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Agreement Between Improvements in Patient Global Impression of Change and Other Measures of Improvement and Attack Resolution Observed in a Phase 2 Trial With Sebetralstat (KVD900) in Patients With Hereditary Angioedema

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Introduction

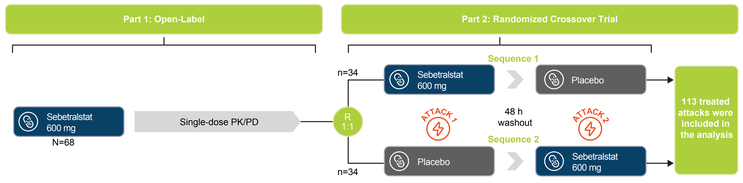
- Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic disease characterized by recurrent episodes of swelling; attacks are painful and can have a significant adverse impact on patients' quality of life[1-4]
- Treatment guidelines for HAE recommend that all patients have access to medications for on-demand treatment and treat attacks as early as possible, aiming to decrease the intensity of symptoms, reduce attack duration, and achieve a more rapid resolution[5-7]
  - Currently, all approved on-demand treatments require parenteral administration, which presents significant challenges with time needed for medication preparation, venous access, and injection-site–associated pain and discomfort[8-11]
  - There remains an unmet need for a safe and effective oral on-demand treatment option for HAE attacks to provide fast administration and reduce treatment burden
- HAE is driven by abnormal functioning of the kallikrein-kinin system, and studies have demonstrated that uncontrolled plasma kallikrein (PKa) activity is a key mechanism responsible for HAE attacks[3,4,12]
- Sebetralstat (KVD900) is a novel investigational oral plasma kallikrein inhibitor for the on-demand treatment of HAE attacks; the efficacy and safety of a single oral dose of sebetralstat 600 mg were evaluated in a phase 2, randomized, double-blind, placebo-controlled crossover trial in people living with HAE type I or II
  - This trial met the primary efficacy endpoint, demonstrating significantly longer time to use of conventional attack treatment with sebetralstat versus placebo
  - Improvements were also observed in patient-reported outcomes measured using the Patient Global Impression of Change (PGI-C) scale, Patient Global Impression of Severity (PGI-S) scale, and visual analog scale (VAS)
- 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 sebetralstat phase 2 trial

Methods

Phase 2 Study Population and Design

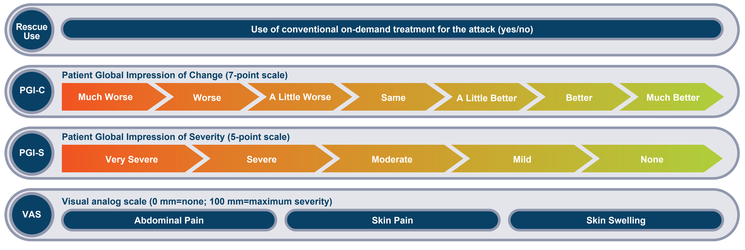
- This phase 2 trial (NCT04208412) included adults aged ≥18 years with HAE type I or II who had experienced at least 3 HAE attacks in the past 93 days and were not on prophylactic therapy
- Following an open-label pharmacokinetic (PK) phase (part 1), patients were randomized to treat 2 eligible HAE attacks with sebetralstat 600 mg or placebo in 1 of 2 sequences in a double-blind crossover trial (part 2) (**Figure 1**)
  - Attacks were not eligible if they involved the face or larynx

Figure 1. Study Design



h, hour; PD, pharmacodynamic; PK, pharmacokinetic; R, randomized.

Figure 2. Efficacy Assessment Scales



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

Efficacy Assessments Included in the Agreement Analyses

- Measures of improvement (within 24 hours of study drug):
  - **PGI-C:** Achievement of "A Little Better" or higher for 2 consecutive timepoints or at least "Better" for 1 timepoint
  - **Use of Rescue Medication:** Defined as use of conventional on-demand treatment for the attack within the assessment period
  - **PGI-S:** Achievement of ≥1 level reduction in severity from baseline
  - **VAS:** Achievement of ≥50% reduction in composite score from baseline
    - VAS composite score is averaged across 3 symptoms: abdominal pain, skin pain, and skin swelling
- Measures of attack resolution (within 24 hours of study drug):
  - **PGI-S:** Rating of "None"
  - **VAS:** All 3 component scores <10 mm for 3 consecutive timepoints
    - Attacks with all 3 VAS components <10 mm at baseline were excluded from the analysis of attack resolution according to VAS and excluded from the analyses presented here

