SCYNEXIS

Ibrexafungerp
Activity against *Pneumocystis*

Stephen A. Barat
Vice-President
Pre-Clinical Research and Early Development

Objectives

- To provide a brief background on *Pneumocystis* pneumonia (PCP).

- To introduce ibrexafungerp (IBX, formerly known as SCY-078), the first representative of a new class of orally-bioavailable glucan synthase inhibitors, and it's activity against *Pneumocystis*.

Pneumocystis- Background

- *Pneumocystis* resides in lung alveoli and can cause a lethal infection known as *Pneumocystis* pneumonia (PCP) in hosts with impaired immune systems
- The incidence of PCP is rising as a result of increased susceptible (non-HIV) patient populations, such as:
  - Solid organ transplant (SOT) recipients
  - Patients with haematologic malignancies
  - Patients receiving immune-modularity therapies for autoimmune and inflammatory conditions
- Currently, the primary treatment for PCP is trimethoprim-sulfamethoxazole (TMP-SMX)
  - TMP-SMX is not well tolerated
  - Mortality rates in non-HIV patients with PCP remain high, and second line agents can be difficult to manage due to drug-drug interactions
- Development of new drugs to treat PCP are needed

White et.al., J. of Fungi 2018, Liu et.al., Oncotarget 2017, Irairt et.al., J. of Fungi 2015

Pneumocystis- Treatment Guidelines

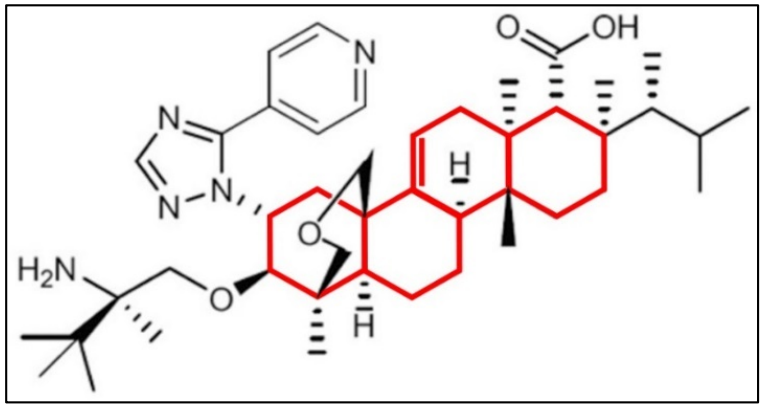
- TMP-SMX is considered as first line therapy for all subject populations (both prophylaxis and treatment)
  - TMP-SMX targets folic acid biosynthesis
    - Trimethoprim targets dihydrofolate reductase
    - Sulfamethoxazole inhibits dihydropteroate synthase
- Recommendations for second line therapy vary based on the patient population:
  - E.g. primaquine+clindamycin, pentamidine, atovaquone or combination therapy of TMP-SMX with caspofungin
- It is noteworthy that prospective clinical trials on the optimal selection of drugs for the treatment of PCP have not been conducted
  - Current therapeutic recommendations in this patient population are based on those mainly in HIV-associated PCP studies and observational studies

Maschmeyer G, et al., J. AntiMicrob Chemo. 2016

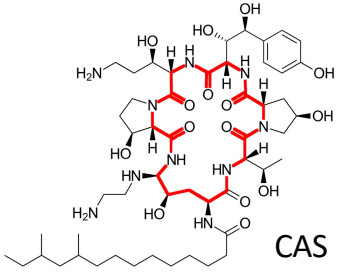
Ibrexafungerp (formerly SCY-078) Overview

Ibrexafungerp
A Novel Triterpenoid Antifungal

Novel Glucan Synthase Inhibitor (GSI)



Structurally distinct from other GSIs (echinocandins)

