Axitinib: A Novel TKI Delivered by Suprachoroidal Injection for AMD

David Brown, MD, FACS
Director of Clinical Research
Retina Consultants of Texas
Houston, TX
Angiogenesis Virtual Meeting
February 12 – 13, 2021
DB Financial Disclosures

Aerie (RG, C), Alcon/Novartis (RG, C), Alexion (C), Allegro (RG, C), Allergan (RG, C), Apellis (RG, C), Astellas (RG), Boehringer-Ingelheim (RG, C), Carl Zeiss Meditec (C), Clearside Biomedical (RG, E, C), Coda Therapeutics (C), Envista (C), 4D Molecular Therapeutics (C), Gemini Therapeutics (RG, C), Google/Verily (C), Genentech/Hoffman-La Roche (RG, C), Graybug (RG, C), Heidelberg Engineering (RG, C), Iconic (C), Irenix (E, C), Janssen (C), Johnson & Johnson (C), Kanghorn Pharma (RG, C), Kodiak Sciences (RG, C), Merck (C), NEI/NIH (RG), Nicox (C), Notal Vision (RG, C), Ohr (RG, C), Ophthotech, OPTOS/Nikon (RG, C), Optovue (RG, C), Pfizer (RG, C), PRN (C), Regeneron/Bayer (RG, C), RegenXbio (RG, C), Samsung Bioepsis (RG, C), Santen (RG, C), SciFlour Life Sciences (C), Second Sight (RG, C), Senju Pharmaceuticals (RG, C), Spark Bio (RG, C), Stealth Biotherapeutics (RG, C), Thrombogenics/Oxurion (RG, C), Tyrogenix (RG, C), Verseon (C), Wyle / NASA (C),

R – Research Grant to Institution.  E = Equity Options  C = Consultant / Scientific Advisory Board

Intellectual Property: Co-patent hold OPTOS “dewarping” algorithms
Inventor: Sub-retinal Injection Micro-kit for Gene Therapy/ Stem Cell Application
Key Takeaways: Axitinib

- **Pan-VEGF inhibition** versus focused VEGF-A inhibition
  - Axitinib is more effective than anti-VEGF-A in in-vitro angiogenesis model\(^1\)
- **Highly potent TKI**
  - >10x more potent than Sunitib and other TKIs (IC50 table)
  - More effective than Sunitib and other TKIs in preclinical angiogenesis model\(^2\)
- **Best biocompatibility** with ocular cells compared with other TKIs\(^3\)

---


Key Takeaways: Suprachoroidal Delivery of Axitinib

CLS-AX (axitinib injectable suspension) delivered via the SCS Microinjector® has potential as a durable therapy for nAMD

- **Targeted high levels in affected tissues via the suprachoroidal space (SCS)**
  - 11x higher in affected tissues than IVT
- **Compartmentalized** delivery to affected posterior tissues
  - Minimizes vitreous floaters, snow globe effect and corneal and anterior segment exposure
- **Pharmacodynamic effect** demonstrated in multiple animal models
- **Prolonged duration** observed in PK studies
  - >1,000 suprachoroidal injections completed to date with the SCS Microinjector®
  - Phase 1/2a clinical trial in nAMD currently enrolling

Sources: Clearside Biomedical preclinical and clinical studies
Axitinib for Suprachoroidal Injection (CLS-AX):

Primary Needs
Durable maintenance of vision and reduced treatment burden in nAMD patients
Axitinib for Suprachoroidal Injection (CLS-AX):

The Opportunity

- Reduce patient burden from monthly injections
  - Pan-VEGF inhibition potentially more efficacious than current approaches
  - Potential to improve long-term, real-world visual outcomes for patients
- Provide physicians with ability to titrate dose based on patient need
- Protect the anterior chamber from exposure to TKIs

**Primary Needs**
Durable maintenance of vision and reduced treatment burden in nAMD patients

TKIs = Tyrosine Kinase Inhibitors
Core Advantages of Treating Via the Suprachoroidal Space

TARGETED
The back of the eye is the location of many irreversible and debilitating visual impairments¹

COMPARTMENTALIZED
Drug is compartmentalized in the suprachoroidal space, which helps keep it away from non-diseased tissues²

BIOAVAILABLE
Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, bathing the choroid and adjacent areas with drug³

for efficacy
for safety
for durability

PK = pharmacokinetic
Suprachoroidal Injection Procedure
Axitinib inhibits angiogenesis in preclinical models

- Axitinib is a pan-VEGF inhibitor
  - Anti-VEGF-A upregulates VEGF-C & VEGF-D
- Axitinib effectively inhibits corneal, retinal and choroidal angiogenesis in multiple preclinical models
- Axitinib has better biocompatibility with ocular cells than other TKIs
Bevacizumab increases angiogenic biomarkers in nAMD patients
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.

