A Phase 2 Study Evaluating an Antisense Oligonucleotide to Prekallikrein in Patients with Hereditary Angioedema


Background

- Hereditary angioedema attacks
  - burdensome, dangerous
  - decreased productivity
  - emotional distress
  - impaired health-related quality of life
- 2021 EAACI/WAO recommended treatment goal\(^1\):
  “...to achieve total control of the disease and to normalize patients’ lives.”
  100% Agreement/Evidence level D
- Prophylactic treatment aims: effectiveness, convenience & safety\(^2\)

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\(^1\) The International WAO/EAACI guideline for the management of hereditary angioedema - the 2021 revision and update, submitted
\(^2\) Fijen et al., Clin Rev Allergy Immunol. 2021
Contact activation route/kallikrein kinin system

PKK-LRx: GalNac oligonucleotide antisense

Targeted delivery of PKK-LRx to hepatocytes leads to significant knockdown of plasma prekallikrein in healthy volunteers

Illustration from Debacker et al., Mol. Ther. 2020; 28: 1759-1771
Methods

KEY INCLUSION CRITERIA
• HAE Type 1 and 2
• ≥ 18 years
• ≥ 2 attacks

PRIMARY OUTCOME
Time normalized number of HAE attacks (per month )

Flow of Trial Participants

F/u: follow-up; OLE: open-label extension
Patients baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PKK-LRx (N=14)</th>
<th>Placebo (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - yrs</td>
<td>37.8 (14.4)</td>
<td>40.0 (13.8)</td>
</tr>
<tr>
<td>Female Sex - n (%)</td>
<td>9 (64.3)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.6 (7.5)</td>
<td>26.2 (3.4)</td>
</tr>
<tr>
<td>C1-INH-HAE Type I - n (%)</td>
<td>13 (92.9)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Age at Onset of Angioedema Symptoms</td>
<td>10.6 (5.6)</td>
<td>16.5 (2.88)</td>
</tr>
<tr>
<td>Number of HAE Attacks in Prior 12 Months</td>
<td>23.1 (16.2)</td>
<td>25.3 (22.9)</td>
</tr>
</tbody>
</table>

Plasma Prekallikrein levels upon treatment with PKK-LRx

- Pharmacodynamic measures by mean percentage change from baseline in plasma Prekallikrein
HAE attacks per individual during screening, treatment and post-treatment periods

Primary Endpoint:
Rate of HAE attacks per month

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PKK-L$_{ag}$ (N=14)</th>
<th>Placebo (N=6)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of attacks per month</td>
<td>Mean (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>0.23 (0.08, 0.39)</td>
<td>2.21 (0.58, 3.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>-90% (-96, -76%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Monthly HAE attack rates

<table>
<thead>
<tr>
<th>Prespecified Secondary Endpoint</th>
<th>PKK-LRx (N=14)</th>
<th>Placebo (N=6)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of attacks per month (Week 5-17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>0.07 (-0.08, 0.23)</td>
<td>2.06 (0.41, 3.72)</td>
<td>0.003</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>-97% (-69, -100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. moderate or severe attacks (Week 1-17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>0.16 (0.03, 0.30)</td>
<td>1.38 (0.08, 2.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>-88% (-96, -66%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. moderate or severe attacks (Week 5-17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>0.05 (0.01, 0.39)</td>
<td>1.20 (0.62, 2.34)</td>
<td>0.004</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>-96% (-100, -65%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Patients Attack Free, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 5-17</td>
<td>12 (92.3%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 9-17</td>
<td>12 (92.3%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 13-17</td>
<td>13 (100.0%)</td>
<td>1 (16.7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Safety

<table>
<thead>
<tr>
<th>Incidence, n (%)</th>
<th>PKK-LRx</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Any Adverse Event</td>
<td>10 (71.4)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Any Drug-Related AE</td>
<td>4 (28.6)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>Highest severity of AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>9 (64.3)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (7.1)</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No SAE’s; no deaths; no discontinuations
Treatment emergent adverse events (TEAEs) Reported for 2 or More Subjects

<table>
<thead>
<tr>
<th>AE</th>
<th>ISIS 721744 80 mg n (%) (n=14)</th>
<th>Placebo n (%) (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache (%)</td>
<td>2 (14.3)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>1 (7.1)</td>
<td>1 (16.7)</td>
</tr>
</tbody>
</table>

Conclusions

- 20 Subjects with HAE type 1 or 2 randomized
- Monthly treatment with 80 mg PKK-LRx resulted in:
  - 90% reduction in angioedema attacks
  - 97% reduction in angioedema attacks (after second dose)
  - 92.3% patients attack free (after second dose)
- No serious adverse events
- Treatment well tolerated
- PKK-LRx is a promising prophylactic treatment in HAE
- Phase 3 in preparation
Acknowledgements

