Pharmacology of KVD824, an Investigational Drug for Prophylaxis of HAE

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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.

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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[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[5-7]
  - Most currently available agents are administered subcutaneously or intravenously[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

HAE, hereditary angioedema; PD, pharmacodynamics; PK, pharmacokinetics.

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.** Banerji A, et al. *N Engl J Med*. 2017;376(8):717-728. **4.** Schmaier AH. *Front Med*. 2018;5:3. **5.** Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3. **6.** Maurer M, et al. *Allergy*. Published online January 10, 2022. doi:10.1111/all.15214. **7.** Bork K, et al. *Allergy Asthma Clin Immunol*. 2021;17(1):40.

Study Design

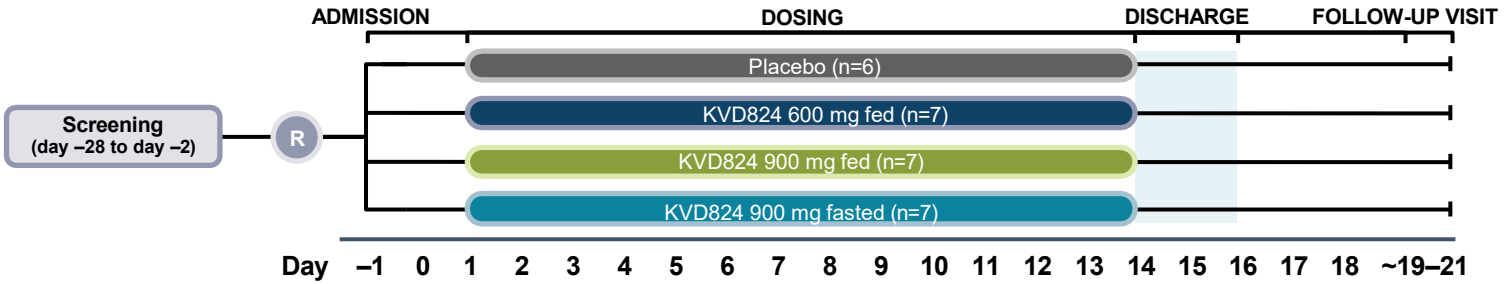
- Phase 1 trial evaluating two different formulations of KVD824[1] in healthy men and women aged 18-55 years with a body mass index range of 18.0-32.0 kg/m^2
- In the single-dose, open-label, nonrandomized, crossover part of the trial, participants received single oral doses of KVD824 600 mg or 900 mg 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.

Reference: 1. ClinicalTrials.gov. Phase 1 crossover study in healthy subjects to evaluate the PK profile of KVD824 following single and multiple doses of modified release (MR) formulations. Accessed September 2, 2022. https://clinicaltrials.gov/ct2/show/NCT05118958

Study Design (continued)

