of importance, suggesting therapeutic benefit for both treatment and prophylaxis of invasive fungal infections.

Disclosures. S. Barat, Scynexis, Inc; Employee, Salary; K. Borrero-Esoda, Scynexis Inc; Consultant, Consulting fee; D. Angulo, Scynexis, Inc; Employee, Salary

1509. Efficacy of Lefamulin Against Staphylococcus aureus-Induced Bacteremia in a Neutropenic and Immunocompetent Murine Model
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Session: 167. Preclinical Study with New Antibiotics and Antifungals
Friday, October 6, 2017: 12:30 PM

Background. S. aureus (SA) is a major human pathogen that causes invasive, clinical infections including bacteremia. Lefamulin (LEF) is the first semi-synthetic, pleuromutilin antibiotic for IV and oral use in humans. LEF is currently in Phase 3 trials for the treatment of community-acquired bacterial pneumonia (CABP). LEF specifically inhibits bacterial protein synthesis by binding to the peptidyltransferase center (PTC) via four H-bonds and other interactions at the A- and P-site resulting in an “induced fit.” LEF has been shown to be highly active against bacterial pathogens causing bacteremia, including SA. This study investigated the efficacy of LEF and comparators against SA in a neutropenic and immunocompetent murine bacteremia model.

Methods. Experimentally induced MSSA bacteremia (inoculum ~2 × 10^7 CFU/mouse) was established in immunocompromised and immunocompetent mice. Infected mice received a single subcutaneous dose of either LEF or comparator (Table 1) 1 hours post-inoculation, mimicking human therapeutic exposures. A control group of infected mice were sacrificed directly before treatment to establish a baseline CFU count and comparison with the bacterial load of treated animals 24 hours post drug administration.

Irrespective of the immune status, LEF showed superior efficacy to linezolid (LZD) and tigecycline (TGC) against MSSA, reducing the bacterial burden more than 4 log_10 CFU/mL within 24 hours (Table 1). A comparable reduction of bacterial burden was observed between LEF and daptomycin (DAP) or vancomycin (VAN) treatment.

Conclusion. LEF showed comparable therapeutic outcome to DAP or VAN in this acute experimental infection model, while showing superior killing as compared with LZD or TGC. The efficacy of LEF was maintained under neutropenic conditions with >4log_10/CFU/mL at clinically relevant exposures. This study supports continued evaluation of LEF for as a potential treatment of staphylococcal bacteremia.

Table 1: Efficacy of lefamulin and reference antibiotics against S. aureus (ATCC 49953)

| Compound | Base [mg/kg] | MIC [µg/mL] | n | Viable Counts [log CFU/mL] Mean ± SD | S. aureus (µg/mL) |
|----------|--------------|-------------|---|---------------------------------------|------------------|
| Non-neutropenic | | | | | |
| Early Control | - | - | 24 | 5.58 ± 0.67 | +0.00 |
| LEF | 70 | 0.06 | 32 | 1.06 ± 0.26 ± | -4.50 |
| VAN | 150 | 1 | 16 | 1.00 ± 0.00 * | -4.58 |
| LZD | 80 | 2 | 16 | 3.61 ± 0.57 ² | -9.57 |
| DAP | 22.5 | 0.25 | 16 | 1.00 ± 0.00 * | -4.58 |
| TGC | 65 | 0.25 | 16 | 1.91 ± 0.68 ° | -8.09 |
| Neutropenic | | | | | |
| Early Control | - | - | 24 | 6.12 ± 0.22 | +0.00 |
| LEF | 70 | 0.06 | 32 | 1.98 ± 0.68 ± | -4.18 |
| VAN | 150 | 1 | 16 | 2.53 ± 0.62 ± | -7.98 |
| LZD | 80 | 2 | 16 | 5.75 ± 1.34 ± | -3.51 |
| DAP | 22.5 | 0.25 | 16 | 1.86 ± 0.62 ± | -4.26 |
| TGC | 65 | 0.25 | 16 | 3.21 ± 0.63 ° | -2.91 |

* P < 0.05 compared with Early Control (Dunnet t method)
² P < 0.05 compared with lefamulin (Bonferroni t-test)

Disclosures. E. Fischer, Nabria Therapeutics AG: Employee and Shareholder, Salary; B. C. Kappes, Nabria Therapeutics AG: Employee and Shareholder, Salary; W. W. Wicha, Nabria Therapeutics AG: Employee and Shareholder, Salary
enzyme). The produg APX001 (APX) is in clinical development and its efficacy was evaluated in an immunocompromised murine model of disseminated C. auris.

**Methods.** MICs were determined by CLSI M27-A3 method. Mice were immuno-compromised for the study. Treatment was initiated 2 hours post challenge. IP treatment groups included a vehicle control, APX 78 mg/kg (mpk) BID, 154 mpk TID, and 108 mpk BID and anidulafungin (AFG) 10mpk BID. Survival was monitored for 16 days post inoculation.

**Results.** APX resulted in significantly better survival than AFG in a murine model of invasive aspergillosis. The exposure needed to achieve efficacy is in line with efficacious exposures reported in the invasive candidiasis models. These results support further development of SCY-078 as an oral antifungal (Table 1).

