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Sebetralstat Effectiveness in the Treatment of Hereditary Angioedema Attacks Rated Mild or Moderate at Baseline in the Phase 2 Trial

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Introduction

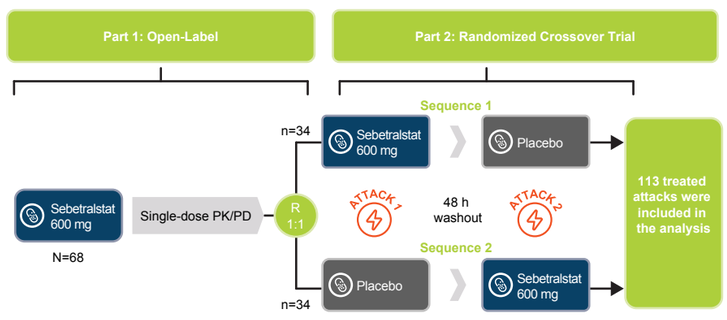
- Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic disease characterized by unpredictable recurrent episodes of swelling; abdominal and peripheral attacks are painful and can have a significant impact on patients' quality of life[1-4]
- Treatment guidelines for HAE recommend 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, finding a private area to administer medication, and injection-site–associated pain and discomfort[8-11]
- HAE is driven by deficiency or dysfunction of C1 inhibitor, which leads to uncontrolled activation of the kallikrein kinin system by plasma kallikrein[4,12]
- Sebetralstat is an investigational oral plasma kallikrein inhibitor for the on-demand treatment of HAE attacks that showed a favorable pharmacokinetic and pharmacodynamic profile and positive efficacy and safety results in a previous phase 2 trial[13-15]
  - Historically, clinical trials in HAE have focused on treatment of moderate to severe attacks[16-18]
  - To better reflect treatment guidelines, which recommend early treatment of all attacks, patients in this trial were advised to administer the study drug within an hour of onset and before the attack reached a "Severe" level on the Patient Global Impression of Severity (PGI-S) scale
  - Here, we present the results of a post hoc analysis of the phase 2 trial to assess the effects of sebetralstat on symptom relief, improvement, and attack resolution analyzed by baseline attack severity (mild or moderate)

Methods

Trial Design

- The randomized, double-blind, placebo-controlled, phase 2 crossover trial design (NCT04208412) is shown in **Figure 1**

Figure 1. Trial Design



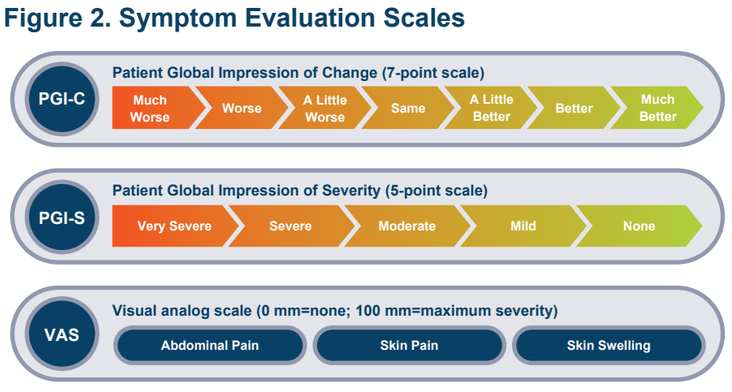
h, hour; PD, pharmacodynamic; PK, pharmacokinetic; R, randomized.

- Enrolled patients were aged ≥18 years with HAE type I or II. Patients 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 with sebetralstat 600 mg or placebo in one of two sequences (**Figure 1**)
  - Attacks that involved the face or larynx were not eligible for treatment with the study drug

Outcome Measures

- Symptom assessment scales are shown in **Figure 2**
- Symptom relief was defined as a rating of at least "A Little Better" for 2 consecutive timepoints on Patient Global Impression of Change (PGI-C) within 12 hours
- Improvement by Patient Global Impression of Severity (PGI-S) was defined as ≥1 level reduction in PGI-S rating within 12 hours
- Attack resolution by PGI-S was defined as a rating of 0 ("None") within 24 hours
- Time to symptom relief by visual analog scale (VAS) was defined as ≥50% reduction from baseline for 3 consecutive timepoints on composite VAS (abdominal pain, skin pain, and skin swelling) scores within 12 hours of study drug

