Background

- Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by episodic swelling attacks
- Patients with HAE synthesize insufficient or non-functioning complement 1 inhibitor (C1-INH)
- HAE attacks are ultimately due to excessive bradykinin release, mediated by uncontrolled plasma kallikrein
- Plasma kallikrein inhibition is a proven therapeutic modality in the treatment of HAE
- A safe and effective oral plasma kallikrein inhibitor will be a major advance in HAE therapy

Objective

- To evaluate the pharmacokinetics, pharmacodynamics and safety of the oral, small molecule plasma kallikrein inhibitor BCX7353 in healthy Western & Japanese subjects

Methods

- Phase I study conducted in the UK
- Healthy subjects (n=122)
- Single ascending dose (SAD): Weekly: subjects: 10, 30, 100, 250 fasted & fed, 500 or 1000mg once daily (n=4 for all, except n=3 for 30mg), vs. placebo (n=2, each cohort)
- Japanese subjects: 100 and 500mg once daily (n=4 for all) vs. placebo (n=2, each cohort)
- Multiple ascending dose (MAD): 125, 250 (Western & Japanese), 500mg x 7 days, 150mg x 14 days (n=10), vs. placebo (n=2, each cohort)
- Serial measurements of drug levels and plasma kallikrein enzyme activity [specific bioassay]
- Mathematical modelling for PK-PD correlations (Emax model), and population PK and PD
- Safety evaluated by clinical and laboratory monitoring

Results

- Demographics
- Japanese healthy subjects

<table>
<thead>
<tr>
<th>Age, mean (SD)</th>
<th>125 (25)</th>
<th>250 (25)</th>
<th>350 (24)</th>
<th>500 (27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M:F</td>
<td>10:2</td>
<td>26:8</td>
<td>7:1</td>
<td>29:11</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25:0.6</td>
<td>25:7</td>
<td>26:6</td>
<td>28:4</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>217 (25)</td>
<td>363 (37)</td>
<td>517 (37)</td>
<td>261 (19)</td>
</tr>
<tr>
<td>Ctau (ng/mL)</td>
<td>101 (25)</td>
<td>158 (40)</td>
<td>235 (32)</td>
<td>112 (23)</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>69 (18)</td>
<td>79 (28)</td>
<td>67 (34)</td>
<td>73 (24)</td>
</tr>
</tbody>
</table>

PK Parameters

<table>
<thead>
<tr>
<th>Dose, mg QD</th>
<th>125 mg QD day 7</th>
<th>250 mg QD day 7</th>
<th>350 mg QD day 14</th>
<th>500 mg QD day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>217±25</td>
<td>363±37</td>
<td>517±37</td>
<td>261±19</td>
</tr>
<tr>
<td>Ctau (ng/mL)</td>
<td>101±25</td>
<td>158±40</td>
<td>235±32</td>
<td>112±23</td>
</tr>
<tr>
<td>Emax (ng/mL)</td>
<td>3,703±214</td>
<td>5,722±214</td>
<td>8,213±214</td>
<td>4,180±210</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>69±18</td>
<td>79±26</td>
<td>67±16</td>
<td>73±24</td>
</tr>
</tbody>
</table>

Safety findings: Single and multiple doses in Western & Japanese Subjects

- No SAEs
- No clinically significant laboratory abnormalities
- 31 of 35 (89%) AEs were mild (grade 1)
- No SAEs
- No clinically significant laboratory abnormalities
- 63 of 70 (90%) AEs were mild (grade 1)
- Four grade 2 events:
  - 100mg Western: moderate (grade 2) nausea and vomiting [2 AEs] (1 subject), moderate (grade 2) hay fever [1 subject]
  - 500mg Japanese cohort: moderate self-limiting diarrhea [1 subject]

Multiple daily doses of 125, 250, 500 mg (7 d), 350 mg (14 d) (N = 50)

- Twelve grade 1 events:
  - 500 mg QD: grade 1 abdominal pain [1 subject], grade 1 diarrhea [1 subject], grade 1 skin rash [1 subject], grade 1 cough [1 subject]
- Six grade 2 events and one grade 3 event:
  - 250 mg GD x 7 Western: grade 2 syncope [1]
  - 350 mg GD x 14 Western: grade 2 upper abdominal pain [1 - discontinued from study]
  - 500 mg QD x 7 Western cohort: grade 2 headache [1], grade 2 diarrhea and upper abdominal pain [1 - discontinued from study], grade 3 skin hypersensitivity reaction [1] (maculopapular rash)

Conclusions

- Once daily administration of the oral small molecule BCX7353 results in sustained drug levels supported by a half-life of 60-70 hrs
- Kallikrein inhibition is sustained over a 24hr dosing interval and is highly correlated to plasma concentrations, r=0.92
- Once daily BCX7353 has a generally well tolerated safety profile
- Clinical studies with HAE patients are planned to assess the efficacy of BCX7353 in reducing the occurrence of attacks

Disclosures: In compliance with the ACC/AHA guidelines on conflict of interest, the speaker/author disclosed the following financial relationships of the speaker/author with companies whose products or services may be related to the medical content of the presentation. Following are the financial relationships of the speaker/author with the companies whose products or services may be related to the medical content of this presentation.

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(1) BioCryst Pharmaceuticals Inc., Durham, NC; (2) Quotient Clinical, Nottingham, United Kingdom; (3) BioCryst Pharmaceuticals Inc. Birmingham, Alabama; (4) PharStat Inc., Raleigh NC