In Vitro Activity of the Novel Agent, Ibrexafungerp (formerly SCY-078) Against *Candida* spp. (Including Fluconazole-Resistant Isolates) Being Developed for the Treatment of Vulvovaginal Candidiasis

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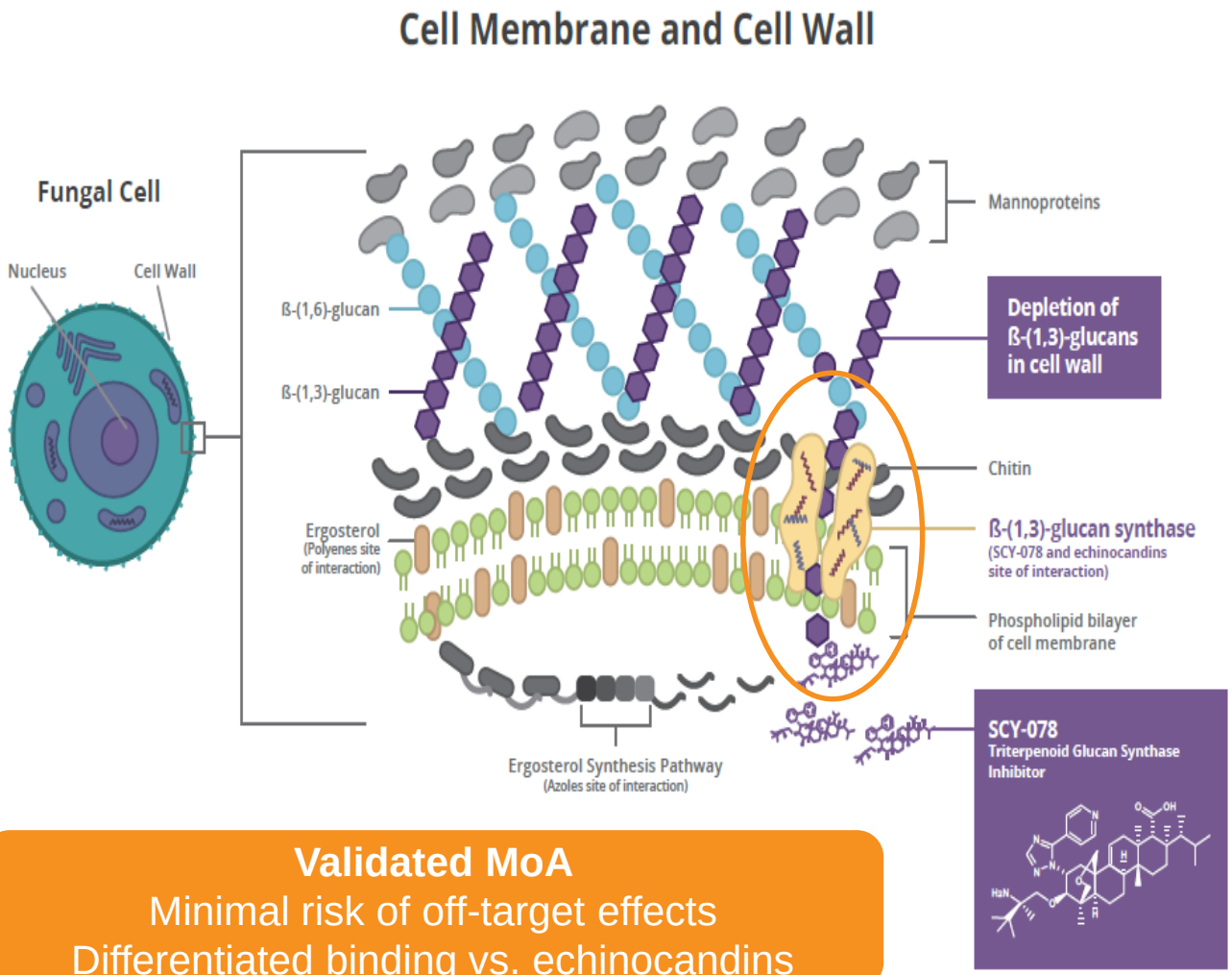
Introduction

