High plasma exposures of KVD900 achieved in First in Human study markedly inhibit plasma prekallikrein activation; early blockade of plasma kallikrein (PKa) may halt attacks in Hereditary Angioedema (HAE) by reducing contact system activation.

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INTRODUCTION

Acute attacks of swelling and pain in hereditary angioedema (HAE) are attributed to increased vascular permeability due to excessive and uncontrolled formation of the proinflammatory peptide hormone bradykinin (BK). BK is generated through cleavage of high molecular weight kininogen (HK) by the serine protease plasma kallikrein (PKa). HAE attacks resolve faster and are shorter after early treatment1. Orally administered treatments that are fast-acting and strongly inhibit plasma kallikrein activity and HK cleavage and, thus, BK production, could provide an effective and convenient approach for the treatment and management of this disease. Although the positive feedback effects of PKa on the activation FXII and FXII cleavage are well documented, the significance of pharmacological inhibition of PKa on the contact system at multiple levels and support the continuing evaluation of KVD900 for the treatment of HAE attacks.

This study examines the effects of KVD900, a rapidly acting, oral, potent (Ki 3 nM), selective inhibitor of PKa (Table 1), with high clinical exposure, on contact system activation and PKa activity in undiluted plasma samples obtained from a phase 1 clinical study.

To evaluate the pharmacodynamic (PD) effects of orally administered KVD900 using ex vivo undiluted plasma assays for plasma kallikrein catalytic activity, and HK, plasma prekallikrein (PPK), and FXII cleavage during contact system activation with dextran sulphate (DXS).

AIM

To evaluate the pharmacodynamic (PD) effects of orally administered KVD900 using ex vivo undiluted plasma assays for plasma kallikrein catalytic activity, and HK, plasma prekallikrein (PPK), and FXII cleavage during contact system activation with dextran sulphate (DXS).

METHODS

• Single doses of KVD900 were administered orally using powder-in capsule formulation or tablet formulation to healthy adult males.
• Samples for pharmacokinetic (PK) and PD assessment were taken at repeated intervals at pre-dose and at the indicated times post-dose.
• Catalytic activity of Pkα in DXS-stimulated (10 µg/mL) plasma samples from the phase 1 study was determined by measuring time-dependent hydrolysis of fluorogenic substrate.
• The time until appearance of detectable PKα activity in DXS-stimulated plasma (lag time) is calculated from the catalytic activity assay. The detection sensitivity of the catalytic activity in plasma is a fluorescence increase to reach 1ΔF units/sec.
• DXS-stimulated cleavage of HK, PPK, and FXII were quantified in undiluted citrated human plasma by capillary-based immunoassay on the Wes System (ProteinSimple).

RESULTS

Ex vivo undiluted plasma assays showed that the 600 mg KVD900 administered in tablet formulation provided >95% inhibition of PKα catalytic activity between 20 mins and 6 hrs post-dose. The tablet formulation will be used in upcoming clinical studies (Figure 2).

The kinetic measurements from the undiluted plasma enzyme assay can be plotted as assay progression curves (Figure 3). These curves highlight that KVD900 does not only have an inhibitory effect on enzyme activity but also increases the time until appearance of catalytic activity during contact system activation (lag time). At early time points post KVD900 administration plasma samples did not display detectable catalytic activity even after prolonged stimulation with the potent activator DXS.