# 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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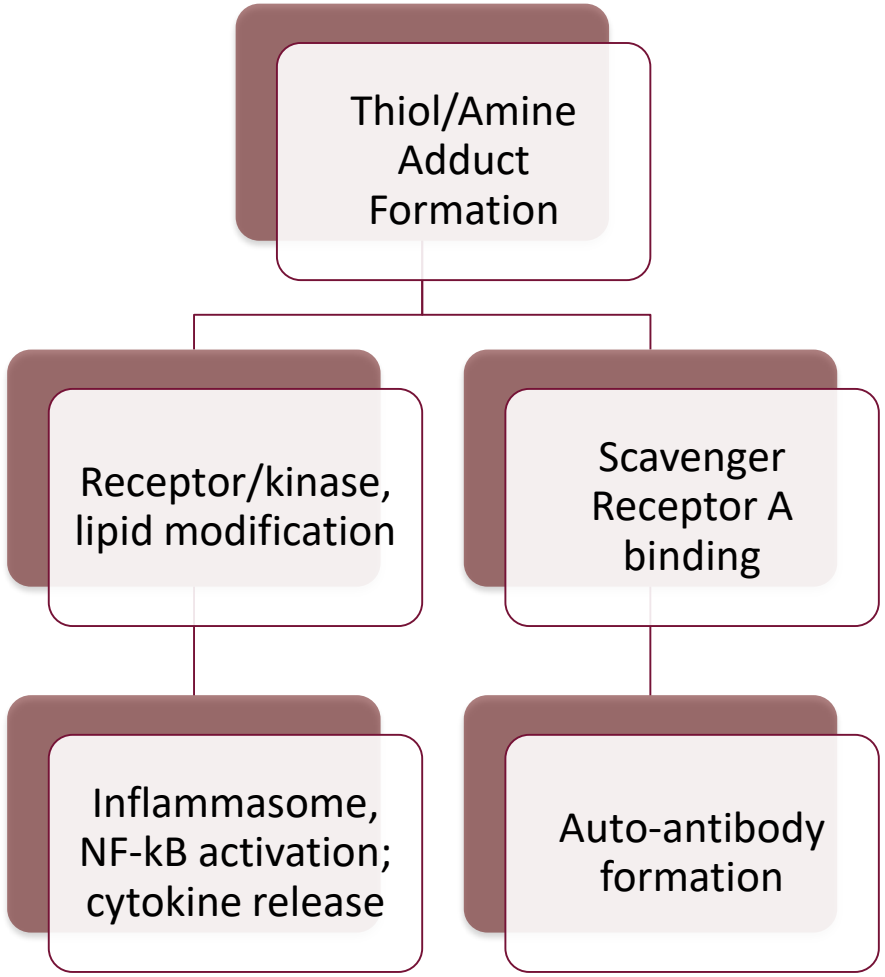
# Aldehydes Are Mediators of Inflammation

- 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-kB/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.**

Cell Mol Biol Lett. 2015 Dec;20(4):647-62. **The advanced lipoxidation end product precursor malondialdehyde induces IL-17E expression and skews lymphocytes to the th17 subset**.

J Leukoc Biol. 2012 Nov;92(5):1055-67. **Proinflammatory effects of malondialdehyde in lymphocytes.**

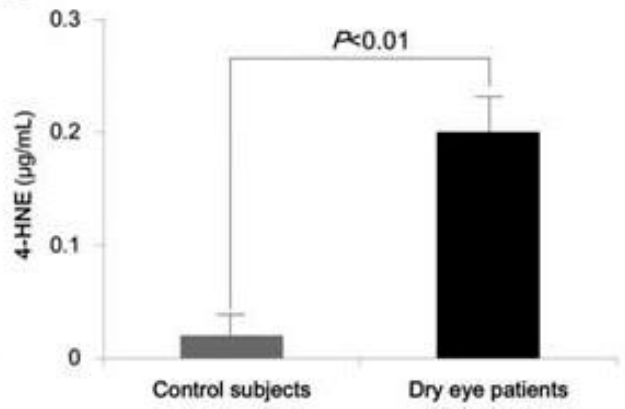
Diabetes. 2008 Apr;57(4):879-88. **Proinflammatory effects of advanced lipoxidation end products in monocytes.**

