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

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Disclosures

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Fungus is the next 'superbug' to threaten human health
The current treatment approaches for IFDs include three main classes of drugs:

- **Polyenes** (amphotericin B [AmB]); Amphotericin B lipid complex; Liposomal Amphotericin)

- **Azoles** (fluconazole, isavuconazole, itraconazole, posaconazole and voriconazole),

- **Echinocandins** (anidulafungin, caspofungin and micafungin)
# Range of activity of antifungal drugs

<table>
<thead>
<tr>
<th>Antifungal spectrum</th>
<th>AMB</th>
<th>5FC</th>
<th>FLU</th>
<th>ITR</th>
<th>VOR</th>
<th>POS</th>
<th>ISA</th>
<th>CAS</th>
<th>MIC</th>
<th>ANI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<td>++</td>
<td>++</td>
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<tr>
<td>Candida glabrata</td>
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<td>++</td>
<td>++</td>
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<tr>
<td>Candida parapsilosis</td>
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<tr>
<td>Candida tropicalis</td>
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<td>++</td>
<td>++</td>
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<tr>
<td>Candida krusei</td>
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<td>+</td>
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<tr>
<td>Candida lusitaniae</td>
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<tr>
<td>Aspergillus fumigatus</td>
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<tr>
<td>Cryptococcus neoformans</td>
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<tr>
<td>Mucorales</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>-</td>
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</tr>
<tr>
<td>Fusarium spp.</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
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</tr>
<tr>
<td>Scedosporium spp.</td>
<td>+</td>
<td>-</td>
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<td>+</td>
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</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>++</td>
<td>-</td>
<td>+</td>
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<td>++</td>
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<tr>
<td>Cocciidioides immitis</td>
<td>++</td>
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<tr>
<td>Histoplasma capsulatum</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>++</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class</th>
<th>Target</th>
<th>Administration</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyene</td>
<td>Ergosterol</td>
<td>Intravenous</td>
<td>Infusion reactions, hepatotoxicity, nephrotoxicity</td>
</tr>
<tr>
<td>Pyrimidine</td>
<td>Nucleic acid</td>
<td>Oral</td>
<td>Bone marrow suppression, liver toxicity</td>
</tr>
<tr>
<td>Azole</td>
<td>Ergosterol</td>
<td>Oral/Intravenous</td>
<td>Gastrointestinal upset, hepatotoxicity, liver failure</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>Cell wall</td>
<td>Intravenous</td>
<td>Infusion reactions, gastrointestinal upset, headache, liver toxicity</td>
</tr>
</tbody>
</table>

5FC, flucytosine; AMB, amphotericin B; ANI, anidulafungin; CAS, caspofungin; FLU, fluconazole; ISA, isavuconazole; ITR, itraconazole; MIC, micafungin; POS, posaconazole; VOR, voriconazole.

Adapted from Nett and Andes (2016).
### Interactions of mould-active azoles (strong CYP3A4 inhibitors) with coadministered targeted therapies

<table>
<thead>
<tr>
<th>COADMINISTERED AGENT</th>
<th>INTERACTION MECHANISM</th>
<th>EFFECT</th>
<th>RECOMMENDATIONS AND ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>Inhibition CYP3A4/2C9</td>
<td>↑ Ibrutinib exposure</td>
<td>420 mg standard dose, 280 mg if Fluco; 140 mg if Posa/vori</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>Inhibition CYP3A4/Pgp</td>
<td>↑ AUC</td>
<td>Monitor for side effect</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>Inhibition CYP3A4/2C9</td>
<td>↑ Ruxolitinib exposure</td>
<td>↓ dose 50%; monitor cytopenias</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Inhibition CYP3A4</td>
<td>↑ Imatinib exposure</td>
<td>Avoid combo</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Inhibition CYP3A4</td>
<td>↑ D. exposure, ↑ QT interval</td>
<td>Avoid combo, monitor ECG</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Inhibition CYP3A4</td>
<td>↑ N. exposure, ↑ QT inter</td>
<td>Avoid combo, monitor ECG</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Substrate CYP3A4</td>
<td>↓ TKI dosage</td>
<td>Avoid combo</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Inhibition CYP3A4</td>
<td>No effect</td>
<td>Monitor QTc</td>
</tr>
<tr>
<td>Midostaurin</td>
<td>Inhibition CYP3A4</td>
<td>↑ adverse reaction</td>
<td>Avoid combo, monitor QTc</td>
</tr>
<tr>
<td>Quirzatinib</td>
<td>Inhibition CYP3A4</td>
<td>↑ Quirzatinib exposure</td>
<td>↓ dose (induc 40 mg -&gt; 20 mg)</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Inhibition CYP3A4</td>
<td>↑ venetoclax exposure</td>
<td>↓ dose 50% if moderate; 75% if potent</td>
</tr>
</tbody>
</table>

