Developing new antifungals for high unmet medical needs: lessons learned and development considerations

FDA Public Workshop Development Considerations of Antifungal Drugs to Address Unmet Medical Need August 4, 2020

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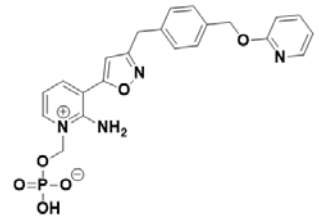
Fosmanogepix novel mechanism of action drug candidate



New MOA : Inhibits inositol acyltransferase Gwt1, pleomorphic effects on fungal cell pathogenicity

- **Broad Spectrum** activity against
  - Yeasts : *Candida, Cryptococcus* - including resistant isolates
  - Molds : *Aspergillus* and the "rare molds" i.e. *Fusarium, Scedosporium, L. prolificans*, Mucorales fungi – including resistant isolates
  - Endemic mycoses : *Blastomyces, Coccidioides, Histoplasma*
- **In Phase 2 studie**s for invasive candidiasis (including *C. auris*), invasive aspergillosis and rare molds in patients with limited treatment options, cryptococcal meningitis, expanded access
- **Wide Tissue Distribution** to deep sites of infection in the lung, kidney, liver and hard-to-access compartments brain and eye
- **IV and Oral Formulations** allows for step-down continuation of care outside of the hospital

Candidemia	**Phase 2:** Topline Data July 2020 [n=20]
Candida auris	**Phase 2:** Enrolling [n=15]
Aspergillus / Rare Molds	**Phase 2:** Enrolling [n=50]
Cryptococcus	**Phase 2:** Clinical Planning
Fusarium	**Expanded Access**

Invasive Fungal Infections are an unmet medical need

High residual mortality despite treatment

- **Invasive fungal infections (IFIs) are associated with high all cause mortality (ACM)**
  - Invasive Candidiasis : Phase 3 trials azoles and candins ACM 10-18% at Day 30
  - Invasive Aspergillosis : Phase 3 trials azoles ACM ~ 20% at 6-wks; ~30% at 12-wks
  - IFI mortality improved with lipid-AmB, second generation mold active azoles and the candins
  - Clinical trial patients are highly selected (e.g. patients who have complicated medical conditions are not eligible for trials) - real world mortality estimated to be higher at 30-95%
- **Limited choice of antifungal drugs** likely to be one of the drivers of high mortality
  - Only three main classes of antifungal drugs – much less than for antibiotics or antivirals
    - Polyenes, azoles and candins
    - Last new class of antifungal drug approved 20 years ago
- **New antifungal drugs are urgently needed** to address the high residual mortality of IFIs

Slide adapted from the Antimicrobial Working Group (AWG) FDA meeting June 2018

Fungal infections recognized as threat to human health in CDC's 2019 Multidrug-Resistance Threat Report

Watch List

AZOLE-RESISTANT
ASPERGILLUS FUMIGATUS

- Increasing percentage of resistance to azole antifungal class- the only class with oral availability
- Emerging as the leading co-infection in patients hospitalized with severe COVID-19 infections

Serious Threat

- Dozens of *Candida* species cause infection, including severe invasive infections
- Increasing percentage of strains are resistant to all antifungal therapies

Urgent Threat

- Multi-drug resistant, difficult to diagnose and hard to eradicate
- Up to 60% mortality
- Cases reported in >40 countries

SARS-CoV-2 pandemic highlights need for new antifungal drugs

Hospitalized patients with severe COVID-19 are at significant risk of invasive fungal infections

30%

Up to 30% of severe COVID-19 patients have also contracted **life-threatening invasive *Aspergillosis* fungal infections**

- Immunosuppressant use for COVID-19 patients may further increase the risk of aspergillosis
- Recent reports of *C. auris* outbreaks in California
- Invasive aspergillosis also occurs in 20% of severe influenza patients with **40-60% mortality**

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COVID-19 Patients Need to Be Tested for Bacteria and Fungi, Not Just the Coronavirus

Many hospitalized victims are developing potentially lethal secondary coinfections such as bacterial pneumonia and sepsis

By Oliver Schacht on April 16, 2020

Los Angeles Times

CALIFORNIA

As COVID-19 spreads, potentially deadly fungus infects L.A. County healthcare facility

By RONG-GONG LIN II | STAFF WRITER

JULY 20, 2020 | 7:57 AM

FIRST OPINION STAT

Antibiotic resistance: the hidden threat lurking behind Covid-19

By JULIE L. GERBERDING / MARCH 23, 2020

ENDPOINTS in FOCUS

'If grippe condemns, the secondary infections execute': What the coronavirus pandemic means for the field of antibiotics

Natalie Grover
Reporter

New antifungal drugs are urgently needed

New antifungal drugs may address the high residual mortality associated with IFIs

- **New antifungal drugs with better drug characteristics**
  - Antimicrobial resistance (AMR) has emerged in *Candida* (including MDR strains e.g. *C. auris*) and *Aspergillus* spp., as well as innate resistant that exists in *Scedosporium* spp., *Lomentospora prolificans*, *Fusarium* spp., and Mucorales fungi
  - **AMR is not the only problem – the following "drug deficiencies" are just as important** existing antifungal drugs can be difficulty to dose adequately due to toxicities, drug interactions (especially with the new cancer agents), poor oral adsorption and/or lack of exposure in some tissue compartments (e.g. brain)
- **Early diagnostic tests**
  - Treatment with appropriate/optimal antifungal therapy may be delayed and/or broad spectrum agents are used before fully establishing the causative fungi

Modern medicine is able to successfully treat diseases (e.g. cancers and transplants) that only a few years ago were universally fatal. However, these life saving treatments makes the patient high risk and vulnerable to invasive fungal infections. Currently, such patients are poorly served as they have limited antifungal drug treatment options. Consequently, there remains a high need for new and novel mechanism of action antifungal drugs that are able to successfully treat life threatening fungal infections.

