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

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Chief Medical Officer
Cidara Therapeutics, Inc.

Rezafungin is in Phase 3 clinical development. Not registered in any country. Registration requirements differ internationally.
Presenter Disclosures

• Employee and shareholder of Cidara Therapeutics, Inc.
What’s Changed for Systemic Fungal Infections in the Past 20 Years?

Clinical Landscape

Evolving epidemiology
- Rising predominance of non-albicans Candida
- Increasing MICs
- Resistance - FKS mutations, pan-azole resistance
- New threat: Candida auris

Complexity of Care
- Older patient population
- Improved outcomes and survival
- Longer periods of neutropenia
- Drug—drug interactions (CYP family)
- Therapeutic drug monitoring needs
- Evidence of inadequate drug exposure in the critically ill, special populations

Increased risk of IFI

Tidal wave of novel chemotherapeutics (midostaurin, vincristine, venetoclax, nilotinib, ibrutinib, and more…)

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  - Resistance - \textit{FKS} mutations, pan-azole resistance
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  - Improved outcomes and survival
  - Longer periods of neutropenia
  - Drug—drug interactions (CYP family)
  - Therapeutic drug monitoring needs
  - Evidence of inadequate drug exposure in the critically ill, special populations

**Antifungal drug approvals**

- Voriconazole
- Posaconazole
- Caspofungin
- Micafungin
- Anidulafungin
- Isavuconazole

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Rezafungin: A Novel Long-Acting Echinocandin With Distinctive Properties in Phase 3

Structural modification increases stability and yields unique chemical & biological properties

<table>
<thead>
<tr>
<th>Properties</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting PK</td>
<td>Once-weekly dosing as in ongoing Phase 3 clinical trials*</td>
</tr>
<tr>
<td>Front-loaded plasma drug exposure</td>
<td>Efficacy: Shorter time to negative blood culture in Phase 2</td>
</tr>
<tr>
<td>Broad spectrum activity</td>
<td>In vivo efficacy vs. Candida, Aspergillus, and Pneumocystis spp.</td>
</tr>
<tr>
<td>Observed absence of toxic degradation products</td>
<td>Safety: lack of hepatotoxicity</td>
</tr>
<tr>
<td>No DDIs and favorable hepatic and renal safety</td>
<td>Compatibility with other medications</td>
</tr>
</tbody>
</table>

* ReSTORE: 1st line treatment of candidemia and/or invasive candidiasis
ReSPECT: 1st line prophylaxis for Candida, Aspergillus, and Pneumocystis spp., in allogeneic blood and marrow transplant patients

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Rezafungin Targets the Fungal Cell Wall


Increased permeability of the cell wall causes osmotic imbalance^2

Rezafungin inhibits production of 1,3-β-D-glucan^2

Fungal cell lysis occurs^2

- Fungicidal against *Candida* spp.
- Fungistatic against *Aspergillus* spp.^2
- Active against *Pneumocystis* spp.^3,^4

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Rezafungin: Potent, Broad-Spectrum Activity Against Candida Species

In Vitro Activity Comparable With Current Echinocandins

<table>
<thead>
<tr>
<th></th>
<th>C. albicans (n=835)</th>
<th>C. glabrata (n=374)</th>
<th>C. tropicalis (n=196)</th>
<th>C. krusei (n=77)</th>
<th>C. parapsilosis (n=329)</th>
<th>C. kefyr (n=52)</th>
<th>C. lusitaniae (n=46)</th>
<th>C. guilliermondii (n=27)</th>
<th>C. dubliniensis (n=22)</th>
<th>C. auris (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rezafungin</td>
<td>0.06</td>
<td>0.12</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>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.03</td>
<td>0.12</td>
<td>0.06</td>
<td>0.12</td>
<td>2</td>
<td>0.06</td>
<td>0.06</td>
<td>2</td>
<td>0.03</td>
<td>0.25</td>
</tr>
<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>1</td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.03</td>
<td>0.03</td>
<td>0.06</td>
<td>0.12</td>
<td>1</td>
<td>0.12</td>
<td>0.25</td>
<td>2</td>
<td>0.03</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*MIC₉₀ (µg/mL)¹⁻³*

- *CLSI broth microdilution methodology was employed for MIC determination (M27-A3).¹⁻³
- †Clinical isolates collected internationally in the JMI Laboratories SENTRY Antimicrobial Surveillance Program (2016-2018).²
- ‡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.³

