Preliminary Findings from a Phase 1 Trial Evaluating the Safety, Tolerability and Biological Activity of OTX-TKI, a Hydrogel-Based, Sustained-Release Intravitreal Axitinib Implant, in Subjects with Neovascular Age-Related Macular Degeneration

FINANCIAL DISCLOSURES

Adverum: Consultant/Advisor, Equity Owner
Alcon Laboratories, Inc.: Consultant/Advisor, Equity Owner
Alimera Sciences, Inc.: Consultant/Advisor
Allergan: Consultant/Advisor
Amgen: Consultant/Advisor
Apellis: Consultant/Advisor
Bausch+Lomb: Consultant/Advisor
Clearside: Consultant/Advisor
Eyepoint: Consultant/Advisor
Genentech: Consultant/Advisor, Grant Support
Helio Vision: Consultant/Advisor
Iridex: Consultant/Advisor
InFocus: Consultant/Advisor, Equity Owner
Notal Vision, Inc.: Consultant/Advisor
Novartis Pharmaceuticals: Consultant/Advisor, Equity Owner
Ocular Therapeutix: Consultant/Advisor
Regeneron Pharmaceuticals, Inc.: Consultant/Advisor, Equity Owner
Regenxbio: Consultant/Advisor
Replenish: Consultant/Advisor, Equity Owner, Patents/Royalty
Santen, Inc.: Consultant/Advisor
Visionary Ventures: Consultant/Advisor, Equity Owner
OTX-TKI TAKE-HOME MESSAGES

- **OTX-TKI was generally well tolerated**
  To date, observed to have a favorable safety profile in both cohorts

- **Preliminary biological signal of clinically-meaningful decrease in retinal fluid**
  Some subjects showed a decrease in intraretinal or subretinal fluid by 2 months

- **Therapy durability suggests extended duration of action**
  In the higher dose cohort, several subjects demonstrated durability of therapy for up to 4.5 months. Patients still being followed in cohort 2, to be further determined

- **Consistent bio-resorption observed**
  Implant biodegraded in all subjects in cohort 1 by 9-10.5 months

- **Implant location observation suggests limited movement**
  Implant was able to be adequately monitored

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**Study is ongoing; continued long-term evaluation of both cohorts**

- Need to establish durability of treatment
- Identify Maximum Tolerated Dose (MTD)
- Understand utility of OTX-TKI with anti-VEGF injection
Unmet Need in Retinal Disease

Problem with Immediate-Release Injections

- Repeated intravitreal injections due to rapid vitreous clearance may cause side effects such as endophthalmitis, damage to the lens, and retinal detachment

- Patient complaints include discomfort, eye pain, decreased vision, increased photosensitivity, and floaters

A New Therapy is Needed

OTX-TKI (Tyrosine Kinase Inhibitor Implant) for Intravitreal Injection

- Polyethylene glycol-based hydrogel fiber containing TKI that biodegrades via ester hydrolysis in the presence of water
- Targeting sustained TKI release for 3 to 6+ months
- Hydrogel degrades and is cleared from the vitreous
- Broader anti-angiogenic profile than anti-VEGF alone and longer duration with sustained delivery
- Small fiber (27-30G needle) with minimal/no visual impact; product can be monitored by physician
- Preservative-free
- Systemic TKI efficacy established in oncology
- Different target than traditional VEGF therapies

Tyrosine Kinase Inhibitors Act Directly on VEGF Receptors

- Axitinib targets VEGFR-1, 2, 3 and PDGFR signaling
- Axitinib acts intracellularly and interferes with cellular signaling through inhibition of the receptor tyrosine kinases
- Anti-VEGF sequesters extracellular VEGF ligands
- Potential for “time to biological onset of action” variability based on intracellular vs extracellular MOA
- Repeated intravitreal injections due to rapid vitreous clearance may cause side effects such as endophthalmitis, damage to the lens, and retinal detachment
- Patient complaints include discomfort, eye pain, decreased vision, increased photosensitivity, and floaters

OTX-TKI Phase 1 Study

**DESIGN**
- Open-label, dose-escalation, feasibility study
- 5 sites in Australia
- 9-month study
- One eye per patient treated
- Key Inclusion criteria:
  - Active primary sub foveal neovascularization (SFNV) secondary to AMD – previously treated or naïve subjects but with retinal fluid present

**OBJECTIVES**
- Safety, tolerability, and biological activity
- Safety evaluations at all visits; mean change in central subfield thickness (CSFT) measured by SD-OCT, BCVA, and clinically-significant leakage on FA and/or OCT-A at 6 months

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**Research Question:**
Does axitinib (a tyrosine kinase inhibitor; TKI) injected into the eye have biological activity?

