ABSTRACT FOR THE 2021 ASRS MEETING

Title:

A Phase 1 Single Dose Study of RZ402: a Novel Orally Administered Plasma Kallikrein Inhibitor to Target Diabetic Macular Edema

Presenters:

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Background:

The plasma kallikrein-kinin system (KKS) promotes vascular inflammation and permeability through bradykinin and related mediators, and is implicated in a number of systemic and local vascular diseases. Plasma kallikrein inhibitors (PKI) are already approved for hereditary angioedema, a systemic vascular leakage syndrome. The KKS is also up-activated in retinal microvascular diseases, and studies have shown it to be both a VEGF-dependent and -independent mediator of DME. Therefore, oral-systemic PKIs offer a potential novel and convenient approach for the treatment of diabetic retinopathy (DR) and/or macular edema (DME). RZ402 is a novel, orally administered, potent and selective plasma kallikrein inhibitor (PKI) which has been shown to reduce retinal vascular leakage in various animal models of DME. A phase 1, first-in-human study was conducted to assess the safety and pharmacokinetics (systemic exposure) of oral RZ402 in a clinical development program for the treatment of DME.

Methods:

A phase 1 randomized, double-masked, placebo-controlled, single-ascending-dose study of RZ402 oral solution in 30 healthy adult male and female subjects was conducted.
Three sequential ascending dose cohorts of 10 subjects each were enrolled, with each cohort receiving single oral doses of RZ402 (or matched placebo in 8:2 fashion) at dose levels of 25-mg

100-mg, and 250-mg. Safety assessments included systemic and ophthalmic evaluations. Serial plasma RZ402 concentrations by LC/MS/MS supported the pharmacokinetic evaluation.

Results:

All 30 subjects completed the study with no discontinuations andsingle doses of RZ402 were generally safe and well tolerated across all dose levels. Overall, 13 subjects (54%) who received RZ402 experienced a total of 18 adverse events (AEs), compared to 2 subjects (33%; 5 AEs) who received placebo. A significant number of the AEs in subjects who received RZ402 were procedure-related (ECG electrode irritation), with only 3 AEs (diarrhea, nausea and headache; all grade 1/mild) in 3 subjects judged by the Investigator as possibly related to the study drug. There was no grade 2 or 3 (severe) or higher AEs nor any serious AEs (SAEs). No clinically meaningful changes in laboratory values, vital signs, or ECG results were observed, and physical and ophthalmic examinations were unremarkable. There were no adverse drug reactions or observed dose-limiting toxicities. Dose-dependent increases in RZ402 concentrations were observed with peak levels at 3 to 4 hours after dose (median) and elimination half-life at 20.2 to 25.6 hours (geometric mean) across the dose groups. Durable and pharmacologically relevant concentrations of RZ402 were observed throughout the intended 24-hour dosing interval.

Conclusion:

RZ402, a novel, orally administered PKI was demonstrated to have a good systemic and ocular safety profile and produced effective serum levels over 24 hours that support a once-a-day oral regimen as a potential treatment for patients with DME. Further clinical studies are warranted and are ongoing.