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Efficacy of the Oral Plasma Kallikrein Inhibitor Sebetralstat (KVD900) by Attack Location in a Phase 2 Clinical Trial in Patients With Hereditary Angioedema

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Background

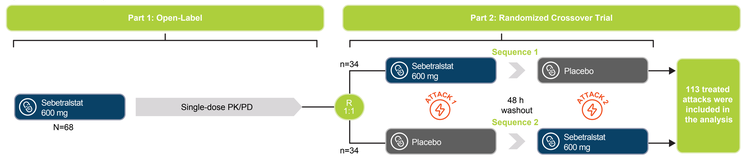
- Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic disease involving abnormal functioning of the kallikrein-kinin system leading to increased vascular permeability and characterized by unpredictable, recurrent, and often painful episodes of swelling of varying severity and location[1-4]
  - Peripheral (also called subcutaneous) attacks affecting the hands, feet, and genitourinary tract are the most common, and may result in disability for 1-5 days[2,3]
  - Abdominal (also called submucosal) attacks are characterized by discomfort, distension, and nausea that can sometimes progress to severe pain with vomiting and diarrhea[2,3]
  - Attacks involving orofacial-pharyngeal zones and upper airways are less common yet potentially life-threatening[5]
    - 1%-3% of attacks affect the larynx and upper airways[5]
- Treatment guidelines for HAE recommend that patients have access to medications for on-demand treatment of HAE attacks and treat every attack as early as possible, aiming to decrease the intensity of symptoms, reduce attack duration, and achieve a more rapid resolution[6-8]
  - Currently, all approved on-demand treatments require parenteral administration, which presents significant challenges with time needed for medication preparation, administration, and injection-site–associated pain and discomfort[9-12]
    - This may cause a delay in patients receiving treatment[13]
  - There remains an unmet need for a safe and effective oral on-demand treatment option for HAE attacks regardless of attack location or severity
- Sebetralstat (KVD900) is a novel investigational oral plasma kallikrein inhibitor for on-demand treatment of HAE attacks
- In a phase 2 randomized clinical trial, a single oral dose of sebetralstat 600 mg was effective in slowing the progression of HAE attacks and was generally safe and well tolerated[14-16]
- This post hoc analysis of data from the phase 2 trial assessed achievement of and time to symptom relief, improvement, and attack resolution following sebetralstat administration by attack location (abdominal or peripheral)

Methods

Trial Design

- Trial design (NCT04208412) is shown in **Figure 1**

Figure 1. Trial Design



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

- Enrolled patients were aged ≥18 years with HAE type I or II who had ≥3 attacks in the past 93 days and were not on prophylactic therapy
- In the crossover part of the trial (part 2), patients were randomized to treat 2 mild to moderate HAE attacks (severe attacks and orofacial-pharyngeal-laryngeal attacks were excluded) with sebetralstat 600 mg or placebo in 1 of 2 sequences (**Figure 1**)
- Attacks that involved the face or larynx were not eligible for treatment with the study drug

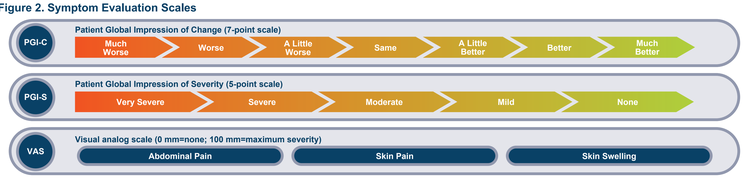
Classification of Attacks

- For this analysis, attacks were categorized as
  - abdominal: included abdominal symptoms at attack onset (with or without peripheral symptoms)
  - peripheral: included only peripheral (and no abdominal) symptoms at attack onset

