Population Pharmacokinetic Model for Intravenous ASN100 in Healthy Subjects

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ABSTRACT

Background: ASN100 is a combination of ASN-1 and ASN-2, two human monoclonal antibodies (mAbs) which selectively bind to 6 *S. aureus* cytotoxins. ASN100 is in development for prevention of *S. aureus* pneumonia in mechanically ventilated patients. A population pharmacokinetic (PK) model was developed for both ASN-1 and ASN-2 following monotherapy or simultaneous administration (ASN100) using dose-escalation data from a first-in-human study.

Methods: A total of 42 healthy subjects received a single 1 hour intravenous (IV) infusion of either ASN-1 or ASN-2 alone (200 to 4000 mg) or ASN100 (3600 or 8000 mg; 1:1 ratio of ASN-1 and ASN-2). Serial PK samples were collected for up to 100 days post-dose and concentrations of ASN-1 and ASN-2 were determined in serum using an enzyme-linked immunosorbent assay (ELISA). Separate linear two-compartment models with zero-order input and first-order elimination were fit to the serum PK data for ASN-1 and ASN-2.

Results: A linear two-compartment model best described the PK data for ASN-1 and ASN-2. There was no evidence of deviation from linear or dose-proportional PK over the dose range studied, differences between monotherapy and combination therapy, or presence of anti-drug antibody formation based upon visual inspection of individual PK profiles. There was excellent agreement between the observed and population mean (r^2 = 0.79 and 0.93) and individual post-hoc predictions (r^2 = 0.88 and 0.98) for ASN-1 and ASN-2, respectively. The population mean clearance (CL) was 0.267 and 0.212 L/day, central volume (Vc) was 3.84 and 4.17 L, distribution CL was 0.586 and 1.23 L/day, and peripheral volume was 3.48 and 3.78 L for ASN-1 and ASN-2, respectively. For parsimony, inter-individual variability was forced to be the same for ASN-1 and ASN-2 and was 22.7% CV for CL, 21.2% CV for Vc, and 34.4% CV for the peripheral volume of distribution (Vp). The mean alpha- and beta-phase elimination half-lives for ASN-1 were 1.91 and 21.6 days and for ASN-2 were 1.08 and 27.5 days, respectively, as calculated using the individual post-hoc parameters.

Conclusion: ASN100 was safe and well tolerated. The PK of both ASN-1 and ASN-2 were linear and dose-proportional over a wide dose range. Although there were slight PK differences between ASN-1 and ASN-2, the PK of both were within the range expected for IgG_1 mAbs.

INTRODUCTION

- *Staphylococcus aureus* is a common pathogen implicated with invasive infections such as hospital-acquired bacterial pneumonia (HABP), including ventilator-associated bacterial pneumonia (VABP).
- *S. aureus* produces a variety of exotoxins during infection and tissue invasion which produce several damaging effects:
  - Destruction of epithelial barrier in the airways by direct cytolytic activity;
  - Targeting of phagocytic cells for lysis thus reducing the host's ability to eliminate bacteria; and
  - Induction of pro-inflammatory responses leading to further tissue damage.
- ASN100 is a combination of ASN-1 and ASN-2, two human monoclonal antibodies (IgG_1) which selectively bind to six *S. aureus* toxins with high affinity thereby potentially neutralizing these toxins prior to exerting their damage.
- ASN100 is currently under development for prevention of *S. aureus* pneumonia in mechanically ventilated patients.
- Arsanis, Inc. recently conducted a first-in-human (FIH) Phase 1 randomized double-blind placebo-controlled ascending single-dose safety trial of ASN100 in healthy subjects, and this data was utilized to develop a population pharmacokinetic (PK) model for both ASN-1 and ASN-2.

OBJECTIVES

- To develop a mammillary structural population PK model to describe the time-course of ASN-1 and ASN-2 in serum following intravenous (IV) administration to healthy subjects when given as monotherapy or as combined ASN100.
- To explore developing a minimal physiologic-based PK (mPBPK) model which is capable of characterizing the time-course of ASN-1 and ASN-2 in serum following IV administration to healthy subjects which may be more physiologically relevant for assessing toxin neutralization in the lung of HABP/VABP patients in future studies.

