The Antifungal Pipeline

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Disclosures

- Received grants, speaker’s fee, ad board honoraria and/or travel support from
  - Gilead Sciences
  - Pfizer Inc.
  - MSD
  - Basilea Pharmaceuticals
  - Astellas
  - Bio-Rad laboratories
  - F2G
  - Scynexis
  - Amplyx
  - Cidara
  - Vical
The current antifungal armamentarium: cellular and biochemical targets

**Ergosterol Synthesis**
- Triazoles (C14-demethylase)
  - Fluconazole
  - Itraconazole
  - Voriconazole
  - Posaconazole
  - Isavuconazole
- Allylamines (squalene epoxidase)
  - Naftifine
  - Terbinafine

**Cell Membrane**
- Polynenes (ergosterol)
  - Amphotericin B
  - Deoxycholate
  - Liposomal
  - Lipid complex

**Cell Wall Synthesis**
- Echinocandins ((1-->3)-β-D-glucan synthase)
  - Caspofungin
  - Micafungin
  - Anidulafungin

**Nucleic Acid Synthesis**
- Fluoropyrimidine (thymidylate synthase)
  - 5-fluorouracil
Isavuconazonium sulfate

- **SECURE-study**
  - Invasive aspergillosis and other filamentous moulds

- **VITAL-study**
  - Mucormycosis, rare fungal infections and renally impaired patients

- **ACTIVE-study**
  - Candidemia and other invasive *Candida* infections

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole</th>
<th>Isavuconazole*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active against Mucorales</td>
<td>No</td>
<td>Active against some</td>
</tr>
<tr>
<td>Food effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>β-cyclodextrin</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Administration</td>
<td>Twice/d following loading dose</td>
<td>Once/d following loading dose</td>
</tr>
<tr>
<td>Predictable PK in adults</td>
<td>No</td>
<td>Yes (up to 600 mg)</td>
</tr>
<tr>
<td>Need for TDM</td>
<td>Yes</td>
<td>Not routinely</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Safety (visual)</td>
<td>++</td>
<td>+ (no visual)</td>
</tr>
<tr>
<td>Clinical experience</td>
<td>Extensive</td>
<td>Limited</td>
</tr>
</tbody>
</table>

### Isavuconazole versus voriconazole (SECURE) study: Primary endpoint (ITT population)

#### All-cause mortality (ACM) through Day 42

<table>
<thead>
<tr>
<th></th>
<th>Isavuconazole (N = 258)</th>
<th>Voriconazole (N = 258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality, n (%)</td>
<td>48 (18.6)</td>
<td>52 (20.2)</td>
</tr>
<tr>
<td>Adjusted treatment difference, % (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-1.0 (-7.8, 5.7)</td>
<td></td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>45 (17.4)</td>
<td>50 (19.4)</td>
</tr>
<tr>
<td>Unknown survival status, n (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (1.2)</td>
<td>2 (0.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isavuconazole–voriconazole calculated by a stratified Cochran–Mantel–Haenszel method (strata: Geographic region, Allogeneic BMT/HSCT, and uncontrolled malignancy status)

<sup>b</sup>Patients with unknown survival status were counted as deaths

Isavuconazole versus voriconazole (SECURE) study: Cumulative incidence of TEAEs over time

TEAEs leading to study drug discontinuation: 14.4% (ISA) vs. 22.8% (VOR); p<0.05

Ullmann A. et al. *ECCMID 2015, Copenhagen Denmark, April 25-25, 2015, EPO18*

### Isavuconazole versus voriconazole (SECURE) study: Most frequent Adverse Events (>10%) by SOC

<table>
<thead>
<tr>
<th>System Organ Class (%)</th>
<th>Isavuconazole (N=257)</th>
<th>Voriconazole (N=259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any AE</td>
<td>96.1</td>
<td>98.5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>33.5#</td>
<td>42.5</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>15.2#</td>
<td>26.6</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>8.9#</td>
<td>16.2</td>
</tr>
</tbody>
</table>