- Vulvovaginal candidiasis (VVC) is a common fungal infection caused by *Candida* spp.
  - Fluconazole is the only approved oral treatment option in the U.S.
    - Patients not responding to or not tolerating fluconazole have limited treatment options including often long and inconvenient topical regimens (e.g. boric acid)
    - There are reported associations between increased pregnancy risks and oral fluconazole (both low- and high-dose) :
      - Any maternal exposure to fluconazole during pregnancy may increase risk of spontaneous abortion and doses higher than 150 mg during the first trimester may increase risk of cardiac septal closure anomalies (1)
- Ibrexafungerp (formerly SCY-078) is a first-in-class, IV/oral, broad-spectrum, glucan synthase inhibitor, currently in Phase 3 development for the treatment of acute VVC and prevention of recurrent VVC.
- The purpose of this study was to evaluate the activity of Ibrexafungerp against *Candida* spp., including fluconazole-resistant isolates

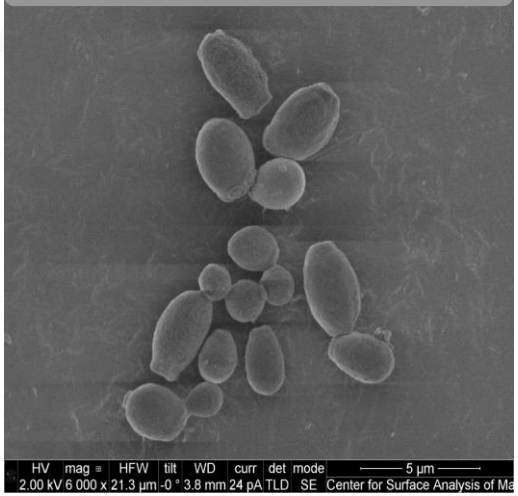
(1) CMAJ 2019 February 19;191:E179-87. doi: 10.1503/cmaj.180963

Ibrexafungerp (SCY-078) MoA: Glucan Synthase Inhibitor

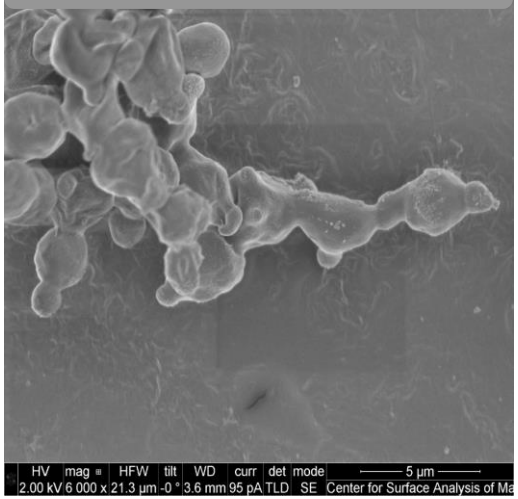


Validated MoA
Minimal risk of off-target effects
Differentiated binding vs. echinocandins

***C. auris* before SCY-078**



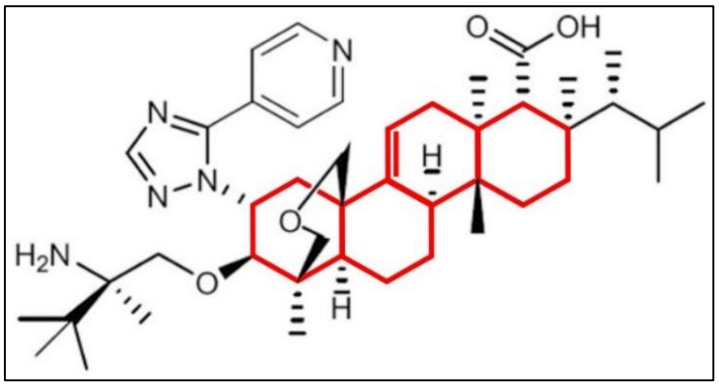
***C. auris* after SCY-078**



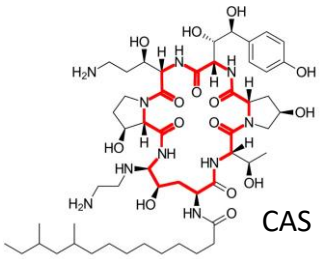
Larkin E., et al. The Emerging Pathogen *Candida auris*: Growth Phenotype, Virulence Factors, Activity of Antifungals, and Effect of SCY-078, a Novel Glucan Synthesis Inhibitor, on Growth Morphology and Biofilm Formation. Antimicrob Agents Chemother. 2017 May; 61(5)

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 *Candida* strains
- Oral and IV formulations
- Favorable safety profile >500 exposed
  - Low risk of drug-drug Interactions
  - No evidence of reproductive or developmental toxicity
- Extensive tissue distribution
  - (V_{dss} > 8 L/kg)
- Active in low pH environments

Methods

- *In vitro* susceptibility (MIC) data for Ibrexafungerp against multiple *Candida* spp. were compiled from 7 independent studies.

