Patient-Level Meta-Analysis of Efficacy and Safety from STRIVE and ReSTORE: Randomized, Double-blinded, Multicenter Phase 2 and Phase 3 Trials of Rezafungin in the Treatment of Candidemia and/or Invasive Candidiasis

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Candidemia and Invasive Candidiasis
“Fungal Diseases as Neglected Pathogens”

- Global annual occurrence of invasive candidiasis: ~700,000\(^1,2\)
- From the Emerging Infections Program: 56% of patients initially treated with fluconazole grew non-*albicans* species and 10.6% fluconazole-treated patients had a fluconazole-resistant isolate\(^3\)
- Guidelines recommend empirical treatment with a first-generation echinocandin for patients with a high risk of invasive candidiasis or candidemia – is it enough?\(^4-6\)
  - Patients classified as low-risk for Candida BSI and therefore left untreated had ~2x higher mortality (69% for untreated vs 35% for treated patients)\(^4\)
  - Dosing of first-generation echinocandins, defined before modern PK/PD era, may be inadequate in the face of increasing echinocandin MICs (*FKS* mutations) and pharmacokinetics in critically ill, moderate-severe hepatic impairment, obesity, ECMO, and burn settings

About Rezafungin

- Next-generation, once-weekly IV echinocandin
- Analog of anidulafungin, designed for increased stability and improved PK\(^1\)
- Long-acting PK enables once-weekly dosing and front-loaded plasma exposure

<table>
<thead>
<tr>
<th>Potential Indication</th>
<th>PHASE 3 TREATMENT TRIAL</th>
<th>PHASE 3 PROPHYLAXIS TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ReSTORE</td>
<td>ReSPECT</td>
</tr>
<tr>
<td>Treatment of candidemia &amp; invasive candidiasis(^2)</td>
<td>Prophylaxis against IFD caused by <em>Aspergillus, Candida &amp; Pneumocystis</em> in allogeneic blood and marrow transplant patients(^3)</td>
<td></td>
</tr>
<tr>
<td>Trial Size</td>
<td>187 patients in primary evaluable population (mITT)(^2)</td>
<td>462 patients(^3)</td>
</tr>
<tr>
<td>Trial Status</td>
<td>Complete(^a)</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

IFD=invasive fungal disease; PK=pharmacokinetics.
\(^a\)Study sites in China are still recruiting patients for submission of rezafungin to the Center for Drug Evaluation in China.
Integrated Analysis of Phase 2 and Phase 3 Data of Rezafungin for the Treatment of Candidemia and/or IC

STRIVE and ReSTORE were Similarly Designed

IC=invasive candidiasis; mITT=modified intent to treat.

The rezafungin arm included optional oral step-down to placebo, to maintain the study blind.

mITT population: all subjects (Ph2+Ph3) who received ≥1 dose of study drug and had documented Candida infection (candidemia and/or IC based on systemic signs and mycological confirmation).

Primary endpoints not pooled were Overall Response (Phase 2) and Global Response (Phase 3).

REZAFUNGIN 400 mg/200 mg\(^a\) once weekly (QWk). (N=139 combined)\(^b\)

CASPOFUNGIN 70 mg/50 mg once daily (QD). (N=155 combined)\(^b\)
with optional oral step-down\(^a\) to fluconazole 6 mg/kg to nearest 200 mg QD

Primary\(^c\): All-cause mortality at Day 30

Adverse events

Secondary/exploratory

– Mycological response at Day 5

– Time to first negative blood culture

IC=invasive candidiasis; mITT=modified intent to treat.

\(^a\)The rezafungin arm included optional oral step-down to placebo, to maintain the study blind.

\(^b\)mITT population: all subjects (Ph2+Ph3) who received ≥1 dose of study drug and had documented Candida infection (candidemia and/or IC based on systemic signs and mycological confirmation).

