Rezafungin: a Novel, Once-Weekly Echinocandin in Phase 3 Development for Treatment and Prevention of Invasive Fungal Disease

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Cidara Therapeutics, Inc
What’s *Not* New in 2019

- No novel antifungal agents developed in the past 12 years
- Morbidity and mortality of invasive fungal disease remain high
- Growing gap between current antifungals and clinical needs of today’s patients
- A return to pre-2000 era? Some novel therapies and medications are contraindicated and/or have drug interactions with the newer azoles
Rezafungin: a novel echinocandin in phase 3
designed for next-generation properties

- Broad spectrum of activity and in vivo efficacy
- Novel PK/PD
- Improved safety
- Increased solubility and stability

“... confers much greater stability, leading to an exceptionally longer half-life and an improved safety profile”

Rezafungin broad-spectrum in vitro activity against common and rare Candida spp.

<table>
<thead>
<tr>
<th></th>
<th>C. albicans (n=1098)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>C. glabrata (n=477)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>C. tropicalis (n=224)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>C. krusei (n=130)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>C. parapsilosis (n=387)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>C. kefyr (n=51)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>C. lusitaniae (n=43)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>C. guilliermondii (n=20)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>C. dubliniensis (n=21)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>C. auris (n=19)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>C. auris (n=100)&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rezafungin</td>
<td>0.06</td>
<td>0.125</td>
<td>0.06</td>
<td>0.06</td>
<td>2</td>
<td>0.12</td>
<td>0.25</td>
<td>1</td>
<td>0.06</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.03</td>
<td>0.125</td>
<td>0.06</td>
<td>0.125</td>
<td>2</td>
<td>0.06</td>
<td>0.06</td>
<td>2</td>
<td>0.06</td>
<td>0.25</td>
<td>NA</td>
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<tr>
<td>Caspofungin</td>
<td>0.03</td>
<td>0.06</td>
<td>0.25</td>
<td>0.5</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td>0.25</td>
<td>1</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

NC = not available.

<sup>a</sup> CLSI broth microdilution methodology was employed for MIC determination (M27-A3).

<sup>b</sup> Clinical isolates collected internationally in the JMI Laboratories SENTRY Antimicrobial Surveillance Program (2014-2017).

<sup>c</sup> Clinical isolates collected in Hungary (2005-2018), except for C. auris obtained from the National Mycology Reference Laboratory (Bristol, UK), tested as part of a retrospective study.

<sup>d</sup> Clinical isolates collected by the CDC, representing each of the 4 known clades of C. auris, including 8 isolates with elevated MICs to one or more echinocandins.

Rezafungin in vitro activity against *Candida auris*

**MIC** <sub>90</sub> of 0.5 µg/mL includes echinocandin-<i>R</i> isolates

Rezafungin MIC Distribution (µg/mL)<sup>a</sup>

<table>
<thead>
<tr>
<th></th>
<th>0.03</th>
<th>0.0625</th>
<th>0.125</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Rezafungin</td>
<td>2</td>
<td>21</td>
<td>28</td>
<td>32</td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

**MICs (µg/mL)<sup>a</sup>** against 8 echinocandin-<i>R</i> isolates

<table>
<thead>
<tr>
<th>Isolate</th>
<th>FKS1 mutation</th>
<th>Rezafungin</th>
<th>Anidulafungin</th>
<th>Caspofungin</th>
<th>Micafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td>B11211</td>
<td>S639P</td>
<td>4</td>
<td>8</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>B12131</td>
<td>S639P</td>
<td>8</td>
<td>8</td>
<td>&gt;16</td>
<td>8</td>
</tr>
<tr>
<td>B12137</td>
<td>S639P</td>
<td>8</td>
<td>8</td>
<td>&gt;16</td>
<td>8</td>
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<tr>
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<td>S639P</td>
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<td>&gt;16</td>
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<tr>
<td>B11858</td>
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<td>4</td>
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<td>B11222</td>
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<td>16</td>
<td>2</td>
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<tr>
<td>B11780</td>
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<td>0.06</td>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
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<tr>
<td>B11784</td>
<td>None</td>
<td>0.5</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>&gt;8</td>
</tr>
</tbody>
</table>

