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Agreement of Patient Global Impression of Change With Attack Resolution or Use of Rescue Medication in Patients With Hereditary Angioedema

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Background

Background

- Hereditary angioedema (HAE) is a rare genetic disease caused by deficiency or dysfunction of C1-inhibitor, a key regulator of the kallikrein-kinin system[1,2]
- Lack of C1-inhibitor leads to uncontrolled activity of plasma kallikrein, which triggers excessive release of bradykinin; this in turn can lead to episodic HAE attacks[3]
- KVD900 is an investigational oral plasma kallikrein inhibitor in development for the on-demand treatment of HAE attacks
- The efficacy and safety of KVD900 was evaluated in a phase 2, randomized, double-blind, placebo-controlled crossover trial in patients with HAE

1. Bork K, et al. *Am J Med*. 2006;119(3):267-274. 2. Levi M, Cohn DM. *Transfus Med Rev*. 2019;33(4):243-247. 3. Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.

Background (continued)

- This trial met the primary efficacy endpoint, demonstrating significantly longer time to use of rescue medication with KVD900 vs placebo
  - Improvements were also observed in patient-reported outcomes (PROs) measured using the Patient Global Impression of Change (PGI-C) scale, Patient Global Impression of Severity (PGI-S) scale, and visual analog scale (VAS)
- The PGI-C scale is a common clinical measure of symptom improvement in various disease conditions, and has also been used to evaluate treatment effect in HAE clinical studies[1,2]
- In this post hoc analysis, we evaluated agreement between improvement observed on the PGI-C scale and 3 other efficacy outcome measures (use of rescue medication, symptom resolution per PGI-S scale, and symptom resolution per VAS) in the KVD900 phase 2 trial

1. Perrot S, Lantéri-Minet M. *Eur J Pain*. 2019;23(6):1117-1128. 2. Craig TJ, et al. *J Allergy Clin Immunol*. 2009;124(4):801-808.

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Methods

Methods

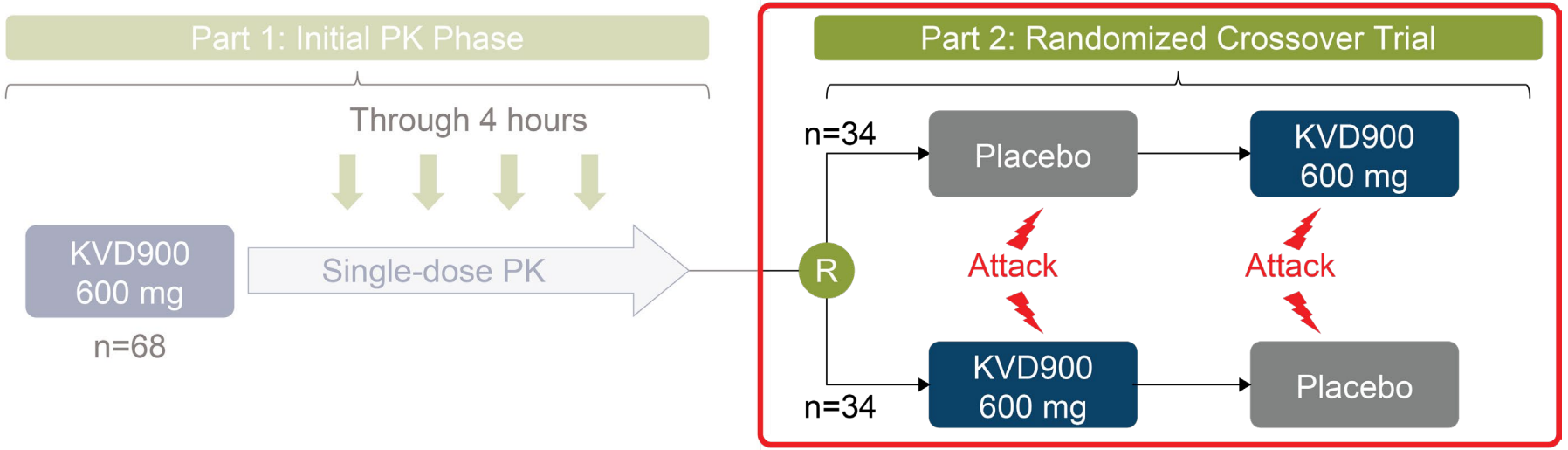
Phase 2 Study Population and Design

- This phase 2 trial (ClinicalTrials.gov ID: NCT04208412) included adult (aged ≥18 years) patients with HAE type I or II who had experienced at least 3 attacks in the past 93 days and were not on prophylactic therapy
- Following an initial open-label pharmacokinetic phase, patients were randomized to treat 2 eligible HAE attacks with KVD900 (600 mg) or placebo in 1 of 2 sequences in a double-blind crossover trial (**Figure 1**)
  - Patients experiencing attacks were eligible for treatment if the attacks were mild or moderate in severity and did not involve the face or larynx

Methods (continued)

Phase 2 Study Population and Design

Figure 1. Study Design



PK, pharmacokinetic; R, randomized.