Slide Courtesy: Prof Tony Pagliuca, KCH
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. <em>Candida</em>, <em>Aspergillus</em>, and <em>Pneumocystis</em> 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
Rezafungin Targets the Fungal Cell Wall

Increased permeability of the cell wall causes osmotic imbalance\(^1\)

Rezafungin inhibits production of \(1,3\-\beta\-D\-glucan\)\(^1\)

Fungal cell lysis occurs\(^1\)

- Fungicidal against \textit{Candida} spp.
- Fungistatic against \textit{Aspergillus} spp.\(^1\)
- Active against \textit{Pneumocystis} spp.\(^2,3\)


Rezafungin: *In Vitro* Activity
Rezafungin: Potent, Broad-Spectrum Activity Against *Candida* Species

*In Vitro Activity Comparable With Current Echinocandins*

<table>
<thead>
<tr>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)&lt;sup&gt;1-3*&lt;/sup&gt;</th>
<th><em>C. albicans</em>&lt;sup&gt;2†&lt;/sup&gt; (n=835)</th>
<th><em>C. glabrata</em>&lt;sup&gt;2†&lt;/sup&gt; (n=374)</th>
<th><em>C. tropicalis</em>&lt;sup&gt;1&lt;/sup&gt; (n=196)</th>
<th><em>C. krusei</em>&lt;sup&gt;1&lt;/sup&gt; (n=77)</th>
<th><em>C. parapsilosis</em>&lt;sup&gt;1&lt;/sup&gt; (n=329)</th>
<th><em>C. kefyr</em>&lt;sup&gt;2†&lt;/sup&gt; (n=52)</th>
<th><em>C. lusitaniae</em>&lt;sup&gt;3‡&lt;/sup&gt; (n=46)</th>
<th><em>C. guilliermondii</em>&lt;sup&gt;3‡&lt;/sup&gt; (n=27)</th>
<th><em>C. dubliensiis</em>&lt;sup&gt;3‡&lt;/sup&gt; (n=22)</th>
<th><em>C. auris</em>&lt;sup&gt;3‡&lt;/sup&gt; (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>0.06</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>
</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>

*CLSI broth microdilution methodology was employed for MIC determination (M27-A3).<sup>1-3</sup>*

<sup>1</sup>Clinical isolates collected internationally in the JMI Laboratories SENTRY Antimicrobial Surveillance Program (2016-2018).<sup>2</sup>

<sup>2</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>3</sup>

CLSI, Clinical and Laboratory Standards Institute; MIC, minimal inhibitory concentration.

# Rezafungin: Potent Activity Against *Aspergillus* Species

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

<table>
<thead>
<tr>
<th>A. <em>fumigatus</em> (n=183)</th>
<th>A. <em>flavus</em> (n=45)</th>
<th>Azole-resistant A. <em>fumigatus</em> (n=31)</th>
<th>A. lentulus (n=11)</th>
<th>A. calidoustus (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rezafungin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEC&lt;sub&gt;90&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.03</td>
<td>0.015</td>
<td><strong>Rezafungin</strong></td>
<td>0.12</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.03</td>
<td>0.015</td>
<td>Posaconazole</td>
<td>4</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>0.03</td>
<td>0.03</td>
<td>Voriconazole</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.015</td>
<td>0.03</td>
<td>Micafungin</td>
<td>0.06</td>
</tr>
</tbody>
</table>

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

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

<sup>‡</sup>Clinical isolates collected in the US and resistance genotypes confirmed by DNA sequence analysis (CYP51A only, n=13; TR<sub>94</sub>L98H, n=2; TR<sub>94</sub>Y121F/T289A, n=2; resistant/no CYP51A mutation, n=6; resistant/CYP51A status unknown, n=8).

