PHENTOLAMINE MESYLATE OPHTHALMIC SOLUTION PROVIDES LONG LASTING PUPIL MODULATION AND IMPROVES VISUAL ACUITY

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I have the following financial interests or relationships to disclose:

- Acufocus
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- Bausch Health (Valeant)
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- Ocunexis
- Ocuphire
- Okogen
- Stuart Pharmaceuticals
- Sun Pharma
- TearLab
- Thea Pharma
PROBLEM: VISION & AGING

Vision Impairment

- **Presbyopia** is an age-related condition (40s and older) when the hardening of the lens and subsequent loss of accommodation make it more difficult to read or see nearby objects. Miosis can enhance depth of focus via the pinhole effect.

- **Dim Light Vision Disturbances** describe a wide range of symptoms affecting the quality of vision at low illumination (low contrast), including glare, halos, and starburst. Ocular aberrations unmasked with larger pupil size generally contribute to these complaints, allowing entry of unfocused rays of light.

Glaucoma

- **Glaucoma** is a group of life-long progressive diseases that are characterized by irreversible damage to the optic nerve and subsequent visual field loss if not properly treated. There is a need for additive therapies to standard of care to further lower intraocular pressure and provide neuroprotection.

**Presbyopia**
U.S. Prevalence: 110+M

**Dim Light Vision Disturbances**
U.S. Prevalence: 15-20M adults

**Glaucoma**
U.S. Prevalence: 3+M
**Phentolamine is a Non-Selective α1 & α2 Adrenergic Antagonist**

- **Reduces Pupil Size via α1 Iris Dilator Blockade**
- **Relaxes (Vasodilates) Smooth Muscle via α1 Smooth Muscle Blockade**

*Note: Phentolamine previously approved using other formulations (IV and IM) for its vasodilation-related effects in pheochromocytoma (Regitine®) and reversing oral anesthesia (OraVerse®)*
ORION-I (NYXG-201) PHASE 2 TRIAL DESIGN

clinicaltrials.gov: NCT03960866

Eligibility Screening
- 5 US sites
- 40 subjects planned

Enrollment
- **39 Patients Enrolled**
- **May to August 2019**

Randomization (1:1)
- 1% Phentolamine Mesylate Ophthalmic Solution (PMOS)
- Placebo
- Daily Dosing of 1 Eyedrop at Bedtime

Inclusion/Exclusion Criteria
- 18 years and older
- Clinical diagnosis of OAG or OHT 22 to 30 mmHg
- Untreated or treated (washout 30 days) with ≤ 2 glaucoma meds
- Otherwise healthy subjects with no pre-existing ocular conditions/procedures

Clinical Sites
- Abrams – Abrams Eye Center – OH
- Dubiner – Clayton Eye Clinical Research – GA
- Hartman – Rochester Ophthalmological Group – NY
- Moroi – UM Kellogg Eye Center – MI
- Smyth-Medina – North Valley Eye Medical Group – CA

Data Readout
- 4Q 2019

30 day washout
- n=20
- 1 eyedrop daily bedtime dose (14 days)

1% PMOS

Placebo

1 eyedrop daily bedtime dose (14 days)

1 eyedrop daily bedtime dose (14 days)

30 day washout
- n=20

1% PMOS
# DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Placebo</th>
<th>1% PMOS</th>
</tr>
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<tbody>
<tr>
<td>n (Full Analysis Set)</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td><strong>Age (years): Mean</strong></td>
<td>63.2</td>
<td>58.1</td>
</tr>
<tr>
<td><strong>Gender: Female n(%)</strong></td>
<td>13 (65%)</td>
<td>9 (47%)</td>
</tr>
<tr>
<td><strong>Race: White n(%)</strong></td>
<td>14 (70%)</td>
<td>11 (58%)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
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<tbody>
<tr>
<td><strong>Study Eye [n(%)]</strong></td>
<td>OD</td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td>10 (50%)</td>
<td>11 (58%)</td>
</tr>
<tr>
<td><strong>Baseline Mean Diurnal IOP (Study Eye) mmHg [mean(SD)]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study Eye</strong></td>
<td>24.38 (2.097)</td>
<td>24.43 (1.675)</td>
</tr>
<tr>
<td><strong>All Eyes</strong></td>
<td>23.75 (2.244)</td>
<td>23.07 (1.662)</td>
</tr>
<tr>
<td><strong>Baseline IOP Category [n(%)]</strong></td>
<td>≥25 mmHg</td>
<td>&lt;25 mmHg</td>
</tr>
<tr>
<td></td>
<td>13 (65%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td></td>
<td>10 (53%)</td>
<td>9 (47%)</td>
</tr>
<tr>
<td><strong>Baseline BCDVA (SD)</strong></td>
<td>Photopic LogMAR (Study Eye)</td>
<td>0.05 (0.11)</td>
</tr>
<tr>
<td></td>
<td>Mesopic LogMAR (Study Eye)</td>
<td>0.17 (0.12)</td>
</tr>
</tbody>
</table>
ORION-I STUDY RESULTS: OVERVIEW

**Primary Endpoint**

- Mean Change in Diurnal IOP at Day 15

**Secondary Endpoints**

- Decrease in Pupil Diameter
- Improvement in DCNVA
- Safety
**PRIMARY ENDPOINT: MEAN CHANGE IN DIURNAL IOP**

Phentolamine Mesylate Ophthalmic Solution Did Not Show a Significant Decrease In IOP After Day 15 But Did Demonstrate A Significant Decrease In Patients With Baseline IOP < 24 mmHg

**All Patients**

![Graph showing mean change in diurnal IOP by visit (study eye)]