*p<0.05

- Other adverse events were not significantly different between isavuconazole and voriconazole

Isavuconazole versus voriconazole (SECURE) study: Cumulative incidence of study drug-related hepatobiliary TEAEs

Ullmann A. et al. ECCMID 2015, Copenhagen Denmark, April 25-25, 2015, EPO18
Isavuconazole versus voriconazole (SECURE) study: Cumulative incidence of study drug-related hepatobiliary TEAEs and lab values

Ullmann A. et al. ECCMID 2015, Copenhagen Denmark, April 25-25, 2015, EPO18
Isavuconazole: exposure-response
Lack of any statistically significant relationship

Outcome
- ACM 42
- OR @ EOT
- MIC pathogen

Drug exposure
- AUCss
- Css
- AUC/MIC

ACM: all cause mortality
OR: overall response
EOT: end of treatment
MIC: minimal inhibitory concentration
AUCss: are under the concentration-time curve at steady state
Css: mean through concentration at steady state

Isavuconazole: exposure-hepatic safety
Lack of any statistically significant relationship

Isavuconazole shortens the QTc interval

A. QTc changes in 26 patients before (pre-Isa) and under treatment with isavuconazole (Isa): mean decrease of 36.5 ± 38.8 msec. (range 7-202 msec.)

B. QTc intervals in a patient with long-term isavuconazole treatment

C. Contra-indicated in patients with familial short QT syndrome

A need for novel antifungal agents (modes of action)

- Gaps in the spectrum of available antifungals
- Emergence of (multi-drug) resistance
- Hazardous drug-drug interactions
- Lack of oral formulations for prolonged (out-patient) therapy
- Acute drug-related toxicities (resulting in early discontinuation) and toxicities associated with prolonged use
- Need for therapeutic drug monitoring due to nonlinear and saturable pharmacokinetics
- Food effects
- Patient compliance

→ Pressing need for new drugs that inhibit novel fungus-specific targets
The antifungal pipeline

Perfect JR. Nat Rev Drug Discov 2017; 16: 603-616
Improving existing antifungals

First generation
- Nystatin
- Amphotericin B
- Flucytosine
- Miconazole (intravenous)
- Ketoconazole (oral)
- Anidulafungin
- Micafungin
- Caspofungin

Second and third generation
- Lipid formulations (reduced toxicity)
- Structural changes to improve activity, safety, pharmacokinetics, etc.

Future generations
- Oral formulations
- Nanoparticles
- Polysaccharide conjugation
- VT-1161 etc. (reduced toxicity, increased half-life)
- SCY078 (oral)
- CD101 (increased stability)

Nature Reviews | Drug Discovery

Perfect JR. Nat Rev Drug Discov 2017; 16: 603-616
Rezafungin (CD101): a more stable echinocandin
(Cidara Therapeutics, San Diego, CA, USA)

- Prolongs half-life (~133 h)
- Allows high exposures
- Eliminates toxic degradation products
- Enables multiple formulations

Structural modification yields improved chemical & biological properties

- Once weekly dosing
- Improved efficacy (less susceptible pathogens)
- Improved safety
- Intravenous and subcutaneous; no oral
Rezafungin: activity against *Candida* and *Aspergillus*

Reza, anidulafungin and caspofungin tested against international clinical surveillance isolates