<sup>a</sup>CLSI BMD methodology, M27-A3

Rezafungin demonstrated activity against *C. auris*

CDC collection of clinical *C. auris* (N=100) had all 4 known clades and 8 isolates with elevated echinocandin MICs
Rezafungin treatment efficacy against *Candida auris* significantly lower fungal burden in immunosuppressed mice

Kidney Tissue Fungal Burden on Days 1, 4, 7, and 10

- Rezafungin-treated mice showed significantly lower *C. auris* fungal burden
  - vs amphotericin B, all days (p<0.0001)\(^a\)
  - vs micafungin, day 10 (p=0.0128)

\(^a\) p=0.023 on day 1 postinfection

# Rezafungin broad-spectrum in vitro activity against Aspergillus spp., including azole-R and cryptic spp.

<table>
<thead>
<tr>
<th></th>
<th>MEC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>azole-R A. fumigatus (n=31)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>A. lentulus (n=11)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>A. calidoustus (n=11)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rezafungin</td>
<td>0.015</td>
<td>0.12</td>
<td>≤0.015</td>
<td>0.5</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.015</td>
<td>0.4</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>0.03</td>
<td>&gt;16</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>a</sup>CLSI broth microdilution methodology was employed for MEC determination (M38-A2).

<sup>b</sup>Clinical isolates collected internationally in the JMI Laboratories SENTRY Antimicrobial Surveillance Program (2014-2017).

<sup>c</sup>Clinical isolates collected in the US and resistance genotypes confirmed by DNA sequence analysis (CYP51A only, n=13; TR<sub>34</sub>/L98H, n=2; TR<sub>46</sub>/Y121F/T289A, n=2; resistant/no CYP51A mutation, n=6; resistant/CYP51A status unknown, n=8). (Wiederhold et al, 2018a; 2018b).

Rezafungin prophylaxis efficacy against *Aspergillus* survival in immunosuppressed mouse model

Rezafungin: one subcutaneous dose of 5, 10 or 20 mg/kg on days -5, -3, or -1 as prophylaxis

10 mg/kg = human dose of 200mg
20 mg/kg = human dose of 400mg

2-3 fold faster clearance in mice than in humans.

Control/Amphotericin B: 3 mg/kg one hour post-infection

CPM = cyclophosphamide

Ong et al. ECCMID 2017; poster EP0703; Ong et al. EHA 2017; poster P645.
Rezafungin prophylaxis efficacy against *Aspergillus* survival in immunosuppressed mouse model

Rezafungin at human equivalent doses: 100% efficacy as prophylaxis against *Aspergillus*, even when administered 5 days pre-infection (≈2 weeks in humans)

CPM=cyclophosphamide.

Ong et al. ECCMID 2017; poster EP0703; Ong et al. EHA 2017; poster P645.
**Pneumocystis pneumonia**
review and reappraisal of a pathogen and its prophylaxis

**Pneumocystis jiroveci (carinii)**

- Opportunistic pathogen of lethal pneumonia (eg, HIV, chemotherapy, corticosteroids)
- Biphasic life cycle: trophic forms and asci/cysts

Current Approach to Prophylaxis

- **TMP-SMX**
  TMP 15-20 mg/kg/d and SMX 75-100 mg/kg/d, PO in 3 divided doses or TMP-SMX DS, 2 tabs TID
- **Dapsone**
  plus pyrimethamine + leucovorin
- **Aerosolized pentamidine**
- **Atovaquone**
  plus pyrimethamine + leucovorin
- **NOT recommended:** oral clindamycin plus primaquine

Cushion et al. ASH, 2016; oral presentation.
Rezafungin prophylaxis efficacy against *Pneumocystis* equivalent to TMP/SMX in immunosuppressed mouse model

Following rezafungin administration at time of *Pneumocystis* inoculation (*P. murina*)

- Rezafungin efficacy equivalent to the gold standard TMP/SMX
- Significant reductions in nuclei and asci even at low doses
- No significant differences in survival

Rezafungin prevented infection and *Pneumocystis* re-activation after cessation of therapy and continued immunosuppression (data not shown; Cushion et al, ASH 2019)
Rezafungin: a novel echinocandin designed for next-generation properties