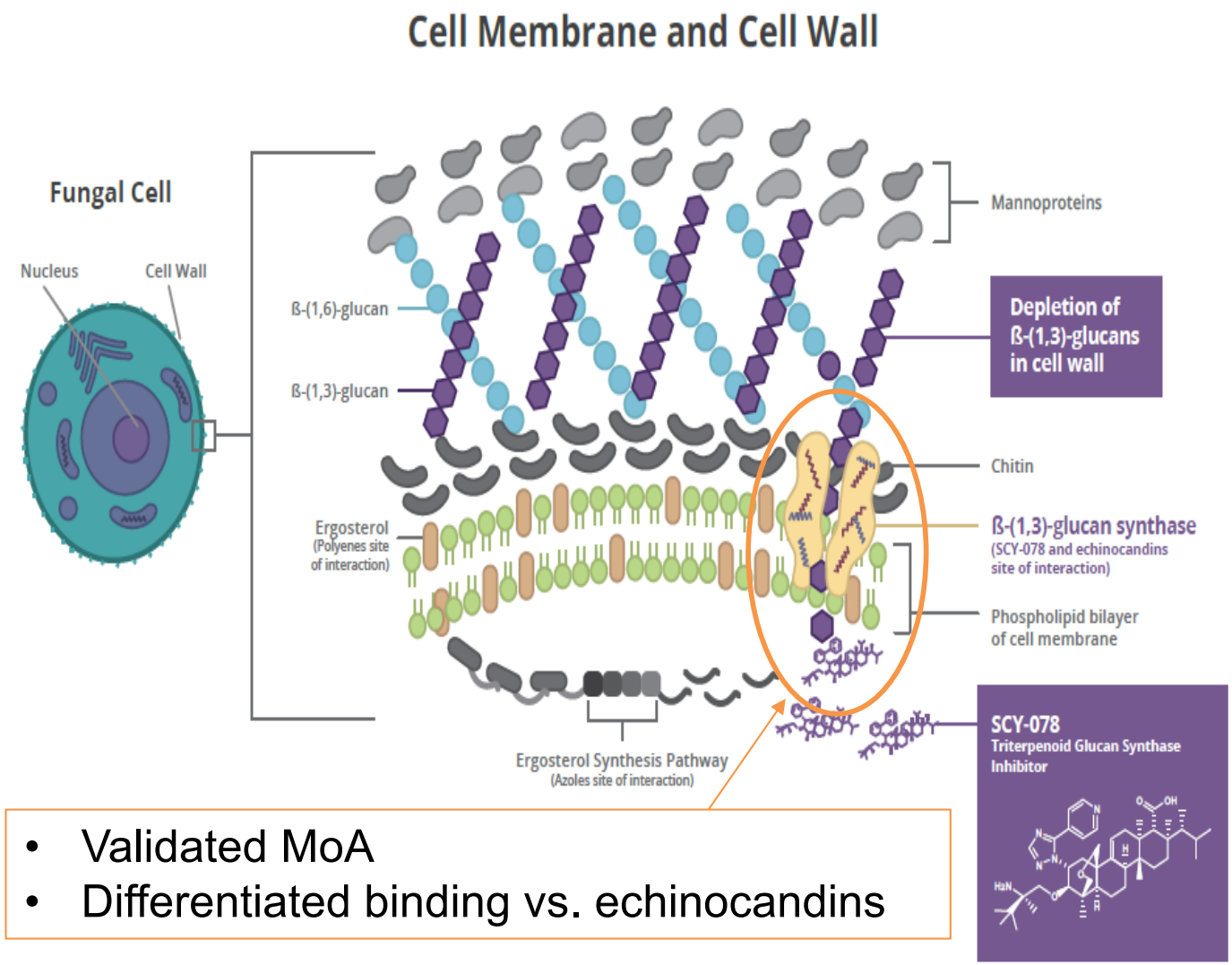


- Different enzyme-drug interaction → lower impact of common FKS mutations
- Oral bioavailability