\(^c\)Primary endpoints not pooled were Overall Response (Phase 2) and Global Response (Phase 3).
Demographics and Characteristics at Baseline
mITT Population – Integrated Analysis of Phase 2 and Phase 3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rezafungin QWk (N=139)</th>
<th>Caspofungin QD (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD, (range)</td>
<td>59.8 ± 15.7 (19, 91)</td>
<td>60.8 ± 15.0 (20, 93)</td>
</tr>
<tr>
<td>≥65 years, n (%)</td>
<td>57 (41.0)</td>
<td>63 (40.6)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>49 (35.3)</td>
<td>65 (41.9)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>24 (17.3)</td>
<td>34 (21.9)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>11 (7.9)</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>White</td>
<td>95 (68.3)</td>
<td>106 (68.4)</td>
</tr>
<tr>
<td>Othera</td>
<td>9 (6.5)</td>
<td>7 (4.5)</td>
</tr>
<tr>
<td>BMI, kg/m², mean ±SD</td>
<td>25.78 ± 7.8</td>
<td>25.12 ± 6.02</td>
</tr>
<tr>
<td>ANC &lt;500 µL b,c, n (%)</td>
<td>7 (5.0)</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candidemia only</td>
<td>100 (71.9)</td>
<td>115 (74.2)</td>
</tr>
<tr>
<td>Invasive candidiasis d</td>
<td>39 (28.1)</td>
<td>40 (25.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>characteristic</th>
<th>Rezafungin QWk (N=139)</th>
<th>Caspofungin QD (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified APACHE II SCORE, n (%)c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>21 (15.1)</td>
<td>26 (16.8)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>116 (83.5)</td>
<td>126 (81.3)</td>
</tr>
<tr>
<td>Geographic region, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>43 (30.9)</td>
<td>46 (29.7)</td>
</tr>
<tr>
<td>Europe/Israel/Turkey</td>
<td>67 (48.2)</td>
<td>76 (49.0)</td>
</tr>
<tr>
<td>Asia Pacific (ex China and Taiwan)</td>
<td>21 (15.1)</td>
<td>27 (17.4)</td>
</tr>
<tr>
<td>China/Taiwan</td>
<td>8 (5.8)</td>
<td>6 (3.9)</td>
</tr>
</tbody>
</table>

aIncludes American Indian or Alaska native and not reported.
bAt randomization.
cReported for patients with data available.
dIC group includes some subjects with both deep tissue infection and candidemia.

Groups were well balanced at baseline (mITT population = 294)

ANC=absolute neutrophil count; APACHE=Acute Physiology and Chronic Health Evaluation II; BMI=body mass index; QD=once daily; QWk=once weekly; SD=standard deviation.
Primary Endpoint: All-Cause Mortality at Day 30
mITT Population – Phase 2, Phase 3, and Integrated

Ph3 established rezafungin NI (20% NI margin)
Difference (95% CI)
2.4 (–9.7 to 14.4)

Difference (95% CI)\(^b\)
–1.5 (–10.7 to 7.7)

Integrated analysis
All-Cause Mortality at Day 30 was comparable between once-weekly rezafungin and once-daily caspofungin

All-Cause Mortality at Day 30, % (n/N)

Phase 2
- Rezafungin once weekly: 8.7% (4/46)
- Caspofungin once daily: 16.4% (10/61)

Phase 3
- Rezafungin once weekly: 23.7% (22/93)
- Caspofungin once daily: 21.3% (20/94)

Integrated
- Rezafungin once weekly: 18.7% (26/139)
- Caspofungin once daily: 19.4% (30/155)

NI=non-inferiority.
\(^a\)Subjects who died on or before Day 30, or with unknown survival status.
\(^b\)Calculated using stratified analysis by study and by part A and B of STRIVE.
Primary endpoint: Cure Rates at Day 14
mITT Population – Phase 2, Phase 3

Phase 2
Overall Cure\(^a\)
- Rezafungin once weekly: 76.1% (35/46)
- Caspofungin once daily: 67.2% (41/61)

Non-integrated analysis
Rates in each trial were comparable between treatments

Phase 3
Global Cure\(^b\)
- Rezafungin once weekly: 59.1% (55/93)
- Caspofungin once daily: 60.6% (57/94)

\(\text{NI=non-inferiority.}\)

\(^a\)Overall Cure (Phase 2): resolution of systemic signs attributable to candidemia or invasive candidiasis AND mycological eradication as demonstrated by a single tissue/fluid culture or 2 negative blood cultures at least 12 hours apart.

\(^b\)Global Cure (Phase 3): investigator assessment of clinical cure AND mycological eradication as demonstrated by a single negative blood or tissue/fluid culture AND (if pertinent) improvement or resolution of evidence of invasive candidiasis on radiographic imaging.
Early Efficacy Outcomes Assessed in Phase 2 and Phase 3 Suggest Potential Benefit of High, Front-Loaded Drug Exposure

Exposure Shape Matters for Antifungal Efficacy

Secondary and Exploratory Endpoints
• Negative blood culture at 24 h and 48 h
• Mycological cure at Day 5
• Time to first negative blood culture

Patient Subgroups
• Positive blood culture proximal to randomization (within 12 hours before or 72 hours after randomization)
• Candidemia-only as final diagnosis (including all with a positive blood culture)