<table>
<thead>
<tr>
<th></th>
<th>Candida MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Aspergillus MEC&lt;sub&gt;90&lt;/sub&gt; (mg/L)&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida</em> spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>albicans (n=655)</td>
<td>0.06</td>
<td>0.015</td>
</tr>
<tr>
<td>glabrata (n=321)</td>
<td>0.125</td>
<td>0.015</td>
</tr>
<tr>
<td>tropicalis (n=206)</td>
<td>0.06</td>
<td>≤0.008</td>
</tr>
<tr>
<td>krusei (n=130)</td>
<td>0.03</td>
<td>≤0.008</td>
</tr>
<tr>
<td>parapsilosis (n=275)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><em>Aspergillus</em> spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fumigatus (n=20)</td>
<td>0.03</td>
<td>0.015</td>
</tr>
<tr>
<td>terreus (n=19)</td>
<td>0.06</td>
<td>≤0.008</td>
</tr>
<tr>
<td>niger (n=16)</td>
<td>0.5</td>
<td>≤0.008</td>
</tr>
<tr>
<td>flavus (n=12)</td>
<td>0.25</td>
<td>0.06</td>
</tr>
</tbody>
</table>

- CLSI broth microdilution methodology was employed for MIC/MEC determination (M27-A3, M38-A2)


<sup>2</sup>*Aspergillus* spp. isolates were collected internationally between 2007 and 2011 and were tested as part of a retrospective study (Pfaller, et al, 2016, JAC)

- The activity of CD101 is comparable to that of other members of the echinocandin class
- Similar results for CD101 activity versus Candida and Aspergillus spp. may be obtained with either CLSI or EUCAST BMD methods.

Rezafungin: superior penetration and accumulation at the site of infection versus micafungin (5mg/kg)

Intra-abdominal invasive candidiasis abscess model

Drug distribution in liver after single dose CD101 at 20 mg/kg determined by MALDI MS Imaging

Zhao et al. Antimicrobial Agents Chemother 2017; 61: e01009-17
Rezafungin PK/PD: Exposure is Key to Improved Efficacy

Caspofungin (14 daily doses)

Rezafungin (4 weekly doses)

**Target**

- Caspofungin: 70mg and 50mg doses
- Rezafungin: 400mg, 400mg, 200mg, 200mg, and 200mg doses

**Free-drug Plasma AUC_{0-24}/MIC Ratio**

**Days of Therapy**

- Caspofungin: 14 days
- Rezafungin: 4 weeks

**MIC**

- Caspofungin: MIC=0.25 for caspofungin
- Rezafungin: MIC=0.12 for CD101

**Bader et al.**

- Emerging Candida glabrata Resistance and Echinocandin Dosing: A Call to Arms! IDWeek 2016
- Overcoming the Resistance Hurdle: PK-PD Target Attainment Analyses of Rezafungin (CD101) for Candida albicans and Candida glabrata. Submitted AAC 2018

**MIC=0.25 for caspofungin. MIC=0.12 for CD101**
STRIVE Part A: Candidemia & Invasive Candidiasis

Rezafungin

400/400/(400)mg n=30
400/200/(200)mg n=30

Week 1
Day 1 5 8 15 22 28 35 42 45 49 56 59

Mycological response
Optional dose
Mycological & clinical response: 1° ENDPOINT
Mycological & clinical response (IC only)
All cause mortality

Caspofungin

70/50/(50)mg n=30

Week 1
Day 1 5 8 15 22 28 35 42 45 49 56 59

70mg Dose 50mg Dose

Analysis Populations:
- The Intent-to-treat (ITT) population: all randomized subjects
- The Safety population: all subjects who received any amount of study drug
- The Microbiological Intent-to-treat population (mITT): all subjects in safety population who had documented Candida infection
# STRIVE Overall Response (Primary Outcome)

**Day 14 – mITT Population**

<table>
<thead>
<tr>
<th>Response</th>
<th>Rezafungin 400 mg/400 mg (QWk) N= 33</th>
<th>Rezafungin 400 mg/200 mg (QWk) N= 31</th>
<th>Caspofungin 70 mg/50 mg (QD) N= 28</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Success</td>
<td>19 (57.6)</td>
<td>22 (71.0)</td>
<td>18 (64.3)</td>
</tr>
<tr>
<td>Failure</td>
<td>7 (21.2)</td>
<td>6 (19.4)</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>7 (21.2)</td>
<td>3 (9.7)</td>
<td>2 (7.1)</td>
</tr>
</tbody>
</table>