Key Attributes

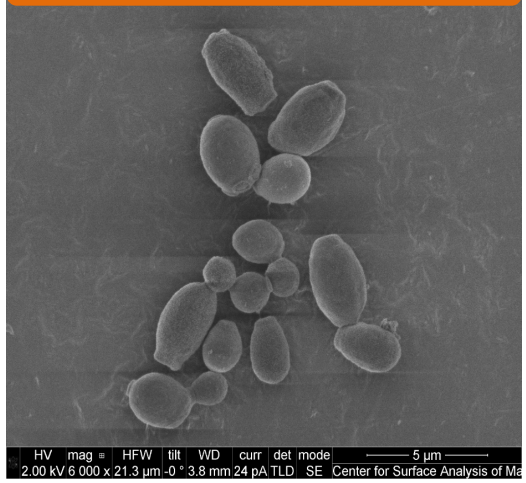
- Activity against:
  - *Candida* spp.
  - *Aspergillus* spp.
  - *Pneumocystis* spp.
- Active against azole-resistant and most echinocandin-resistant strains
- Oral and IV formulations
- Favorable safety profile >500 exposed
  - Low risk of drug-drug Interactions
- Extensive tissue distribution
  - (V_{dss} > 8 L/kg)

Ibrexafungerp MoA: Glucan Synthase Inhibitor

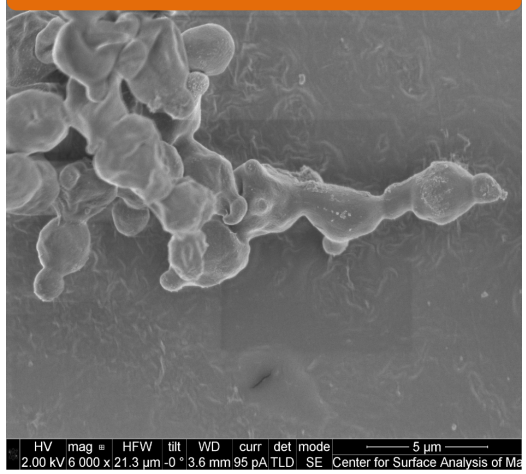


- Validated MoA
- Differentiated binding vs. echinocandins

C. auris before SCY-078



C. auris after SCY-078



IBX - evaluated against >2000 clinical isolates of *Candida* spp. *in vitro*

Species	N	MIC_{90} range (μg/mL)*
C. albicans	≈600	0.06 – 0.25
C. glabrata	≈400	0.25 – 0.5
C. parapsilosis	≈300	0.25 – 0.5
C. tropicalis	≈200	0.125 – 0.25
C. krusei	≈150	0.5 - 1
C. auris	≈140	0.5 - 1
C. guilliermondii	≈45	1 - 4
C. lusitanaie	≈30	0.25 - 4
C. dubliniensis	≈20	0.06 – 0.25
C. orthopsilosis	≈15	0.06 - 1
C. peliculosa	≈15	0.25 - 2
C. kefyr	≈15	0.06 - 1
C. other	≈45	0.03 - 4

Data from 8 independent studies: Pfaller et al 2013 and 2017, Shell et al 2017, Marcos-Zabrano et al 2017, Personal communications from Dr. M. Ghannoum, Dr. P. Pappas and Dr. G. Quindos. MIC_{50} ranges shown for spp. with >100 isolates

Ibrexafungerp has *in vitro* activity against isolates of all of the *Candida* spp. tested with MIC_{90} values ranging from 0.03 μg/mL to 4 μg/mL

IBX – *In Vivo* Activity Against Fungal Species

- Ibrexafungerp has demonstrated activity in multiple murine models of Invasive Candidiasis
  - The models evaluated the activity of ibrexafungerp *in vivo* activity against *C. albicans*, *C. glabrata, C. tropicalis, C. parapsilosis* and *C. auris* strains
    - The studies included WT and echinocandin-resistant isolates
    - Treatment with ibrexafungerp resulted in improved mortality and decreased fungal kidney burden across all of the *Candida* spp. evaluated, including echinocandin-resistant strains.
- Ibrexafungerp has demonstrated activity in murine and rabbit models of Aspergillosis
  - Murine models on invasive aspergillosis evaluated the activity of ibrexafungerp *in vivo* both WT and azole-resistant strains
    - Treatment with ibrexafungerp resulted in improved mortality, decreased fungal kidney burden and decreased galactomannan index against both WT and azole-resistant strains
  - A rabbit model of pulmonary aspergillosis evaluated the activity of ibrexafungerp in combination with isavuconazole
    - Addition of ibrexafungerp to isavuconazole resulted in significant improvements in survival, pulmonary infarct scores and decreased galactomannan antigenemia in serum and bronchoalveolar lavage

