KVD900, a new oral on-demand treatment of hereditary angioedema attacks achieves complete plasma kallikrein suppression: safety, tolerability, pharmacokinetic and pharmacodynamic results from a phase I first-in-human study

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Saturday May 25, 2019  O-25 11:00 – 12:30
Background

• HAE attacks are unpredictable in frequency and severity\(^1\)

• Immediate access to on-demand treatment for HAE attacks is mandatory\(^2\)

• Early initiation of on-demand treatment significantly shortens attack duration\(^3,4\)

• A rapid oral, on-demand treatment may stop attacks early at onset, addressing a significant worldwide need of HAE patients

Early on-demand initiation during time-critical window may stop attacks early at onset

Intervene early during PKa activation

Early inhibition of plasma kallikrein activation may pre-empt swelling and pain
Objectives

Evaluate single doses of KVD900 (powder in capsule & tablet):

• safety and tolerability
• pharmacokinetics (PK)
• pharmacodynamics (PD)
• exposure fasted vs. fed
Methods - setup

• Phase 1 study in healthy, adult male volunteers (18y to 55y) in three parts:
  – Part A: single ascending dose, capsules, 5 mg to 600 mg, random: n=6 active, 2 placebo, empty stomach
  – Part B: single dose capsule vs. tablet x-over, 100 mg, n=8, empty stomach
  – Part C: single dose tablet, empty stomach vs full meal, x-over, 600 mg, n=12
Methods – study schema

**Single-dose (caps):**
- Safety, PK & PD
  - n=6 & 2 × 8
  - Capsule vs. tablet
  - n=8

**Single-dose: fasted vs. fed n=12**

**Healthy subjects,**
- male, > 18y,
- randomized to active & placebo

- Placebo 5mg
- Placebo 10mg
- Placebo 20mg
- Placebo 40mg
- Placebo 80mg
- Placebo 160mg
- Placebo 300mg
- Placebo 600mg

- Capsule 100mg
- Tablet 100mg

- Fed 600mg
- Fasted 600mg

-wash-out
Methods - Analytics

• Tandem MS-MS for KVD900 concentrations

• Dextran sulfate (DXS) stimulation:
  – fluorogenic enzyme assay (whole plasma)
  – capillary-based high molecular weight kininogen (HK) cleavage immunoassay (whole plasma)
Plasma Kallikrein activation pathway

- Factor XII
- Factor XIIa
- Plasma Prekallikrein
- Plasma Kallikrein
- PKa Enzyme Assay
- High Molecular Weight Kininogen
- HK Cleavage Assay
- Brady-Kinin

Both tests measure the activity of plasma kallikrein in cleaving target substrates.

- Increased vascular permeability
- Pro-inflammatory
- Vaso-active
Results - Safety

- No SAEs reported
- 25/26 AEs were mild
  - One moderate (headache at 10mg)
  - No GI AEs considered related to KVD900
- No subjects withdrawn
- No clinically significant changes in vital signs, ECG, safety labs

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>AEs</th>
<th>Verbatim Reported Symptom</th>
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<tbody>
<tr>
<td>5mg</td>
<td>6</td>
<td>2</td>
<td>Back pain, dizziness (possibly related)</td>
</tr>
<tr>
<td>10mg</td>
<td>6</td>
<td>1</td>
<td>Headache (moderate)</td>
</tr>
<tr>
<td>20mg</td>
<td>6</td>
<td>1</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>40mg</td>
<td>6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>80mg</td>
<td>6</td>
<td>1</td>
<td>Cough</td>
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<tr>
<td>160mg</td>
<td>6</td>
<td>3</td>
<td>URTI, myalgia, nasopharyngitis</td>
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<tr>
<td>300mg</td>
<td>6</td>
<td>-</td>
<td>-</td>
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<tr>
<td>600mg</td>
<td>6</td>
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</tr>
<tr>
<td>100mg (bridge)</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>600mg (fasted vs. fed)</td>
<td>12</td>
<td>15</td>
<td>5 x headache (1 possibly, 3 probably related)</td>
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<td></td>
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<td></td>
<td>3 x fatigue (2 possibly related)</td>
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<td>2 x lethargy (probably related)</td>
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<td></td>
<td></td>
<td></td>
<td>1 x each: vomiting, folliculitis, eczema, arthropod bite, presyncope</td>
</tr>
<tr>
<td>Placebo</td>
<td>16</td>
<td>3</td>
<td>Back pain, oral herpes, oropharyngeal pain</td>
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</tbody>
</table>
Pharmacokinetics – capsules, ascending single doses

KVD900 rapidly achieves maximal plasma exposure

KVD900 (ng/ml)

Cohort 8 600 mg
Cohort 7 300 mg
Cohort 6 160 mg
Cohort 5 80 mg
Cohort 4 40 mg
Cohort 3 20 mg
Cohort 2 10 mg
Cohort 1 5 mg

Hours

Mean±/SEM
Pharmacokinetics – capsules vs. tablet (100mg)

The KVD900 tablet formulation further exceeds the fast absorption seen with the capsule.
Pharmacokinetics – Fasted vs. fed

KVD900 concentrations rapidly exceed multiples of IC$_{50}$ within 20 minutes irrespective of food intake.
Pharmacodynamics – PKa enzyme assay (600 mg tablet)

KVD900 achieves instantaneous PKa enzyme inhibition and maintains near complete suppression of activity for 8 hrs.
Pharmacodynamics – HK cleavage assay

The level of HK protection afforded by C1INH is sustained for 10hrs.
## Pharmacodynamics – Preservation of HK

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<tr>
<th>No DXS</th>
<th>DXS @ 17°</th>
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### Controls

### Ph. 1 subjects

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<tr>
<th></th>
<th>pre-dose</th>
<th>1 hr</th>
<th>6 hrs</th>
<th>8 hrs</th>
<th>10 hrs</th>
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<tbody>
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<tr>
<td>Subj. 6</td>
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HK cleavage protection is upheld for up to 12 hrs
Conclusions

- First-in-human study of KVD900 in 68 subjects
- Single oral administration of up to 600 mg KVD900 is generally safe and well tolerated without any severe adverse events and no related GI events
- KVD900 achieves rapid suppression of plasma kallikrein activity
- KVD900 achieves sustained protection of intact HK
- KVD900 concentrations rapidly exceed multiples of IC50 within 20 minutes irrespective of food intake
- Phase 2 study currently ongoing to evaluate potential of KVD900 for on-demand suppression of HAE attacks