On-demand Oral Treatment With KVD900 for HAE Attacks Achieves Rapid Exposure and Improves Patient Outcomes

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Background

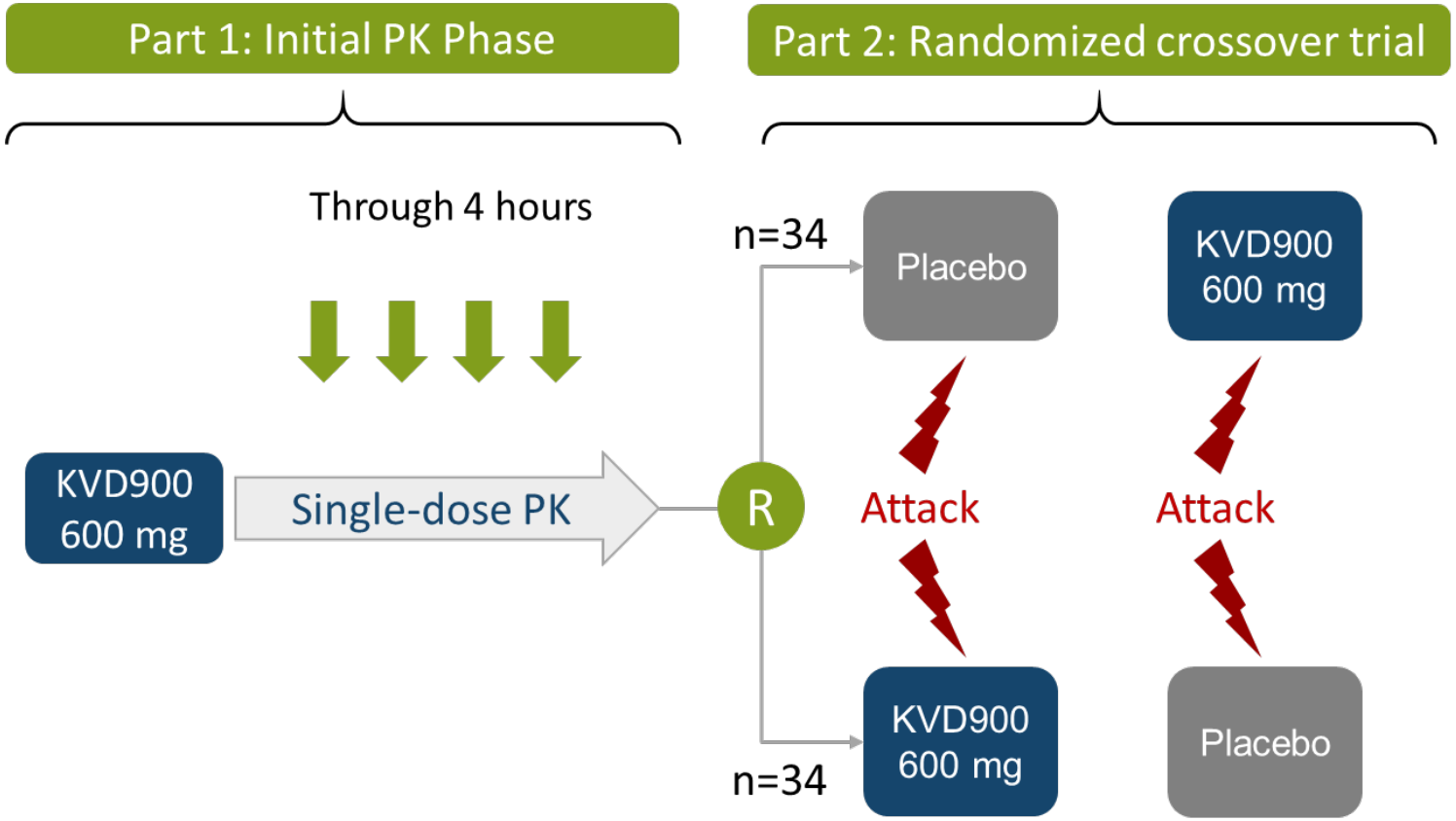
- Guidelines recommend effective on-demand therapy for every patient with HAE to reduce symptom severity and attack duration[1,2]
- The rate at which a drug reaches therapeutic concentrations in plasma may influence speed of onset of therapeutic effects
- KVD900 is an investigational oral plasma kallikrein inhibitor in development for the treatment of acute HAE attacks
- We evaluated pharmacokinetics of KVD900 and its relationship to patient-reported outcomes in the treatment of HAE attacks (NCT04208412)

HAE, hereditary angioedema.

