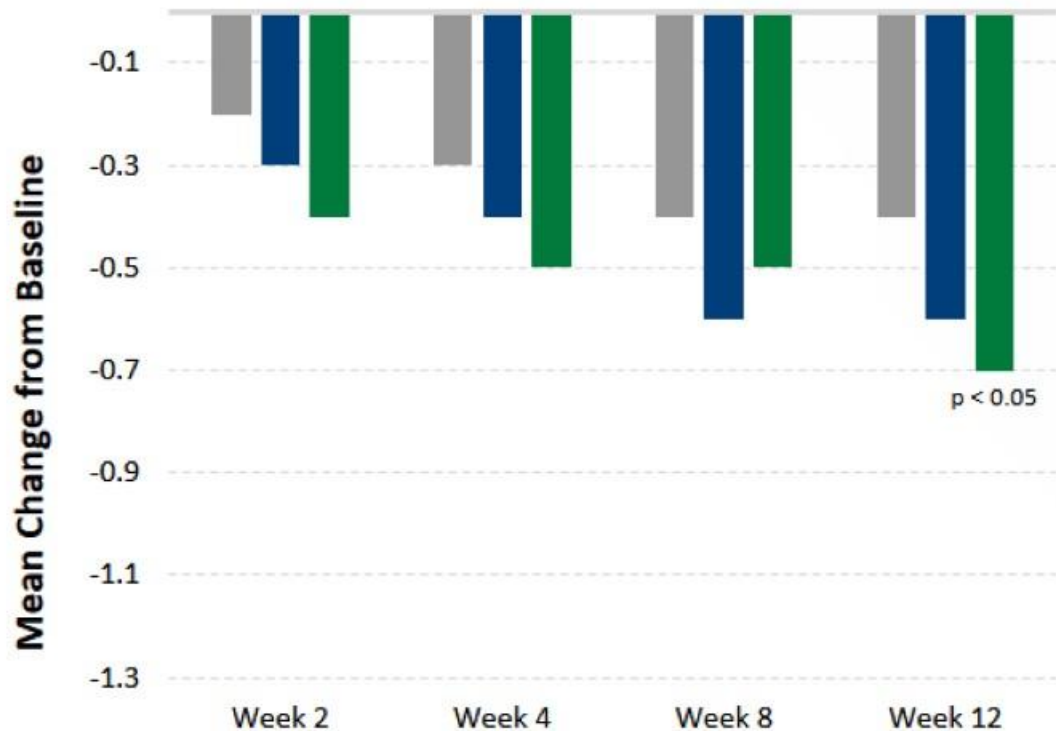
# Drug Potency Supported by Ocular Discomfort Improvement vs. Vehicle in Higher Baseline Patients

OD & 4-Symptom Questionnaire: Overall Ocular Discomfort (0-5)

Total Population (N=100 | 100 | 100)

ITT Population with Observed Data Only

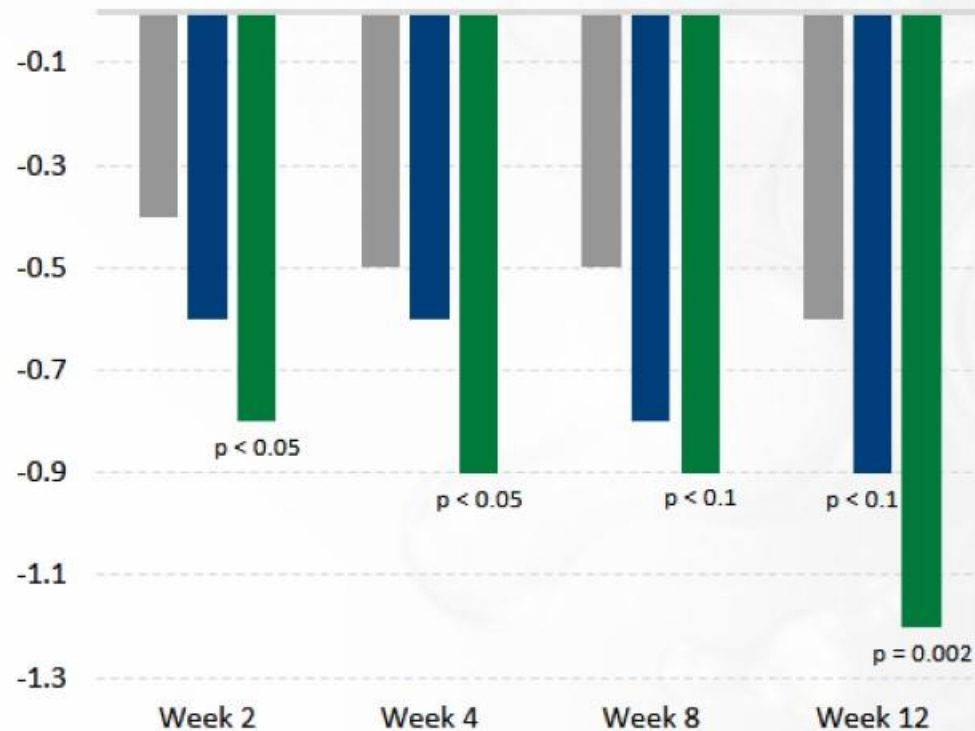
Total Population Average Baseline Score = 2.9



Above Median Baseline Population (N=69 | 65 | 64)

ITT Population with Observed Data Only

Above Median Population Average Baseline Score = 3.4



VS.

