PHENTOLAMINE MESYLATE OPHTHALMIC SOLUTION REDUCES TIME TO RECOVERY OF MEDICALLY-INDUCED MYDRIASIS IN A PHASE 2 TRIAL

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I have the following financial interests or relationships to disclose:

- Aerie Pharmaceuticals
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- Alcon Labs
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- Allergan Inc
- Allysta pharmaceuticals
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- Sight Sciences
- Silk Technologies
- Sun Pharmaceuticals
- Surface Inc.
- Tarsus Medical
- TearLab
- Topcon
- Visant Medical
- Visionix
- Vital Tears
- Vmax
- Yolia
Medically-induced pupil dilation is a necessary tool for routine ophthalmoscopy…

….but the many hours of recovery time impairs vision leading to:

- Photophobia (sensitivity to light)
- Cycloplegia (loss of accommodation)
- Subjective “Discomfort” of Vision
- Halos and Glare
- Difficulty Reading and Driving
Parasympathetic innervation stimulates circular muscles

Sympathetic (primarily $\alpha_1$) innervation stimulates radial muscles

Mydriatic Agents

- Tropicamide (anti-cholinergic)
  - Parasympathetic innervation stimulates circular muscles

- Phenylephrine ($\alpha_1$ agonist)
  - Sympathetic (primarily $\alpha_1$) innervation stimulates radial muscles

Phentolamine is a Non-selective $\alpha_1$ & $\alpha_2$ Adrenergic Antagonist

Reduces Pupil Size via $\alpha_1$ Iris Dilator Blockade

Relaxes (Vasodilates) Smooth Muscle via $\alpha_1$ Smooth Muscle Blockade

Reversal of Mydriasis

Note: Phentolamine previously approved using other formulations (IV and IM) for its vasodilation-related effects in pheochromocytoma (Regitine®) and reversing oral anesthesia (OraVerse®)

1% Phentolamine Mesylate Ophthalmic Solution (Nyxol®)
MIRA-1 (NYXRM-201) PHASE 2 TRIAL DESIGN

Eligibility Screening
4 US sites
32 subjects

Randomization (1:1)
• 1% Phentolamine Mesylate Ophthalmic Solution (PMOS)
• Placebo

1% PMOS

Mydriatic Agent A n=16
1 drop after 1 hour

Mydriatic Agent B n=16
1 drop after 1 hour

Mydriatic Agent B n=16
1 drop after 1 hour

Mydriatic Agent A n=16
1 drop after 1 hour

Placebo

Day 1

Data Readout 4Q 2019

Day 8

Enrollment
• 32/32 Patients Enrolled
• August – Sept 2019

Inclusion/Exclusion Criteria
• 18 years and older
• Otherwise healthy subjects with no pre-existing ocular conditions/procedures
• Protocol based on Rev-Eyes (an alpha1 blocker FDA approved in 1990)

Clinical Sites
• Foster – Athens Eye Care – OH
• Kannarr – Kannarr Eye Care – KS
• Karpecki – Kentucky Eye Institute – KY
• Montaquila – West Bay Eye Associates – RI

Eligibility Screening

* Half subjects 2.5% Phenylephrine & half subjects 1% Tropicamide
Primary Endpoint

Mean change in pupil diameter from mydriatic maximum diameter at 2 hours

Secondary Endpoints

Mean & percent change from baseline ($\leq 0.2$ mm) in pupil diameter from mydriatic maximum diameter at 30 min, 1, 2, 4, & 6 hours

Visual Function

• Binocular accommodation (within 1 diopter)
• Near & distance VA assessments

Safety

• HR & BP
• IOP
• Adverse Effects (conjunctival hyperemia)
• Ocular discomfort
• No loss of VA
**DEMOGRAPHICS**

*Double-Masked Placebo-controlled Randomized, 2-arm Crossover Phase 2 Study With Patients Treated With Both Phentolamine Mesylate Ophthalmic Solution & Placebo*

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Placebo to PMOS</th>
<th>PMOS to Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (Full Analysis Set)</strong></td>
<td>15</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td><strong>Age (years): Median</strong></td>
<td>30.0</td>
<td>26.0</td>
<td>27.0</td>
</tr>
<tr>
<td><strong>Gender: Female n(%)</strong></td>
<td>10 (67%)</td>
<td>9 (44%)</td>
<td>19 (61%)</td>
</tr>
<tr>
<td><strong>Race: White n(%)</strong></td>
<td>14 (93%)</td>
<td>15 (94%)</td>
<td>29 (94%)</td>
</tr>
<tr>
<td><strong>Brown Iris color: n(%)</strong></td>
<td>15 (100%)</td>
<td>16 (100%)</td>
<td>31 (100%)</td>
</tr>
</tbody>
</table>
**PRIMARY ENDPOINT: MEAN PUPIL DIAMETER**

