All-cause and attributable mortality in invasive candidiasis and/or candidaemia with rezafungin and caspofungin treatment: outcomes from the ReSTORE trial

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About Rezafungin

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

### PHASE 3 TREATMENT TRIAL | PHASE 3 PROPHYLAXIS TRIAL
---|---
**Potential Indication** | **Prophylaxis against IFD caused by *Aspergillus, Candida & Pneumocystis* in allogeneic blood and marrow transplant patients\(^3\)**

<table>
<thead>
<tr>
<th>Treatment of candidaemia &amp; invasive candidiasis(^2)</th>
<th><strong>Trial Size</strong></th>
<th>187 patients in primary evaluable population (mITT)(^2)</th>
<th>462 patients(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Status</strong></td>
<td>Complete(^a)</td>
<td>Ongoing</td>
<td></td>
</tr>
</tbody>
</table>

*Study sites in China are still recruiting patients for submission of rezafungin to the Center for Drug Evaluation in China.*

References:

Abbreviations:
IFD, invasive fungal disease; PK, pharmacokinetics.
Introduction/background

ReSTORE (NCT03667690) was a global, randomised, double-blind, double-dummy, Phase 3 non-inferiority trial, evaluating the efficacy and safety of rezafungin and caspofungin in the treatment of candidaemia and/or invasive candidiasis.¹

References

ReSTORE study design

**Rezafungin**
- Dose: 400/200 mg (QWk) N=93 (mITT population)
- Week 1: 400 mg
  - Day 1, 5, 14
- Optional dose: 200 mg
  - Day 30

**Caspofungin**
- Dose: 70/50 mg (QD) N=94 (mITT population)
- Week 1: 70 mg
  - Day 1
- Optional dose: 50 mg
  - Days 2 to 28

**Global cure (EMA Primary Endpoint)**
- Week 1: 2
- Week 2 to 4: 3
- Week 5: 5

**ACM (FDA Primary Endpoint)**
- Week 6 to 7
- Week 8: 6
- Week 9: 7

**End of follow-up period**
- Week 9

- Adults diagnosed with candidaemia and/or invasive candidiasis (by systemic manifestations and mycological confirmation) were randomised to receive rezafungin once-weekly IV infusion (Week 1: 400 mg; Weeks 2–4: 200 mg) or once daily caspofungin (Day 1: 70 mg; Days 2–28: 50 mg) for ≥14 days (≤4 weeks)

- Oral step-down treatment (caspofungin arm: fluconazole; rezafungin arm: placebo), was allowed from Day 4 for subjects with resolved/stable signs and symptoms of C/IC and negative blood cultures

**References**

**Abbreviations:**
- ACM, all-cause mortality
- IV, intravenous
- mITT, modified intention to treat
ReSTORE analysis methodology

• The current analysis examined all-cause mortality (ACM) and therapeutic step-down data from the ReSTORE trial¹

• Endpoints examined (mITT population):*
  – Day 30 (-2 days) ACM (20% non-inferiority margin)
  – Deaths attributable to candidaemia/invasive candidiasis through Day 59 (independent data review committee assessment)
  – Duration of treatment exposure
  – The proportion receiving step-down therapy

*All randomised subjects receiving ≥1 study drug dose

References

Abbreviations:
ACM, all-cause mortality; mITT, modified intention to treat.
Results: study population

The analysis included 93 subjects in the rezafungin arm and 94 in the caspofungin arm (mITT population).\(^1\)

<table>
<thead>
<tr>
<th>Baseline demographics and characteristics (mITT population)</th>
<th>Rezafungin (400/200 mg) (N=93)</th>
<th>Caspofungin (70/50 mg) (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (range), years</td>
<td>59.5 ± 15.8 (19–89)</td>
<td>61.9 ± 14.6 (20–91)</td>
</tr>
<tr>
<td>Age &lt;65 years, n (%)</td>
<td>55 (59.1)</td>
<td>56 (59.6)</td>
</tr>
<tr>
<td>Age ≥65 years, n (%)</td>
<td>38 (40.9)</td>
<td>38 (40.4)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62 (66.7)</td>
<td>56 (59.6)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (33.3)</td>
<td>38 (40.4)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>23 (24.7)</td>
<td>31 (33.0)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>5 (5.4)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>White</td>
<td>59 (63.4)</td>
<td>55 (58.5)</td>
</tr>
<tr>
<td>Other/not reported</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Final diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candidaemia-only, n (%)</td>
<td>64 (68.8)</td>
<td>67 (71.3)</td>
</tr>
<tr>
<td>Invasive candidiasis, n (%)(^a)</td>
<td>29 (31.2)</td>
<td>27 (28.7)</td>
</tr>
<tr>
<td>Modified APACHE II score(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>12.3 ± 7.54</td>
<td>13.0 ± 7.18</td>
</tr>
<tr>
<td>≥20, n (%)</td>
<td>12 (12.9)</td>
<td>17 (18.21)</td>
</tr>
<tr>
<td>&lt;20, n (%)</td>
<td>80 (86.0)</td>
<td>77 (81.9)</td>
</tr>
<tr>
<td>Mean BMI, kg/m(^2) ± SD</td>
<td>25.5 ± 7.19</td>
<td>24.3 ± 6.22</td>
</tr>
<tr>
<td>ANC &lt;500/μL, n (%)</td>
<td>7 (7.5)</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>Mechanically ventilated at baseline, n (%)</td>
<td>16 (17.2)</td>
<td>28 (29.8)</td>
</tr>
</tbody>
</table>

mITT population: all subjects with documented *Candida* infection based on central laboratory evaluation (blood culture or a culture from a normally sterile site obtained ≤4 days [96 hours] before randomisation) receiving ≥1 dose of study drug.