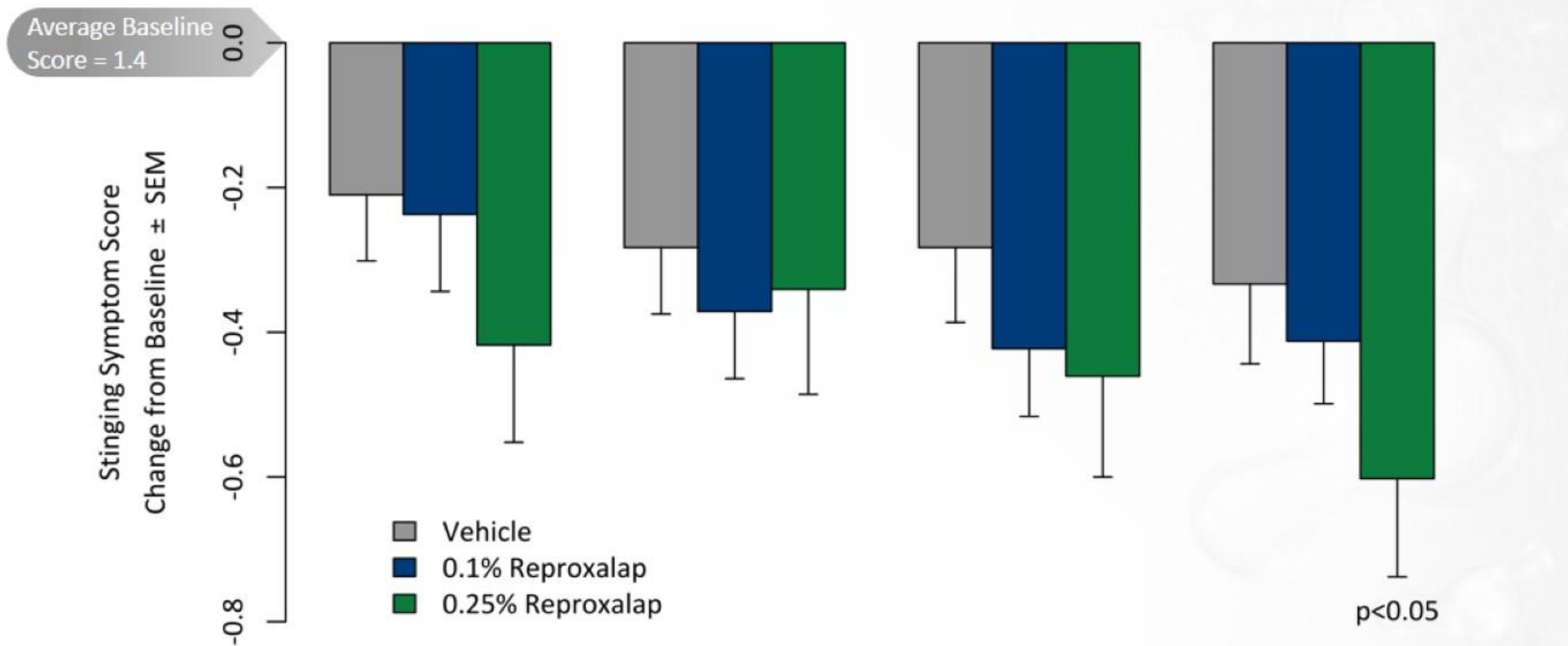
p values subject to change based on quality control analysis  
Source: Reproxalap DED Phase 2b clinical trial results

■ Vehicle ■ Reproxalap (0.1%) ■ Reproxalap (0.25%)

OD = Ocular Discomfort

# Ocular Stinging Symptom Results Support Observed Improvement in Ocular Dryness Score

OD & 4-Symptom Questionnaire: Stinging (0-5)



p values subject to change based on quality control analysis  
Source: Reproxalap DED Phase 2b clinical trial results

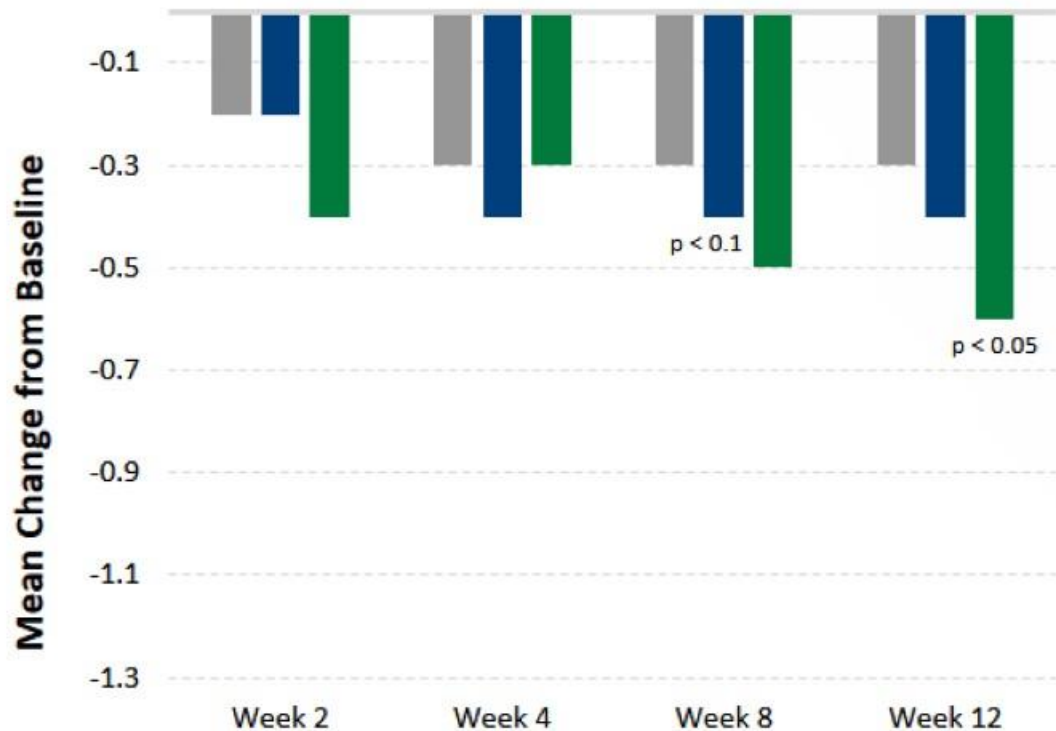
# Drug Potency Supported by Ocular Stinging Improvement vs. Vehicle in Higher Baseline Patients

OD & 4-Symptom Questionnaire: Stinging (0-5)

Total Population (N=100 | 100 | 100)