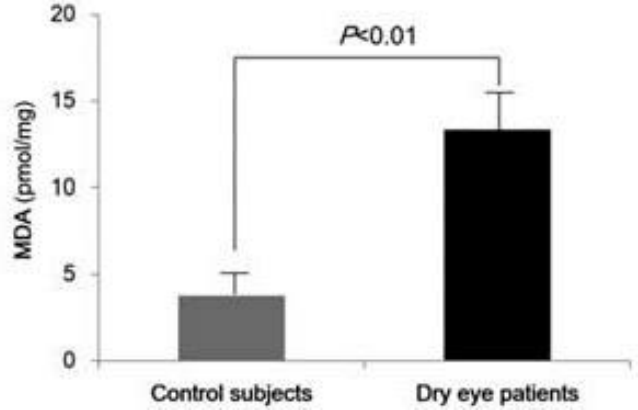
Free Radic Biol Med. 2012 Sep 15;53(6):1226-38. **Identification of novel bioactive aldehyde-modified phosphatidylethanolamines formed by lipid peroxidation.**

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.**

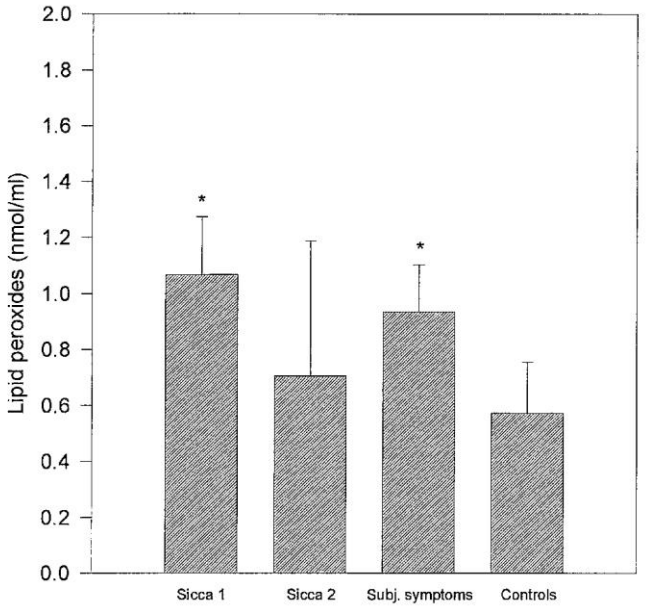
Alcohol Clin Exp Res. 2002 Feb;26(2):158-64. **In vitro exposure to malondialdehyde-acetaldehyde adducted protein inhibits cell proliferation and viability**.

