KVD900 as a Single Dose, Rapid, Oral Plasma Kallikrein Inhibitor for the On-Demand Treatment of Hereditary Angioedema Attacks: Pharmacokinetic and Pharmacodynamic results from a Phase 1 Single Ascending Dose Study.

Sally L. Hampton[1], Gian Marco De Donatis[1], Nivetha Murugesan[2], Louise J. Rushbrooke[1], Lily Li[2], Edward Duckworth[1], Michael D. Smith[2], Rachel M. Morten[1], Andreas Maetzel[2], Christopher M. Yea[1] and Edward P. Feener[2]. KalVista Pharmaceuticals, [1]Salisbury, United Kingdom, [2]Cambridge, MA, USA

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) (Figure 1). HAE attacks resolve faster and are shorter after early treatment[1]. 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. KVD900 is a novel, potent (Ki 3 nM), selective inhibitor of PKa (Table 1, closely-related serine proteases) being developed as a single dose, rapid, oral inhibitor for the on demand treatment of HAE attacks.

Pharmacodynamic measures of inhibition of exogenously activated PKa enzyme and inhibition of cleavage of physiological substrate HK before and after receiving KVD900, in undiluted plasma, provide valuable insight into the inhibitory potential as an innovative on-demand HAE treatment.

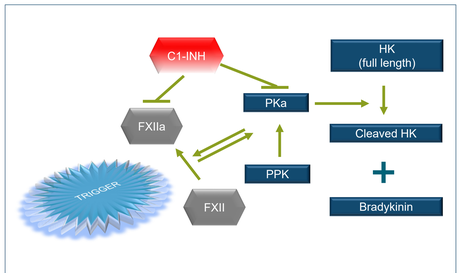


Figure 1: Activation of the contact system. Triggers of attacks in HAE include stress, anxiety, mechanical trauma, infection, hormonal changes, and other factors.

Table 1: KVD900 closely-related serine protease selectivity

Enzyme	IC_{50}
Tissue Kallikrein	>10 μM
FXIIa	>40 μM
FXIa	>40 μM
FXa	>10 μM
FVIIa	>10 μM
Plasmin	>40 μM
Thrombin	>40 μM
Trypsin	>40 μM

AIM

To evaluate the pharmacodynamic (PD) effects of orally administered KVD900 using *ex vivo* whole plasma assays for plasma kallikrein catalytic activity and HK cleavage, in samples from a Phase 1 Single Ascending Dose Study in healthy adult males.

METHODS

- A randomized, double-blind, placebo-controlled single ascending dose and crossover studies for food effect and capsule/tablet formulations.
- 64 healthy male participants (n=6 active, 2 placebo per cohort, 8 cohorts) were administered single ascending doses of KVD900 5, 10, 20, 40, 80, 160, 300 or 600 mg in a capsule.
- 8 participants were administered 100 mg KVD900 in a crossover study of the capsule and a tablet formulation.
- 12 participants were administered 600 mg KVD900 in a food effect crossover study.
- Samples for pharmacokinetic (PK) and PD assessment were taken at repeated intervals over 48 hours.
- PD measurements were determined in dextran sulfate (DXS) stimulated undiluted plasma using a fluorogenic enzyme assay and capillary based HK cleavage immunoassay.
- Catalytic activity of PKa in DXS-stimulated (Sigma; 10 μg/mL) plasma samples from KVD900 phase 1 study was determined by the time-dependent hydrolysis of fluorogenic substrate in all samples from all parts of the study.
- DXS-stimulated cleavage of HK in undiluted plasma was quantified by capillary-based immunoassay on the Wes System (ProteinSimple) using monoclonal anti-HK antibody and chemiluminescence-based detection. Plasma kallikrein mediated HK cleavage in undiluted citrated human plasma was induced by contact system activation with DXS (6.25 μg/ml) at 4°C in selected samples from the SAD phase.

RESULTS

Orally administered KVD900 achieved rapid and dose-dependent plasma exposure over the range of doses tested from 5 mg to 600 mg (Figure 2, Table 2).

The mean plasma exposure following the 600 mg dose of KVD900 was 3162 +/- 1031 ng/mL at 30 min and 3680 +/- 846 ng/mL at 1 hr.

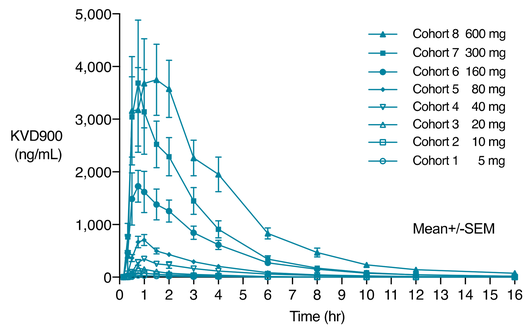


Table 2: KVD900 SAD PK parameters

Dose (mg)	C_{max} (ng/mL) Mean (95% CI)
5	38.7 (28.3, 52.9)
10	80.7 (59.0, 110)
20	169 (124, 231)
40	357 (261, 488)
80	684 (500, 935)
160	1,970 (1440, 2700)
300	3,910 (2860, 5340)
600	4,830 (3530, 6610)

Mean PK parameters of KVD900 n=6 in each SAD cohort

Figure 2: Plasma concentrations of KVD900 0-24 hours post-dose; capsule formulation, fasted state

Enzyme assays in activated undiluted plasma were performed on samples from each SAD cohort (Figure 3A). KVD900 doses 160 mg and above demonstrated >90% average inhibition of plasma kallikrein catalytic activity between 45 min and 2 hr for cohort 6, between 20 min and 4 hr for cohort 7. A 600 mg dose of KVD900 (cohort 8) provided >90% inhibition of plasma kallikrein catalytic activity between 30 min and 6 hr post-dose and >50% inhibition for 10hr (Figure 3B).