- The combined studies consisted of a total of 774 isolates with 242 being fluconazole-resistant (FLU-R) and 532 wild-type (WT) isolates of *C. albicans, C. glabrata, C. tropicalis* and *C. parapsilosis*.

- Isolates with Ibrexafungerp MIC values >2-fold dilutions as compared to WT MIC_{50} values were considered resistant.

- FLU-R was defined for *Candida* spp. per CLSI M27-S4

Results:
Activity of Ibrexafungerp against *Candida albicans*

(N)	IBX MIC_{50} (Range, ug/mL)	IBX MIC (Range)	FLU MIC_{50} (Range)	FLU MIC (Range)
C. albicans				
WT (216)	0.008 – 0.125	0.008 - 2	0.125 – 0.5	0.06 - 2
FLU-R (45)	<0.03 – 0.125	0.008 - 2	64 - >128	4 - >128

Results:
Activity of Ibrexafungerp against *Candida glabrata*

(N)	IBX MIC_{50} (Range, ug/mL)	IBX MIC (Range)	FLU MIC_{50} (Range)	FLU MIC (Range)
C. glabrata				
WT (215)	0.125 – 0.5	0.015 - 4	4 -32	0.06 - 32
FLU-R (185)	0.5	0.06 - 2	64 - >128	64 - >128

Results:
Activity of Ibrexafungerp against *Candida tropicalis*

(N)	IBX MIC_{50} (Range, ug/mL)	IBX MIC (Range)	FLU MIC_{50} (Range)	FLU MIC (Range)
C. tropicalis				
WT (47)	0.25	0.06 - 2	0.25 – 0.5	0.125 - 1
FLU-R (6)	NA	0.125 - 1	NA	16 - 128

Results:
Activity of Ibrexafungerp against *Candida parapsilosis*

(N)	IBX MIC_{50} (Range, ug/mL)	IBX MIC (Range)	FLU MIC_{50} (Range)	FLU MIC (Range)
C. parapsilosis				
WT (54)	0.25 – 0.5	0.125 - 4	0.5 - 1	0.25 - 2
FLU-R (6)	NA	0.25 – 0.5	NA	8 - 64

Ibrexafungerp: Summary and Conclusion

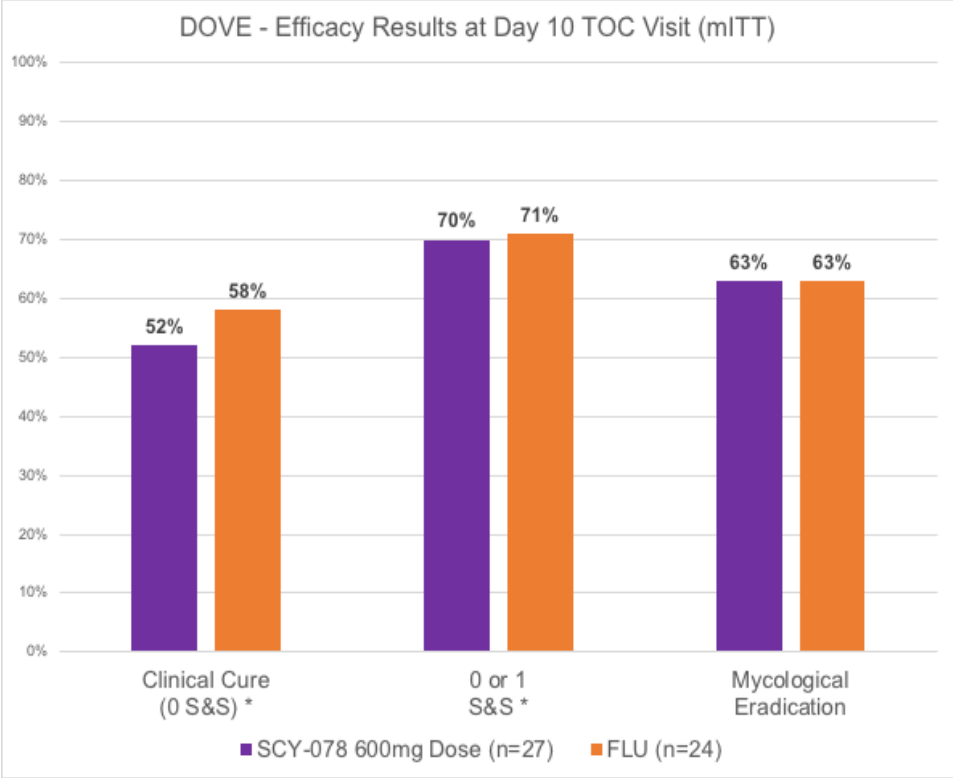
- In this study, IBX displayed similar MIC values against both WT and FLU-R *Candida* spp.
  - IBX was active (MIC within 2 dilutions of WT) against 99% (240/242) of the FLU-R isolates tested in these studies.
- Previously reported:
  - IBX has enhanced anti-*Candida* activity at pH 4.5
  - IBX concentrates in vaginal tissues (based on preclinical data)
- Also being presented at ACOG (e-posters on Saturday, May 4):
  - IBX shows no reproductive or developmental harm
  - Phase 2b VVC study (DOVE) supports the selection of ibrexafungerp 600mg-dose for Phase 3 registration studies in VVC
- **Collectively, the data indicate that IBX is a highly-promising, oral antifungal agent for the treatment of VVC, including infections caused by fluconazole-resistant isolates.**

