Pharmacology of KVD824, an Investigational Drug for Prophylaxis of HAE

Vesna Grivcheva-Panovska,1 Michael D. Smith,2 Edward J. Duckworth,2 Sally L. Hampton,2 Christopher M. Yea,2 Peter J. Mutch,2 Matt Iverson,2 Erik Hansen,2 Edward P. Feener2

1University Clinic of Dermatology, School of Medicine, University Saints Cyril and Methodius, Skopje, North Macedonia; 2KalVista Pharmaceuticals, Salisbury, UK, and Cambridge, MA, US

Presented during the Bradykinin Symposium, September 15–16, 2022, Berlin, Germany
Disclosures

VGP has served as a consultant for KalVista Pharmaceuticals and as principal investigator for CSL Behring, Pharming, BioCryst, and KalVista. MDS, EJD, SLH, CMY, PJM, MI, EH, and EPF are employees of KalVista Pharmaceuticals.

Acknowledgments

The study was supported by KalVista Pharmaceuticals. Medical writing assistance was provided under the direction of the authors by Courtney Niland, PhD, of Cadent, a Syneos Health group company, and was supported by KalVista Pharmaceuticals.
Background

- HAE is a rare genetic disease involving the kallikrein-kinin system marked by excessive generation of plasma kallikrein, leading to increased vascular permeability and characterized by recurrent and episodic attacks of swelling\(^\text{1-4}\)

- Treatment guidelines for HAE recommend that long-term prophylactic treatment be considered for patients with HAE to reduce the overall occurrence of attacks\(^\text{5-7}\)
  - Most currently available agents are administered subcutaneously or intravenously\(^\text{5-7}\)

- KVD824 is a novel oral plasma kallikrein inhibitor in development for prophylaxis in HAE

- Here, we report PK, PD, and safety analyses of KVD824 administration from a phase 1 trial in healthy volunteers

Study Design

• Phase 1 trial evaluating two different formulations of KVD824\(^1\) in healthy men and women aged 18-55 years with a body mass index range of 18.0-32.0 kg/m\(^2\)

• In the single-dose, open-label, nonrandomized, crossover part of the trial, participants received single oral doses of KVD824 600 mg or 900 mg as modified-release tablets or immediate-release capsules in a fed or fasted state

• PK analyses from the single-dose treatment group were used to select appropriate modified-release formulation for the multidose part of the trial

PK, pharmacokinetic.
In the multiple-dose, randomized, double-blind, placebo-controlled part of the trial, participants were randomized to receive placebo or modified-release formulation of KVD824 600 mg (standard meal), KVD824 900 mg (standard meal), or KVD824 900 mg (fasted) twice daily for 14 days.

- Blood samples from this multidose study were collected for the PK/PD analyses.

Disposition of Study Participants

All Participants
- Enrolled (n=16)
- Dosed (n=16)
- Completed (n=15)
- Discontinued (did not attend; lost to follow-up) (n=1)

Single-Dose Part
- Placebo
  - Enrolled (n=6)
  - Dosed (n=6)
  - Completed (n=6)

Multiple-Dose Part
- KVD824 600 mg Fed
  - Enrolled (n=7)
  - Dosed (n=7)
  - Completed (n=7)
- KVD824 900 mg Fed
  - Enrolled (n=7)
  - Dosed (n=7)
  - Completed (n=7)
- KVD824 900 mg Fasted
  - Enrolled (n=7)
  - Dosed (n=7)
  - Completed (n=7)

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Plasma Concentrations and PK Parameters of KVD824

<table>
<thead>
<tr>
<th>Day</th>
<th>Tmax (h)</th>
<th>Cmax (ng/mL)</th>
<th>AUC0–tau (ng•h/mL)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 (mean)</td>
<td>3.717</td>
<td>2,020</td>
<td>8,420</td>
<td>NC</td>
</tr>
<tr>
<td>Day 14 (mean)</td>
<td>3.860</td>
<td>2,410</td>
<td>12,200</td>
<td>9.743</td>
</tr>
</tbody>
</table>

- Twice-daily administration of KVD824 900 mg (fed) resulted in steady-state geometric mean C_{max} >2000 ng/mL

AUC, area under the curve; C_{max}, maximum plasma concentration; h, hours; NC, not calculated; PK, pharmacokinetic; t_{1/2}, half-life; T_{max}, time to C_{max}.
Inhibition of Plasma Kallikrein Activity by KVD824

