Rezafungin (CD101)

Taylor Sandison, MD MPH
Chief Medical Officer
Rezafungin: a novel echinocandin designed for next-generation properties

- Broad spectrum of activity and in vivo efficacy
- Novel PK/PD
- Improved safety
- Increased solubility and stability

"... confers much greater stability, leading to an exceptionally longer half-life and an improved safety profile"

Rezafungin: a novel echinocandin designed for next-generation properties

“... confers much greater stability, leading to an exceptionally longer half-life and an improved safety profile”

- Broad spectrum of activity and in vivo efficacy
  → *Candida*, *Aspergillus*, *Pneumocystis* including a subset of azole- and echinocandin-R isolates
  → Potential prevention of resistance

- Novel PK/PD
- Improved safety
- Increased solubility and stability
Rezafungin broad-spectrum in vitro activity against common and rare Candida spp.

<table>
<thead>
<tr>
<th></th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C. albicans (n=1098)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C. glabrata (n=477)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C. tropicalis (n=224)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C. krusei (n=130)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C. parapsilosis (n=387)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C. kefyr (n=51)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C. lusitaniae (n=43)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C. guilliermondii (n=20)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C. dubliniensis (n=21)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C. auris (n=19)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C. auris (n=100)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rezafungin</td>
<td>0.06</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.03</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>0.03</td>
</tr>
</tbody>
</table>

NC=not available.

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

<sup>b</sup>Clinical isolates collected internationally in the JMI Laboratories SENTRY Antimicrobial Surveillance Program (2014-2017).

<sup>c</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>d</sup>Clinical isolates collected by the CDC, representing each of the 4 known clades of C. auris, including 8 isolates with elevated MICs to one or more echinocandins.

Rezafungin in vitro activity against *Candida auris*  
**MIC$_{90}$ of 0.5 µg/mL includes echinocandin-R isolates**

<table>
<thead>
<tr>
<th>Isolate</th>
<th>FKS1 mutation</th>
<th>Rezafungin</th>
<th>Anidulafungin</th>
<th>Caspofungin</th>
<th>Micafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td>B11211</td>
<td>S639P</td>
<td>4</td>
<td>8</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>B11222</td>
<td>None</td>
<td>0.25</td>
<td>2</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>B11780</td>
<td>None</td>
<td>0.06</td>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>B11784</td>
<td>None</td>
<td>0.5</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>&gt;8</td>
</tr>
<tr>
<td>B11858</td>
<td>None</td>
<td>0.25</td>
<td>4</td>
<td>&gt;16</td>
<td>1</td>
</tr>
<tr>
<td>B12131</td>
<td>S639P</td>
<td>8</td>
<td>8</td>
<td>&gt;16</td>
<td>8</td>
</tr>
<tr>
<td>B12137</td>
<td>S639P</td>
<td>8</td>
<td>8</td>
<td>&gt;16</td>
<td>8</td>
</tr>
<tr>
<td>B12149</td>
<td>S639P</td>
<td>8</td>
<td>8</td>
<td>&gt;16</td>
<td>8</td>
</tr>
</tbody>
</table>

Rezafungin demonstrated activity against *C. auris*

CDC collection of clinical *C. auris* (N=100) had all 4 known clades and 8 isolates with elevated echinocandin MICs

---

Rezafungin broad-spectrum in vitro activity against Aspergillus spp., including azole-R and cryptic spp.

<table>
<thead>
<tr>
<th></th>
<th>A. fumigatus (n=261)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>A. terreus (n=19)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>A. niger (n=16)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>A. flavus (n=43)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>azole-R</th>
<th>A. fumigatus (n=31)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>A. lentulus (n=11)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>A. calidoustus (n=11)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rezafungin</strong></td>
<td><strong>0.015</strong></td>
<td><strong>0.015</strong></td>
<td>≤0.008</td>
<td><strong>0.015</strong></td>
<td><strong>0.12</strong></td>
<td>≤0.015</td>
<td>0.6</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Anidulafungin</strong></td>
<td>0.015</td>
<td>0.015</td>
<td>≤0.008</td>
<td>0.015</td>
<td>Posaconazole</td>
<td>0.4</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Caspofungin</strong></td>
<td>0.03</td>
<td>0.125</td>
<td>0.06</td>
<td>0.03</td>
<td>Voriconazole</td>
<td>&gt;16</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

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

<sup>b</sup> Clinical isolates collected internationally in the JMI Laboratories SENTRY Antimicrobial Surveillance Program (2014-2017).