ITT Population with Observed Data Only

Total Population Average Baseline Score = 1.4

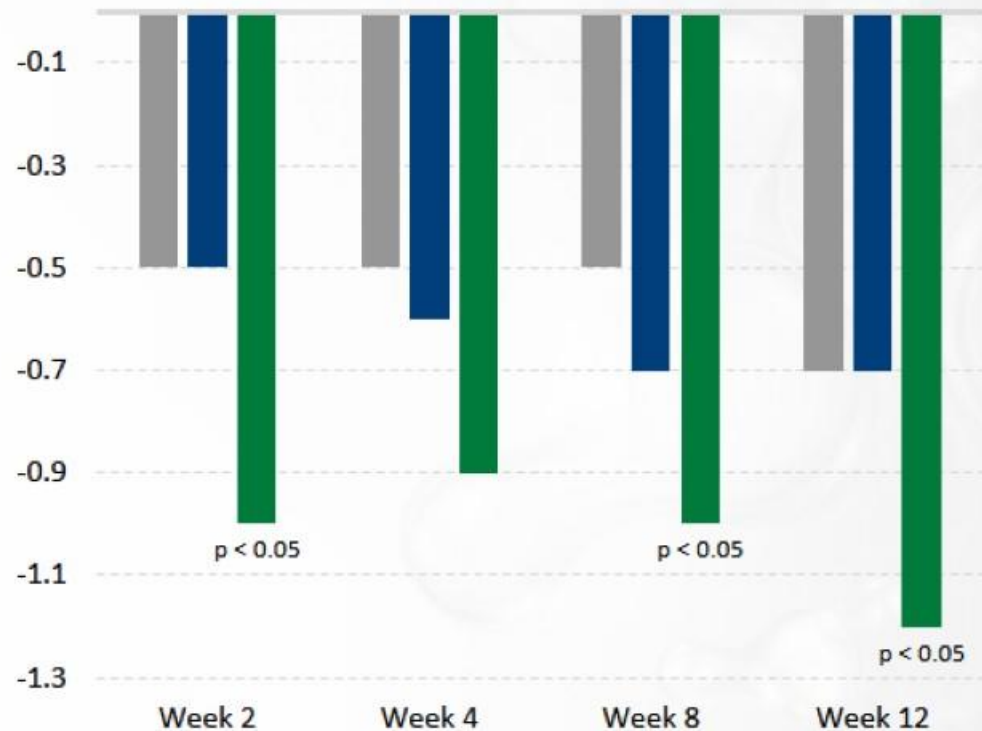


VS.

Above Median Baseline Population (N=66 | 56 | 67)

ITT Population with Observed Data Only

Above Median Population Average Baseline Score = 2.2



p values subject to change based on quality control analysis  
Source: Reproxalap DED Phase 2b clinical trial results

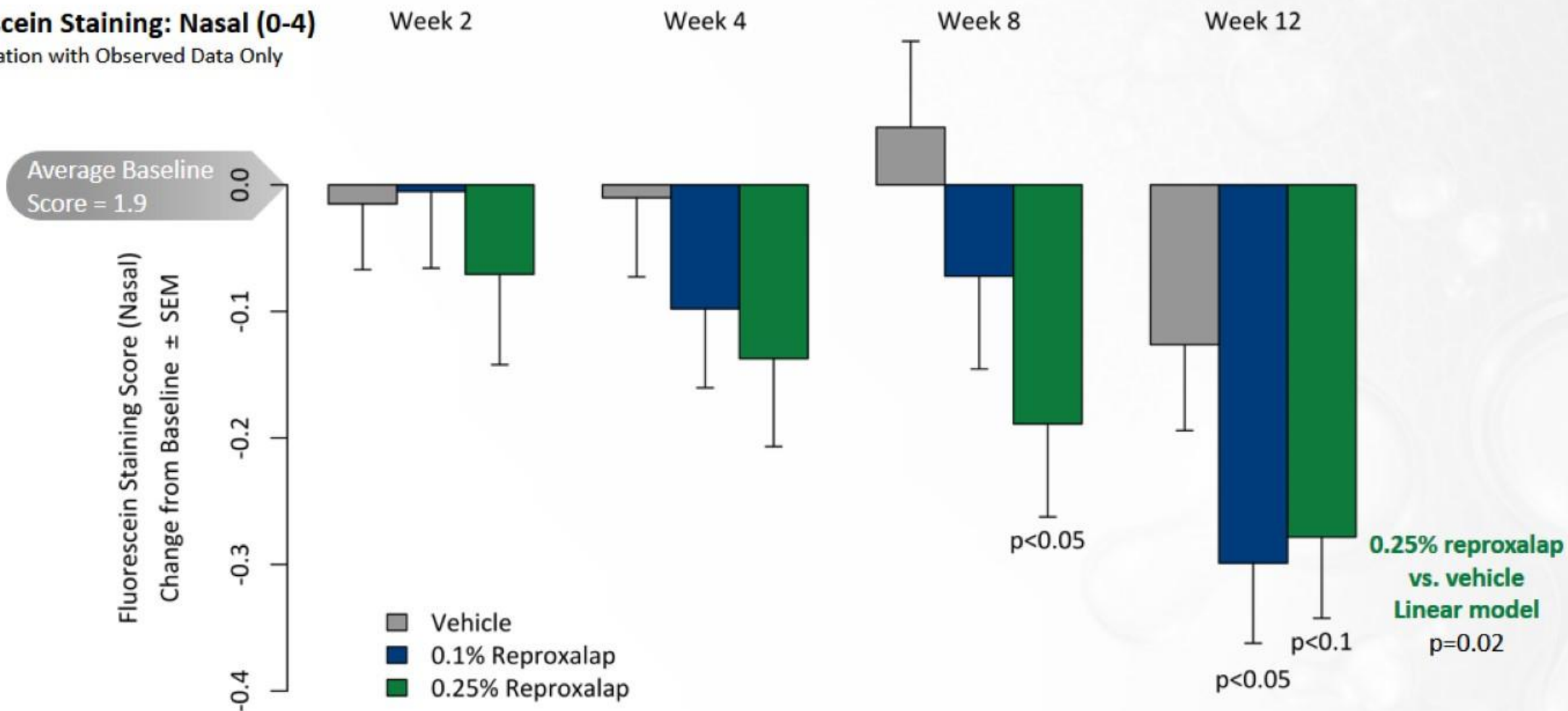
■ Vehicle ■ Reproxalap (0.1%) ■ Reproxalap (0.25%)

