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Response Drivers in Sebetralstat Placebo-controlled Clinical Trials

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Background

- Sebetralstat, an oral plasma kallikrein inhibitor, has recently been approved for on-demand treatment of HAE attacks in patients ≥12 years old in the US, Europe, Japan, and other countries[1-4]
- Pooled analysis of the phase 2 and phase 3 randomized, placebo-controlled trials of sebetralstat in participants with HAE prioritized early treatment, aiming to intervene before symptomatic progression[5,6]
  - In those trials, sebetralstat 300 mg and 600 mg met the primary endpoint[5,6]
  - Time to beginning of symptom relief, assessed using the Patient Global Impression of Change (PGI-C) scale, was the primary endpoint in the phase 3 trial and secondary endpoint in the phase 2 trial[5,6]

Objective

- The objective of this analysis was to evaluate the factors that predict time to beginning of symptom relief for individuals treating attacks with sebetralstat

Methods

Clinical Trial Designs

- Data were pooled from participants in the phase 2 and phase 3 randomized crossover trials (**Table 1**)

Table 1. Key Features of Phase 2 and Phase 3 Trials

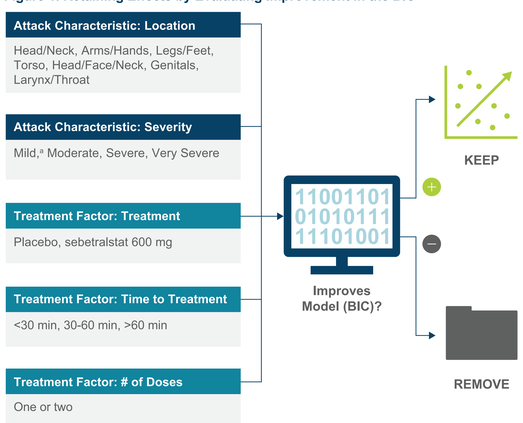
	Phase 2 (NCT04208412)[8]	Phase 3 (NCT05259917)[9]
Key inclusion criteria	• ≥18 years old • ≥3 attacks in 3 months	• ≥12 years old • ≥2 attacks in 3 months
LTP status	• LTP not allowed	• Stable LTP allowed
Treatment	• Sebetralstat 600 mg • Placebo	• Sebetralstat 300 mg • Sebetralstat 600 mg • Placebo
Second administration	• Not allowed	• Allowed ≥3 hours after first administration
Eligible attacks	• Attacks to be treated within an hour of onset and before reaching "severe" level on PGI-S • Facial or laryngeal attacks were not eligible	• Participants were advised to treat at the earliest recognition of an attack • Attacks of all severity and in all locations were eligible, excluding laryngeal attacks that were considered "severe" by the participant
Endpoints	Primary Endpoint • Time to conventional attack treatment Secondary Endpoints • **Time to beginning of symptom relief[a]** • Time to complete attack resolution	Primary Endpoint • **Time to beginning of symptom relief[a]** Key Secondary Endpoints • Time to reduction in severity • Time to complete attack resolution

[a]Time to beginning of symptom relief was defined as a rating of "A Little Better" on the PGI-C scale at 2 or more consecutive time points within 12 hours of first administration.
LTP, long-term prophylaxis; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

Statistical Approach

- Parametric time-to-event modeling was utilized; the Gompertz probability distribution was used to describe the hazard function (out of 8 different distributions evaluated for baseline hazard)
- The impact of each effect was evaluated using stepwise univariate addition, retaining the effect that caused the largest improvements in Bayesian information criterion (BIC) (**Figure 1**)
- Simulation was performed using the final model
  - Simulation included 5000 simulated patients randomly assigned to treatment and time between attack and first dose
  - Random variability in response was included in the simulations

Figure 1. Retaining Effects by Evaluating Improvement in the BIC

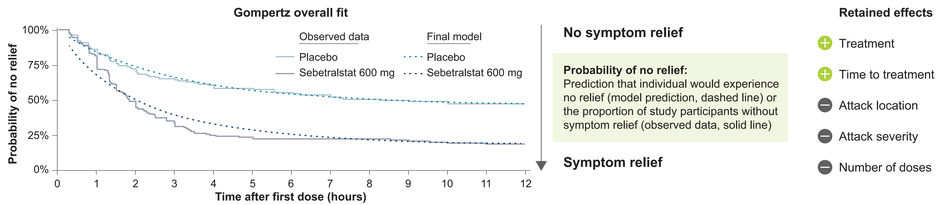


[a]Attacks rated as "None" were included as mild.
BIC, Bayesian information criterion; min, minutes.

