Poster ID: 500

Rapid Plasma Kallikrein Inhibition Following Oral KVD900 Is Associated With Early Symptom Relief in Patients With Hereditary Angioedema

Edward J. Duckworth,* Edward P. Feener, Christopher M. Yea, Paul Audhya, Sally L. Hampton, Michael D. Smith

KalVista Pharmaceuticals, Salisbury, UK, and Cambridge, MA, USA

*Presenting author

Background

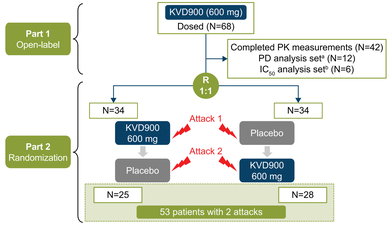
- Hereditary angioedema (HAE) is a rare genetic disease characterized by recurrent, often painful episodes of swelling of the skin and mucosal membranes[1,2]
- Previous studies have demonstrated that plasma kallikrein (PKa) activity is increased during attacks in patients with HAE and that uncontrolled PKa enzyme activity is a primary cause of HAE attacks[3-5]
- KVD900 is an investigational oral PKa inhibitor for the on-demand treatment of HAE
- We evaluated pharmacokinetics (PK), pharmacodynamics (PD), and time to symptom relief in adult patients with HAE treated with KVD900 in a placebo-controlled phase 2 trial

Methods

Study Population and Design

- This randomized, double-blind, placebo-controlled, phase 2 crossover trial (ClinicalTrials.gov identifier: NCT04208412) included adult patients aged ≥18 years with HAE type I or II who had experienced at least 3 attacks in the past 93 days and were not receiving prophylactic therapy
- In part 1 of the trial, an open-label, single 600 mg dose of KVD900 was administered to the patients in the clinic for assessment of PK and PD parameters (**Figure 1**)

Figure 1. Study Design



In part 1 of the trial, HAE patients received an open-label, single 600 mg dose of KVD900 for assessment of PK and PD parameters. Plasma samples from 42 patients were collected for assessment of PK parameters. Plasma samples from a subset (N=12) of those patients were randomly selected to evaluate PD parameters. Plasma samples from a separate subset (N=6) of patients in the PK set were randomly selected for IC_{50} evaluations. In part 2, 34 patients were randomized to sequence 1 (600 mg KVD900; placebo) and 34 patients were randomized to sequence 2 (placebo; 600 mg KVD900). A total of 53 patients completed treatment of 2 attacks.
[a]PD analysis set is a subset of patients included in the PK analysis. [b]IC_{50} analysis set is a subset of patients included in the PK analysis.
IC_{50}, half maximal inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; PKa, plasma kallikrein; R, randomized.

- In part 2 of the trial, patients were randomized to receive either 600 mg of KVD900 for the first attack followed by placebo for the second attack, or placebo for the first attack followed by 600 mg of KVD900 for the second attack
  - Attacks were eligible for treatment if they were mild or moderate in severity (not severe) and did not involve the face or larynx
  - For eligible attacks, study treatment was to be taken within 1 hour of attack onset

PK and PD Assay Methods

- In part 1 of the trial, plasma samples for PK and PD assessment were taken predose and at repeated intervals beginning 15 minutes after oral dosing and up to 4 hours postdose
- PK parameters included plasma concentration over time, maximum observed concentration (C_{max}), and time to C_{max} (T_{max})
- For PD analyses, PKa enzyme activity was measured in plasma using the fluorescent substrate H-D-Pro-Phe-Arg-AFC
  - The contact system in plasma was stimulated by dextran sulfate (DXS), leading to PKa generation from pre-kallikrein. PKa activity was estimated based on the maximum rate of fluorescence increase
- Plasma samples from 6 patients with HAE from the phase 2 trial and 6 healthy volunteers from a separate phase 1 trial were randomly selected for KVD900 IC_{50} determination using predose plasma
  - To determine the PKa plasma IC_{50}, KVD900 (at 8 concentrations) was preincubated for 5 minutes in plasma prior to DXS stimulation and determination of PKa enzyme activity
- Plasma samples from 12 patients with HAE from the phase 2 trial PK set were randomly selected to analyze the PD of dosed KVD900
  - Stimulated PKa activity in postdose plasma samples was calculated as a percentage of PKa activity observed in predose samples