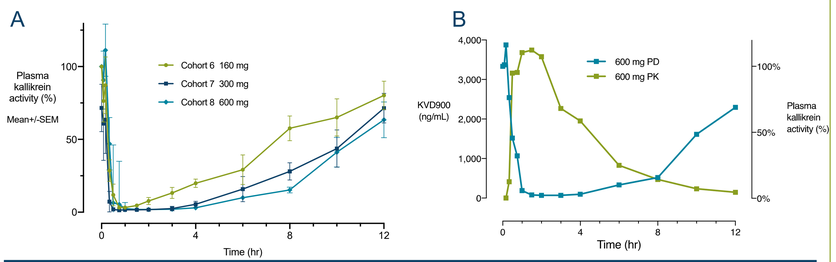
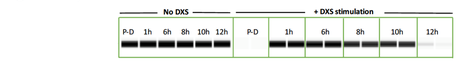
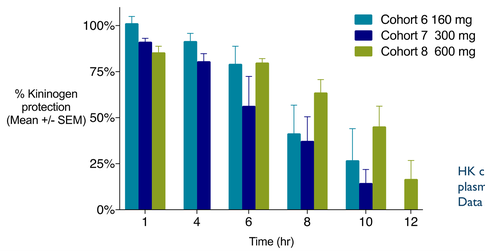


Figure 3: Mean Enzyme activity in DXS-activated undiluted plasma from SAD cohorts 6-8 (A) and PK/PD profile at 600 mg (B)

Doses of KVD900 starting at 160 mg were able to inhibit plasma kallikrein catalytic activity above 90% for an increasing amount of time. The duration of these PD effects was dose proportional. KVD900 also protected HK from DXS-stimulated cleavage in undiluted plasma for at least 10 hr following a single 600 mg dose (Figure 4).



Representative Wes System gel image.
Duplicate undiluted plasma samples +/- DXS stimulation from a single subject in cohort 8 who received 600 mg KVD900 compared with pre-dose (P-D).



HK cleavage evaluated following DXS stimulation of undiluted plasma samples at selected time points from cohorts 6-8. Data are expressed as Mean +/- SEM, n=6.

Figure 4: Mean percent HK protection in DXS-activated undiluted plasma; SAD cohort 6 (160 mg), 7 (300 mg) and 8 (600 mg)

RESULTS

In a formulation crossover study the KVD900 tablet provided an even more rapid absorption profile than capsules, with maximal concentration (C_{max}) being reached at Tmax 30 min (Figure 5, Table 3).

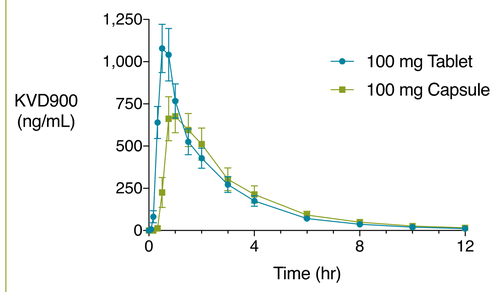


Table 3: KVD900 Crossover PK parameters

Parameter	100mg Tablet	100mg Capsule
Tmax (Hours)	0.5	1.1
Cmax (ng/mL)	1180	772
AUC0-inf (ng*hr/mL)	2140	2000

Mean PK parameters of KVD900 n=8 in each condition

Figure 5: Mean Enzyme activity in DXS-activated undiluted plasma from SAD cohorts (A) and PK/PD profile at 600 mg (B)

No significant food-effect was observed on the PD profile of 600 mg KVD900 tablet provided in fed and fasted state. KVD900's effects are rapidly observed in fed and fasted state with plasma kallikrein inhibition of >90% achieved by 30 minutes in both states. (Figure 6).

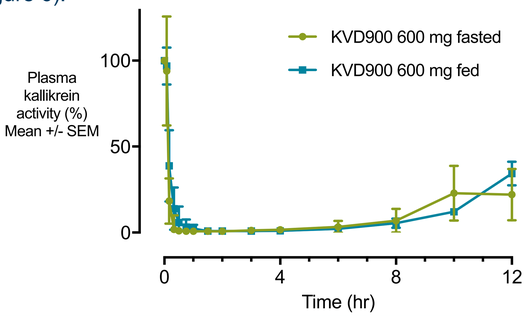


Figure 6: Plasma enzyme activity following 600 mg KVD900 tablet in Fed and Fasted state

SUMMARY & CONCLUSIONS

- KVD900 displays rapid, dose dependent and high plasma exposure
- PD studies in DXS stimulated undiluted plasma demonstrate that KVD900 provided rapid and highly effective plasma kallikrein inhibition and protection of HK cleavage
- A single 600 mg dose provided >90% PKa inhibition and protection of HK cleavage at 1 hr
- The PD effects of KVD900 were maintained up to 12 hr
- These pharmacokinetic and pharmacodynamic properties of KVD900 make it well suited as a rapidly acting oral treatment of HAE attacks

REFERENCES

[1]Maurer M et al. PLoS ONE 2013;8(2): e53773. doi:10.1371/journal.pone.0053773

CONFLICT OF INTEREST DISCLOSURE

- SLH, GMDD, NM, LJR, LL, EJD, MDS, RMM, AM, CMY and EPF are employees of KalVista Pharmaceuticals.