- Following the first dose, stimulated plasma kallikrein activity was inhibited by >50% within 30 minutes
- >50% inhibition (geometric mean) was maintained over a 12-hour period with twice-daily dosing (fed), with a maximum inhibition of >95%

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Sustained Inhibition of Plasma Kallikrein with KVD824

• Oral KVD824 administered twice-daily (fed) achieved rapid plasma exposure with sustained high levels of plasma kallikrein inhibition (n=6)

Error bars represent SEM.
IC_{50}, half maximal inhibitory concentration.
## Safety of KVD824

### Treatment-Emergent Adverse Events in the Multiple-Dose Part of the Trial

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=6)</th>
<th>KVD824 600 mg Fed (n=7)</th>
<th>KVD824 900 mg Fed (n=7)</th>
<th>KVD824 900 mg Fasted (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) Events</td>
<td>n (%) Events</td>
<td>n (%) Events</td>
<td>n (%) Events</td>
</tr>
<tr>
<td><strong>Any TEAE</strong></td>
<td>2 (33.3) 4</td>
<td>3 (42.9) 5</td>
<td>5 (71.4) 7</td>
<td>4 (57.1) 19</td>
</tr>
<tr>
<td>Headache</td>
<td>0 0</td>
<td>2 (28.6) 2</td>
<td>0 0</td>
<td>2 (28.6) 4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
<td>0 0</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (16.7) 1</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Vessel puncture site bruiseb</td>
<td>1 (16.7) 1</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
<td>0 0</td>
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<tr>
<td>Catheter site hematomaa</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Medical device site reactionb</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Vessel puncture site painb</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 2</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (16.7) 2</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Night sweats</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
<td>0 0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
<td>0 0</td>
</tr>
<tr>
<td>Pollakiuria</td>
<td>0 0</td>
<td>0 0</td>
<td>2 (28.6) 2</td>
<td>0 0</td>
</tr>
<tr>
<td>Contusion</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
</tr>
<tr>
<td>Transaminases increased</td>
<td>0 0</td>
<td>0 0</td>
<td>1 (14.3) 1</td>
<td>0 0</td>
</tr>
</tbody>
</table>

*aTotal number of events.

*bAEs associated with blood sample collecting procedure.

AE, adverse event; TEAE, treatment-emergent adverse event.

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**Highlights – most frequently reported TEAEs**

- Headache
- Dizziness
- Back pain
- Joint stiffness
- Joint swelling
- Muscle spasms
- Musculoskeletal chest pain
- Vessel puncture site bruise
- Catheter site hematoma
- Medical device site reaction
- Vessel puncture site pain
- Abdominal pain
- Constipation
- Dysphagia
- Nausea
- Epistaxis
- Night sweats
- Pruritus
- Rash maculopapular
- Pollakiuria
- Transaminases increased
Safety of KVD824 (continued)

- No deaths, serious AEs, or severe AEs were reported
- 31 TEAEs were reported in 12 (57.1%) healthy volunteers who received KVD824 and 4 TEAEs in 2 (33.3%) volunteers who received placebo
- All TEAEs were mild, and no volunteer discontinued due to a TEAE
  - Most frequently reported events were headaches (4 events), pollakiuria (2 events), epistaxis (2 events)
  - 5 TEAEs considered possibly related to active treatment were: joint stiffness (1), joint swelling (1), muscle spasms (1), pruritus (1), and transaminases increased (1)
  - 1 TEAE considered possibly related to placebo was nausea
- Gastrointestinal TEAEs were reported in 3 (14.3%) volunteers receiving KVD824 (constipation, abdominal pain, dysphagia) and 1 (16.7%) volunteer receiving placebo (nausea)

AE, adverse event; TEAE, treatment-emergent adverse event.

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Summary

• Healthy participants receiving single or multiple doses of modified-release oral KVD824 achieved rapid plasma exposure

• Modified-release twice-daily oral KVD824 resulted in high levels of sustained plasma kallikrein inhibition in the multiple dose part of the trial

• KVD824 was found to be generally safe and well tolerated, with only mild TEAEs reported

• Phase 2 clinical trial KOMPLETE evaluating modified-release twice-daily KVD824 for prophylaxis in HAE is ongoing¹

HAE, hereditary angioedema; TEAE, treatment-emergent adverse event.