IBX – Rationale for Activity Against *Pneumocystis*

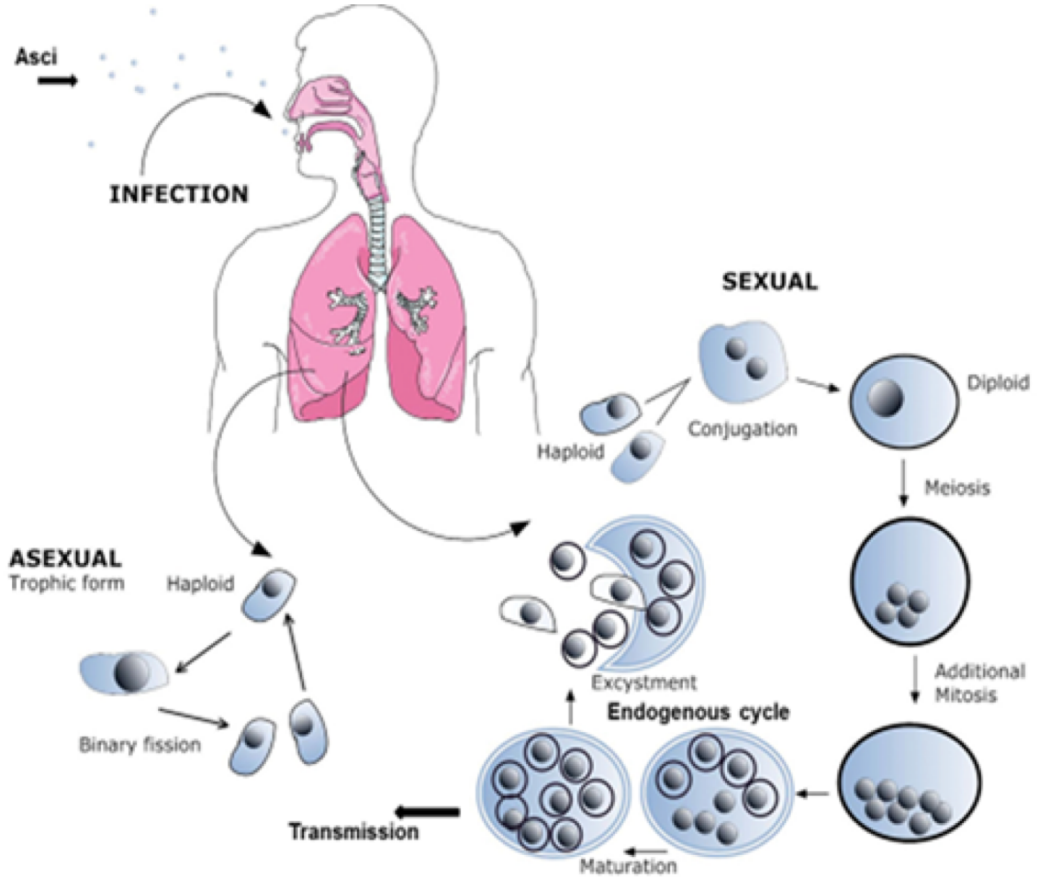


Figure 2. New proposed life cycle of Pneumocystis. A new concept of the life cycle of Pneumocystis is proposed that includes both the pulmonary stages (endogenous cycle) and the extra-pulmonary stages of infection and transmission. **Endogenous cycle**: inhaled asci arrive at the alveoli, ascospores are released, attach to the Alveolar Epithelial Cells 1 (AEC1), replicate asexually and at some point begin sexual replication via a primary homothallic mechanism. Resulting asci participate in the endogenous cycle and also the extra-pulmonary stage by releasing asci (**transmission**) to complete the life cycle by **infection** of the next host.

