A Multi-Center, Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled Phase 2b Dry Eye Disease Clinical Trial to Evaluate the Safety and Efficacy of Topical Ocular Reproxalap, a Novel RASP Inhibitor.

John D Sheppard, MD, MMSc, FACS
Professor of Ophthalmology, Microbiology & Molecular Biology
Eastern Virginia Medical School
President, Virginia Eye Consultants
Partner, Cincinnati Vision Partners

ARVO: May 1st, 2019
Disclosures

- Alcon: Research Grants, Speaker, Advisor
- Aldeyra Pharmaceuticals: Advisory Board, Clinical Research
- Allergan: Research Grants, Speaker, Advisory Board, Media Spokesman
- Bausch & Lomb, Ista, Valeant: Research Grants, Speaker, Advisory Boards
- Abbvie: Research, Advisor, Spokesman
- BioTissue: Advisory Board, Clinical Research
- Clearside Ophthalmics: Advisor, Research
- Doctors Allergy Formula: Advisor, Investor
- EyeGate Research: Advisory Board, Research, Shareholder, Speaker
- EyeRx Research: Clinical Research, Stock Ownership
- Imprimis Pharma: Advisory Board
- Isis Pharmaceuticals: Research, Advisory Board
- Inspire/Merck Pharmaceuticals: Research, Speaker, Advisory Board
- Insite: Research Grants
- Kala Pharmaceuticals: Research, Advisory Board
- Kowa Pharmaceuticals: Advisor
- Lacrisiences: Shareholder, Advisor
- LayerBio: Advisor, Investor
- Lumenis: Speaker
- Lux Biosciences: Advisory, Research Grants
- MG Therapeutics: Advisory Board
- Provision Network: Owner
- NovaBay: Advisory Board, Researcher
- Novartis/Ciba Vision: Speaker, Advisor
- NiCox: Advisory Board
- Omeros: Advisory Board
- OcuCure: Advisory Board, Shareholder
- OcuHub: Advisor, Investor
- Oculeve: Advisor, Clinical Research
- Pfizer: Research, Speaker
- RPS: Advisory, Research, Investor
- Rutech: Clinical Investigator, Advisory Board
- Santen: Research, Speaker, Advisory Board
- Shire, SarCode Biosciences: Advisory Board, Shareholder, Research Grant
- Syedgen: Advisory Board
- Science Based Health: Research, Advisory, Spokesman
- Senju: Research Grants
- Srathspey Crowne: Investor
- Stemnion: Advisory Board, Investigator
- Talia Technology: Speaker, Advisory Board
- Tear Lab: Advisory Board, Speaker, Shareholder
- Tear Science: Advisory Board, Speaker
- Topcon: Clinical Research Grant
- Topivert: Consultant
- Vistakon: Advisory Board, Clinical Research
- Xoma, Servier: Clinical Investigator, Advisor
- 1-800-DOCTORS: Advisory Board, Shareholder
- Virginia Eye Consultants & Surgery Center: Owner
Blockade of RASP: A Novel Therapeutic Approach

RASP Binding
- Reproxalap rapidly binds to RASP in a reaction that is essentially irreversible in vivo
- Reproxalap out-competes endogenous RASP targets

Adduct Transport
- Reproxalap-RASP adducts are transported inside the cell

Adduct Degradation
- Reproxalap-RASP adducts are degraded within hours

RASP = Reactive Aldehyde Species
RASP Are Elevated in Tears of Dry Eye Disease Patients


Reproxalap Demonstrated RASP Reduction in DED Phase 2a Trial Which Correlated with Sign Improvement in Individual Patients

Pre-Treatment = Day 0, Post-Treatment = Day 28.

Pooled data from Phase 2a clinical trial presented at ARVO 2018
Reproxalap’s Novel Mechanism of Action has the Potential to Address the Two Major Forms of Dry Eye Disease

Insufficient tear volume and increased evaporation lead to cycle of inflammation and cell damage

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.
Phase 2b Dry Eye Disease Clinical Trial Design

• **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, and history of use or desire to use eye drops for dry eye symptoms within 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
    • Corneal fluorescein staining score of ≥ 2 in at least one region (e.g., inferior, superior, or central)
    • Sum corneal fluorescein staining score of ≥ 4
    • Total lissamine green conjunctival score of ≥ 2
    • 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 Design

### Phase 2b Dry Eye Disease Clinical Trial

**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)**
  - Reproxalap 0.1% (N = 100)
  - Reproxalap 0.25% (N = 100)
Reproxalap Improved Ocular Dryness vs. Vehicle

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

Average Baseline Score = 3.1

OD = Ocular Discomfort

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

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

**Above Median Population Average Baseline Score = 3.6**

Mean Change from Baseline

<table>
<thead>
<tr>
<th>Week</th>
<th>Vehicle</th>
<th>Reproxalap (0.1%)</th>
<th>Reproxalap (0.25%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0</td>
<td>-0.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>-0.4</td>
<td>-0.3</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>-0.6</td>
<td>-0.5</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>-0.8</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