<sup>c</sup> Clinical isolates collected in the US and resistance genotypes confirmed by DNA sequence analysis (CYP51A only, n=13; TR<sub>34</sub>/L98H, n=2; TR<sub>34</sub>/Y121F/T289A, n=2; resistant/no CYP51A mutation, n=6; resistant/CYP51A status unknown, n=8). (Wiederhold et al, 2018a; 2018b).

Rezafungin treatment efficacy against *Candida auris* significantly lower fungal burden in immunosuppressed mice

Rezafungin-treated mice showed significantly lower *C. auris* fungal burden

• vs amphotericin B, all days (p<0.0001)\(^a\)
• vs micafungin, day 10 (p=0.0128)

\(^a\) p=0.023 on day 1 postinfection

Rezafungin prophylaxis efficacy against Aspergillus survival in immunosuppressed mouse model

Rezafungin: one subcutaneous dose of 5, 10 or 20 mg/kg as prophylaxis
10 mg/kg ≈ human dose of 200mg
20 mg/kg ≈ human dose of 400mg
2-3 fold faster clearance in mice than in humans.

Control/Amphotericin B: 3 mg/kg one hour after infection

CPM=cyclophosphamide

Ong et al. ECCMID 2017; poster EP0703; Ong et al. EHA 2017; poster P645.
Rezafungin prophylaxis efficacy against *Aspergillus* survival in immunosuppressed mouse model

Rezafungin at human equivalent doses demonstrated 100% efficacy as prophylaxis against *Aspergillus*, even when administered 5 days pre-infection (≈2 weeks in humans)

CPM = cyclophosphamide.

Ong et al. ECCMID 2017; poster EP0703; Ong et al. EHA 2017; poster P645.
Pneumocystis pneumonia
review and reappraisal of a pathogen and its prophylaxis

Pneumocystis jiroveci (carinii)
• Obligate fungi
• Opportunistic pathogen of lethal pneumonia
  HIV-infected, chemotherapy, corticosteroids, other diseases states
• Biphasic life cycle
  asexual - trophic forms
  asexual - asci/cysts

Current Approach to Prophylaxis
• TMP-SMX: TMP 15–20 mg/kg/d and SMX 75–100 mg/kg/d, PO in 3 divided doses or TMP-SMX DS, 2 tablets TID
• Dapsone
  plus pyrimethamine + leucovorin
• Aerosolized pentamidine
• Atovaquone
  plus pyrimethamine + leucovorin
• NOT recommended: oral clindamycin plus primaquine

Cushion et al. ASH, 2016; oral presentation.
Rezafungin prophylaxis efficacy against *Pneumocystis* equivalent to TMP/SMX in immunosuppressed mouse model

Rezafungin administered at time of *Pneumocystis* inoculation (*P. murina*)

- Rezafungin significantly reduced counts of both nuclei and asci
- No significant differences in survival rates
- Rezafungin efficacy equivalent to the gold standard TMP/SMX
- Efficacy seen with much lower doses than required for *Candida* or *Aspergillus* models

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Nuclei Counts</th>
<th>Study 2</th>
<th>Asci Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/S</td>
<td>20 mg/kg/3x/wk</td>
<td>0.5 mg/kg/1x/wk</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg/1x/wk</td>
<td>0.5 mg/kg/2x/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/kg/3x/wk</td>
<td>0.5 mg/kg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2 mg/kg/3x/wk</td>
<td>5 mg/kg 1x/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2 mg/kg/1x/wk</td>
<td>5 mg/kg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 mg/kg/3x/wk</td>
<td>C/S</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg/1x/wk</td>
<td>0.5 mg/kg/1x/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/kg/3x/wk</td>
<td>0.5 mg/kg/2x/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2 mg/kg/3x/wk</td>
<td>0.5 mg/kg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2 mg/kg/1x/wk</td>
<td>5 mg/kg 1x/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 mg/kg/3x/wk</td>
<td>C/S</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg/1x/wk</td>
<td>0.5 mg/kg/1x/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/kg/3x/wk</td>
<td>0.5 mg/kg/2x/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2 mg/kg/3x/wk</td>
<td>0.5 mg/kg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2 mg/kg/1x/wk</td>
<td>5 mg/kg 1x/wk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05 vs C/S (control/steroid only)

