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

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Purpose:
As a potent, selective tyrosine kinase inhibitor, axitinib inhibits VEGF receptors 1, 2, and 3. Pan-VEGF inhibition may be more effective versus current anti-VEGF-A monotherapy, which upregulates other angiogenic factors, including VEGF-C and VEGF-D. In animal models, axitinib inhibits corneal, retinal, and choroidal angiogenesis. Consequently, the potential of CLS-AX as long-acting therapy for nAMD was assessed.

Methods:
Ocular distribution and pharmacokinetics of CLS-AX were assessed in Dutch-Belted pigmented rabbits. A suprachoroidal injection (100 µL) of CLS-AX was administered to each eye as 0.03 mg/eye (group 1) or 0.1 mg/eye (group 2). Efficacy of CLS-AX was evaluated in laser-induced choroidal neovascularization (CNV) models in rats and pigs. Brown Norway rats (n=10) were dosed once weekly for two weeks (0.2 mg/5 µL/eye), Weanling pigs (n=8) were treated with 4 mg of CLS-AX in the right eye (OD) and with saline in the left eye (OS). Retinal lesions were evaluated on fundus photography, fluorescein angiography (FA) and on retinal flat mount tissue (n=16 eyes) by measuring the Isolectin B4 (IB4) signal.

Results:
CLS-AX was generally well tolerated with no signs of toxicity. No axitinib was detected in either plasma or aqueous humor. Sustained, high exposure of axitinib was observed throughout the 10-week study, highest in the sclera/choroid/RPE > retina > vitreous; consequently, preliminary estimation of human ocular levels suggests that suprachoroidal CLS-AX may provide axitinib levels in choroid-retina that are >1000X higher than the in-vitro IC50 value, through 6 months. In rats, CLS-AX significantly decreased the incidence of severe (Grade IV) lesions by Day 21 versus the control. In pigs, CLS-AX significantly reduced fluorescein leakage at weeks 1 and 2 (p<0.009 for both) versus the control. IB4 quantification indicated significantly reduced growth of new blood vessels (p=0.03) at the site of the retinal laser lesion as compared to saline treatment.

Conclusions:
CLS-AX was well tolerated with durability in the suprachoroidal space. Results from the laser CNV studies corroborate others, showing inhibition of neovascularization in animal models. Given this PD effect, the ability to directly target affected tissues, and intrinsic highly potent pan-VEGF inhibition through receptor blockade, suprachoroidal CLS-AX has potential as long-acting therapy for nAMD.