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Relationship Between PGI-C Scale and Other PROs in KVD900 Trial in Hereditary Angioedema

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Background

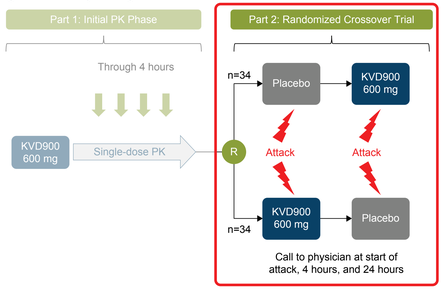
- Hereditary angioedema (HAE) is a rare genetic disease caused by deficiency in or dysfunction of the C1-inhibitor, and is characterized by episodic attacks[1]
- KVD900 is an investigational oral plasma kallikrein inhibitor for the treatment of HAE attacks
  - KVD900 was evaluated in a phase 2, placebo-controlled, double-blind, crossover trial in patients with HAE experiencing mild-to-moderate attacks
- Given the lack of a "gold standard," several patient-reported outcomes (PROs) were collected to capture the patient experience
  - The Patient Global Impression of Change (PGI-C) scale has been used in HAE studies and assesses improvement in overall symptoms. PGI-C has been validated in a number of other episodic diseases against well-established measures of pain intensity, pain interference in daily life, and treatment effectiveness[2]
- We investigated the association between patients' scores on the PGI-C scale and 2 other PRO measures in the KVD900 phase 2 trial after the main study results were reported

Methods

Study Population and Design

- Patients in this phase 2 trial (ClinicalTrials.gov ID: NCT04208412) were adults aged ≥18 years with HAE type I or II, were not on prophylactic therapy, and had experienced at least 3 attacks in the past 93 days
- In this study, an open-label single 600 mg dose of KVD900 was administered to the patients in the clinic for assessment of pharmacokinetic parameters (Part 1) (**Figure 1**)
- Patients were then randomized to treat 2 eligible HAE attacks within 1 hour of onset with KVD900 (600 mg) or placebo in 1 of 2 sequences in a crossover trial (Part 2)
  - Patients experiencing attacks were eligible for treatment if the attacks were mild or moderate in severity (not severe) and did not involve the face or larynx, and if they had a sufficient washout period of prior on-demand treatment with ready access to conventional on-demand treatment for rescue if they deemed necessary
  - This poster presents data from Part 2 of this phase 2 study

Figure 1. Study Design

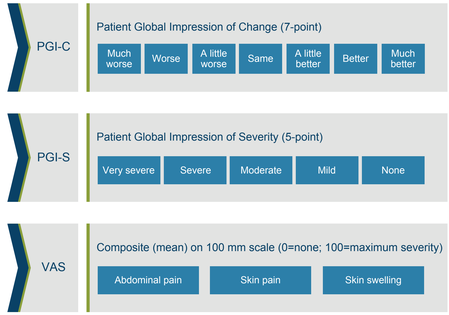


PK, pharmacokinetic; R, randomized.

Outcome Measures and Statistical Analyses

- The PGI-C assessed symptom improvement on a 7-point scale from "much better" to "much worse" (**Figure 2**)
  - PGI-C was analyzed as time to reach "a little better"/"better" or higher improvement for 2 consecutive time points (ie, with persistence)
- A visual analogue scale (VAS) measured severity of HAE attack symptoms on a 100 mm scale ranging from 0 (none) to 100 (very severe)
  - Composite VAS score was averaged across 3 symptoms: abdominal pain, skin pain, and skin swelling
  - Improvement was defined as a 50% reduction at 3 consecutive time points from baseline in composite VAS
- The Patient Global Impression of Severity (PGI-S) assessed HAE attack severity on a 5-point Likert-type scale from "none" to "very severe"
  - PGI-S score improvement was defined as a decrease in attack severity by ≥1 level from baseline

Figure 2. PRO Measures



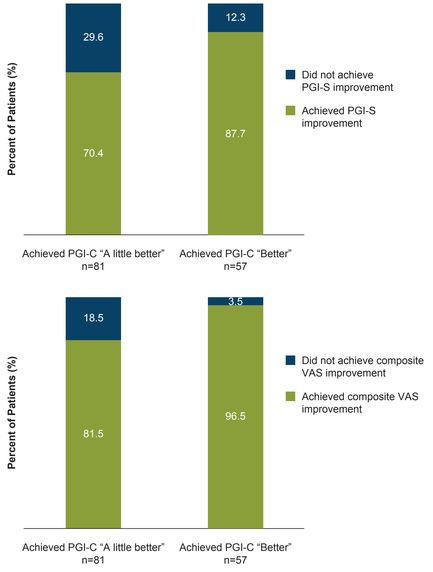
PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome; VAS, visual analogue scale.