Outcomes in the Initial Days of Treatment
mITT Population – Integrated – Secondary and Exploratory Endpoints

**Exploratory Endpoint:**
Negative Blood Culture

**Day 1**
- At 24 hours: 60.0% (63/105) for Rezafungin, 49.1% (57/116) for Caspofungin
- At 48 hours: 77.7% (80/103) for Rezafungin, 63.5% (73/115) for Caspofungin

**Day 5**
- At 24 hours: 80.0% (80/100) for Rezafungin, 77.7% (78/103) for Caspofungin
- At 48 hours: 63.5% (73/115) for Rezafungin, 67.8% (78/115) for Caspofungin

**Secondary Endpoint:**
Efficacy at Day 5

- Rezafungin once weekly vs. Caspofungin once daily:
  - Difference (95% CI): 12.9 (1.5 to 24.3)

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aSubjects with positive blood culture at Screening.
bCalculated using stratified analysis by study and by part A and B of STRIVE.
cMycological eradication rates for subjects with candidemia only.
Mycological Eradication at Day 5
mITT Population – Integrated – Secondary Endpoint

Integrated analysis

More pronounced effect in patients with a positive blood culture proximal to randomization

Suggests benefit from the potential clinical effect of front-loaded exposure

Difference (95% CI)

80.0% (80/100)

75.5% (40/53)

Difference (95% CI)

67.8% (78/115)

54.9% (39/71)

**Candidemia Only**

**Positive Blood Culture Proximal to Randomization**

Rezafungin once weekly

Caspofungin once daily

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*a* Calculated using stratified analysis by study and by part A and B of STRIVE.

*b* Positive culture from blood drawn within 12 hours prior to randomization or within 72 hours after randomization.
Exploratory Endpoint: Faster Time to First Negative Blood Culture

mITT Population – Integrated

Integrated analysis

Rezafungin once weekly eradicated fungi faster than caspofungin once daily

- Pooled Rezafungin (400/200 mg)
- Pooled Caspofungin (70/50 mg)

Log-Rank Test p-value (pooled) = 0.0051

p-value for the pooled groups is from a stratified log-rank test with Study ID and part as a stratum.
Exploratory Endpoint: Faster Time to First Negative Blood Culture

mITT Population – Integrated

Integrated analysis: a more pronounced effect for rezafungin seen in patients with positive blood culture proximal to randomization

Patients with positive blood culture at Screening

Patients with positive blood culture proximal to randomization

P-values for the pooled groups is from a stratified log-rank test with Study ID and part as a stratum.

*Positive culture from blood drawn within 12 hours prior to randomization or within 72 hours after randomization.
### Summary of Adverse Events
**Safety Population – Integrated**

Rezafungin was generally well tolerated and had a similar safety profile to caspofungin.

<table>
<thead>
<tr>
<th>Adverse Event (AE)</th>
<th>Proportion of Patients Who Experienced an AE, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rezafungin once weekly N=151</td>
</tr>
<tr>
<td>≥1 TEAE</td>
<td>138 (91.4)</td>
</tr>
<tr>
<td>Study drug-related</td>
<td>22 (14.6)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Caspofungin once daily N=166</td>
</tr>
<tr>
<td>Serious AE</td>
<td>83 (55.0)</td>
</tr>
<tr>
<td>Study drug-related</td>
<td>3 (2.0)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>TEAE leading to study drug discontinuation</td>
<td>14 (9.3)</td>
</tr>
<tr>
<td></td>
<td>15 (9.0)</td>
</tr>
</tbody>
</table>

AE: adverse event; TEAE: treatment-emergent AE.

<sup>a</sup>5 AEs assigned as study drug-related in the rezafungin group, including 2 serious AEs, were associated with placebo administration during blinded study drug administration.
Summary

• Rezafungin is a next-generation once-weekly echinocandin in development for treatment of candidemia and IC and for prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp. in blood and marrow transplantation.

• Rezafungin was found to be non-inferior to caspofungin for both of its primary endpoints (all-cause mortality at Day 30, US FDA; global cure at Day 14, EMA) – Latebreaker Poster #L0244.

• Rezafungin had a similar safety profile to that of caspofungin.

• In an exploratory analysis, rezafungin had a faster time to negative blood culture, suggesting the potential clinical effect of front-loaded exposure.

• Integrated analysis of the Phase 2 and Phase 3 trials for rezafungin supports the conclusion that rezafungin is efficacious for the treatment of candidemia and IC.