Multiple-Dose Part of the Trial



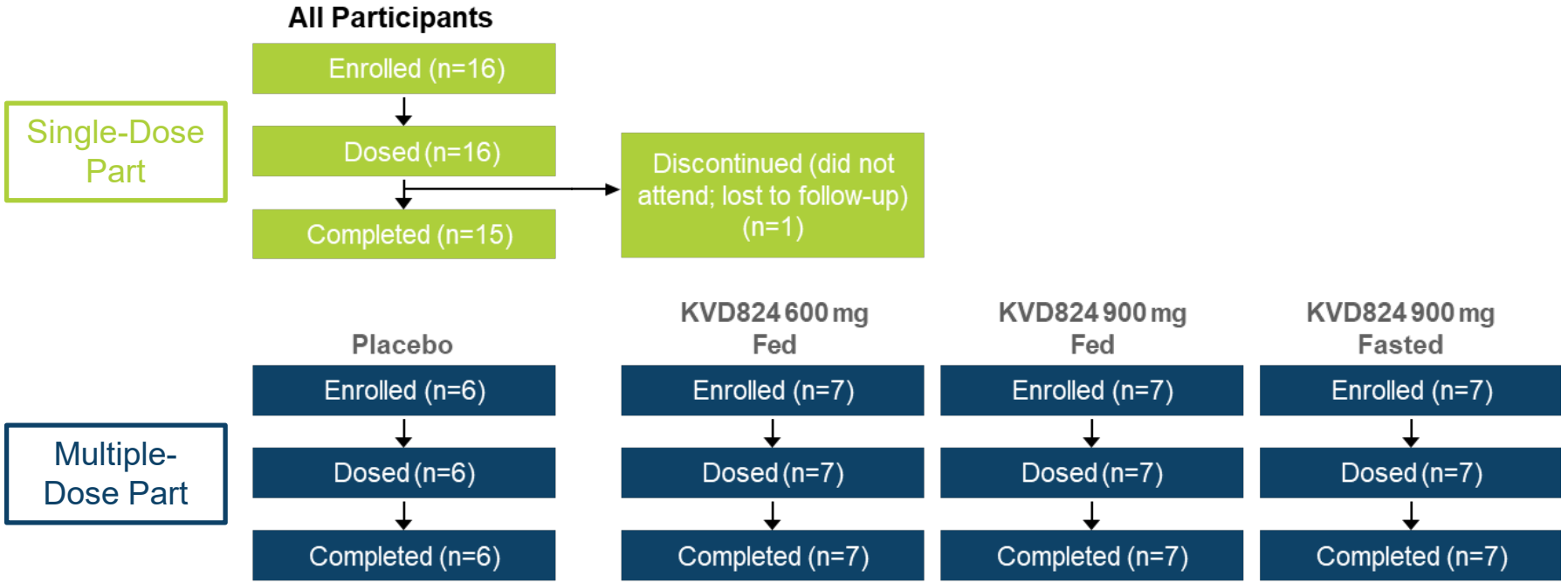
In the multiple-dose, randomized, double-blind, placebo-controlled part of the trial,[1] participants were randomized to receive placebo or modified-release formulation of KVD824 600 mg (standard meal), KVD824 900 mg (standard meal), or KVD824 900 mg (fasted) twice daily for 14 days

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

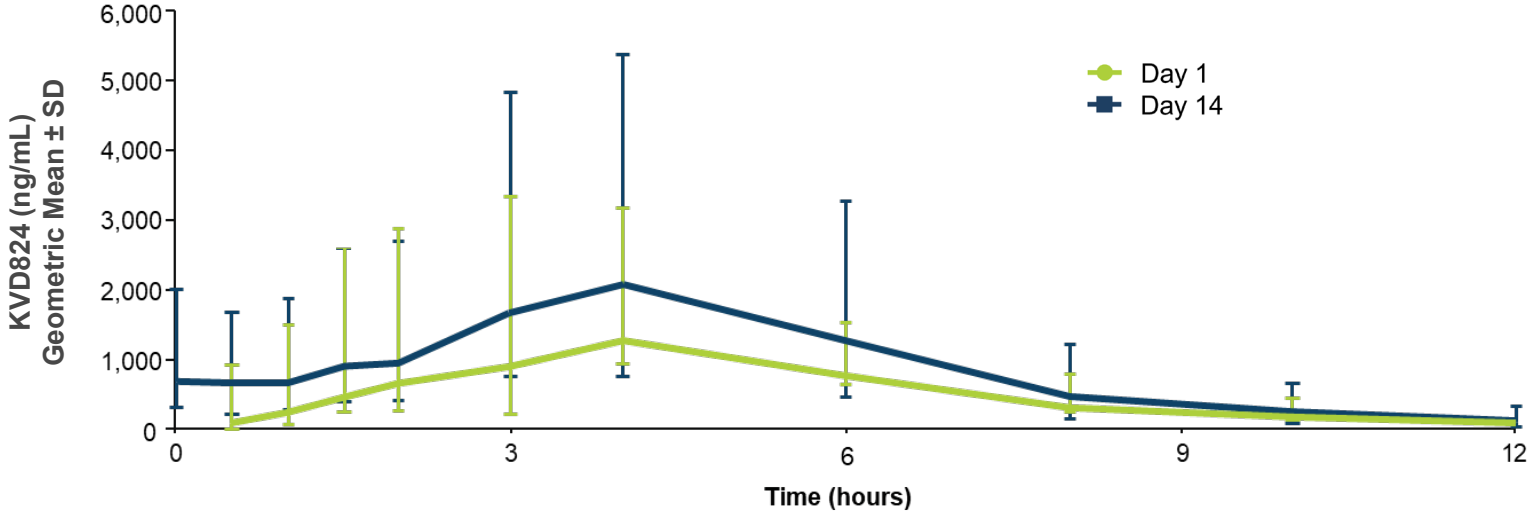
PD, pharmacodynamic; PK, pharmacokinetic; R, randomization.

