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Nonclinical safety and pharmacology of RZ402, a plasma kallikrein inhibitor, for the treatment of diabetic macular edema as a daily oral therapy

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Abstract

Purpose : Excessive retinal vascular permeability (VP) is the key defining pathology underlying the development of diabetic macular edema (DME). The serine protease plasma kallikrein (PK) generates the vasoactive peptide bradykinin, a known mediator of VP. PK-null mice are protected from increased retinal VP induced by diabetes, or by VEGF, and we previously showed that systemic administration of the selective small-molecule PK inhibitor (PKI) RZ402 (formerly ASP440) normalized the elevated retinal VP in rodent models of diabetes (Diabetes 60:1590–1598, 2011.) We are developing RZ402 as a potential treatment for DME.

Methods : Single and repeat-dose toxicology, respiratory safety, cardiovascular safety, neurobehavioral and toxicokinetic studies were performed in Sprague-Dawley (SD) rats, cynomolgus monkeys, or both. Oral dosing was carried out via gavage of a suspension of RZ402 in 0.4% hydroxymethyl cellulose. Administered p.o. doses ranged from 0, 70, 100, 200, 300, 400, 800 and 1000 mg/kg. Drug exposure was determined by analyzing plasma samples by LC-MS/MS.

Results : RZ402 exhibited excellent ADME properties in rat and monkey, with moderate clearance, excreted renally as the unchanged parent drug. Plasma levels of drug were maintained above the previously established EC50 level of 50 nM for up to 24h after oral dosing. No adverse effects were observed following seven-day repeat oral dosing in rats at up to 1000 mg/kg, at therapeutic exposure multiples >500-fold. RZ402 was well-tolerated and exhibited dose-proportional exposures up to 800 mg/kg when dosed orally in monkeys, and repeat oral dosing for seven days at up to 400 mg/kg did not result in adverse clinical observations nor any meaningful changes in hematology and clinical chemistry measures. No histopathological changes were observed in any organs. Additionally, no adverse effects were observed in respiratory and CNS safety pharmacology studies in rats (dosed orally at up to 1000 mg/kg) or in a cardiovascular safety pharmacology study in monkeys (dosed orally at up to 400 mg/kg).

Conclusions : In summary, RZ402 is a safe and effective preclinical drug candidate for DME, with an ADME and safety profile in rodent and non-rodent species supporting the potential for once-daily oral dosing in the clinic.

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