*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)

Average Baseline Score = 2.9

- 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 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

<table>
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<tr>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.1</td>
<td>-0.3</td>
<td>-0.5</td>
<td>-0.7</td>
</tr>
<tr>
<td>-0.9</td>
<td>-0.7</td>
<td>-0.5</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

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

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

ITT Population with Observed Data Only

Above Median Population Average Baseline Score = 3.4

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<tr>
<td>-0.1</td>
<td>-0.3</td>
<td>-0.5</td>
<td>-0.7</td>
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<tr>
<td>-0.9</td>
<td>-0.7</td>
<td>-0.5</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

p < 0.05

p = 0.002

OD = Ocular Discomfort
Reproxalap Improved Ocular Staining vs. Vehicle

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

Average Baseline Score = 1.9

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

0.25% reproxalap vs. vehicle
MMRM Week 2-12
p=0.02

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

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
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 both Ocular Dryness and Staining

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

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

- **Probability of Symptom-Free (Ocular Dryness Score = 0)**
  - 0.25% Reproxalap vs. Vehicle

*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
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

**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)

Source: Reproxalap DED Phase 2b clinical trial results

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

ITT Population with Observed Data Only
Conclusions

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 has conducted an EOP2 meeting with the FDA, agreeing on adaptive Phase 3 clinical trial design, primary endpoints and analysis strategy

• **Phase 3 clinical program started 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
Adaptive Phase 3 Dry Eye Disease Clinical Trial Design

**Phase 3 Dry Eye Disease Clinical Trial: Part 1**

<table>
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<th>Visit 4</th>
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<th>Visit 7</th>
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<th>Visit 9</th>
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<tbody>
<tr>
<td>Week -2</td>
<td>Day 1</td>
<td>Wk 1</td>
<td>Wk 2</td>
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<td>Wk 5</td>
<td>Wk 6</td>
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<td>Wk 10</td>
<td>Wk 11</td>
</tr>
<tr>
<td>Screening</td>
<td>Treatment</td>
<td>Reproxalap 0.25% (N = 100) QID</td>
<td>Vehicle (N = 100) QID</td>
<td>Reproxalap 0.25% (N = 100) QID to BID</td>
<td>Vehicle (N = 100) QID to BID</td>
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**Phase 3 Dry Eye Disease Clinical Trial: Part 1 and 2**

- **Primary objective:** Evaluate efficacy of reproxalap ophthalmic solution (0.25%) vs. vehicle on co-primary symptom and sign endpoints
- **Population selection and design:** Same as used for Phase 2b

**Phase 3 Dry Eye Disease Clinical Trial: Part 2**

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<td>Treatment Regimen tbd (QID or QID to BID)</td>
<td>Reproxalap 0.25% (N = 200-400)</td>
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- Confirmed sample size
- Confirmed dosing regimen

**Phase 3 Dry Eye Disease Clinical Trial: Part 1 and 2**

- **Primary objective:** Evaluate efficacy of reproxalap ophthalmic solution (0.25%) vs. vehicle on co-primary symptom and sign endpoints
- **Population selection and design:** Same as used for Phase 2b

**Phase 3 Dry Eye Disease Clinical Trial: Part 2**

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- Confirmed sample size
- Confirmed dosing regimen
Phase 3 Primary Endpoint Strategy: Dry Eye Disease Symptom and Sign Endpoints Achieved in Phase 2b Clinical Trial with MMRM

**Primary Symptom Endpoint for Phase 3 DED**

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

Baseline Score ≥ 3
(N=69 | 69)

Week 2 | Week 4 | Week 8 | Week 12
---|---|---|---
0 | 0 | 0 | 0
-0.2 | -0.2 | -0.2 | -0.2
-0.4 | -0.4 | -0.4 | -0.4
-0.6 | -0.6 | -0.6 | -0.6
-0.8 | -0.8 | -0.8 | -0.8

Mean Change from Baseline

**Fluorescein Staining: Nasal (0-4)**

Baseline Score ≥ 2
(N=62 | 56)

Week 2 | Week 4 | Week 8 | Week 12
---|---|---|---
0 | 0 | 0 | 0
-0.1 | -0.1 | -0.1 | -0.1
-0.2 | -0.2 | -0.2 | -0.2
-0.3 | -0.3 | -0.3 | -0.3
-0.4 | -0.4 | -0.4 | -0.4

Mean Change from Baseline

**MMRM p values**

- **Primary Symptom Endpoint**
  - **MMRM p = 0.0048**

- **Primary Sign Endpoint**
  - **MMRM p = 0.0007**

*p values subject to change based on quality control analysis

Source: Reproxalap DED Phase 2b clinical trial results

**Vehicle**  **Reproxalap (0.25%)**

*p<0.05  **p<0.01

OD = Ocular Discomfort

MMRM = Mixed effect Model Repeated Measures
Thank You

ARVO  May 1, 2019  Vancouver, BC