Excluding Indeterminate Response*

<table>
<thead>
<tr>
<th>Response</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19/26 (73.1)</td>
<td>22/28 (78.6)</td>
<td>18/26 (69.2)</td>
</tr>
<tr>
<td>Success</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>7/26 (26.9)</td>
<td>6/28 (21.4)</td>
<td>8/26 (30.8)</td>
</tr>
</tbody>
</table>

*Indeterminate response indicates inability to assess outcome due to missing data point(s)
Rezafungin shows equivalent efficacy to TMP/SMX in PCP prophylaxis mouse model

Prophylaxis with rezafungin, which blocked cyst/asci formation, offers a new means to prevent PCP

STUDY DESIGN

10 mice per arm
Infected with *P. murina* by intranasal inoculation
Immunosuppression with dexamethasone throughout study
CD101 was administered at the same time the mice were infected
Quantification of PCP from lung
Rezafungin: Potential for Simplified Single Drug Paradigm

Day  -10  0  10  20  30  40  50  60  70  80
SOC for *Candida* and *Aspergillus*

SOC for *Pneumocystis* (PCP)

Risk of IFI

High
Low

Pre-engraftment
Post-engraftment

Transplant  Engraftment

Rezafungin
SCY-078: (triterpene) β-(1,3) glucan synthase inhibitor
(Scynexis [spin-off of Sanofi], Jersey City, NJ, USA)

- Activity against:
  - Cidal against Candida spp (also R and C. auris)
  - High activity against Candida biofilms
  - Aspergillus spp (also azole-R)
  - Pneumocystis spp
  - Paecilomyces variotii
  - No activity Mucorales/Fusarium

- Oral and IV formulations

- Favorable safety profile

- Low risk of drug-drug Interactions (not a CYP substrate nor inhibitor)

- High tissue penetration (Vdss > 8 L/kg) but no CNS penetration

- No QTc effect expected

- IC50 against purified glucan synthase from C. albicans is 0.6 ng/mL

- Different enzyme-drug interaction → lower impact of common fks mutations

- Oral bioavailability

- Structurally distinct from other GSIs (echinocandins)
SCY-078 in combination with azole for invasive pulmonary aspergillosis - Rabbit model

- Neutropenic rabbit model of pulmonary aspergillosis
- Treatment for 12 days
- N=6 / group (QD doses):
  - SCY-078 (IV) at 2.5 or 7.5mg/kg
  - Isavuconazole (PO) 40mg/kg
  - SCY-078 2.5 + Isavuconazole
  - SCY-078 7.5 + Isavuconazole

- p<0.05, prolonged survival in SCY2.5+ISA40 and SCY7.5+ISA40 -treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and ISA40

Angulo D. at TIMM 2017
SCY-078 - Phase 2 in Invasive Candidiasis (Step Down) - Completed

Design:

Echinocandin IV

Oral SCY-078 – 1000mg (D1), 500mg QD

Oral SCY-078 – 1250mg (D1), 750mg QD

Standard of Care
Fluconazole 800 LD-400mg/d po or Micafungin 100mg IV/d
14 to 28 days (at least 14 days after first negative culture)

Results:

Pop PK = SCY-078 PO, 750mg QD achieves target exposure (AUC$_{0-24hr}$ of 15 µM·hr)
AEs frequency and severity - comparable for all groups

Global Response at EOT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Favorable</th>
<th>Reasons for Unfavorable</th>
</tr>
</thead>
</table>
| SCY-078 500 mg     | 5 (71.4)  | 1. Never received study drug  
                     |            | 2. Discontinued due to a non-drug related AE |
| N = 7 n (%)        |           |                         |
| SCY-078 750 mg     | 6 (85.7)  | 1. Withdraw consent after one dose |
| N = 7 n (%)        |           |                         |
| Fluconazole 400 mg | 5 (71.4)  | 1. Died (abdominal sepsis)  
| N =7 n (%)         |            | 2. Discontinued (new + blood culture for Candida spp;) |
SCY-078 Phase 2 Study in Moderate and Severe Vulvovaginal Candidiasis (VVC): proof-of-concept

