Phase 2 Clinical Trial To Evaluate The Efficacy Of Phentolamine Ophthalmic Solution And Low-Dose Pilocarpine For The Treatment Of Presbyopia

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- Sun Pharma
- TearLab
- Thea Pharm
Phentolamine Ophth. Solution (POS) + Low-Dose Pilocarpine (LDP) Combination

Moderate Use Of Iris Dilator And Iris Sphincter Muscles To Improve Near Vision

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**0.75% POS**

- Iris Dilator Muscle Inhibition
- Alpha1/2 antagonist approved decades ago 505(b)(2)
- Novel MOA on iris dilator with 24+ hour durability with moderate 1+mm pupil reduction
- No daytime redness with chronic evening dosing of POS
- Well-tolerated with no systemic effects
- Stable, preservative-free, single use vial

**0.4% LDP**

- Iris Sphincter Muscle Activation
- Cholinergic agonist approved decades ago 505(b)(2)
- Known MOA on sphincter muscle with more potent miotic effects at approved doses (1%, 2%, 4%)
- Chronic daily dosing of LDP in daytime
- Low concentration avoids known tolerability issues:
  - headache and browache
  - redness
  - accommodative spasm causing loss of distance vision especially at night

Source: POS (Nyxol®) data from 8 completed trials; Pilocarpine Product label

1.5 to 2.5 mm PD reduction moves toward the pin-hole (1.6 to 2.5 mm, up to <3 mm)

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Presbyopia VEGA-1 Phase 2 Design

Randomized, Double-Masked, Placebo-Controlled Multi-Center One-Week Trial

Endpoints

Primary: % of subjects with ≥ 3 lines of improvement in distance-corrected near visual acuity comparing POS + LDP vs placebo alone at 1 hour

Secondary:
• % of subjects with ≥ 2 and ≥ 3 lines gained at time points from 30 min to 6 hours in photopic and mesopic lighting comparing POS + LDP vs placebo, POS alone, and LDP alone
• No loss of distance vision
• Pupil diameter at time points
• Safety and tolerability (redness)

Eligibility Criteria

- Males or females ≥ 40 and ≤ 64 years of age
- BCDVA of 0.0 LogMAR (20/20 Snellen equivalent) or better in each eye under photopic conditions
- DCNVA of 0.4 LogMAR (20/50 Snellen equivalent) or worse under photopic conditions in each eye & binocularly
# Demographics and Baseline Characteristics

*Treatment And Placebo Arms Were Balanced In the VEGA-1 Phase 2 Clinical Trial*

<table>
<thead>
<tr>
<th></th>
<th>Placebo Alone N=43</th>
<th>POS Alone N=30</th>
<th>LDP Alone N=31</th>
<th>POS+LDP Alone N=43</th>
<th>Total N=147</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years): Median (Range)</strong></td>
<td>52 (42-62)</td>
<td>54 (41-60)</td>
<td>52 (44-64)</td>
<td>53 (43-63)</td>
<td>53 (41-64)</td>
</tr>
<tr>
<td><strong>Sex: Male n (%) Female n (%)</strong></td>
<td>15 (35%) 28 (65%)</td>
<td>7 (23%) 23 (77%)</td>
<td>13 (42%) 18 (58%)</td>
<td>5 (12%) 38 (88%)</td>
<td>40 (27%) 107 (73%)</td>
</tr>
<tr>
<td><em><em>Race: White n (%) Other</em> n (%)</em>*</td>
<td>37 (86%) 6 (14%)</td>
<td>26 (87%) 1 (3%)</td>
<td>28 (90%) 3 (10%)</td>
<td>40 (93%) 3 (7%)</td>
<td>131 (89%) 15 (11%)</td>
</tr>
<tr>
<td><strong>Dark Iris Color: n (%)</strong></td>
<td>18 (42%)</td>
<td>12 (40%)</td>
<td>12 (39%)</td>
<td>18 (42%)</td>
<td>60 (41%)</td>
</tr>
<tr>
<td><strong>Light Iris Color: n (%)</strong></td>
<td>25 (58%)</td>
<td>18 (60%)</td>
<td>19 (61%)</td>
<td>25.1 (58%)</td>
<td>87 (59%)</td>
</tr>
<tr>
<td><strong>Photopic DCNVA Mean Letters read- Binocular (Snellen Equiv.) 70 letters = 20/20</strong></td>
<td>46 (20/63)</td>
<td>45 (20/63)</td>
<td>48 (20/63)</td>
<td>46 (20/63)</td>
<td>46 (20/63)</td>
</tr>
<tr>
<td><strong>Photopic BCDVA Mean Letters read- Binocular (Snellen Equiv.) 55 letters = 20/20</strong></td>
<td>62 (20/15)</td>
<td>61 (20/15)</td>
<td>60 (20/15)</td>
<td>61 (20/15)</td>
<td>61 (20/15)</td>
</tr>
<tr>
<td><strong>Photopic Pupil Diameter Mean (mm)</strong></td>
<td>4.3</td>
<td>4.5</td>
<td>4.3</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Mesopic Pupil Diameter Mean (mm)</strong></td>
<td>5.1</td>
<td>5.0</td>
<td>5.0</td>
<td>5.1</td>
<td>5.1</td>
</tr>
<tr>
<td><strong>IOP (mmHg)</strong></td>
<td>13.5</td>
<td>14.8</td>
<td>13.9</td>
<td>14.4</td>
<td>14.1</td>
</tr>
</tbody>
</table>

