**Pharmacokinetics (PK) and Pharmacodynamics (PD) of a New Direct Thrombin Inhibitor (DPOC-4088)**

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**Background**

- DPOC-4088 is an orally active, potent, rapidly binding, reversible direct thrombin inhibitor in clinical development as a once-daily oral treatment.
- DPOC-4088 inhibits plasma coagulation triggered via the intrinsic or extrinsic pathway and effectively interferes with whole blood clotting.

**Methods**

- **Randomized, open-label, 4-period crossover, single oral dose study.**
- **12 eligible young (18-45 years of age) healthy male subjects.**
- **Each subject received 4 treatments (random order) with DPOC-4088 PR formulations.**
- **Plasma concentrations of DPOC-4088 were determined by validated liquid chromatography/mass spectrophotometry (LC/MS) methods.**

**PK Results**

- **Tale 1: PK of Two Doses and Two PR Formulations of DPOC-4088**

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>100 mg, 16 hr</th>
<th>100 mg, 20 hr</th>
<th>200 mg, 16 hr</th>
<th>200 mg, 20 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, nM</td>
<td>122</td>
<td>122</td>
<td>121</td>
<td>121</td>
</tr>
<tr>
<td>Cmax/C12 hr</td>
<td>2.8</td>
<td>2.9</td>
<td>2.2</td>
<td>2.6</td>
</tr>
<tr>
<td>T1/2 terminal</td>
<td>3.7</td>
<td>2.6</td>
<td>3.1</td>
<td>3.4</td>
</tr>
<tr>
<td>AUC, nM.hour</td>
<td>1099</td>
<td>1099</td>
<td>1099</td>
<td>1099</td>
</tr>
</tbody>
</table>

**PD Results**

- **Table 2: PD of Two Doses and Two PR Formulations of DPOC-4088**

<table>
<thead>
<tr>
<th>PD Parameter</th>
<th>100 mg, 16 hr</th>
<th>100 mg, 20 hr</th>
<th>200 mg, 16 hr</th>
<th>200 mg, 20 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax/C12 hr</td>
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<td>1099</td>
<td>1099</td>
<td>1099</td>
</tr>
</tbody>
</table>

**Safety Results**

- **Single oral doses of 100 mg and 200 mg DPOC-4088 in both the 16 and 20 hr PR release formulations were well-tolerated.**
- **Overall, 27 AEs occurred in 9 subjects, all were grade 1 except for one grade 2 headache and one grade 2 neck pain, both unlikely to be treatment-related.**
- **Headache and oropharyngeal pain were the only AEs reported in more than 2 subjects.**
- **Grade 1 epistaxis occurred in one subject ~30 minutes post-dosing (200 mg dose).**
- **No SAEs occurred and no clinically significant abnormalities were observed in safety labs, ECGs, vital signs or physical examinations.**

**Conclusions**

- **Increasing the DPOC-4088 dose from 100 to 200 mg resulted in a dose proportional increase in Cmax and exposure (AUC∞).**
- **The 20 hr PR formulation exhibited a significantly lower Cmax than the 16 hr PR formulation.**
- **The effect of DPOC-4088 on ECT, aPTT, TT and PT (INR) was dose-dependent for both the 16 hr and 20 hr PR formulations.**
- **The 20 hr PR formulation of DPOC-4088 was well-tolerated and is expected to show a favorable peak-to-trough ratio during multiple dosing.**