OD = Ocular Discomfort

# Proposed Co-Primary Endpoint: Reproxalap Improved Ocular Staining vs. Vehicle

## Fluorescein Staining: Nasal (0-4)

ITT Population with Observed Data Only



p values subject to change based on quality control analysis

Source: Reproxalap DED Phase 2b clinical trial results

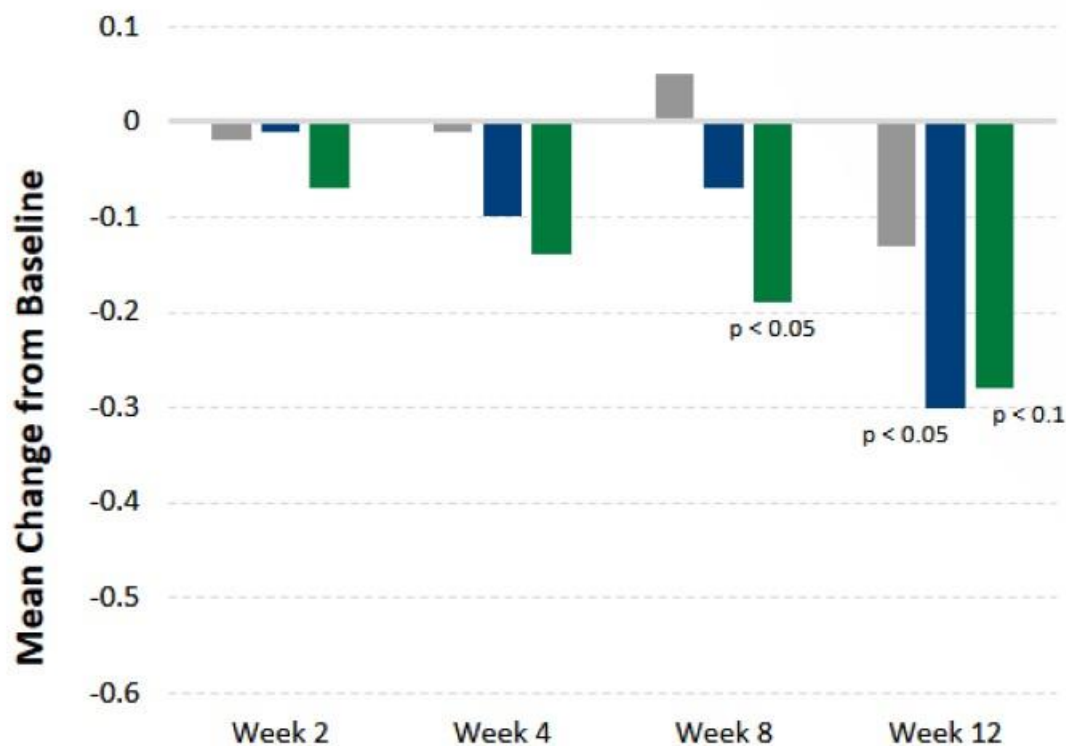
# Drug Potency Supported by Ocular Staining Improvement vs. Vehicle in Higher Baseline Patients

## Fluorescein Staining: Nasal (0-4)

Total Population (N=100 | 100 | 100)

ITT Population with Observed Data Only

Total Population Average Baseline Score = 1.9

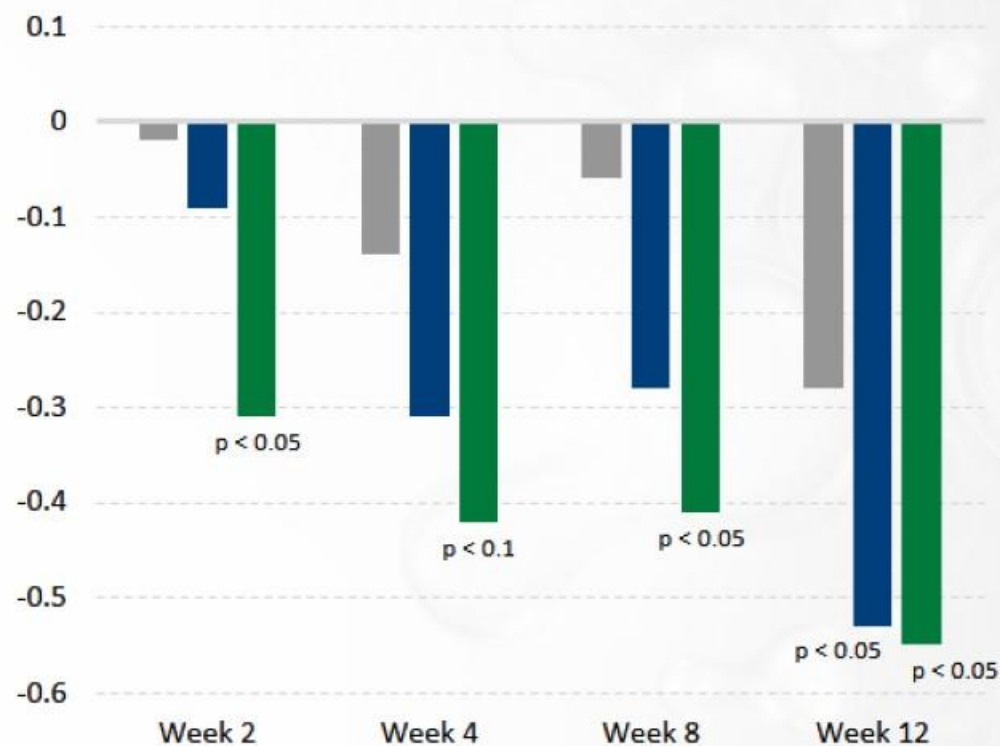


VS.