Why New Antifungals Are Desperately Needed
https://www.labiotech.eu/medical/new-antifungals-development/

Development of antifungal drugs have unique challenges

- Antifungal clinical trials have always been **difficult to recruit patients** due to the relatively small number patients with the specific invasive fungal infection (orphan population)
- Clinical trials in orphan populations require a global search for eligible patients, with a high number of sites (many will enroll zero patients) to offset low enrollment rates
- Clinical trials in IFIs are logistically complex, take a long time to conduct and are require much resources (people and money) – enrollment costs are very high @ $100-200,000/patient
- Phase 3 RCTs in invasive candidiasis and invasive aspergillosis have historically required ~300-600 patients – however, the **recruitment rate per site are very low**
  - Invasive Candidiasis 1.9 patients/site/year
  - Invasive Aspergillosis 1.5 patients/site/year
- More recently, clinical trials are being conducted in patients with limited or no treatment options – which increases the scarcity of patients who are eligible for the trials
- These logistical challenges discourage sponsors and investors to develop antifungal drugs

Limited or no treatment options due to resistance, contraindication, intolerance or lack of clinical response to standard of care antifungal therapy

Invasive Candidiasis – RCT trial logistics (chronological order)

Site enrolls on average 1.9 (range 0.6 – 3.5) patients per year

Study	Enrolled	Duration (month)	Enr/Mo	Sites	#/site/mo	Year(s)	Regions	Paper
ISAVU vs CASPO	450	88	5	113	0.05 [a]	Dec 2006 – Mar 2015	Americas, CEE, ME, Asia, Africa	Kullberg
MICA vs CASPO	595	19	31	167	0.19	Sept 2004 – Apr 2006	North America, EU, Brazil, India	Pappas
ANID vs FLUCO	261	19	14	47 [b]	0.29	Mar 2003 – Oct 2004	North America, EU	Reboli
MICA vs AmB	531	21	25	115	0.22	Jan 2003 – Nov 2004	Americas, CEE, ME, Asia, Africa, Australia	Kuse
VORI vs AmB/FLUCO	422	52	8	101	0.08	Sept 1998 – Jan 2003	Americas, CEE, ME, Asia	Kullberg
CASPO vs AmB	239	44	5	56	0.10	Nov 1997 – Jun 2001	Americas, CEE, ME, Asia, Australia	Mora-Duarte
FLUCO vs AmB/FLUCO	236	45	5	27	0.19	Jul 1995 – Apr 1999	US	Rex

[a] Study design hampered recruitment: Required ≥ 10 days of initial treatment with IV drug. Also, use of another azole not as attractive in the presence of the echinocandins.
[b] 1 center enrolled 25 pts (~10%) of total n

Invasive Aspergillosis – RCT trial logistics (chronological order)

Site enrolls on average 1.5 (range 1.2 – 1.9) patients per year

Study	Enrolled	Duration (month)	Enr/Mo	Sites	#/site/mo	Year(s)	Regions	Paper
ANID + VORI vs VORI	459	30	15.3	93	0.16	Jul 2008 – Jan 2011	Americas, CEE, Asia	Marr
ISAV vs VORI	527	47 [a]	11.2	107	0.10	Mar 2007 – Mar 2013	Americas, CEE, ME, Asia, NZ, AUS	Maertens
VORI vs AmB	391	39	10.0	95	0.11	Jul 1997 – Oct 2000	Americas, EU, ISR, India, AUS	Herbrecht

[a] Enrollment was suspended from Jan 2009 to Mar 2011 (25 months) to allow for completion of nonclinical toxicity studies and licensing activities
[b] Possible or probable IFI

IFI unmet medical need – summary

IFI drug development would benefit from a new paradigm for demonstrating "substantial evidence" similar to other orphan drugs to treat life threatening rare diseases

- IDSA, pharmaceutical companies, governments and regulatory agencies have acknowledged the need for new antimicrobial drugs to combat antimicrobial resistance
- Clinical trials in IFIs have historically been difficult to conduct – over the last few years it has become harder to enroll patients who are eligible/suitable for clinical trials; we anticipate this trend to continue
- Drugs to treat life-threatening rare diseases have been approved based on small data sets that support the ***substantial evidence of effectiveness*** required for approval of all drugs
- FDA has issued the LPAD pathway guidance document, for drugs intended to ***treat a serious or life-threatening infection in a limited population of patients with unmet needs*** and ***permits the risk-benefit assessment to flexibly consider severity, rarity, and prevalence of infection the drug is intended to treat,*** however ***LPAD pathway does not alter FDA approval standards***
- Two drugs (Arikayce and Pretomanid) have been approved through the LPAD pathway, it is unclear how far this flexibility might extend in the approval of new antifungal drugs that address high unmet medical need for a rare life threatening invasive fungal infections