Results

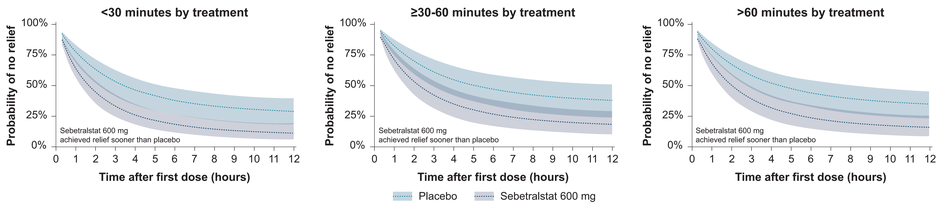
- The Gompertz model was found to generally reproduce the observed data (**Figure 2**)

Figure 2. Model Predictions Versus Observed Data



- The likelihood of symptom relief was achieved sooner with sebetralstat 600 mg when taken within 30 minutes of attack onset (**Figure 3**)
- Regardless of the time to treatment administration, the likelihood of symptom relief was achieved sooner with sebetralstat 600 mg than placebo
- The probability of symptom relief following sebetralstat 600 mg treatment was similar regardless of attack location, baseline severity, and number of doses

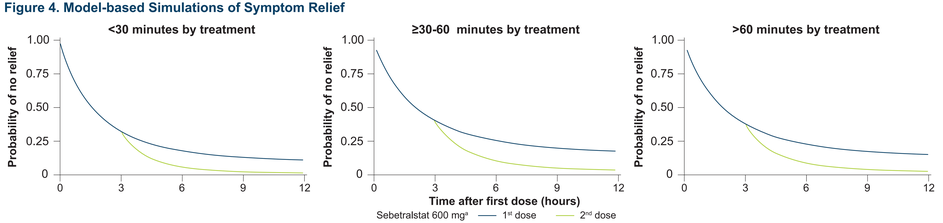
Figure 3. Key Predictors of Symptom Relief



Gompertz probability distribution was used to describe hazard function. Plots represent medians with 95% confidence intervals.

- In model-based simulations of time to symptom relief, a patient who administers 1 dose of sebetralstat 600 mg for an attack had a probability of experiencing symptom relief within 12 hours of 88.5% (95% CI: 81.5%-94.5%), 81.9% (95% CI: 70.5%-90.5%), and 84.4% (95% CI: 75.2%-92.2%) if administered within 30 minutes, between 30-60 minutes, and after 60 minutes, respectively (**Figure 4**)
  - The model also predicts use of a second dose provides incremental benefit within 12 hours

Figure 4. Model-based Simulations of Symptom Relief



[a]Simulations assumed that the 2nd dose of sebetralstat had the same efficacy as the first dose. The simulations ignore the probability that patients who did not respond to the 1st dose are "non-responders" and may not respond to subsequent doses. Plots represent medians.

Conclusions

- **Overall, the likelihood of symptom relief was achieved sooner with sebetralstat 600 mg than with placebo, regardless of time to treatment**
- **The model suggests earlier time to treatment associates with an earlier likelihood of achieving symptom relief with sebetralstat 600 mg**
  - **The earliest likelihood for symptom relief was achieved when sebetralstat 600 mg was taken <30 minutes after attack onset**
- **The model further suggests that sebetralstat works equally as well across different attack locations and severities**
- **Simulations determined that the vast majority of patients experience beginning of symptom relief within 12 hours after a single dose of sebetralstat 600 mg**
- **As an oral treatment, sebetralstat enables early administration, which was the strongest predictor of symptom relief**

References

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