Cushion et al. ASH 2016, oral presentation; Cushion and Ashbaugh. TCT 2019; poster.
Rezafungin: a novel echinocandin designed for next-generation properties

- Broad spectrum of activity and in vivo efficacy
- Novel PK/PD
  - Prolonged $t_{1/2}$ (~130 h)
  - High drug exposure
  - Maximized pharmacometric drivers of efficacy
- Improved safety
- Increased solubility and stability

“... confers much greater stability, leading to an exceptionally longer half-life and an improved safety profile”

Rezafungin: exposure shape matters
PK/PD determinant of antifungal efficacy

Antimicrobials with:
Concentration-dependent killing
Long half-life
Safety

Allows
Front-Loaded
Dosing*

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

Dose fractionation of rezafungin 2 mg/kg in neutropenic mice
(n=5/group)

*High drug exposure early in therapy

Rezafungin *C. albicans* and *C. glabrata* target attainment

**RZF: 400 once weekly**

**RZF: 400 mg once then 200 mg once weekly**

Lakota et al. ID Week, 2018; poster 1390.
Rezafungin dosing: front-loaded and once-weekly

Distributions of weekly AUC:MIC ratios


Target above which efficacy is observed in the mouse model.
‘Silent epidemic’ of antifungal underdosing
PK/PD target attainment against Candida glabrata

Anidulafungin 200 mg followed by 100 mg q24h (MIC=0.12 µg/mL)

Micafungin 100 mg q24h (MIC=0.03 µg/mL)

Caspofungin 70 mg followed by 50 mg q24h (MIC=0.12 µg/mL)

Rezafungin optimized PK/PD matters

*Target attainment in treatment of less susceptible Candida*

Echinocandin target attainment percent probabilities for current echinocandins

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>C. albicans</th>
<th>C. glabrata</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anidulafungin</td>
<td>Caspofungin</td>
</tr>
<tr>
<td>0.008</td>
<td>100&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>100</td>
</tr>
<tr>
<td>0.015</td>
<td>99.1</td>
<td>100</td>
</tr>
<tr>
<td>0.03</td>
<td>52.7</td>
<td>100</td>
</tr>
<tr>
<td>0.06</td>
<td>0.90</td>
<td>97.9</td>
</tr>
<tr>
<td>0.12</td>
<td>0</td>
<td>76.7</td>
</tr>
<tr>
<td>0.25</td>
<td>0</td>
<td>35.7</td>
</tr>
<tr>
<td>0.5</td>
<td>0</td>
<td>12.1</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>4.4</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1.35</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Shading reflects relative probability of PK/PD target attainment.
## Echinocandin target attainment percent probabilities for current echinocandins and rezafungin

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>C. albicans</th>
<th>C. glabrata</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anidulafungin</td>
<td>Caspofungin</td>
</tr>
<tr>
<td>0.008</td>
<td>100&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>100</td>
</tr>
<tr>
<td>0.015</td>
<td>99.1</td>
<td>100</td>
</tr>
<tr>
<td>0.03</td>
<td>52.7</td>
<td>100</td>
</tr>
<tr>
<td>0.06</td>
<td>0.90</td>
<td>97.9</td>
</tr>
<tr>
<td>0.12</td>
<td>0</td>
<td>76.7</td>
</tr>
<tr>
<td>0.25</td>
<td>0</td>
<td>35.7</td>
</tr>
<tr>
<td>0.5</td>
<td>0</td>
<td>12.1</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>4.4</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1.35</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Bader et al. IDWeek 2017; poster 833.
Distinctive pharmacokinetics of rezafungin
Long half-life... and more

“... confers much greater stability, leading to an exceptionally longer half-life and an improved safety profile”

- Broad spectrum of activity and in vivo efficacy
- Novel PK/PD
  - Prolonged $t_{1/2}$ (~130 h)
  - High drug exposure
  - Maximized pharmacometric drivers of efficacy
- Improved safety
- Increased solubility and stability

Distinctive pharmacokinetics of rezafungin
Long half-life... and more

- Novel PK/PD
  - Prolonged $t_{1/2}$ (~130 h)
  - High drug exposure
  - Maximized pharmacometric drivers of efficacy

