Development considerations for *Candida auris*

Development Considerations of Antifungal Drugs to Address Unmet Medical Need

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David Angulo, MD
Chief Medical Officer at SCYNEXIS

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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 \((V_{dss} > 5 \text{ L/kg})\)
- 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 powered 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.

  - *In vitro, in vivo* evidence of activity - efficacy
  - PK/PD target attainment
  - Safety in sufficient number of patients
  - Evidence of clinical efficacy

- 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