**Patients with Baseline IOP <24 mmHG**

![Graph showing mean change in diurnal IOP by visit, subjects with baseline IOP < 24 mmHG (study eye)]
SECONDARY ENDPOINT: MEAN CHANGE IN PUPIL DIAMETER

Phentolamine Mesylate Ophthalmic Solution Showed A Consistent 20% Mean Reduction (~1 mm) In Pupil Diameter From Baseline In Both Photopic And Mesopic Conditions That Is Sustained Over 24 Hours With Bedtime Daily Dosing

Photopic
Baseline Pupil Diameter: Placebo 3.6 mm, Nyxol 3.6 mm

Mesopic
Baseline Pupil Diameter: Placebo 4.6 mm, Nyxol 4.7 mm

![Graphs showing pupil diameter change in photopic and mesopic conditions over days 8, 15, and 16.](image-url)
SECONDARY ENDPOINT: MEAN CHANGE IN PUPIL DIAMETER

One-third of subjects who were given Phentolamine Mesylate Ophthalmic Solution had ≥30% reduction in pupil diameter in both photopic & mesopic conditions.

Percent of subjects achieving percent reductions from baseline in photopic conditions (Study Eye):

- Placebo (n = 20):
  - ≥10% Reduction: 15%
  - ≥15% Reduction: 15%
  - ≥20% Reduction: 10%
  - ≥25% Reduction: 5%
  - ≥30% Reduction: 0%

- 1% PMOS (n = 19):
  - ≥10% Reduction: 63%
  - ≥15% Reduction: 42%
  - ≥20% Reduction: 32%
  - ≥25% Reduction: 32%
  - ≥30% Reduction: *p=0.012

Percent of subjects achieving percent reductions from baseline in mesopic conditions (Study Eye):

- Placebo (n = 20):
  - ≥10% Reduction: 20%
  - ≥15% Reduction: 10%
  - ≥20% Reduction: 5%
  - ≥25% Reduction: 0%
  - ≥30% Reduction: 0%

- 1% PMOS (n = 19):
  - ≥10% Reduction: 79%
  - ≥15% Reduction: 68%
  - ≥20% Reduction: 47%
  - ≥25% Reduction: 37%
  - ≥30% Reduction: *p=0.042
SECONDARY ENDPOINT: VISUAL ACUITY

~60% of subjects who were given Phentolamine Mesylate Ophthalmic Solution had ≥ 1 line of improvement in distance-corrected near visual acuity (DCNVA) at day 15 in both photopic & mesopic conditions.

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**Photopic Conditions (Study Eye):**

- Placebo (n = 20): 20% improvement ≥ 1 line, 0% ≥ 2 lines, 0% ≥ 3 lines.
- 1% PMOS (n = 19): 63% improvement ≥ 1 line.

*P = 0.0259

**Mesopic Conditions (Study Eye):**

- Placebo (n = 20): 15% improvement ≥ 1 line, 5% ≥ 2 lines, 0% ≥ 3 lines.
- 1% PMOS (n = 19): 58% improvement ≥ 1 line.

*P = 0.0143
SECONDARY ENDPOINT: OVERALL SAFETY & TOLERABILITY

No SAEs, Minimal AEs, And No Changes In BP & Heart Rate Observed With Phentolamine Mesylate Ophthalmic Solution

<table>
<thead>
<tr>
<th>Adverse Effect (AE)</th>
<th>Phentolamine (n=19)</th>
<th>Placebo (n=20)</th>
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<tbody>
<tr>
<td>Conjunctival Hyperemia</td>
<td>3 (16%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Eye Pruritus</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Instillation site burn/pain</td>
<td>3 (16%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
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Mean Systolic Blood Pressure

Mean Heart Rate (beats/min)

Note: Mean Diastolic Blood Pressure also demonstrated no significant difference between treatment arms.
SECONDARY ENDPOINT (SAFETY): CONJUNCTIVAL HYPEREMIA

Phentolamine Mesylate Ophthalmic Solution Dosed At Bedtime Did Not Demonstrate A Statistically Significant Difference From Placebo For Redness At Day 8 And Day 15.

Percent of Subjects with Conjunctival Hyperemia at 8am in the Study Eye

Day 8
- Placebo: 10%
- 1% PMOS: 10%

Day 15
- Placebo: 10%
- 1% PMOS: 10%

p=0.3899  p=0.3476
CONCLUSIONS

• IOP Findings
  • IOP endpoint not met as change from baseline in mean diurnal IOP was not significantly different between arms
  • However, post-hoc analysis showed a reduction in IOP favoring PMOS observed in patients with IOPs < 24 mmHg

• Additional Efficacy Findings
  • Consistent with prior trials, a mean reduction in pupil diameter of approximately 20% (~1 mm or more) was seen with PMOS vs. placebo
    • One-third of subjects in PMOS arm had ≥ 30% reduction in pupil diameter
  • Daily bedtime dose demonstrated sustained pupil diameter effects over 24 hours
  • Statistically significant 1-line-or-greater improvement in DCNVA with PMOS

• Safety Findings
  • Consistent with prior trials, all TEAEs were mild in severity
  • PMOS dosed at bedtime did not demonstrate a statistically significant difference in redness from placebo
  • No serious TEAEs and no systemic effects of BP/HR observed with PMOS
  • No worsening in visual acuity

• Next Steps
  • Planning Phase 3 registration clinical trials to investigate the effect of 1% Phentolamine Mesylate Ophthalmic Solution (PMOS) in patients with dim light/night vision disturbances
  • Planning Phase 2 trial in presbyopia with another miotic agent to achieve the pinhole size for near vision improvement
THANK YOU

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