Pharmacokinetics and Ocular Tolerability of Suprachoroidal CLS-AX (axitinib injectable suspension)

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1. Clearside Biomedical, Inc.
Financial Disclosures

- LM: Commercial Relationship(s); Clearside Biomedical, Inc.: Code E (Employment); Clearside Biomedical, Inc.: Code I (Personal Financial Interest)
- VK: Commercial Relationship(s); Clearside Biomedical, Inc.: Code E (Employment); Clearside Biomedical, Inc.: Code I (Personal Financial Interest)
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Inhibition of multiple VEGF receptors by CLS-AX may provide more complete blockade of the neo-angiogenesis process associated with nAMD versus currently available monotherapy

- Anti-VEGF-A drugs provide clinically sub-optimal efficacy and create an unmet need to develop new drugs and optimize drug delivery techniques with the goal of improving and maintaining visual acuity\(^1,3,5\)

- Axitinib is a potent and highly selective pan-VEGF receptor inhibitor\(^2\)

- Approved as an oral agent for renal cell carcinoma (Inlyta\(^\circledR\))

- A recent Phase 2 study demonstrated that targeting VEGF-A, VEGF-C & VEGF-D may result in improved efficacy compared to targeting VEGF-A alone\(^6\)

CLS-AX, administered suprachoroidally, has the potential to be a longer-acting therapy for nAMD Treatment

- Directly targets drug delivery to the back of the eye at high doses
- Potentially lower drug concentrations are needed at dosing compared to other routes of administration
- Minimizes drug exposure to non-diseased tissues
- Less invasive, in-office procedure

Reference: Clearside Biomedical Inc.
Suprachoroidal injection results in posterior and circumferential drug delivery

- Administered drug flows **posteriorly and circumferentially** in the suprachoroidal space within the posterior segment.
- Suprachoroidal injections are administered **4 – 4.5 mm from the limbus**, in the superior temporal quadrant.
- Each injection utilizes a proprietary **SCS Microinjector®** device.

Reference: Clearside Biomedical Inc.
Assess the durability (PK) and ocular tolerability of suprachoroidally administered CLS-AX (axitinib injectable suspension) in Dutch Belted (pigmented) rabbits during a 10-week study.
Methods

- CLS-AX was administered as a single bilateral injection to the suprachoroidal space at a dose of **0.03 mg/eye** or **0.1 mg/eye** (n=2 animals per group/ time-point)

- Clinical ocular exams were performed via **indirect ophthalmoscopy** and **slit-lamp biomicroscopy** at pre-dose and at wks. 1, 2 and 4. **OCT** was performed at pre-dose, wk. 6 and wk. 9 or 10

- **Plasma** samples were collected at predose and on days 2, 8, 15, 31, 45, 61, 66 and 68. **RPE-choroid-sclera (RCS), retina, aqueous humor** and **vitreous humor** samples were collected at terminal end-points

- Bioanalytical assays were performed via an LC-MS/MS method. Pharmacokinetic parameters were calculated using Phoenix WinNonlin (Version 6.4)
Generally, CLS-AX was well tolerated in DB rabbits

- No ophthalmic abnormalities were observed in any of the animals beyond wk. 1
  - On study day 3, there was an observation of moderately severe (+3) aqueous flare in one animal and mild (+1) conjunctival hyperemia in 5 animals

- OCT showed no evidence of abnormalities and choroidal or retinal degeneration for the duration of the study
CLS-AX injected suprachoroidally exhibited high, efficacious and sustained levels of axitinib to posterior ocular tissues

Axitinib concentrations within the RCS (drug depot) and retina were maintained 3-5 log orders above IC$_{50}$ over the study duration

Plasma and aqueous humor levels of axitinib were below the limit of quantitation
Area Under the Curve (AUC) values for CLS-AX were maintained at high levels in the Retina and RCS for the duration of the study.

**RCS (drug depot)**
- 0.1 mg dose: 55,600 µg.hr/g
- 0.03 mg dose: 8,120 µg.hr/g

**Retina**
- 0.1 mg dose: 674 µg.hr/g
- 0.03 mg dose: 414 µg.hr/g

**Vitreous Humor**
- No quantifiable axitinib beyond day 7 post-dose

No axitinib detected in the aqueous humor*  
No axitinib detected in plasma*  

*LLOQ = 1 ng/mL
Conclusion

CLS-AX administered via **suprachoroidal injection**, provided **sustained, targeted, high levels** of axitinib to the back of the eye and was **well-tolerated**. Given this durability, intrinsic high potency and pan-VEGF inhibition, CLS-AX administered suprachoroidally has the potential to be a bi-annual therapy for nAMD.
THANK YOU!