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

Rezafungin: *In Vivo* Efficacy
Rezafungin Treatment: Disseminated Aspergillosis Mouse Model

Survival Following Treatment - *Aspergillus fumigatus*

**Study Design**
- ICR mice, n=10/arm, CPM-immunosuppressed
- *A. fumigatus* (ATCC 13073) $2 \times 10^4$ on Day 0
- Study drugs administered 1 h post-infection, as single dose or fractionated doses (bid x 5 days)
  - Amphotericin B 3 mg/kg total IP
  - Rezafungin 2 mg/kg total IP
- Rezafungin 20 mg/kg = human dose of 400 mg

100% survival rates with single dose or fractionated doses (bid x 5 days) of rezafungin or amphotericin B

Survival following single dose of rezafungin 2 mg/kg comparable to amphotericin B

CPM, cyclophosphamide; IP, intraperitoneal.
Rezafungin Prophylaxis: Invasive Candidiasis Mouse Model

Kidney Tissue Fungal Burden Following Administration of Prophylaxis – *Candida albicans*

![Graph showing fungal burden 24 hours after infection in CPM-induced neutropenic mouse model](image)

Rezafungin reduction of fungal burden is dependent on dose and timing of prophylaxis administration

At 20 mg/kg, rezafungin reduced CFU burden regardless of when prophylaxis was administered

CFU, colony-forming units; CPM; cyclophosphamide.

Survival Following Administration of Prophylaxis - *Aspergillus fumigatus*

**Study Design**

- ICR mice, n=6/arm, CPM-immunosuppressed
- *A. fumigatus* (ATCC 13073), 1.85x10⁴ on Day 0
- Study drugs administered
  - Amphotericin B 3 mg/kg IP one hour after infection as positive control
  - Rezafungin 5 mg/kg SC one hour after infection as positive control
  - Rezafungin 5 mg/kg SC, 10 mg/kg SC, or 20 mg/kg SC on Day -5, Day -3, or Day -1
  - Rezafungin 10 mg/kg = human dose of 200 mg
  - Rezafungin 20 mg/kg = human dose of 400 mg

Rezafungin reduction of fungal burden is dependent on dose and timing of prophylaxis administration

- 100% prophylaxis efficacy against *A. fumigatus* at human equivalent doses (10 and 20 mg/kg)
- Prophylaxis efficacious even administered 5 days pre-infection
- Longer durations of clinical protection may be seen as half-life >3 times that in mouse

CPM, cyclophosphamide; IP, intraperitoneal; SC, subcutaneous.

Rezafungin: PK/PD
Rezafungin High Exposure for Sustained Fungicidal Activity

Exposure Shape Matters for Antifungal Efficacy

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

High drug exposure early in therapy

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

Rezafungin: Phase 1 Data
Long Half-Life Enables Once-Weekly Dosing

Plasma Concentrations of Rezafungin In Healthy Adults

Single dose¹

Multiple doses¹

PK studies for single- and multiple-ascending doses reveal consistent results

Phase 3 Prophylaxis Trial Dosing Designed to Cover *Aspergillus*

**Simulated Rezafungin Plasma Concentration Profiles**

Rezafungin 400 mg initial dose followed by 200 mg once weekly selected for Phase 3

**Study Design**

1. Population PK model developed using Phase 1 data
2. Monte Carlo simulation conducted using baseline demographic data from 100 BMT patients
3. Simulated rezafungin plasma concentration profiles following rezafungin 400 mg initially and 200 mg weekly thereafter) displayed relative to *A. fumigatus* MEC<sub>100</sub> (≤0.03 ug/mL)<sup>2</sup>

>90% of simulated BMT patients had rezafungin concentrations above the *A. fumigatus* MEC<sub>100</sub> for 12 weeks

Lower doses of rezafungin expected to prevent *Pneumocystis* and *Candida* infections

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BMT, blood and marrow transplantation; MEC, minimal effective concentration.