Figure 2. Symptom Evaluation Scales



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

Results

Baseline Attack Severity

- The median time from recognition of attack onset to oral administration of study drug was 30 minutes
- Baseline attack severity was categorized using PGI-S
  - 26 (48%) of sebetralstat-treated attacks were categorized as mild and 28 (52%) were categorized as moderate
  - 31 (57%) of placebo-treated attacks were categorized as mild and 23 (43%) were categorized as moderate
  - Paired observations for each patient who treated two attacks (n=53) showed a nearly even distribution of mild/mild, moderate/moderate, and mixed severity (mild/moderate and moderate/mild) (**Table 1**)

Table 1. Severity of Attacks by PGI-S

Severity of 2 Attacks by PGI-S	Number of Patients
Mild/Mild	18
Mild/Moderate	11
Moderate/Mild	6
Moderate/Moderate	18

Mild includes mild and lower severity; moderate includes moderate and higher severity.
PGI-S, Patient Global Impression of Severity.

Symptom Relief by PGI-C

- Attacks of both mild and moderate severity that were treated with sebetralstat were more likely to achieve symptom relief by PGI-C within 12 hours compared to those treated with placebo (**Table 2**; **Figure 3**)

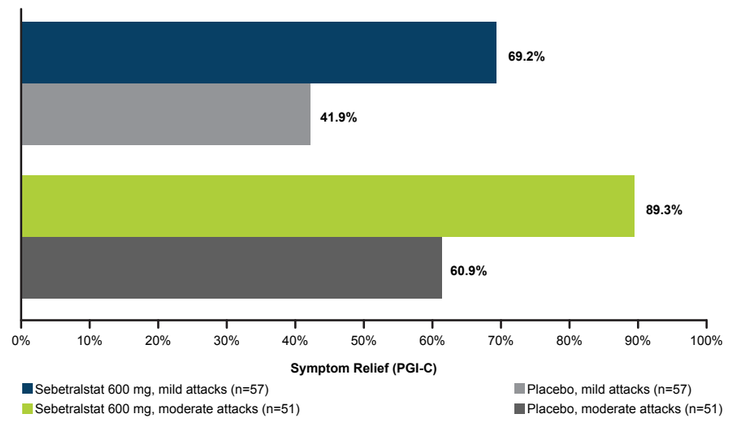
Table 2. Achievement of Outcome Measures by Baseline Attack Severity

Outcome Measurement	Baseline Attack Severity	Sebetralstat (n=54)	Placebo (n=54)
Symptom Relief by PGI-C	Mild	69.2% (18/26)	41.9% (13/31)
	Moderate	89.3% (25/28)	60.9% (14/23)
Improvement by PGI-S	Mild	34.6% (9/26)	9.7% (3/31)
	Moderate	78.6% (22/28)	52.2% (12/23)
Attack Resolution by PGI-S	Mild	53.8% (14/26)	22.6% (7/31)
	Moderate	53.6% (15/28)	34.8% (8/23)
Symptom Relief by VAS	Mild	65.4% (17/26)	22.6% (7/31)
	Moderate	64.3% (18/28)	43.5% (10/23)

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

- The placebo-adjusted symptom relief by PGI-C for mild and moderate attacks was similar

Figure 3. Achievement of Symptom Relief By PGI-C Within 12 Hours of Study Drug by Baseline Attack Severity