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**EVALUATION VISITS**
- **Cohort 1:** 200 µg (n=6)
- **Cohort 2:** 400 µg (n=6)
- **Cohort 3a:** 600 µg (n=6)
- **Cohort 3b:** 400 µg + anti-VEGF (n=6)

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### Cohort 1 & 2: Safety Overview

#### Total Adverse Events

<table>
<thead>
<tr>
<th>Number of subjects with:</th>
<th>OTX-TKI 200 µg N=6</th>
<th>OTX-TKI 400 µg N=6</th>
<th>Total (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Events (AEs)</td>
<td>17</td>
<td>14</td>
<td>31</td>
</tr>
<tr>
<td>Ocular AEs</td>
<td>15</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Serious Ocular AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>By severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>14</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Opacities around OTX-TKI implant</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tiny pigmented Keratic Precipitates*</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Foreign material (fiber and reflective particles)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Event did not require treatment

Interim look; Unmonitored data
## Cohort 1 & 2: Safety Overview
### Ocular Adverse Events (Study Eye)

*To date, no inflammation requiring steroid treatment has been observed in any subject*

<table>
<thead>
<tr>
<th>Number of subjects with:</th>
<th>OTX-TKI 200 µg N=6</th>
<th>OTX-TKI 400 µg N=6</th>
<th>Total (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiny pigmented Keratic Precipitates</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Subconjunctival hemorrhage following injection</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Subretinal hemorrhage</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pain following injection</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Progressive/increased subretinal fluid</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Discomfort/difficulty opening eyes upon waking</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Opacities around OTX-TKI implant</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Visual distortion</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Increased geographic atrophy</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Foreign material (fiber and reflective particles)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Cohort 2: SD-OCT Evaluation

Subject 1: History of EYLEA Q4 Weeks (OD)  

<table>
<thead>
<tr>
<th>Time</th>
<th>CSFT (µm)</th>
<th>BCVA</th>
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<tbody>
<tr>
<td>BASELINE</td>
<td>473</td>
<td>-0.04 (20/18)</td>
</tr>
<tr>
<td>MONTH 2</td>
<td>368</td>
<td>-0.06 (20/17)</td>
</tr>
<tr>
<td>MONTH 3</td>
<td>337</td>
<td>-0.06 (20/17)</td>
</tr>
<tr>
<td>MONTH 4.5</td>
<td>224</td>
<td>0.30 (20/40)</td>
</tr>
<tr>
<td>MONTH 5</td>
<td>225</td>
<td>-0.02 (20/19)</td>
</tr>
</tbody>
</table>

Subject 2: Treatment Naïve Subject (OS)  

<table>
<thead>
<tr>
<th>Time</th>
<th>CSFT (µm)</th>
<th>BCVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE</td>
<td>513</td>
<td>1.40 @ 1m (20/502)</td>
</tr>
<tr>
<td>MONTH 2</td>
<td>343</td>
<td>1.40 @ 1m (20/502)</td>
</tr>
<tr>
<td>MONTH 3</td>
<td>316</td>
<td>1.48 @ 1m (20/604)</td>
</tr>
<tr>
<td>MONTH 4.5</td>
<td>354</td>
<td>1.36 @ 1m (20/458)</td>
</tr>
</tbody>
</table>

Received anti-VEGF injection
Change in Best Corrected Visual Acuity and Central Subfield Thickness Values: Cohort 2

*All BCVA and CSFT values compared to Baseline visit

NOTE: Interim review, unmonitored data

*Denotes administration of rescue therapy
OTX-TKI Conclusions

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