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

David M Brown MD
Thomas Ciulla MD MBA, Viral Kansara PhD
Financial Disclosures

• D. Brown: Relevant: Clearside Biomedical, Advisor, Clinical Trial Support

• T. Ciulla:
  – Clearside Biomedical, Inc.
    • Employee, stockholder
    • Salary, stock, stock options

• V. Kansara:
  – Clearside Biomedical, Inc.
    • Employee, stockholder
    • Salary, stock, stock options
Axitinib for Suprachoroidal Injection (CLS-AX): A Potential Solution for Treatment Burden

Primary Need
Durable maintenance of vision and reduced treatment burden in neovascular AMD patients
Suprachoroidal Injection Procedure
Core Advantages of Treating Via the Suprachoroidal Space

**TARGETED**
The back of the eye is the location of many irreversible and debilitating visual impairments\(^1\)

**COMPARTMENTALIZED**
Drug is compartmentalized in the suprachoroidal space, which helps keep it away from non-diseased tissues\(^2\)

**BIOAVAILABLE**
Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, bathing the choroid and adjacent areas with drug\(^3\)

---

Axitinib: A Novel Tyrosine Kinase Inhibitor (TKI)

- Anti-VEGF-A upregulates VEGF-C & VEGF-D: TKIs block VEGF A/B/C
- Axitinib inhibits corneal, retinal and choroidal angiogenesis in multiple preclinical models
- Axitinib is more biocompatible with ocular cells than other TKIs
Bevacizumab injection increases angiogenic biomarkers in nAMD patients
Axitinib inhibits angiogenic sprouts more potently than anti-VEGF-A, anti-PDGF-B and combination thereof
# Tyrosine Kinase Inhibitors: Potency

**Table: Inhibitory concentrations (IC50 in nmol) for targets with multtargeted TKIs.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>VEGFR1</th>
<th>VEGFR2</th>
<th>VEGFR3</th>
<th>PDGFRα</th>
<th>PDGFRβ</th>
<th>c-Kit</th>
<th>RET</th>
<th>RAF</th>
<th>FLT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1–0.3</td>
<td>5</td>
<td>1.6</td>
<td>1.7</td>
<td>&gt;1000</td>
<td>NA</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>10</td>
<td>30</td>
<td>47</td>
<td>71</td>
<td>84</td>
<td>74</td>
<td>&gt;1000</td>
<td>NA</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>5–10</td>
<td>10</td>
<td>13</td>
<td>100–200</td>
<td>NA</td>
<td>1–10</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>NA</td>
<td>90</td>
<td>20</td>
<td>50–60</td>
<td>50–60</td>
<td>68</td>
<td>100–150</td>
<td>5–10</td>
<td>46</td>
</tr>
</tbody>
</table>

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

Figure 5

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.
Oral Axitinib caused 71% area regression of laser-induced CNV compared to vehicle-treatment (p < 0.001) in Mice.

In vitro safety evaluations of axitinib, pazopanib and sorafenib for intraocular use

Axitinib, pazopanib, or sorafenib (0.1 to 100 µg/mL)

- Primary human optic nerve head astrocytes
- Trabecular meshwork cells
- Retinal pigment epithelium
- Human corneal endothelial & lens epithelial cells
AMD Vascular Endothelial Growth Factor Treatment Approaches

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

Suprachoroidal Axitinib May Improve Outcomes with Its Broad VEGF Blockade

- Inhibits VEGFR-1, VEGFR-2, VEGFR-3
- Inhibited corneal, retinal, and choroidal angiogenesis in animal models\(^3\)-\(^7\)
- More effective than other TKIs for experimental corneal neovascularization in animal models
- Better ocular cell biocompatibility than other TKIs\(^8\)

Sources:
Suprachoroidal injection of axitinib (CLS-AX) provides targeted delivery relative to IVT injection at same dose

Values: area under the curve ratios, SCS / IVT

- SCS: 1 mg/eye, 100 µL
- IVT: 1 mg/eye, 25 µL

Single bilateral injection, 1-wk rabbit PK studies

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

- -
Plasma
SCS CLS-AX at or below level of detection

SCS: Suprachoroidal Injection
IVT: Intravitreal Injection
PK: Pharmacokinetic
CLS-AX: axitinib injectable suspension
LLOQ: lower limit of quantification, 0.15 mg/mL.
Suprachoroidal axitinib maintains levels above IC50 for 60+ days in rabbit model

Axitinib Concentration over Time
By Ocular Tissue

Axitinib Concentration over Time
By Ocular Tissue

Axitinib IC50: 0.12 ng/mL

Single bilateral SC injection
0.1 mL/eye
Group 1: 0.03 mg/eye
Group 2: 0.1 mg/eye
Suprachoroidal axitinib reduces CNV lesion severity versus control in rat model

**METHOD**
- Laser CNV: 4 lesions per eye
- \(N=20\) eyes (\(n=10\) specimens, bilateral SC injections)
- Two (2) doses, days 1 & 8, 0.4 mg/eye/dose

**RESULTS**
- At Day 21: CLS-AX lesion reduction in severe (Grade IV) lesions versus control – see graph

FLUOROSCEIN ANGIOGRAPHY GRADING SCALE

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CLS-AX</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Lesions Grade IV Day 21</td>
<td>88.8%</td>
<td>63.3%</td>
</tr>
</tbody>
</table>

\(<Fisher's Exact p-value = .0002>\)
Suprachoroidal axitinib reduces fluorescein leakage and new vessel growth in pig model

METHOD
• Laser CNV created 6 lesions per eye
• N=8 Weanling Pigs
  – OD: 4mg/ 0.1 mL Suprachoroidal CLS-AX
  – OS: 0.1 mL Saline
• Single dose followed by imaging at week 1 and week 2

RESULTS
• SC CLS-AX significantly reduced fluorescein leakage
  – 10.5% @ week 1 (p=0.009)
  – 16.0% @ week 2 (p=0.0015)
• SC CLS-AX significantly reduced growth of new blood vessels
  – 18% reduction vs. saline treatment (p=0.03)
Suprachoroidal axitinib: Iso-lectin B4 staining shows reduction in vascular staining in pigs

<table>
<thead>
<tr>
<th>Axitinib inhibits blood vessel growth (Iso-lectin B4 staining on retina flatmount)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong> (vehicle treated)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Large area of <em>vascular</em> staining (red)</td>
</tr>
</tbody>
</table>
Suprachoroidal Axitinib in Animal Models

Across all animal models

- Suprachoroidal axitinib was well tolerated in all species
- No overt signs of toxicity
- Sustained, high exposure observed in ocular tissues through 10 weeks
  - Highest levels in the sclera/choroid/RPE > retina > vitreous
- No quantifiable axitinib detected in plasma or aqueous humor
Conclusion

• Suprachoroidal CLS-AX has potential as a bi-annual therapy for nAMD
• Intrinsic high potency, pan-VEGF inhibition through receptor blockade
• Prolonged duration observed in PK studies
• Pharmacodynamic effect demonstrated in multiple animal models
• Targeted therapy for affected tissue layers via suprachoroidal injection
• IND submission is planned this year, followed by a Phase 1/2a clinical trial in neovascular AMD