Development considerations for Coccidioidomycosis

Coccidioidomycosis (Valley Fever): Considerations for Development of Antifungal Drugs

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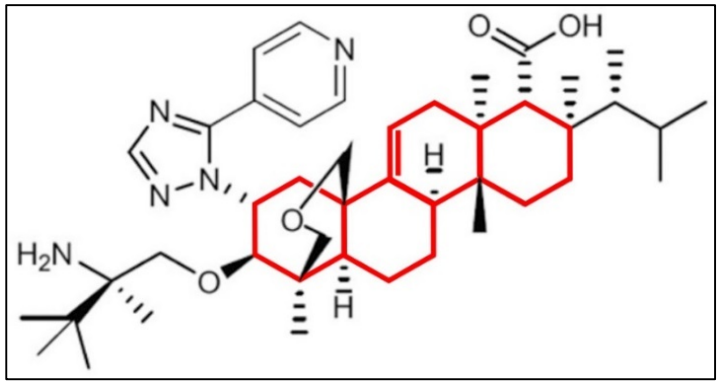
Disclosures: employee and shareholder of SCYNEXIS, Inc

Ibrexafungerp (SCY-078)

Novel Glucan Synthase Inhibitor (GSI)



Structurally distinct from other GSIs (echinocandins)

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

Attributes / Development

- *In vitro* and *in vivo* activity against:
  - *Candida* spp
  - *Aspergillus* spp
  - *Pneumocystis* spp
  - ***Coccidioides* spp**
- Extensive tissue distribution (V_{dss} > 5 L/kg)
- In clinical development for:
  - Invasive candidiasis (P2 study completed)
  - Vulvovaginal candidiasis (P3 studies completed)
  - Recurrent VVC (P3 study ongoing)
  - Invasive aspergillosis (P2 study ongoing)
  - *Candida auris* infection (P3 ongoing)
  - Refractory invasive fungal diseases including coccidioidomycosis (P3 ongoing)

Products with labeled indications for the treatment of Coccidioidomycosis in the US

• Fluconazole	NO
• Itraconazole	NO
• Amphotericin B deoxycholate	YES
• Ambisome	NO
• Posaconazole	NO
• Echinocandins	NO

IDSA 2016 guideline: *No clinical studies exist to guide the optimal dose or duration of fluconazole or other antifungal therapy for persons with primary pulmonary coccidioidomycosis.*[1]

1. Galgiani J, et al. IDSA Guideline - Coccidioidomycosis. Clin Infect Dis 2016

Complexities of coccidioidomycosis trials

- The number of cases are limited

  ~150,000 cases a year but the majority do not receive antifungal treatment

  15,611 cases reported in 2018[1]

  - Efficacy Study of Fluconazole to Treat Coccidioidomycosis Pneumonia (Valley Fever) – NIAID 2015-2018[2]
    - Conducted in 9 sites in Arizona and California
    - Planned for 1000 CAP in endemic regions - Enrolled 72 subjects and “Terminated for lack of feasibility”
    - Potential issues with the feasibility of the design

1. https://www.cdc.gov/fungal/diseases/coccidioidomycosis/statistics.html
2. Clinical trials .gov study ID: NCT02663674

Complexities of coccidioidomycosis trials

- Treatment duration is long
  - Likely requires long-term toxicology studies
  - Multiple efficacy assessment and long treatment duration increases drop-out rates and overall cost of the trial
  - Requires a significant amount of clinical trial supplies

- Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Mycoses Study Group[1]
  - 198 patients with chronic pulmonary, soft tissue, or skeletal coccidioidal infections.
  - Oral fluconazole (FLU), 400 mg/d, or itraconazole (ITRA), 200 mg twice daily.
  - Endpoint: scoring system including symptoms, appearance of lesions and antibody titers
  - Primary timepoint 8 months – data was available for 67/94 of FLU and 78/97 of ITRA subjects

1. Galgiani J, et al. Ann Intern Med, 2000

Market implications

- ~12,000 treated a year
- What would be the percent of market share of a new agent ?
  - Depends on differentiating attributes
  - However, currently available treatment options will likely continue to be used in a significant proportion of patients
- Market access:
  - Would the new agent need to be superior to SOC for favorable market access?
  - Or, would it be used only as second line therapy?

Developing drugs for Coccidioidomycosis, why so few runners in this race?

- Clinical trials are complex – long (to enroll and follow up)
- Cost/time of development via traditional Phase 2, Phase 3 RCT vs. SOC is significant
- Market opportunity is limited and unlikely to grow significantly
- Difficult to predict market access before Phase 3 data
- Return on investment will likely take long time

- Difficult-to-fund development program via traditional investors

What could be done to promote drug development for this unmet need?

- Non-dilutive funding to support Phase 2 / 3
- Activate coccidioidomycosis clinical trial networks
  - Site-by-site approach is costly and takes long time (4-12month) to set up a site
    - contract negotiation
    - research and ethics committee review
- Re-evaluation of endpoints and trial designs
  - Including “salvage therapy”
- Streamlined regulatory paths
- Ensure commercial sustainability of the product once in the market