enzyme). The prodrug 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 immunocompromised for the study. Treatment was initiated 2 hours post challenge. IP treatment groups included a vehicle control, APX 78mg/kg (mpk) BID, 78mpk TID, and 104mpk BID, and anidulafungin (AFG) 10mpk BID. Survival was monitored for 16d post inoculation.

Results. *Susceptibility*. APXA had significantly lower MIC_{50} and MIC_{90} values (concentration that inhibits 50 and 90% of the tested isolates, respectively) than the other tested antifungals with a MIC_{90} of 0.031 µg/mL (Table 1).

Survival. 100% mortality in the vehicle-treated control group occurred by 6d. Significant efficacy was observed in all APX treatment groups with 90, 100, and 80% survival observed respectively for APX 78 mpk BID; 78 mpk TID and 104 mpk BID. AFG treatment resulted in 50% survival at 16d. Mice in all of the APX treated groups had a significantly higher % survival compared with the AFG and vehicle groups.

Conclusion. APXA was the most active antifungal agent *in vitro*. The prodrug 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

	APXA	flucytosine	amphotericin B	AFG	caspofungin	fluconazole	itraconazole	micafungin	posaconazole	voriconazole
	24h	48h	48h	24h	24h	24h	48h	48h	24h	48h	48h
	50%	50%	100%	50%	50%	50%	50%	50%	50%	50%	50%
Range	0.002-0.063	0.5-1	2-4	0.125-0.25	0.25-1	1->64	2->64	<0.063-1	0.25-2	0.25-1	<0.063-2
MIC_{50}	0.004	0.5	4	0.125	0.5	16	>64	0.5	1	0.25	0.5
MIC_{90}	0.031	1	4	0.25	1	>64	>64	1	1	0.5	2

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

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), triterpenoid 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 5 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. The primary endpoint was survival at day 14, secondary endpoints were changes in fungal kidney burden and serum galactomannan index (GM). Pharmacokinetic analysis was conducted on blood samples at Day 7.

Results. SCY-078 was well tolerated at all doses. Treatment with SCY-078 at 15 mg/kg/day and 20 mg/kg/day significantly increased mean survival in all strains ($P \leq 0.003$). SCY-078 also resulted in significant reductions in fungal kidney burden ($P < 0.05$) and serum GM levels ($P < 0.005$) in all strains. Primary and secondary efficacy endpoints were also met in the groups treated with IP administration of CSP or AMB. Plasma levels of SCY-078 ranged from ≈15–20 µM*hr (AUC_{0-12}) with C_{max} ranging from ≈ 1–1.6 µg/mL for the two dose groups.

Conclusion. SCY-078 demonstrated potent activity against WT and azole-resistant strains of *A. fumigatus* 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 treatment for IA infections.

Disclosures. **K. Borroto-Esoda**, Scynexis Inc: Consultant, Consulting fee; **S. Barat**, Scynexis, Inc: Employee, Salary; **D. Angulo**, Scynexis, Inc: Employee, Salary; **K. Holden**, Evotec (UK) Ltd.: Employee, Salary; **P. Warn**, Evotec (UK) Ltd.: Employee, Salary

1512. *In Vivo* Efficacy of Cefiderocol against Carbapenem-Resistant Gram-Negative Bacilli in Murine Urinary Tract Infection Models

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Background. Cefiderocol (S-649266), a novel siderophore cephalosporin, shows potent activity against carbapenem-resistant Gram-negative bacilli. In the cefiderocol global surveillance study that focused on carbapenem-resistant Gram-negatives (SIDERO-CR-2014/2016), the most frequent bacterial species recovered from patients with urinary tract infection (UTI) were *K. pneumonia*e and *P. aeruginosa*. The purpose of this study was to evaluate the *in vivo* efficacy of cefiderocol againt carbapenem-resistant *K. pneumoniae* and *P. aeruginosa*in murine UTI models.

Methods. Cefiderocol, ceftazidime/avibactam (CZA), ceftolozane/tazobactam (C/T), meropenem (MEM) and cefepime (FEP) were used as the test compounds. Four test strains of *E. coli* EC-14, *K. pneumoniae* VA-357 harboring KPC-2, *P. aeruginosa* SR10163 (FEP-resistant strain), and NUBL-1122 harboring IMP-1 were used. MIC was determined by broth microdilution method. As recommended by CLSI, cefiderocol was tested in iron-depleted cation-adjusted Mueller Hinton broth. ICR female mice (n = 3–6) were infected by transurethral inoculation (ca. 2×10^5CFU/mouse). Treatment was initiated 4, 10, 28, 34 hours post-infection. Viable cells in kidney tissue at 48 hours post-infection were counted.

Results. Against VA-357 (KPC-2), cefiderocol and CZA had the MICs of 1 and 2 µg/mL, respectively, and they showed ≥ 3-$\log_{10}$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), cefiderocol of 100 mg/kg significantly decreased the viable cells with ≥ 3-$\log_{10}$CFU (MIC, 1 µg/mL), while CZA, C/T, MEM and FEP did not show the bactericidal efficacy (MIC, ≥32 µg/mL). All the test compounds showed dose-dependent decrease in the viable cells in kidneys against ceftazidime-susceptible and -resistant strains of EC-14 and SR10163, respectively, in a reflection of their MICs.

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

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1513. Absorption, Distribution, and Excretion of ^{14}C-APX001 after Single-Dose Administration to Rats and Monkeys

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Background. APX001 is a small-molecule therapeutic agent in clinical development for the treatment of invasive fungal infections (IFI).

Methods. The absorption, distribution and excretion profiles of [^{14}C]APX001-derived radioactivity were determined in rats (albino and pigmented) and monkeys. Rats (some implanted with bile duct cannulae) were administered a single 100 mg/kg oral dose or a 30 mg/kg intravenous (IV) dose. Monkeys were administered a single 6 mg/kg IV dose. Samples of blood, urine, feces and bile, as well as carcasses, were collected through 168 hours after dosing. Samples were analyzed for total radioactivity content by liquid scintillation counting, and carcasses were analyzed by quantitative whole-body autoradiography.

Results. [^{14}C]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 C_{max} values included bile, abdominal fat, reproductive fat, subcutaneous fat, and liver, but radioactivity was also detected in tissues associated with IFI, including lung, brain and eye. In monkeys, the highest C_{max} 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 lung, brain and eye tissues. In pigmented rats, radiocarbon was densely distributed into pigmented tissue and more slowly cleared than from other tissues.

Mean recovery of radioactivity in rats was approximately 95–100%. In bile duct-intact rats, >90% of radioactivity was recovered in feces. In cannulated rats, biliary excretion of radioactivity was the major route of elimination and accounted for 88.8% of the dose, whereas urinary and fecal excretion of radioactivity was minor and accounted for 2.56% and 5.42% of the dose, respectively. In monkeys, the overall recovery of radioactivity was 87.6%, and was eliminated in feces (49.8% of dose) and to a lesser extent in urine (20.6% of dose).

Conclusion. Together, the results indicate that APX001-related radioactivity is extensively distributed to major tissues (including tissues relevant to IFI) in both rats and monkeys and cleared primarily by biliary/fecal excretion.

Disclosures. **R. Mansbach**, Amplyx Pharmaceuticals Inc.: Consultant, Consulting fee; **K. J. Shaw**, Amplyx Pharmaceuticals Inc.: Employee, Salary; **M. R. Hodges**, Amplyx Pharmaceuticals: Employee, Salary; **S. Coleman**, Covance Laboratories: Employee, Salary; **M. E. Fitzsimmons**, Covance Laboratories: Employee, Salary