Development considerations for *Candida auris*

Development Considerations of Antifungal Drugs to Address Unmet Medical Need

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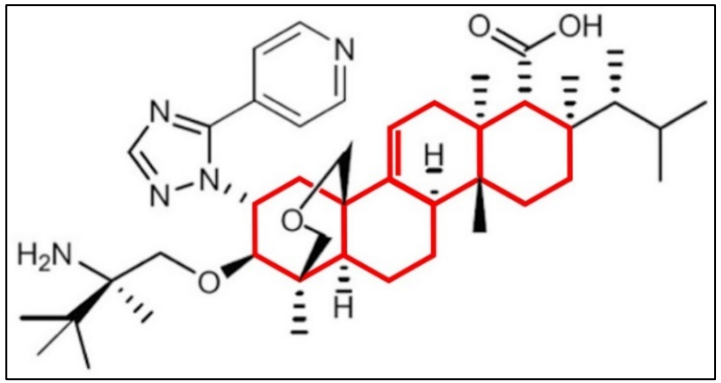
Disclosures: employee and shareholder of SCYNEXIS, Inc

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
    - Including *Candida auris*
  - *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)
  - Refractory invasive fungal diseases (P3 ongoing)
  - *Candida auris* infection (P3 ongoing)

Developing new antifungals for *Candida auris* Regulatory Background

- FDA:
  - Invasive Candidiasis
    - Single pivotal, randomized, controlled trial (RCT), typically noninferiority
  - LPAD Pathway
    - Based on a benefit-risk assessment that more flexibly takes into account the *severity, rarity or prevalence* of the infection and the *lack of alternatives* available.
    - The drug is intended to treat *serious or life-threatening infection* in a *limited* population with *unmet needs*
    - *A streamlined clinical development program* for a limited population may involve smaller, shorter, or fewer clinical trials.
    - *Substantial* evidence of effectiveness must be provided
      - Acceptance of a greater uncertainty based on risk-benefit assessment

Typical antifungal development path for invasive candidiasis

- A Phase 2 dose POC / dose ranging study
- A Phase 3, randomized, controlled, double blind, properly power study to demonstrate non-inferiority to SOC
  - Size of P3 study (NCT03667690) in invasive candidiasis IC : ~220
    - Candidemia incidence in US (cdc.gov): 25,000/year
    - Enrolling ~220 subjects takes ~2 years in 64 centers worldwide
  - Estimated time for Phase 2 and 3 completion is 4-5 years with estimated cost >$60M

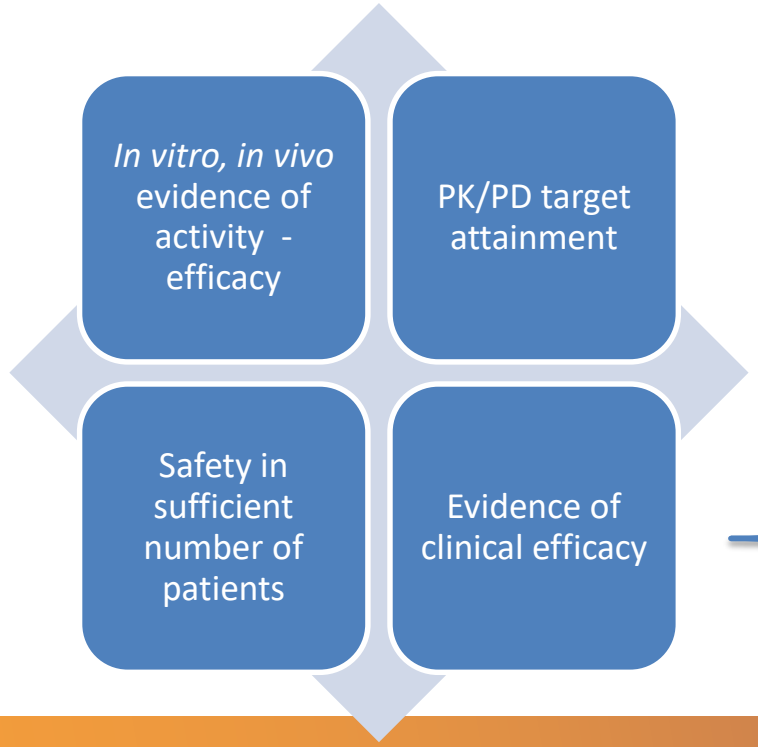
Development of antifungals for *C.auris*

- Enrolling patients with *C.auris* in clinical trials is difficult:
  - Limited number of patients (~500/year in US) and many heavily treated
  - High mortality – difficult to enroll
  - Multiple centers/countries are needed (trials are $$$$ and long)
  - Need to chase the hotspot
- Clinical evidence from a statistically powered RCT in patients with *C.auris* is unlikely to be feasible

- Alternative approaches are needed to generate substantial evidence of effectiveness
  - A well-balanced definition of “substantial”, in-light-of the *unmet medical need* , will facilitate/accelerate availability of new therapies

Potential paths for development of antifungals for *C.auris*

- For uncommon, MDR fungal infections, where clinical data will be limited, other sources should be considered to compile the substantial evidence of effectiveness



- RCT in invasive candidiasis, enriched with *C.auris* population
- RCT in other candida (or other fungal?) diseases
  + PLUS
  – A small study in *C.auris* patients:
    - Non-randomized compared versus external controls (contemporaneous and/or historical)
    - RCT (but not necessarily powered)
- Other alternatives: Multiple studies (smaller) in different fungal diseases

Development Opportunities

- We need to identify **efficient development paths** for new therapeutics for this challenging infection, that are:
  - Well-defined
  - Streamlined
  - Feasible within a reasonable timeframe
  - Endorsed by regulatory authorities, scientific community and executable within the industry framework
  - Supported by funding

- Alternative development approaches seems justified based on:
  - unmet need
  - limited number cases,
  - high mortality,
  - high rate of MDR,
  - transmission potential, potential public health impact,
  - available non-clinical models to supplement clinical data