- Each measure was completed at 30-minute intervals from 0 to 4 hours after administration of study drug, followed by 1-hour intervals to 12 hours, and then 3-hour intervals to 24 hours
- Post hoc analyses evaluated the association among PGI-C, VAS, and PGI-S over a 24-hour period from treatment for all attacks, regardless of treatment received
  - Cross-tabulations of PGI-C endpoints versus the VAS and PGI-S endpoints were produced. In these cross-tabulations, the PGI-C was assessed in relation to VAS and PGI-S endpoints
  - 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 between endpoints

Results

- Sixty patients completed treatment for at least 1 HAE attack (n=113 attacks)
- Of attacks that achieved a PGI-C score of "a little better" or higher with persistence (ie, 2 consecutive time points) within 24 hours, 70.4% (57/81) also achieved PGI-S improvement, and 81.5% (66/81) achieved composite VAS improvement within 24 hours (**Figure 3**)
  - Conversely, of attacks that did not achieve PGI-C improvement of "a little better" or higher with persistence, 93.8% (30/32) did not achieve PGI-S improvement, and 93.8% (30/32) did not achieve composite VAS improvement
- Of attacks that achieved a PGI-C score of "better" or higher with persistence within 24 hours, 87.7% (50/57) also achieved PGI-S improvement, and 96.5% (55/57) achieved composite VAS improvement within 24 hours
  - Conversely, of attacks that did not achieve PGI-C improvement of "better," 83.9% (47/56) did not achieve PGI-S improvement, and 76.8% (43/56) did not achieve composite VAS improvement

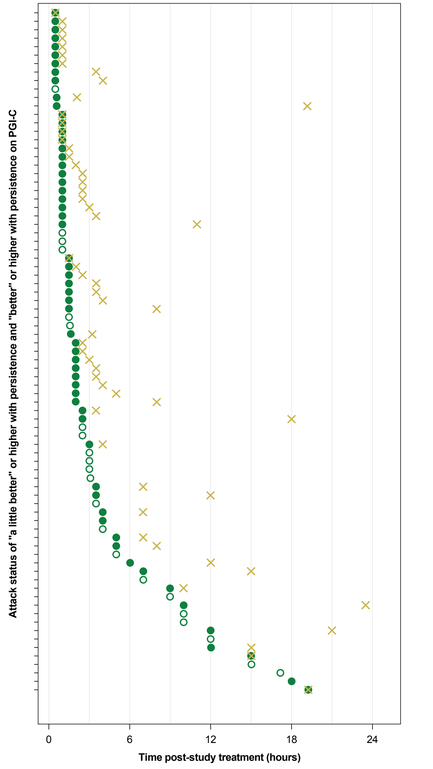
Figure 3. Agreement of PGI-C With Other PROs



PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PROs, patient-reported outcomes; VAS, visual analogue scale.

- The majority of attacks rated "a little better" or higher with persistence achieved "better" or higher with persistence within the assessment period, irrespective of treatment received (KVD900 or placebo) (**Figure 4**)

Figure 4. Time to PGI-C Rating



Time to PGI-C rating "a little better" or higher with persistence and time to "better" or higher with persistence for attacks that achieved PGI-C rating "a little better" or higher with persistence assessed within 24 hours post-study treatment (N=81)

- Descriptive comparisons of the PGI-C, VAS, and PGI-S measures showed moderate to substantial agreement (**Table 1**)

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

PGI-C Outcome (2 Consecutive Time Points)	Comparator Outcome (Single Time Point)	Sensitivity	Specificity	Cohen's Kappa*
PGI-C: "A little better"	PGI-S improvement	0.97	0.56	0.53
PGI-C: "A little better"	Composite VAS improvement	0.97	0.67	0.67
PGI-C: "Better"	PGI-S improvement	0.85	0.87	0.72
PGI-C: "Better"	Composite VAS improvement	0.81	0.96	0.73

*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 analogue scale.

- PGI-C scoring of "a little better" or higher with persistence had 97% sensitivity compared with composite VAS and PGI-S improvement
- Cohen's kappa was 0.72 and 0.73 for PGI-C scoring of "better" or higher with persistence compared with PGI-S and composite VAS improvements, respectively, indicating substantial agreement
  - Cohen's kappa was 0.53 and 0.67 for PGI-C scoring of "a little better" or higher with persistence compared with PGI-S and composite VAS improvements, indicating moderate and substantial agreement, respectively

Conclusions

- Compared with PGI-S and composite VAS improvements, PGI-C scoring of "a little better" with persistence was a sensitive endpoint for identifying improvement within 24 hours
- The majority of attacks that achieved PGI-C "a little better" went on to achieve PGI-C "better" at a later time
- A PGI-C rating of "better" with persistence is more specific but less sensitive than a PGI-C rating of "a little better"
- Moderate to substantial agreement between PGI-C and other PROs suggests that improvement on PGI-C was clinically significant from the patients' perspective

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Disclosures

PA and CY are employees of KalVista Pharmaceuticals, Inc. PW is an employee of Veramed Limited, and acts as a Consultant Statistician for KalVista.

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