# 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>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>CYP3A4, P-gp</td>
<td>↔ ( C_{\text{max}} ) \downarrow AUC \sim 15%</td>
<td>No change in dose</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>CYP2C8, OATP</td>
<td>↔ ( C_{\text{max}} ) \uparrow AUC \sim 15%</td>
<td>No change in dose</td>
</tr>
<tr>
<td>Metformin</td>
<td>OCT, MATEs</td>
<td>↔ ( C_{\text{max}} ) ↔ AUC</td>
<td>No change in dose</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>BCRP, OATP</td>
<td>\uparrow ( C_{\text{max}} ) \sim 12% \uparrow AUC \sim 15%</td>
<td>No change in dose</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>OATP</td>
<td>↔ ( C_{\text{max}} ) ↔ AUC</td>
<td>No change in dose</td>
</tr>
<tr>
<td>Caffeine</td>
<td>CYP1A2</td>
<td>↔ ( C_{\text{max}} ) ↔ AUC</td>
<td>No change in dose</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>CYP2B6</td>
<td>↔ ( C_{\text{max}} ) ↔ AUC</td>
<td>No change in dose</td>
</tr>
<tr>
<td>Midazolam</td>
<td>CYP3A</td>
<td>↔ ( C_{\text{max}} ) ↔ AUC</td>
<td>No change in dose</td>
</tr>
<tr>
<td>Digoxin</td>
<td>CYP2B6</td>
<td>↔ ( C_{\text{max}} ) ↔ AUC</td>
<td>No change in dose</td>
</tr>
</tbody>
</table>

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

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

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.

¹ Ong, et al. EBMT19 2019; poster B196.
Rezafungin Lack of Effect on QT Interval in Healthy Adults

- First definitive QT/QTc study completed for any echinocandin
- Rezafungin IV injection in single doses up to 1400 mg did not prolong the QT interval\(^1\)

\[\text{Rezafungin Concentration (ng/mL)}\]

\[\text{Moxifloxacin Concentration (ng/mL)}\]

\[\text{Intercept} = -0.222 \text{ msec}; \text{Slope} = -0.000014 \text{ msec/(ng/mL)}\]

\[\text{P value} = 0.7379; 90\% \text{CI for slope is -0.000085 to 0.000056}\]

\[\text{Intercept} = -3.114 \text{ msec}; \text{Slope} = 0.004785 \text{ msec/(ng/mL)}\]

\[\text{P value} = <.0001; 90\% \text{CI for slope is 0.002859 to 0.006711}\]

Rezafungin at supratherapeutic doses did not impact QT interval, cardiac contractility, or ejection fraction

Rezafungin Phase 2 Treatment Trial
Study design\textsuperscript{1,2}
A Phase 2, prospective, double-blind, randomized trial conducted in 63 centers across 10 countries

Study aims\textsuperscript{1,2}
Evaluate the safety and efficacy of once-weekly IV rezafungin vs once-daily caspofungin in the treatment of candidemia and/or IC

Primary efficacy endpoint\textsuperscript{1-4}
Overall response (mycological eradication and resolution of signs of candidemia and/or IC) at Day 14 (mITT population; all randomized subjects who received any amount of study drug and who had documented \textit{Candida} infection)

Secondary efficacy endpoints\textsuperscript{1-4}
\begin{itemize}
\item Mycological eradication at Day 5 and Day 28 (mITT population)
\item Principal investigator assessment of clinical response at Day 14
\item Time to first of two negative blood cultures
\item All-cause mortality at Day 30
\end{itemize}

Safety endpoints\textsuperscript{1-4}
TEAEs, SAEs, mortality (safety population)
Rezafungin demonstrated similar efficacy vs. caspofungin
Overall Response by *Candida* Species at Day 14 (mITT Population)³

Rezafungin efficacy compared with caspofungin consistent in variety of *Candida* species

Rezafungin 400 mg/400 mg weekly (N=76)
- Rezafungin 400 mg/200 mg weekly (N=46)
- Caspofungin 70 mg/50 mg daily (N=61)

³ mITT, microbiological intent-to-treat.