70 subjects had cultured-confirmed VVC (per protocol population)

Efficacy Evaluation at Day 24 (per protocol population)

<table>
<thead>
<tr>
<th></th>
<th>SCY-078 1250mg (D1), 750mg (D2-3) (n= 24)</th>
<th>SCY-078 1250mg (D1), 750mg (D2-5) (n= 26)</th>
<th>SCY-078 (Combined) (n= 50)</th>
<th>Fluconazole 150mg (D1) (n= 20)</th>
<th>% Δ SCY-078 (combined) vs. Fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Cure</strong></td>
<td>19 79.2%</td>
<td>19 73.1%</td>
<td>38 76%</td>
<td>13 65%</td>
<td>+11%</td>
</tr>
<tr>
<td><strong>Recurrences Requiring Antifungal Therapy</strong></td>
<td>1 4.2%</td>
<td>1 3.8%</td>
<td>2 4%</td>
<td>3 15%</td>
<td>-11%</td>
</tr>
</tbody>
</table>

- The rate of mycological eradication at Day 24 and Month 4 was 70% and 74% for the SCY-078 combined arms vs. 65% and 60% for the fluconazole arm

- There were no severe or serious adverse events in any treatment groups. A higher rate of GI adverse events (e.g., nausea, diarrhea) were reported in the SCY-078 treatment arms, which were mild to moderate in severity and transient in nature
SCY-078: ongoing clinical trials

• **FURI:** Phase 3, open-label study in patients that are refractory to or intolerant of approved antifungal agents
  • Intended population includes:
    • Invasive candidiasis, including *C. auris*
    • Chronic disseminated candidiasis
    • Severe mucocutaneous candidiasis
  • Sites opened in the US and in EU

• **DOVE:** Phase 2, randomized, double blind, dose-finding study in patients with acute VVC
  • Exploring 5 dose regimens of oral SCY-078 vs. Fluconazole
  • Sites opened in the US
Orotomides: inhibitors of pyrimidine biosynthesis
(F901318, F2G Ltd, Manchester, UK)

[Diagram of pyrimidine biosynthesis]

- Orotomides inhibit dihydroorotate dehydrogenase (DHODH)

Oliver JD et al. PNAS 2016; 113: 12809-12814
**F901318: In vitro active against all major Aspergillus spp., including *A. terreus***

<table>
<thead>
<tr>
<th>Aspergillus spp.</th>
<th>GeoMean (mg/L)</th>
<th>F901318</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. fumigatus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=44)</td>
<td>GeoMean</td>
<td>0.037</td>
<td>0.700</td>
<td>0.590</td>
</tr>
<tr>
<td></td>
<td>MIC50</td>
<td>0.040</td>
<td>0.630</td>
<td>0.630</td>
</tr>
<tr>
<td></td>
<td>MIC90</td>
<td>0.040</td>
<td>5.0</td>
<td>1.250</td>
</tr>
<tr>
<td><strong>A. terreus</strong></td>
<td>GeoMean</td>
<td>0.013</td>
<td>0.112</td>
<td>0.290</td>
</tr>
<tr>
<td>(n=17)</td>
<td>MIC50</td>
<td>0.020</td>
<td>0.630</td>
<td>0.310</td>
</tr>
<tr>
<td></td>
<td>MIC90</td>
<td>0.040</td>
<td>0.630</td>
<td>0.630</td>
</tr>
<tr>
<td><strong>A. niger</strong></td>
<td>GeoMean</td>
<td>0.048</td>
<td>0.274</td>
<td>0.368</td>
</tr>
<tr>
<td>(n=15)</td>
<td>MIC50</td>
<td>0.04</td>
<td>0.31</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>MIC90</td>
<td>0.08</td>
<td>1.25</td>
<td>1.25</td>
</tr>
<tr>
<td><strong>A. flavus</strong></td>
<td>GeoMean</td>
<td>0.031</td>
<td>0.466</td>
<td>0.582</td>
</tr>
<tr>
<td>(n=17)</td>
<td>MIC50</td>
<td>0.04</td>
<td>0.63</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>MIC90</td>
<td>0.04</td>
<td>1.25</td>
<td>0.63</td>
</tr>
</tbody>
</table>