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Rezafungin: Potent Activity Against *Aspergillus* Species

*In Vitro Activity Includes Azole-Resistant Strains and Cryptic Species*

<table>
<thead>
<tr>
<th></th>
<th>MEC&lt;sub&gt;90&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>A. fumigatus</em> (n=183)&lt;sup&gt;1†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rezafungin</td>
<td>0.03</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.03</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>0.03</td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MEC&lt;sub&gt;90&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Azole-resistant</em> <em>A. fumigatus</em> (n=31)&lt;sup&gt;2‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rezafungin</td>
<td>0.12</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>4</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*CLSI broth microdilution methodology was employed for MEC and MIC determination (M38-A2).*<sup>2</sup>

<sup>1</sup>Clinical isolates collected internationally in the JMI Laboratories SENTRY Antimicrobial Surveillance Program (2016-2018).<sup>3</sup>

<sup>2</sup>Clinical isolates collected in the US and resistance genotypes confirmed by DNA sequence analysis (CYP51A only, n=13; TR<sub>trn/L98H</sub>, n=2; TR<sub>trn/Y112F/T289A</sub>, n=2; resistant/no CYP51A mutation, n=6; resistant/CYP51A status unknown, n=8).<sup>3</sup>

CLSI, Clinical and Laboratory Standards Institute; CYP, cytochrome P450; MEC, minimal effective concentration; MIC, minimal inhibitory concentration.

Rezafungin: *In Vivo* Efficacy

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Efficacy of Rezafungin in Prophylactic Mouse Models of Invasive Candidiasis, Aspergillosis, and *Pneumocystis* Pneumonia

Lynn Miesel, Melanie T. Cushion, Alan Ashbaugh, Santiago R. Lopez, Voon Ong

Survival – *A. fumigatus* (ATCC 13073) 1.85x10⁴ on Day 0

Kidney Tissue Fungal Burden – *Pneumocystis murina* 2x10⁶ on Day 0

- 100% prophylaxis efficacy against *A. fumigatus* at human equivalent doses (10 and 20 mg/kg)
- Prophylaxis efficacy against *Pneumocystis* comparable to TMP-SMX (standard of care) at human equivalent doses

*ps<0.05 vs. control.
C/S, control steroid; CPM, cyclophosphamide; LOD, limit of detection; TMP/SMX, trimethoprim-sulfamethoxazole.


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Rezafungin: PK/PD

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Rezafungin High Exposure for Sustained Fungicidal Activity

Exposure Shape Matters for Antifungal Efficacy

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

Simulated dose fractionation of rezafungin in healthy mice, total dose 2 mg/kg

Fungal burden in neutropenic mice following Candida albicans infection and 2 mg/kg rezafungin


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Rezafungin PK/PD Target Attainment by MIC Associated With Net Fungal Stasis and CFU Reductions From Baseline

Percent Probability Against Worldwide C. albicans and C. glabrata MIC Distributions

Study Design

- Population PK model, non-clinical PK/PD targets, and *in vitro* surveillance data used to simulate probabilities of target attainment
- Simulated administration of rezafungin 400 mg
- Highest rezafungin MIC values in *fks* mutants observed were 0.25 mg/L for *C. albicans* and 2 mg/L for *C. glabrata*

Rezafungin 400 mg simulated to achieve high percent probabilities of PK/PD target attainment, providing efficacy for majority of patients

Single dose of rezafungin 400 mg simulated to reduce fungal burden, even in some *fks* mutant *Candida* isolates

CFU, colony-forming units; MIC, minimal inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic.

Rezafungin Demonstrates High Probability of PK/PD Target Attainment

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>C. albicans(^1,2)</th>
<th>C. glabrata(^1,2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Micafungin</td>
<td>Anidulafungin</td>
</tr>
<tr>
<td>0.008</td>
<td>99.4</td>
<td>100</td>
</tr>
<tr>
<td>0.015</td>
<td>71.2</td>
<td>99.1</td>
</tr>
<tr>
<td>0.03</td>
<td>10.1</td>
<td>52.7</td>
</tr>
<tr>
<td>0.06</td>
<td>0.1</td>
<td>0.90</td>
</tr>
<tr>
<td>0.12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Shading reflects relative probability of PK/PD target attainment 1 week after dose (stasis).

Rezafungin high probability of PK/PD target attainment against *C. albicans* and *C. glabrata* in Monte Carlo simulations

MIC, minimal inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic.