1. Betschel S, et al. *Allergy Asthma Clin Immunol*. 2019;15:72. 2. Maurer M, et al. *Allergy*. 2018;73(8):1575-1596.

Study Design

- Patients (aged ≥18 years) with HAE type I or II participated in a two-part phase 2 study (NCT04208412)
- Part 1: single 600-mg dose of open-label KVD900 administered in the clinic
- Part 2: double-blind, placebo-controlled crossover trial in which each patient treated 2 mild or moderate HAE attacks with KVD900 and placebo



HAE, hereditary angioedema; PK, pharmacokinetics; R, randomized.

Outcome Measures

Pharmacokinetic parameters

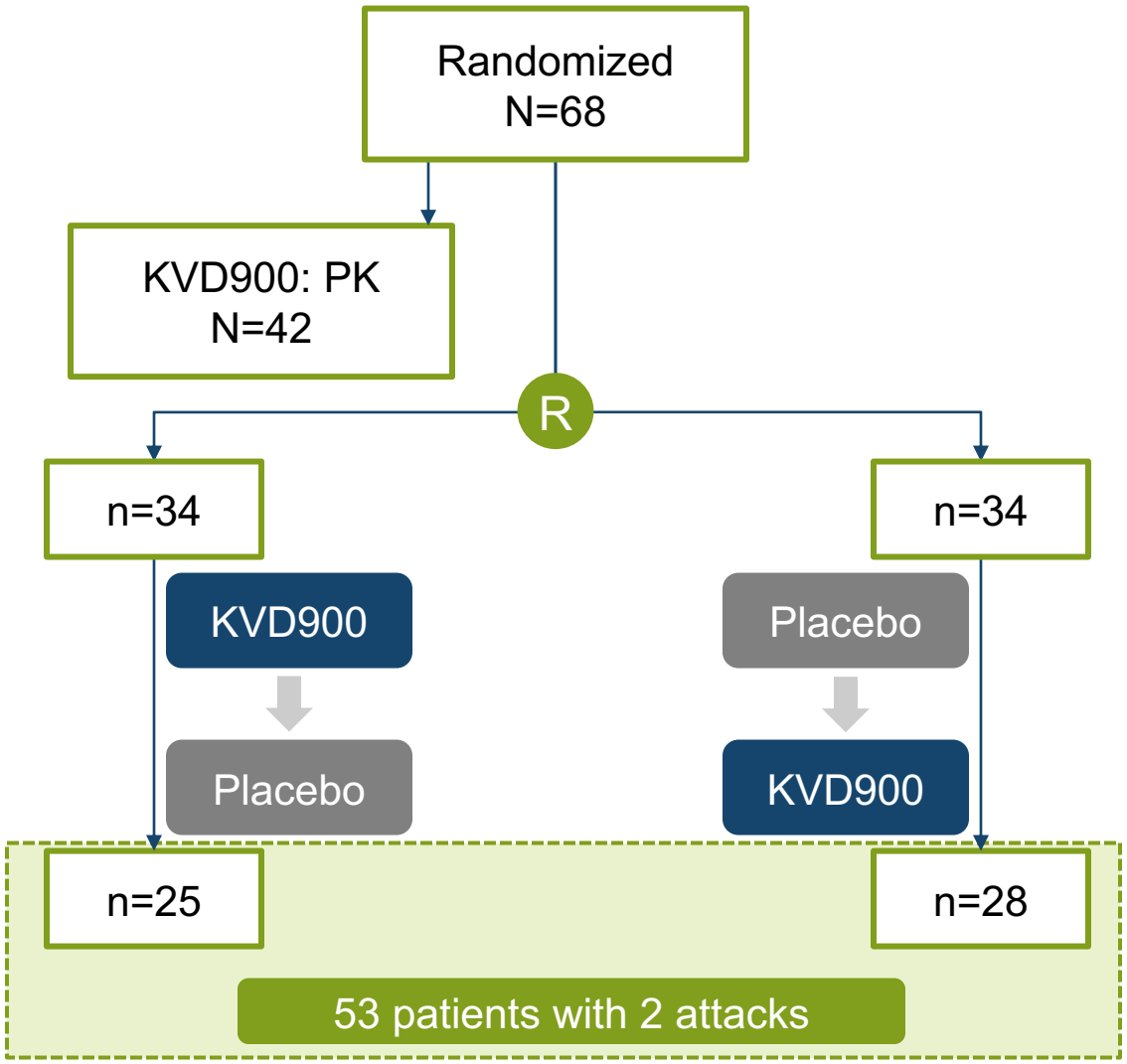
- Plasma concentration over time, maximum observed concentration (C_{max}), and time to C_{max} (T_{max})

