Agreement of Patient Global Impression of Change With Attack Resolution or Use of Rescue Medication in Patients With Hereditary Angioedema

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Methods

Phase 2 Study Population and Design

This phase 2 trial (ClinicalTrials.gov ID: NCT02004812) included adult patients with HAE type I or II who had experienced at least 1 HAE attack in the 24 hours before screening and who had been diagnosed with episodic HAE attacks caused by deficiency or dysfunction of C1-inhibitor, a key regulator of the kallikrein-kinin system.

Following an initial open-label pharmacokinetic phase, patients were randomized to receive 2 eligible HAE attacks with KVD900 (600 mg) or placebo as indicated in Table 1.

In this phase 3 analysis, we evaluated agreement between improvement in the PGI-C scale and attack resolution or use of rescue medication (end points for the primary efficacy endpoint) according to a visual analogue scale (VAS) and Patient Global Impression of Change (PGI-C) scale.

Study Design

- Hereditary angioedema (HAE) is a rare genetic disease caused by deficiency or dysfunction of C1-inhibitor, a key regulator of the kallikrein-kinin system.
- Lack of C1-inhibitor leads to uncontrolled activity of plasma kallikrein, which triggers excessive release of bradykinin, a vasoactive mediator.
- KVD900 is an investigational oral plasma kallikrein inhibitor in development for the on-demand treatment of HAE attacks.

This study was supported by KalVista Pharmaceuticals Ltd. Medical writing assistance was provided under the direction of the authors by Courtney Niland, PhD, of Cadent Medical Communications, LLC.

Disclosures

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**Figure 1. Study Design**

**Statistical Analysis**

Cross-tabulation analysis was used to evaluate agreement between improvements achieved on the PGI-C scale and 3 other outcome measures: rescue medication use, attack resolution according to PGI-S, and attack resolution according to VAS per hour of attack study administration.

- The sensitivity and specificity of the PGI-C endpoint compared with each comparator was assessed using standard sensitivity and specificity calculations.
- Cohen's kappa was calculated to assess the agreement (consistency) between the outcomes.

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

**Conclusions**

This study analyzed that achieving improvement on the PGI-C scale was associated with achieving attack resolution and reduced need for rescue medication in patients with HAE.

Patients who reported improvement on the PGI-C scale within 24 hours were less likely to use rescue medication and more likely to achieve attack resolution within the 24-hour assessment period.

Conclusions

- Sixty patients completed trial for at least 1 HAE attack (n=113 attacks).
- A PGI-C score of "Better" or higher for 2 consecutive time points was achieved in 71.7% (81/113) of attacks within the 24-hour assessment period.
- Attacks that achieved a PGI-C score of "Better" or higher for 2 consecutive time points were less likely to result in use of rescue medication and more likely to achieve attack resolution by PGI-S and VAS compared with attacks that did not achieve PGI-C "Better" or higher for 1 time point.
- Sensitivity, specificity, and Cohen's kappa are summarized in Table 1.
- Cohen's kappa was used to moderate agreement of PGI-C "Better" for 2 time points with use of rescue medication, PGI-S, and VAS measures.
- Cohen's kappa indicated moderate agreement of PGI-C "Better" for 1 time point with no use of rescue medication, PGI-S, and VAS measures.
- A PGI-C score of "Better" for 2 time points was slightly more sensitive in identifying attack resolution within 24 hours than a PGI-C score of "Better" for 1 time point, but was less specific.

**Table 2. Sensitivity, Specificity, and Cohen's Kappa for PGI-C Outcome Within 24 Hours From Administration of Study Drug**

**Figure 3. Rescue Medication Use and Attack Resolution in Attacks That Achieved or Did Not Achieve PGI-C "A Little Better" for 2 Consecutive Time Points Within 24 Hours**

**Figure 2. Outcome Measures**

**Figure 3. Rescue Medication Use and Attack Resolution in Attacks That Achieved or Did Not Achieve PGI-C "A Little Better" for 2 Consecutive Time Points Within 24 Hours**

- Ninety-nine percent (99%) of attacks achieved a PGI-C score of "A Little Better" or higher for 2 consecutive time points.
- Ninety-four percent (94%) of attacks achieved a PGI-C score of "Better" or higher for 2 consecutive time points.
- Ninety percent (90%) of attacks achieved a PGI-C score of "Much Better" or higher for 2 consecutive time points.

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

**Results**

**Table 2. Sensitivity, Specificity, and Cohen’s Kappa for PGI-C Outcome Within 24 Hours From Administration of Study Drug**

**Statistical Analysis**

- Cross-tabulation analysis was used to evaluate agreement between improvements achieved on the PGI-C scale and 3 other outcome measures: rescue medication use, attack resolution according to PGI-S, and attack resolution according to VAS per hour of attack study administration.

- The sensitivity and specificity of the PGI-C endpoint compared with each comparator was assessed using standard sensitivity and specificity calculations.
- Cohen's kappa was calculated to assess the agreement (consistency) between the outcomes.

- Effects of PGI-C ranged from slight (kappa = 0.01) to moderate (kappa = 0.44) for sensitivity and specificity calculations.