Reproxalap
Phase 2b Dry Eye Disease Results

September 2018
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Dry Eye Disease: A Chronic Disease with Inadequate Therapy

Large Disease Burden

- 20 million adults in the U.S. estimated to suffer from Dry Eye Disease (DED)
- Women are twice as likely to suffer from DED than men
- DED increases with age, with those over age 50 three times more likely to suffer from DED
- DED can significantly affect vision-related quality of life

Under-served Patient Population

- Only 5% of diagnosed DED patients utilize current Rx treatments for dry eye disease

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
    • ≥ 2 on OD & 4-Symptom Questionnaire (in at least one symptom score)
    • Schirmer’s Test < 10 mm and ≥ 1 mm
    • Tear Film Break-Up Time ≤ 5 sec
    • ≥ 2 staining score in at least one corneal region, and ≥ 4 in sum corneal
    • ≥ 2 staining score in sum conjunctival
    • Demonstrate Controlled Adverse Environment (CAE) response

Visit 1
Week -2
Visit 2
Day 1
Visit 3
Week 2
Visit 4
Week 4
Visit 5
Week 8
Visit 6
Week 12

Screening
Treatment (QID)

Vehicle (N = 100)

Vehicle
Reproxalap 0.1% (N = 100)

Reproxalap 0.25% (N = 100)

-Wk 2 -Wk 1 Wk 1 Wk 2 Wk 3 Wk 4 Wk 5 Wk 6 Wk 7 Wk 8 Wk 9 Wk 10 Wk 11 Wk 12

OD = Ocular Discomfort
QID = four times daily
Source: Reproxalap DED Phase 2b clinical trial protocol
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**
- OD&4S: Ocular Discomfort
  - p < 0.001
- OD&4S: Dryness
  - p < 0.001
- OD&4S: Stinging
  - p < 0.001
- OD&4S: Grittiness
  - p < 0.001
- OD&4S: Burning
  - p < 0.001
- SANDE: Severity
  - p < 0.001

**Symptom Frequency Measures**
- ODS
  - p < 0.001
- OSDI
  - p < 0.001
- SANDE: Frequency
  - p < 0.001

**Tear Quantity and Quality Signs**
- Schirmer’s Test
  - p < 0.001
- TFBUT
  - p < 0.001
- Osmolarity
  - p = 0.001

**Ocular Surface Damage Signs (Stains)**
- Fluorescein
  - Conjunctival: Nasal
    - p < 0.001
  - Conjunctival: Temporal
    - p < 0.001
  - Corneal: Inferior
    - p = 0.003
  - Corneal: Central
    - p = 0.001
  - Corneal: Superior
    - p < 0.001
- Lissamine Green
  - Conjunctival: Nasal
    - p < 0.001
  - Conjunctival: Temporal
    - p < 0.001
  - Corneal: Inferior
    - p = 0.001
  - Corneal: Central
    - p < 0.001
  - Corneal: Superior
    - p < 0.001

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

ITT Population with Observed Data Only

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

ALDEYRA THERAPEUTICS™
Proposed Co-Primary Endpoint: Reproxalap Improved Ocular Dryness vs. Vehicle

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

Week 2
Week 4
Week 8
Week 12

ITT Population with Observed Data Only

Average Baseline Score = 3.1

Dryness Symptom Score
Change from Baseline ± SEM

Vehicle
0.1% Reproxalap
0.25% Reproxalap

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

Above Median Baseline Population (N=79 | 69 | 69)
ITT Population with Observed Data Only

Total Population Average Baseline Score = 3.1
Above Median Population Average Baseline Score = 3.6

Mean Change from Baseline

Week 2  Week 4  Week 8  Week 12
p < 0.05

Vehicle  Reproxalap (0.1%)  Reproxalap (0.25%)

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

OD = Ocular Discomfort
Ocular Discomfort Symptom Results Support Observed Improvement in Ocular Dryness Score

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

Week 2

Week 4

Week 8

Week 12

Average Baseline Score = 2.9

OD = Ocular Discomfort

p values subject to change based on quality control analysis

Source: Reproxalap DED Phase 2b clinical trial results

Vehicle

0.1% Reproxalap

0.25% Reproxalap

p < 0.05
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

Mean Change from Baseline

Week 2 | Week 4 | Week 8 | Week 12
Vehicle | Reproxalap (0.1%) | Reproxalap (0.25%)

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

OD = Ocular Discomfort
Ocular Stinging Symptom Results Support Observed Improvement in Ocular Dryness Score

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

- **Week 2**
- **Week 4**
- **Week 8**
- **Week 12**

*ITT Population with Observed Data Only*

Average Baseline Score = 1.4

**Change from Baseline ± SEM**

- **Vehicle**
- **0.1% Reproxalap**
- **0.25% Reproxalap**

*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 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

Above Median Baseline Population (N=66 | 56 | 67)
ITT Population with Observed Data Only

Above Median Population Average Baseline Score = 2.2

Mean Change from Baseline

Week 2  Week 4  Week 8  Week 12

-1.1  -0.9  -0.7  -0.5

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

VS.