# RASP Are Elevated in Tears of Dry Eye Disease Patients



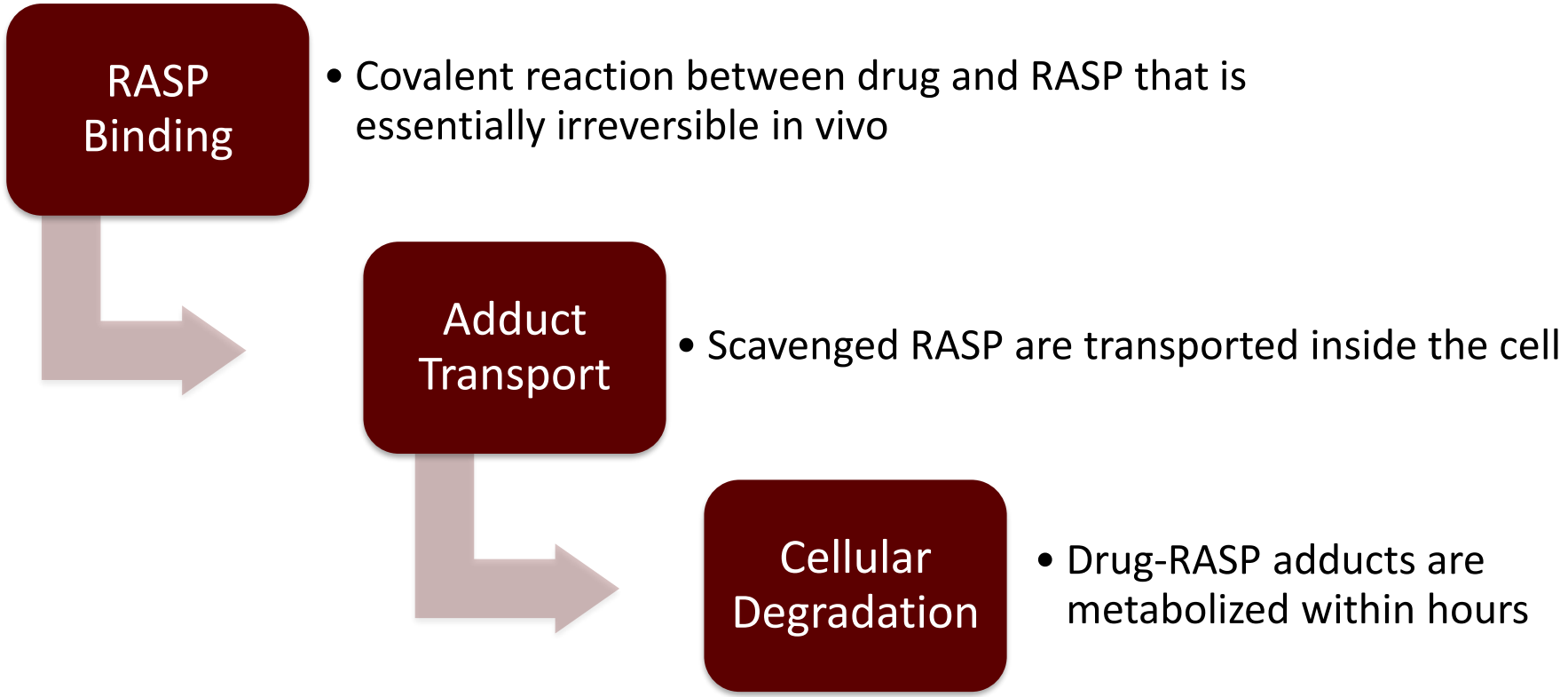




Curr Eye Res. 41:1143-9, 2016.




Graefe's Arch Clin Exp Ophthalmol. 233:694-8, 1995.

# RASP Scavengers Represent A Novel Therapeutic Approach



# Dry Eye Disease
# Phase 2a Clinical Design

| | |
|---|---|
| **Design** | Randomized, Double-Masked, Clinical Trial |
| **Dosing** | Topical Ocular Reproxalap (ADX-102) Formulations:<br>• Current Formulation 0.5%<br>• Current Formulation 0.1%<br>• 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.