Source: VEGA-1 TLR Table 14.1.2.2 Demographics and Baseline Characteristics (PP Population). Snellen Conversion Chart.
Primary Endpoint: % Of Subjects ≥ 15 Letter Gain In Photopic DCNVA At 1 Hour

Primary Endpoint Was Met For POS + LDP Gaining ≥ 15 Letters Near Vision In PP Population

VEGA-1 Phase 2 Trial

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Placebo (n=43)</th>
<th>POS+LDP (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Note: PP population differs from mITT by only one subject; results were essentially identical.

Source: VEGA-1 TLR Table 14.2.1.2 % of Subjects With Improvement From Baseline in Photopic DCNVA by Time Point (PP Population). 15 letters is 3 lines and 10 letters is 2 lines.
Secondary Endpoint: % Of Subjects $\geq$ 15 Letter Gain At All Timepoints

POS + LDP Had Strong Response With $\geq$ 15 Letter Gain From 30 Min To 6 Hours

VEGA-1 Phase 2 Trial

Percent of Subjects with $\geq$ 15 Letters DCNVA Improvement from Baseline (PP Population)

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Placebo (n=43)</th>
<th>POS+LDP (n=43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16%</td>
<td>14%</td>
<td>0.09</td>
</tr>
<tr>
<td>0.5</td>
<td>14%</td>
<td>14%</td>
<td>0.09</td>
</tr>
<tr>
<td>1</td>
<td>28%</td>
<td>61%</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>2</td>
<td>16%</td>
<td>16%</td>
<td>0.09</td>
</tr>
<tr>
<td>3</td>
<td>47%</td>
<td>47%</td>
<td>0.02</td>
</tr>
<tr>
<td>4</td>
<td>21%</td>
<td>21%</td>
<td>0.02</td>
</tr>
<tr>
<td>6</td>
<td>19%</td>
<td>37%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Durable benefit over 6 hours

Rapid onset of efficacy

Source: VEGA-1 TLR Table 14.2.1.2 Percent of Subjects with Improvement From Baseline in Photopic DCNVA by Time Point (PP Population). 15 letters is 3 lines.
Secondary Endpoint: Snellen Equiv. DCNVA Baseline vs. 1 Hour Post POS+LDP

POS+LDP Had A Dramatic Effect On Near Vision With A Clear Improvement Shift

26% Placebo Adjusted Response ≤ 20/40 for POS+LDP Combo at 1 Hour (p=0.02) Compared to AGN 13% Placebo Adjusted (p = 0.02) photopic DCNVA

Source: VEGA-1 TLR Table 14.2.24.1 Percent of Subjects with Photopic DCNVA by Time Point (PP Population); Novartis/Encore Materials, ASCRS 2021 Allergan Abstracts
Secondary Endpoint: % of Subjects $\geq$ 15 Letter Gain In Near & $\leq$ 5 Letter Loss In Distance

Phase 3 Approval Endpoint Also Showed Early Onset & Durable Near Vision Gain Without Loss Of Distance

### VEGA-1 Phase 2 Trial

#### Percent of Subjects with 15 Letter Improvement in DCNVA and $\leq$ 5 Letter Loss in BCDVA Binocular

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Placebo (n=43)</th>
<th>POS+LDP (n=43)</th>
<th>POS (n=30)</th>
<th>LDP (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>14%</td>
<td>33%</td>
<td>26%</td>
<td>28%</td>
</tr>
<tr>
<td>1</td>
<td>14%</td>
<td>42%</td>
<td>30%</td>
<td>14%</td>
</tr>
<tr>
<td>2</td>
<td>14%</td>
<td>39%</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

- $p<0.0001$
- $p=0.03$
- $p=0.008$
- $p=0.004$
- $p=0.01$
- $p<0.0001$
- $p=0.2$
- $p=0.001$
- $p=0.0001$
- $p=0.06$
- $p=0.0009$