Week 2  Week 4  Week 8  Week 12

-1.3  -1.1  -0.9  -0.7

p < 0.05

OD = Ocular Discomfort
Proposed Co-Primary Endpoint:
Reproxalap Improved Ocular Staining vs. Vehicle

Fluorescein Staining: Nasal (0-4)
ITT Population with Observed Data Only

Average Baseline Score = 1.9

<table>
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<tr>
<th>Week</th>
<th>Vehicle</th>
<th>0.1% Reproxalap</th>
<th>0.25% Reproxalap</th>
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<td>Week 2</td>
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<td>Week 12</td>
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</table>

Change from Baseline ± SEM

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

Above Median Baseline Population (N=59 | 56 | 62)
ITT Population with Observed Data Only

Above Median Population Average Baseline Score = 2.3

Mean Change from Baseline

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<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
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<tr>
<td>Vehicle</td>
<td>Reproxalap (0.1%)</td>
<td>Reproxalap (0.25%)</td>
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p values subject to change based on quality control analysis
Source: Reproxalap DED Phase 2b clinical trial results
Ocular Staining Responder Analyses Demonstrate Statistical Superiority of Reproxalap Over Vehicle

**Fluorescein Staining (Nasal)**
ITT Population with Observed Data Only

**OD&4S: Ocular Dryness and Fluorescein Staining (Nasal)**
ITT Population with Observed Data Only

Probability of Response for Staining

```
Responser Probability
(Nasal Fluorescein Staining Effect Size 1)
```

- **0.25% Reproxalap**
- **Vehicle**

```
Week of Treatment
```

\[ p = 0.006 \]

\[ GEE \ p = 0.020 \]

- **Clinically significant response in 2 weeks**
- **Statistically significant response in symptom and sign vs. vehicle**

Probability of Response for both Ocular Dryness and Staining

```
Responser Probability
(Dryness and Staining Effect Size 1)
```

- **0.25% Reproxalap**
- **Vehicle**

```
Week of Treatment
```

\[ p = 0.032 \]

\[ GEE \ p = 0.037 \]

*p values subject to change based on quality control analysis*  
**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

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

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

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<th>0.1% reproxalap</th>
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<td>3/100 (3%)</td>
<td>12/100 (12%)</td>
<td>1/100 (1%)</td>
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- 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

**AQUEOUS DEFICIENT DRY EYE**
- Produces aqueous fluid
- Lacrimal gland
- Insufficient tear volume and increased evaporation lead to cycle of inflammation and cell damage

**EVAPORATIVE DRY EYE**
- Contributes to tear film instability
- Meibomian gland
- Produces lipid

**DRY EYE DISEASE**
- ↑ Inflammatory cytokines
- ↑ Tear osmolarity
- ↑ Cell death (cornea, conjunctiva)

**Statistically significant RASP biomarker reduction demonstrated with reproxalap in dry eye disease**

**Phase 2a clinical trial**

*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

• **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
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 ≥1)**

- **0.25% Reproxalap**
- **Vehicle**

- **Week of Treatment**:
  - 0 2 4 6 8 10 12

- **Responder Probability (Ocular Dryness Symptom Effect Size ≥1)**
  - **GEE p = 0.041**
  - **p = 0.019**

- **Clinically significant response in 2 weeks**
- **Statistically significant symptom-free response vs. vehicle**

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

- **0.25% Reproxalap**
- **Vehicle**

- **Week of Treatment**:
  - 0 2 4 6 8 10 12

- **Responder Probability (Ocular Dryness Symptom Score of 0)**
  - **GEE p = 0.013**
  - **p = 0.049**
  - **p = 0.045**

**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.

**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.

**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.

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

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

**Anticipated Milestones**
- Reproxalap dry eye disease Phase 3 clinical trial program initiation 2019
- Reproxalap allergic conjunctivitis ALLEVIATE Phase 3 trial results late 2018/early 2019

*Ocular itch endpoint to be included (as secondary)*

*Contingent on funding, regulatory review, and other factors.*
## Deep and Innovative Pipeline

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

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

Research Collaboration janssen

Research Collaboration (undisclosed)
Two
Mechanisms of action in development

Seven
Successful Phase 2 Clinical Trials 2016-2018

Four
Phase 3 Clinical Trials Ongoing or Expected to Initiate

Phase 2 count includes mesothelioma investigator-sponsored trial; Phase 3 trials contingent on funding, regulatory review, and other factors.