Evaluating Safety, Tolerability and Biological Activity of OTX-TKI, a Hydrogel-Based, Sustained-Release Intravitreal Axitinib Implant, in Subjects with Neovascular Age-Related Macular Degeneration

Interim Analysis of a Phase 1 Clinical Trial

**UNMET NEED IN RETINAL DISEASE**

**Problem with Immediate-Release Injections**

- Repeated intravitreal anti-VEGF injections are necessary to reach and maintain effective concentrations due to rapid vitreous clearance.¹⁻³
- Multiple visits and injections challenging for patients/families, 98% of retina specialists prefer treat and extend (TAE) paradigm³

**Tyrosine Kinase Inhibitors Act Directly on VEGF Receptors⁵**

- Axitinib targets VEGFR-1, 2, 3 and PDGFR signaling
- Axitinib acts intracellularly and interferes with cellular signaling through inhibition of the receptor tyrosine kinases, potentially varying the “time to biological onset of action” based on intracellular vs extracellular MOA of anti-VEGF
- Axitinib is more potent compared to other TKIs (e.g., sunitinib, sorafenib and pazopanib)⁶ and has greater biocompatibility with ocular cell lines⁷

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

Hydrogel Implant incorporates axitinib, a small molecule tyrosine kinase inhibitor, delivered by intravitreal injection

- Polyethylene glycol-based hydrogel fiber containing TKI biodegrades via ester hydrolysis in the presence of water
- Goal of sustained TKI release for 4 to 6+ months
- Hydrogel degrades; cleared from the vitreous
- Potential for broader anti-angiogenic profile Vs anti-VEGF
- Goal of longer duration with sustained delivery without surgical intervention
- Small fiber (minimal/no visual impact; product can be monitored by physician)
- Preservative-free
- Systemic TKI efficacy established in oncology
Question: Does axitinib (a tyrosine kinase inhibitor; TKI) injected into the eye have biological activity?

**DESIGN**
- Open-label, dose-escalation, feasibility study
- 5 sites in Australia
- 9-month study
- One eye per patient treated
- Key Inclusion criteria:
  - Active primary subfoveal 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

**EVALUATION VISITS**
- Screening
- OTX-TKI (actively enrolling subjects)
- Baseline
- Day 3
- Day 7
- Month 1
- Month 2
- Month 3
- Month 4.5
- Month 6
- Month 7.5
- Month 9
- Month 11

**Cohorts**
- Cohort 1: 200 µg (n=6)
- Cohort 2: 400 µg (n=7)
- Cohort 3a: 600 µg
- Cohort 3b: 400 µg + anti-VEGF

**PHARMACOKINETIC (PK) SAMPLING TIMEPOINTS (Cohorts 1 and 2 only)**
- Month 11

**NOTE:** Interim review, unmonitored data; Data cut on October 23rd 2020
Cohort 1 & 2: MEAN CHANGE IN CENTRAL SUBFIELD THICKNESS VALUES & BEST CORRECTED VISUAL ACUITY

*All BCVA and CSFT values compared to Baseline visit

NOTE: Interim review, unmonitored data; Data cut on October 23rd, 2020 (Cohorts 1 & 2 only)
COHORT 2 (400 µg) & 3a (600 µg): SD-OCT EVALUATION

**Cohort 2: Subject 1 (OD): History of Aflibercept Q4 Weeks for 16 months**

<table>
<thead>
<tr>
<th>Phase</th>
<th>CSFT (µm)</th>
<th>BCVA</th>
</tr>
</thead>
<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 4.5</td>
<td>224</td>
<td>0.30 (20/40)</td>
</tr>
<tr>
<td>Month 6</td>
<td>234</td>
<td>-0.08 (20/17)</td>
</tr>
<tr>
<td>Month 7.5</td>
<td>295</td>
<td>-0.08 (20/17)</td>
</tr>
<tr>
<td>Month 9</td>
<td>272</td>
<td>-0.06 (20/17)</td>
</tr>
<tr>
<td>Month 11</td>
<td>275</td>
<td>0.02 (20/21)</td>
</tr>
</tbody>
</table>

**Cohort 3a: Subject 1 (OS): Treatment Naïve Subject**

<table>
<thead>
<tr>
<th>Phase</th>
<th>CSFT (µm)</th>
<th>BCVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>484</td>
<td>0.58 (20/76)</td>
</tr>
<tr>
<td>Month 2</td>
<td>236</td>
<td>0.22 (20/33)</td>
</tr>
<tr>
<td>Month 3</td>
<td>232</td>
<td>0.24 (20/40)</td>
</tr>
</tbody>
</table>

*NOTE: Interim review; unmonitored data; Data cut on October 23rd, 2020*
### Adverse Events

<table>
<thead>
<tr>
<th>Number of subjects with:</th>
<th>Cohort 1 200 µg n=6</th>
<th>Cohort 2 400 µg n=7</th>
<th>Total n=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Events (AEs)</td>
<td>14</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>Ocular AEs</td>
<td>12</td>
<td>12</td>
<td>24</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>12</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related Ocular AEs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

- No subjects had IOP elevation
- No subjects needed ocular steroids

### Percentage of Subjects Without Needing Rescue Medications

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>At 3 months % (n/N)</th>
<th>At 6 months % (n/N)</th>
<th>At 7.5 months % (n/N)</th>
<th>At 9 months % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 (200 µg)</td>
<td>66.7 (4/6)</td>
<td>50 (3/6)</td>
<td>50 (3/6)</td>
<td>50 (3/6)</td>
</tr>
<tr>
<td>Cohort 2 (400 µg)</td>
<td>71.4 (5/7)</td>
<td>57.1 (4/7)</td>
<td>42.9 (3/7)</td>
<td>20 (1/5)*</td>
</tr>
</tbody>
</table>

* Only 5 of 7 subjects reached 9 months in the study.

**NOTE:** Interim review, unmonitored data; Data cut on October 23rd, 2020. (Cohorts 1 & 2 only)

**Pharmacokinetics**

Plasma concentrations of axitinib were below the limit of quantification of assay (BLQ) <0.1 ng/ml at all sampled timepoints in all subjects in Cohorts 1 & 2.
OTX-TKI CONCLUSIONS:

- **OTX-TKI was generally well tolerated**
  To date, observed to have a favorable safety profile, with no ocular serious adverse events; No measurable systemic exposure to axitinib observed in Cohorts 1-2

- **Preliminary biological signal of clinically-meaningful decrease in retinal fluid**
  Some subjects showed a decrease in intraretinal or subretinal fluid by 2 months in 400 µg Cohort 2 and 600 µg Cohort 3

- **Therapy durability suggests extended duration of action**
  In the 400 µg Cohort 2, several subjects demonstrated durability of therapy for up to 6 months and one subject demonstrated durability to 11 months

- **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: Next steps**

- **Continued long-term evaluation of OTX-TKI cohorts:** Need to establish durability of treatment
- **New high-dose 600 µg Cohort 3 currently enrolling:** Evaluate tolerability with a higher dose & explore OTX-TKI with an initial anti-VEGF injection

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