Venetoclax and Ibrutinib Pharmacokinetics
Unaltered when Coadministered with Rezafungin

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Chief Medical Officer

Abstract #02227
Disclosures

• This presentation reports data from a Phase 1 study that was funded by Cidara Therapeutics
• All authors are employees and shareholders of Cidara Therapeutics
Rezafungin: A Novel Once-Weekly 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 rezafungin Phase 3 clinical trials(^a)</td>
</tr>
<tr>
<td>Front-loaded plasma drug exposure</td>
<td>Efficacy: Shorter time to negative blood culture</td>
</tr>
<tr>
<td>Broad spectrum activity</td>
<td><em>In vivo</em> 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: No observed hepatotoxicity</td>
</tr>
<tr>
<td>No DDIs and favorable hepatic and renal safety</td>
<td>Compatibility with commonly used medications</td>
</tr>
</tbody>
</table>

\(^a\)ReSTORE: 1\(^{st}\)-line treatment of candidemia and/or invasive candidiasis (completed; study sites in China still recruiting for submission of rezafungin to the Center for Drug Evaluation in China). ReSPECT: 1\(^{st}\)-line prophylaxis against invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp., in allogeneic blood and marrow transplant patients (ongoing).
# Rezafungin Phase 3 Program:
## Two Global, Double-Blind, Randomized Trials vs SOC

<table>
<thead>
<tr>
<th><strong>TARGET INDICATION</strong></th>
<th><strong>PHASE 3 TREATMENT TRIAL</strong></th>
<th><strong>PHASE 3 PROPHYLAXIS TRIAL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of Candidemia and Invasive Candidiasis</td>
<td>Prophylaxis Against IFD caused by <em>Aspergillus, Candida &amp; Pneumocystis</em> in Allogeneic Blood and Marrow Transplant Patients</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>TRIAL SIZE</strong></th>
<th><strong>PHASE 3 TREATMENT TRIAL</strong></th>
<th><strong>PHASE 3 PROPHYLAXIS TRIAL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>187 Patients(^a)(^1) (20% noninferiority margin)</td>
<td>462 Patients(^2) (12.5% noninferiority margin)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PRIMARY ENDPOINT</strong></th>
<th><strong>PHASE 3 TREATMENT TRIAL</strong></th>
<th><strong>PHASE 3 PROPHYLAXIS TRIAL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 30 All-Cause Mortality (FDA) Day 14 Global Response (EMA)</td>
<td>Day 90 Fungal-Free Survival</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>COMPARATOR</strong></th>
<th><strong>PHASE 3 TREATMENT TRIAL</strong></th>
<th><strong>PHASE 3 PROPHYLAXIS TRIAL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin with Optional Step Down to Fluco</td>
<td>Fluconazole, Posaconazole (if GVHD) and Bactrim</td>
<td></td>
</tr>
</tbody>
</table>

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GVHD=graft versus host disease; IFD=invasive fungal disease; SOC=standard of care.

\(^a\)Study sites in China are still recruiting patients for submission of rezafungin to the Center for Drug Evaluation in China.

Increasing Patient Population with Higher Risk of IFD Underscores Need for Safe, Effective Antifungals

• The overall patient population vulnerable to IFD is growing\textsuperscript{1-5}
  – Elderly, critically ill (now including severe Covid)
  – Post-surgical, post-transplantation, patients on immunosuppressive therapy

• Antifungal prophylaxis is often used for such patients\textsuperscript{6,7} but most commonly used antifungal agents (eg, azoles) can alter the pharmacokinetics of other drugs, including commonly used cancer agents\textsuperscript{8,9}
  – CYP3A4 interactions with anastrazol, exemestane, paclitaxel, irinotecan, letrozole, docetaxel, tamoxifen

DDI=drug-drug interaction; IFD=invasive fungal disease. 
Potential Complications Between Current Antifungal Agents and Newer Therapies Further Underscore Unmet Needs

DDIs are common and may preclude optimal treatment

- DDIs with newer agents may lead to\(^1\)-\(^6\):
  - Need to reduce dose of primary treatment, such as venetoclax and ibrutinib
  - Need for TDM
  - Delay or discontinuation of antifungal prophylaxis
- Azole-based prophylaxis was discontinued due to toxicity in 14% of patients with newly diagnosed AML treated with venetoclax-containing regimens\(^2\):
  - Mostly hepatotoxicity
  - Also, QTc prolongation, hallucinations, rash, neuropathy, arthralgias, and GI upset

### Kinase inhibitors
- BTK (eg, Imbruvica)
- mTOR (eg, Afinitor)
- JAK (eg, Jakafi, Xeljanz)
- BCR (eg, Venclexta)
- Src (eg, Bosulif, Sprycel)
- PI3K\(\delta\) (eg, Zydelig)

### Immunotherapies
- PD-1 (eg, Opdivo, Keytruda)
- PD-L1 (eg, Tecentriq)
- CTLA-4 (eg, Yervoy)
- Interleukins (eg, Aldesleukin)
- CAR-T cell (eg, Kymriah, Yescarta)
- B cell (eg, Rituxan, Gazyva)

with more to come...