- Extensive distribution
  - uniform tissue penetration across major organs (rat model) up to 4-fold higher compared to plasma
  - limited CNS penetration
  - Elimination similar across all tissues

Rezafungin penetrates & accumulates vs micafungin including difficult-to-treat infection (IAC mouse model)

A single dose of rezafungin 20 mg/kg or 2-3 doses of micafungin 5 mg/kg on day 3 post-infection with C. albicans

MALDI-MS imaging assessed drug penetration at site of infection in an IAC mouse model.
Rezafungin penetrates & accumulates vs micafungin including difficult-to-treat infection (IAC mouse model)

- 6- to 8-fold higher RZF exposure at site of infection
- Multidose MCF did not reach tissue drug levels achieved with single dose RZF

IAC = intraabdominal candidiasis; GMS = Gömöri methenamine silver stain; MALDI MS = matrix-assisted laser desorption/ionization mass spectrometry; MCF = micafungin; RZF = rezafungin.

Rezafungin distributes to key sites for infection higher levels and longer duration in ELF vs micafungin

RZF Concentrations

- >20-fold higher than MEC\(_{90}\) for \(A. \text{ fumigatus}\) and \(A. \text{ flavus}\) (0.015 \(\mu\)g/mL) after 3 days in mice
  - plasma: 3 \(\mu\)g/mL
  - ELF: 4 \(\mu\)g/mL
- Comparable human levels after 1 week expected, based on RZF plasma \(t_{1/2}\) (133 h, human vs. 21 h, mouse)

ELF = epithelial lining fluid.
Ong et al. HTIDE, 2018; poster.
Rezafungin: a novel echinocandin designed for next-generation properties

- Broad spectrum of activity and in vivo efficacy
- Novel PK/PD
- Improved safety
- Increased solubility and stability

“... confers much greater stability, leading to an exceptionally longer half-life and an improved safety profile”

Rezafungin preclinical safety vs anidulafungin
normal findings vs elevated enzymes and necrosis


Normal Plasma Liver Enzymes
Normal Liver Histology

Plasma Liver Enzymes Elevated
Hepatocellular Necrosis

20-min IV Infusion via Tail Vein at Comparable Plasma Exposures

2-week Rat Hepatotoxicity Screening Study
**Rezafungin Phase 1 drug-drug interaction study**

*No changes in dose required when rezafungin coadministered*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Possible Mechanism(s)</th>
<th>Observations</th>
<th>Suggested Action</th>
</tr>
</thead>
</table>
| Tacrolimus   | CYP3A4, P-gp          | ↓AUC ~15%    | No change in dose |}
| Repaglinide  | CYP2C8, OATP          | ↑AUC ~15%    |                  |
| Metformin    | OCT, MATEs            |              |                  |
| Rosuvastatin | BCRP, OATP            | ↑C\text{max} ~12% ↑AUC ~15% |                  |
| Pitavastatin | OATP                  |              |                  |
| Caffeine     | CYP1A2                |              |                  |
| Efavirenz    | CYP2B6                |              |                  |
| Midazolam    | CYP3A                 |              |                  |
| Digoxin      | CYP2B6                |              |                  |

- Single-center, RCT (N=26)
- Substrate drugs dosed alone for 3 weeks, then again with rezafungin for 3 weeks
- Designed to assess the effect of rezafungin on the PK of multiple drugs

Ong et al. TCT 2019; poster 535.
Rezafungin: a novel echinocandin designed for next-generation properties

“... confers much greater stability, leading to an exceptionally longer half-life and an improved safety profile”

- Broad spectrum of activity and in vivo efficacy
- Novel PK/PD
- Improved safety

\[ \text{Rezafungin} \]

- **Increased solubility and stability**
  - Multiple formulations (IV, SC)