\(^a\) Patients who progressed from candidaemia to invasive candidiasis based on radiological and/or tissue/fluid culture assessment through Day 14.

\(^b\) Reported for patients with APACHE II score data available.

References
Results: Day 30 ACM rate

Day 30 ACM rate was **23.7%** (rezafungin arm) and **21.3%** (caspofungin arm).†

References


†US FDA primary endpoint†
Results: Day 30 ACM versus other Phase 3 echinocandin data

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 30 ACM (%)</th>
<th>ACU</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin (^2)</td>
<td>25.3%</td>
<td>63/249</td>
<td></td>
</tr>
<tr>
<td>Micafungin (^2)</td>
<td>28.3%</td>
<td>153/541</td>
<td></td>
</tr>
<tr>
<td>Anidulafungin (^2)</td>
<td>22.7%</td>
<td>29/128</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations:
ACM, all-cause mortality.
Results: deaths attributable to candidaemia/invasive candidiasis

Through Day 59, 5 (5.4%) deaths were attributable to candidaemia/invasive candidiasis in the rezafungin arm and 7 (7.4%) in the caspofungin arm.*

<table>
<thead>
<tr>
<th>Patient classification, n(%)</th>
<th>Attributable deaths**†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rezafungin (400/200 mg)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Cardiorespiratory failure</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>

*Independent data review committee assessment.
†Data were missing for 1 death in the rezafungin group, which the treating investigator considered not attributable to candidaemia/invasive candidiasis.

References

Abbreviations:
mITT, modified intention to treat.
Results: duration of IV therapy and step-down data

- Median duration of IV therapy exposure was 14 days in both arms.
- A switch to oral therapy was implemented for 25.8% (24/93) of the rezafungin arm and 36.2% (34/94) of the caspofungin arm.
- Overall, 83.4% (20/24; rezafungin arm) and 61.8% (21/34; caspofungin arm) of patients receiving oral step-down treatment met the criteria for step down by Day 7–9.

Abbreviations:
IV, intravenous.

References
Conclusions

- Rezafungin for injection demonstrated non-inferiority, versus caspofungin, concerning Day 30 ACM.
- Mortality due to candidaemia/invasive candidiasis was low in both treatment groups during the study period.
- Median duration of IV therapy was similar in both arms, with >25% of patients meeting oral step-down criteria in each treatment group.

References

Abbreviations:
ACM, all-cause mortality; IV, intravenous.
Disclosures and funding

Disclosures

**GR Thompson**: grants and consulting fees from Amplyx, Astellas, Cidara, F2G, and Manye; grants from Merck; and data safety monitoring board membership for Pfizer, outside of the submitted work.

**OA Cornely**: reports grants or contracts from Amplyx, Basilea, Bundesministerium für Bildung und Forschung, Cidara, German Center for Infection Research, European Union Directorate-General for Research and Innovation (101037867), F2G, Gilead, Matinas, MedPace, MSD, Mundipharma, Octapharma, Pfizer, and Scynexis; consulting fees from AbbVie, Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, IQVIA, Janssen, Matinas, MedPace, Menarini, Molecular Partners, Noxxon, Octapharma, Parades, Pfizer, Pharma Support America, Scynexis, and Seres; honoraria from Abbott, AbbVie, Al-Jazeera Pharmaceuticals, Astellas, Gilead, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, Nosando, Pfizer, and Shionogi; payment for expert testimony from Cidara; data safety monitoring board or advisory board membership for Actelion, Allerica, Cidara, Entasis, IQVIA, Janssen, MedPace, Paratek, Pharma Support America, Pulmocide, Shionogi, and The Prime Meridian Group; a patent at the German Patent and Trade Mark Office (DE 10 2021 113 007.7); stocks from CoRe Consulting; and is a board member of German Society for Haematology and Medical Oncology, Deutsche Gesellschaft für Information und Wissen, ECMM European Confederation of Medical Mycology, International Society for Human & Animal Mycology, Mycoses Study Group–Education and Research Consortium, and Wiley, outside of the submitted work.

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**BJ Kullberg**: independent data review committee membership for Cidara. GRT reports grants and consulting fees from Amplyx, Astellas, Cidara, F2G, and Manye; grants from Merck; and data safety monitoring board membership for Pfizer, outside of the submitted work.

**M Kolleff**: grants from Barnes-Jewish Hospital Foundation and consulting fees from Merck, Pfizer, and Shionogi, outside of the submitted work.

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**M Bassetti**: honoraria from and membership of data safety monitoring board or advisory board for Angelini, Cidara, Gilead, Menarini, MSD, Pfizer, and Shionogi, outside of the submitted work.

**AF Das**: consulting fees from Cidara.

**PG Pappas**: grants from and data review committee membership for Cidara; grants from Astellas, Scynexis, and Merck; and advisory board membership for F2G, outside of the submitted work.

**T Sandison**: employee of and stocks in Cidara. All other authors declare no competing interests.

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**STRIVE study**: Cidara Therapeutics were involved in trial design, execution, and data analysis. Cidara Therapeutics and Mundipharma were involved in trial reporting.