Suprachoroidal CLS-AX (axitinib injectable suspension) as a Potential Long-Acting Therapy for Neovascular Age-Related Macular Degeneration (nAMD)

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Financial Disclosures

- **R. Bhisitkul:**
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Axitinib Inhibits VEGF 1, 2, 3 Receptors

Current AMD Therapies predominantly focus on VEGF-A blockade, not VEGF Receptors

- Anti-VEGF-A increases VEGF-C $^1$ & VEGF-D$^2$
- Broad VEGF blockade may improve outcomes
- A Phase 2 study yielded better AMD outcomes with anti-VEGF-A,C,D vs anti-VEGF-A$^3$

Suprachoroidal Axitinib provides broad VEGF blockade

- Inhibits VEGFR-1, VEGFR-2, VEGFR-3
- Inhibited corneal, retinal, and choroidal angiogenesis in animal models$^4$$^8$
- More effective than other TKIs for experimental corneal neovascularization in animal models
- Better ocular cell biocompatibility than other TKIs$^9$

Sources:
Axitinib inhibits angiogenic sprouts more potently than anti-VEGF-A, anti-PDGF-B and combination thereof.

Topical axitinib more effectively inhibits experimental murine corneal neovascularization than sunitinib, sorafenib (at same dose)

Figure 5. Selection of tyrosine kinase receptor inhibitor drugs. Screening of tyrosine kinase inhibitor drugs loaded nanowafers for their relative therapeutic efficacy in inhibiting corneal neovascularization after 10 days of treatment. Representative 3D reconstructed corneal images of fluorescence confocal microscopy: (a) healthy cornea (control); (b) untreated ocular burn (control); (c) blank PVA-NW; (d) Sora-NW; (e) Suni-NW; (f) Axi-NW. (g) Quantification of corneal neovascularization volume. n = 3 animals, *P < 0.05 vs OB control and P < 0.05 vs PVA-NW, **P < 0.01. All error bars represent standard deviation from the mean.
DIRECTED TO CHORIO-RETINA

The macula and posterior pole are the key locations of many common retinal diseases

for efficacy

COMPARTMENTALIZED

Drug is compartmentalized in the suprachoroidal space, away from non-diseased anterior segment tissues

for safety

BIOAVAILABLE

Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, providing the choroid and adjacent areas with drug

for durability

Suprachoroidal Injection of CLS-AX: Targeted, Durable in Preclinical Model

Targeted Delivery relative to IVT at Same Dose
- 11X SCS vs IVT (Retina / RPE-choroid-sclera)
- 0.003X SCS vs IVT (Vitreous humor)

Aqueous Humor
SCS CLS-AX at or below level of detection

Values: area under the curve ratios, SCS / IVT
Rabbit Model
SCS: 1 mg/eye, 100 μL | IVT: 1 mg/eye, 25 μL
Single bilateral injection, 1-wk rabbit PK studies

Durable, High Drug Levels Maintained in the Retina

Abbreviations:
Source: Based on Clearside Biomedical preclinical data

- High Retina Levels: Sufficient to block VEGF pathway
- Low Plasma Levels: <1 ng/mL
Suprachoroidal Injection of CLS-AX: Iso-lectin B4 staining shows reduction in retinal vascular staining in pigs

Axitinib inhibits blood vessel growth
(Iso-lectin B4 staining on retina flatmount)

Control
(vehicle treated)

CLS-AX treated eyes

#1

#2

Large area of vascular staining (red)

Significant reduction in vascular staining (red)

Abbreviations: CLS-AX: Axitinib injectable suspension
Source: Based on Clearside Biomedical preclinical data
CLS-AX Phase 1/2a Clinical Trial in Wet AMD

Trial Design
- Open-label study to assess the safety and tolerability of single doses of CLS-AX administered through suprachoroidal injection
- 3 Cohorts of 5 patients each: n=15
- Dose-escalation will begin at 0.03 mg CLS-AX; proceed to next cohort following review by Safety Monitoring Committee

Cohort Enrollment and Treatment

<table>
<thead>
<tr>
<th>Screening</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg aflibercept dosed at screening (day -28)</td>
<td>CLS-AX dosed at baseline</td>
<td>Aflibercept as needed</td>
<td>Aflibercept as needed</td>
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Key Inclusion Criteria
- Active subfoveal choroidal neovascularization secondary to AMD
- Two or more anti-VEGF treatments in the 4 months preceding the screening visit with a meaningful response
- BCVA score of ≥ 20 letters (20/400) and ≤ 75 letters (20/32) with < 5 letters change between screening and baseline to ensure patient stability after anti-VEGF

Primary Endpoint
- Safety and tolerability over 3 months of a single dose of suprachoroidally injected CLS-AX following IVT aflibercept

Note: aflibercept is dosed via intravitreal injection (IVT); CLS-AX is dosed via suprachoroidal injection
Axitinib (CLS-AX) for Suprachoroidal Injection

**Potential Benefits**

- Intrinsic high potency, pan-VEGF inhibition through receptor blockade
- Targeted therapy for affected tissue layers via suprachoroidal injection
- Prolonged duration observed in PK studies
- IND accepted, Phase 1/2a clinical trial in nAMD to begin enrolling in 2020