Outcome Measures

- In part 2 of the trial, symptom relief was assessed using the Patient Global Impression of Change (PGI-C) measure on a 7-point scale from "Much Worse" to "Much Better," with 3 highest scores of "A Little Better," "Better," and "Much Better"
  - The PGI-C was completed at 30-minute intervals from 0.5 to 4 hours, 1-hour intervals to 12 hours, and 3-hour intervals to 24 hours
  - Time to symptom relief (PGI-C score of "A Little Better" or higher for 2 consecutive time points) was assessed within 12 hours of study drug administration

Statistical Analyses

- Unpaired *t* test was used to test significance between IC_{50} values, with $P<0.05$ indicating statistical significance
- *P* value for time to symptom relief data was determined using Gehan's generalized Wilcoxon test with $P<0.05$ indicating statistical significance

Results

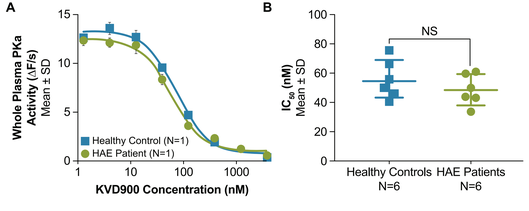
Patients

- Among the 68 dosed patients, 42 were included in the PK set (part 1), and 53 completed treatment of 2 attacks (part 2) (**Figure 1**)
- For the 68 patients, mean (standard deviation [SD]) age was 38.3 (13.23) years, 37 (54%) were women, and mean (SD) body mass index was 27.3 (5.47)

PK Analyses

- KVD900 was rapidly absorbed following a single oral 600 mg dose, with a geometric mean plasma concentration of 501 ng/mL at 15 minutes, the first time point evaluated (**Figure 2**)
  - Plasma levels of KVD900 reached maximum values (geometric mean C_{max}: 6080 ng/mL) with an observed median T_{max} of 1.0 hour
  - The mean PK profiles of selected samples from patients for the PD analysis (N=12) were similar to those of the full PK set (N=42; **Figure 2**)

Figure 3. IC_{50} in Predose Plasma

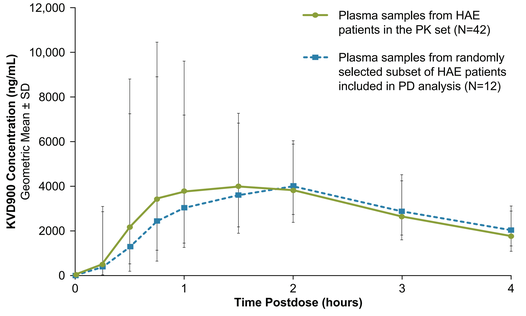


(A) Representative data from n=2 technical replicates of a single healthy control and a single HAE patient show the effect of exogenously added KVD900 on DXS-stimulated PKa activity measured using H-D-Pro-Phe-Arg-AFC. (B) Plasma samples from 6 patients with HAE from the phase 2 trial and 6 healthy volunteers (healthy controls) from a separate phase 1 trial were randomly selected for KVD900 IC_{50} determination. ΔF/s, change in fluorescence per second; DXS, dextran sulfate; HAE, hereditary angioedema; IC_{50}, half maximal inhibitory concentration; NS, nonsignificant; PKa, plasma kallikrein.