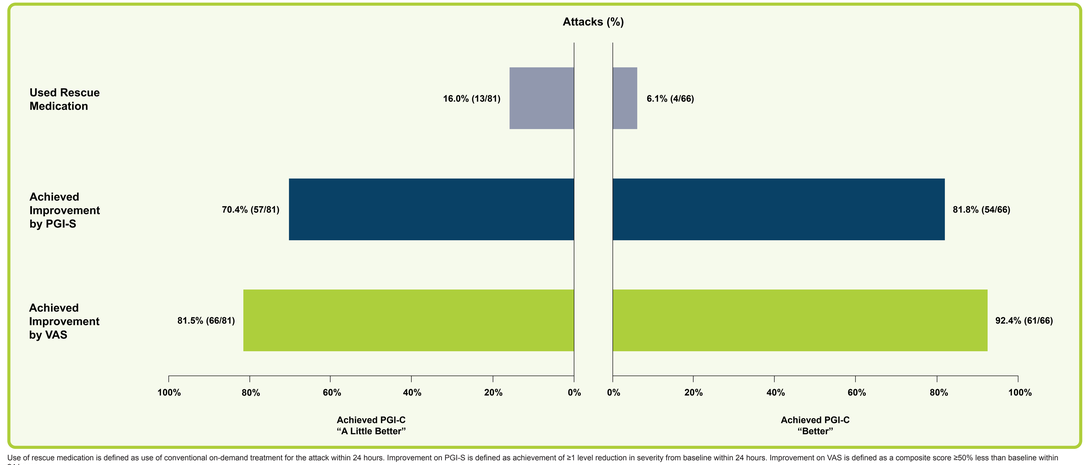
Statistical Analysis

- A post hoc cross-tabulation analysis was used to evaluate agreement between improvements achieved on the PGI-C scale and 5 other outcome measures: rescue medication use, improvement according to PGI-S, improvement according to VAS, 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 were assessed using standard sensitivity and specificity calculations
  - Cohen's kappa was calculated to assess the agreement (consistency) between the outcomes

Results

- A PGI-C score of "A Little Better" or higher for 2 consecutive timepoints was achieved in 71.7% (81/113) of attacks within 24 hours of study drug administration
  - Attacks that achieved a PGI-C score of "A Little Better" or higher for 2 consecutive timepoints were less likely to need rescue medication (16.0% [13/81] vs 65.6% [21/32]) and more likely to achieve improvement on PGI-S (70.4% [57/81] vs 6.3% [2/32]) and VAS (81.5% [66/81] vs 6.3% [2/32]) compared with attacks that did not achieve a PGI-C score of "A Little Better" or higher for 2 consecutive timepoints (**Figure 3**)

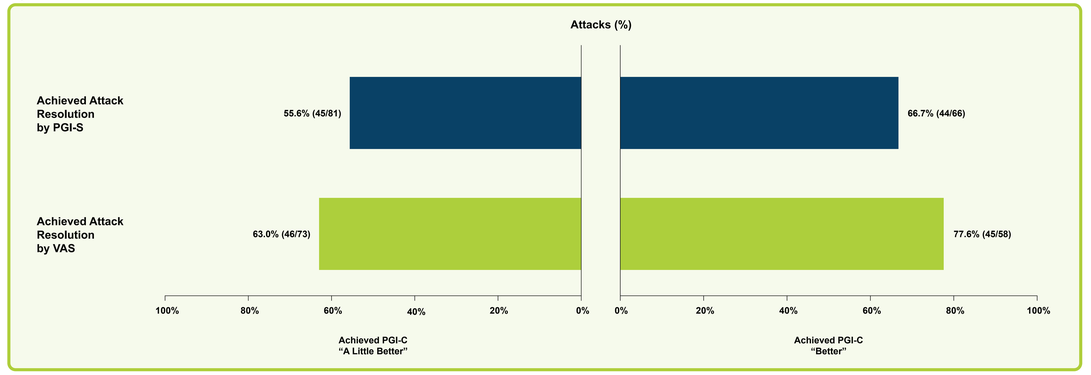
Figure 3. Improvement by Other Outcome Measures in Attacks That Achieved a PGI-C Score of "A Little Better" for 2 Consecutive Timepoints or "Better" for 1 Timepoint Within 24 Hours



Use of rescue medication is defined as use of conventional on-demand treatment for the attack within 24 hours. Improvement on PGI-S is defined as achievement of ≥1 level reduction in severity from baseline within 24 hours. Improvement on VAS is defined as a composite score ≥50% less than baseline within 24 hours.
PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; VAS, visual analog scale.