METHODS

Data

- Data were obtained from a a randomized, Phase 1 FIH study of the safety, tolerability, and PK of ASN-1 and ASN-2 in 52 healthy subjects 18-55 years of age after monotherapy or dosing of the ASN100 combination.
- In Part 1, 40 subjects were randomized evenly into one of 10 cohorts.
  - In Cohorts 1, 3, 5, and 7, subjects were randomized (3:1) to receive a single IV dose of ASN-1 (200, 600, 1800, and 4000 mg, respectively) or placebo.
  - In Cohorts 2, 4, 6, and 8, subjects were to be randomized (3:1) to receive a single IV dose of ASN-2 (200, 600, 1800, and 4000 mg, respectively) or placebo.
  - In Cohorts 9 and 10, subjects were to be administered single 3600 mg (Cohort 9) or 8000 mg (Cohort 10) IV doses of ASN100.
  - Blood samples for PK evaluations were to be collected pre-dose, at the end of infusion, 1, 2, 3, 4, 5, 6, 12, and 24 hours post-dose, and 7, 14, 21, 38, 58, 78, and 98 days post-dose.
  - Immunogenicity of ASN-1 and ASN-2 was tested pre-dose,14, 38 and 98 days post-dose.
- In Part 2, 12 subjects were studied to assess lung penetration after a single IV ASN100 dose of 3600 mg (Cohort 11, N=6) or 8000 mg (Cohort 12, N=6).
  - Blood samples for PK evaluations were to be collected pre-dose, at the end of infusion, 1, 2, 3, 4, 5, 6, 12, and 24 hours post-dose, and at 8 and 30 days post-dose.
  - Immunogenicity of ASN-1 and ASN-2 was tested pre-dose and 30 days post-dose.
- ASN-1 and ASN-2 concentrations in serum were determined using ELISA with a lower limit of quantification of 1 µg/mL for both ASN-1 and ASN-2.

Mammillary Population PK Model

- Separate two-compartment models (2-CMT) with zero-order IV input (k_0) and first order elimination (**Figure 1**) were used to characterize the serum ASN-1 and ASN-2 PK data using NONMEM Version 7.2 (FOCEI method).
- Clearance (CL), central volume of distribution (Vc), distribution CL (CLd) and the peripheral volume of distribution (Vp) were estimated.
- Interindividual variability (ω^2) was estimated for CL, Vc and Vp using exponential error models assuming log-normal parameter distributions.
- Residual variability (σ^2) was estimated using a proportional error model.

Minimal Physiologic-Based PK Model

- Separate mPBPK models were developed for ASN-1 and ASN-2 in NONMEM.
- The mPBPK model (**Figure 4**) assumed that ASN-1 and ASN-2 distribution was limited to the interstitial fluid and minimally accounted for distribution from the serum into two composite tissue compartments representing tissues with tight and leaky junctions, respectively [1, 2].
- Physiological parameters for the mPBPK, such as lymphatic flow rates and interstitial fluid volumes for tissues were obtained from the literature [1] for different species (including, rat, cynomolgus monkey, and humans) and allometric relationships were derived and fixed.
  - This included serum volume (V_S), interstitial fluid volume (V_{ISF}), lymph volume (V_L), and total lymphatic flow (L).
  - The lymphatic capillary reflection coefficient (σ_L) was fixed to 0.2.
  - The volume of the leaky tissues (V_{Leaky}) was calculated as $0.35 \bullet V_{ISF} \bullet Kp$, where Kp represents the fraction of the interstitial fluid to which ASN-1 and ASN-2 is available to distribute.
  - The volume of the tight tissues (V_{Tight}) was calculated as $0.65 \bullet V_{ISF} \bullet Kp$.
  - The lymphatic flow to tight tissues (L_1) was calculated as 0.33•L, while the lymphatic flow to leaky tissues (L_2) was calculated as 0.67•L.
- Drug-specific parameters such as the reflection coefficients for tight (σ_1) or leaky (σ_2) tissues, and drug clearance (CL_S) were estimated; during model development it was deemed necessary to also estimate V_S.

