grant, Research support; Pfizer: Commercial grant, Research support; Roche: Commercial grant, Research support; Melinta: Industrial partner, Research support; MedImmune (AZ): Industrial partner (IMI), Research support; NIHR England: Grant Investigator, Grant recipient; MRC (UK): Grant Investigator, Grant recipient; Innovate UK: Grant Investigator, Grant recipient. Newton Fund (FCO): Grant Investigator, Grant recipient. **S. K. Cammarata**, Melinta Therapeutics, Inc.: Employee, Salary. **K. Fusaro**, Melinta Therapeutics: Employee, Salary. **J. S. Loutit**, The Medicines Company: Employee and Shareholder, Salary

1388. Dose Discrimination for ASN100: Bridging from Rabbit Survival Data to Predicted Activity in Humans Using a Minimal Physiologically Based Pharmacokinetic (mPBPK) Model

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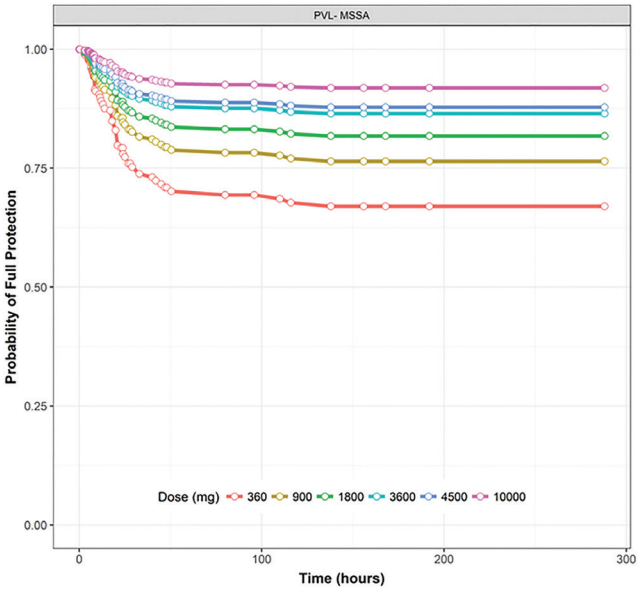
Background. ASN100 is a combination of two co-administered fully human monoclonal antibodies (mAbs), ASN-1 and ASN-2, that together neutralize the six cytotoxins critical to *S. aureus* pneumonia pathogenesis. ASN100 is in development for prevention of *S. aureus* pneumonia in mechanically ventilated patients. A pharmacometric approach to dose discrimination in humans was taken in order to bridge from dose-ranging, survival studies in rabbits to anticipated human exposures using a mPBPK model derived from data from rabbits (infected and noninfected) and noninfected humans [IDWeek 2017, Poster 1849]. Survival in rabbits was assumed to be indicative of a protective effect through ASN100 neutralization of *S. aureus* toxins.

Methods. Data from studies in rabbits (placebo through 20 mg/kg single doses of ASN100, four strains representing MRSA and MSSA isolates with different toxin profiles) were pooled with data from a PK and efficacy study in infected rabbits (placebo and 40 mg/kg ASN100) [IDWeek 2017, Poster 1844]. A Cox proportional hazards model was used to relate survival to both strain and mAb exposure. Monte Carlo simulation was then applied to generate ASN100 exposures for simulated patients given a range of ASN100 doses and infection with each strain (n = 500 per scenario) using a mPBPK model. Using the Cox model, the probability of full protection from toxins (i.e., predicted survival) was estimated for each simulated patient.

Results. Cox models showed that survival in rabbits is dependent on both strain and ASN100 exposure in lung epithelial lining fluid (ELF). At human doses simulated (360–10,000 mg of ASN100), full or substantial protection is expected for all four strains tested. For the most virulent strain tested in the rabbit pneumonia study (a PVL-negative MSSA, Figure 1), the clinical dose of 3,600 mg of ASN100 provides substantially higher predicted effect relative to lower doses, while doses above 3,600 mg are not predicted to provide significant additional protection.

Conclusion. A pharmacometric approach allowed for the translation of rabbit survival data to infected patients as well as discrimination of potential clinical doses. These results support the ASN100 dose of 3,600 mg currently being evaluated in a Phase 2 *S. aureus* pneumonia prevention trial.