MIC50 (MIC90) = MIC (mg/L inhibiting 50% (90%) of strains. **VORI** = voriconazole, **POSA** = posaconazole
F901318: In vitro active against azole-resistant *A. fumigatus* with defined cyp51A mutations

<table>
<thead>
<tr>
<th>Isolate</th>
<th>cyp51A amino acid substitutions</th>
<th>Itraconazole</th>
<th>Posaconazole</th>
<th>Voriconazole</th>
<th>F901318</th>
</tr>
</thead>
<tbody>
<tr>
<td>F6919</td>
<td>M220K</td>
<td>&gt;8</td>
<td>&gt;8</td>
<td>1</td>
<td>0.08</td>
</tr>
<tr>
<td>F7075</td>
<td>G54E</td>
<td>&gt;8</td>
<td>&gt;8</td>
<td>0.5</td>
<td>0.08</td>
</tr>
<tr>
<td>F11628</td>
<td>G138C</td>
<td>&gt;8</td>
<td>2</td>
<td>8</td>
<td>0.04</td>
</tr>
<tr>
<td>F12219</td>
<td>G54R</td>
<td>&gt;8</td>
<td>2</td>
<td>0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>F12636</td>
<td>G54E</td>
<td>&gt;8</td>
<td>2</td>
<td>0.25</td>
<td>0.04</td>
</tr>
<tr>
<td>F12776</td>
<td>Y431C</td>
<td>&gt;8</td>
<td>2</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>F13619</td>
<td>H147Y G448S</td>
<td>8</td>
<td>1</td>
<td>&gt;8</td>
<td>0.04</td>
</tr>
<tr>
<td>F13747</td>
<td>G434C</td>
<td>&gt;8</td>
<td>1</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>F14403</td>
<td>G54R</td>
<td>&gt;8</td>
<td>2</td>
<td>0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>F16134</td>
<td>M220K</td>
<td>&gt;8</td>
<td>&gt;8</td>
<td>2</td>
<td>0.04</td>
</tr>
<tr>
<td>F16157</td>
<td>G54V</td>
<td>&gt;8</td>
<td>2</td>
<td>0.5</td>
<td>0.04</td>
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<tr>
<td>F16216</td>
<td>L98H+TR</td>
<td>&gt;8</td>
<td>1</td>
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<tr>
<td>F17294</td>
<td>L98H+TR</td>
<td>&gt;8</td>
<td>1</td>
<td>4</td>
<td>0.04</td>
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</tbody>
</table>
F901318 has the potential to address some of the unmet medical needs

- Novel mechanism of action – inhibitor of pyrimidine biosynthesis
  - Potent dihydroorotate dehydrogenase (DHODH) inhibitor
  - Highly selective for fungal enzyme relative to the human equivalent (900-fold difference)

- Active against all major species of *Aspergillus*
  - Activity includes strains resistant to azoles and amphotericin
  - Unrelated mechanism of action and no cross-resistance with existing drugs

- Active against *Scedosporium* spp. as well as a number of other rare and resistant moulds

- No activity against Zygomycetes, *Candida* spp., and *Cryptococcus* spp.

