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SCY-078 Demonstrates Significant Tissue Penetration in Rats and Mice Following Oral or IV Administration

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BACKGROUND

The ability of a pharmacologic agent to reach target organ(s) in therapeutically-meaningful concentrations is one of the fundamental considerations when developing effective, anti-infective treatments. 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. Tissue distribution studies were conducted in rats and mice to evaluate the profile of distribution of SCY-078 following oral or IV administration.

METHODS

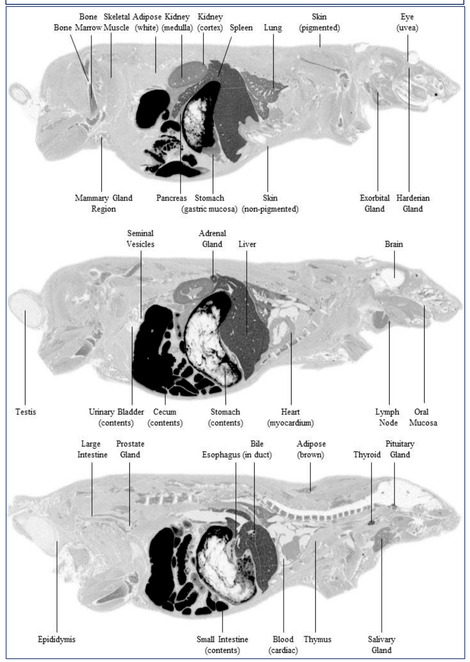
Blood, tissue, fluid or whole-body concentrations of SCY-078 were evaluated in rats and mice according to the following table:

Animal	Dose	Sample collection
Sprague Dawley rat	Single dose ^{3}H-SCY-078 5 mg/kg PO	Carcass and plasma at post-dose time points ranging from 0.083 to 168 hours
Han Wistar or Long Evans (pigmented) rat	Single dose ^{14}C-SCY-078 15 mg/kg PO Or 5 mg/kg IV	Carcass and plasma at post-dose time points ranging from 0.083 to 168 hours
CD-1 mouse	Seven days of 3, 6.25, 12, 25, 50, or 100 mg/kg BID PO	• Blood samples collected from each animal at post-dose time points ranging from 0.25 to 60 hours • Kidneys collected 2 0r 60 hours post-dose • Bronchoalveolar lavage fluid (BALF) collected 2, 12, or 24 hours post-dose

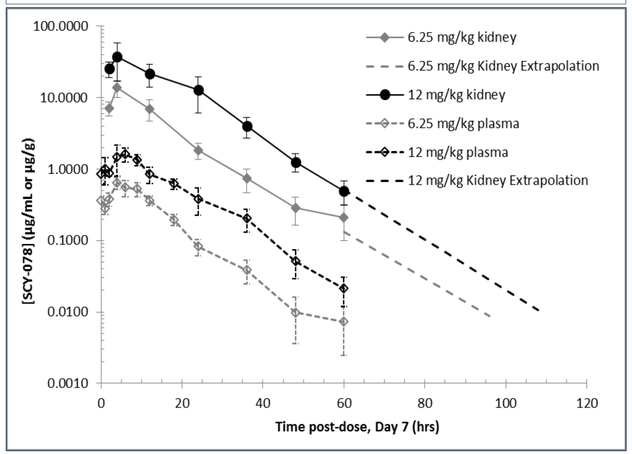
RESULTS

SCY-078 distributed rapidly into tissues following administration. In rats, T_{max} in whole blood, plasma and tissues following oral dosing was reached by 4 hrs. Blood to plasma ratio was < 1.0 indicating low partitioning into erythrocytes. High concentrations were noted in pituitary, spleen, liver, adrenals, lymph nodes, thyroid, bone marrow, thymus, lungs, kidneys and vagina. Tissue:blood ratios in rats ranged from approximately 15- to 50-fold. In mice, kidney concentrations were approximately 20-fold greater than plasma at all doses studied, and the kidney:plasma ratio increased in a dose-related fashion indicating enhanced tissue distribution from greater unbound fractions in plasma. In lungs, exposures in epithelial lining fluid were generally 4-fold greater than plasma and the epithelial lining fluid:plasma ratio increased up to 13-fold at the highest plasma concentrations. Concentrations in vaginal tissue and secretions also exceeded those in plasma, and increased in a dose-dependent manner to as much as 10-fold.

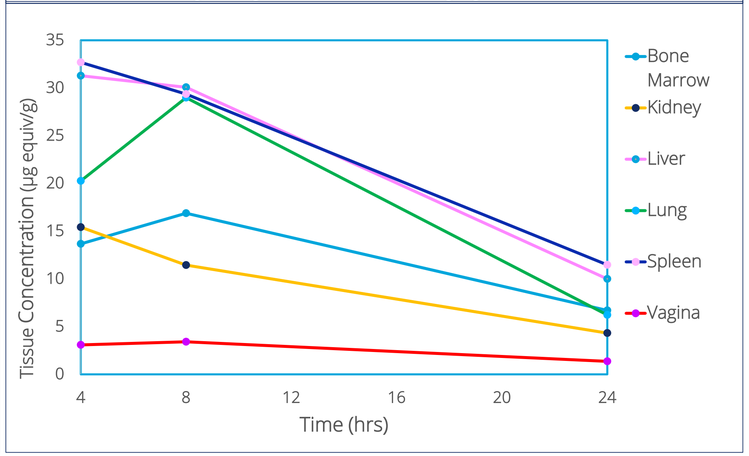
Whole-body Autoradiogram of the Radioactivity Distribution in a Male Pigmented LE Rat at 4h Following a Single Oral Dose of [^{14} C]SCY-078 at a Target Dose of 15 mg/kg



Plasma and Kidney Sample Concentrations in CD-1 Mice Following Seven Days of Oral BID Dosing vs. Time Profiles of SCY-078



Tissue Concentration vs. Time for Select Tissues of of Female Long-Evans Rats Following a Single Oral Dose of 15 mg/kg of [^{14} C]SCY-078



CONCLUSION

SCY-078 demonstrates significant tissue penetration, indicating an intrinsic ability to reach clinically meaningful levels in various potential target organs of importance, suggesting therapeutic benefit for both treatment and prophylaxis of invasive fungal infections.

For additional information, contact us at info@scynexis.com.