- Broad spectrum of activity and in vivo efficacy
- Novel PK/PD
  - Prolonged t₁/₂ (~130 h)
  - High drug exposure
  - Maximized pharmacometric drivers of efficacy
- Improved safety
- Increased solubility and stability
Rezafungin: exposure shape matters
PK/PD determinant of antifungal efficacy

High drug exposure following once-weekly dosing resulted in greater fungal killing than divided doses (same weekly exposure)

Dose fractionation of rezafungin 2 mg/kg in neutropenic mice (n=5/grp)

### Echinocandin target attainment percent probabilities for current echinocandins

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>C. albicans</th>
<th>C. glabrata</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anidulafungin</td>
<td>Caspofungin</td>
</tr>
<tr>
<td>0.008</td>
<td>100&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>100</td>
</tr>
<tr>
<td>0.015</td>
<td>99.1</td>
<td>100</td>
</tr>
<tr>
<td>0.03</td>
<td>52.7</td>
<td>100</td>
</tr>
<tr>
<td>0.06</td>
<td>0.90</td>
<td>97.9</td>
</tr>
<tr>
<td>0.12</td>
<td>0</td>
<td>76.7</td>
</tr>
<tr>
<td>0.25</td>
<td>0</td>
<td>35.7</td>
</tr>
<tr>
<td>0.5</td>
<td>0</td>
<td>12.1</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>4.4</td>
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<tr>
<td>2</td>
<td>0</td>
<td>1.35</td>
</tr>
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<td>4</td>
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<td>0.25</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Shading reflects relative probability of PK/PD target attainment

Bader et al. IDWeek 2017; poster 833.
Echinocandin target attainment percent probabilities for current echinocandins and rezafungin

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>C. albicans</th>
<th></th>
<th></th>
<th>C. glabrata</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anidulafungin</td>
<td>Caspofungin</td>
<td>Rezafungin</td>
<td></td>
<td>Anidulafungin</td>
<td>Caspofungin</td>
</tr>
<tr>
<td>0.008</td>
<td>100&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>100</td>
<td>100</td>
<td>0.008</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>0.015</td>
<td>99.1</td>
<td>100</td>
<td>100</td>
<td>0.015</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>0.03</td>
<td>52.7</td>
<td>100</td>
<td>100</td>
<td>0.03</td>
<td>99.2</td>
<td>100</td>
</tr>
<tr>
<td>0.06</td>
<td>0.90</td>
<td>97.9</td>
<td>100</td>
<td>0.06</td>
<td>54.3</td>
<td>100</td>
</tr>
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<td>0</td>
<td>76.7</td>
<td>100</td>
<td>0.12</td>
<td>0.95</td>
<td>100</td>
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<tr>
<td>0.25</td>
<td>0</td>
<td>35.7</td>
<td>100</td>
<td>0.25</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>0.5</td>
<td>0</td>
<td>12.1</td>
<td>90.55</td>
<td>0.5</td>
<td>0</td>
<td>97.0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>4.4</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>73.2</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1.35</td>
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<td>2</td>
<td>0</td>
<td>33.9</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0.25</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>11.3</td>
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<tr>
<td>8</td>
<td>0</td>
<td>0.05</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>4.35</td>
</tr>
</tbody>
</table>

Shading reflects relative probability of PK/PD target attainment

Bader et al. IDWeek 2017; poster 833.
Rezafungin: a novel echinocandin *designed for next-generation properties*

- Broad spectrum of activity and in vivo efficacy
- Novel PK/PD
  - Prolonged $t_{1/2}$ (~130 h)
  - High drug exposure
  - Maximized pharmacometric drivers of efficacy
- Improved safety
- Increased solubility and stability

Distinctive pharmacokinetics of rezafungin

long half-life... and more

→ Extensive distribution
  • uniform tissue penetration across major organs (rat model) up to 4-fold higher compared to plasma
  • limited CNS penetration
→ Elimination similar across all tissues

• Increased solubility and stability
Rezafungin penetrates & accumulates vs micafungin including difficult-to-treat infection (IAC mouse model)

Single dose rezafungin 20 mg/kg or 2-3 doses of micafungin 5 mg/kg on day 3 post-infection with *C. albicans*

MALDI-MS imaging assessed drug penetration at site of infection in an IAC mouse model

- 6- to 8-fold higher RZF exposure at site of infection
- Multidose MCF did not reach tissue drug levels achieved with single dose RZF

IAC = intraabdominal candidiasis; GMS = Gömöri methenamine silver stain; MALDI MS = matrix-assisted laser desorption/ionization mass spectrometry; MCF = micafungin; RZF = rezafungin.

