Safety and pharmacokinetics of ASN100, a monoclonal antibody combination for the prevention and treatment of *Staphylococcus aureus* infections, from an single ascending dose Phase 1 clinical study in healthy adult volunteers

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Study design, aims and endpoints

**Background**

With widespread growing concern regarding antibiotic resistance, novel antibacterial therapeutic approaches are needed. Monoclonal antibodies are well-suited for the prevention and treatment of acute bacterial infections with their high specificity and long half-lives. *S. aureus* is a human pathogen that is capable of causing a wide spectrum of infections ranging from mild conditions to severe diseases including sepsis and pneumonia. The observed limited impact of antibodies on *S. aureus* colonization of the airways (Stulak, 2017), prevention of infections by this organism represent a significant unmet medical need. *Staphylococcus aureus* pathogenesis involves the action of multiple toxins. ASN-1 is a novel, investigational product, a monoclonal antibody combination of two fully human IgG1 monoclonal antibodies, ASN-1 and ASN-2, that together target six *S. aureus* toxins (Rouha, 2015, Badarau, 2016). ASN-1 targets alpha-hemolysin (Hla) and four leukocidins (HlgAB, HlgCB, LukED, LukSF(PV)).

**Subject demographics**

- Characteristics
  - Plasma, all dose levels (n=10)
  - ASN-1 alone, all dose levels (n=12)
  - ASN-2 alone, all dose levels (n=12)
  - ASN100, all dose levels (n=6)

<table>
<thead>
<tr>
<th>Group</th>
<th>ASN-1 Dose (mg)</th>
<th>ASN-2 Dose (mg)</th>
<th>Ratio</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASN-1, 200 mg</td>
<td>100.3</td>
<td>194.1</td>
<td>0.53</td>
<td>12</td>
</tr>
<tr>
<td>ASN-1, 600 mg</td>
<td>184.7</td>
<td>651.6</td>
<td>0.28</td>
<td>16</td>
</tr>
<tr>
<td>ASN-1, 1800 mg</td>
<td>577.6</td>
<td>1839.0</td>
<td>0.32</td>
<td>18</td>
</tr>
<tr>
<td>ASN-2, 200 mg</td>
<td>1867.3</td>
<td>3394.2</td>
<td>0.55</td>
<td>14</td>
</tr>
<tr>
<td>ASN-2, 600 mg</td>
<td>2508.7</td>
<td>5033.0</td>
<td>0.50</td>
<td>16</td>
</tr>
<tr>
<td>ASN-2, 1800 mg</td>
<td>7352.7</td>
<td>16347.2</td>
<td>0.45</td>
<td>17</td>
</tr>
</tbody>
</table>

| ASN100, 4000 mg   | 4000 mg         | 4000 mg         | 1     | 15       |

<table>
<thead>
<tr>
<th>ASN-1 Dose (mg)</th>
<th>ASN-2 Dose (mg)</th>
<th>Ratio</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASN-1 (4000 mg)</td>
<td>200 mg</td>
<td>0.01</td>
<td>12</td>
</tr>
<tr>
<td>ASN-2 (4000 mg)</td>
<td>200 mg</td>
<td>0.01</td>
<td>12</td>
</tr>
</tbody>
</table>

**Dose escalation was successfully completed.**

- No dose limiting toxicities were observed.
  - Fifty-seven AEs occurred in 24 of 30 (80%) subjects receiving active drug and in 9 of 10 (90%) subjects receiving placebo.
  - All AEs were transient, mild or moderate in severity and resolved without intervention.
  - No new safety signals were observed with increasing dose escalation.
  - Two AEs (one episode of headache [subject receiving 200 mg ASN-1 alone, one of fatigue [subject receiving 4000 mg ASN-2]) were possibly related to study drug.
  - One unrelated serious adverse event (SAE) was reported [fractured metallic bone requiring surgery].
  - No treatment-emergent anti-drug antibody responses detected.
  - 2 subjects were confirmed to have ADAs against ASN-1 prior to dosing; these did not seem to impact the observed safety profile.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo, all dose levels (n=18)</th>
<th>ASN-1 alone, all dose levels (n=24)</th>
<th>ASN-1/ASN-2, all dose levels (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK sampling</td>
<td>pre-dosing; 1, 2, 3, 4, 5, 6, 7, 12, 24 hours; 7, 14, 21, 38, 58, 78, 98 days post-dosing</td>
<td>pre-dosing; 1, 2, 3, 4, 5, 6, 7, 12, 24 hours; 7, 14, 21, 38, 58, 78, 98 days post-dosing</td>
<td>pre-dosing; 1, 2, 3, 4, 5, 6, 7, 12, 24 hours; 7, 14, 21, 38, 58, 78, 98 days post-dosing</td>
</tr>
</tbody>
</table>

**Pharmacokinetic analysis**

**Safety results**

- ASN100 was safe and well tolerated at doses up to 8000 mg (4000 mg ASN-1 and 4000 mg ASN-2).
  - Dose escalation completed from 200 mg of ASN-1 or ASN-2 administered separately up to 8000 mg (4000 mg ASN-1 + 4000 mg ASN-2).
  - No drug-related SAEs
  - Only 2 possibly drug-related AE of mild severity recorded
  - No increase in AE frequency with dose escalation
  - No treatment-emergent ADAs detected up to day 98
  - ASN-1 and ASN-2 exhibited linear serum pharmacokinetics with limited inter-subject variability either when administered alone or simultaneously
  - Serum half-life of ASN-1 and ASN-2 as well as distribution volume were in line with previously reported profiles of human IgG1 mAbs

**Conclusions**

The observed favourable safety profile supports continued clinical development of ASN100 for the prevention and treatment of serious *S. aureus* infections, including pneumonia.

**References**


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