Patient Global Impression of Change (PGI-C)

- Symptom improvement assessed on a 7-point scale from “much worse” to “much better,” with 3 highest scores “a little better,” “better,” and “much better”
- Measured at 30-minute intervals from 0.5 to 4 hours, 1-hour intervals to 12 hours, then 3-hour intervals to 24 hours
- Analyzed as time to reach “a little better” or higher improvement for 2 consecutive time points (or “better” or higher at any time point) within 12 and 24 hours

A selection of secondary and exploratory endpoints from the study are presented in this presentation. The full list of outcome measures from the study is available at https://clinicaltrials.gov/ct2/show/NCT04208412.
C_{max}, maximum observed concentration; PGI-C, Patient Global Impression of Change; T_{max}, time to C_{max}.

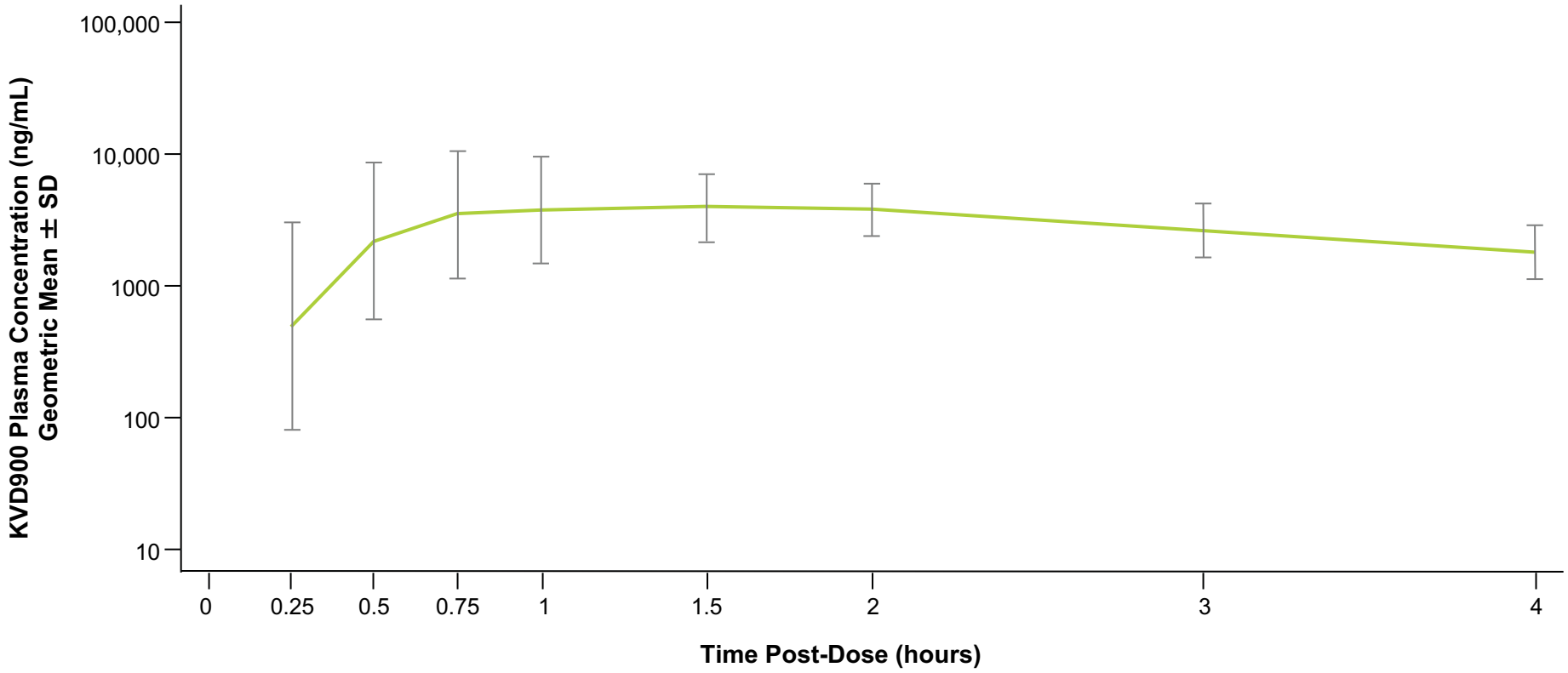
Study Flow and Baseline Demographics



Demographic Characteristics (N=68)	
Age, years Mean (SD) Range	 38.3 (13.23) 19-68
Gender M/F, n	 31/37
BMI, kg/m^2 Mean (SD) Range	 27.3 (5.47) 18.8-40.9

A total of 9 patients (26.5%) from the sequence 1 arm (KVD900-Placebo) withdrew early from the study; n=1 Withdrawal by Subject; n=8 Other. A total of 6 patients (17.6%) from the sequence 2 arm (Placebo-KVD900) withdrew early from the study; n=1 Lost to Follow-up; n=5 Other. Patients with Other as primary reason for withdrawal were withdrawn due to early discontinuation of the study as enough patients had completed the study.
BMI, body mass index; F, female; M, male; PK, pharmacokinetics; R, randomized; SD, standard deviation.

Plasma KVD900 Concentration Over Time



- KVD900 was rapidly absorbed, with measurable concentrations detected at 0.25 hours
- Plasma levels reached C_{max} of 6080 ng/mL (geometric mean) within 1 hour (median T_{max})

Based on N=42 patients in the pharmacokinetic set.

C_{max}, maximum observed concentration; SD, standard deviation; T_{max}, time to C_{max}.

Time to Symptom Improvement (PGI-C)