Reference: 1. ClinicalTrials.gov. Phase 1 crossover study in healthy subjects to evaluate the PK profile of KVD824 following single and multiple doses of modified release (MR) formulations. Accessed September 2, 2022. https://clinicaltrials.gov/ct2/show/NCT05118958

Disposition of Study Participants



Plasma Concentrations and PK Parameters of KVD824



	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0–tau}$ (ng•h/mL)	$t_{1/2}$ (h)
Day 1 (mean)	3.717	2,020	8,420	NC
Day 14 (mean)	3.860	2,410	12,200	9.743

- 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}.

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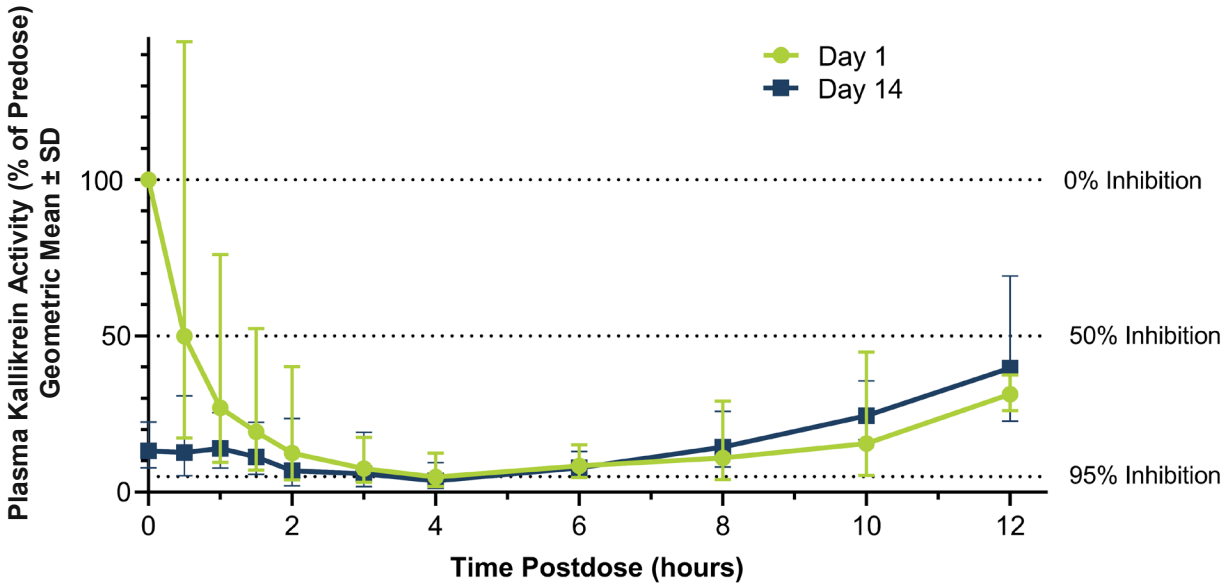
Inhibition of Plasma Kallikrein Activity by KVD824



