Pharmacokinetics, Safety, Pharmacodynamics, and Potency of ATN-249, a Novel Oral Plasma Kallikrein Inhibitor for Hereditary Angioedema

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Disclosures

- CMO for Attune Pharmaceuticals, Inc.
- ATN-249 is an investigational agent which has not been approved by the FDA or the EMA
HAE Therapy

- Plasma derived C1-INH for prophylaxis – 2008
- Acute therapies within a year
- Lanadelumab and C1-INHsc recently approved

- Strong unmet need for effective, well tolerated, safe oral therapies with improved:
  - Quality of life
  - Convenience
ATN-249 – A New Oral Kallikrein Inhibitor

- Well characterized mechanism of action\(^1\)
- >1000 compounds synthesized
- ATN-249 selected on basis of chemical structure, selectivity and potency for plasma kallikrein and kallikrein inhibition
- Pre-clinical profile supported further development

Phase 1 Single Ascending Dose (SAD)\(^1\)

**Design**
- 7 cohorts with 8 subjects randomized 6:2 with placebo
- 50, 100 (fasted/fed), 150, 200, 400, & 800 mg QD

**Results**
- **Exposure:** Increased in a dose-dependent manner
- **PK:** Low to moderate between-subject variability
- **Safety:** Well tolerated:
  - No moderate/severe TEAEs
  - No drug-related TEAEs
  - No SAEs
  - No dose limiting toxicity

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\(^1\) Poster “Pharmacokinetics and Safety of ATN-249, a Novel Oral Plasma Kallikrein Inhibitor for Hereditary Angioedema” presented at WSAAI, January 20-24, 2019
Phase 1 Multiple Ascending Dose (MAD)

**Design**
- 4 cohorts with 8 subjects randomized 6:2 with placebo
- 100, 200, 400 mg QD, & 300 mg BID
- 14 days of repeated dosing

**Results**
- **PK:** Predictable and dose-linear with low to moderate between-subject variability
- **Safety:**
  - Well-tolerated
  - No drug related TEAEs
- **PD:** Trough levels well above the therapeutically relevant concentrations needed for inhibition
Exposure increased in a dose-dependent manner
Multiple Ascending Dose PK

Plasma Concentration, Day 14

Exposure increased in a dose-dependent manner
## Multiple Ascending Dose PK Parameters

### Day 14

<table>
<thead>
<tr>
<th>Parameter Mean (% CV)</th>
<th>100 QD</th>
<th>200 QD</th>
<th>400 QD</th>
<th>300 BID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC&lt;sub&gt;τ&lt;/sub&gt; (ng*hr/mL)</strong></td>
<td>4592 (26.9)</td>
<td>9749 (27.2)</td>
<td>16390 (47.8)</td>
<td>28740 (26.4)</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;avg&lt;/sub&gt; (ng/mL)</strong></td>
<td>191 (26.9)</td>
<td>406 (27.2)</td>
<td>683 (47.8)</td>
<td>1198 (26.4)</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</strong></td>
<td>496 (22.7)</td>
<td>1202 (26.1)</td>
<td>2010 (60.5)</td>
<td>2040 (28.6)</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;min&lt;/sub&gt; (ng/mL)</strong></td>
<td>47 (36.0)</td>
<td>92 (44.5)</td>
<td>153 (45.1)</td>
<td>527 (28.2)</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (Hours)</strong></td>
<td>2.4 (35.6)</td>
<td>2.2 (49.9)</td>
<td>1.9 (43.2)</td>
<td>1.9 (43.2)</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;1/2&lt;/sub&gt; (Hours)</strong></td>
<td>10.9 (8.1)</td>
<td>10.5 (30.3)</td>
<td>11.7 (20.4)</td>
<td>7.7 (7.6)</td>
</tr>
</tbody>
</table>

- **AUC**, **C<sub>avg</sub>**, **C<sub>max</sub>**, and **C<sub>min</sub>** increased proportionally with dose
- **T<sub>max</sub>** and **T<sub>1/2</sub>** consistent across dose cohorts
Multiple Ascending Dose Safety Summary