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Rezafungin Sustained Tissue Distribution *In Vivo*

**Rat PK Models**

**Uniform tissue distribution across liver, kidney, lungs, and spleen**

**Similar half-life/elimination in organs**

AUC, area under the curve.

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Rezafungin Distribution to Key Sites in Infection

Drug Concentrations in Plasma and ELF\(^1\)

Micafungin

<table>
<thead>
<tr>
<th>Time post-dose (h)</th>
<th>Mean Concentration (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>48</td>
<td>2</td>
</tr>
<tr>
<td>72</td>
<td>0</td>
</tr>
</tbody>
</table>

Plasma  
ELF

Rezafungin

<table>
<thead>
<tr>
<th>Time post-dose (h)</th>
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<tbody>
<tr>
<td>0</td>
<td>35</td>
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<td>30</td>
</tr>
<tr>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>72</td>
<td>5</td>
</tr>
</tbody>
</table>

Plasma  
ELF

Study Design

- Study drugs administered IP as a single dose in CD-1 mice
  - Micafungin 5 mg/kg (≈ human dose of 100 mg)
  - Rezafungin 20 mg/kg (≈ human dose of 400 mg)
- Comparable levels in humans expected after 1 week due to rezafungin plasma half-life (133 h in human, 21 h in mouse)

Micafungin distribution into mouse ELF is similar to that observed in humans, suggesting that this model may be predictive of distribution in humans

Rezafungin concentrations >20-fold higher than MEC\(_{90}\) (0.015 μg/mL) against *Aspergillus fumigatus* and *A. flavus* in plasma (3 μg/mL) and ELF (4 μg/mL) after 3 days

High levels and long duration in ELF reinforce potential for rezafungin efficacy with once-weekly dosing

ELF, epithelial lining fluid; MEC, minimal effective concentration.


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Rezafungin Tissue Penetration With a Single Dose (Zhao et al, 2017)

*In vivo* Comparison of Drug Penetration in the Liver

**Study Design**
- CD-1 mice, no immunosuppression
- *C. albicans* (SC5314), $1 \times 10^7$ on Day 0
- Study drugs administered on Day 3 post-infection
  - Micafungin 5 mg/kg 2-3 daily doses ($5 \text{ mg/kg} \approx \text{human dose of } 100 \text{ mg}$)
  - Rezafungin 20 mg/kg single dose ($20 \text{ mg/kg} \approx \text{human dose of } 400 \text{ mg}$)
- MALDI-MSI to assess drug penetration at infection site

- Multiple doses of micafungin did not reach tissue drug levels achieved with single dose of rezafungin
- Rezafungin accumulated in necrotic areas of each lesion at 48 and 72 hours

GMS, Gomori methenamine silver; H&E, hematoxylin and eosin; MALDI-MSI, matrix-assisted laser desorption ionization mass spectrometry imaging.

Rezafungin Tissue Penetration With a Single Dose (Zhao et al, 2017)

Drug Levels of Rezafungin and Micafungin vs Mutant Prevention Concentration

Study Design

- CD-1 mice, no immunosuppression
- *C. albicans* (SC5314), 1x10^7 on Day 0
- Study drugs administered on Day 3 post-infection
  - Micafungin 5 mg/kg 2-3 daily doses (5 mg/kg ≈ human dose of 100 mg)
  - Rezafungin 20 mg/kg single dose (20 mg/kg ≈ human dose of 400 mg)
- Tissue drug levels measured at infection site, in lesions and in uninvolved/surrounding tissues

Rezafungin drug levels above the MPC for *C. albicans* and *C. glabrata*

* *p<0.001.
MALDI-MSI, matrix-assisted laser desorption ionization mass spectrometry imaging.

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## Evidence of Rezafungin Safety and Consistent Drug Exposures Across Populations

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Consistent rezafungin exposures observed, including in a wide range of renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic Impairment</td>
<td>No clinically relevant differences in mean exposure observed between moderate or severe hepatic impairment and healthy controls</td>
</tr>
<tr>
<td>Drug-Drug Interaction Studies</td>
<td>No notable drug interactions</td>
</tr>
<tr>
<td></td>
<td>No dose adjustments with rezafungin coadministration</td>
</tr>
<tr>
<td>QT Interval Study</td>
<td>Lack of effect on QT interval in healthy adults</td>
</tr>
</tbody>
</table>

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Rezafungin PK Profile in Healthy Adults