The *Pneumocystis* life cycle contains an asexual mode of replication via binary fission of the trophic form and a sexual mode resulting in formation of an ascus (cyst)

The cyst form of *Pneumocystis* spp. contains **β-1,3-D-glucan**, the target of IBX activity

Murine Models of *Pneumocystis* Pneumonia

- Murine models of PCP - designed to mimic the immunosuppressive states in humans that have been associated with PCP - have been shown to be effective in determining the potential activity of experimental treatments
  - Prophylaxis model – mice are immunosuppressed with corticosteroids and infection is established by intranasal inoculation with *P. murina.* Treatment is initiated at the time of infection and continued for six weeks. Efficacy is based on the reduction of organism burden (nuclei and asci) between the treatment groups and the negative control group as determined by microscopic evaluation
  - Therapeutic model - The study is conducted in two phases
    - Phase 1 – immunosuppressed mice are exposed to infected mice for 2 weeks to establish infection
    - Phase 2 – once infection has been established, mice are treated for up to 3 weeks. Efficacy is based on evaluation for the presence of the trophic and cyst forms by staining and microscopic examination and survival.
- TMP-SMX is used as the positive control in both studies.

IBX: Activity in a Murine Prophylaxis model of PCP

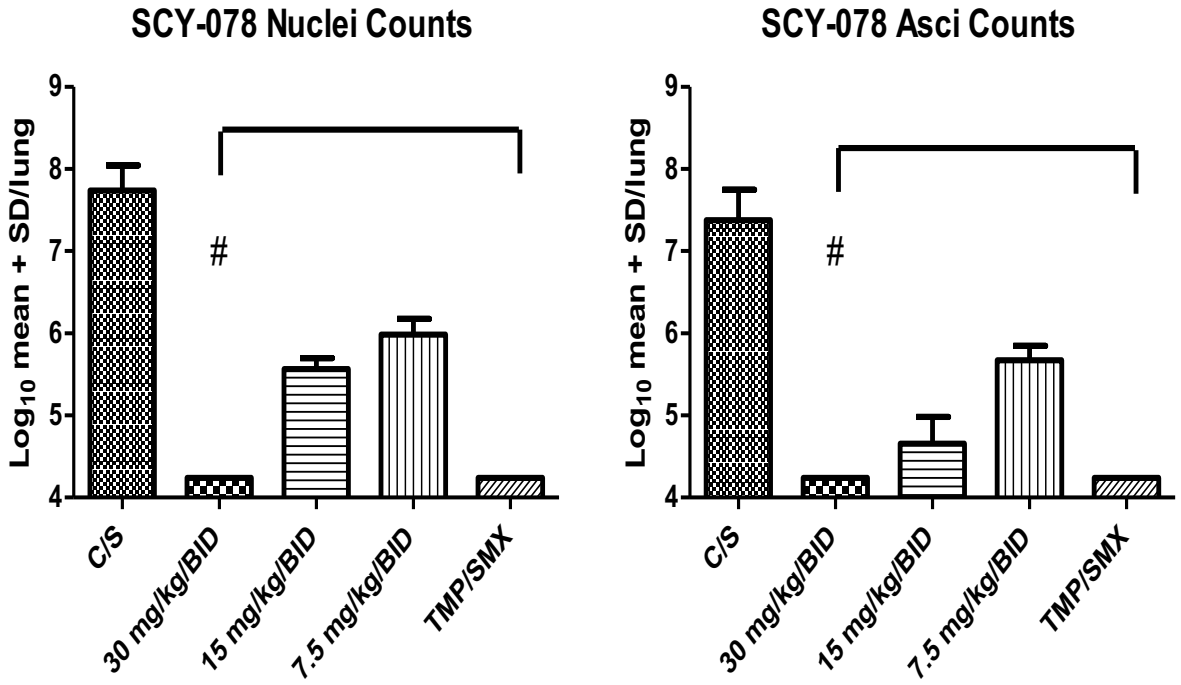
