Long-acting potential of suprachoroidally delivered BCX4161, a selective plasma kallikrein inhibitor, for diabetic macular edema

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BCX4161 is a potent and selective inhibitor of human plasma kallikrein activity. Elevated plasma kallikrein (PKal) levels have been reported in the vitreous humor of patients with diabetic macular edema (DME). Inhibition of PKal activity can be an effective therapeutic strategy for the treatment of DME. Suprachoroidal delivery of BCX4161 suspension may result in sustained and safe therapeutic drug levels in the retina-choroid. Hence, the purpose of this study was to assess ocular pharmacokinetics (PK), durability and tolerability of suprachoroidally delivered BCX4161 in rabbits.

Methods

- A 100µL volume of BCX4161 suspension was administered bilaterally to male Dutch-Belted (DB) pigmented rabbits (N=2-3/timepoint) at a dose of 0.5mg/eye using a proprietary SCS Microinjector® with a 700µm needle attached.
- Ocular tolerability was assessed via clinical examinations including slit-lamp, indirect ophthalmoscopy and IOP measurements.
- Ocular tissues (RPE-choroid-sclera(RCS), retina, vitreous humor, aqueous humor) and blood were collected at various predetermined intervals over the 3-month study duration.
- During tissue harvesting, an 8mm biopsy punch was used to collect the central retina and central RCS around the optic nerve.
- Drug levels were assayed via an LC-MS/MS method.

Results

- BCX4161 delivered suprachoroidally was generally well tolerated in rabbits with no overt signs of toxicity observed over the study duration.
- Sustained and high BCX4161 levels were detected in the RCS (Fig.1) and the retina (Fig.2) during the 12-week study.
- Cmax levels in the retina tissues were ~75µg/gm and 13µg/gm in the peripheral retina and central retina respectively.
- At the end of the study, mean BCX4161 levels in the peripheral retina and central retina were 21µg/gm and 30µg/gm respectively, corresponding to 2-3 orders of magnitude higher than the IC50 (5.8nM) levels reported in a human plasma ex-vivo assay.
- Levels of BCX4161 in the dose depot (RCS) were 1-2 orders of magnitude higher than concentrations in the retina while the retina drug levels were 1-2 orders of magnitude higher than the vitreous humor.
- Moderate to low drug levels were detected in the vitreous humor (Fig.3).
- Minimum to low levels of BCX4161 were detected in a few aqueous humor (Fig.3) and plasma (Fig.4) samples, supporting limited systemic drug exposure and systemic effect.

Conclusions

- Suprachoroidally administered BCX4161 suspension provided sustained and targeted delivery of BCX4161 to the chorioretina tissues while minimizing systemic exposure and drug levels in the anterior segment.
- BCX4161 administered via the suprachoroidal route utilizing the proprietary SCS Microinjector® has the potential to be a safe, effective and long-acting therapy for the treatment of DME.

References