On-demand Oral Treatment With KVD900 for HAE Attacks Achieves Rapid Exposure and Improves Patient Outcomes

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Guidelines recommend effective on-demand therapy for every patient with HAE to reduce symptom severity and attack duration\(^1,2\)

The rate at which a drug reaches therapeutic concentrations in plasma may influence speed of onset of therapeutic effects

KVD900 is an investigational oral plasma kallikrein inhibitor in development for the treatment of acute HAE attacks

We evaluated pharmacokinetics of KVD900 and its relationship to patient-reported outcomes in the treatment of HAE attacks (NCT04208412)

HAE, hereditary angioedema.
Study Design

- Patients (aged ≥18 years) with HAE type I or II participated in a two-part phase 2 study (NCT04208412)
- Part 1: single 600-mg dose of open-label KVD900 administered in the clinic
- Part 2: double-blind, placebo-controlled crossover trial in which each patient treated 2 mild or moderate HAE attacks with KVD900 and placebo

HAE, hereditary angioedema; PK, pharmacokinetics; R, randomized.
Outcome Measures

Pharmacokinetic parameters

• Plasma concentration over time, maximum observed concentration ($C_{\text{max}}$), and time to $C_{\text{max}}$ ($T_{\text{max}}$)

Patient Global Impression of Change (PGI-C)

• Symptom improvement assessed on a 7-point scale from “much worse” to “much better,” with 3 highest scores “a little better,” “better,” and “much better”
• Measured at 30-minute intervals from 0.5 to 4 hours, 1-hour intervals to 12 hours, then 3-hour intervals to 24 hours
• Analyzed as time to reach “a little better” or higher improvement for 2 consecutive time points (or “better” or higher at any time point) within 12 and 24 hours

A selection of secondary and exploratory endpoints from the study are presented in this presentation. The full list of outcome measures from the study is available at https://clinicaltrials.gov/ct2/show/NCT04208412.

$C_{\text{max}}$, maximum observed concentration; PGI-C, Patient Global Impression of Change; $T_{\text{max}}$, time to $C_{\text{max}}$. 
Study Flow and Baseline Demographics

A total of 9 patients (26.5%) from the sequence 1 arm (KVD900-Placebo) withdrew early from the study; n=1 Withdrawal by Subject; n=8 Other. A total of 6 patients (17.6%) from the sequence 2 arm (Placebo-KVD900) withdrew early from the study; n=1 Lost to Follow-up; n=5 Other. Patients with Other as primary reason for withdrawal were withdrawn due to early discontinuation of the study as enough patients had completed the study.

BMI, body mass index; F, female; M, male; PK, pharmacokinetics; R, randomized; SD, standard deviation.

### Demographic Characteristics (N=68)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>Mean (SD) 38.3 (13.23)</td>
</tr>
<tr>
<td></td>
<td>Range 19-68</td>
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<tr>
<td><strong>Gender</strong></td>
<td>M/F, n 31/37</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>Mean (SD) 27.3 (5.47)</td>
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<td>Range 18.8-40.9</td>
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</tbody>
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### Randomized N=68

- KVD900: PK N=42
  - n=34
  - n=28
- Placebo
  - n=25
  - n=28

### 53 patients with 2 attacks

BMI, body mass index; F, female; M, male; PK, pharmacokinetics; R, randomized; SD, standard deviation.
KVD900 was rapidly absorbed, with measurable concentrations detected at 0.25 hours.

Plasma levels reached $C_{\text{max}}$ of 6080 ng/mL (geometric mean) within 1 hour (median $T_{\text{max}}$).
## Time to Symptom Improvement (PGI-C)

### Median (95% CI) Time to Symptom Improvement (Hours)

<table>
<thead>
<tr>
<th></th>
<th>“A Little Better” or Higher Improvement for 2 Consecutive Time Points</th>
<th>“Better” or Higher Improvement for Any Time Point</th>
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<tbody>
<tr>
<td></td>
<td>Within 12 Hours</td>
<td>Within 24 Hours</td>
</tr>
<tr>
<td>KVD900</td>
<td>1.6 (1.5–3.0)</td>
<td>1.6 (1.5–3.0)</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.0 (4.0–NC)</td>
<td>9.0 (4.0–17.2)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
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- Median time to symptom improvement was significantly shorter with KVD900 than with placebo (as indicated by a rating on the PGI-C of “a little better” for 2 consecutive time points or “better” for any 1 time point)

KVD900 treatment vs placebo analyzed using Gehan’s generalized Wilcoxon test in the Full Analysis Set (n=53). Findings for “a little better” or higher are for 2 consecutive time points. Findings for “better” or higher are at any 1 time point. Censoring occurred where an attack rating did not occur, or conventional attack treatment was used within the studied period post study drug dosing.

CI, confidence interval; NC, noncalculable; PGI-C, Patient Global Impression of Change.
Proportion of Patients With Symptom Improvement (PGI-C)

“A Little Better” or Higher Improvement (%)

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<thead>
<tr>
<th></th>
<th>KVD900</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Within 12 Hours</td>
<td>83.0</td>
<td>50.9</td>
</tr>
<tr>
<td>Within 24 Hours</td>
<td>84.9</td>
<td>64.2</td>
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n= 44 27

Within 12 Hours (P=0.0018) Within 24 Hours (P=0.0309)

“Better” or Higher Improvement (%)

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<thead>
<tr>
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<th>KVD900</th>
<th>Placebo</th>
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<tr>
<td>Within 12 Hours</td>
<td>58.5</td>
<td>35.8</td>
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<tr>
<td>Within 24 Hours</td>
<td>67.9</td>
<td>47.2</td>
</tr>
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n= 31 19 36 25

Within 12 Hours (P=0.0319) Within 24 Hours (P=0.0593)

• A higher percentage of patients rated HAE attacks “a little better”/“better” or higher within 12 and 24 hours with KVD900 treatment compared with placebo

KVD900 treatment vs placebo analyzed using Prescott’s test in the Full Analysis Set (n=53). Findings for “a little better” or higher are for 2 consecutive time points. Findings for “better” or higher are at any 1 time point. HAE, hereditary angioedema; PGI-C, Patient Global Impression of Change.
Conclusions

Treatment of HAE attacks with KVD900 achieved rapid plasma exposure and faster improvements in initial symptom relief compared with placebo.

Development of an exposure-response model for KVD900 would further elucidate the relationship between pharmacokinetic and pharmacodynamic measures and clinical outcomes.

Acknowledgments
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