Study Design

- C3H/HeN mice (10 per group) were infected by intranasal inoculation of *P. murina* at 2 x 10^6/50 µl. The immune systems of the mice were suppressed by the addition of dexamethasone at 4 mg/liter to acidified drinking water.
- Treatment with oral IBX (7.5 mg/kg, 15 mg/kg, or 30 mg/kg BID), trimethoprim/sulfamethoxazole (TMP/SMX 50/250 mg/kg, 3X/week as positive control), or vehicle control was started at the time of inoculation and was continued for six weeks.
- Efficacy analysis was based on the reduction of organism burden between the treatment groups and the vehicle control group as determined by microscopic evaluation (total nuclei and asci counts) in lung tissue as well as survival at the end of treatment. Statistical significance is accepted at a *p* value ≤ 0.05.

IBX: Activity in a murine prophylaxis model of PCP

Results

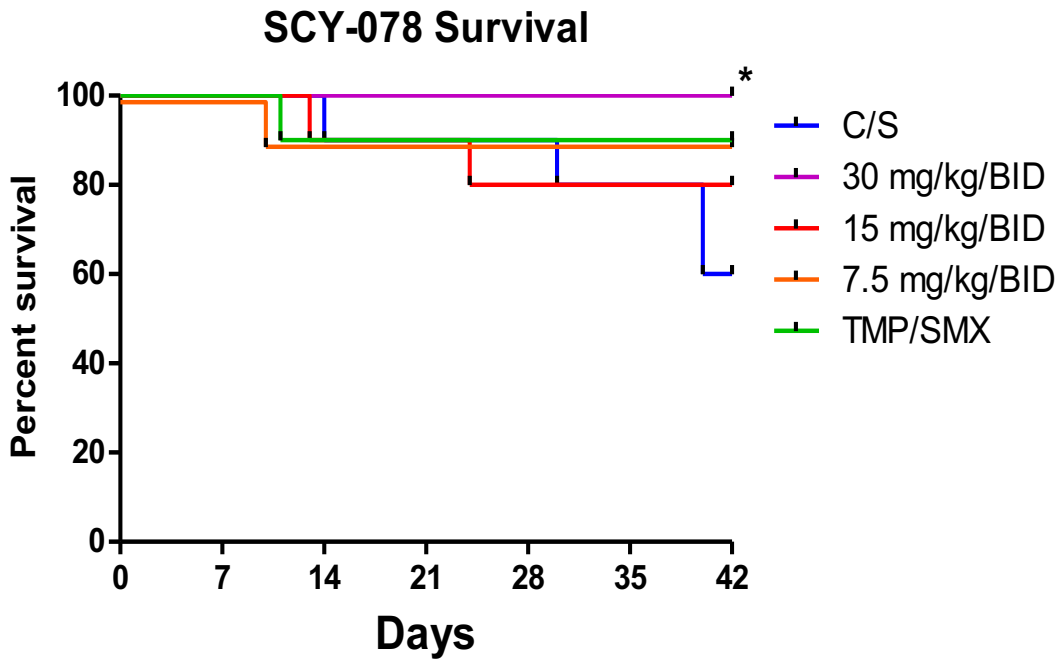
- IBX at all 3 dose levels significantly reduced both nuclei and asci burden versus the vehicle treated control group (C/S).
- IBX at 30 mg/kg performed equally as well as the gold standard for treatment of *Pneumocystis* pneumonia (TMP/SMX) at reducing the asci burden and nuclei counts.



IBX: Activity in a murine prophylaxis model of PCP

Results

- IBX at 30 mg/kg showed a significant improvement in survival versus the vehicle treated control group.



* denotes statistical significant difference between treatment group and C/S group.

