ReSTORE: Efficacy and Safety Results of the Phase 3, Noninferiority Trial of Rezafungin in the Treatment of Candidemia and/or Invasive Candidiasis (IC)

G.R. Thompson III,¹ A. Soriano,² O.A. Cornely,³ B. J. Kullberg,⁴ M. Kollef,⁵ J. Vazquez,⁶ P.M. Honore,⁷ M. Bassetti,⁸ J. Pullman,⁹ M. Chayakulkeeree,¹⁰ I. Poromanski,¹¹ C. Dignani,¹² A.F. Das,¹³ T. Sandison,¹³ P.G. Pappas¹⁴ on behalf of the ReSTORE Trial investigators

¹Univ of California Davis Medical Center, Davis, CA, USA; ²Hospital Clinic de Barcelona, IDIBAPS, Univ of Barcelona, Spain; ³Univ of Cologne and Univ Hospital Cologne, Excellence Center for Medical Mycology (ECMM), Cologne, Germany; ⁴Radboud Univ Medical Center, Nijmegen, The Netherlands; ⁵Washington Univ, St. Louis, MO, USA; ⁶Augusta Univ, Augusta, GA, USA; ⁷Brugman Univ Hospital, Brussels, Belgium; ⁸Univ of Genoa, Genoa, Italy; ⁹Mercury Street Medical, Butte, MT, USA; ¹⁰Mahidol Univ, Bangkok, Thailand; ¹¹Univ Multiprofile Hospital Active Treatment and Emergency Medicine N.I. Pirogov EAD, Sofia, Bulgaria; ¹²PSI-CRO, Durham, NC, USA; ¹³Cidara Therapeutics, Inc., San Diego, CA, USA; ¹⁴Univ of Alabama at Birmingham, Birmingham, AL, USA

ECCMID 2022 Poster #L0244
Acknowledgements

• The patients, investigators, and site personnel who participated in ReSTORE are gratefully acknowledged.

Disclosures

• Presenter (G.R. Thompson, III): Research grants (Astellas, Cidara, Mayne, Merck, Scynexis, F2G); Advisory (Astellas, Cidara, Mayne, F2G, Pfizer)

• Funding/Support: Poster preparation support was provided by T. Chung (Cidara Therapeutics). Cidara Therapeutics sponsored and funded the ReSTORE trial and had a role in the trial design, data collection, and analysis, and in the decision to submit these data for presentation.
ReSTORE: a Phase 3 Global Trial of Rezafungin in the Treatment of Candidemia and/or IC

- Rezafungin is a next-generation 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.
- Study Objective: To evaluate the efficacy and safety of rezafungin once weekly vs caspofungin once daily, with optional oral step-down to fluconazole in the caspofungin arm, in the treatment of documented candidemia and/or IC.

To maintain blinding, the rezafungin arm included oral placebo administered once daily.

N values are presented for the mITT population, comprising all subjects in safety population who had documented Candida infection.

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

Study Design of ReSTORE (NCT03667690)
- Prospective, multicenter, double-blind, double-dummy, 1:1 randomized, controlled, non-inferiority trial

Study arms were well matched at baseline (as shown in Table 1 of the Poster Abstract)

*N=94 (mITT)

400/200 mg Weekly
- Week 1: 6
- Day 5: 2

3: Global Cure (1° ENDPOINT – EMA)
- 4: Optional Dose
- 5: All-Cause Mortality (1° ENDPOINT – FDA)

9: End of Follow-up Period

70/50 mg Daily (with optional oral fluconazole step-down)
- Week 1: 6
- Day 2: 5

N=93 (mITT)

End of Follow-up Period

To maintain blinding, the rezafungin arm included oral placebo administered once daily.

Documented candidemia and/or IC based on systemic signs and mycological confirmation.

N values are presented for the mITT population, comprising all subjects in safety population who had documented Candida infection.

Global Cure defined as Clinical Cure (as assessed by the Primary Investigator), Mycological Eradication and Radiological Cure (for qualifying invasive candidiasis patients only).
## Primary Endpoints: Global Cure at Day 14 and All-Cause Mortality at Day 30

### Modified Intent-To-Treat (mITT) Population

#### Global response at Day 14 (±1 day)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Proportion of Patients, % (n)</th>
<th>Rezafungin 400/200 mg weekly N=93</th>
<th>Caspofungin 70/50 mg daily N=94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Cure(^a) at Day 14</td>
<td>59.1 (55)</td>
<td>60.6 (57)</td>
<td></td>
</tr>
<tr>
<td>Difference (95% CI)(^b)</td>
<td>–1.1 (–14.9 to 12.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>30.1 (28)</td>
<td>30.9 (29)</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>10.8 (10)</td>
<td>8.5 (8)</td>
<td></td>
</tr>
</tbody>
</table>

