# SCY-078: A First-in-class, Orally-bioavailable, Glucan Synthase Inhibitor has Activity Alone and is Synergistic with Azole Antifungal Agents against *Aspergillus* spp.

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## BACKGROUND

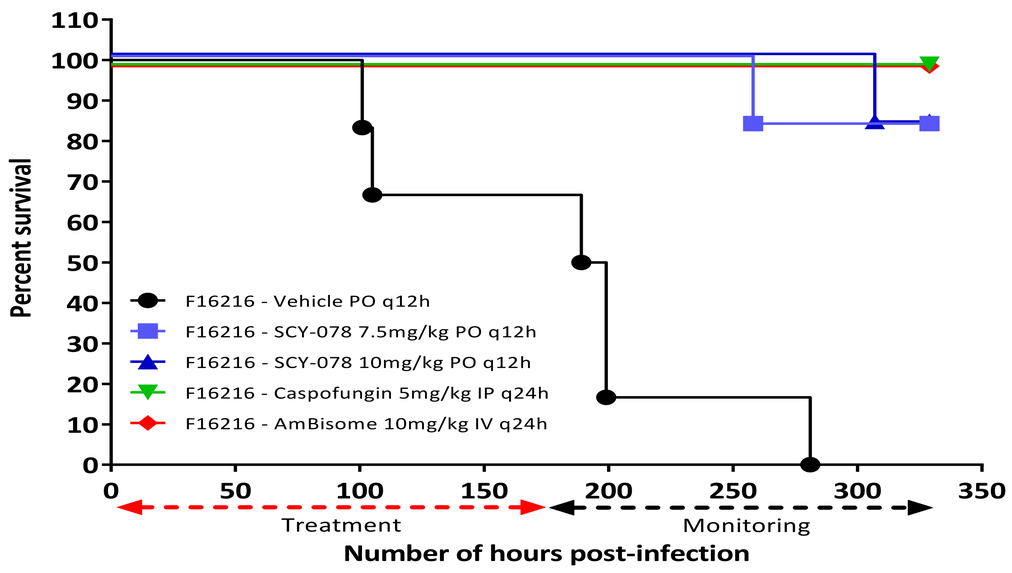
SCY-078 is a novel, oral and intravenous (IV), triterpenoid-class glucan synthase inhibitor with broad-spectrum activity against *Candida*, *Aspergillus* and *Pneumocystis* spp. currently in clinical development for use in the treatment of multiple serious fungal infections. Invasive aspergillosis (IA) continues to be a disease of high morbidity and mortality, especially in immunocompromised patients. Triazoles have become the drug of choice for the treatment of IA, but with suboptimal clinical outcomes and a growing concern of azole-resistant *Aspergillus*, there is a need for new agents and strategies for treatment of this disease. To understand the *in vitro* and *in vivo* activity of SCY-078 alone and in combination with other antifungal agents against *Aspergillus*, SCY-078 was tested against both susceptible and azole-resistant isolates of *Aspergillus* spp. as a single agent and in combination with azoles.

## METHODS

- The *in vitro* activity of SCY-078 against *Aspergillus* spp. isolates was evaluated by 4 independent laboratories using CLSI (M38-A2) and/or EUCAST methods. The combined studies included 480 unique isolates, the majority of which were *A. fumigatus* (N=175), *A. flavus* (N=102), *A. terreus* (n=99) and *A. niger* (N=56) as well as 20 azole-resistant isolates. Activity determinations were based on the Minimum Effective Concentration (MEC), the lowest concentration to exhibit small, rounded, compact hyphal forms as compared to hyphal growth in the control well, indicating gross morphological changes.
- The *in vitro* activity of SCY-078 in combination with voriconazole, isavuconazole and amphotericin B against wild-type (WT) and azole-resistant *Aspergillus* strains was evaluated using a checkerboard combination test method.
- The *in vivo* activity of SCY-078 was assessed against wild-type and azole-resistant (TR34, L98H) *A. fumigatus* strains in neutropenic ICR mice. Mice were infected via the lateral tail vein, and antifungal therapy was initiated 5 hours post infection and maintained for 7 days. Efficacy was evaluated by determination of kidney fungal burden.
- The *in vivo* activity of SCY-078 alone and in combination with isavuconazole was evaluated in a rabbit model of pulmonary aspergillosis. Neutropenic female New Zealand white rabbits were infected via endotracheal inoculation and antifungal therapy was initiated 24 hours after inoculation and continued for 12 days. Efficacy was evaluated by determination of lung injury (infarct score) and survival.

