Selectivity, Potency, and Exposure Evaluation of ATN-249, A New Oral Kallikrein Inhibitor for Hereditary Angioedema

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BACKGROUND
- Hereditary angioedema (HAE) is a rare, potentially life-threatening disease characterized by acute skin and mucosal edema
- HAE may result in recurrent skin swelling, abdominal pain, laryngeal edema, nonerythematous rash, tingling sensations, anxiety, mood changes, or exhaustion
- HAE is caused by a deficiency of C1 inhibitor (C1-INH), which leads to increased levels of plasma kallikrein
- Increased levels of plasma kallikrein lead to elevated levels of bradykinin, which causes vasodilation, inflammation, and edema
- Currently, there is no cure for HAE

MATERIALS & METHODS
- ATN-249 is a novel, orally-administered plasma kallikrein inhibitor that potentially treats HAE by blocking kallikrein-mediated production of bradykinin
- ATN-249 was >2000-fold more selective at inhibiting plasma kallikrein versus other closely related serine proteases (Table 1)
- In biochemical inhibition, ATN-249 had an IC₅₀ of 2.7nM vs 25.4nM for C1-INH; in contact activation assays, the EC₅₀ was 8.2nM vs 92.4nM, respectively (Figure 2)
- A single oral dose of ATN-249 at 15mg/kg provided 24-hour exposure (C₀₋₂₄) 30-fold greater than EC₅₀ (Figure 3)
- No adverse events were observed at the highest dose (300mg/kg), setting the no-observed-adverse-effect-level (NOAEL) at 300mg/kg

RESULTS
- ATN-249 was 9- to 11-fold more potent than C1-INH at inhibiting plasma kallikrein both in biochemical inhibition and contact activation assays

OBJECTIVES
The objective of this preclinical study was to evaluate the selectivity of ATN-249, as well as the potency, pharmacokinetic exposure, and safety of ATN-249 as compared to C1 inhibitor (C1-INH)

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Figure 1: Overview of Hereditary Angioedema and C1-INH Pathway-Specific Treatment Options

Figure 2: Potency of ATN-249 and C1-INH Plasma Kallikrein Inhibition (Percent)

Figure 3: Pharmacokinetic Exposure of ATN-249 After a Single Oral Dosing at 15mg/kg in Monkeys

Table 1: Selectivity of ATN-249

<table>
<thead>
<tr>
<th>Serine Protease</th>
<th>ATN-249 (nM)</th>
<th>C1-INH (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Kallikrein</td>
<td>2.7</td>
<td>N/A</td>
</tr>
<tr>
<td>Tissue Kallikrein</td>
<td>&gt;20,000</td>
<td>&gt;105,000</td>
</tr>
<tr>
<td>Plasmin</td>
<td>&gt;7,000</td>
<td>&gt;7,000</td>
</tr>
<tr>
<td>Factor Xa</td>
<td>&gt;50,000</td>
<td>&gt;50,000</td>
</tr>
<tr>
<td>Factor VIIa</td>
<td>&gt;50,000</td>
<td>&gt;50,000</td>
</tr>
<tr>
<td>Tissue Plasminogen Activator (IPA)</td>
<td>&gt;100,000</td>
<td>&gt;100,000</td>
</tr>
</tbody>
</table>

CONCLUSIONS/DISCUSSIONS
- ATN-249 was highly selective at plasma kallikrein inhibition compared to other closely related serine proteases
- ATN-249 demonstrated ~10-fold greater plasma kallikrein inhibition relative to C1-INH in both biochemical inhibition and contact activation assays — an ex-vivo assay that closely represents clinical pharmacology
- After a single dose, ATN-249 at 15mg/kg provided 24-hour exposure 30-fold greater than EC₅₀ and 20-fold below the NOAEL
- These results suggest a wide therapeutic window and once-daily dosing potential
- ATN-249 may be a potent, safe, orally-administered plasma kallikrein inhibitor for treatment of HAE

References: