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A prospective, phase 2, multicentre, open-label, randomized, comparative study to estimate the safety, tolerability, pharmacokinetics, and efficacy of oral SCY-078 vs standard-of-care following initial intravenous echinocandin therapy in the treatment of invasive candidiasis (including candidaemia) in hospitalized non-neutropenic adults (mycoses study group 010)

Peter G. Pappas*[1], John Pullman[2], George Thompson[3], Andrej Spec[4], Ellis Tobin[5], Jose Vazquez[6], David Angulo Gonzalez[7], Silvia Helou[8]

[1]*University of Alabama-Birmingham*

[2]*Mercury Street Medical*

[3]*Uc-Davis; Infectious Diseases*

[4]*Washington University St Louis*

[5]*Albany Medical Center*

[6]*Georgia Regents University*

[7]*Scynexis, Inc.*

[8]*Scynexis, Inc.; R&d*

Background: SCY-078 is an oral and (intravenous) IV, semi-synthetic triterpene antifungal, structurally distinct glucan synthase inhibitor in development for the treatment for fungal infections caused by *Candida* and *Aspergillus* species.The purpose of this study was to evaluate the safety of 2 dosing regimens of oral SCY-078 in subjects with invasive candidiasis (IC), to identify the dose to achieve a target exposure (15.4 μM/hr) in > 80% of the intended population, and to provide a preliminary assessment of the efficacy and safety of orally administered SCY-078 vs. standard of care (SOC) following initial IV echinocandin therapy.

Material/methods: In this study, all subjects with documented IC received an IV echinocandin for 3 to 10 days and were subsequently randomized to receive step-down oral therapy in a 1:1:1 ratio to one of the 3 treatment arms: oral SCY-078 1000mg loading dose followed by 500mg QD, oral SCY-078 1250mg loading dose followed by 750mg QD, or SOC (oral fluconazole 800mg loading followed by 400mg QD or IV micafungin 100mg QD) for up to 28 days. Plasma samples from SCY-078 subjects were collected to evaluate exposure by population PK modeling. Safety was assessed throughout the study and global response was evaluated at end of treatment and at the 6 week follow up visit.

Results: Out of 27 subjects enrolled, 7 were randomized to received SCY-078 500mg, 7 to receive SCY-078 750mg, 8 to receive the SOC (7 received fluconazole and 1 received micafungin due to fluconazole-resistant isolate) and 5 did not meet criteria for randomization. The interim population PK analysis indicates that the SCY-078 750mg regimen is predicted to achieve the target exposure of at least 15.4 μM•hr. at steady state in approximately 85% of the population. The rate of adverse events (AEs) and serious AEs were similar among subjects receiving SCY-078 or fluconazole. The most common AEs for all groups were gastrointestinal (GI); diarrhea, abdominal pain, nausea and vomiting. GI events were mild or moderate; none resulted in discontinuation. Similar favorable global response rates were reported among all treatment groups: 6 of 7 (86%) in the SCY-078 750mg group, 5 of 7 (71%) in the SCY-078 500mg group and 5 of 7 (71%) in the fluconazole group . The one subject treated with micafungin had favorable global response.

Conclusions: The oral dose of SCY-078 estimated to achieve the target exposure in subjects with IC is 750mg QD. This dose was well-tolerated and achieved favorable global response rate similar to SOC.