Oral Axitinib caused 71% area regression of laser-induced CNV compared to vehicle-treatment (p < 0.001) in Mice
Axitinib is >10x more potent than other TKIs

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
CLS-AX May Address Unmet Needs in Neovascular AMD

Treatment Burden

At 1 year, “real-world” patients receive only 6-7 injections\textsuperscript{4,5}

Under-treatment contributes to poor real-world outcomes

Limited Outcomes

At 1 year, with on-label anti-VEGF dosing \textsuperscript{1-3}:
~1/5 of patients lose BCVA
~1/2 do not achieve \geq 20/40
~2/3 do not gain \geq 3 lines BCVA

At 1 year, “real-world” patients improve by only 1-3 letters\textsuperscript{4,5}

Ceiling of Efficacy

Increased anti-VEGF dosage or more intense regimens yield no additional BCVA benefit\textsuperscript{1,6,7}

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\textsuperscript{1} & VEGF-D\textsuperscript{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\textsuperscript{3-7}
- More effective than other TKIs for experimental corneal neovascularization in animal models
- Better ocular cell biocompatibility than other TKIs\textsuperscript{8}

Sources:
Suprachoroidal injection of axitinib provides targeted delivery relative to IVT injection of equivalent dose.

Values: area under the curve ratios, SCS / IVT

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

- **11x SCS vs IVT**
  - Retina / RPE-choroid-sclera

- **0.003X SCS vs IVT**
  - Vitreous humor

**SCS**: Suprachoroidal Injection
**IVT**: Intravitreal Injection
**PK**: Pharmacokinetic
**CLS-AX**: axitinib injectable suspension
**LLOQ**: lower limit of quantification, 0.15 mg/mL

Single bilateral injection, 1-wk rabbit PK studies
Suprachoroidal injection of axitinib maintains levels above IC50 for 60+ days in rabbit model

Axitinib Concentration over Time

By Ocular Tissue

---

Axitinib Concentration (ng/mL or mg/g)

Time (days)

0.1 mL/eye
Group 1: 0.03 mg/eye
Group 2: 0.1 mg/eye

Axitinib IC50: 0.12 ng/mL
Suprachoroidal injection of 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 ANGIGRAPHY 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>
<tbody>
<tr>
<td><img src="image" alt="Grade 0" /></td>
<td><img src="image" alt="Grade I" /></td>
<td><img src="image" alt="Grade II" /></td>
<td><img src="image" alt="Grade III" /></td>
<td><img src="image" alt="Grade IV" /></td>
</tr>
</tbody>
</table>

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

*Fisher’s Exact p-value = .0002
Suprachoroidal injection of 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 injection of axitinib: Iso-lectin B4 staining shows reduction in vascular staining in pigs

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

- Control (vehicle treated)
  - Large area of vascular staining (red)
- CLS-AX treated eyes
  - #1: Significant reduction in vascular staining (red)
  - #2: Significant reduction in vascular staining (red)
Suprachoroidal injection of axitinib was well tolerated in animals

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
OASIS: Phase 1/2A clinical study to evaluate safety and tolerability of CLS-AX in nAMD

**Primary Endpoint**
Evaluate **safety and tolerability** over 3 months of a single dose of CLS-AX given via suprachoroidal injection following IVT aflibercept

**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
OASIS: Phase 1/2A clinical study to evaluate safety and tolerability of CLS-AX in nAMD

- Open-label study to assess the safety and tolerability of a single dose of CLS-AX administered through suprachoroidal injection
- 3 Cohorts with 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
Suprachoroidal Administration of CLS-AX: Potential Impacts in nAMD

• Suprachoroidal injection of CLS-AX may have the potential to:
  – Reduce treatment burden via durability in the SCS with the customized CLS-AX formulation
  – Improve patient outcomes via targeted delivery to diseased tissues and via potency relative to other tyrosine kinase inhibitors (TKIs)
  – Optimize safety with compartmentalized delivery
  – Minimize the ceiling of efficacy via pan-VEGF inhibition

• Phase 1/2a OASIS clinical trial for nAMD currently enrolling