## Above Median Baseline Population (N=59 | 56 | 62)

ITT Population with Observed Data Only

Above Median Population Average Baseline Score = 2.3



p values subject to change based on quality control analysis  
Source: Reproxalap DED Phase 2b clinical trial results

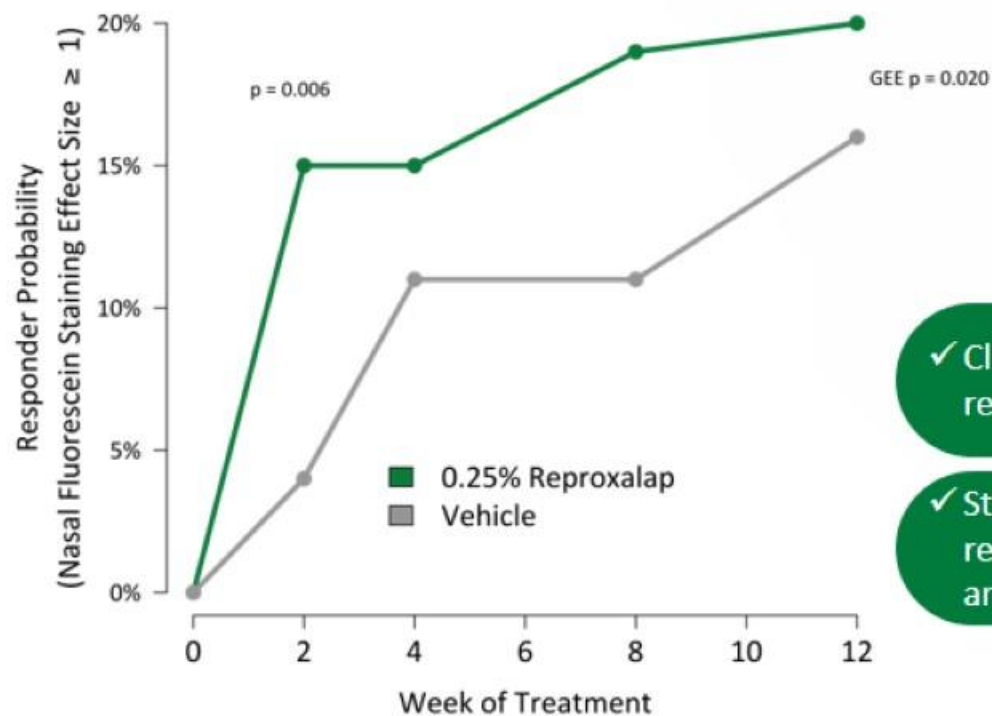
■ Vehicle ■ Reproxalap (0.1%) ■ Reproxalap (0.25%)

# Ocular Staining Responder Analyses Demonstrate Statistical Superiority of Reproxalap Over Vehicle

## Fluorescein Staining (Nasal)

ITT Population with Observed Data Only

Probability of Response for Staining



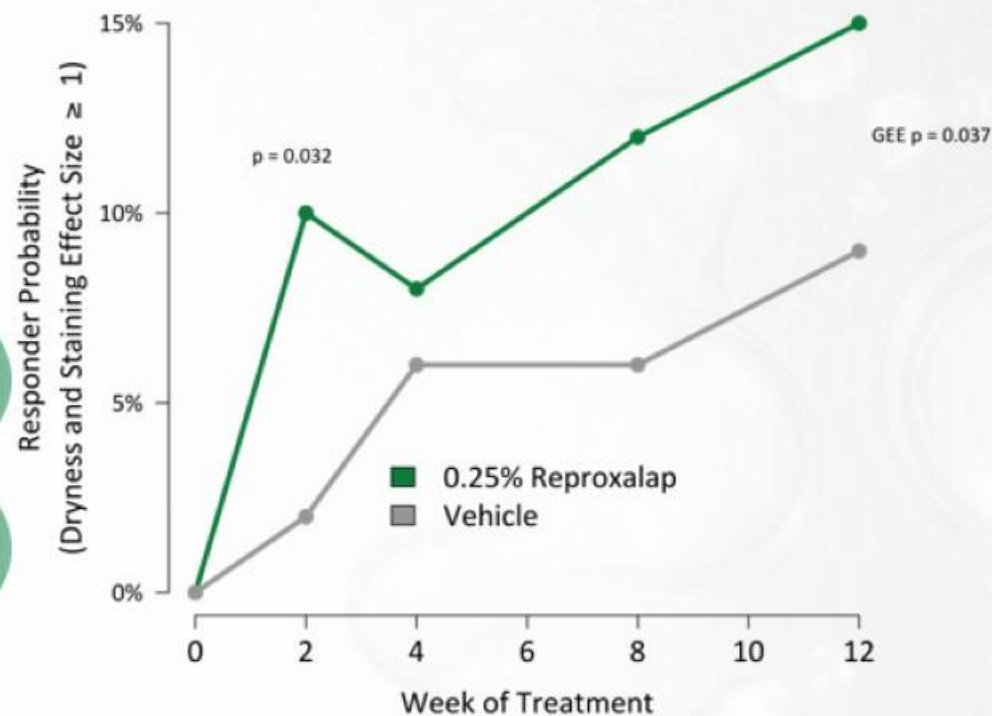
✓ Clinically significant response in 2 weeks

✓ Statistically significant response in symptom and sign vs. vehicle

## OD&4S: Ocular Dryness and Fluorescein Staining (Nasal)

ITT Population with Observed Data Only

Probability of Response for both Ocular Dryness and Staining



p values subject to change based on quality control analysis  
Source: Reproxalap DED Phase 2b clinical trial results

OD&4S = Ocular Discomfort & 4 Symptom  
Effect Size = Change from Baseline / Standard Deviation at Baseline