Figure 1. Median probability of predicted protective effect of various doses of ASN100 vs. a PVL-negative MSSA based on mPBPK-based scaling of ELF exposures from rabbits to humans



Note: Full Protection defined as the amount of toxin neutralization associated with survival in the rabbit studies

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1389. Pharmacokinetic/Pharmacodynamic (PK/PD) Evaluation of a Novel Aminomethylcycline Antibiotic, KBP-7072, in the Neutropenic Murine Pneumonia Model Against *S. aureus* (SA) and *S. pneumoniae* (SPN)

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Background. KBP-7072 is a novel aminomethylcycline antibiotic with broad-spectrum activity that includes organisms with drug-resistance to β-lactams and tetracyclines. We examined the PK/PD relationship between KBP-7072 drug exposures and treatment effect using a neutropenic murine pneumonia model against a diverse group of SA and SPN.

Methods. Five SAs (three MRSAs) and six SPNs (three PCNs NS, two Tet^R) strains were used. MICs were determined by CLSI Methods. Plasma and ELF PK was determined after SC dosing (range 1–256 mg/kg). Lung burden was assessed by CFU counts at the beginning and end of therapy (24 hours). Infected mice were treated with KBP-7072 by SC route: SA dose range 0.25–64 mg/kg/6 hours, SPN dose range 0.06–16 mg/kg/6 hours. The Emax Hill equation was used to model the dose–response data to the PK/PD index AUC/MIC. The magnitude of the PK/PD index (plasma free and ELF total concentrations) associated with net stasis, 1- and 2-log kill were determined in the pneumonia model for all strains.

Results. SA MICs were 0.25 mg/L for all isolates and SPN MICs were 0.008–0.016 mg/L. Plasma PK of KBP-7072 included: Cmax 0.12–25.2 mg/L, $AUC_{0-\infty}$ 1.1–234 mg hour/L, $T_{1/2}$ 3.2–4.6 h. ELF PK by urea correction methods included: Cmax 0.06–13.3 mg/L, $AUC_{0-\infty}$ 0.4–95 mg hour/L, $T_{1/2}$ 3.1–4 hours. ELF penetration based on free plasma drug concentrations (77.5% bound) ranged from 82 to 238%. AUC was linear over the dose range (R^2 = 0.99). Potent dose-dependent cidal activity (3–5 log kill) was observed against all strains. AUC/MIC was a robust predictor of efficacy (SA R^2 = 0.89, SPN R^2 0.80). Median static, 1- and 2-log kill AUC/MIC values are shown in the table.

Group	Stasis Plasma fAUC/MIC	Stasis ELF AUC/MIC	1-Log Kill Plasma fAUC/MIC	1-Log Kill ELF AUC/MIC	2-Log Kill Plasma fAUC/MIC	2-Log Kill ELF AUC/MIC
SA	0.97	1.72	2.48	4.41	5.81	7.51
SPN	1.12	1.99	3.68	6.54	13.06	23.22

Conclusion. KBP-7072 demonstrated potent *in vivo* efficacy against SA and SPN, including strains with elevated minocycline MIC and β-lactam resistance, in the neutropenic murine pneumonia model. A 3–5 log kill was observed and AUC/MIC was strongly associated with efficacy. The AUC/MIC target for net stasis was comparable between SA and SPN at a plasma fAUC/MIC target of ~1 and ELF AUC/MIC target ~2. Cidal targets were similarly very low. All targets were numerically lower than comparative tetracyclines. These results should prove useful for clinical dosing regimen optimization.

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1390. Pharmacokinetic-Pharmacodynamic (PK-PD) Target Attainment Analyses to Support Rezafungin (RZF) Dose Selection in Treatment of *Candida*

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Background. RZF is a novel antifungal of the echinocandin class with distinctive pharmacokinetics that support weekly dosing intervals. RZF is being developed for the treatment of candidemia and invasive candidiasis (IC) and the prevention of invasive fungal infections. A previously developed population PK model based on Phase 1 intravenous (IV) data [AAC 2018; e02603–17] was refined using IV data from additional Phase 1 and Phase 2 (STRIVE) studies.