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

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### Background

With worldwide 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 antibiotic resistance of *S. aureus* and the observed limited impact of antibiotics on *S. aureus* colonization of the airways (Stalik, 2017), prevention of infections by this organism represent a significant unmet medical need. *Staphylococcus aureus* pathogenesis involves the action of multiple toxins. ASN100 is a novel, investigational product, a monoclonal antibody combination of two fully human IgG1 monoclonal antibodies, ASN-1 and ASN-2, that together neutralizes at least 5 *S. aureus* toxins (Rouha, 2015, Badarau, 2016). ASN-1 targets alpha-hemolysin (Hla) and four leukocidins (HlgA, HlgB, LukED, and LukSF/PV) and ASN-2 targets the recently discovered, potent leukocidin LukGK (lukAB). To support further evaluation of ASN100 for the prevention and treatment of *S. aureus* infectious diseases, a Phase 1, first-in-human study was conducted to assess the safety, tolerability and pharmacokinetics of ASN-1 and ASN-2 alone and in combination.

### Study design, aims and endpoints

The ASN100-01 (EudraCT 2015-003144-39) study was a first-in-human, double-blind, randomized, placebo controlled single ascending dose Phase 1 study.

- **40 normal healthy volunteers (NHVs) enrolled in the study**
- **Primary objective**
  - Evaluate the safety and tolerability of a single intravenous (IV) dose of ASN100 and its individual antibody components (ASN-1 and ASN-2) administered to healthy adults
- **Secondary objective**
  - Evaluate the pharmacokinetics of ASN100 and its components ASN-1 and ASN-2 and to measure ADA levels in serum against both antibodies
- **Inclusion criteria**
  - healthy adults aged 18 to 55 years
  - weight 60 to 100 kg, BMI = 30 kg/m²
  - normal electrocardiogram
  - negative screening assessment for human immunodeficiency virus or viral hepatitis (Hepatitis B or C)
- **Exclusion criteria**
  - current or prior use of immunoglobulin products within the previous 100 days
  - history of anaphylaxis, documented severe hypersensitivity reaction or severe injection site reaction
  - current or recent (< 1 month) immunosuppressive therapy with steroids, immunomodulators or anti-inflammatory drugs other than NSAIDs.

Subjects were randomized into 6 groups

<table>
<thead>
<tr>
<th>Dose</th>
<th>Antibody</th>
<th>Randomization</th>
<th>R of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg</td>
<td>ASN-1</td>
<td>1:1 active:placebo</td>
<td>8 (4 ASN-1, 4 ASN-2)</td>
</tr>
<tr>
<td>600 mg</td>
<td>ASN-1</td>
<td>1:1 active:placebo</td>
<td>8 (4 ASN-1, 4 ASN-2)</td>
</tr>
<tr>
<td>1800 mg</td>
<td>ASN-1</td>
<td>1:1 active:placebo</td>
<td>8 (4 ASN-1, 4 ASN-2)</td>
</tr>
<tr>
<td>4000 mg</td>
<td>ASN-1</td>
<td>1:1 active:placebo</td>
<td>8 (4 ASN-1, 4 ASN-2)</td>
</tr>
<tr>
<td>1800 mg + 1800 mg</td>
<td>ASN-1</td>
<td>1:1 active:placebo</td>
<td>4</td>
</tr>
<tr>
<td>4000 mg + 4000 mg</td>
<td>ASN-1</td>
<td>1:1 active:placebo</td>
<td>6</td>
</tr>
</tbody>
</table>

Administration of study drug

- **ASN-1** and/or **ASN-2 were administered intravenously, alone or simultaneously, over 50 to 60 minutes

Follow-up, PK and ADA sampling

- **subjects were monitored for 24 hours after dosing and followed for 98 days**
- **PK sampling: pre-dosing, 1, 2, 3, 4, 5, 6, 12, 24 hours, 7, 14, 21, 38, 58, 78, 90 days post-dosing**
- **ADA sampling: pre-dosing, 14, 38 and 90 days post-dosing**

### Pharmacokinetics

The summary of mean serum PK parameters for ASN100 and ASN-2.

<table>
<thead>
<tr>
<th>ASN100 dose (mg)</th>
<th>Cmax (μg/mL)</th>
<th>t1/2 (h)</th>
<th>AUC0-t (μg*h/mL)</th>
<th>AUC0-Inf (μg*h/mL)</th>
<th>Clearance (L/h)</th>
<th>VSS (L)</th>
<th>Half-life (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASN-1, 200 mg</td>
<td>100.3</td>
<td>194.0</td>
<td>19441</td>
<td>0.00107</td>
<td>6.89</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td>ASN-1, 600 mg</td>
<td>184.7</td>
<td>605.15</td>
<td>64516</td>
<td>0.0095</td>
<td>6.63</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>ASN-1, 1800 mg</td>
<td>577.6</td>
<td>1839.30</td>
<td>315138</td>
<td>0.0108</td>
<td>8.02</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>ASN-2, 200 mg</td>
<td>1867.3</td>
<td>393474</td>
<td>531318</td>
<td>0.0116</td>
<td>7.00</td>
<td>19.7</td>
<td></td>
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<tr>
<td>ASN-2, 600 mg</td>
<td>550.3</td>
<td>201314</td>
<td>233625</td>
<td>0.0086</td>
<td>6.89</td>
<td>24.1</td>
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<tr>
<td>ASN-2, 1800 mg</td>
<td>752.1</td>
<td>303329</td>
<td>316427</td>
<td>0.0129</td>
<td>8.24</td>
<td>20.3</td>
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<tr>
<td>ASN-2, 4000 mg</td>
<td>161.3</td>
<td>24242</td>
<td>25701</td>
<td>0.0075</td>
<td>6.54</td>
<td>23.9</td>
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<tr>
<td>ASN-2, 600 mg</td>
<td>183.2</td>
<td>67100</td>
<td>70440</td>
<td>0.00936</td>
<td>6.10</td>
<td>21.7</td>
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<tr>
<td>ASN-2, 1800 mg</td>
<td>543.0</td>
<td>244728</td>
<td>207655</td>
<td>0.00868</td>
<td>6.38</td>
<td>28.3</td>
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<tr>
<td>ASN-2, 4000 mg</td>
<td>467.7</td>
<td>250887</td>
<td>296315</td>
<td>0.00627</td>
<td>7.55</td>
<td>36.3</td>
<td></td>
</tr>
<tr>
<td>ASN-2, 600 mg</td>
<td>1074.8</td>
<td>437901</td>
<td>503209</td>
<td>0.00816</td>
<td>8.26</td>
<td>32.3</td>
<td></td>
</tr>
</tbody>
</table>

### Conclusions

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 ASN100 (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 AEs 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.**

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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