- 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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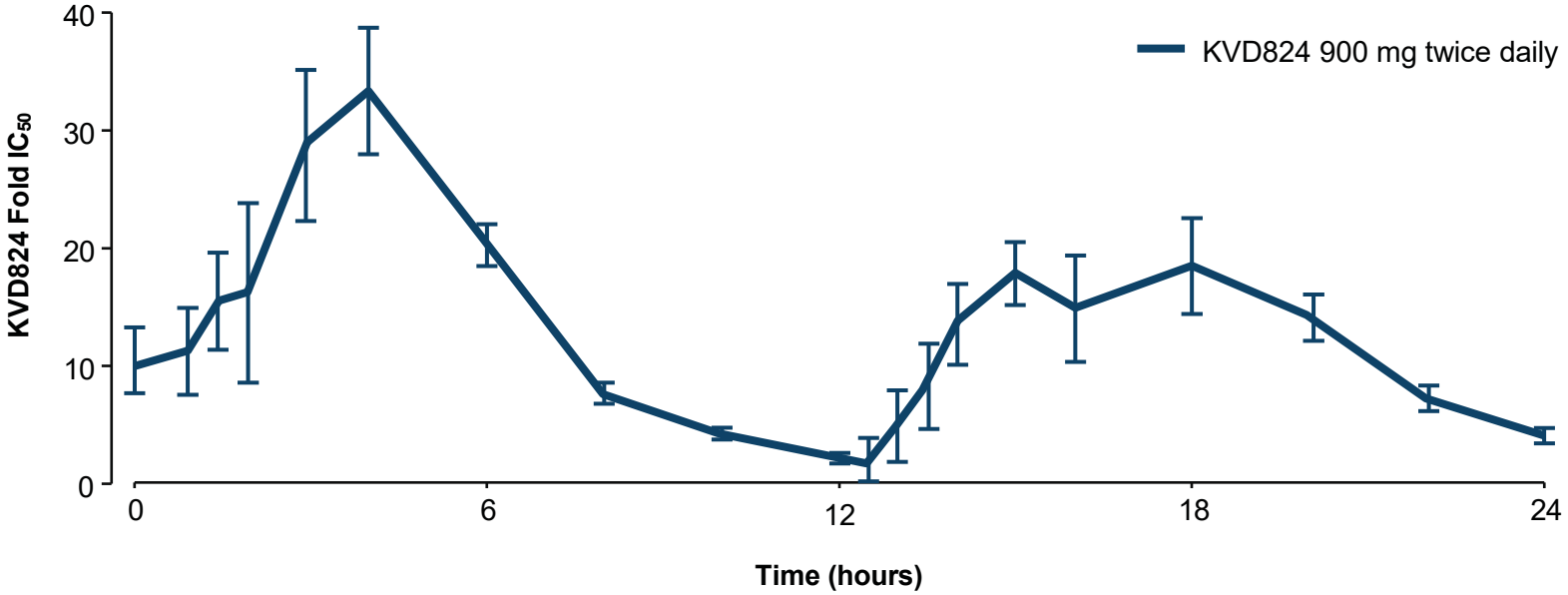
Sustained Inhibition of Plasma Kallikrein with KVD824



- 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

	Placebo (n=6)		KVD824 600 mg Fed (n=7)		KVD824 900 mg Fed (n=7)		KVD824 900 mg Fasted (n=7)	
	n (%)	Events[a]	n (%)	Events[a]	n (%)	Events[a]	n (%)	Events[a]
Any TEAE	2 (33.3)	4	3 (42.9)	5	5 (71.4)	7	4 (57.1)	19
Headache	0	0	2 (28.6)	2	0	0	2 (28.6)	4
Dizziness	0	0	0	0	1 (14.3)	1	0	0
Back pain	1 (16.7)	1	0	0	0	0	1 (14.3)	1
Joint stiffness	0	0	0	0	0	0	1 (14.3)	1
Joint swelling	0	0	0	0	0	0	1 (14.3)	1
Muscle spasms	0	0	0	0	0	0	1 (14.3)	1
Musculoskeletal chest pain	0	0	0	0	0	0	1 (14.3)	1
Vessel puncture site bruise[b]	1 (16.7)	1	0	0	1 (14.3)	1	0	0
Catheter site hematoma[b]	0	0	0	0	0	0	1 (14.3)	1
Medical device site reaction[b]	0	0	0	0	0	0	1 (14.3)	1
Vessel puncture site pain[b]	0	0	1 (14.3)	1	0	0	0	0
Abdominal pain	0	0	1 (14.3)	1	0	0	0	0
Constipation	0	0	0	0	0	0	1 (14.3)	2
Dysphagia	0	0	0	0	0	0	1 (14.3)	1
Nausea	1 (16.7)	2	0	0	0	0	0	0
Epistaxis	0	0	1 (14.3)	1	0	0	1 (14.3)	1
Nasal congestion	0	0	0	0	0	0	1 (14.3)	1
Oropharyngeal pain	0	0	0	0	0	0	1 (14.3)	1
Night sweats	0	0	0	0	1 (14.3)	1	0	0
Pruritus	0	0	0	0	0	0	1 (14.3)	1
Rash maculopapular	0	0	0	0	1 (14.3)	1	0	0
Pollakiuria	0	0	0	0	2 (28.6)	2	0	0
Contusion	0	0	0	0	0	0	1 (14.3)	1
Transaminases increased	0	0	0	0	1 (14.3)	1	0	0

[a]Total number of events.
[b]AEs associated with blood sample collecting procedure.
AE, adverse event; TEAE, treatment-emergent adverse event.

highlights – most frequently reported TEAEs

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.

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 ongoing[1]

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

Reference: 1. ClinicalTrials.gov. A trial to evaluate the efficacy and safety of different doses of KVD824 for prophylactic treatment of HAE type I or II (KVD824-201). Accessed September 2, 2022. https://clinicaltrials.gov/ct2/show/NCT05055258