Rezafungin distributes to key sites for infection *higher levels and longer duration in ELF vs micafungin*

**RZF Concentrations**

- >20-fold higher than MEC$_{90}$ for *A. fumigatus* and *A. flavus* (0.015 µg/mL) after 3 days in mice
  - plasma: 3 µg/mL
  - ELF: 4 µg/mL
- Comparable human levels after 1 week expected, based on RZF plasma $t_{1/2}$ (133 h, human vs. 21 h, mouse)

ELF = epithelial lining fluid.

Ong et al. HTIDE, 2018; poster.
Rezafungin: a novel echinocandin designed for next-generation properties

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- Novel PK/PD
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Rezafungin preclinical safety vs anidulafungin

**normal findings vs elevated enzymes and necrosis**


- **Rezafungin**
  - Normal Plasma Liver Enzymes
  - Normal Liver Histology

- **Anidulafungin**
  - Plasma Liver Enzymes Elevated
  - Hepatocellular Necrosis

2-week Rat Hepatotoxicity Screening Study

20-min IV Infusion via Tail Vein at Comparable Plasma Exposures
Rezafungin Phase 1 drug-drug interaction study

*no changes in dose required when rezafungin coadministered*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Possible Mechanism(s)</th>
<th>Observations</th>
<th>Suggested Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>CYP3A4, P-gp</td>
<td>↓$C_{\text{max}}$ AUC ~15%</td>
<td>No change in dose</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>CYP2C8, OATP</td>
<td>↑$C_{\text{max}}$ AUC ~15%</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>OCT, MATEs</td>
<td>↓$C_{\text{max}}$, ↓AUC</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>BCRP, OATP</td>
<td>↑$C_{\text{max}}$ ~12%, ↑AUC ~15%</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>OATP</td>
<td>↓$C_{\text{max}}$, ↓AUC</td>
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</tr>
<tr>
<td>Caffeine</td>
<td>CYP1A2</td>
<td>↑$C_{\text{max}}$, ↑AUC</td>
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<tr>
<td>Efavirenz</td>
<td>CYP2B6</td>
<td>↓$C_{\text{max}}$, ↓AUC</td>
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<td>Midazolam</td>
<td>CYP3A</td>
<td>↓$C_{\text{max}}$, ↓AUC</td>
<td></td>
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<tr>
<td>Digoxin</td>
<td>CYP2B6</td>
<td>↓$C_{\text{max}}$, ↓AUC</td>
<td></td>
</tr>
</tbody>
</table>

Ong et al. TCT 2019; poster 535.

- Single-center, RCT (N=26)
- Substrate drugs dosed alone for 3 weeks, then again with rezafungin for 3 weeks
- No dose change needed for common medications when coadministered with rezafungin
Rezafungin Phase 1 QTc interval study
No clinically significant effects

- Cardiovascular safety of systemic antifungals
  - Posaconazole - prolongs QT interval; 
    torsades de pointes (rare)
  - Amphotericin B - abnormal cardiac conduction

- First echinocandin to undergo definitive QT/QTc study
- No effects on QT/QTc interval observed at supratherapeutic doses

STRIVE Phase 2 trial of rezafungin treatment

candidemia & invasive candidiasis

Clinicaltrials.gov; NCT02734862

**OBJECTIVES**

To establish:

- Safety and tolerability
- Clinical and mycological efficacy across timepoints
- Efficacy vs caspofungin
- Dosing regimen for Phase 3
### STRIVE demographics and baseline characteristics

**ITT Population**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rezafungin 400 mg/400 mg QWk N= 81</th>
<th>Rezafungin 400 mg Wk1/200 mg QWk N= 57</th>
<th>Caspofungin 70 mg/50 mg QD N= 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>%, except where noted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Mean [Range]</td>
<td>60 y [24-88]</td>
<td>60 y [24-91]</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Candidemia</td>
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<td>80.7</td>
</tr>
<tr>
<td></td>
<td>IC</td>
<td>23.5</td>
<td>19.3</td>
</tr>
<tr>
<td>APACHE II&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>28.4</td>
<td>26.3</td>
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<td></td>
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<td>24.6</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>13.4</td>
<td>14.1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Numbers of subjects with scores not calculated/missing not shown.

