Predict Long-Term HAE Attack Prevention with STAR-0215

Mechanistic Modeling and Simulations

Introduction
Inhibition of plasma kallikrein is a validated mechanism for prevention of hereditary angioedema (HAE) attacks. Clinically, STAR-0215 demonstrated a long circulating half-life (estimated up to 117 days) and prolonged plasma kallikrein inhibition (through at least 84 days). Simulations of different dose regimens were performed using a mechanistic quantitative systems pharmacology (QSP) model to explore the potential for the reduction of HAE attacks.

Objective
Evaluate the potential for long-acting HAE attack suppression by STAR-0215 with administration every three months (84 days) or every six months (168 days).

Methods
A simplified QSP model was established based on published reaction parameters for the plasma kallikrein-kininogen pathway in the vascular space and adjacent to the endothelial surface. The human pharmacokinetic (PK) parameters of STAR-0215 were derived from healthy adult subject results in the Phase 1a trial. The virtual cohorts were established using human PK parameters and their variabilities identified from healthy subjects. The reduction in monthly HAE attack rate starting at the 1st month of treatment, for both Q3 and Q6 month regimens.

Results
- QSP model showed that effective HAE attack prevention could be achieved with the following dosing regimens:
  - A 600mg SC loading dose, followed by 300mg SC maintenance dose every 3 months
  - 600mg SC loading doses on Days 1 and 28, followed by 600mg every 6 months

Both pharmacometric and QSP models showed subcutaneously administered STAR-0215 could potentially sustain required PK exposure for 86% of treated HAE patients to be attack-free during the first 6 months of treatment for the Q3 and Q6 month regimens, respectively.

Conclusions
STAR-0215 is a novel, potent and selective long-acting monoclonal antibody plasma kallikrein inhibitor for the potential treatment of HAE. Results from both pharmacometrics and QSP models support STAR-0215 administration once every 3 or 6 months for long-acting robust suppression of HAE attacks.

Jou-Ku Chung1, Haobin Luo2, John Tolsma2, Pradeep Bista1, Andy Nichols1, Chris Morabito1
1Astria Therapeutics, Boston, MA, USA; 2iRES Group, Needham, MA, USA

Poster P-05
Presented at the 13th C1-Inhibitor Deficiency and Angioedema Workshop

Dose Regimens Simulated

Regimen 1 (Q3 Month) - 600 mg SC loading dose followed by 300 mg SC maintenance doses every 3 months
Regimen 2 (Q6 Month) - 600 mg SC loading doses on days 1 and 28, followed by 600 mg SC maintenance dose every 6 months

Results – Pharmacometric Model Shows STAR-0215 Could Sustain Exposure Above Target Threshold with Both Q3 and Q6 Month Regimens

Results - QSP Model Predicts STAR-0215 May Produce Robust and Long-Lasting HAE Attack Suppression

A population simulation using virtual patients (n=500 per cohort)
- Model estimated a ≥90% reduction in monthly HAE attack rate starting at the 1st month of treatment, for both Q3 and Q6 month dose regimens

Method Figure 1 – Simplified QSP Model Diagram

Method Figure 2 – STAR-0215 PK in Healthy Adult Human Subjects in a Phase 1a Trial

Non-Compartmental PK Parameters of STAR-0215 From a Phase 1a Trial in Healthy Human Subjects

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>T0 (Days)</th>
<th>Tmax (Days)</th>
<th>Cmax (µg/mL)</th>
<th>AUC0-84 (µg.d/mL)</th>
<th>Clast (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg (n=7)</td>
<td>65</td>
<td>19</td>
<td>1.9</td>
<td>1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>300 mg (n=6)</td>
<td>25</td>
<td>16</td>
<td>2.1</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>600 mg (n=6)</td>
<td>105</td>
<td>8</td>
<td>24.9</td>
<td>1411</td>
<td>12.5</td>
</tr>
<tr>
<td>600 mg (n=6)</td>
<td>43</td>
<td>4</td>
<td>9.1</td>
<td>301</td>
<td>4.3</td>
</tr>
</tbody>
</table>

AUC0-84 = area under the concentration versus time curve from the start of administration to 84 days post-dose; Cmax = maximum drug concentration; SD = standard deviation; CL = clearance; t1/2 = terminal half-life; Tmax = time to maximum drug concentration; Vc = volume of distribution.

Note: Treatment was a single subcutaneous dose of STAR-0215 administered on Day 1 as follows: 100 mg, 300 mg, 600 mg ± placebo.

Results from both pharmacometrics and QSP models support STAR-0215 administration once every 3 or 6 months for long-acting robust suppression of HAE attacks.