P201

# Ibrexafungerp (formerly SCY-078) Demonstrates Activity Against *Candida auris*: *In Vitro*, *In Vivo* and Clinical Case Studies of Candidemia

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## BACKGROUND

*Candida auris* is a growing global threat; a pathogen associated with high mortality (up to 60%), multi-drug resistance, the ability to spread from person-to-person and surface-to-person, presenting high risk for outbreaks in healthcare facilities. Ibrexafungerp is a novel IV/oral glucan synthase inhibitor (triterpenoid) antifungal with activity against *Candida*, *Aspergillus* and *Pneumocystis* spp, in Phase 3 development. Given the potent activity of ibrexafungerp against *Candida* spp., Scynexis has embarked on a development program to understand the activity and effectiveness against *Candida auris*. We will present the current preclinical and clinical data sets of ibrexafungerp against *Candida auris*.

## METHODS

*In vitro* studies tested IBX against >100 clinical isolates of *C. auris*. Isolates represent each of the four known clades of *C. auris* and originate from countries all over the world. The collection includes isolates with elevated MICs against the echinocandins. All isolates were evaluated using broth microdilution methods as described in standards of the Clinical and Laboratory Standards Institute reference methodology M27-A3. (Tables 1 and 2, Berkow et al, AAC 2017). Other *in vitro* studies evaluated the effects of IBX against *C. auris* biofilms as previously described (Figure 1, Larkin et al, AAC 2017). The *in vivo* activity of IBX against *C.auris* was evaluated using a disseminated murine model (Figure 2, Ghannoum, ASM Microbe 2019) and a cutaneous infection guinea pig model (Figure 3, Ghannoum, ASM Microbe 2019). In humans, an ongoing open-label trial of ibrexafungerp for treatment of patients with infections caused by *C. auris* (the CARES study) has been initiated in the USA and India. We present two patient cases from the CARES study. (Table 3, Juneja, ECCMID 2019)

## RESULTS

Table 1: Ibrexafungerp MIC distribution across 100 clinical *C. auris* isolates μg/ml)

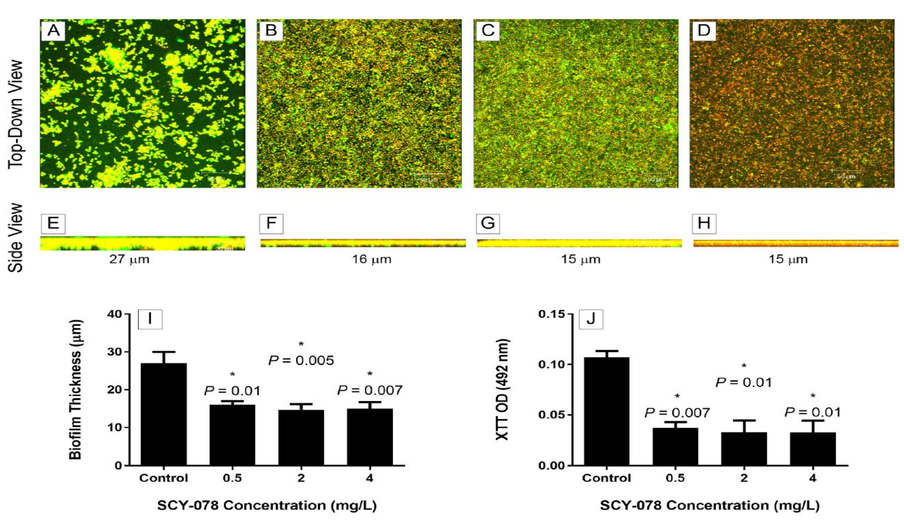
| MIC | 0.03 | 0.0625 | 0.125 | 0.25 | 0.5 | 1 | 2 | 4 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| # of Isolates | | 4 | 3 | 12 | 31 | 46 | 4 | | |