- ~20% invasive candidiasis in overall population
- Treatment groups well balanced and matched
**STRIVE Candida species at enrollment**

*mITT Population*

### Total (196 isolates)

- **C. albicans**: 46%
- **C. glabrata**: 19%
- **C. parapsilosis**: 14%
- **C. tropicalis**: 11%
- **C. dubliniensis**: 3%
- **C. krusei**: 3%
- **Other**: 4%

*Other: C. fermentati, C. intermedia, C. kefyr, C. metapsilosis, C. rugosa, C. utilis (n=1 each), and C. guilliermondii (n=2)*

### EU only (128 isolates)

- **C. albicans**: 44%
- **C. glabrata**: 16%
- **C. parapsilosis**: 18%
- **C. dubliniensis**: 2%
- **C. kefyr, C. rugosa, C. utilis**: (n=1 each) and **C. guilliermondii**: (n=2)
- **C. tropicalis**: 13%
- **Other**: 4%
STRIVE summary of rezafungin efficacy results

mITT Population

- Overall Response D14: 46%, 76.1%, 41%
- PI Assessment of Clinical Response D14: 53%, 37%, 43%
- All-Cause Mortality D30: 15.8%, 4.3%, 13.1%

1° endpoint component Ph3 – EMA

- Rezafungin 400mg/400mg QWk (N=76)
- Rezafungin 400mg/200mg QWk (N=46)
- Caspofungin 70mg/50mg QD (N=61)
STRIVE PI assessment of clinical response by *Candida* species

**Day 14 - mITT Population**

<table>
<thead>
<tr>
<th>Species</th>
<th>57.9</th>
<th>84.2</th>
<th>92.3</th>
<th>80.0</th>
<th>55.6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rezafungin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg/400mg QWk</td>
<td>(N=76)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg/200 mg QWk</td>
<td>(N=46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caspofungin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 mg/50 mg QD</td>
<td>(N=61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. of isolates:

* C. albicans: 38, 19, 34
* C. glabrata: 13, 14, 10
* C. parapsilosis: 10, 7, 11
* C. tropicalis: 9, 7, 6
### STRIVE overall response

**Day 5 - mITT Population**

<table>
<thead>
<tr>
<th>Overall Response</th>
<th>Rezafungin 400 mg/400 mg QWk N= 76</th>
<th>Rezafungin 400 mg/200 mg QWk N= 46</th>
<th>Caspofungin 70 mg/50 mg QD N= 61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>42 (55.3)</td>
<td>34 (73.9)</td>
<td>34 (55.7)</td>
</tr>
<tr>
<td>Failure</td>
<td>24 (31.6)</td>
<td>10 (21.7)</td>
<td>24 (39.3)</td>
</tr>
</tbody>
</table>

aIndeterminate outcomes (those unable to be assessed due to missing data point[s]) not shown. mITT = microbiological intent-to-treat (all who received study drug and had documented Candida infection.

• **Day 5 outcomes reflect initial dose of 400 mg in both RZF-treated arms**
STRIVE time to negative blood culture

Greatest difference ~24 hours after first dose

Hours Since First Dose

- RZF Group 1
- RZF Group 2
- Caspofungin

Probability of Negative Blood Culture

- 1.0
- 0.8
- 0.6
- 0.4
- 0.2
- 0.0

Time (hours)
### STRIVE summary of adverse events

**Safety Population**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rezafungin 400 mg/400 mg QWk N=81</th>
<th>Rezafungin 400 mg Wk1/200 mg QWk N=53</th>
<th>All Rezafungin (Pooled) N=134</th>
<th>Caspofungin 70 mg/50 mg QD N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 TEAE</td>
<td>71 (87.7)</td>
<td>49 (92.5)</td>
<td>120 (89.6)</td>
<td>55 (80.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>29 (35.8)</td>
<td>17 (32.1)</td>
<td>46 (34.3)</td>
<td>26 (38.2)</td>
</tr>
<tr>
<td>Study drug-related</td>
<td>7 (8.6)</td>
<td>6 (11.3)</td>
<td>13 (9.7)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>TEAE leading to study D/C</td>
<td>6 (7.4)</td>
<td>1 (1.9)</td>
<td>7 (5.2)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>35 (43.2)</td>
<td>28 (52.8)</td>
<td>63 (47.0)</td>
<td>29 (42.6)</td>
</tr>
<tr>
<td>Study drug-related</td>
<td>1 (1.2)</td>
<td>1 (1.9)</td>
<td>2 (1.5)</td>
<td>2 (2.9)</td>
</tr>
</tbody>
</table>