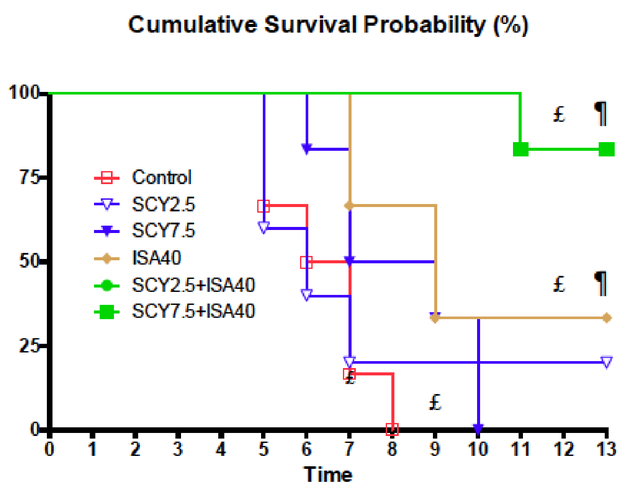
## RESULTS

### Survival following treatment of disseminated *A. fumigatus* (azole-resistant) infection with various anti-fungal agents in a murine model[c]




Similar results were obtained against a WT strain of *A. fumigatus*

### Treatment with SCY-078 and Isavuconazole resulted in prolonged survival compared to monotherapy in a rabbit model[d]




¶, p<0.05, prolonged survival in SCY2.5+ISA40 and SCY7.5+ISA40 -treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and ISA40

£, p<0.01, prolonged survival of rabbits treated with SCY2.5+ISA40, SCY7.5+ISA40, ISA40 alone in comparison to that of UC

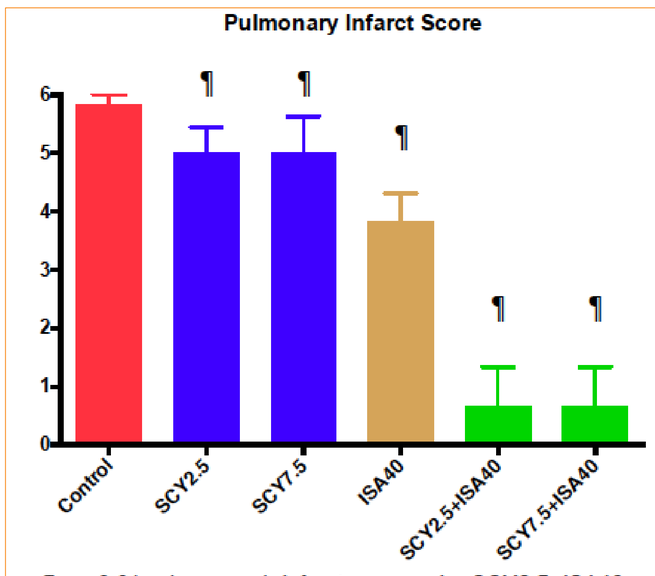
When tested *in vitro,* the MEC ranges (mg/ml) for SCY-078 alone against *Aspergillus* strains were as follows: *A. fumigatus* (N=175) 0.008-4; *A. flavus* (N=102) 0.0015-0.25; *A. terreus* (n=99) 0.008-0.25; *A. niger* (N=56) 0.008-0.5*; A. nidulans* (9) <0.063-0.125; *A. glaucus* (5) <0.063-0.125; *A. versicolor* (8) <0.063-0.25; and azole-resistant *Aspergillus* (20), <0.03-0.5.[a] The antifungal activity in combination is displayed in the table below, synergistic activity was observed in the majority of the tests with no antagonistic activity shown in any combination.