GEE = Generalized Estimating Equations

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

## Improvement Effect Size at Week 12

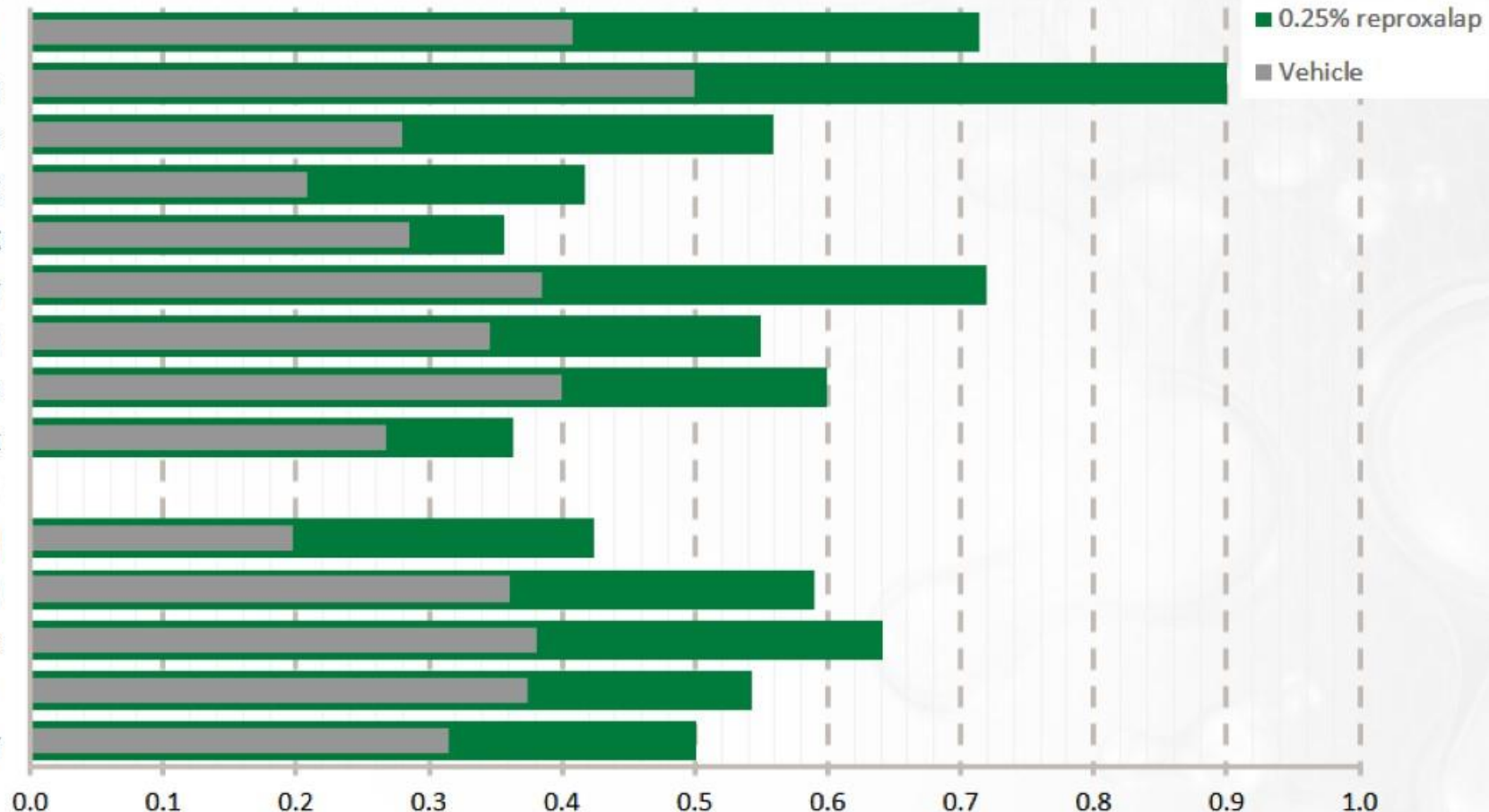
ITT Population with Observed Data Only

### 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



SANDE = Symptom Assessment in Dry Eye

Average improvement effect size across both eyes for tear quality and tear quantity measures

(Schirmer's Test, Tear Film Break-Up Time, and Osmolarity)