Long Plasma Half-Life and Minimal Metabolism Following IV Administration

Study Design
- Healthy human subjects, N=9
- Single 400 mg dose of radiolabeled rezafungin administered IV
- Collected blood, urine, and fecal samples over 60 days

Rezafungin accounted for ~77% total radiocarbon AUC
Metabolites accounted for <10% total plasma radioactivity AUC exposure
Consistent rezafungin exposures observed over a wide range of renal function

Rezafungin minimally metabolized and mainly excreted unchanged in feces
No dose adjustment expected for renal impairment

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AUC, area under the curve.
Rezafungin in Renal and Hepatic Impairment

**Details of Analyses**
- Exposure ($C_{\text{max}}$) following rezafungin 400 mg
  - By Renal Function: from subjects in STRIVE, estimated using a population PK model and Bayesian estimation
  - By Hepatic Function: from subjects with moderate or severe hepatic impairment (HI; Child-Pugh class B or C) and healthy matched controls in an open-label study

- Consistent RZF exposures over a wide range of renal function were observed in STRIVE data

- Mean RZF exposure in moderate or severe HI was modestly reduced (up to ~30% lower) vs matched healthy subjects

- Of 9 AEs in 7 subjects, 1 was considered related to rezafungin (mild headache in subject with moderate HI)

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*Renal impairment did not appear to affect rezafungin safety or efficacy in STRIVE

Differences in mean exposure in moderate or severe HI and healthy controls were not clinically relevant

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*Geometric Means with 95% confidence intervals.
Flanagan et al, SCCM 2020; Flanagan et al ICHS 2021; Cidara Therapeutics, Data on file (submitted, TIMM 2021)

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Rezafungin Demonstrated No Notable Drug-Drug Interactions

### Drug Interaction Study In Healthy Adults

<table>
<thead>
<tr>
<th>DRUG</th>
<th>POSSIBLE MECHANISM(S)</th>
<th>OBSERVATIONS</th>
<th>SUGGESTED ACTION</th>
</tr>
</thead>
</table>
| Tacrolimus    | CYP3A4, P-gp          | $\leftrightarrow C_{\text{max}}$  
$\downarrow$ AUC ~15% | No change in dose |
| Repaglinide   | CYP2C8, OATP          | $\leftrightarrow C_{\text{max}}$  
$\uparrow$ AUC ~15% | No change in dose |
| Metformin     | OCT, MATEs            | $\leftrightarrow C_{\text{max}}$  
$\leftrightarrow$ AUC | No change in dose |
| Rosuvastatin  | BCRP, OATP            | $\uparrow C_{\text{max}}$ ~12%  
$\uparrow$ AUC ~15% | No change in dose |
| Pitavastatin  | OATP                  | $\leftrightarrow C_{\text{max}}$  
$\leftrightarrow$ AUC | No change in dose |
| Caffeine      | CYP1A2                | $\leftrightarrow C_{\text{max}}$  
$\leftrightarrow$ AUC | No change in dose |
| Efavirenz     | CYP2B6                | $\leftrightarrow C_{\text{max}}$  
$\leftrightarrow$ AUC | No change in dose |
| Midazolam     | CYP3A                 | $\leftrightarrow C_{\text{max}}$  
$\leftrightarrow$ AUC | No change in dose |
| Digoxin       | CYP2B6                | $\leftrightarrow C_{\text{max}}$  
$\leftrightarrow$ AUC | No change in dose |

Single-center, open-label trial (N=26). Substrate drugs dosed alone for 3 weeks, then with rezafungin for 3 weeks.\(^1\)

No dose adjustments required for these commonly used drugs when rezafungin is co-administered.

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AUC, area under the curve; BCRP, breast cancer resistance protein; $C_{\text{max}}$, maximum plasma concentration; CYP, cytochrome P450; MATEs, multidrug and toxin extrusion protein; OATP, organic anion transporting polypeptides; OCT, organic cation transporter; P-gp, P-glycoprotein.