Key Efficacy Results of P2b DOVE Study

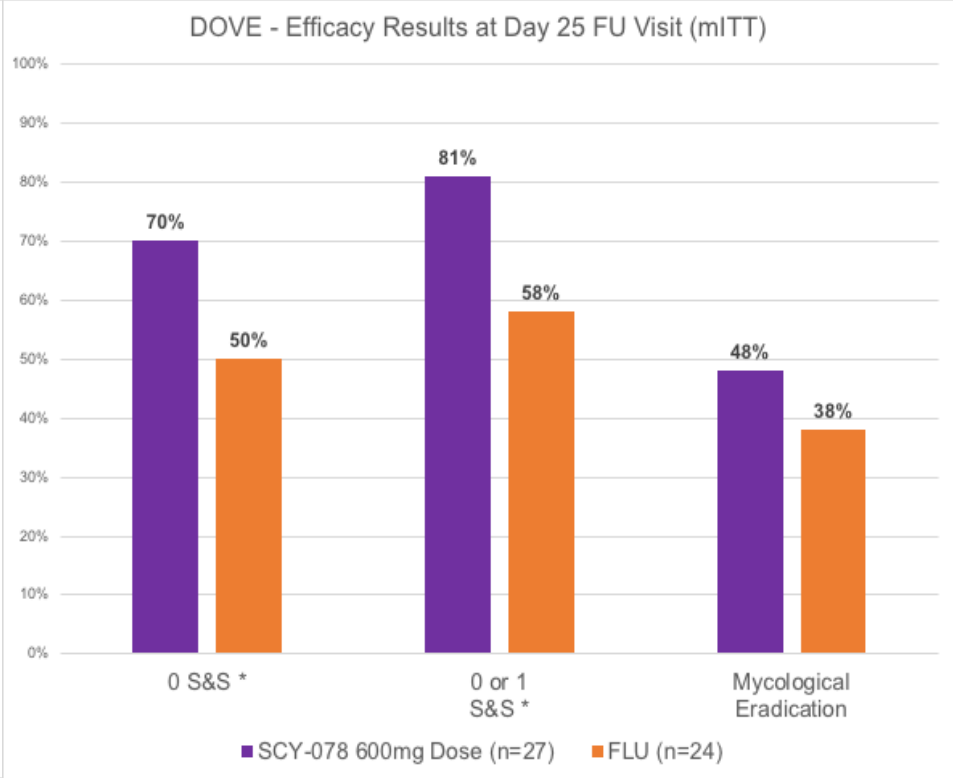
Randomized, multi-center, double-blind, active-controlled, dose-finding study of 5 dose regimens of Ibrexafungerp compared to Fluconazole 150 mg single day dose.

Ibrexafungerp 600 mg daily dose (300 mg BID)

Day 10



Day 25



Ibrexafungerp Phase 3 Studies in VVC

VANISH:

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

- Sites in the US and Europe

CANDLE:

Phase 3 pivotal randomized, double-blind, in patients with recurrent VVC.

- Sites in the US and Europe

SCYNEXIS

Thank you