### SCY-078 demonstrated synergistic *in vitro* activity when combined with azoles or AmphiB against WT and azole-resistant* *Aspergillus*[b]

| | SCY-078+VORI | | SCY-078+ISA | | SCY-078+AMB | |
|---|---|---|---|---|---|---|
| **Isolate** | FICI | Interpretation† | FICI | Interpretation† | FICI | Interpretation† |
| **20438** | 0.27 | S | 0.5 | S | 0.13 | S |
| | 0.31 | S | 0.5 | S | 0.13 | S |
| **28378** | 0.31 | S | 0.16 | S | 0.25 | S |
| | 0.19 | S | 0.28 | S | 0.25 | S |
| **28382** | 0.31 | S | 0.27 | S | 0.25 | S |
| | 0.5 | S | 0.03 | S | 0.13 | S |
| **28401** | 0.28 | S | 0.31 | S | 0.25 | S |
| | 0.27 | S | 0.31 | S | 0.13 | S |
| ***28383** | 1 | NI | 0.51 | NI | 1 | NI |
| | 1 | NI | 1.02 | NI | 1.03 | NI |
| ***28500** | 1.25 | NI | 1.03 | NI | 0.25 | S |
| | 1.13 | NI | 1.25 | NI | 0.28 | S |

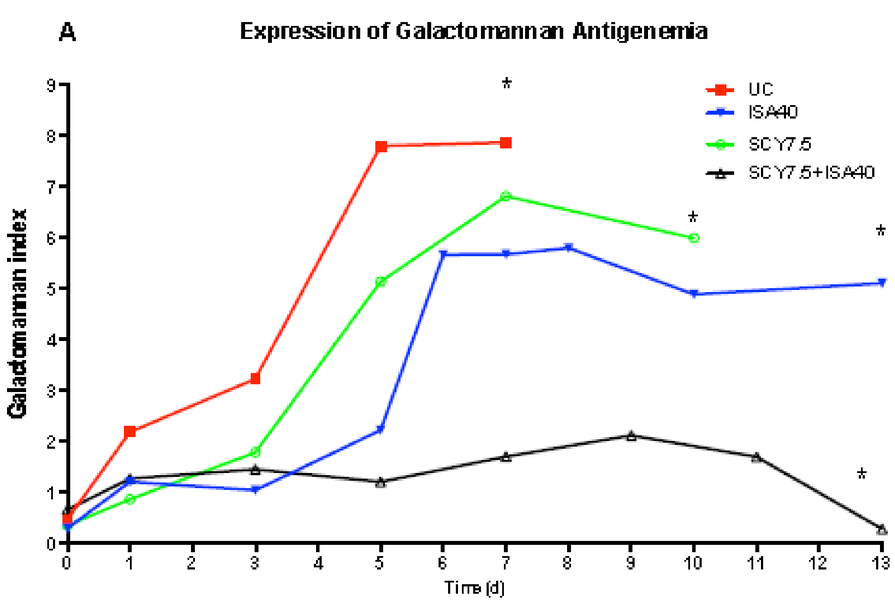
*Azole-resistant strains, S (Synergistic: FICI ≤ 0.5); NI (no interaction: FICI > 0.5 ≤ 4.0)

### Treatment with SCY-078 and Isavuconazole resulted in decreased pulmonary infarct scores compared to monotherapy[d]




¶, p<0.01, decreased infarct scores in SCY2.5+ISA40 and SCY7.5+ISA40 -treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and ISA40

### Lower GMI in rabbits treated with combination regimen of SCY7.5+ISA40 in comparison to that of single therapy of SCY7.5, ISA40, and untreated controls[d]




*p<0.05; lower GMI in rabbits treated with combination therapy in comparison to that of single drug therapy

## CONCLUSION

SCY-078 demonstrated potent *in vitro* and *in vivo* activity against wild-type and azole-resistant strains of *Aspergillus*. SCY-078 demonstrated synergistic activity with other antifungal agents *in vitro* and *in vivo* against *Aspergillus fumigatus*. These results support further development of SCY-078 for invasive *Aspergillus* infections.

[a]Data on file
[b]SCY-078, a Novel Oral Glucan Synthase Inhibitor, for the Treatment of Invasive Aspergillosis: Evaluation of Antifungal Activity Singly and in Combination. Ghannoum M et al., Antimicrob Agents Chemother. 2018 Apr 2
[c]SCY-078 Demonstrates Significant Antifungal Activity in a Murine Model of Invasive Aspergillosis, Borroto-Esoda et al, IDWeek 2017
[d]Combination Therapy with SCY-078 and Isavuconazole for Treatment of Experimental Invasive Pulmonary Aspergillosis, Walsh et al. Advances Against Aspergillosis 2018