Table 2: Ibrexafungerp MIC data compared to isolates with elevated echinocandin MICs

| | Minimum Inhibitory Concentration (μg/ml) | | | |
|---|---|---|---|---|
| Isolate | Anidulafungin | Caspofungin | Micafungin | Ibrexafungerp |
| 1 | 8 | 1 | 4 | 1 |
| 2 | 16 | 1 | 4 | 1 |
| 3 | 1 | 16 | 1 | 1 |
| 4 | 2 | 16 | 2 | 1 |
| 5 | 4 | 0.5 | 0.5 | 0.5 |
| 6 | >16 | >16 | >8 | 0.5 |
| 7 | 4 | >16 | 1 | 1 |

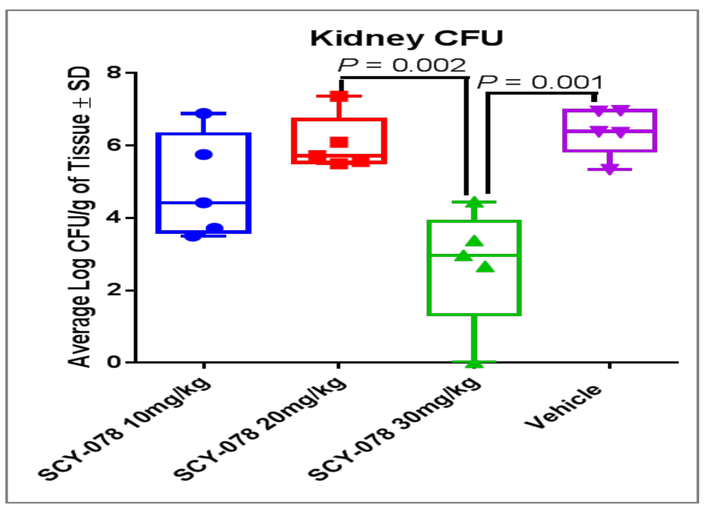
Ibrexafungerp demonstrated consistent MIC's against *Candida auris* species with echinocandin-susceptible and –resistant isolates

Figure 1: Confocal scanning laser microscopy analyses of the effect of Ibrexafungerp on biofilms formed by *C. auris*



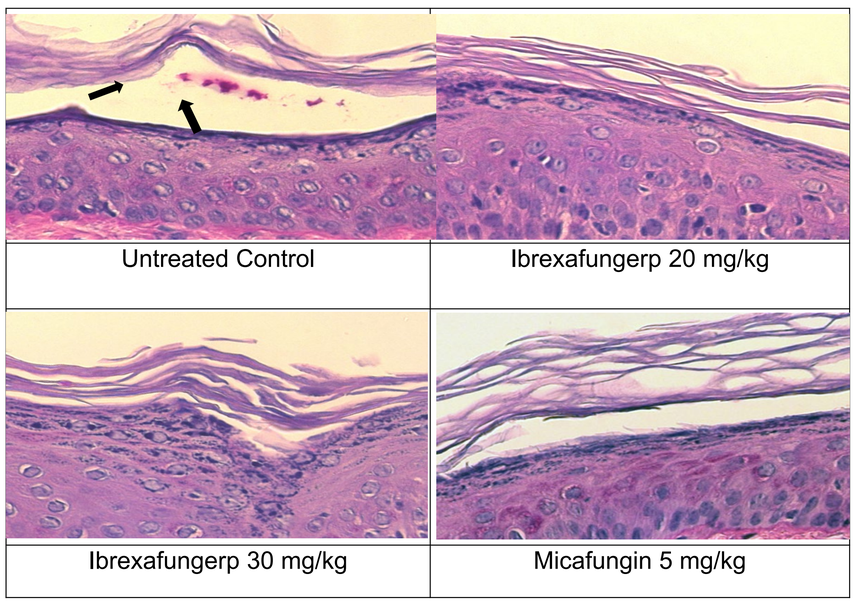

Biofilms formed by *C. auris* MRL 31102 were exposed to: (A, E) No drug (Control), or IBX at different concentrations: (B, F) 0.5 mg/L, (C, G) 2 mg/L, or (D, H) 4 mg/L. Panels A-D show the top-down views, while panels E-H show side views of untreated and treated biofilms (magnification, ×25). Panels I and J show the thickness and metabolic activity, respectively, of untreated (Control) and IBX treated biofilms. **P*-value compared to untreated control (no drug). *P*-value of <0.05 was considered significant. All experiments were done in triplicate, bars represent mean ± SD. IBX exhibited potent activity against biofilms formed by *C. auris* strains.