Outcome Measures

- Symptom relief was defined as a score of "A Little Better" or higher for 2 consecutive timepoints within 12 hours of study drug administration on the Patient Global Impression of Change (PGI-C) scale
- Baseline attack severity was evaluated by Patient Global Impression of Severity (PGI-S) scale (numeric values from 0 to 4 were used to align with categorical PGI-S scores from "None" to "Very Severe") and by individual component (abdominal pain, skin pain, skin swelling) and composite (mean of the components) scores on a 100-mm visual analog scale (VAS)
- Improvement on PGI-S scale was defined as improvement from baseline by 1 or more levels within 12 hours
- Attack resolution was defined as:
  - PGI-S score of 0 ("None") within 24 hours
  - Attack resolution was also defined as a score <10 mm for all VAS components for 3 consecutive timepoints within 24 hours
    - Attacks where all 3 VAS components were <10 mm at baseline were excluded from the analysis
- Results are presented using descriptive statistics; symptom evaluation scales are shown in **Figure 2**

Figure 2. Symptom Evaluation Scales



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

Results

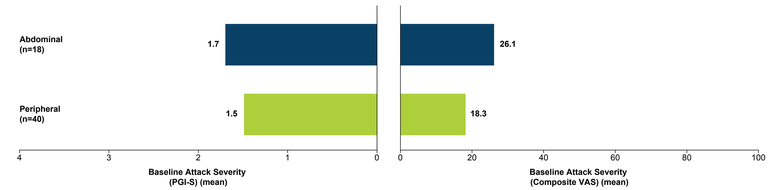
Attack Characteristics

- 113 attacks were treated in the trial, of which 58 were treated with sebetralstat
- Of sebetralstat-treated attacks, 18 (31.0%) were categorized as abdominal and 40 (69.0%) as peripheral
  - Of the attacks classified as abdominal, 2 (11.1%) attacks included both abdominal and peripheral symptoms (abdomen and genitals; abdomen and arm)
  - Peripheral attacks most commonly occurred in the arms or legs (62.5%) followed by the genitourinary tract (15.0%), hand (12.5%), and other locations (eg, buttock, shoulder, foot) (10.0%)

Baseline Attack Severity

- There was a tendency for abdominal attacks to be rated as more severe than peripheral attacks at baseline (**Figure 3**)

Figure 3. Baseline Severity of Attacks (PGI-S and Composite VAS) by Attack Location



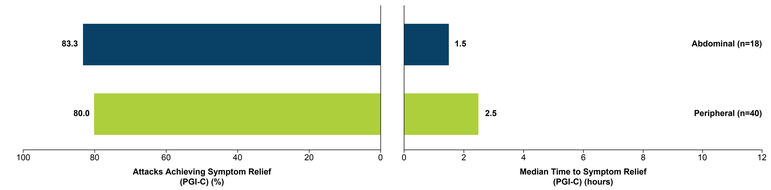
PGI-S, Patient Global Impression of Severity; VAS, visual analog scale.

- Mean VAS component scores at baseline by attack location
  - Skin pain: 13.8 (abdominal), 18.0 (peripheral)
  - Skin swelling: 23.2 (abdominal), 34.9 (peripheral)
  - Abdominal pain: 41.2 (abdominal), 2.2 (peripheral)

Symptom Relief

- 83.3% of attacks in abdominal and 80.0% in peripheral locations achieved symptom relief as assessed on PGI-C within 12 hours (**Figure 4, left panel**)
- Median time to symptom relief (PGI-C) within 12 hours was slightly shorter for abdominal attacks compared with peripheral attacks (**Figure 4, right panel**)

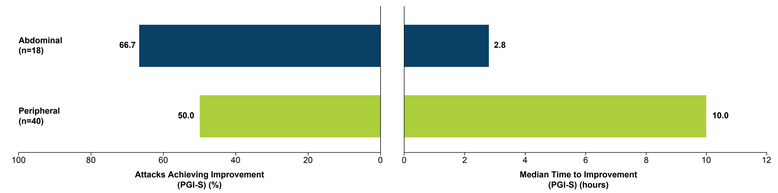
Figure 4. Achievement of Symptom Relief and Time to Symptom Relief (PGI-C) Within 12 Hours by Attack Location



Symptom relief was defined as a score of "A Little Better" or higher for 2 consecutive timepoints within 12 hours of study drug administration on the PGI-C scale.
PGI-C, Patient Global Impression of Change.