D/C=discontinuation; TEAE (treatment-emergent adverse event)=AE that occurs after first dose of study drug is administered.
<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Rezafungin 400 mg/400 mg QWk N=81</th>
<th>Rezafungin 400 mg Wk1/200 mg QWk N=53</th>
<th>All Rezafungin (Pooled) N=134</th>
<th>Caspofungin 70 mg/50 mg QD N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalemia</td>
<td>13 (16.0)</td>
<td>9 (17.0)</td>
<td>22 (16.4)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (8.6)</td>
<td>11 (20.8)</td>
<td>18 (13.4)</td>
<td>10 (14.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (7.4)</td>
<td>8 (15.1)</td>
<td>14 (10.4)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (11.1)</td>
<td>4 (7.5)</td>
<td>13 (9.7)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (7.4)</td>
<td>7 (13.2)</td>
<td>13 (9.7)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (4.9)</td>
<td>8 (15.1)</td>
<td>12 (9.0)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5 (6.2)</td>
<td>6 (11.3)</td>
<td>11 (8.2)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>9 (11.1)</td>
<td>1 (1.9)</td>
<td>10 (7.5)</td>
<td>3 (4.4)</td>
</tr>
</tbody>
</table>
Phase 3 ReSTORE trial of rezafungin treatment

candidemia & invasive candidiasis

Rezafungin
400/200/(200)mg n=92

Week 1
Day 1 2 3 4 5 6 7 8 9
Global Response
Optional dose
Global Response (1° ENDPOINT – EMA)
30(-2) 35 42 45 49 56 59
Global Response & All cause mortality (1° ENDPOINT – FDA)

Caspofungin
70/50/(50)mg n=92

Week 1
Day 1 2 3 4 5 6 7 8 9
70mg Dose
50mg Dose
Global Response & All cause mortality (1° ENDPOINT – FDA)
Rezafungin antifungal prophylaxis

Potential simplified single-drug paradigm

Antifungal prophylaxis in allogeneic blood and marrow transplant setting

Current Antifungal Prophylaxis Regimens

- Fluconazole
- Fluconazole or Posaconazole or Voriconazole
- Posaconazole or Voriconazole or Bactrim, dapsone or atovaquone

Rezafungin

SOC for Candida and Aspergillus

SOC for Pneumocystis

Candida, Aspergillus and Pneumocystis
Planned Phase 3 antifungal prophylaxis trial in BMT

**Rezafungin Arm (n=~300)**

- Week 1: Rezafungin
- Week 2: Rezafungin
- Week 3: Rezafungin
- Week 4: Rezafungin
- Week 5: Rezafungin
- Week 12: Rezafungin
- Week 13: Rezafungin
- Day 1: Rezafungin

**Comparator Arm (n=~150)**

- Week 1: Azole
- Week 2: Azole
- Week 3: Azole
- Week 4: Azole
- Week 5: Azole
- Week 12: Azole
- Week 13: Azole
- Week 17: Azole
- Day 1: Azole

1° Endpoint: Fungal Free Survival at Day 90

Follow up

Size and timing pending additional regulatory input

*Fluconazole to start in all patients. Posaconazole optional in patients who develop GVHD per label.
What’s *New* in Antifungals: Rezafungin

- A novel echinocandin designed for flexibility, safety, and efficacy
  - Broad spectrum
  - Robust in vivo efficacy
  - Long half-life, front-loaded exposure, extensive distribution
  - Safety profile includes no/low DDI potential

- Phase 3 development
  - Treatment of candidemia and IC - underway
  - Prophylaxis against IFD [candidemia, aspergillosis, and PCP] in BMT recipients - 1Q20

- Rezafungin demonstrates potential as a next-generation antifungal with novel properties to face today’s challenges in treatment and prevention of invasive fungal disease
Thank You