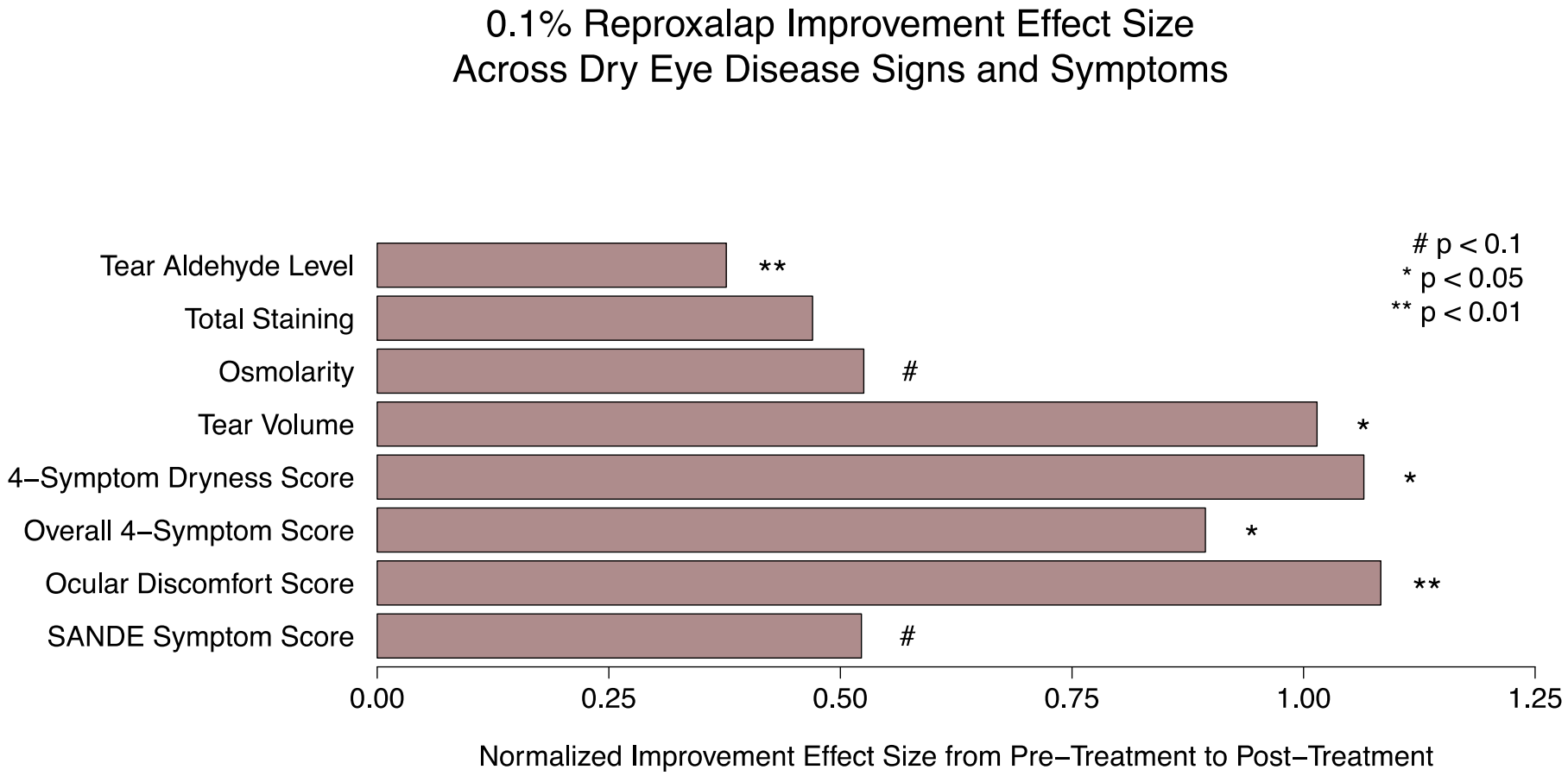
# Inclusion Criteria: Active Disease

- 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

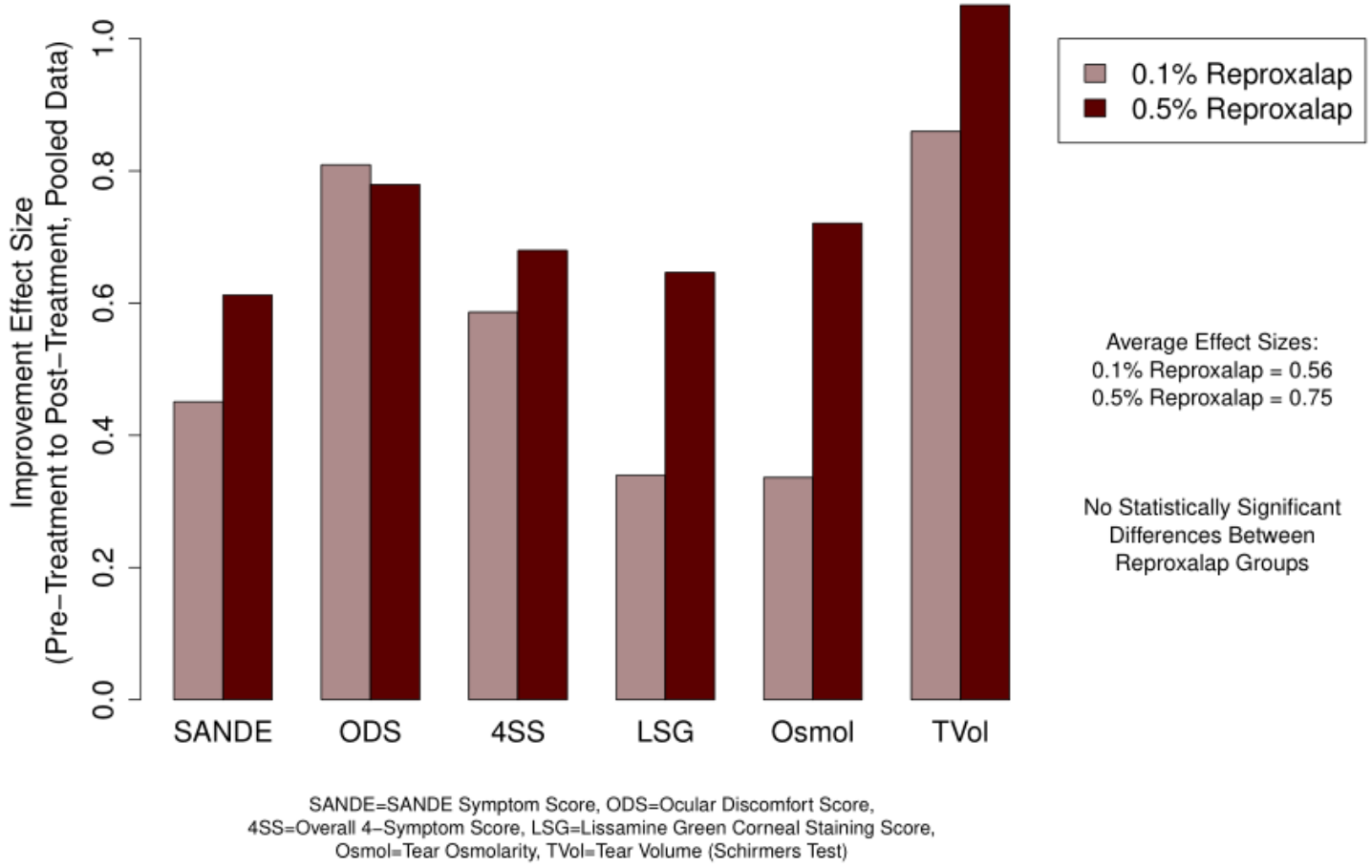
| Endpoint (Pooled Data) | Pre-Treatment | Post-Treatment (Day 28) | p value* |
|---|---|---|---|
| Symptom Assessment in Dry Eye (SANDE) Score | 61 | 52 | p = 0.003 |
| Ocular Discomfort Score | 2.3 | 1.5 | p = 0.00002 |
| Overall 4-Symptom Score | 2.6 | 2.0 | p = 0.0004 |
| Tear Volume (Schirmer Test) | 5.6 | 8.3 | p = 0.008 |
| Osmolarity | 304 | 294 | p = 0.003 |
| Total Staining (Lissamine Green) | 5.2 | 4.3 | p = 0.002 |