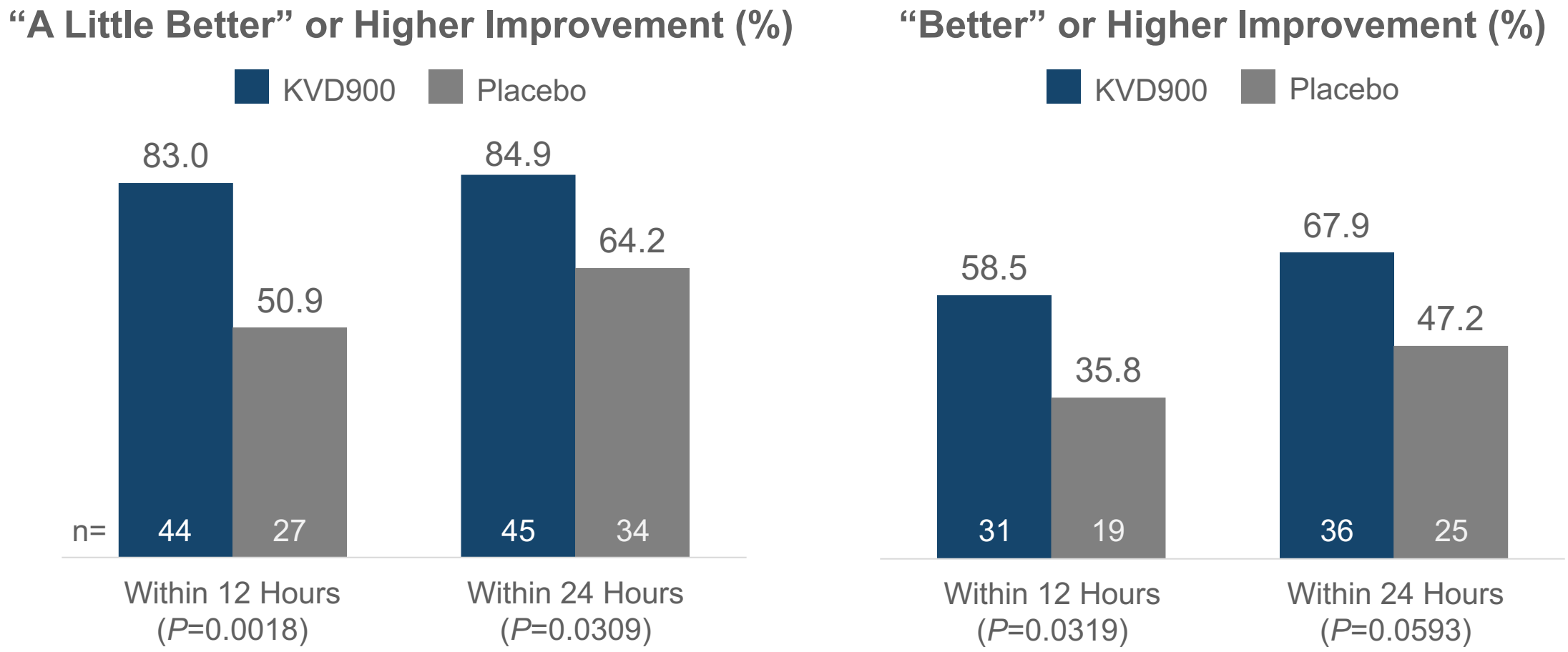
Median (95% CI) Time to Symptom Improvement (Hours)

	"A Little Better" or Higher Improvement for 2 Consecutive Time Points		"Better" or Higher Improvement for Any Time Point	
	Within 12 Hours	**Within 24 Hours**	**Within 12 Hours**	**Within 24 Hours**
KVD900	1.6 (1.5–3.0)	1.6 (1.5–3.0)	5.0 (2.1–NC)	5.0 (2.1–15.0)
Placebo	9.0 (4.0–NC)	9.0 (4.0–17.2)	NC (9.0–NC)	15.0 (9.0–23.5)
P value	<0.0001	<0.0001	0.0003	0.0036

- Median time to symptom improvement was significantly shorter with KVD900 than with placebo (as indicated by a rating on the PGI-C of "a little better" for 2 consecutive time points or "better" for any 1 time point)

KVD900 treatment vs placebo analyzed using Gehan's generalized Wilcoxon test in the Full Analysis Set (n=53). Findings for "a little better" or higher are for 2 consecutive time points. Findings for "better" or higher are at any 1 time point. Censoring occurred where an attack rating did not occur, or conventional attack treatment was used within the studied period post study drug dosing.
CI, confidence interval; NC, noncalculable; PGI-C, Patient Global Impression of Change.

Proportion of Patients With Symptom Improvement (PGI-C)



- A higher percentage of patients rated HAE attacks "a little better"/"better" or higher within 12 and 24 hours with KVD900 treatment compared with placebo

KVD900 treatment vs placebo analyzed using Prescott's test in the Full Analysis Set (n=53). Findings for "a little better" or higher are for 2 consecutive time points. Findings for "better" or higher are at any 1 time point.
HAE, hereditary angioedema; PGI-C, Patient Global Impression of Change.

Conclusions

- Treatment of HAE attacks with KVD900 achieved rapid plasma exposure and faster improvements in initial symptom relief compared with placebo
- Development of an exposure-response model for KVD900 would further elucidate the relationship between pharmacokinetic and pharmacodynamic measures and clinical outcomes

Acknowledgments

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