- A PGI-C score of "Better" or higher was achieved in 58.4% (66/113) of attacks within 24 hours of study drug administration
  - Attacks that achieved a PGI-C score of "Better" or higher for 1 timepoint were less likely to use rescue medication (6.1% [4/66] vs 63.8% [30/47]) and more likely to achieve improvement on PGI-S (81.8% [54/66] vs 10.6% [5/47]) and VAS (92.4% [61/66] vs 14.9% [7/47]) compared with attacks that did not achieve a PGI-C score of "Better" or higher for 1 timepoint (**Figure 3**)
- Attacks that achieved a PGI-C score of "A Little Better" or higher for 2 consecutive timepoints were more likely to achieve attack resolution on PGI-S (55.6% [45/81] vs 3.1% [1/32]) and VAS (63.0% [46/73] vs 4.2% [1/24]) compared with attacks that did not achieve a PGI-C score of "A Little Better" or higher for 2 consecutive timepoints (**Figure 4**)
- Attacks that achieved a PGI-C score of "Better" or higher for 1 timepoint were more likely to achieve attack resolution on PGI-S (66.7% [44/66] vs 4.3% [2/47]) and VAS (77.6% [45/58] vs 5.1% [2/39]) compared with attacks that did not achieve a PGI-C score of "Better" or higher for 1 timepoint (**Figure 4**)

Figure 4. Attack Resolution in Attacks That Achieved PGI-C Score "A Little Better" for 2 Consecutive Timepoints or "Better" for 1 Timepoint Within 24 Hours



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 timepoints. 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.

- Of attacks where "A Little Better" (2 consecutive timepoints) was achieved within 4 hours, 82.3% (51/62) also achieved "Better" (1 timepoint) within 24 hours; of attacks where "A Little Better" (2 consecutive timepoints) was achieved within 12 hours, 80.0% (60/75) also achieved "Better" (1 timepoint) within 24 hours
- Sensitivity, specificity, and Cohen's kappa are summarized in **Table 1**
  - Cohen's kappa indicated fair to substantial agreement of PGI-C "A Little Better" for 2 timepoints with no use of rescue medication, PGI-S, and VAS measures (**Table 1**)
    - Cohen's kappa indicated moderate to substantial agreement of PGI-C "Better" for 1 timepoint with no use of rescue medication, improvement on PGI-S, and improvement on VAS
    - Cohen's kappa indicated fair to substantial agreement between PGI-C improvements and attack resolution

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

PGI-C Outcome	Comparator Outcome	Sensitivity	Specificity	Cohen's Kappa*
"A Little Better" for 2 timepoints	No use of rescue medication	0.86	0.62	0.49
"A Little Better" for 2 timepoints	Improvement on PGI-S	0.97	0.56	0.53
"A Little Better" for 2 timepoints	Improvement on VAS	0.97	0.67	0.67
"A Little Better" for 2 timepoints	Attack resolution on PGI-S	0.98	0.46	0.39
"A Little Better" for 2 timepoints	Attack resolution on VAS	0.98	0.46	0.43
"Better" for 1 timepoint	No use of rescue medication	0.78	0.88	0.60
"Better" for 1 timepoint	Improvement on PGI-S	0.92	0.78	0.70
"Better" for 1 timepoint	Improvement on VAS	0.90	0.89	0.78
"Better" for 1 timepoint	Attack resolution on PGI-S	0.96	0.67	0.59
"Better" for 1 timepoint	Attack resolution on 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.

- Across each comparison, PGI-C "A Little Better" showed higher sensitivity but somewhat lower specificity versus PGI-C "Better"

Conclusions

- These results demonstrate that improvements observed on the PGI-C scale were in agreement with other measures of improvement or attack resolution in the phase 2 trial of oral on-demand drug candidate sebetralstat, further validating PGI-C as a meaningful measure of efficacy in people living with HAE
- This analysis supported the choice of PGI-C "A Little Better" for 2 timepoints as the primary endpoint for the phase 3 KONFIDENT trial (NCT05259917)

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Disclosures

PKA, MDS, and CMY are employees of KalVista Pharmaceuticals. PW is an employee of Veramed Limited and acts as a consultant statistician for KalVista Pharmaceuticals. DC has received speaker fees and/or consultancy fees from BioCryst, CSL Behring, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Pharming, Pharvaris, and Shire/Takeda.

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