Methods (continued)

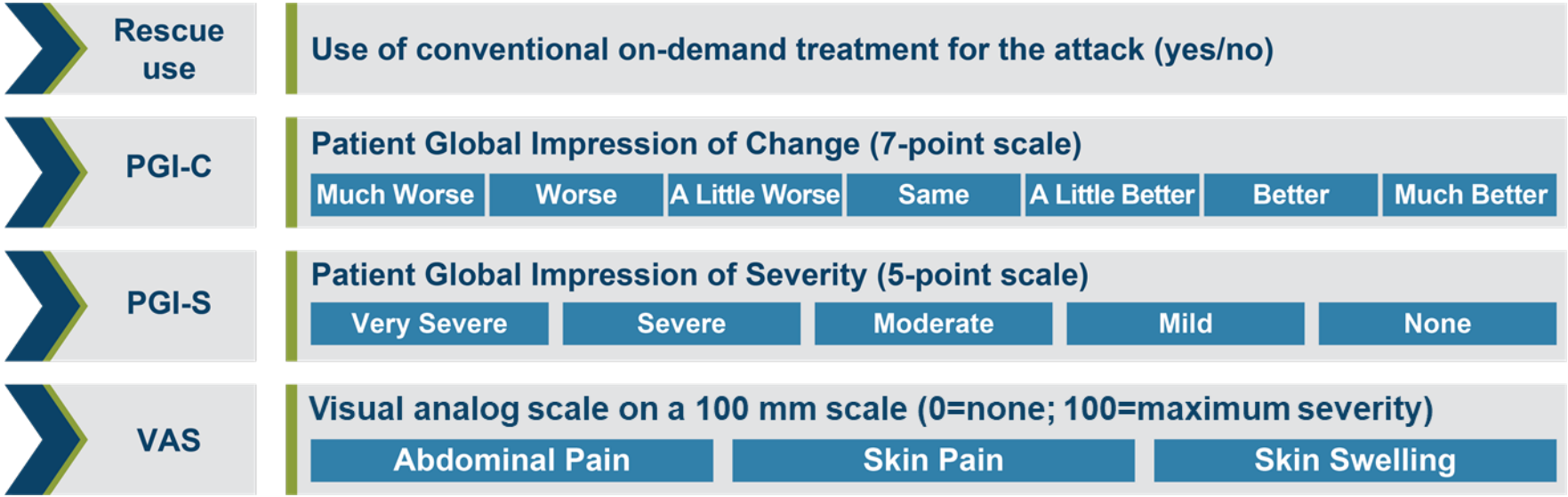
Outcome Measures Included in Post Hoc Analysis

- Improvement per PGI-C scale was assessed in 2 ways: 1) achievement of “A Little Better” or higher for 2 consecutive time points and 2) achievement of “Better” or higher for 1 time point (**Figure 2**)
- Use of rescue medication was defined as use of conventional on-demand treatment for the attack within the assessment period
- Attack resolution per PGI-S scale was defined as a PGI-S rating of “None”
- Attack resolution per VAS was defined as all 3 VAS component scores being <10 for 3 consecutive time points
  - Attacks with all 3 VAS components being <10 at baseline were excluded from the analysis of attack resolution according to VAS

Methods (continued)

Outcome Measures Included in Post Hoc Analysis

Figure 2. Outcome Measures



The PGI-C assessed symptom improvement on a 7-point scale from “Much Better” to “Much Worse.” The PGI-S assessed HAE attack severity on a 5-point scale from “None” to “Very Severe.” The VAS measured severity of HAE attack symptoms on a 100-mm scale ranging from 0 (none) to 100 (maximum severity).

HAE, hereditary angioedema.