RESULTS

- ASN100 was safe and well tolerated in healthy subjects, and there were no anti-drug antibodies formed as a result of treatment with ASN100.
- Both the mammillary 2-CMT (**Table 1**)and the mPBPK (**Table 2**) models provided an excellent fit to the ASN-1 and ASN-2 serum PK data.
- As shown in **Figure 2**, there was excellent agreement between the observed serum ASN-1and ASN-2 concentrations and both the population mean predictions (r^2 of 0.79 and 0.93, respectively,) and the individual post-hoc predicted concentrations (r^2 of 0.88 and 0.98, respectively).
- The population mean CL was 0.267 and 0.212 L/day and Vc was 3.84 and 4.17 L for ASN-1 and ASN-2, respectively.
- The mean alpha- and beta-phase elimination half-lives for ASN-1 were 1.91 and 21.6 days and for ASN-2 were 1.08 and 27.5 days, respectively, as calculated using the individual post-hoc parameters.
- Visual predictive checks (VPC) performed using the mammillary 2-CMT model showed reasonable agreement between the 10th, 50th and 90th percentiles of the observed and simulated serum ASN-1 and ASN-2 PK data (**Figure 3**).
- The mPBPK provided nearly identical predictions as the 2-CMT model (**Figure 5**) suggesting this may be expanded to predict drug concentrations in lung.

Figure 1. Mammillary 2-CMT model

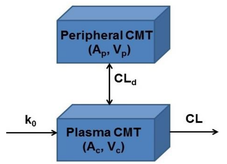


Table 1. Mammillary 2-CMT model parameter estimates for ASN-1 and ASN-2

Parameter	ASN-1		ASN-2	
	Final estimate	%SEM	Final estimate	%SEM
CL (L/day)	0.267	6.33	0.212	6.18
Vc (L)	3.84	4.84	4.17	6.24
CLd (L/day)	0.586	17.9	1.23	11.9
Vp (L)	3.48	11.7	3.78	15.4
ω^2 for CL[a]	0.0515 (22.7% CV)	24.3	0.0515 (22.7% CV)	24.3
ω^2 for Vc[a]	0.0449 (21.2% CV)	32.3	0.0449 (21.2% CV)	32.3
ω^2 for Vp[a]	0.118 (34.4% CV)	34.4	0.118 (34.4% CV)	34.4
Residual variability (σ^2)	0.0429 (20.7% CV)	5.59	0.0220 (14.8% CV)	4.64

a. For parsimony and to avoid over-parameterization, all IIV terms were forced to the same magnitudes for both ASN-1 and ASN-2

Figure 2. VPC, stratified by dose group, using the mammillary 2-CMT model

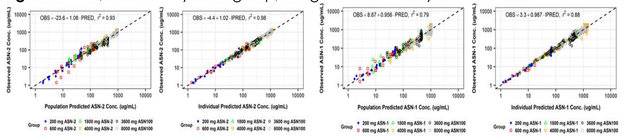
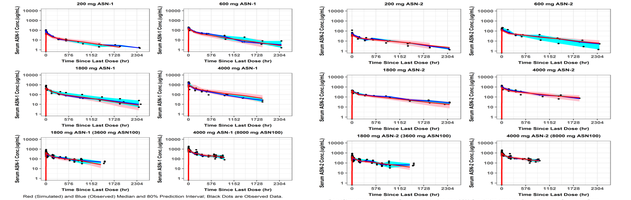


Figure 3. VPC, stratified by dose group, using the mammillary 2-CMT model



Red (Simulated) and Blue (Observed) Median and 90% Prediction Interval, Black Dots are Observed Data.