# Improvement Effect Sizes Were Robust and Statistically Significant in Phase 2a Clinical Trial



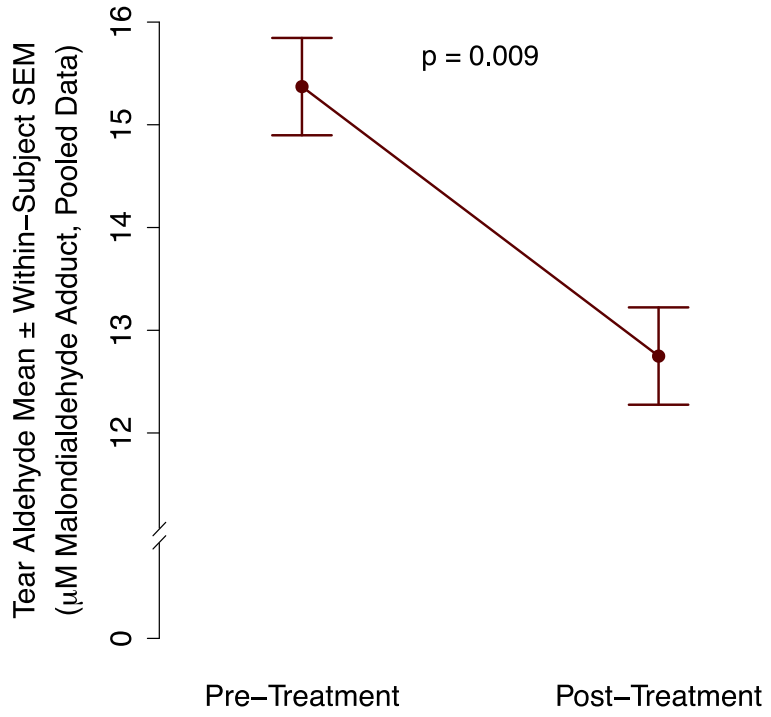

Effect size = Mean difference from Day 0 to Day 28 / Standard Deviation of Day 0.

# A Dose Response Was Observed in Phase 2a Dry Eye Disease Clinical Trial

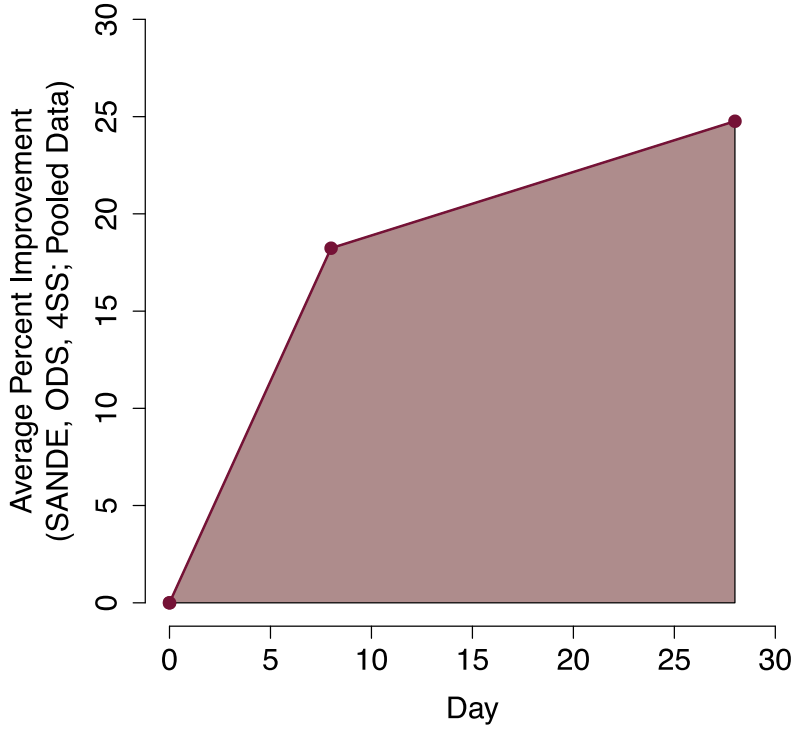



Effect size = Mean difference from Day 0 to Day 28 / Standard Deviation of Day 0.