Methods
Statistical Analysis

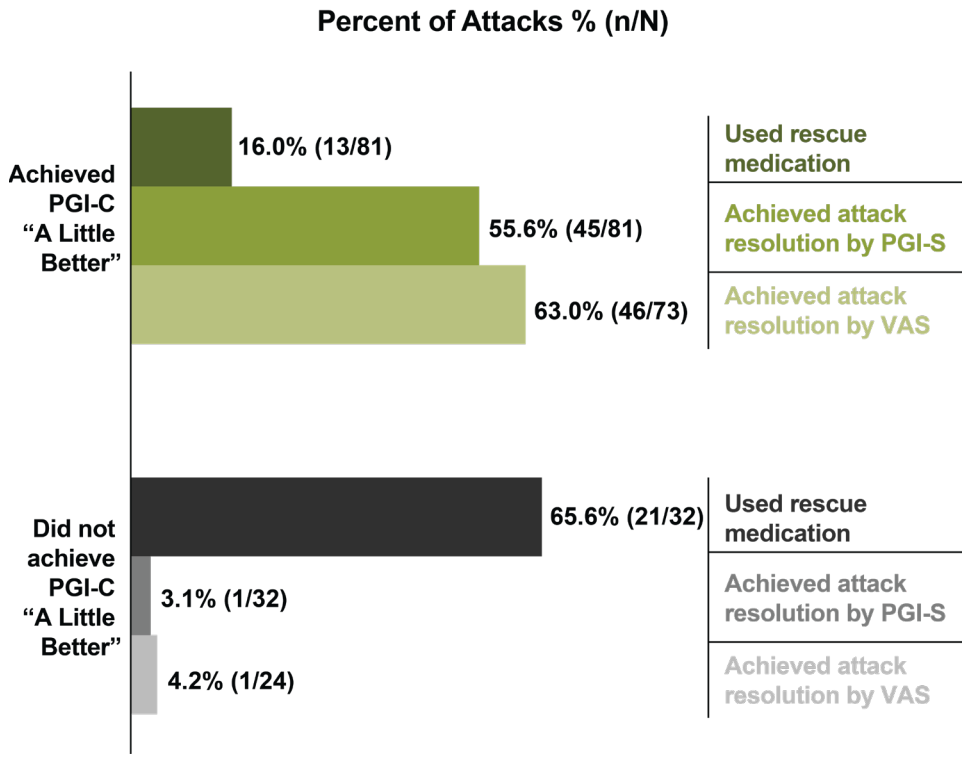
- Cross-tabulation analysis was used to evaluate agreement between improvements achieved on the PGI-C scale and 3 other outcome measures: rescue medication use, attack resolution according to PGI-S, and attack resolution according to VAS over a 24-hour period after study drug administration
  - The sensitivity and specificity of the PGI-C endpoint compared with each comparator was assessed using standard sensitivity and specificity calculations
  - Cohen's kappa was calculated to assess the agreement (consistency) between the outcomes

Results

Results

- 60 patients completed treatment for at least 1 HAE attack (n=113 attacks)
- A PGI-C score of “A Little Better” or higher for 2 consecutive time points was achieved in 71.7% (81/113) of attacks within the 24-hour assessment period
  - Attacks that achieved a PGI-C score of “A Little Better” or higher for 2 consecutive time points were less likely to result in use of rescue medication and more likely to achieve attack resolution by PGI-S and VAS compared with attacks that did not achieve PGI-C “A Little Better” or higher for 2 consecutive time points (**Figure 3**)
- A PGI-C score of “Better” or higher was achieved in 58.4% (66/113) of attacks within the 24-hour assessment period
  - Attacks that achieved a PGI-C score of “Better” or higher for 1 time point were less likely to result in use of rescue medication and more likely to achieve attack resolution by PGI-S and VAS compared with attacks that did not achieve PGI-C “Better” or higher for 1 time point (**Figure 4**)

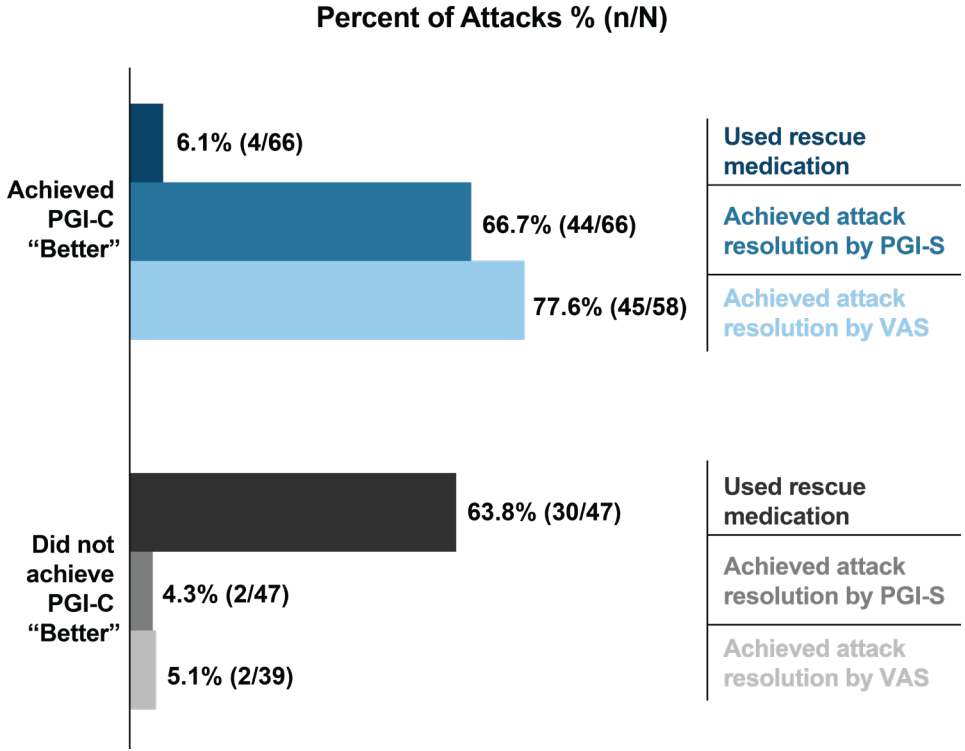
Figure 3. Rescue Medication Use and Attack Resolution in Attacks That Achieved or Did Not Achieve PGI-C "A Little Better" for 2 Consecutive Time Points Within 24 Hours