PD Analyses

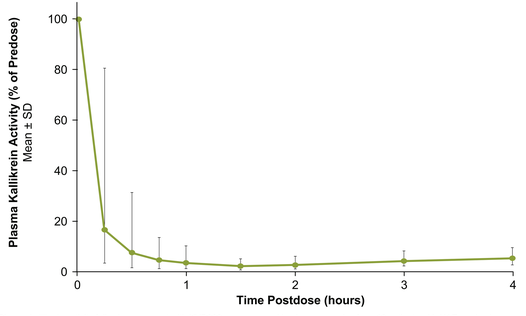
- Inhibition of DXS-stimulated PKa activity by exogenous KVD900 was similar in predose plasma of patients with HAE and healthy volunteers (**Figure 3A**)
  - The KVD900 IC_{50} was not significantly different between patients with HAE and healthy volunteers (mean [SD] 47.5 [10.4] and 54.4 [13.1], respectively; $P=0.3153$) (**Figure 3B**)
- Following oral administration of KVD900, stimulated PKa activity in plasma was inhibited >80% within 15 minutes (**Figure 4**)
  - Near-complete inhibition (≥95%) of PKa activity was observed within 1 hour following oral administration of KVD900 and maintained through 4 hours (the last time point measured)

Figure 2. Plasma KVD900 Pharmacokinetics Following Oral Dosing



Concentration of KVD900 over time following oral administration of a single dose of KVD900 (600 mg) was assessed in plasma samples from 42 HAE patients in the PK set and a subset of 12 HAE patients randomly selected to be included in PD analysis.
HAE, hereditary angioedema; PD, pharmacodynamic; PK, pharmacokinetic.

Figure 4. Orally Administered KVD900 Rapidly Inhibits Plasma Kallikrein Activity in Patients With HAE

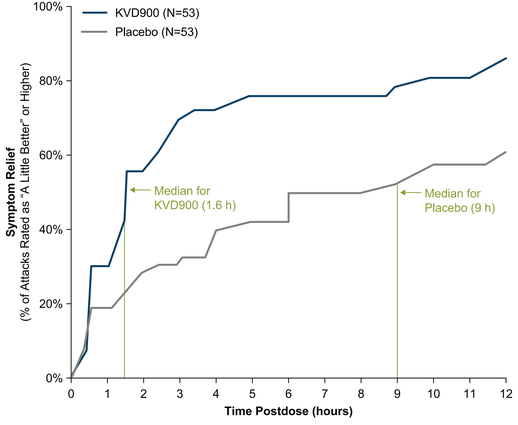


Plasma kallikrein activity following treatment with KVD900 was assessed in plasma samples from 12 patients with HAE randomly selected from the phase 2 trial PK set. PKa activity is shown as a percentage of PKa activity in the predose samples.
HAE, hereditary angioedema; PK, pharmacokinetic; PKa, plasma kallikrein.

Symptom Improvement

- Median time to symptom relief was significantly shorter following treatment with KVD900 compared with placebo (1.6 [95% confidence interval (CI), 1.5-3.0] vs 9.0 [95% CI, 4.0-noncalculable] hours; $P<0.0001$) (**Figure 5**)

Figure 5. KVD900 Provides Fast Symptom Relief



Achievement of symptom relief based on PGI-C, where symptom relief is defined as "A Little Better" or higher on the PGI-C for 2 consecutive time points.
PGI-C, Patient Global Impression of Change.

Conclusions

- Oral administration of KVD900 achieved rapid plasma exposure and near-complete inhibition of PKa activity in patients with HAE
- Time to symptom relief was significantly shorter for patients treated with KVD900 versus placebo
- Rapid PKa inhibition following oral KVD900 was associated with early symptom relief in patients with HAE

Acknowledgments

The study was supported by KalVista Pharmaceuticals Ltd. Medical writing assistance was provided under the direction of the authors by Lisa Baker, PhD, and Brittany Eldridge, PhD, of Cadent Medical Communications, a Syneos Health group company, and was supported by KalVista Pharmaceuticals, Inc.

Presented during the AAAAI Annual Meeting; February 25–28, 2022; Phoenix, AZ.

Disclosures

All authors are employees of KalVista Pharmaceuticals, Salisbury, UK, and Cambridge, MA, USA.

References

1. Bork K, et al. *Am J Med*. 2006;119(3):267-274.
2. Longhurst H, Cicardi M. *Lancet*. 2012;379(9814):474-481.
3. Suffritti C, et al. *Clin Exp Allergy*. 2014;44(12):1503-1514.
4. Banerji A, et al. *N Engl J Med*. 2017;376(8):717-728.
5. Schmaier AH. *Front Med*. 2018;5:3.