**Conclusion.** APX was the most active antifungal agent in vitro. The produg APX resulted in significantly better survival than AFG in a C. auris disseminated infection model. Thus APX may be a viable treatment for C. auris infections.

**Table 1: Susceptibility of 16 C. auris isolates against antifungals**

| Antifungals | Minimum Inhibitory Concentration (MIC) (µg/mL) |
|-------------|-----------------------------------------------|
| Caspofungin (CSP) | 154 |
| Itraconazole (ITZ) | 154 |
| Fluconazole (FLC) | 154 |
| Amphotericin B (AMB) | 154 |
| Voriconazole (VRC) | 154 |
| Posaconazole (POS) | 154 |
| Flucytoxine (FLX) | 154 |
| Anidulafungin (AFG) | 154 |

**Disclosures.** K. J. Shaw, Amplyx Pharmaceuticals Inc.: Employee; Salary; M. Ghanounou, Amplyx Pharmaceuticals: Consultant, Research Contractor and Scientific Advisor, Consulting fee and Research grant; Cidara Therapeutics: Consultant and Research Contractor; Consulting fee and Research grant.

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1511. **SCY-078 Demonstrates Significant Antifungal Activity in a Murine Model of Invasive Aspergillosis**

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**Background.** Azoles are the most common anti-fungal agents for the treatment of Aspergillus infections. Echinocandins have demonstrated utility in Aspergillus infections, but are limited in use due to a lack of oral bioavailability. SCY-078 is a novel, oral and intravenous (IV), tripterpenoid glucan synthase inhibitor with activity against Aspergillus and Candida, currently in clinical development for the treatment of invasive fungal infections. This study was conducted to evaluate the in vivo antifungal activity of SCY-078 in a murine model of invasive aspergillosis (IA).

**Methods.** The in vivo activity of SCY-078 was assessed against a wild type (WT) and two azole-resistant A. fumigatus strains in neutropenic ICR mice. Five groups of mice (6/group) were infected IV into the lateral tail vein. Antifungal therapy was initiated 2 hours post infection and maintained for 7 days. SCY-078 was administered orally as a loading dose of 15 mg/kg or 20 mg/kg followed by BID maintenance doses of 7.5 or 10 mg/kg, respectively. Caspofungin (CSP) and amphotericin B (AMB) were administered QD by intraperitoneal injection (IP) at doses of 5 mg/kg and 10 mg/kg, respectively. SCY-078 was administered 5 hours post infection and maintained for 7 days. SCY-078 was administered intravenously at doses of 7.5, 10, and 20 mg/kg by IP injection (ca. 2 × 105 CFU/mouse). Treatment was initiated 4, 10, 28, 34 hours post-infection. Viable cell counts in lungs at 48 hours post-infection were counted.

**Results.** Against CPA-357 (KPC-2), ceftazidime and CZA had the MICs of 1 and 2 µg/mL, respectively, and they showed >3-log CFU from the initial therapy with 100 mg/kg treatment. These efficacy were superior to those of C/T, MEM and FEP at the same dose. Against NUBL-1122 (IMP-1), ceftazidime of 100 mg/kg significantly decreased the viable cells with ≥ 3-log values included

**Conclusion.** Ceftazidime exhibited in vivo bactericidal activity against carbapenem-resistant K. pneumoniae and P. aeruginosa in the UTI models, suggesting that ceftazidime is promising antibacterial agent for the treatment of UTI infections caused by these resistant strains.

**Disclosures.** S. Matsumoto, SHIONOGI & CO., LTD.: Employee, Salary; S. Kanazawa, SHIONOGI & CO., LTD.: Employee, Salary; R. Nakamura, SHIONOGI & CO., LTD.: Employee, Salary; M. Tsuji, Shionogi & Co.: Employee, Salary; T. Sato, SHIONOGI & CO., LTD.: Employee, Salary; Y. Yamano, SHIONOGI & CO., LTD.: Employee, Salary

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**Background.** APX001 is a small-molecule therapeutic agent in clinical development for the treatment of invasive fungal infections. In vivo, APX001-derived radioactivity was rapidly and extensively absorbed and extensively distributed to most tissues for both routes of administration in both species. In rats, tissues with the highest radioactivity Cmax values included liver, abdominal fat, reproductive fat, subcutaneous fat, and liver, but radioactivity was also detected in lungs, brain, and eye tissues. In monkeys, the highest Cmax values were in bile, urine, uveal tract, bone marrow, abdominal fat, liver, and kidney cortex. Liver and kidney were the tissues with highest radioactivity, but as in the rat, radioactivity was also detected in lungs, brain, and eye tissues. In pigs, radiocarbon was densely distributed into pigmented tissue and more slowly cleared than from other tissues.

**Results.** Mean recovery of radioactivity in rats was approximately 95–100%. In bile duct-injured animals, the most frequent bacterial species recovered were Acinetobacter baumannii, Escherichia coli, and Klebsiella pneumoniae. The radioactivity was also detected in the kidneys of rats and monkeys with ≥ 3-log CFU from the initial therapy with 100 mg/kg treatment. These efficacy were superior to those of C/T, MEM and FEP at the same dose. Against NUBL-1122 (IMP-1), ceftazidime of 100 mg/kg significantly decreased the viable cells with ≥ 3-log values included