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

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Purpose

BCX4161 is a potent and selective inhibitor of human plasma kallikrein activity[1]. Elevated plasma kallikrein (PKal) levels have been reported in the vitreous humor of patients with diabetic macular edema (DME)[1]. Inhibition of PKal activity can be an effective therapeutic strategy for the treatment of DME[2]. 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
- C_{max} 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 IC_{50} (5.8nM) levels reported in a human plasma ex-vivo assay[1].
- 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

Fig. 1

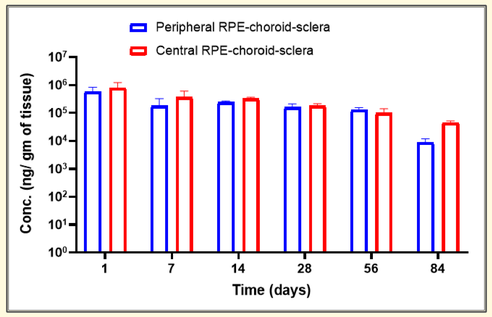


Fig. 2

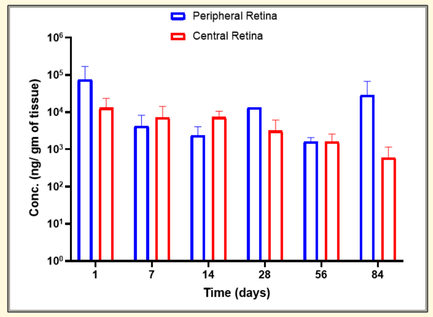


Fig. 3

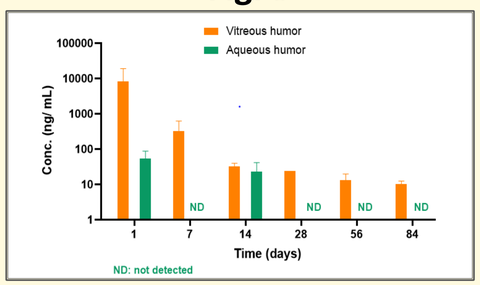
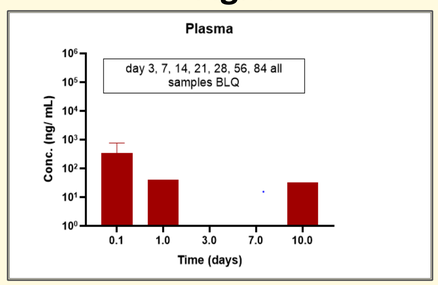


Fig. 4



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

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