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Repeat Oral Dose SCY-247 Exceeds Exposures Associated with Efficacy in Murine Models of Invasive Candidiasis with Low Potential for Drug-Drug Interactions with Key CYP450s

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BACKGROUND

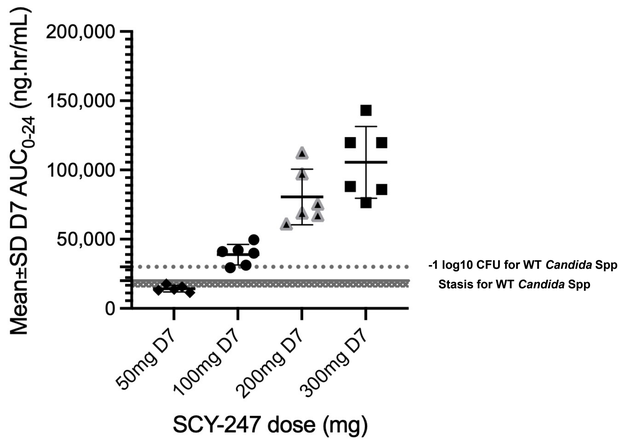
SCY-247 is a second-generation IV/oral triterpenoid antifungal. Herein we report preliminary safety and pharmacokinetic (PK) data from a phase 1 study following repeat oral SCY-247 administration to healthy participants, correlation with exposures associated with efficacy in murine models of invasive candidiasis (IC), and drug-drug interaction (DDI) potential with key CYP450s.

METHODS

24 participants received once daily oral doses of 50, 100, 200 or 300mg SCY-247. Safety, tolerability and plasma PK data were obtained per panel (6 active, 2 placebo). Steady-state AUC_{0-24} exposures on day 7 of treatment were compared to those associated with efficacy in murine models of IC. Potential for inhibiting or inducing CYP450 isoforms was assessed *in vitro* using methods supportive of an FDA Investigational New Drug (IND) Application. 12 healthy human volunteers completed a drug-drug interaction evaluation of oral midazolam and oral SCY-247. Participants received midazolam 2mg on Day 1, SCY-247 loading dose of 300mg BID on Day 3 followed by maintenance SCY-247 300mg QD from Days 4 to 7, midazolam co-administered with SCY-247 on Day 8 and continued SCY-247 QD on Day 9.

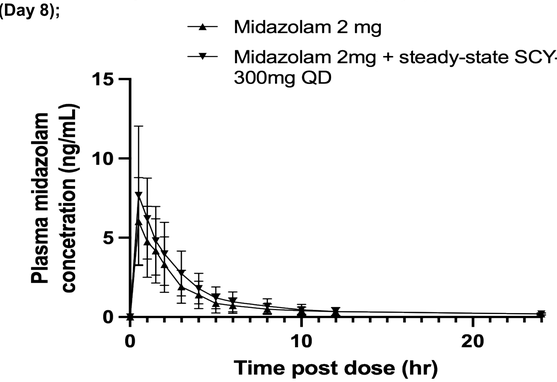
RESULTS

Figure 1: SCY-247 Mean AUC_{0-24} in humans



SCY-247 demonstrated efficacy in murine models of *C. auris*, *C. glabrata*. or *C. albicans* infections as either stasis or a ~≥1 log_{10} CFU kidney reduction (range -0.74 to -3.85log_{10} CFU) versus infected pre-treatment control with AUC_{0-24} ~20hr.µg/mL and ~30hr.µg/mL, respectively. For an echinocandin–resistant (rECH) S629P *C. glabrata* model, the same endpoints were achieved at ~15hr.µg/mL and ~55hr.µg/mL. SCY-247 was well-tolerated in healthy human participants. Plasma AUC_{0-24} (Figure 1) increased dose proportionally. Correlation of exposures in humans versus those with significant treatment effect in mice supported a daily human dose of ≥100mg SCY-247.

Figure 2: Midazolam plasma concentrations alone (Day 1) and in combination with steady-state levels of SCY-247 (Day 8);



In vitro, SCY-247 did not induce human CYP450s 1A2, 2B6 or 3A4. IC50 values for inhibition of 2C9 and 2C19 were >30µM and were ~24µM (midazolam) or >30µM (testosterone) for 3A. These concentrations are ~10-fold higher than the 100mg steady-state Cmax thereby supportive of low risk of DDI's. A phase 1 drug-drug interaction study of midazolam and a supra-therapeutic dose of SCY-247 (300 mg) showed that SCY-247 was a weak CYP3A4 inhibitor, (Figure 2) geometric mean C_{max} and AUC_{0-last} for midazolam, without and with SCY-247, were 5.81 and 7.34 ng/mL; and 14.62 and 20.42 hr.ng/mL, respectively.

CONCLUSION

SCY-247 was well-tolerated at repeat oral doses. Exposures achieved exceeding those associated with efficacy in murine models of IC and indicate low potential for clinically meaningful CYP-based DDIs.

For additional information contact SCYNEXIS at info@scynexis.com

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Disclosures: David Angulo, MD is an employee and shareholder of SCYNEXIS, Inc.