Serum and lung pharmacokinetics of ASN100, a monoclonal antibody combination for the prevention and treatment of Staphylococcus aureus pneumonia

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1. Abstract

Background: Monoclonal antibodies (mAbs) are well-suited for the prevention and treatment of acute bacterial infections. ASN100 is a combination of two fully human IgG1 mAbs, ASN-1 and ASN-2 that together neutralize six Staphylococcus aureus cytotoxins, alpha-hemolysin (Hla) and five leukocidins (HlgA, HlgB, LukA, LukB, LukD)* that are important in the pathogenesis of S. aureus pneumonia (Rouho et al., Badarou et al.). We aimed to characterize the pharmacokinetics (PK) of ASN100 in both serum and lung epithelial lining fluid (ELF) in male and female healthy volunteers.

Methods: The safety, tolerability, and serum and lung PK of single intravenous infusion of ASN100 was evaluated in a Phase 1 study. Eight subjects (5:1 randomization) in two double-blind cohorts received ASN100 (doses of 3600 mg or 8000 mg) or placebo. ASN-1 and ASN-2 were administered in a fixed dose 1:1 ratio. Twelve subjects received ASN100 open-label at doses of 3600 mg or 8000 mg and each underwent two bronchoalveolar lavage (BAL) fluid collections either on days 1 and 3 or on days 2 and 8 post-dosing. ASN-1 and ASN-2 concentrations were determined by ELISA. The ELF concentrations were normalized based on urea concentration in serum and BAL fluid.

Results: No dose limiting toxicity was observed. Treatment-emergent adverse events (TEAEs) showed no association of increased incidence with higher dose. All TEAEs were mild or moderate in severity, with 83% of subjects receiving ASN100 reporting at least one TEAE versus 90% of placebo subjects. A dose proportional increase in serum peak and exposure (AUC) of ASN-1 and ASN-2 was observed and the serum PK of ASN-1 and ASN-2 was comparable (approximate half-life of each antibody was 3 weeks). Penetration of ASN-1 and ASN-2 into the ELF was observed at the first post-dose time point of 24 hours, peak concentrations were observed after day 2 and the mAbs remained detectable for 30 days.

Conclusions: ASN100 was safe and well tolerated at doses up to 8000 mg (4000 mg ASN-1 and 4000 mg ASN-2). The PK profiles of ASN-1 and ASN-2 were comparable following single and multiple administration. Significant levels of each mAb were demonstrated between day 1 and 30 post-dosing. These data supported clinical development of ASN100 for the prevention and treatment of S. aureus pneumonia.

2. Study design, objectives

The ASN100-01 [EudraCT 2015-003144-39] study was a first-in-human, double-blind, randomized, placebo controlled single ascending dose Phase 1 study with an open-label extension assessing lung pharmacokinetics. Primary objectives: Evaluate the safety and tolerability of a single intravenous (IV) dose of ASN100 and its individual antibody components (ASN-1 and ASN-2).

Secondary objectives: 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 ≤100 kg, BMI ≤30 kg/m², normal electrocardiogram, normal screening assessment for human immunodeficiency virus or viral hepatitis (Hepatitis A, B, C). Exclusion criteria: current or prior use of immunoglobulin products within the previous 100 days; history of anaphylaxis or severe hypersensitivity reaction; severe injection site reaction; current (<1 month) immunosuppressive therapy with steroids, immunmodulators or anti-inflammatory drugs other than NSAIDs.

Subjects were randomized into 6 groups (double-blind phase) or allocated to 2 groups (open-label phase)

3. Subject demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo, all doses collected</th>
<th>1800 mg ASN-1 + 1800 mg ASN-2</th>
<th>Mean (SD) ASN-2 Concentration (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (%) Male/Female</td>
<td>6/6 (100), 6/6 (100)</td>
<td>6/6 (100), 6/6 (100)</td>
<td>308 ± 2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>25.0 (15.0)</td>
<td>25.0 (15.0)</td>
<td>17.9 (4.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.1 (7.7)</td>
<td>78.1 (7.7)</td>
<td>17.9 (4.4)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178.0 (8.4)</td>
<td>178.0 (8.4)</td>
<td>17.9 (4.4)</td>
</tr>
</tbody>
</table>

4. Safety results

Dose escalation was successfully completed up to 4000 mg ASN-1 + 4000 mg ASN-2 doses.

• No dose limiting toxicities were observed.
• Sixty-eight TEAEs occurred in 46 of 48 (95.8%) subjects receiving active drug and twenty-three TEAEs in 9 of 10 (90%) subjects receiving placebo.
• All TEAEs were moderate in severity and resolved without intervention. TEAEs had no association of increased incidence with dose escalation.
• Two TEAEs (one episode of headache [subject receiving 200 mg ASN-1 active], one of fatigue [subject receiving 8000 mg ASN100 active]) were possibly related to study drug.
• One unrelated serious adverse event (SAE) was reported (fractured metatarsal bone requiring surgery).
• No treatment-emergent anti-drug antibody responses detected.
• Three subjects were confirmed to have ADA against ASN-1 prior to dosing; these did not seem to impact the observed PK profile.

5. Serum pharmacokinetics

The serum pharmacokinetics of ASN-1 and ASN-2 following intravenous administration, administered singly or simultaneously

The summary of mean serum PK parameters for ASN-1 and ASN-2.

| Dose level |ASN-1|ASN-2|
|____________|____|_____|
| Mean (SD) [μg/mL] | 165.3 ± 25.0 | 257.01 ± 23.9 |
| Half-life [days] | 23.9 | 23.9 |

6. Lung and serum pharmacokinetics

The lung (epithelial lining fluid) and serum pharmacokinetics of ASN-1 and ASN-2 following intravenous administration at two dose levels.

| Dose level |ASN-1|ASN-2|
|____________|____|_____|
| Mean (SD) [μg/mL] | 543.0 ± 260507.8 | 28.3 |
| Half-life [days] | 28.3 | 28.3 |

7. Conclusions

ASN100 was safe and well tolerated; and ASN100 was present in lung epithelial lining fluid following intravenous administration.

• 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 TEAEs of mild severity recorded (1 episode of headache, 1 fatigue).
• No increase in TEAE 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 drug distribution volume were in line with previously reported profiles of human IgG mAbs.
• ASN-1 and ASN-2 was detected in lung epithelial lining fluid as early as day 1.

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

8. References


9. Support / Acknowledgements

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10. Disclosures and Contact

Disclosures: ZM and EN are employees for Arsanis Biosciences GmbH, FL, SL and CS are employees of Arsanis, Inc.; and ZM, FL, SL, EN and CS are shareholders in Arsanis, Inc.

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