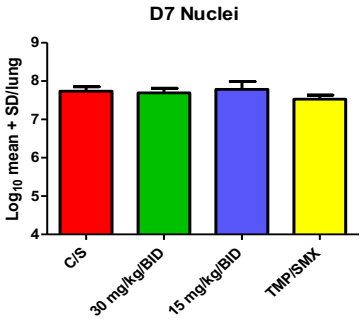
IBX: Activity in a murine treatment model of PCP

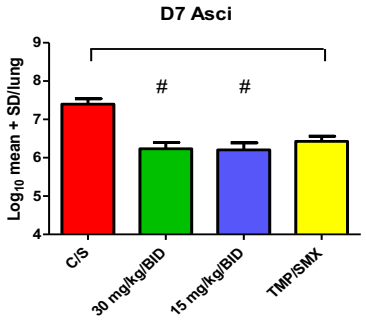
Study Design

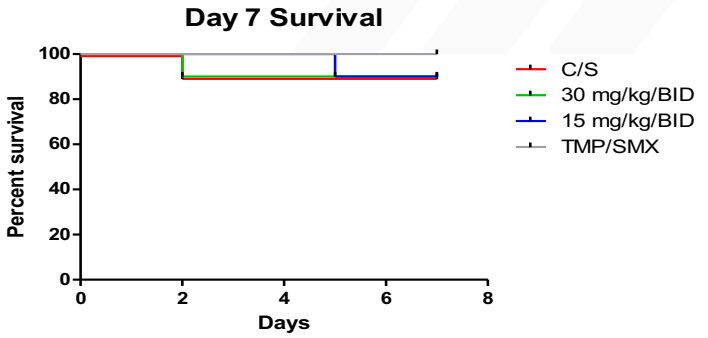
- C3H/HeN mice (10/group) were infected with *P. murina* pneumonia through exposure to mice with a fulminant *P. murina* infection (seed mice). Mice were immune suppressed by the addition of dexamethasone at 4 mg/liter to the drinking water. The seed mice were rotated within the cages for 2 weeks and then removed.
- After the mice developed a moderate infection level (approximately 5 weeks), the mice were divided into a negative control group (control steroid), positive control group (TMP/SMX 50/250 mg/kg, QD) and IBX (15 and 30 mg/kg, BID) treatment groups. Treatments were administered by oral gavage (PO) for up to 3 weeks.
- Mice were euthanized by CO_2 and lungs processed for analysis. Slides were made from the lung homogenates at different dilutions and stained (Diff-Quik to quantify the nuclei and cresyl echt violet to quantify the asci).
- Efficacy was based on a reduction of organism burden between the treatment groups and the negative control group as determined by microscopic evaluation. Efficacy analysis was based on quantification of nuclei (all life cycle stages) and asci.

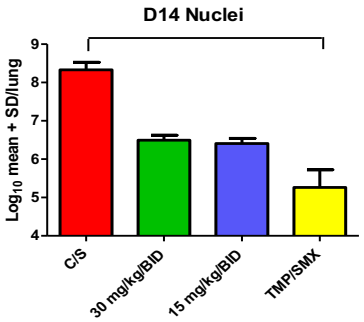
IBX: Activity in a murine treatment model of PCP

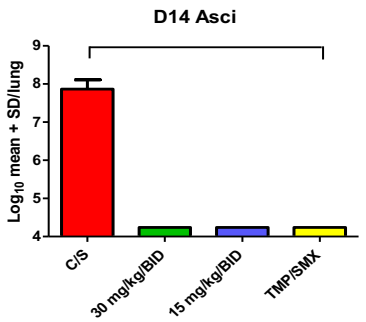
SCY-078 significantly reduced nuclei and asci at all dose levels