Improvement Effect size = Change from Baseline / Standard Deviation at Baseline

Source: Reproxalap DED Phase 2b clinical trial results



## Reproxalap: No Observed Safety Concerns and Generally Well Tolerated

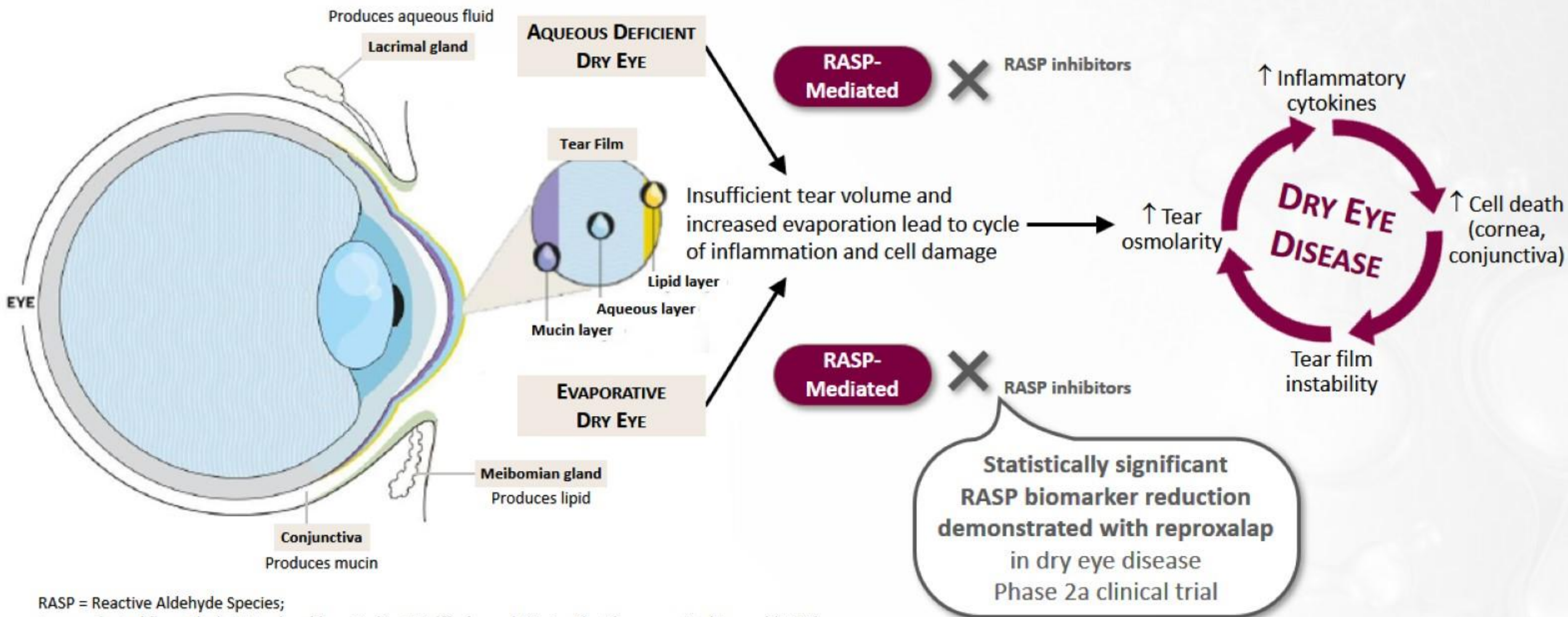
- Consistent with prior topical reproxalap clinical experience in over 500 patients, no observed safety concerns, and predominantly mild instillation site irritation reported

	0.1% reproxalap	0.25% reproxalap	Vehicle
Discontinuations	3/100 (3%)	12/100 (12%)	1/100 (1%)

- Rates consistent with recent Phase 2 dry eye disease clinical trials

Source: Reproxalap DED Phase 2b clinical trial results

# Reproxalap's Novel Mechanism of Action has the Potential to Address the Two Major Forms of Dry Eye Disease



RASP = Reactive Aldehyde Species;  
 Image adapted from Alisdair Macdonald as cited in J Wolffsohn and J Craig, The Pharmaceutical Journal (2017);  
 RASP activity as shown based on published literature and Aldeyra data on file.

# Reproxalap: A Novel Drug Candidate for the Treatment of Dry Eye Disease

## Positive Phase 2b Clinical Trial Results

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## Reproxalap Planned Phase 3 Dry Eye Disease Program

- Two Phase 3 clinical trials expected to be initiated in 2019, following discussion with regulatory authorities
- First Phase 3 clinical trial is an adaptive two-stage design; expected initiation in 2019
  - Stage 1: Protocol optimization and sample size confirmation (12 weeks)
  - Stage 2: Randomized, double masked, two-arm, parallel-group design, reproxalap vs vehicle (12 weeks)
- Primary endpoints: Ocular dryness score and ocular staining
- Secondary endpoints include ocular itch, based on positive reproxalap allergic conjunctivitis program results and high comorbidity of allergic conjunctivitis in dry eye disease patients
- Estimated sample size of 400-500 per arm with approximately 90% statistical power
- Second Phase 3 clinical trial expected to initiate in 2019

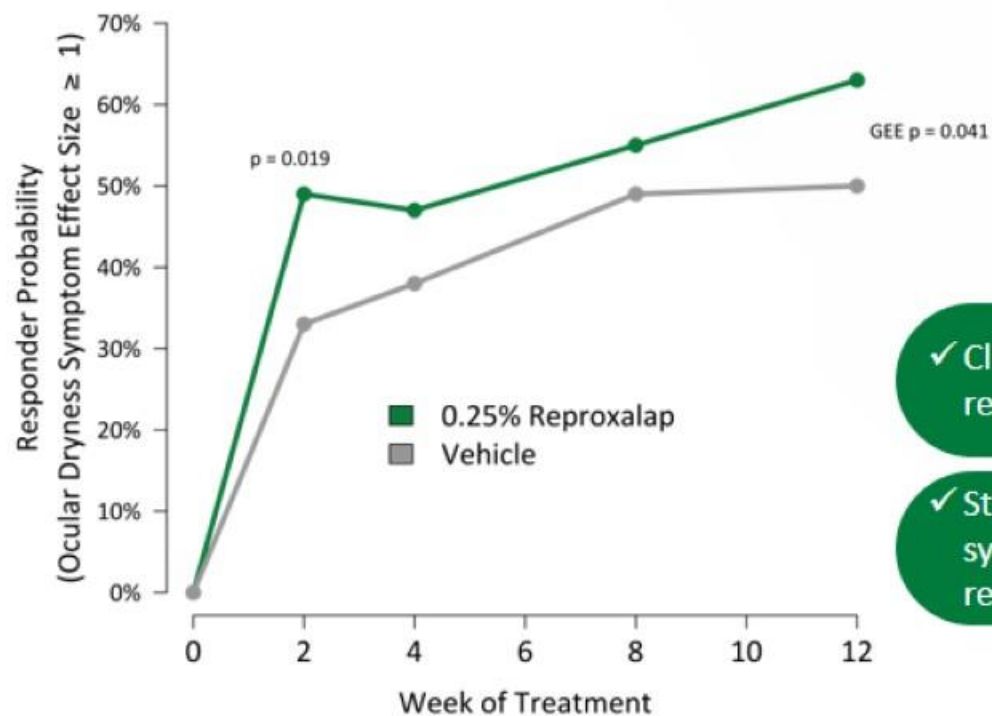
Contingent on funding, regulatory review, and other factors.