# Cidara Therapeutics Pipeline

**Rezafungin subcutaneous for outpatient/clinic**

<table>
<thead>
<tr>
<th>Program</th>
<th>Indication</th>
<th>Discovery</th>
<th>Research/ in vitro</th>
<th>in vivo</th>
<th>IND-enabling</th>
<th>Ph 1</th>
<th>Ph 2</th>
<th>Ph 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rezafungin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rezafungin IV</td>
<td>Treatment (Candida)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rezafungin IV</td>
<td>Fungal prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rezafungin Subcutaneous</td>
<td>Fungal Infections</td>
<td></td>
<td></td>
<td></td>
<td>With NIH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cloudbreak Immunotherapy Platform</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiviral Conjugates (AVC)</td>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RSV, HIV, Dengue, Zika</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASM Microbe 2019
REZAFUNGIN
CLINICAL TRIAL PROGRAM
Rezafungin treatment studies
Phase 2 STRIVE

**Phase 2**

- Part A met objectives of establishing clinical safety and efficacy and determining dosing for Phase 3 (400 mg/200 mg)
- Part B enrollment completed; anticipated topline data mid-2019

**Phase 3**

- Enrollment underway, similar to STRIVE in design except a more severe patient population is expected (~25% invasive candidiasis vs ~10% in STRIVE Part A)
Rezafungin treatment of candidemia and IC
Phase 2 trial design

Rezafungin
400/400/(400) mg  n=35
400/200/(200) mg  n=36

Caspofungin
70/50/(50) mg  n=36

Analysis Populations:
- Intent-to-treat (ITT): all randomized subjects
- Safety: all subjects who received any amount of study drug
- Microbiological Intent-to-treat (mITT): all subjects in safety population who had documented *Candida* infection
Rezafungin efficacy in treatment of candidemia and IC

*Excluding Indeterminate Response (inability to assess outcome due to missing data point[s]).

Phase 2 results support dose selection for Phase 3

<table>
<thead>
<tr>
<th>Part A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response D14</td>
</tr>
<tr>
<td>Invasive Candidiasis Patients</td>
</tr>
<tr>
<td>Response - High APACHE II Score Patients</td>
</tr>
<tr>
<td>Investigator Assessment D14</td>
</tr>
<tr>
<td>All Cause Mortality D30</td>
</tr>
</tbody>
</table>

400/200/(200)mg QWk
Dose selected for P3
Rezafungin treatment studies
Phase 3 RESTORE

**Phase 2**

- Part A met objectives of establishing clinical safety and efficacy and determining dosing for Phase 3 (400 mg/200 mg)
- Part B enrollment completed; anticipated topline data mid-2019

**Phase 3**

- Enrollment underway, similar to STRIVE in design except a more severe patient population is expected (~25% invasive candidiasis vs ~10% in STRIVE Part A)
Today’s antifungal prophylaxis paradigm
multiple agents with multiple considerations

Comprehensive antifungal prophylaxis requires one or more azole plus an anti-PCP agent

SOC for *Candida* and *Aspergillus*
SOC for *Pneumocystis* pneumonia (PCP)

Risk of IFI

Day
-10. 0 10 20 30 40 50 60 70 80

Pre-engraftment  Engraftment  Post-engraftment

Fluconazole
Fluconazole
Posaconazole or voriconazole
Posaconazole or voriconazole

Anti-PCP: TMP/SMX, dapsone, atovaquone

HSCT: hematopoietic stem cell transplantation; TMP/SMX: Trimethoprim/sulfamethoxazole (co-trimoxazole, Bactrim).
Rezafungin for antifungal prophylaxis
potential to improve and simplify today’s paradigm

Safety vs polyenes, azoles, and TMP-SMX
No DDIs or myelosuppression
Once-weekly dosing (IV or SC) with no drug monitoring required
Unique PK profile may be advantageous against resistant pathogens

SOC for Candida, Aspergillus, and Pneumocystis pneumonia (PCP)

Risk of IFI

Day
-10  0  10  20  30  40  50  60  70  80

Transplant  Pre-engraftment  Engraftment  Post-engraftment
Rezafungin prophylaxis in patients receiving allogeneic BMT

**Phase 3 trial design**

Adaptive design: interim analysis @ 50% enrollment for futility/sample size.

Approximately 25-30 sites globally; size and timing pending additional regulatory input.