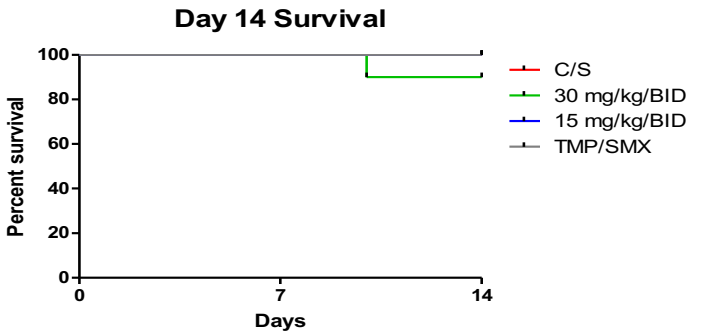


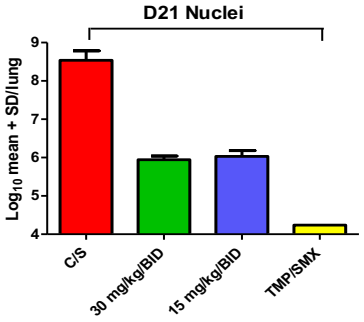


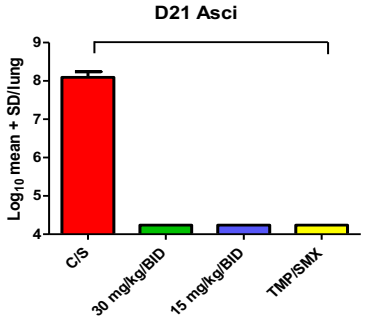


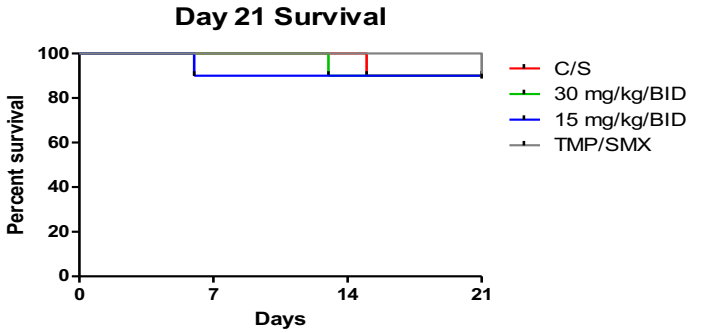












IBX: Activity in a murine Treatment model of PCP

- Both dose levels of IBX were significantly better than the gold standard for treating PCP (TMP/SMX) at reducing asci burden by Day 7.
- Both dose levels of IBX significantly reduced nuclei and asci levels at Days 14 and 21, as compared to the negative control.
- There was no microscopically detectable asci by Day 14 and a significant reduction in nuclei at Days 14 and 21.

Ibrexafungerp: Summary and Next Steps

- IBX performed equally as well as the gold standard for treatment of *Pneumocystis* pneumonia at reducing the asci burden in murine models of *Pneumocystis*.
  - While a dose-response was observed in the prophylaxis study, there were no differences in response between the 15 mg/kg and the 30 mg/kg groups in the treatment study.
- Additional studies are currently ongoing/planned to further investigate dose-response, treatment durability, etc.

Conclusions

- The number of patients with non-HIV related PCP is increasing, and mortality rates remain high in this patient population
- Current treatments have various limitations.
- IBX, as the first representative of a new class of oral antifungal agents with demonstrated activity against *Pneumocystis* murine models, may present a potential option, for either prophylaxis or treatment of PCP, and merits clinical investigation.

Ibrexafungerp Ongoing Clinical Trials

VANISH: Phase 3 pivotal (2 studies), randomized, double-blind, in patients with acute VVC. Single day IBX treatment.

- Sites in US and Europe

SCYNERGIA: Phase 2, randomized, double-blind, in patients with Invasive Pulmonary Aspergillosis. IBX in combination with Azole.

- Sites in US and Europe (recruiting centers)

FURI: Phase 3, open-label in patients with *Candida* spp. infections that are refractory to or intolerant of approved antifungal agents

- Sites in the US, Germany, Austria, Netherlands, UK and Spain

CARES: Phase 3, open-label in patients with *Candida auris* infections

- Sites in US and India

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Thank you