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P0164 In vitro activity of SCY-078, a novel IV/oral glucan synthase inhibitor, against Aspergillus spp., alone or in combination with other antifungal therapies

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Background: Invasive aspergillosis (IA) remains a major cause of death among the immunocompromised population, including those receiving long-term immunosuppressive therapy. In light of increased azole resistance, administration limitations (intravenous only) of existing echinocandins (ECH) and toxicity associated with amphotericin B (AM), new antifungal agents and treatment approaches (e.g., combination therapy) for the treatment of IA are clearly needed. SCY-078 is the first in class triterpenoid antifungal, a novel class of glucan synthase inhibitors, with broad *in vitro* and *in vivo* activity against a broad spectrum of *Candida* and *Aspergillus*.

Materials/methods: The test panel of clinical *Aspergillus* strains (*n*=311) included *A. fumigatus, A. terreus, A. flavus, A. niger, A. glaucus, A. ustus, A. versicolor,* and *A. westerdijkiae.* Seventeen of these had reduced susceptibility to AM, voriconazole (VOR), and/or ECH. Susceptibility testing was performed according to CLSI M38-A2 microdilution assay, with SCY-078 inhibition endpoints determined by minimum effective concentration (MEC). Combination testing of SCY-078 with AM, isavuconazole (ISA), or VOR was performed in a checkerboard microdilution assay, with interactions scored by Fractional Inhibitory Concentration Index (FICI).

Results: SCY-078 showed potent antifungal activity against this panel of *Aspergillus fumigatus* and non-*fumigatus* strains (MEC_{90} = 0.125 µg/ml) as compared to AM (MIC_{90} = 8 µg/ml) and VOR (MIC_{90} = 2 µg/ml). SCY-078 showed fungistatic behavior against the *Aspergillus* strains tested. Combination testing of SCY-078 with ISA or VOR against *A. fumigatus* demonstrated synergistic activity against the majority of the azole-susceptible strains tested, while SCY-078 in combination with AM was synergistic against the azole-susceptible strains as well as a known *cyp51A* mutant in *A. fumigatus*.

Conclusions: Further studies of SCY-078 are warranted, as this novel glucan synthase inhibitor may prove to be an important additional antifungal for first-line or salvage therapy and mono or combination treatment of IA.