Non-inferiority (NI) achieved; lower bound of 95% CI was within 20% NI margin

#### All-cause mortality at Day 30 (–2 days)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Proportion of Patients, % (n)</th>
<th>Rezafungin 400/200 mg weekly N=93</th>
<th>Caspofungin 70/50 mg daily N=94</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACM at Day 30</td>
<td>23.7 (22)</td>
<td>21.3 (20)</td>
<td></td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>2.4 (–9.7, 14.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known deceased</td>
<td>20.4 (19)</td>
<td>18.1 (17)</td>
<td></td>
</tr>
<tr>
<td>Unknown survival</td>
<td>3.2 (3)</td>
<td>3.2 (3)</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>76.3 (71)</td>
<td>78.7 (74)</td>
<td></td>
</tr>
</tbody>
</table>

Non-inferiority (NI) achieved; upper bound of 95% CI was within the 20% NI margin

---

\(^a\)Defined as 1) clinical cure as assessed by the investigator; 2) radiological cure for those patients with IC documented by radiologic/imaging evidence at baseline; and 3) mycological eradication, as confirmed by an independent DRC.

\(^b\)Adjusted for the two randomization strata and APACHE II score/ANC at screening.
Global Cure and Mycological Eradication at Days 5, 14, and 30

**mITT Population – Secondary and Exploratory Endpoints**

Global cure\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Day 5</th>
<th>Day 14</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of Patients (n/N)</td>
<td>55.9% (52/93)</td>
<td>59.1% (55/93)</td>
<td>49.5% (46/93)</td>
</tr>
<tr>
<td></td>
<td>52.1% (49/94)</td>
<td>60.6% (57/94)</td>
<td>48.9% (46/94)</td>
</tr>
</tbody>
</table>

Mycological Eradication\(^b\)

<table>
<thead>
<tr>
<th></th>
<th>Day 5</th>
<th>Day 14</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of Patients (n/N)</td>
<td>78.1% (50/64)</td>
<td>68.7% (46/67)</td>
<td>71.9% (46/64)</td>
</tr>
<tr>
<td></td>
<td>62.5% (40/64)</td>
<td>59.7% (40/67)</td>
<td>70.1% (47/67)</td>
</tr>
</tbody>
</table>

\(^a\)Defined as 1) clinical cure as assessed by the investigator; 2) radiological cure for those patients with IC documented by radiologic/imaging evidence at baseline; and 3) mycological eradication, as confirmed by an independent DRC.

\(^b\)Subjects with candidemia only.
Outcomes in the Initial Days of Treatment

mITT Population – Secondary and Exploratory Endpoints

**Negative Blood Culture**

- **At 24 hours**
  - 53.7% (36/67) for Rezafungin 400/200 mg weekly
  - 46.2% (30/65) for Caspofungin 70/50 mg daily

- **At 48 hours**
  - 74.2% (49/66) for Rezafungin 400/200 mg weekly
  - 64.1% (41/64) for Caspofungin 70/50 mg daily

**Efficacy Endpoints**

- **At 24 hours**
  - 78.1% (50/64) for Mycological Eradication
  - 55.9% (52/93) for Global Cure

- **At 5 Days**
  - 68.7% (46/67) for Mycological Eradication
  - 52.1% (49/94) for Global Cure

---

*Subjects with positive blood culture before randomization.*

*Mycological eradication rates for subjects with candidemia only.*
Time to Negative Blood Culture

mITT and mITT2 – Exploratory Endpoint – Subjects with Positive Blood Culture Before Randomization (Candidemia-only)

- **mITT**: Subjects who received at least one dose of study drug and had a positive culture from blood or other normally sterile site up to 96 hours before randomization.
- **mITT2**: Subjects in mITT who had a positive blood culture within 12h prior to or within 72h after randomization.
<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 400/200 mg weekly N=98</td>
</tr>
<tr>
<td>≥1 TEAE</td>
<td>89 (90.8)</td>
</tr>
<tr>
<td>Study drug-related&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16 (16.3)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>55 (56.1)</td>
</tr>
<tr>
<td>Study drug-related&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>AE leading to study drug discontinuation</td>
<td>13 (13.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Study drug-related AEs may be considered related to study drug or placebo due to investigator blinding.

5 AEs in the rezafungin arm were considered related to placebo administration.

0 AEs in the caspofungin arm were considered related to placebo administration.

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

• The ReSTORE trial evaluated the efficacy and safety of rezafungin QWk vs caspofungin QD in the treatment of documented candidemia and/or IC

• 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)

• Exploratory endpoints of early efficacy (mycological eradication and global cure at Day 5, time to negative blood culture) support the conclusion that rezafungin is efficacious for the treatment of candidemia and IC

• Rates of AEs and SAEs were similar between study arms

25 April 2022, 8:30 – Session “Emerging Clinical Data and Interventional Studies”
Results from Integrated Analysis of Rezafungin Ph2/Ph3 Trials