Allysta Pharmaceuticals, Inc.

Science driven. Results focused.

Henry Hsu MD, CEO
Dry Eye Challenge: A Heterogenous Multifactorial Disease

Optimal Approach:
Address multiple aspects to improve outcomes

- Inflammation
  - Proinflammatory cytokines
  - Inflammatory cell response
- Epithelial cell damage (cornea)
- Tear film disruption (goblet cells, Meibomian glands)
Novel Approach Yields Promising Results

**Key Findings**

Topical adiponectin:

- ↓ Corneal damage
- ↓ Inflammatory cytokine levels
- ↓ T cell infiltrate (CD4+T cells)
- ↑ Goblet cell density (mucin)
- ↑ Tear integrity (breakup time)
- ↑ Tear volume

**Therapeutic Effect of Topical Adiponectin in a Mouse Model of Desiccating Stress–Induced Dry Eye (Yoon, IOVS. 2013)**

- **Corneal Damage**
  - * P < 0.05 vs BSS
  - † P < 0.05 vs EDE.

**IL-1 β, TNF-α, and INF- γ ( Conjunctiva )**

<table>
<thead>
<tr>
<th>pg/mL</th>
<th>IL-1β</th>
<th>TNF-α</th>
<th>IFN-γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>UT (normal)</td>
<td>1.08 †† $</td>
<td>0.50 †† $</td>
<td>25.9 †† $</td>
</tr>
<tr>
<td>EDE (untreated dry eye)</td>
<td>6.82</td>
<td>1.59</td>
<td>47.93</td>
</tr>
<tr>
<td>0.0001% adiponectin</td>
<td>6.81</td>
<td>1.21</td>
<td>43.45</td>
</tr>
<tr>
<td>0.001% adiponectin</td>
<td>1.30 ††</td>
<td>0.55 ††</td>
<td>31.95 ††</td>
</tr>
<tr>
<td>0.01% adiponectin</td>
<td>1.22 ††</td>
<td>0.52 ††</td>
<td>31.44 ††</td>
</tr>
</tbody>
</table>

**T Cells (conjunctiva) by Flow Cytometry**

- **Goblet Cell Density**
Rationale for Targeting Adiponectin Pathway

- A unique “protective” hormone with multiple beneficial actions:
  - Inhibit inflammation (cellular, cytokine) (NF-κb, TNF-α)
  - Epithelial cell growth factor following injury (Akt)
  - Reverses insulin resistance (AMPK)

- Protects against adverse effects of obesity (inflammation, metabolic derangements)

- Broad actions on multiple organs/cell types
  - Receptors present in ocular tissue

How to harness benefits for ocular disease?
ALY688: An Optimized Adiponectin Analogue

Adiponectin protein is a poor drug candidate

1.) Identification of Binding Domain

2.) Optimization

ALY688: peptide agonist
- Activates adipo receptors
- Stable in biological fluids (tears)
- Topical eye drop formulation (BID)

Scherer, Diabetes (2006)
Otvos, BMC Bio (2011)
ALY688 (vs Adipo) in Dry Eye

**ALY688** as effective as **adipo** protein:
- Decreased corneal damage
- Increased tear volume
- Increase break up time

**ALY688** more effective than cyclosporin
Efficacy Confirmed in Rabbit Dry Eye Model (Atropine)

ALY688 improved corneal staining, tear integrity, and tear volume

(Crawford, 2019, ARVO)
ALY688 Accelerates Corneal Wound Healing

Decrease in Area of Corneal Epithelial Defect following Alkali Burn

* p < 0.01 for ADP355 and Adipo vs BSS

(Rapid improvement in corneal defect size)

(Yoon, et. al. ARVO, 2018)
ALY688 Improves Multiple Aspects of Dry Eye Disease

**Inciting Factors:**

- Decrease tear production
- Increased tear evaporation
- Loss of tear integrity

**Inflammatory Cascade:**

- Cytokines
- WBCs

**Corneal surface damage**

- Promote corneal healing

**Tear Film Disruption**

- Reduce inflammation
- Improve tear integrity and tear volume

ALY688

- Increase tear production
- Reduced tear evaporation
- Improve tear integrity

ALLYSTA
ALY688-201 Clinical Trial

- Phase 1/2a randomized, double-masked, vehicle-controlled study in US

- Dry eye patients with moderate to early severe dry eye signs and symptoms (N=120)

- Treatment groups (8 weeks dosing period)
  - ALY688 Ophthalmic Solution (0.1%)
  - ALY688 Ophthalmic Solution (0.4%)
  - Vehicle Ophthalmic Solution

- Primary objective: Evaluate safety and tolerability of ALY688
  - Additional endpoints: effects on signs (corneal staining) and symptoms (dry eye scoring); change in ocular surface cytokines, inflammatory cells

- IND submission: October 2019
- Data available: Mid-2020
Allysta Management and Advisors

MANAGEMENT TEAM

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DRY EYE SCIENTIFIC ADVISORY BOARD

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Allysta Pharmaceuticals

- Based in SF Bay area

- Pipeline includes ALY688 SC sustained release formulation (once/weekly) being developed for NASH and obesity-related metabolic disease
  - Clinical trials to begin 2H, 2020

- Financing: Morningside Ventures (Boston)