Source: VEGA-1 TLR Table 14.2.2.2 Percent of Subjects with $\geq$ 15 Letters of Improvement in Photopic DCNVA and $< 5$ Letters of Loss in Photopic Binocular BCDVA by Time Point (PP Population)
Secondary Endpoint: Change In Photopic/Mesopic BCDVA At 1 Hour
Treatment With POS And/Or LDP Did Not Reduce BCDVA And Had A Modest Beneficial Effect

VEGA-1 Phase 2 Trial

Percent of Subjects With Improvement or Loss From Baseline in Photopic BCDVA at 1 hour

Source: VEGA-1 TLR Table 14.2.8.1 and 14.2.10.1 Percent of Subjects With Improvement or Loss From Baseline in Photopic and Mesopic BCDVA by Time Point (PP)
Secondary Endpoint: Mean Pupil Diameter Over Time

Achieved Pupil Size ~2mm In POS+LDP Consistent With 3-line Improvement In Near Vision

Source: VEGA-1 TLR Table 14.2.12.1 Observed Values and Change from Baseline in Photopic Pupil Diameter by Time Point (PP Population)
Secondary Endpoint: Safety Findings

*POS+LDP Combination Was Well Tolerated With A Favorable Safety Profile In VEGA-1 Trial*

<table>
<thead>
<tr>
<th></th>
<th>Placebo Alone n=45</th>
<th>POS Alone n=30</th>
<th>LDP Alone n=31</th>
<th>POS+LDP n=44</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Treatment Emergent Adverse Events (n)</strong></td>
<td>4</td>
<td>18</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td><strong>TEAEs by Severity (n [%])</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (2.2%)</td>
<td>6 (20%)</td>
<td>6 (19.4%)</td>
<td>13 (29.5%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (2.2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td><strong>AEs Occurring in ≥ 5% of subjects (n [%])</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instillation Site Pain (Mild)</td>
<td>1 (2.2%)</td>
<td>3 (10%)</td>
<td>0 (0%)</td>
<td>4 (9.1%)</td>
</tr>
<tr>
<td>Instillation Site Erythema (Mild)</td>
<td>0 (0%)</td>
<td>3 (10%)</td>
<td>2 (6.5%)</td>
<td>5 (11.4%)</td>
</tr>
<tr>
<td>Conjunctival Hyperemia (Mild)</td>
<td>0 (0%)</td>
<td>2 (6.7%)</td>
<td>0 (0%)</td>
<td>2 (4.5%)</td>
</tr>
<tr>
<td>Eye Disorders (Mild)</td>
<td>1 (2.2%)</td>
<td>2 (6.7%)</td>
<td>4 (12.9%)</td>
<td>5 (11.4%)</td>
</tr>
</tbody>
</table>

• No deaths, no serious AEs, and 1 withdrawal due to AEs (on POS alone)
• 0% Headaches or Browaches reported for POS+LDP and POS alone
• Only 1 subject in LDP alone arm reported mild headache
• Almost all AEs were mild and most common was mild instillation site discomfort
• Distance visual acuity not adversely affected (as shown earlier)
• No change in IOP

Conjunctival Hyperemia CCLRU Scale for Reference

Source: VEGA-1 TLR Table 14.3.1.1 Overall Summary of Treatment Emergent Adverse Events (TEAE) (Safety Population)
Table 14.3.1.3 Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Severity (Safety Population)
Summary Of Positive VEGA-1 Phase 2 Results

POS + LDP Efficacy Data With A Favorable Safety Profile In Presbyopia

- **Met the primary endpoint** with statistical significance for binocular photopic near vision at 1 hour
  - 61% POS+ LDP gained 15 letters (3 lines) or more vs. 28% Placebo (33% Placebo Adjusted)
- **Met the Phase 3 co-primary endpoint** vs. placebo gaining 15 letters (3 lines) near vision with less than 5 letters of distance vision loss
- **Met many key secondary endpoints**
  - Rapid onset at 30 min
  - Durable near vision improvement through at least 6 hours
  - POS+LDP was numerically better than each component through 2-hours
  - A majority of subjects treated with the combination achieved near acuity of 20/30 or better
  - Sustained significant reduction in PD over at least 18 hours due the durability effects of POS
  - Near vision efficacy seen monocularly and binocularly
  - Also, efficacy data in both light and dark iris colors
- **Favorable safety profile for POS + LDP**
  - No serious AEs
  - No systemic AEs were observed in >5% subjects
  - No headaches, no browaches, and no blurry vision AEs were reported
  - Only mild, transient conjunctival hyperemia observed in <5% of subjects
- **Positive Phase 2 results lead to advancing Phase 3 presbyopia program**
Thank you for your attention!

DR. JAY S. PEPOSE

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