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

Michael R. Hodges, MD
Chief Medical Officer Amplyx Pharmaceuticals Inc.
Disclosures: employee and Amplyx shareholder
**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, Coccioidioides, Histoplasma*
- **In Phase 2 studies** 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*

- Phase 2: Enrolling [n=50]

*Rare Molds*

*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**

**DRUG-RESISTANT CANDIDA SPECIES**

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

**Urgent Threat**

**DRUG-RESISTANT CANDIDA AURIS**

- 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

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 Schmitt on April 16, 2020

**Los Angeles Times**

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

**STAT**

Antibiotic resistance: the hidden threat lurking behind Covid-19

By Julie L. Gerberding / March 23, 2020

**ENDPOINTS in FOCUS**

‘If gripe condemns, the secondary infections execute’: What the coronavirus pandemic means for the field of antibiotics

By 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.
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Enrolled</th>
<th>Duration (month)</th>
<th>Enr/Mo</th>
<th>Sites</th>
<th>#/site/mo</th>
<th>Year(s)</th>
<th>Regions</th>
<th>Paper</th>
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<td>ISAVU vs CASPO</td>
<td>450</td>
<td>88</td>
<td>5</td>
<td>113</td>
<td>0.05 a</td>
<td>Dec 2006 – Mar 2015</td>
<td>Americas, CEE, ME, Asia, Africa</td>
<td>Kullberg</td>
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<td>19</td>
<td>31</td>
<td>167</td>
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<td>ANID vs FLUCO</td>
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<td>19</td>
<td>14</td>
<td>47 b</td>
<td>0.29</td>
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<td>MICA vs AmB</td>
<td>531</td>
<td>21</td>
<td>25</td>
<td>115</td>
<td>0.22</td>
<td>Jan 2003 – Nov 2004</td>
<td>Americas, CEE, ME, Asia, Africa, Australia</td>
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<td>VORI vs AmB/FLUCO</td>
<td>422</td>
<td>52</td>
<td>8</td>
<td>101</td>
<td>0.08</td>
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<td>Americas, CEE, ME, Asia</td>
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<td>239</td>
<td>44</td>
<td>5</td>
<td>56</td>
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<td>Nov 1997 – Jun 2001</td>
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<td>FLUCO vs AmB/FLUCO</td>
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<td>45</td>
<td>5</td>
<td>27</td>
<td>0.19</td>
<td>Jul 1995 – Apr 1999</td>
<td>US</td>
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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*

<table>
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<tr>
<th>Study</th>
<th>Enrolled</th>
<th>Duration (month)</th>
<th>Enr/Mo</th>
<th>Sites</th>
<th>#/site/mo</th>
<th>Year(s)</th>
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<th>Paper</th>
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<td>459</td>
<td>30</td>
<td>15.3</td>
<td>93</td>
<td>0.16</td>
<td>Jul 2008 – Jan 2011</td>
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<td>ISAV vs VORI</td>
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<td>11.2</td>
<td>107</td>
<td>0.10</td>
<td>Mar 2007 – Mar 2013</td>
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<tr>
<td>VORI vs AmB</td>
<td>391</td>
<td>39</td>
<td>10.0</td>
<td>95</td>
<td>0.11</td>
<td>Jul 1997 – Oct 2000</td>
<td>Americas, EU, ISR, India, AUS</td>
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*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.