- 113 TEAEs
  - None related to investigational drug
  - 86 drug arm & 27 placebo arm
  - Majority were mild: 106 mild & 7 moderate

- 1 SAE – Not related to investigational drug
  - Asymptomatic cardiac arrhythmia

- No clinically significant laboratory or EKG abnormalities

- One subject withdrew on Day 15 as requested due to personal issues
## TEAEs – Instance & Type >10% of Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ATN-249 (N=24)</th>
<th>Placebo (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td></td>
</tr>
<tr>
<td>Total TEAEs</td>
<td>95.8 (23)</td>
<td>86</td>
</tr>
<tr>
<td>By type (&gt;10%):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>50.0 (12)</td>
<td>22</td>
</tr>
<tr>
<td>General disorders &amp; cannulation site conditions</td>
<td>41.7 (10)</td>
<td>12</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>41.7 (10)</td>
<td>21</td>
</tr>
<tr>
<td>Skin &amp; subcutaneous tissue disorders</td>
<td>20.8 (5)</td>
<td>7</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>16.7 (4)</td>
<td>4</td>
</tr>
<tr>
<td>Infections &amp; infestations</td>
<td>16.7 (4)</td>
<td>5</td>
</tr>
<tr>
<td>Injury, poisoning &amp; procedural complications</td>
<td>16.7 (4)</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal &amp; connective tissue disorders</td>
<td>16.7 (4)</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory, thoracic &amp; mediastinal disorders</td>
<td>12.5 (3)</td>
<td>1</td>
</tr>
</tbody>
</table>

- Comparable safety profile vs. placebo
- TEAEs were self limited and not drug related
Biochemical Inhibition of Plasma Kallikrein

<table>
<thead>
<tr>
<th>Name</th>
<th>IC_{50} (nM)</th>
<th>IC_{90} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATN-249</td>
<td>1.8</td>
<td>13.1</td>
</tr>
<tr>
<td>ATN-111</td>
<td>0.8</td>
<td>4.3</td>
</tr>
<tr>
<td>Lanadelumab</td>
<td>0.4</td>
<td>3.3</td>
</tr>
<tr>
<td>C1-INH</td>
<td>29.0</td>
<td>191.6</td>
</tr>
</tbody>
</table>

- 16-fold higher potency vs. C1-INH
- 4-fold lower potency vs. lanadelumab
Inhibition of Plasma Kallikrein via Contact Assay Activation (Elagic Acid) in Diluted Human Plasma

<table>
<thead>
<tr>
<th>Name</th>
<th>EC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>EC&lt;sub&gt;90&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATN-249</td>
<td>2.7</td>
<td>19.9</td>
</tr>
<tr>
<td>ATN-111</td>
<td>0.9</td>
<td>5.4</td>
</tr>
<tr>
<td>Lanadelumab</td>
<td>0.7</td>
<td>10.8</td>
</tr>
<tr>
<td>C1-INH</td>
<td>40.7</td>
<td>593.7</td>
</tr>
</tbody>
</table>

- 15-fold higher potency vs. C1-INH
- 4-fold lower potency vs. lanadelumab
Western Blot Analysis of Cleaved HMWK\(^1\) in Healthy Volunteers’ Whole Plasma Activated by DXS

- **ATN-249**: >80% inhibition of cleaved kininogen at 125-250 nM
- **Lanadelumab**: >80% inhibition at 25-50 nM

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\(^1\) High-molecular-weight kininogen
Multiple Ascending Dose PK

Plasma Concentration, Day 14

Dosing as low as 100 mg BID is expected to achieve the trough concentration needed for inhibition.
Conclusions and Discussion

◆ MAD:
  – **PK**: Predictable and dose-linear with low to moderate between-subject variability
  – **Safety**: Well-tolerated and no drug related TEAEs
  – **PD**: Trough levels well above the therapeutically relevant concentrations

◆ In vitro inhibition comparable to lanadelumab

◆ Potentially a best-in-class safe, oral plasma kallikrein inhibitor for prophylactic treatment of HAE

◆ Phase 2 study planned
Thank You