# Reproxalap's Differentiated Product Profile Evidenced by Responder Analyses – Rapid and Symptom-Free (Ocular Dryness)

## OD & 4-Symptom Questionnaire: Dryness

ITT Population with Observed Data Only

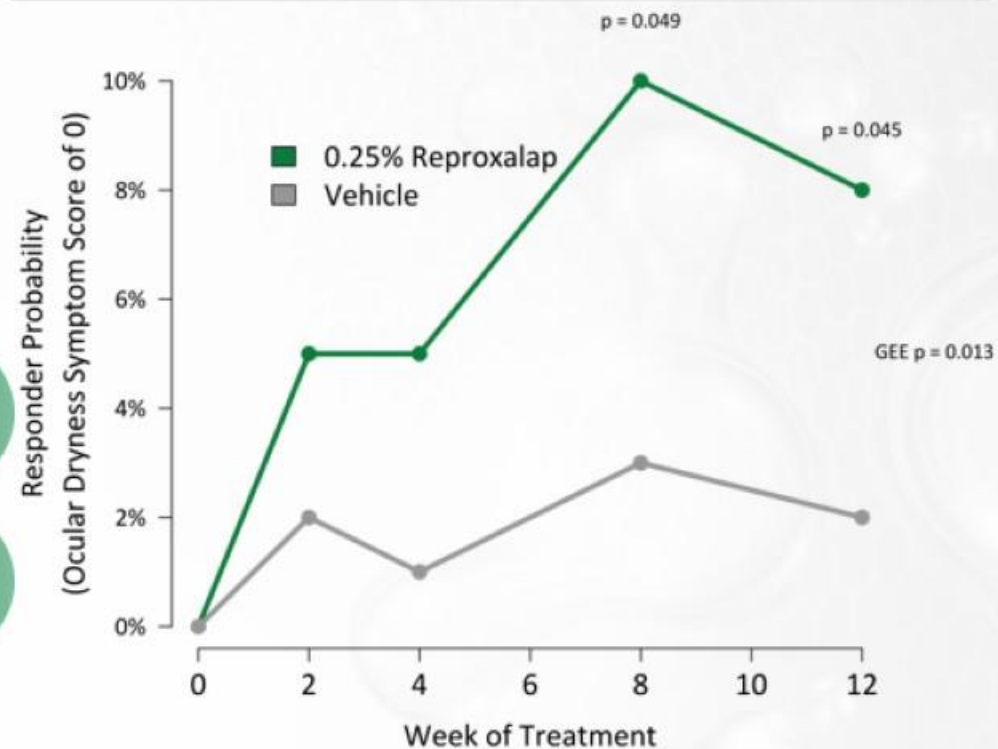
Probability of Response (Improvement Effect Size  $\geq 1$ )



✓ Clinically significant response in 2 weeks

✓ Statistically significant symptom-free response vs. vehicle

Probability of Symptom-Free (Ocular Dryness Score = 0)



p values subject to change based on quality control analysis  
Source: Reproxalap DED Phase 2b clinical trial results

OD = Ocular Discomfort  
Effect Size = Change from Baseline / Standard Deviation at Baseline

GEE = Generalized Estimating Equations

# Reproxalap: A Unique and Novel Product Candidate for Dry Eye Disease

## Patients & Physicians Not Satisfied



Current prescription options **may take up to six weeks or longer** to have an effect

Up to  
**75%**

of patients with DED **are not satisfied with current prescription options**

Up to  
**50%**

of patients **treated for DED** with current therapies **fail and discontinue** according to prescribing physicians

## A Unique Opportunity

### Reproxalap



**Early and consistent symptom improvements** in Phase 2b clinical trial



**Broad symptom and sign improvements** in Phase 2b clinical trial



**Novel mechanism of action** and differentiated approach to treat DED

Sources: Aldeyra primary patient market research, primary physician market research, secondary market research, and estimates; Clin Ophthalmol. 2009; 3: 405–412.

# Reproxalap: Late-Stage Development for Dry Eye Disease and Allergic Conjunctivitis – Two Medical Conditions with Significant Overlap

## Dry Eye Disease

- ✓ Initiated reproxalap **Phase 2b clinical trial in dry eye disease January 2018**
- ✓ **Positive** reproxalap dry eye disease **Phase 2b clinical trial results September 2018**

## Anticipated Milestones\*

- New** Reproxalap dry eye disease **Phase 3 clinical trial program initiation 2019**  
↳ *Ocular itch endpoint to be included (as secondary)*

## Allergic Conjunctivitis


- ✓ Initiated reproxalap **ALLEVIATE Phase 3 clinical trial in allergic conjunctivitis April 2018**

## Anticipated Milestones\*

- Reproxalap allergic conjunctivitis ALLEVIATE Phase 3 trial **results late 2018/early 2019**

\*Contingent on funding, regulatory review, and other factors.

# Deep and Innovative Pipeline

Mechanism	Compound	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Next Expected Milestone
RASP Inhibitors	Reproxalap Ocular	Dry Eye Disease	✓ ✓				Phase 3 initiation 2019
		Allergic Conjunctivitis	✓ ✓				Phase 3 results late 2018 / 2019
		Noninfectious Anterior Uveitis	✓				Phase 3 results 2019
	Reproxalap Dermal	Sjögren-Larsson Syndrome	✓				Phase 3, Part 1 results 2019
	ADX-629 Systemic	Autoimmune Disease					
	ADX-103	Retinal Disease					
	Not Disclosed	Systemic Inflammatory Disease		Research Collaboration 			
Hsp90 Inhibitors	ADX-1612	PTLD					
		Ovarian Cancer				Investigator-Sponsored Trial	
		Mesothelioma	✓				Phase 2 initiation 2019
	ADX-1615	Autoimmune Disease					
		Cancer					
Anti-Inflammatory	Not Disclosed	Ocular Inflammation	Research Collaboration (undisclosed)				

RASP = Reactive Aldehyde Species  
 PTLD = Post-Transplant Lymphoproliferative Disorder

✓ = Positive Phase 2 clinical trial data reported in 2016 – 2018





ALDEYRA

THERAPEUTICS™

Two

Mechanisms of  
action in  
development

Seven

Successful Phase 2  
Clinical Trials  
2016-2018

Four

Phase 3 Clinical  
Trials Ongoing or  
Expected to  
Initiate