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 significant economic and personal impact on patients and their caregivers.

Treatment guidelines for HAE recommend that immediate and appropriate management strategies are used for an on-demand treatment and that attacks are only as possible among the most severe. Many treatments are available for HAE, including conventional on-demand treatment (e.g., desmopressin [DDAVP], plasma-derived antihemophilic factor [AHF], and C1-esterase inhibitor, C1-INH) and prophylactic treatment with C1-INH concentrates or recombinant C1-INH.

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 were evaluated in an open-label, proof-of-concept, phase 2 study in patients with HAE (NCT04060141).

Methods

Phase 2 Study Population and Design

This phase 2, double-blind, randomized, placebo-controlled study enrolled adults aged 18 years or older who had experienced at least 3 HAE attacks in the past 30 days and who were expected to have ≥ 3 attacks during the study period at a single investigator site (Figure 1).

Methods continued...

Results

A phase 2 dose of 600 mg can be administered for the primary endpoint, and a 24-hour treatment period was used to evaluate the primary endpoint.

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

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cohen’s Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.98</td>
<td>0.92</td>
<td>0.60</td>
</tr>
<tr>
<td>PGI-C “Better”</td>
<td>0.98</td>
<td>0.92</td>
<td>0.60</td>
</tr>
</tbody>
</table>

The use of rescue medication is defined as use of conventional on-demand treatment for the attack within 24 hours. Improvement on VAS is defined as a composite score ≥ 50% less than baseline within 24 hours. Improvement on PGI-S is defined as a score of “Much Better” or “Better” in 2 consecutive timepoints.

Figure 1: Study Design

Figure 2: Efficacy Assessment Scales

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

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

Conclusions

• These results demonstrate that improvements observed on the PGI-C score were in agreement with other measures of improvement and attack resolution in the phase 2 trial of an on-demand drug candidate for HAE. Further validating PGI-C is a meaningful measure of efficacy for people living with HAE.

• The 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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References