RESULTS

Figure 4. mPBPK model diagram

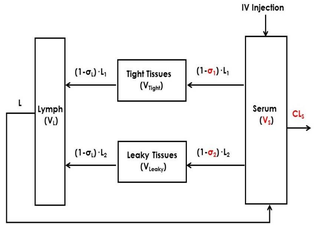


Figure 5. Comparison of individual post-hoc predictions for ASN-1 between 2-CMT and mPBPK models

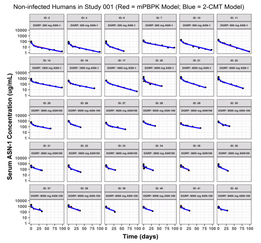


Table 2. mPBPK model parameter estimates for ASN-1 and ASN-2

Parameter	ASN-1		ASN-2	
	Final estimate	%SEM	Final estimate	%SEM
CL_S (L/day)	0.268	5.04	0.205	4.87
Lymph reflection coefficient, σ_L	0.2	FIXED	0.2	FIXED
Tight tissues reflection coefficient, σ_1	0.897	3.47	0.897	3.47
Leaky tissues reflection coefficient, σ_2	0.752	5.74	0.693	7.98
Serum volume, V_S (L) coefficient	3.65	3.42	3.65	3.42
V_S-weight power	1	FIXED	1	FIXED
Interstitial fluid volume, V_{ISF} (mL)[a]	221	FIXED	221	FIXED
V_{ISF}-weight power	0.999	FIXED	0.999	FIXED
Lymph fluid volume, V_L (mL)[a]	74.4	FIXED	74.4	FIXED
V_L-weight power	1.01	FIXED	1.01	FIXED
Total lymphatic flow, L (mL/hr)[a]	4.92	FIXED	4.92	FIXED
L-weight power	0.73	FIXED	0.73	FIXED
Fraction of V_{ISF} for mAb distribution, K_p	0.8	FIXED	0.8	FIXED
Volume of leaky tissues, V_{Leaky} (mL)	$0.35 \bullet V_{ISF} \bullet K_p$	FIXED	$0.35 \bullet V_{ISF} \bullet K_p$	FIXED
Volume of tight tissues, V_{Tight} (mL)	$0.65 \bullet V_{ISF} \bullet K_p$	FIXED	$0.65 \bullet V_{ISF} \bullet K_p$	FIXED
Lymph flow, tight tissues, L_1 (mL/hr)	0.33•L	FIXED	0.33•L	FIXED
Lymph flow, leaky tissues, L_2 (mL/hr)	0.67•L	FIXED	0.67•L	FIXED
ω^2 for CL_S	0.0532 (23.1% CV)	24.3	0.0532 (23.1% CV)	24.3
ω^2 for V_S	0.0496 (22.3% CV)	22.3	0.0496 (22.3% CV)	22.3
ω^2 for σ_2	0.0323 (42.1% CV)	18.0	0.0323 (42.1% CV)	18.0
Residual variability (σ^2)	0.0542 (23.3% CV)	21.2	0.0247 (15.7% CV)	19.5

a. Not centered around any reference body weight (only V_S was centered around a weight of 70 kg.

CONCLUSIONS

- A mammillary linear 2-CMT model best described the time-course of both ASN-1 and ASN-2 in serum following monotherapy or combined administration as ASN100.
- A mPBPK model was also successfully developed to adequately describe the time-course of both ASN-1 and ASN-2 in serum following monotherapy or combined administration as ASN100. This more physiologically relevant model will allow for future expansion to characterize ASN-1 and ASN-2 penetration and toxin neutralization in the lungs of patients with *S. aureus* pulmonary disease.

REFERENCES

1. Zhao J, Cao Y, Jusko WJ. Across-species scaling of monoclonal antibody pharmacokinetics using a minimal PBPK model. *Pharm Res.* 2015 Oct;32(10):3269-81.
2. Cao Y, Jusko WJ. Incorporating target-mediated drug disposition in a minimal physiologically-based pharmacokinetic model for monoclonal antibodies. *J Pharmacokinet Pharmacodyn*. 2014 Aug;41(4):375-87.