All time points prior to rescue medication use within the assessment period are considered. Attack resolution according to PGI-S is defined as a PGI-S rating of "None." Attack resolution according to VAS is defined as all 3 VAS component scores being <10 for 3 consecutive time points. Attacks with all VAS components scoring <10 at baseline were excluded.

PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; VAS, visual analog scale.

Figure 4. Rescue Medication Use and Attack Resolution in Attacks That Achieved or Did Not Achieve PGI-C "Better" for 1 Time Point Within 24 Hours



All time points prior to rescue medication use within the assessment period are considered. Attack resolution according to PGI-S is defined as a PGI-S rating of "None." Attack resolution according to VAS is defined as all 3 VAS component scores being <10 for 3 consecutive time points. Attacks with all VAS components scoring <10 at baseline were excluded

PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; VAS, visual analog scale

Results (continued)

- Sensitivity, specificity, and Cohen's kappa are summarized in **Table 1**
- Cohen's kappa indicated fair to moderate agreement of PGI-C "A Little Better" for 2 time points with no use of rescue medication, PGI-S, and VAS measures
  - Cohen's kappa indicated moderate to substantial agreement of PGI-C "Better" for 1 time point with no use of rescue medication, PGI-S, and VAS measures
- A PGI-C score of "A Little Better" for 2 time points was slightly more sensitive at identifying attack resolution and no use of rescue medication within 24 hours than a PGI-C score of "Better" for 1 time point, but was less specific

Table 1. Sensitivity, Specificity, and Cohen's Kappa for PGI-C Outcome Within 24 Hours From Administration of Study Drug

PGI-C Outcome	Comparator Outcome	Sensitivity	Specificity	Cohen's Kappa*
"A Little Better" for 2 time points	No use of rescue medication	0.86	0.62	0.49
"A Little Better" for 2 time points	Attack resolution by PGI-S	0.98	0.46	0.39
"A Little Better" for 2 time points	Attack resolution by VAS	0.98	0.46	0.43
"Better" for 1 time point	No use of rescue medication	0.78	0.88	0.60
"Better" for 1 time point	Attack resolution by PGI-S	0.96	0.67	0.59
"Better" for 1 time point	Attack resolution by VAS	0.96	0.74	0.69

*A Cohen's kappa value of 0.01–0.20 indicates none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement between the variables.

PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; VAS, visual analog scale.

Conclusions

Conclusions

- This analysis suggests that achieving improvement on the PGI-C scale was associated with achieving attack resolution and a reduced need for rescue medication in patients with HAE
- Patients who reported improvement on the PGI-C scale within 24 hours were less likely to use rescue medication and more likely to achieve attack resolution
- Based on a Cohen's kappa analysis, fair to substantial agreement between PGI-C and other PROs assessing attack resolution and use of rescue medication suggests that improvement on the PGI-C scale was clinically meaningful
- A PGI-C score of "A Little Better" for 2 consecutive time points was a slightly more sensitive outcome for identifying attack resolution and no use of rescue medication within 24 hours than a PGI-C score of "Better" for 1 time point, albeit less specific

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Disclosures

Paul Audhya and Christopher Yea are employees of KalVista Pharmaceuticals. Peter Williams is an employee of Veramed Limited, and acts as a consultant statistician for KalVista. Danny Cohn has received speaker fees and/or consultancy fees from BioCryst, CSL Behring, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Pharming, Pharvaris, and Shire/Takeda.