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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. Due to the antibiotic resistance of *S. aureus* and the observed limited impact of antibiotics on *S. aureus* colonization of the airways (Stulik, 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 IgG1κ monoclonal antibodies, ASN-1 and ASN-2, that together neutralize six *S. aureus* toxins (Rouha, 2015; Badarau, 2016). ASN-1 targets alpha-hemolysin (Hla) and four leukocidins (HlgAB, HlgCB, LukED, and LukSF/PVL) and ASN-2 targets the recently discovered, potent leukocidin LukGH (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

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

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, 98 days post-dosing
- ADA sampling: pre-dosing; 14, 38 and 98 days post-dosing

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=6)
Sex (n [%])				
Male	6 (60.0)	9 (75.0)	9 (75.0)	6 (100.0)
Female	4 (40.0)	3 (25.0)	3 (25.0)	0
Race (n [%])				
Caucasian	10 (100.0)	11 (91.7)	11 (91.7)	6 (100.0)
Afro-American	0	0	1 (8.3)	0
Asian	0	1 (8.3)	0	0
Age, years (mean ± SD)	29 (6.36)	30 (8.04)	35 (10.17)	30 (5.35)
Body weight, kg (mean ± SD)	78 (12.77)	78 (11.44)	76 (10.15)	80 (12.12)
Height, cm (mean ± SD)	179 (10.49)	178 (7.76)	179 (8.49)	181 (6.96)
Body Mass Index, kg/m² (mean ± SD)	24 (3.37)	24 (3.01)	24 (3.09)	24 (2.69)

Safety results

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.
  - AEs had no association of increased incidence with dose escalation.
  - Two AEs (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.

- 2 subjects were confirmed to have ADAs against ASN-1 prior to dosing; these did not seem to impact the observed PK profile.

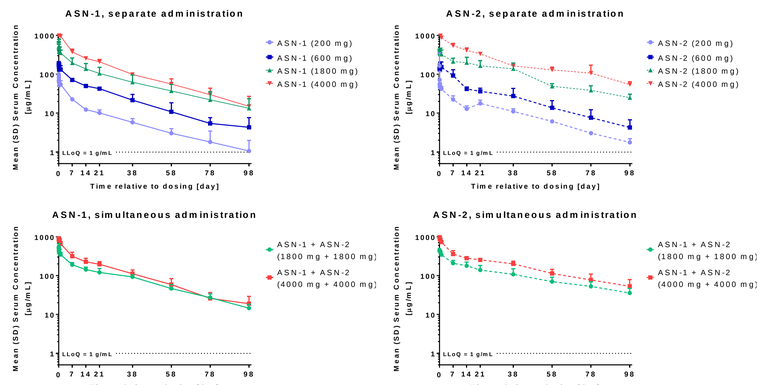
Serum pharmacokinetics

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

ASN-1 dose (No. of subjects)	Cmax [µg/mL]	AUC0-d98 [µg*h/mL]	AUC0-inf [µg*h/mL]	Clearance [L/h]	VSS [L]	Half-life [days]
ASN-1, 200 mg (n=3)	100.3	17948	19411	0.0107	6.89	25.3
ASN-1, 600 mg (n=3)	184.7	60515	64516	0.0095	6.63	25.0
ASN-1, 1800 mg (n=3)	577.6	172066	183930	0.0108	8.02	24.0
ASN-1, 4000 mg (n=3)	1867.8	339474	351387	0.0116	7.00	19.7
ASN-1/ASN-2, 1800 + 1800 mg (n=3)	550.3	201134	213265	0.0086	6.89	24.1
ASN-1/ASN-2, 4000 + 4000 mg (n=3)	975.2	302392	316427	0.0129	8.24	20.3

ASN-2 dose (No. of subjects)	Cmax [µg/mL]	AUC0-d98 [µg*h/mL]	AUC0-inf [µg*h/mL]	Clearance [L/h]	VSS [L]	Half-life [days]
ASN-2, 200 mg (n=3)	165.3	24242	25701	0.00795	6.54	23.9
ASN-2, 600 mg (n=3)	183.2	67100	70440	0.00936	6.10	21.7
ASN-2, 1800 mg (n=3)	543.0	244728	269507	0.00686	6.38	28.3
ASN-2, 4000 mg (n=3)	1341.6	530058	593307	0.00678	6.78	32.8
ASN-1/ASN-2, 1800 + 1800 mg (n=3)	467.7	250887	296315	0.00627	7.55	36.3
ASN-1/ASN-2, 4000 + 4000 mg (n=3)	1074.8	437901	503209	0.00816	8.26	32.3

Serum pharmacokinetics



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 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

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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