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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 wild type (WT) and azole-resistant (TR34, L98H) *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 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.

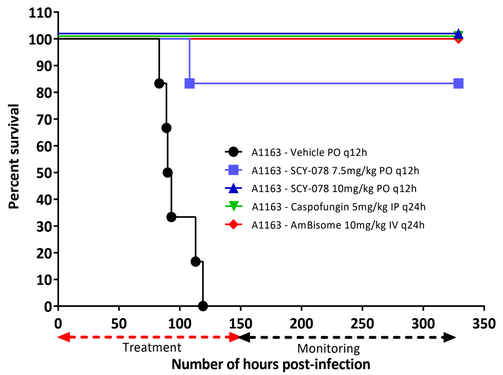
Endpoints:

- Primary: survival at day 14
- Secondary: changes in fungal kidney burden and serum galactomannan index (GM). Pharmacokinetic analysis was conducted on blood samples at Day 7.

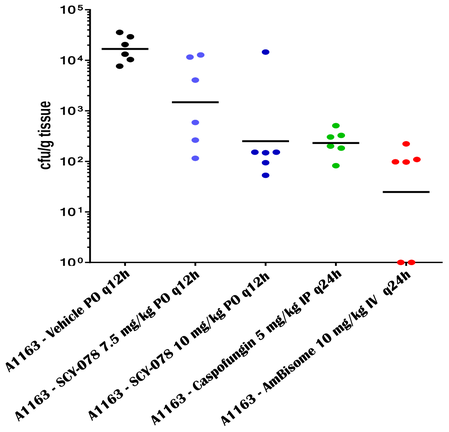
RESULTS

SCY-078 was well-tolerated at all doses. Treatment with SCY-078 at 7.5 mg/kg/day and 10 mg/kg/day BID 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.

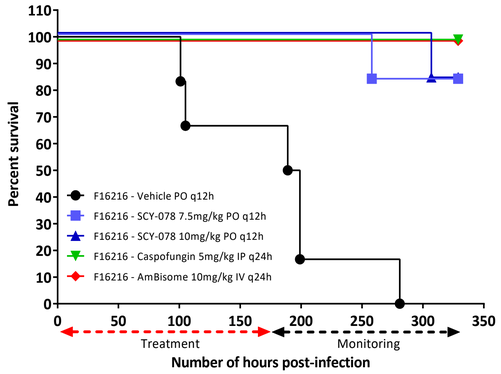
Survival Following Treatment of Disseminated *A.fumigatus* (WT) Infection with Various Anti-fungal Agents



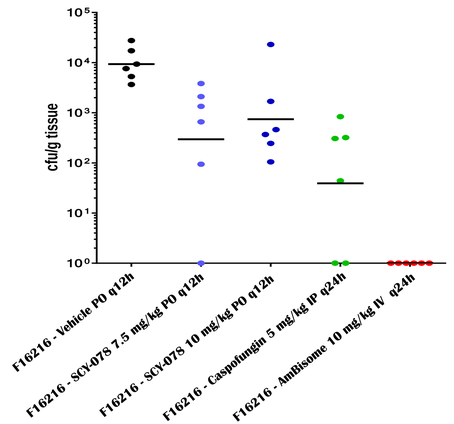
Mean Kidney Burden of *A. fumigatus* (WT) Following Treatment with Various Anti-fungal Agents



Survival Following Treatment of Disseminated *A.fumigatus* (azole-resistant) Infection with Various Anti-fungal Agents



Mean Kidney Burden of *A. fumigatus* (azole-resistant) Following Treatment with Various Anti-fungal Agents



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.

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