Phentolamine Mesylate Ophthalmic Solution Demonstrated A Significant Reduction In Pupil Diameter At 2 Hours After Eyes Were Dilated With Either Phenylephrine Or Tropicamide

Reduction in Pupil Diameter after Patients Received either Phenylephrine 2.5% or Tropicamide 1.0% in Study Eye

Reduction in Pupil Diameter after Patients Received Phenylephrine 2.5% in Study Eye

Reduction in Pupil Diameter after Patients Received Tropicamide 1.0% in Study Eye

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

**MYDRIATIC**

Phentolamine Mesylate Ophthalmic Solution Demonstrated A Significant Reduction In Pupil Diameter At 2 Hours After Eyes Were Dilated With Either Phenylephrine Or Tropicamide.
SECONDARY ENDPOINT: PUPIL DIAMETER RETURN TO BASELINE

Phentolamine Mesylate Ophthalmic Solution Demonstrated A Significant Return To Pupil Diameter Baseline 2 Hours After Eyes Were Dilated With Either Phenylephrine Or Tropicamide

Percent of Subjects Returning to ≤ 0.2 mm within Baseline after Treatment with either Phenylephrine or Tropicamide

- **Placebo**
  - 0%: 7%
  - 1 hour: 7%
  - 2 hours: 16%
  - 4 hours: 29%
  - 6 hours: 23%

- **PMOS (Phentolamine Mesylate Ophthalmic Solution)**
  - 0%: 68%
  - 1 hour: 77%
  - 2 hours: 23%
  - 4 hours: 68%
  - 6 hours: 100%

- **p-values**
  - 0%: 0.1094
  - 1 hour: 0.0262
  - 2 hours: 0.0001

ARVO Abstract: #3365340
Phentolamine Mesylate Ophthalmic Solution Had An Average Time Savings Of 2 Hours To Return Pupil Diameter At Or Below Baseline
SECONDARY ENDPOINT: ACCOMMODATION

Phentolamine Mesylate Ophthalmic Solution Demonstrates A Faster Return Of Accommodative Power Compared To Placebo In Subjects Treated With Tropicamide Mydriatic Agent

Percent of Subjects Returning to Accommodation within ≤ 1 D of Baseline in at least one eye after Treatment with Tropicamide

- Placebo: n=16
- PMOS: n=16

- 0 hours: Placebo 25%, PMOS 19%
- 2 hours: Placebo 25%, PMOS 63%
- 4 hours: Placebo 56%, PMOS 75%

p=0.0084
SECONDARY ENDPOINT: OVERALL SAFETY AND TOLERABILITY

No SAEs, No Changes In Blood Pressure & Heart Rate, & Minimal AEs (Redness) Observed With Phentolamine Mesylate Ophthalmic Solution

<table>
<thead>
<tr>
<th>Adverse Effect (AE)</th>
<th>PMOS (n=31)</th>
<th>Placebo (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival Hyperemia</td>
<td>11 (35.5%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**Systolic BP**

**Diastolic BP**

**Heart Rate**

PMOS

Placebo
There is a mild-moderate eye redness with Phentolamine Mesylate Ophthalmic Solution in the first 2 hours that diminishes over the next 4 hours.

- Subjects were given an option to use Lumify (brimonidine) at 2 hours to reduce any mild-to-moderate redness; no subjects requested Lumify.
- Conjunctival hyperemia trended towards baseline levels at 6 hours with drug.
CONCLUSIONS

- **Reversal of Mydriasis Efficacy**
  - Primary endpoint met with Phentolamine Mesylate Ophthalmic Solution (PMOS) significantly decreased pupil diameter from baseline at 2 hours compared to placebo
    - Difference was significant from 1 through 6 hours
    - Pupil diameter differences were maintained when analyzed separately by the mydriatic agents, phenylephrine and tropicamide
    - Consistent with prior trials, PMOS was shown to decrease pupil diameter ~20% and improve visual acuity in multiple lighting conditions

- **Accommodation Efficacy**
  - In eyes dilated with tropicamide, treatment with PMOS resulted in unchanged accommodation from baseline compared with placebo at 2 hours

- **Safety Findings**
  - Consistent with prior trials, PMOS was observed to cause a mild, transient conjunctival hyperemia that peaked in the first hour and declined steadily thereafter to baseline by 6 hours
  - No Lumify requested to reverse mild redness
  - No serious TEAEs and no systemic effects of BP/HR observed with PMOS

- **Next Steps**
  - Planning Phase 3 registration clinical trials to investigate the effect of 1% PMOS in Reversal of Mydriasis indication
    - Trials will include balance of dark and light iris colors as well as evaluate the further efficacy of 1 vs 2 PMOS eyedrops
THANK YOU

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