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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 (HlgAB, HlgCB, LukED, LukSF [PVL] and LukGH) that are important in the pathogenesis of *S. aureus* pneumonia (*Rouha et al., Badarau 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 (3:1 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 30 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 concentrations 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 81% 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 were comparable (approximate half-life of each antibody was 3 weeks). Penetration of ASN-1 and ASN-2 into the ELF of the lung was observed at the first post-dose time point of 24 hours, peak concentrations were observed after day 2 and the mAbs remained detectable at day 30.
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 simultaneous administration. Significant lung concentrations of each mAb were demonstrated between day 1 and 30 post-dosing. These data support continued 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 objective: Evaluate the safety and tolerability of a single intravenous (IV) dose of ASN100 and its individual antibody components (ASN-1 and ASN-2)
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/m^2, 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/recent (<1 month) immunosuppressive therapy with steroids, immunomodulators or anti-inflammatory drugs other than NSAIDs.
Subjects were randomized into 6 groups (double-blind phase) or allocated to 2 groups (open-label phase)

Dose	Antibody	Randomization ratio	# of subjects
200 mg	ASN-1 or ASN-2	3:1 active:placebo	8 (4 ASN-1, 4 ASN-2)
600 mg	ASN-1 or ASN-2	3:1 active:placebo	8 (4 ASN-1, 4 ASN-2)
1800 mg	ASN-1 or ASN-2	3:1 active:placebo	8 (4 ASN-1, 4 ASN-2)
4000 mg	ASN-1 or ASN-2	3:1 active:placebo	8 (4 ASN-1, 4 ASN-2)
1800 mg + 1800 mg	ASN-1 and ASN-2	3:1 active:placebo	4
4000 mg + 4000 mg	ASN-1 and ASN-2	3:1 active:placebo	4
1800 mg + 1800 mg	ASN-1 and ASN-2	All active, open-label	6
4000 mg + 4000 mg	ASN-1 and ASN-2	All active, open-label	6

Administration of study drug: ASN-1 and/or ASN-2 were administered intravenously, alone or simultaneously
Follow-up, PK and ADA sampling: subjects were followed for 98 days (double-blind phase) or 30/37 days (open-label phase; duration of follow-up was dependent on timing of BAL sampling) for adverse events, PK and ADA

Study phase	Pre-dosing	1h	2h	3h	4h	5h	6h	12h	24h	2d	7d	8d	14d	21d	30d	37d	38d	58d	78d	98d
Double blind	PK + ADA	PK	PK	PK	PK	PK	PK	PK	PK		PK		PK + ADA	PK			PK + ADA	PK	PK	PK + ADA
Open-label	PK + ADA	PK	PK	PK	PK	PK	PK	PK	PK	BAL PK*		BAL§ PK			BAL§ PK + ADA	PK#				

* BAL and PK sampling only for 2 subjects per group; § BAL only for 2 subjects per group; # Only for subjects undergoing BAL on day 30

3. Subject demographics

Characteristic	Placebo, 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=18)
Sex (n [%])				
Male	6 (60.0)	9 (75.0)	9 (75.0)	17 (94.4)
Female	4 (40.0)	3 (25.0)	3 (25.0)	1 (5.6)
Race (n [%])				
Caucasian	10 (100.0)	11 (91.7)	11 (91.7)	17 (94.4)
Afro-American	0	0	1 (8.3)	0
Asian	0	1 (8.3)	0	1 (5.6)
Age, years (mean ± SD)	29 (6.36)	30 (8.04)	35 (10.17)	29 (8.52)
Body weight, kg (mean ± SD)	78 (12.77)	78 (11.44)	76 (10.15)	76 (10.38)
Height, cm (mean ± SD)	179 (10.49)	178 (7.76)	179 (8.49)	180.7 (9.75)
Body Mass Index, kg/m^2 (mean ± SD)	24 (3.37)	24 (3.01)	24 (3.09)	23 (2.40)

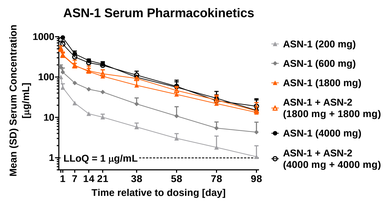
4. Safety results

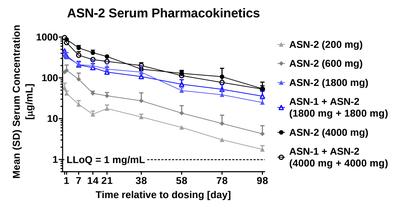
Dose escalation was successfully completed up to 4000 mg ASN-1 + 4000 mg ASN-2 doses.
- No dose limiting toxicities were observed.
- Sixty-eight TEAEs occurred in 34 of 42 (81%) subjects receiving active drug and twenty-three TEAEs in 9 of 10 (90%) subjects receiving placebo.
  - All TEAEs were transient, mild or 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.
- 3 subjects were confirmed to have ADAs 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



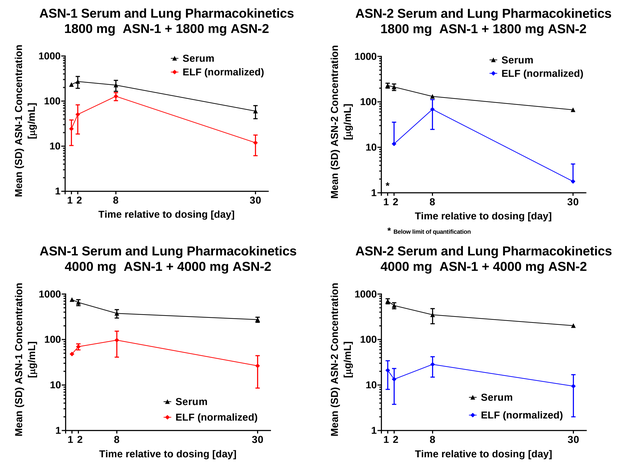


The summary of mean serum PK parameters for ASN-1 and ASN-2.

	ASN-1			ASN-2		
Dose level	Cmax [µg/mL]	$AUC_{0\text{-}inf}$ [µg*h/mL]	Half-life [days]	Cmax [µg/mL]	$AUC_{0\text{-}inf}$ [µg*h/mL]	Half-life [days]
200 mg (n=3)	100.3	19411	25.3	165.3	25701	23.9
600 mg (n=3)	184.7	64516	25.0	183.2	70440	21.7
1800 mg (n=3)	577.6	183930	24.0	543.0	269507	28.3
4000 mg (n=3)	1867.8	351387	19.7	1341.6	593307	32.8
ASN-1/ASN-2, 1800 + 1800 mg (n=3)	550.3	213265	24.1	467.7	296315	36.3
ASN-1/ASN-2, 1800 + 1800 mg (n=6) Open-label	637.5	135631	14.0	371.6	151232	22.8
ASN-1/ASN-2, 4000 + 4000 mg (n=3)	975.2	316427	20.3	1074.8	503209	32.3
ASN-1/ASN-2, 4000 + 4000 mg (n=6) Open-label	1251.5	342449	13.2	1094.5	382996	18.3

6. Lung and serum pharmacokinetics

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



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 distribution volume were in line with previously reported profiles of human IgG1κ mAbs
- ASN-1 and ASN-2 was detected in lung epitehelial 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

Rouha H, Badarau A, Visram ZC, et al. MAbs 2015;7(1):243-54.
Badarau A, Rouha H, Malafa S, et al. MAbs 2016;8(7):1347-60.

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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