- [Intravenous and] oral routes of administration

- Animal PK-PD and initial human PK data suggest therapeutic exposures can be achieved in man; efficacy based on \( C_{\text{min}} \)

- Toxicology studies to date have not revealed major safety concerns

- No safety concerns in initial IV SAD & MAD studies in healthy volunteers

- Weak interaction with CYP 3A4
VL-2397 (ASP2397)  
(Vical Inc, San Diego, CA, USA)

- Discovered by Astellas Pharma from leaf litter fungus in Malaysia in 2007
  - Extensive nonclinical development studies were conducted
  - Vical in-licensed in March 2015

- Naturally-occurring siderophore isolated from *Acremonium* species

- Cyclic hexapeptide resembling the siderophore ferrichrome, able to chelate aluminum

- IV formulation only
VL-2397 Novel Mechanism of Action

- Active transport into *A. fumigatus* occurs via Sit1
- Mammalian cells lack Sit1 transporter
- Activity results from effect on an (unknown) intracellular target
- Low propensity for clinically significant DDIs
- Low risk for nephrotoxicity or hepatotoxicity
- Predictable PK and no apparent accumulation

Adapted from Denning *Science* 2015
**VL-2397: *In Vitro* Antifungal Activity**

Susceptible fungal pathogens (MIC ≤ 2)

<table>
<thead>
<tr>
<th>Fungal Species</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspergillus species</strong></td>
<td><em>A. fumigatus</em>, <em>A. terreus</em>, <em>A. flavus</em>, <em>A. nidulans</em>, including azole-R species</td>
</tr>
<tr>
<td><strong>Candida species</strong></td>
<td><em>C. glabrata</em>, <em>C. kefyr</em></td>
</tr>
<tr>
<td><strong>Other yeast species</strong></td>
<td><em>Cryptococcus neoformans</em></td>
</tr>
<tr>
<td></td>
<td><em>Trichosporon asahii</em></td>
</tr>
</tbody>
</table>

Assayed in inactivated human serum-containing media

MIC, minimal inhibitory concentration
VL-2397 Rapid Activity Against Aspergillus Including Drug-Resistant Isolates

Rapid Onset of Antifungal Activity

in Vitro

Activity vs. Azole-Resistant Aspergillus in Vivo

N = 10 mice /group
PSCZ: Posaconazole

Nakamura, ICAAC, 2014
VL-2397 Phase 2 Design: Invasive Aspergillosis

- Global, multicenter, randomized, open-label study
- N= 200 adults with AML, ALL or allo-HCT recipients
- 2:1 randomization VL-2397 to active comparator
  - Comparator: Physician’s choice of voriconazole, isavuconazole or liposomal amphotericin B
- 6 weeks of antifungal treatment
  - 4 weeks of VL-2397 followed by 2 weeks of comparator
- Primary endpoint: All-cause mortality at 4 weeks
  - Key secondary endpoint: ACM at 6 weeks
- Non-inferiority design
- If successful: FDA can grant limited use indication approval
APX001 (E1210) Glycosylphosphatidylinositol biosynthesis (Amplyx, San Diego, CA, USA)

- First in class novel mechanism of action – inhibition of Gwt1
- Broad spectrum yeasts and moulds – including resistant isolates (e.g., Candida auris, Mucorales fungi) but maybe not Candida krusei (?)
- Oral & IV formulations – 1 hour infusions with ~90% oral bioavailability
- Excellent Phase 1 PK profile – once day dosing with low variability and no food effect
- Safe and well tolerated in Phase 1 up to 14-days in healthy volunteers
  - Target AUCs achieved with no clinically significant safety signals
- Favorable Drug-Drug Interaction potential
- Wide tissue distribution including lung, renal and brain

