1511. SCY-078 Demonstrates Significant Antifungal Activity in a Murine Model of Invasive Aspergillosis
Katyna Borroto-Esda, PhD1; Stephen Barat, PhD1; David Angulo, MD2; Kirsty Holden, PhD1; and Peter Warn, PhD1, 2

SCY-078 is a novel, orally administered antifungal prodrug in clinical development for the treatment of invasive fungal infections. Pharmacokinetic analysis was conducted on blood samples at Day 7. SCY-078 also resulted in significant reductions in fungal kidney burden and microbial counts in major tissues, including tissues relevant to IFI.

Methods. SCY-078 is a novel, orally administered antifungal. Pharmacokinetic analysis was conducted on blood samples at Day 7. SCY-078 was administered orally as a loading dose of 15 mg/kg or 20 mg/kg followed by BID maintenance doses 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 for 7 days. SCY-078 was administered in the murine model of invasive aspergillosis (IA).

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 ≤ 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 IF administration of SCF or AMB. Plasma levels of SCY-078 ranged from 15-26 μM hr (AUC0-∞) with Cmax ranging from 1-1.6 μM/mL for the two dose groups.

Conclusion. SCY-078 demonstrated potent activity against WT andazole-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-Esda, 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

Session: 167. Preclinical Study with New Antibiotics and Antifungals

1513. Absorption, Distribution, and Excretion of [14C]-APX001 after Single-Dose Administration to Rats and Monkeys
Robert Mandshu1, PhD1; Karen J. Shaw, PhD1; Michael R. Hodges, MBBS, BSc1; Samantha Cole1, PhD1; and Elinor A. Simmons, PhD2

APX001 (APX) is in clinical development as a potential therapy for the treatment of invasive fungal infections (IFI).

Methods. The absorption, distribution and excretion profiles of [14C]-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 10 mg/kg IV dose. Samples of blood, urine, feces, bile, as well as carcasses, were collected throughout 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. [14C]-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 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 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 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 it 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. Mandshu, 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