- 66.7% of abdominal attacks and 50.0% of peripheral attacks improved on PGI-S within 12 hours (**Figure 5, left panel**)
- Based on PGI-S, median time to improvement within 12 hours was shorter for abdominal attacks (**Figure 5, right panel**)

Figure 5. Achievement of Symptom Improvement and Time to Symptom Improvement (PGI-S) Within 12 Hours by Attack Location

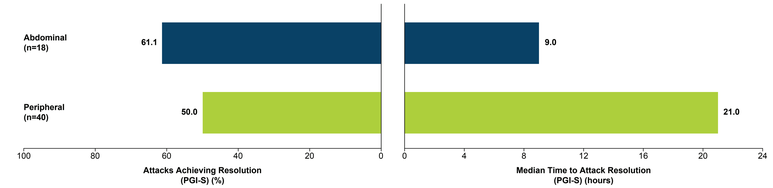


Improvement on PGI-S scale was defined as improvement from baseline by 1 or more levels within 12 hours.
PGI-S, Patient Global Impression of Severity.

Attack Resolution

- More abdominal (61.1%) than peripheral (50.0%) attacks achieved resolution within 24 hours on PGI-S (**Figure 6, left panel**)
- Median time to attack resolution (PGI-S) was 9 and 21 hours for abdominal and peripheral attacks, respectively (**Figure 6, right panel**)

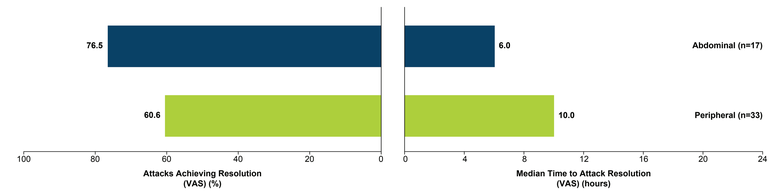
Figure 6. Resolution of Attacks and Time to Attack Resolution (PGI-S) Within 24 Hours by Attack Location



Attack resolution was defined as a PGI-S score of 0 ("None") within 24 hours.
PGI-S, Patient Global Impression of Severity.

- More abdominal (76.5%) than peripheral (60.6%) attacks achieved resolution within 24 hours on VAS (**Figure 7, left panel**)
- Median time to attack resolution (VAS) was 6 and 10 hours for abdominal and peripheral attacks, respectively (**Figure 7, right panel**)

Figure 7. Resolution of Attacks and Time to Attack Resolution (VAS) Within 24 Hours by Attack Location



Attack resolution was defined as a score <10 mm for all VAS components for 3 consecutive timepoints within 24 hours.
VAS, visual analog scale.

Conclusions

- Sebetralstat treatment resulted in rapid symptom relief for both abdominal and peripheral attacks, with approximately 80% achieving symptom relief within 12 hours regardless of attack location as evaluated by a score of "A Little Better" or higher for 2 consecutive timepoints on the PGI-C scale
  - Abdominal attacks tended to resolve more quickly than peripheral attacks as evaluated on PGI-S and VAS scales
  - Faster symptom relief for abdominal versus peripheral attacks observed in this study is consistent with previously reported findings for other acute therapies[17,18]
- The results of this post hoc analysis demonstrate that sebetralstat provides symptom relief and attack resolution for people living with HAE, regardless of abdominal or peripheral attack location

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Disclosures

EAP was the principal investigator and reviewed and approved the study report. AZ has received speaker/consultancy fees from BioCryst, CSL Behring, Pharming, and Takeda. DMC has received speaker fees and/or consultancy fees from BioCryst, CSL Behring, Ionis Pharmaceuticals, KalVista, Pharming, Pharvaris, and Shire/Takeda. PW is an employee of Veramed Limited, and acts as a consultant statistician for KalVista. PKA, CMY, and MDS are employees of KalVista Pharmaceuticals.

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