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BKR=B-cell antigen receptor; BTK=Bruton’s tyrosine kinase; CAR=Chimeric antigen receptor; CTLA-4=Cytotoxic T-lymphocyte antigen-4; JAK=Janus kinase; mTOR=Mammalian target of rapamycin; PI3K\(\delta\)=Phosphoinositide 3-kinase delta isoform; PD-1=Programmed cell death protein 1; PD-L1=Programmed death-ligand 1; TDM=therapeutic drug monitoring; TKI=tyrosine kinase inhibitor.
Rezafungin Demonstrated
No Notable Drug-Drug Interactions (DDIs)

Drug Interaction Study in Healthy Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Possible Mechanism</th>
<th>Observations</th>
<th>Suggested Action</th>
</tr>
</thead>
</table>
| Tacrolimus    | CYP3A4, P-gp       | $\leftrightarrow C_{\text{max}}$  
$\downarrow $ AUC $\sim$15% | No change in dose |
| Repaglinide   | CYP2C8, OATP       | $\leftrightarrow C_{\text{max}}$  
$\uparrow$ AUC $\sim$15% | No change in dose |
| Metformin     | OCT, MATEs         | $\leftrightarrow C_{\text{max}}$  
$\leftrightarrow$ AUC | No change in dose |
| Rosuvastatin  | BCRP, OATP         | $\uparrow C_{\text{max}}$  
$\uparrow$ AUC $\sim$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       | P-gp               | $\leftrightarrow C_{\text{max}}$  
$\leftrightarrow$ 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.

¹ Ong, et al. EBMT19 2019; poster B196.
Study Background and Objective

• Following a previous Phase 1 study of rezafungin against common/sensitive drug substrates for a variety of drug metabolizing enzymes and transporter proteins, this study was conducted to evaluate the effect of rezafungin on increasingly used anticancer agents, including venetoclax and ibrutinib
DDI Study Design
Open-Label Study in Healthy Adults

- 32 healthy inpatients (16 male [Group 1] and 16 female [Group 2])
- Ibrutinib and venetoclax each administered alone and with rezafungin IV (400 mg then 200 mg once weekly)
- Suitable washout periods between dosing
- Plasma concentrations of ibrutinib and venetoclax determined using validated LC-MS/MS methodologies

Note: There is no Day 0 (Day 1 follows Day −1).
*a Coadministered drugs given orally ≤2 minutes after the start of rezafungin IV.

CRU=clinical research unit; LC-MS/MS=liquid chromatography with tandem mass spectrometry.
Result: Rezafungin PK as Expected – No Differences in Rezafungin Exposure with ConMeds

Weekly Rezafungin AUC for 400 mg Followed by 200 mg/Week

As seen in Population PK modeling:
- Sex is not significant covariate
- Albumin and BSA are significant covariates in the model
- Slightly higher exposure in females may be due to underlying BSA differences

AUC=area under the curve; BSA=body surface area; F=females; M=males; PK=pharmacokinetics.

To be presented separately.
Result: No Clinically Meaningful DDIs between Venetoclax and Rezafungin

Venetoclax concentration over time

Pharmacokinetics of Venetoclax ± Rezafungin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Venetoclax Alone</th>
<th>Venetoclax with Rezafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>AUC\textsubscript{0-\infty}, ng\cdot h/mL</td>
<td>16</td>
<td>3341</td>
</tr>
<tr>
<td>C\textsubscript{max}, ng/mL</td>
<td>16</td>
<td>274</td>
</tr>
<tr>
<td>t\textsubscript{1/2}, h</td>
<td>16</td>
<td>17.2</td>
</tr>
<tr>
<td>T\textsubscript{max}, h</td>
<td>16</td>
<td>4</td>
</tr>
</tbody>
</table>
**Result:** No Clinically Meaningful DDIs between Ibrutinib and Rezafungin

**Ibrutinib concentration over time**

### Pharmacokinetics of Ibrutinib ± Rezafungin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ibrutinib Alone</th>
<th>Ibrutinib with Rezafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ), pg( \cdot )h/mL</td>
<td>32</td>
<td>315613</td>
</tr>
<tr>
<td>( C_{\text{max}} ), pg/mL</td>
<td>32</td>
<td>91323</td>
</tr>
<tr>
<td>( t_{1/2} ), h</td>
<td>32</td>
<td>7.7</td>
</tr>
<tr>
<td>( T_{\text{max}} ), h</td>
<td>32</td>
<td>2</td>
</tr>
</tbody>
</table>

[Diagram showing Ibrutinib concentration over time with mean concentration (ng/mL) on the y-axis and time (hours) on the x-axis, highlighting the pharmacokinetics of Ibrutinib alone and with Rezafungin with data points for each parameter.]
**Result: No Safety Findings of Concern**

**TEAE by drug**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Period 1 ( Alone )</th>
<th>Period 2 ( w/ Rezafungin )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>2 (5.9)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>2 (5.9)</td>
<td>6 (18.8)</td>
</tr>
</tbody>
</table>

- No SAEs or discontinuations due to AE
- Majority of AEs were mild to moderate; one severe AE*

*Severe AE: abdominal pain considered related to administration of rezafungin and venetoclax
  - Started on Day 16, ~1 day after coadministration of both drugs
  - Subject was transported but not admitted to hospital that day; underwent ultrasounds and CT scan; received ketorolac tromethamine and morphine sulfate IV
  - Subject returned to CRU that evening with diagnosis of “gas in the intestines”
  - Event considered resolved ~2 days from onset

CT=computed tomography.
Conclusions

• DDIs due to CYP3A4 interactions between azoles and treatments for hematologic malignancies and/or GVHD may lead to down-dosing, such as venetoclax and ibrutinib, or avoiding antifungal prophylaxis altogether.

• Previous DDI study of rezafungin showed no meaningful interactions with commonly used drugs.

• The present DDI study showed that no dose adjustments of either venetoclax or ibrutinib are necessary when given in combination with rezafungin.

• Rezafungin is a novel once-weekly echinocandin in Phase 3 development for treatment of candidemia/invasive candidiasis and for prevention of IFD caused by *Candida, Aspergillus, and Pneumocystis* spp.