1. Thompson, et al. ID week 2020;poster 1284.
Time to negative blood culture was significantly lower in the pooled rezafungin group compared to caspofungin Post-hoc log-rank test p = 0.0016

Rezafungin efficacy early in treatment course suggests clinical effect of front-loaded plasma drug exposure and its importance as a pharmacometric predictor of efficacy

All Rezafungin (Pooled) 103 25 13 10 5 5 5 3 2
Caspofungin 53 23 17 11 9 9 8 8 6

mITT, microbiological intention-to-treat.
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 Phase 3 Development
# Rezafungin Phase 3 Development Plan

<table>
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<th>Potential Indication</th>
<th>PHASE 3 TREATMENT TRIAL</th>
<th>PHASE 3 PROPHYLAXIS TRIAL</th>
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<td>Treatment of candidemia &amp; invasive candidiasis&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Prophylaxis against IFD caused by <em>Aspergillus</em>, <em>Candida</em> &amp; <em>Pneumocystis</em> in allogeneic blood and marrow transplant patients&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Trial Size</td>
<td>184 evaluable patients Primary Evaluable Population Size&lt;sup&gt;2&lt;/sup&gt;</td>
<td>462 patients&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>Trial Status</td>
<td>Ongoing</td>
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IFD, invasive fungal disease.

Rezafungin Phase 3 Treatment Trial
Study design
A Phase 3, prospective, double-blind, randomized, international, multicenter trial

Study aims
Evaluate the efficacy and safety of once-weekly IV rezafungin vs once-daily caspofungin followed by optional oral fluconazole step-down in the treatment of candidemia and/or IC

Primary efficacy endpoint
- US FDA: noninferiority in subjects randomized to rezafungin compared with caspofungin, on ACM at Day 30 (±2 days) (mITT population)
- EMA: noninferiority in subjects randomized to rezafungin compared with caspofungin, on global cure and mycological eradication at Day 14 (±1 day) (mITT population)

Evaluated population
- mITT population: all subjects in safety population who had documented Candida infection
- 184 patients in primary evaluable population

ACM, all-cause mortality; EMA, European Medicines Agency; IC, invasive candidiasis; mITT, microbiological intent-to-treat.

Phase 3 Trial Design Mirrors STRIVE Phase 2 Trial

**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

*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
Rezafungin: The Potential For a Simplified Single Drug Paradigm

Antifungal Prophylaxis in Allogeneic Blood and Marrow Transplant Setting


Rezafungin prophylaxis could prevent *Candida, Aspergillus, and Pneumocystis* infections—including drug-resistant species.
Study design
A Phase 3, prospective, randomized, double-blind, international, multicenter trial

Study aims
Evaluate the efficacy and safety of once-weekly IV rezafungin compared with standard of care (azole plus TMP/SMX) against IFD caused by Aspergillus, Candida, and Pneumocystis in allogeneic blood and marrow transplant patients

Primary efficacy endpoint
Fungal-free survival at Day 90 (±7 days) compared to standard of care

Enrolled population
462 enrolled patients

IFD, invasive fungal disease; TMP/SMX, trimethoprim-sulfamethoxazole.
Trial Design

**REZAFUNGIN**  
(N=300)  
400/200 mg once weekly

**COMPARATOR**  
(N=150)  
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.

Summary of 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**
  - Serves 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

**Potential role in tougher-to-treat documented Candida infections, early hospital discharge, outpatient treatment when step-down oral therapy is not warranted, and prophylaxis to replace azoles and Bactrim® for certain immunocompromised/high-risk patients**