A Randomized, Double-Masked, Parallel-Group, Phase 2a Dry Eye Disease Clinical Trial to Evaluate the Safety and Efficacy of Topical Ocular ADX-102 (Reproxalap), a Novel Aldehyde Sequestering Agent

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Aldehydes Are Mediators of Inflammation

- Aldehydes covalently bind thiol (Michael addition) and amine (Schiff base) residues on proteins.

- Direct protein binding leads to conformational changes in proteins, resulting in dysfunctional proteins, which in turn initiate a pro-inflammatory signaling cascade.

- Aldehyde-protein adducts are ligands for Scavenger Receptor A, subsequently leading to auto-antibody formation against the adducted protein.
The Scientific Literature Supports the Toxicity of Pro-Inflammatory Reactive Aldehyde Species (RASP)

**Cardiovasc Res.** 2010 Nov 1;88(2):352-9. HNE-induced 5-LO expression is regulated by NF-κB/ERK and Sp1/p38 MAPK pathways via EGF receptor in murine macrophages.

**Biofactors.** 2005;24(1-4):229-36. Role of 4-hydroxy-2,3-nonenal in the pathogenesis of fibrosis.


**Diabetes.** 2008 Apr;57(4):879-88. Proinflammatory effects of advanced lipoxidation end products in monocytes.


**Proc Natl Acad Sci U S A.** 2007 Aug 14;104(33):13519-24. 4-hydroxynonenal, an endogenous aldehyde, causes pain and neurogenic inflammation through activation of the irritant receptor TRPA1.

RASP Are Elevated in Tears of Dry Eye Disease Patients


RASP Scavengers Represent A Novel Therapeutic Approach

- **RASP Binding**
  - Covalent reaction between drug and RASP that is essentially irreversible in vivo

- **Adduct Transport**
  - Scavenged RASP are transported inside the cell

- **Cellular Degradation**
  - Drug-RASP adducts are metabolized within hours
## Dry Eye Disease
### Phase 2a Clinical Design

**Design**

Randomized, Double-Masked, Clinical Trial

**Dosing**

Topical Ocular Reproxalap (ADX-102) Formulations:
- Current Formulation 0.5%
- Current Formulation 0.1%
- Novel Lipid Formulation 0.5%

**Enrollment**

51 Dry Eye Patients with Active Disease

**Treatment Time**

4 Weeks

**Clinic Visits**

Day 1, Week 1, Week 4

Further information can be found on www.clinicaltrials.gov: Trial #NCT03162783.
Inclusion Criteria: Active Disease

• History of dry eye for at least 6 months
• History of use or desire to use eye drops for dry eye symptoms within 6 months
• Score of ≥ 2 on the Ora Calibra® Ocular Discomfort & 4-symptom questionnaire in at least one symptom
• Schirmer’s Test score of ≤ 10 mm and ≥ 1 mm
• Tear film break-up time (TFBUT) ≤ 5 seconds
• Corneal fluorescein staining score of ≥ 2 in at least one region (e.g. inferior, superior, or central)
• Sum corneal fluorescein staining score of ≥ 4, based on the sum of the inferior, superior, and central regions
• Total lissamine green conjunctival score of ≥ 2, based on the sum of the temporal and nasal regions
Reproxalap Improved Numerous Dry Eye Disease Signs and Symptoms in Phase 2a Clinical Trial

<table>
<thead>
<tr>
<th>Endpoint (Pooled Data)</th>
<th>Pre-Treatment</th>
<th>Post-Treatment (Day 28)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Assessment in Dry Eye (SANDE) Score</td>
<td>61</td>
<td>52</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>Ocular Discomfort Score</td>
<td>2.3</td>
<td>1.5</td>
<td>p = 0.0002</td>
</tr>
<tr>
<td>Overall 4-Symptom Score</td>
<td>2.6</td>
<td>2.0</td>
<td>p = 0.0004</td>
</tr>
<tr>
<td>Tear Volume (Schirmer Test)</td>
<td>5.6</td>
<td>8.3</td>
<td>p = 0.008</td>
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<tr>
<td>Osmolarity</td>
<td>304</td>
<td>294</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>Total Staining (Lissamine Green)</td>
<td>5.2</td>
<td>4.3</td>
<td>p = 0.002</td>
</tr>
</tbody>
</table>
Improvement Effect Sizes Were Robust and Statistically Significant in Phase 2a Clinical Trial

0.1% Reproxalap Improvement Effect Size Across Dry Eye Disease Signs and Symptoms

Effect size = Mean difference from Day 0 to Day 28 / Standard Deviation of Day 0.
A Dose Response Was Observed in Phase 2a Dry Eye Disease Clinical Trial

Effect size = Mean difference from Day 0 to Day 28 / Standard Deviation of Day 0.
Drug Activity in Phase 2a Clinical Trial Supported by Biomarker Reduction and Increasing Efficacy over Time

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

SANDE=Symptom Assessment in Dry Eye Score, ODS=Ocular Discomfort Score, 4SS=Overall 4-Symptom Score
Aldehyde Reduction Correlated with Sign Improvement Within Individual Patients

Pooled data from Phase 2a clinical trial.
Aldehyde Reduction Correlated with Sign Improvement Within Individual Patients

Pooled data from Phase 2a clinical trial.
Phase 2a Clinical Trial Safety Summary

- No observed safety concerns
- Transient stinging consistent with other eye drops and prior reproxalap clinical experience
- Tolerability of 0.1% reproxalap consistent with standard of care in the dry eye disease population
Conclusions

- Reproxalap demonstrated statistically significant and clinically relevant improvement in a broad range of dry eye disease signs and symptoms:
  - Rapid onset of activity within one week of dosing
  - Improvement increased over time, and a modest dose-response was observed

- Reproxalap activity in dry eye disease supported by pro-inflammatory aldehyde biomarker levels

- Primary objective of trial achieved:
  
  0.1% reproxalap, which demonstrated consistent statistically and clinically significant activity and was the best-tolerated formulation, selected to advance to Phase 2b
**Dry Eye Disease**
**Phase 2b Clinical Design**

Initiated Q1 2018; Results expected H2 2018

| Groups                  | • 0.1% Reproxalap  
|                        | • 0.25% Reproxalap  
|                        | • Vehicle          |
| Randomization          | Double-Masked 1:1:1 |
| Treatment              | 12 Weeks, Topical Ocular |
| Enrollment             | 300 Patients with Dry Eye Disease |
| Endpoints              | Standard Dry Eye Disease Signs and Symptoms |

Further information can be found on [www.clinicaltrials.gov](http://www.clinicaltrials.gov): Trial #NCT03404115.