Rezafungin Phase 2 Treatment Trial

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Trial Not Powered for Inferential Statistical Analysis

mITT N=183

**REZAFUNGIN**
(N=122)*
400/400 mg N=76
400/200 mg N=46

**CASPOFUNGIN**
(N=61)*
70/50 mg

Optional Oral Fluconazole Step-down
800/400 mg

**Analysis Population**
- Intent-to-treat (ITT)
- Safety
- Microbiological Intent-to-treat (mITT) and had documented *Candida* infection

**Definition**
- All Randomized
- and received ≥1 dose of study drug

**N**
- 207
- 202 (97.6%)
- 183 (88.4%)

* ~21% invasive candidiasis (ITT)

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IC, invasive candidiasis; ITT, intent-to-treat; mITT, microbiological intent-to-treat
Summary of Rezafungin Efficacy (mITT Population)\textsuperscript{1}

<table>
<thead>
<tr>
<th></th>
<th>Rezafungin 400 mg/400 mg weekly (N=76)</th>
<th>Rezafungin 400 mg/200 mg weekly (N=46)</th>
<th>Caspofungin 70 mg/50 mg daily (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Day 14</td>
<td>60.5</td>
<td>69.7</td>
<td>70.5</td>
</tr>
<tr>
<td>PI Assessment of Clinical Response Day 14</td>
<td>67.2</td>
<td>80.4</td>
<td>43</td>
</tr>
<tr>
<td>All-Cause Mortality Day 30</td>
<td>15.8</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

EMA, European Medicines Agency; FDA, Food and Drug Administration; mITT, microbiological intent-to-treat; PI, principal investigator.


Rezafungin demonstrated similar efficacy vs. caspofungin

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### Efficacy Outcomes at Day 5 (mITT Population)\(^1\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rezafungin 400 mg/400 mg weekly</td>
<td>76</td>
</tr>
<tr>
<td>Rezafungin 400 mg/200 mg weekly</td>
<td>46</td>
</tr>
<tr>
<td>Rezafungin Pooled</td>
<td>122</td>
</tr>
<tr>
<td>Caspofungin 70 mg/50 mg daily</td>
<td>61</td>
</tr>
</tbody>
</table>

Note initial dose of 400 mg in both rezafungin-treated arms.

Rezafungin efficacy compared with caspofungin evident by day 5

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mITT, microbiological intention-to-treat.

Time to Negative Blood Culture

mITT: All randomized patients who received study drug and had documented Candida infection

Pooled rezafungin vs Caspofungin ($p=0.0016$ posthoc log-rank test)

- Rezafungin efficacy early in treatment course suggests clinical effect of high, front-loaded plasma drug exposure

mITT, microbiological intention-to-treat.
Time to Negative Blood Culture

mITT: All randomized patients who received study drug and had documented *Candida* infection

mITT2: Patients in mITT with positive blood culture within 12h before and 72h after enrollment

- Rezafungin efficacy early in treatment course suggests clinical effect of high, front-loaded plasma drug exposure
- More pronounced effect in mITT2 suggests patients with active infection may be more likely to benefit from potential clinical effect of front-loaded exposure

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mITT, microbiological intention-to-treat.

Efficacy Endpoints During Initial Days of Treatment (mITT Population – Patients with Candidemia Only)

Day 1

**Negative Blood Culture**

At 24 hours

- Pooled Rezafungin: 74.7% (71/96)
- Caspofungin: 53.3% (27/50)

At 48 hours

- Pooled Rezafungin: 84.5% (80/93)
- Caspofungin: 64.4% (32/49)

Day 5

**Efficacy Endpoints at Day 5**

- **Mycological Cure**
  - Pooled Rezafungin: 73.1% (68/93)
  - Caspofungin: 58.3% (28/48)

- **Overall Success**
  - Pooled Rezafungin: 64.5% (60/93)
  - Caspofungin: 52.1% (25/48)

---

mITT, microbiological intention-to-treat.

Time to Negative Blood Culture (mITT Population)\(^1\)

1. Data on file from STRIVE Phase 2 clinical trial.
2. Data on file. Of patients with confirmed Candida infection (positive blood culture), mITT population (%; n/N).

Rezafungin is in Phase 3 clinical development. Not registered in any country. Registration requirements differ internationally.
### Summary of Adverse Events (Safety Population)\(^1\)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rezafungin 400 mg/400 mg Weekly N=81</th>
<th>Rezafungin 400 mg/200 mg Weekly N=53</th>
<th>All Rezafungin (Pooled) N=134</th>
<th>Caspofungin 70 mg/50 mg Daily N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<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>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>

No concerning trends with rezafungin safety

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## Treatment-Emergent Adverse Events (≥10%, Safety Population)\(^1\)

<table>
<thead>
<tr>
<th>Treatment-emergent Adverse Event</th>
<th>Rezafungin 400 mg/400 mg Weekly N=81</th>
<th>Rezafungin 400 mg/200 mg Weekly N=53</th>
<th>All Rezafungin (Pooled) N=134</th>
<th>Caspofungin 70 mg/50 mg Daily 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>