### 1° Endpoint: Day 90 Fungal-Free Survival

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>12</th>
<th>13</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rezafungin (n=300)</td>
<td><img src="image1" alt="Week 1" /></td>
<td><img src="image2" alt="Week 2" /></td>
<td><img src="image3" alt="Week 3" /></td>
<td><img src="image4" alt="Week 4" /></td>
<td><img src="image5" alt="Week 5" /></td>
<td><img src="image6" alt="Week 12" /></td>
<td><img src="image7" alt="Week 13" /></td>
<td><img src="image8" alt="Week 17" /></td>
</tr>
<tr>
<td>Azole placebo</td>
<td><img src="image9" alt="Week 1" /></td>
<td><img src="image10" alt="Week 2" /></td>
<td><img src="image11" alt="Week 3" /></td>
<td><img src="image12" alt="Week 4" /></td>
<td><img src="image13" alt="Week 5" /></td>
<td><img src="image14" alt="Week 12" /></td>
<td><img src="image15" alt="Week 13" /></td>
<td><img src="image16" alt="Week 17" /></td>
</tr>
<tr>
<td>Bactrim placebo</td>
<td><img src="image17" alt="Week 1" /></td>
<td><img src="image18" alt="Week 2" /></td>
<td><img src="image19" alt="Week 3" /></td>
<td><img src="image20" alt="Week 4" /></td>
<td><img src="image21" alt="Week 5" /></td>
<td><img src="image22" alt="Week 12" /></td>
<td><img src="image23" alt="Week 13" /></td>
<td><img src="image24" alt="Week 17" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>12</th>
<th>13</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard of Care (n=150)</td>
<td><img src="image25" alt="Week 1" /></td>
<td><img src="image26" alt="Week 2" /></td>
<td><img src="image27" alt="Week 3" /></td>
<td><img src="image28" alt="Week 4" /></td>
<td><img src="image29" alt="Week 5" /></td>
<td><img src="image30" alt="Week 12" /></td>
<td><img src="image31" alt="Week 13" /></td>
<td><img src="image32" alt="Week 17" /></td>
</tr>
<tr>
<td>Rezafungin Placebo</td>
<td><img src="image33" alt="Week 1" /></td>
<td><img src="image34" alt="Week 2" /></td>
<td><img src="image35" alt="Week 3" /></td>
<td><img src="image36" alt="Week 4" /></td>
<td><img src="image37" alt="Week 5" /></td>
<td><img src="image38" alt="Week 12" /></td>
<td><img src="image39" alt="Week 13" /></td>
<td><img src="image40" alt="Week 17" /></td>
</tr>
<tr>
<td>Azole*</td>
<td><img src="image41" alt="Week 1" /></td>
<td><img src="image42" alt="Week 2" /></td>
<td><img src="image43" alt="Week 3" /></td>
<td><img src="image44" alt="Week 4" /></td>
<td><img src="image45" alt="Week 5" /></td>
<td><img src="image46" alt="Week 12" /></td>
<td><img src="image47" alt="Week 13" /></td>
<td><img src="image48" alt="Week 17" /></td>
</tr>
<tr>
<td>Bactrim</td>
<td><img src="image49" alt="Week 1" /></td>
<td><img src="image50" alt="Week 2" /></td>
<td><img src="image51" alt="Week 3" /></td>
<td><img src="image52" alt="Week 4" /></td>
<td><img src="image53" alt="Week 5" /></td>
<td><img src="image54" alt="Week 12" /></td>
<td><img src="image55" alt="Week 13" /></td>
<td><img src="image56" alt="Week 17" /></td>
</tr>
</tbody>
</table>

*Fluconazole to start in all patients. Posaconazole optional in patients who develop GVHD per label.

Adaptive design: interim analysis @ 50% enrollment for futility/sample size.

Approximately 25-30 sites globally; size and timing pending additional regulatory input.
Rezafungin for treatment and prophylaxis

novel and unique properties of a next-generation echinocandin

• **Potent and Broad-Spectrum** against *Candida*, *Aspergillus*, and *Pneumocystis*:
  including *Candida auris* and subset of azole- and echinocandin-resistant isolates

• **Enhanced PK**: once-weekly, high-exposure, front-loaded dosing and greater tissue
  penetration maximizes pharmacometrics of efficacy and may prevent resistance

• **Safety and DDI profile of the echinocandin class**: spares myelosuppression, TDM,
  hepatic & renal toxicity, non-compliance, and complications of
  managing/avoiding DDIs

• **Dosing & Administration**: inpatient and outpatient use dosed once-weekly, earlier
  hospital discharge, multiple formulations