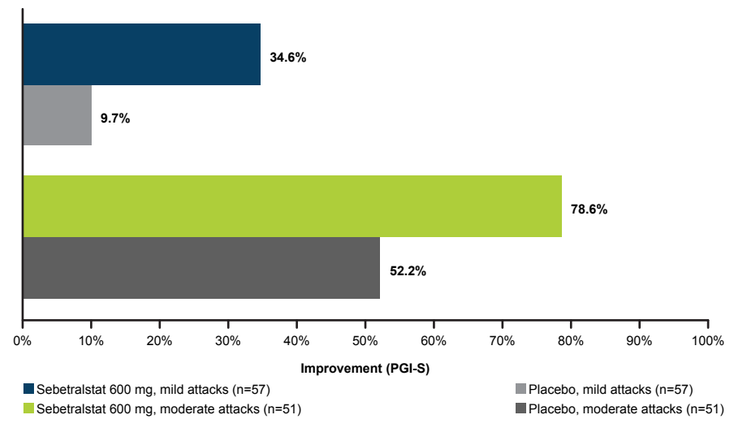


PGI-C, Patient Global Impression of Change

Improvement by PGI-S

- Attacks of both mild and moderate severity that were treated with sebetralstat were more likely to achieve improvement by PGI-S compared to those treated with placebo (**Table 2**; **Figure 4**)
- Placebo-adjusted improvement by PGI-S was similar for mild and moderate attacks

Figure 4. Achievement of Improvement by PGI-S Within 12 Hours of Study Drug by Baseline Attack Severity

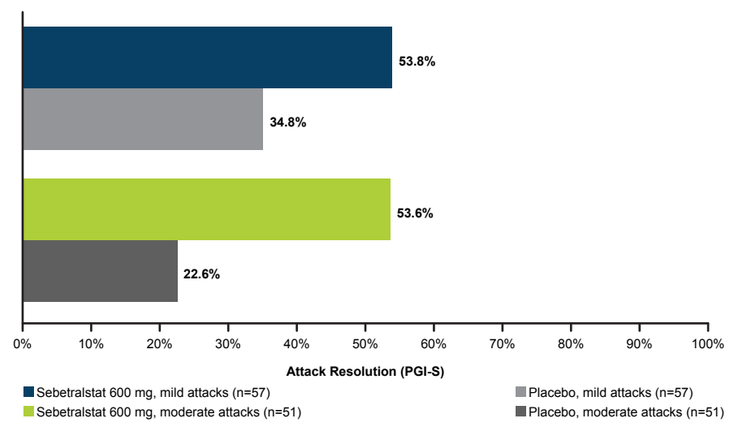


PGI-S, Patient Global Impression of Severity.

Attack Resolution

- Attacks of both mild and moderate severity that were treated with sebetralstat were more likely to achieve attack resolution by PGI-S compared to those treated with placebo (**Table 2**; **Figure 5**)
- Placebo-adjusted attack resolution by PGI-S (%) was similar for mild and moderate attacks

Figure 5. Achievement of Attack Resolution by PGI-S Within 24 Hours of Study Drug by Baseline Attack Severity

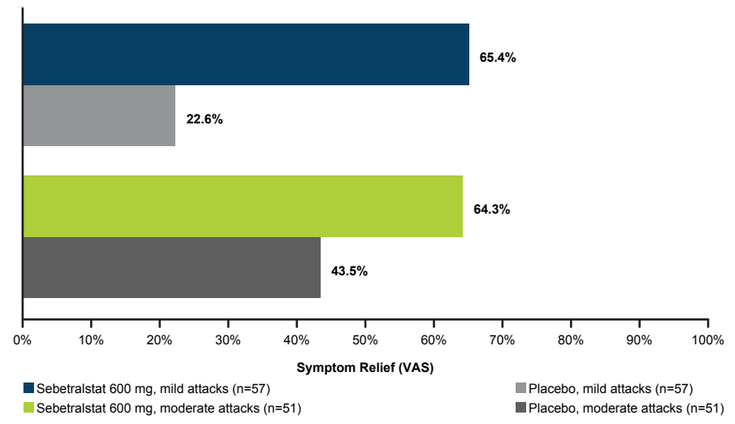


PGI-S, Patient Global Impression of Severity.

Symptom Relief by VAS

- Attacks of both mild and moderate severity that were treated with sebetralstat were more likely to achieve symptom relief by VAS compared to those treated with placebo (**Table 2**; **Figure 6**)
- Placebo-adjusted symptom relief by VAS was higher for mild compared with moderate attacks

Figure 6. Achievement of Symptom Relief by VAS Within 12 Hours of Study Drug by Baseline Attack Severity



VAS, visual analog scale.

Conclusion

- Sebetralstat treatment provided relief of mild and moderate HAE attacks, showing meaningful treatment effect regardless of baseline attack severity, as shown by PGI-C, PGI-S, and VAS

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