1385. Efficacy of Cefazidime–Avibactam in Combination with Aztreonam (COMBINE): Solutions for Metallo-β-Lactamase Producing-Enterobacteriaceae (MBL)

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Background. Novel antibiotics will not be available to combat the threat of MBL until 2021. One strategy to overcome MBLs is to combine CAZ-AVI + ATM. ATM is not held back by the MBL and ATM offers protection for ATM and CAZ vs. ESBLs and AmpCs. The combination also offers a theoretical advantage to inactivating multiple PBP2s by using dual β-lactam therapy. Our objective was to define optimal dosing profiles for clinical use of ATM to add to CAZ-AVI in the hollow fiber infection model (HFIM).

Methods. Each col. ARLG-1013 (bldCAZ, bltAVI, bltCTX, bltCMY, bltKPC) and K. pneumoniae ARLG-1002 (bldCAZ, bltAVI, bltCTX, bltCMY) were studied at a 7.5 log, CFU/mL in the HFIM. Human dosing regimens of CAZ-AVI 2 g/0.5 g q8h (2 hours infusion) and ATM 2 g q6h (2 hours infusion) were simulated in alone and in combination. Continuous infusion (CI) regimens of CAZ-AVI 6.5/1.5 g per day CI + ATM 6 g/day CI and q6h regimens were given simultaneously and sequentially (ATM given 2 hours after CAZ-AVI). Resistant subpopulations were profiled on single (ATM), double (CAZ-AVI) and triple (ATM/CAZ-AVI) drug plates containing 2/2/4, 8/8/4, or 32/32/4 mg/L over 7 days.

Results. Against E. coli ARLG-1013, ATM alone mirrored growth control (+3.14 at 168 hours) (All units Log, CFU/mL change vs. baseline). CAZ-AVI alone showed some intrinsic activity (+1.19 at 168 hours). CAZ-AVI 2g/0.5g q8h (2 hours infusion) + ATM 2g q6h resulted in a subpopulation of resistant E. coli (bldCMY, bltKPC). ATM and CAZ-AVI was highly synergistic and strongly synergistic against MBL Enterobacteriaceae in HFIM. ATM efficacy in combination was driven by it’s β-lactam. A Phase I study will assess safety to provide patients a critically important solution against “untreatable” Gram negatives.

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1387. Phase I Study to Evaluate the Safety and Pharmacokinetics (PK) of Single and Multiple Ascending Doses (SAD/MAD) of Intravenous (IV) Minocycline in Healthy Male Volunteers

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Background. Carbapenem-resistant Acinetobacter baumannii infections are defined by the WHO as a critical threat. IV minocycline is approved in the United States for treatment of Acinetobacter infections at doses up to 200 mg BD. This study investigated safety and PK of single and multiple doses of IV minocycline, including doses higher than approved in the United States.

Methods. This was a randomized, double blind, placebo-controlled, SAD/MAD study of 6 doses (100–600 mg) of IV minocycline. Healthy adult subjects received a single dose of minocycline or placebo on Day 1, and 15 doses BD starting on Day 4. Safety was assessed throughout the study. Serial blood and urine samples were collected for PK assessment.

Results. Sixty-nine healthy subjects were randomized. 49 were included in the PK analysis. (Serious adverse event; AE) occurred in 55 subjects (79.9%) requiring temporary study drug-related AEs; dizziness 40 (58.0%) and nausea 34 (49.3%) were the most common. All related AEs were mild except for seven subjects with moderate nausea and/or dizziness. Dosing in the 400 mg cohort was discontinued due to AEs, therefore MAD escalation was stopped. Subsequent cohorts were escalated for SAD and loading dose only.

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SAD Mean (SD) PK Parameters

| Dose (mg) | 100 | 200 | 300 | 400 | 500 | 600 |
|---|---|---|---|---|---|---|
| N | 8 | 8 | 8 | 8 | 9 | 9 |
| Cmax (mg/L) | 0.99 (0.2) | 1.89 (0.4) | 3.23 (1.2) | 4.93 (1.8) | 4.36 (0.8) | 7.02 (2.4) |
| T_{1/2} (h) | 11.05 (2.1) | 13.70 (2.3) | 16.62 (3.9) | 17.65 (2.1) | 14.44 (2.7) | 17.27 (3.8) |
| AUC (mg*h/L) | 9.73 (1.4) | 25.30 (6.9) | 38.26 (13.8) | 36.04 (11.2) | 25.73 (20.3) | 53.85 (29.4) |
| CI (L/h) | 10.49 (1.8) | 8.21 (2.2) | 8.29 (1.2) | 8.71 (1.1) | 10.25 (0.3) | 8.70 (2.8) |
| Vss (L) | 156 (36.7) | 148 (36.6) | 158 (45.4) | 142 (38.0) | 179 (45.6) | 153 (52.8) |

AUC, area under the drug concentration–time curve; Cmax, maximum observed drug concentration; T_{1/2}, half-life; CI, plasma clearance; Vss, volume of distribution at steady state. N, number of subjects.

Conclusion. Single IV doses of minocycline up to 600 mg were tolerated reasonably well, but the maximum tolerated multi-dose was 300 mg BD. Most common AEs were mild nausea and dizziness with evidence of increasing incidence but not increasing severity with increasing dose. Exposure increased in a dose proportional fashion with exception of the 500 mg dose. The dosage regimen selected for further studies will be a 600 mg loading dose followed by 300 mg BD.

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138. 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 cytotokins 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 2a 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

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

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**Background.** KBP-7072 is a novel aminomycillin 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 neutrophile murine pneumonia model against a diverse group of SA and SPN.

**Methods.** Five SAs (three MRSA) and six SPNs (three PCNs NS, two TetSR) 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 0.12–35.2 mg/L, AUC0-∞ 1.1–234 mg.hour/L, T1/2 1.1–2.46 h. ELF PK by urea correction methods included: Cmax 0.06–13.3 mg/L, AUC0-∞ 0.4–95 mg.hour/L, T1/2 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 (R² = 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 R² = 0.89, SPN R² = 0.80). Median static, 1- and 2-log kill AUC/MIC values are shown in the table.

|               | Stasis Plasma | Stasis ELF | 1-Log Kill Plasma/AUC/MIC | 1-Log Kill ELF/AUC/MIC | 2-Log Kill Plasma/AUC/MIC | 2-Log Kill ELF/AUC/MIC |
|---------------|---------------|------------|---------------------------|------------------------|---------------------------|------------------------|
| Group         | AUC/MIC       | AUC/MIC    | AUC/MIC                   | AUC/MIC                | AUC/MIC                   | 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 neutrophile murine pneumonia model. A 3–5 log kill was observed against all strains. Cidal effect was strongly associated with efficacy. The AUC/MIC target for net stasis was comparable between SA and SPN at a plasma AUC/MIC target of ~1 and ELF AUC/MIC target ~2. Cidal targets were similar 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 Bezafungin (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; e2603–17) was refined using IV data from additional Phase 1 and Phase 2 (STRIDE) studies.

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