# Drug Activity in Phase 2a Clinical Trial Supported by Biomarker Reduction and Increasing Efficacy over Time

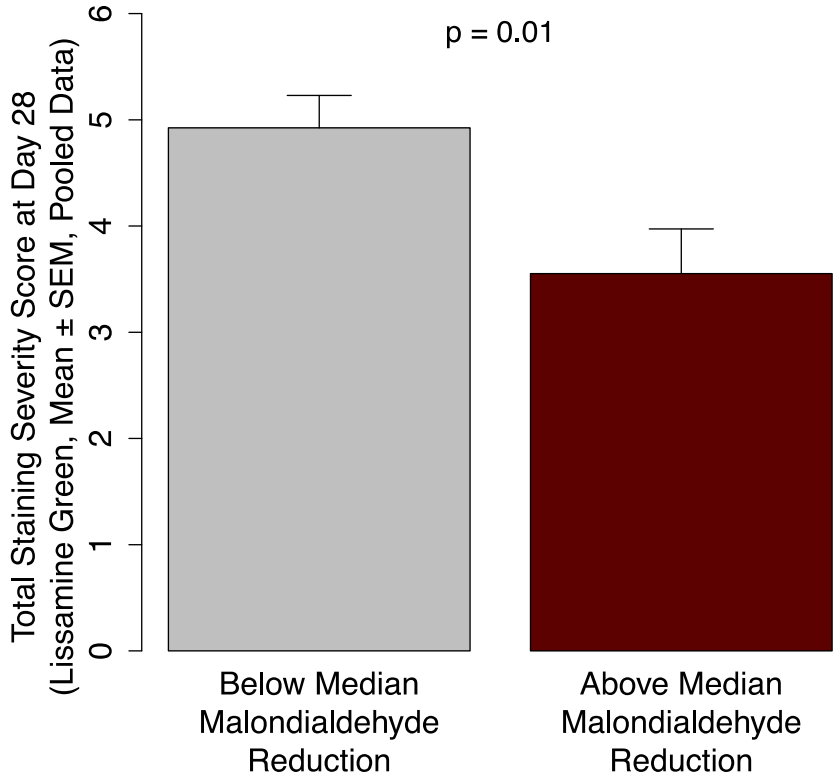



Pre-Treatment = Day 0, Post-Treatment = Day 28.




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.

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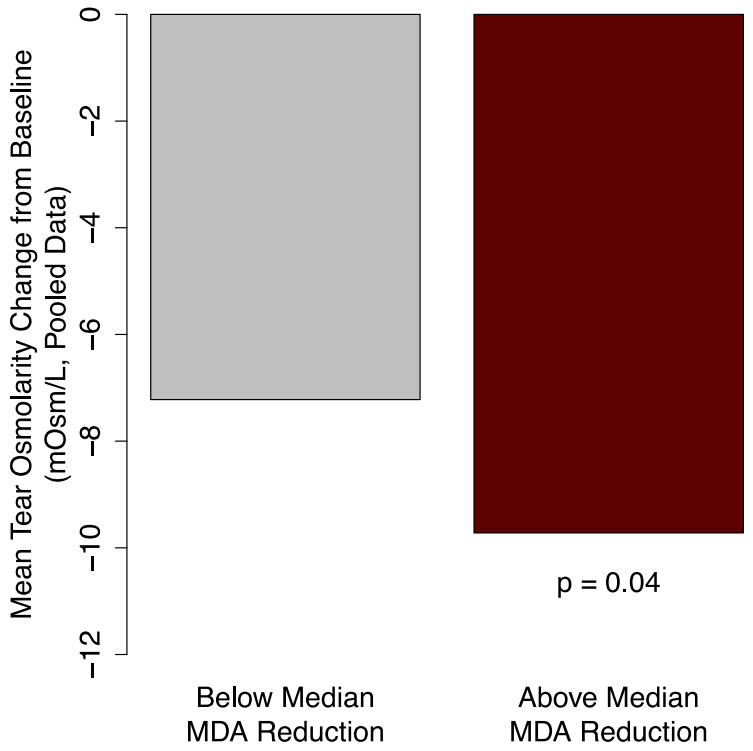


Pooled data from Phase 2a clinical trial.

# 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<br>• 0.25% Reproxalap<br>• 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: Trial #NCT03404115.