EFFECT OF MODERATE HEPATIC IMPAIRMENT ON THE SAFETY AND PHARMACOKINETICS OF REZAFUNGIN

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Introduction - Rezafungin

• Novel echinocandin antifungal that inhibits the synthesis of 1,3-β-D-glucan
• In Phase 3 development for treatment candidemia and invasive candidiasis and for prevention of IFD caused by *Candida* and *Aspergillus* spp. and *Pneumocystis jirovecii*
• Mass balance studies have demonstrated that elimination of rezafungin is primarily in the feces as unchanged rezafungin
• An open-label, single-dose study was conducted to investigate the safety, tolerability, and PK of rezafungin in subjects with hepatic impairment and healthy subjects

IFD=invasive fungal disease; PK=pharmacokinetics.
Study Design

• Open-label study to investigate the safety, tolerability, and PK of rezafungin

<table>
<thead>
<tr>
<th>Subjects</th>
<th>N</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate hepatic impairment</td>
<td>8</td>
<td>Single rezafungin 400-mg, 1-hr IV infusion</td>
</tr>
<tr>
<td>(Child-Pugh Class B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal hepatic function*</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

*matched for age (within ± 10 years of mean for hepatic impaired group); sex (similar M:F ratios); and BMI (within ± 20% of mean for hepatic impaired group)

Plasma Sampling                  | Collection Schedule                                                                 |
----------------------------------|--------------------------------------------------------------------------------------|
Rezafungin PK                    | at end of infusion and 1.5, 3, 6, 8, 12, 24, 48, 96, 168, and 336 h post-dose     |
Rezafungin protein binding       | prior to dosing (spiked), at 45 min post start of infusion, and at 72 h post infusion |

• Vital signs, physical examinations, 12-lead ECGs, clinical laboratory assessments, AEs, and concomitant medication usage were evaluated for all subjects through the Day 32 Follow-up visit

AE=adverse event; BMI=body mass index; ECG=electrocardiogram.
Results

- Sixteen subjects (4 male and 4 females/group) were enrolled and completed the study

**Mean (+SD) Plasma Rezafungin Concentration-Time Profiles After Single 400-mg IV Infusion of Rezafungin**

- Rezafungin concentrations were similar between groups
- Declined in multi-exponential manner
- Were >20-fold above detection limits (50 ng/mL) at the last collection time of 2 weeks post dose
# Results

Plasma Rezafungin PK in Subjects with Moderate Hepatic Impairment or Normal Hepatic Function After a Single Dose of IV Rezafungin 400 mg

<table>
<thead>
<tr>
<th>Group</th>
<th>Statistic</th>
<th>$C_{\text{max}}$ (μg/mL)</th>
<th>$t_{\text{max}}^a$ (h)</th>
<th>$\text{AUC}_{0-\infty}$ (μg·h/mL)</th>
<th>$t_{1/2}$ (h)</th>
<th>CL (L/h)</th>
<th>$V_z$ (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate Hepatic Impairment</td>
<td>Mean</td>
<td>17.9</td>
<td>1</td>
<td>1210</td>
<td>110.27</td>
<td>0.353</td>
<td>55.1</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.23</td>
<td>(1.00-1.00)</td>
<td>329</td>
<td>11.81</td>
<td>0.0919</td>
<td>10.8</td>
</tr>
<tr>
<td>Normal Hepatic Function</td>
<td>Mean</td>
<td>20.6</td>
<td>1</td>
<td>1780</td>
<td>123.1</td>
<td>0.237</td>
<td>42.3</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>5.88</td>
<td>(1.00-1.50)</td>
<td>456</td>
<td>18.91</td>
<td>0.0559</td>
<td>12.9</td>
</tr>
</tbody>
</table>

N=8 per group.

$^a$Median (Min – Max) are reported for $t_{\text{max}}$
Results

Plasma Rezafungin Unbound $C_{\text{max}}$ and $AUC_{0-\infty}$ in Subjects with Moderate Hepatic Impairment or Normal Hepatic Function After a Single Dose of IV Rezafungin 400 mg
# Results - Safety

## Treatment Emergent AE Severity in Subjects with Moderate Hepatic Impairment or Normal Hepatic Function After a Single Dose of IV Rezafungin 400 mg

<table>
<thead>
<tr>
<th>Adverse Event&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Moderate Hepatic Impaired N=8 n (%)</th>
<th>Normal Hepatic Function N = 8 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adverse Event Severity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>At least one TEAE</td>
<td>3 (37.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (12.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (12.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (12.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion site extravasation</td>
<td>1 (12.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adverse events are coded using MedDRA version 22.1

AE=adverse event; TEAE=treatment-emergent AE.
Conclusions

• Systemic exposure of rezafungin, though modestly reduced in subjects with moderate hepatic impairment, remained within the range observed in subjects with normal hepatic function

• Importantly, these minor differences are not indicative of reduced drug clearance that can be associated with hepatic impairment and are likely to reflect variability between small groups of subjects

• This study demonstrated that dose adjustment of rezafungin is not warranted in subjects with moderate hepatic impairment, and that it was safe to study subjects with severe hepatic impairment (ongoing)

• Rezafungin was safe and well tolerated in subjects with moderate hepatic impairment