No concerning trends with rezafungin safety

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Conclusions

Rezafungin 400 mg/200 mg dose demonstrated highest overall response, lowest all-cause mortality, and more rapid clearance of candidemia in STRIVE trial

Rezafungin 400 mg/200 mg dose now in Phase 3 trials

Adverse event data demonstrate the safety of rezafungin and its once-weekly dosing regimen

Rezafungin is in Phase 3 clinical development. Not registered in any country Registration requirements differ internationally
**Global Response** is defined as Clinical Response (as assessed by the Primary Investigator), Mycological Response and Radiological Response (for qualifying invasive candidiasis patients only).

EMA, European Medicines Agency; FDA, Food and Drug Administration.


### Phase 3 Trial Design Mirrors STRIVE Phase 2 Trial
Prospective, randomized, double-blind, international, >100 centers

**REZAFUNGIN**
N=92 in mITT population
400/200 mg

**CASPOFUNGIN**
N=92 in mITT population
70/50 mg

Optional Oral Fluconazole Step-down
6 mg/kg to nearest 200 mg

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*Global Response is defined as Clinical Response (as assessed by the Primary Investigator), Mycological Response and Radiological Response (for qualifying invasive candidiasis patients only).

EMA, European Medicines Agency; FDA, Food and Drug Administration.  
Rezafungin Phase 3 Prophylaxis Trial in Allogeneic BMT

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Rezafungin: The Potential For a Simplified Single Drug Paradigm

Antifungal Prophylaxis in Allogeneic Blood and Marrow Transplant Setting\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Current Antifungal Prophylaxis Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
</tr>
<tr>
<td>Fluconazole → Posaconazole or voriconazole</td>
</tr>
<tr>
<td>Posaconazole or voriconazole</td>
</tr>
<tr>
<td>Bactrim®, dapsone, or atovaquone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rezafungin Regimen in Ongoing Phase 3 Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rezafungin 400/200 mg once weekly</td>
</tr>
</tbody>
</table>

Transplant               Day
-10  0  10  20  30  40  50  60  70  80  90

Standard of care for
- Candida and Aspergillus
- Pneumocystis


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Trial Design

Phase 3, Prospective, Randomized, Double-Blind, International, Multicenter Trial¹

To evaluate efficacy and safety of rezafungin vs standard of care (azole plus TMP/SMX) against IFD caused by *Aspergillus*, *Candida*, and *Pneumocystis* in allogeneic BMT patients.

REZAFUNGIN (N=308)
400/200 mg once weekly

COMPARATOR (N=154)
400 mg fluconazole QD*
80 mg TMP/400 mg SMX QD

*Patients with acute GVHD can be switched to posaconazole

GVHD, graft-versus-host disease; IFD, invasive fungal disease; SMX, sulfamethoxazole; TMP, trimethoprim.

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Ongoing Phase 3 Trial
IFD Prophylaxis in allogeneic BMT

1º Endpoint: Fungal-free survival at Day 90

462 patients enrolled

Follow-up
Rezafungin for Treatment and Prophylaxis

Unique Properties of a Next-Generation Echinocandin

- **Potent and broad-spectrum activity** against *Candida, Aspergillus, and Pneumocystis*
  - includes *C. auris*, subset of azole- and echinocandin-resistant isolates, *Aspergillus* activity includes azole-resistant species

- **Enhanced PK**
  - extended half-life (~130 hours), once-weekly front-loaded dosing, and greater tissue penetration compared with micafungin
  - Front-loaded dosing may improve early outcomes, time to negative blood culture, and day 5 outcomes compared with caspofungin

- **Safety and DDI profile of the echinocandin class**
  - may spare myelosuppression, TDM, hepatic and renal toxicity, non-compliance, and complications of managing/avoiding DDIs

- **Dosing and administration**
  - once-weekly use inpatient and outpatient may support earlier hospital discharge

- **Phase 2 STRIVE trial**
  - demonstrated rezafungin safety and efficacy for 1st line treatment of documented candidemia and/or invasive candidiasis

- **Phase 3 ongoing**
  - ReSTORE: 1st line treatment of candidemia and/or invasive candidiasis v caspofungin, 2-4 weeks
  - ReSPECT: 1st line prophylaxis of *Candida, Aspergillus, and Pneumocystis* in alloBMT ± GVHD, vs fluconazole/posaconazole/Bactrim®, 90 days

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