- **Principle investigators**
  - Jonathan A. Bernstein (Cincinnati, Ohio)
  - Timothy Craig (Hershey, Pennsylvania)
  - William R. Lumry (Dallas, Texas)
  - Michael E. Manning (Scottsdale, Arizona)
  - Jason Raasch (Plymouth, Massachusetts)
  - Raffi Tachdjian (Los Angeles, California)
On-demand Oral Treatment With KVD900 for HAE Attacks Achieves Rapid Exposure and Improves Patient Outcomes

Jonathan A. Bernstein,1 Huamin H. Li,2 Chris M. Yea,3 Andreas Maetzel,4 Paul K. Audhya,3 Peter Williams,5 Aleena Banerji,6 Marc A. Riedl7

1University of Cincinnati College of Medicine and Bernstein Clinical Research Center, LLC, Cincinnati, OH, USA; 2Institute for Asthma and Allergy, Wheaton, MD, USA; 3KalVista Pharmaceuticals, Inc., Cambridge, MA, USA; 4Institute of Health Policy & Management, University of Toronto Dalla Lana School of Public Health, Toronto, ON, Canada; 5Veramed Limited, Twickenham, UK; 6Massachusetts General Hospital, Boston, MA, USA; 7University of California, San Diego, La Jolla, CA, USA

ACAAI Annual Meeting, November 4–8, 2021, New Orleans, LA

Presentation ID: A022

Background

Guidelines recommend effective on-demand therapy for every patient with HAE to reduce symptom severity and attack duration1,2

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

Outcome Measures

Pharmacokinetic parameters

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

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.
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.

KVD900: PK N=42

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

53 patients with 2 attacks

Plasma KVD900 Concentration Over Time

- 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 $T_{\text{max}}$)

Based on N=42 patients in the pharmacokinetic set.

$C_{\text{max}}$, maximum observed concentration; SD, standard deviation; $T_{\text{max}}$, time to $C_{\text{max}}$. 
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>
</tr>
</thead>
<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>
</tbody>
</table>

- 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).

Proportion of Patients With Symptom Improvement (PGI-C)

<table>
<thead>
<tr>
<th></th>
<th>“A Little Better” or Higher Improvement (%)</th>
<th>“Better” or Higher Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“A Little Better” or Higher Improvement (%)</td>
<td>KVD900</td>
</tr>
<tr>
<td></td>
<td>Within 12 Hours (P=0.0018)</td>
<td>83.0</td>
</tr>
<tr>
<td></td>
<td>Within 24 Hours (P=0.0309)</td>
<td>84.9</td>
</tr>
</tbody>
</table>

- 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.
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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HAE, hereditary angioedema.
Multi-Site Retrospective Evaluation of Fire Ant Venom Immunotherapy Efficacy and Safety

Hyun J. Park, MD, PhD1; David J. Schwartz, MD1

1 Allergy, Immunology, and Immunizations Clinic, Walter Reed National Military Medical Center, Bethesda, MD

Disclaimer: The views expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.

Introduction

• Imported fire ant (IFA) immunotherapy is the only disease modifying treatment against IFA hypersensitivity.
• IFA hypersensitivity is a significant military readiness matter.
• IFA venom immunotherapy (VIT) safety and efficacy studies are scarce.
• 11 military health facilities collaboration for a retrospective study to review active IFA VIT patients.
**Methods**

**Partnership Site Locations**

![Map of partnership site locations across the United States.](image)

**Disclaimer:** The views expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.

**Results**

**Patient Source Subset Counts**

- **USACAEL Total:** 876
- **DoD Only Total:** 809
- **11 Partnership Sites:** 491
- **Active IFA VIT:** 137
- **IFA Challenged:** 28

- **Patient Count from United States Army Centralized Allergen Extract Laboratory (USACAEL)**
  - 2016 to Q1 2021
- **Patient Count from Chart review at Partnerships**
  - Q1 2021

**Disclaimer:** The views expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.
Results

Subject Subsets and Adverse Events

SR Pre-VIT: 97.81% (134/137)
Maintenance: 73.72% (101/137)
SR to VIT: 2.92% (4/137)
Epi for SR to VIT: 1.46% (2/137)

SR - Systemic Reaction, Epi - Epinephrine, VIT - Fire Ant Venom Immunotherapy

Sting Challenge Reaction Distribution

Local Irritation or Less: 67.86% (19/28)
Large Swelling: 17.86% (5/28)
Systemic Cutaneous: 7.14% (2/28)
Anaphylaxis: 7.14% (2/28)

Disclaimer: The views expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.
Conclusion

- Substantial proportion of subjects on IFA VIT had protection to re-exposure with few adverse events.
- IFA immunotherapy is a safe disease modifying treatment against IFA hypersensitivity.