1 Gwt1 GPI-anchored wall transfer protein 1
## Antifungal agents in clinical phase of development: summary

<table>
<thead>
<tr>
<th>Agent</th>
<th>Action mechanism</th>
<th>Advantage</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT-1161</td>
<td>Inhibitor of lanosterol demethylase</td>
<td>Tetrazole moiety with high affinity to the fungal CYP51</td>
<td>Candida infections</td>
</tr>
<tr>
<td>VT-1129</td>
<td>Inhibitor of lanosterol demethylase</td>
<td>Tetrazole moiety with high affinity to the fungal CYP51</td>
<td>Cryptococcal meningoencephalitis</td>
</tr>
<tr>
<td>SCY-078</td>
<td>Glucan synthase inhibitor</td>
<td>Oral bioavailability, activity despite resistance mutations</td>
<td>Invasive Candida infections</td>
</tr>
<tr>
<td>CD101</td>
<td>Glucan synthase inhibitor</td>
<td>Increased half-life, reduced toxicity</td>
<td>Invasive Candida infections, Aspergillus infections</td>
</tr>
<tr>
<td>CAMB</td>
<td>Ergosterol binding, pore formation in the fungal membrane, K and Mg efflux resulting in cell death</td>
<td>Oral bioavailability, reduced toxicity, broad spectrum activity</td>
<td>Candida and Aspergillus infections, Cryptococcal meningoencephalitis</td>
</tr>
<tr>
<td>MAT2203</td>
<td>Ergosterol binding, formation of pores in the fungal membrane, K and Mg efflux resulting in cell death</td>
<td>Oral bioavailability, reduced toxicity, broad spectrum activity</td>
<td>Invasive Candidiasis, Aspergilosis</td>
</tr>
<tr>
<td>Nikkomycin Z</td>
<td>Inhibits fungal wall synthesis through inhibition of chitin synthases</td>
<td>Fungal specific target</td>
<td>Coccidioidomycosis, histoplasmosis and blastomycosis</td>
</tr>
<tr>
<td>APX001</td>
<td>Inhibits Gwt1, GPI-anchor protein synthesis</td>
<td>Fungal specific target, affects multiple virulence factors</td>
<td>Candida spp, Aspergillus spp, Scedosporium</td>
</tr>
<tr>
<td>F901318</td>
<td>Inhibits DHODH, pyrimidine synthesis pathway.</td>
<td>Fungal specific target, broad spectrum antifungal</td>
<td>Aspergillus spp, Dimorphic fungi, Scedosporium, Fusarium spp</td>
</tr>
</tbody>
</table>
# Invasive aspergillosis: First line therapy recommendations

<table>
<thead>
<tr>
<th>Drugs</th>
<th>IDSA¹</th>
<th>ECIL²</th>
<th>ESCMID-ECMM-ERS³</th>
<th>Australia⁴</th>
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</thead>
<tbody>
<tr>
<td>AmB DC</td>
<td></td>
<td>A against</td>
<td>DI</td>
<td>Alternative</td>
</tr>
<tr>
<td>AmB-LS</td>
<td>Strong Moderate quality</td>
<td>BI</td>
<td>BII</td>
<td>Alternative</td>
</tr>
<tr>
<td>ABLC</td>
<td>Weak Low quality</td>
<td>BII</td>
<td>CIII</td>
<td></td>
</tr>
<tr>
<td>ABCD</td>
<td>Weak Low quality</td>
<td>CI</td>
<td>DI</td>
<td></td>
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<tr>
<td>Itraconazole</td>
<td></td>
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<td>CIII</td>
<td>CIII</td>
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<tr>
<td>Posaconazole</td>
<td></td>
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<tr>
<td><strong>Voriconazole</strong></td>
<td><strong>Strong High quality</strong></td>
<td><strong>AI</strong></td>
<td><strong>AI</strong></td>
<td><strong>Recommended</strong></td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Not recommended</td>
<td>CII</td>
<td>CII</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>Weak recommendation; moderate-quality evidence</td>
<td></td>
<td>CIII</td>
<td></td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td><strong>Weak Moderate quality</strong></td>
<td>Discouraged</td>
<td>CI</td>
<td>No supportive evidence</td>
</tr>
</tbody>
</table>

Thanks for listening....