The First In Vitro and In Vivo Assessment of Anfibatide, a Novel Glycoprotein Ib Antagonist, In Mice and In a Phase I Human Clinical Trial

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Introduction

Platelets in hemostasis: physiologic role

Platelets in thrombosis: pathologic role

Glycoprotein Ib-IX-V complex

Platelet rupture leads to thrombosis: The No. 1 killer worldwide.
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Anfibatide

Purified protein

Molecular weight: 29799.7

Three-step purification

Model of Anfibatide complex with GPIb

Anfibatide with GPIb

vWF-A1 with GPIb
Anfibatide strongly inhibited Ristocetin-induced (GPIb- and vWF-mediated) platelet aggregation

Anfibatide inhibited thrombus formation in two arteriole murine models
Anfibatide strongly inhibited platelet adhesion and thrombus formation in *ex vivo* flow chamber in both murine and human blood

Anfibatide dissolved the preformed thrombus
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### Phase I Clinical Trial

- Provided informed consent and met all inclusion/exclusion criteria
- 94 patients were randomized

**Single dose groups**
8 groups, N=64

<table>
<thead>
<tr>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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</thead>
<tbody>
<tr>
<td>Dose (μg/60kg)</td>
<td>33</td>
<td>66</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>N</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

**Multi-dose groups**
3 groups, N=30

<table>
<thead>
<tr>
<th>Group</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose (μg/60kg)</td>
<td>33</td>
<td>66</td>
<td>1.0</td>
</tr>
<tr>
<td>Constant rate injection</td>
<td>Start time (h)</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Dose</td>
<td>0.12 μg/60kg/h for 24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>6</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

### Pharmacokinetics of Anfibatide

- Blood concentration of Anfibatide (ng/mL) vs. Time after Anfibatide administration (h)

### GPIb occupancy

- GPIb receptor occupancy (%) vs. Time after Anfibatide administration (h)
Anfibatide did not significantly decrease platelet count or prolong bleeding time

Summary of Safety Assessment
- No serious adverse events or deaths during study
- No serious allergic reactions occurred or antibodies detected
- No abnormal biochemistry or hematology parameters
- No significant change in ECG or blood pressure
- No significant effect on coagulation or fibrinolysis

Anfibatide is a safe and potent anti-platelet reagent with great potential for future anti-thrombotic therapy.
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