Figure 2: Ibrexafungerp lowers tissue fungal burden in a murine disseminated model of *Candida auris*




Data showed that tissue fungal burdens were lower than vehicle controls in all treatment groups, with the highest reduction in tissue burden observed in the 30 mg/kg dosing group (Table 1, Fig. 1). The 14-day survival rate was comparable across the active groups, with animals in the ibrexafungerp 10, 20 and 30 mg/kg groups having survival rates of 60%, 70% and 60%, respectively, compared to the vehicle group which had a survival rate of 20% (Table 2). Exposures in mice dosed with ibrexafungerp 10, 20 or 30 mg/kg BID are consistent with steady-state plasma exposure ($AUC_{0\text{-}24}$) values of 8.4, 24.3 and 40.2 ug*hr/mL, respectively.

Figure 3: Ibrexafungerp treatment in a guinea pig model of *Candida auris* cutaneous infection




Histological examination showed that no fungal elements were observed in the biopsy samples treated with ibrexafungerp or micafungin, as opposed to the untreated control group (arrow) (Figure 3)

Table 2: We present our experience with 2 cases of candidemia due to *C.auris* that we enrolled in the CARES study.

| Demographics | Medical History | Microbiology Day, relative to IBX start | Description | Antifungal therapy Day, relative to Ibrexafungerp start |
|---|---|---|---|---|
| 58 years old<br>Male<br>Asian | Diabetes Mellitus, acute ischemic stroke, popliteal thrombosis, liver, spleen and kidney infarcts, and prolonged ICU stay. | Paired blood cultures:<br>Day -11 *Candida auris*<br>Fluconazole MIC >64<br>Voriconazole MIC 2<br>Ampho B MIC 0.5<br>Micafungin MIC 0.12<br><br>Day -4 *Candida auris*<br>Day +3 Negative<br>Day +5 Negative<br>Day +12 Negative | The patient developed aspiration pneumonia and septic shock. He was initially treated with antibiotics and subsequently empirically added fluconazole. *C. auris* was recovered from blood culture and antifungal therapy was switched to micafungin. Clinical improvement was observed but blood culture collected after micafungin remained positive and ibrexafungerp was initiated. Blood cultures became negative, the patient continued to improve and completed 17 days of ibrexafungerp. The patient was considered to have achieved complete response at end of therapy (EOT), per investigator's assessment.<br><br>The patient subsequently developed sepsis due to *K. pneumonia* and died of septic shock and multiple organ failure on Day 43 after EOT. | Fluconazole IV<br>from -10 to Day -5<br><br>Micafungin IV<br>from Day -5 to Day -1<br><br>Ibrexafungerp<br>from Day 1 to Day +17<br><br>Ibrexafungerp related AEs included, loose stools (mild) from Day +2 to Day + 4 |
| 64 years old<br>Female<br>Asian | Diabetes Mellitus, Hypertension, Chronic Kidney Diseases on Maintenance Hemodialysis | Paired blood cultures:<br>Day -3 *Candida auris*<br>Day +3 *Candida auris*<br>Day +9 Negative<br>Day +21 Negative | The patient presented with a LRTI, fever and hypotension. The patient was started on antibiotics and showed improvement but fever persisted. *C. auris* was isolated from blood cultures and ibrexafungerp was initiated. The patient's blood cultures became negative and the patient continued to improve completing 22 days of ibrexafungerp. The patient was considered to have achieved complete response at EOT, per investigator's assessment. At the end of the 6 week follow up, the patient was alive and with no evidence of recurrence of the fungal infection. | Ibrexafungerp<br>from Day 1 to Day +22<br><br>No Ibrexafungerp related AEs were observed |

## CONCLUSION

This data demonstrate that ibrexafungerp possess potent *in vitro* and *in vivo* activity as well as promising clinical activity. Therefore, continued clinical evaluation of ibrexafungerp as an option to treat *C. auris* infections is warranted