Phase 2 STRIVE Clinical Trial of Rezafungin for the Treatment of Candidemia and/or Invasive Candidiasis: Results Stratified by Baseline Renal Function

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INTRODUCTION AND PURPOSE
Rezafungin is a novel once-weekly echinocandin antifungal in development for treatment as well as prevention (prophylaxis) of invasive fungal infections. STRIVE (NCT02734882) is a global, randomized, double-blind, placebo-controlled, Phase 2 trial evaluating the safety and efficacy of IV rezafungin (RZF) in the treatment of candidemia and/or invasive candidiasis compared with standard-care IV caspofungin with optional oral steptidom. Following completion of the first part of STRIVE (“Part A”), enrollment was continued (“Part B”) to achieve the target safety database, with Part B completion expected in 2019. Patient populations at risk of invasive fungal infections often have underlying disease or conditions or are receiving medications that may affect renal function. This analysis evaluated outcomes by baseline renal function in patients treated with RZF in the completed Part A of STRIVE.

METHODS
Patients were randomized to 1 of 3 treatment arms and treated for 14 to 21 days (Figure 1) as previously described.1

![Image](image_url)

Figure 1. Treatment arms in the STRIVE trial

107 Randomized Patients (ITT) → 92 in mITT
Rezafungin (400 mg Q Week)
Rezafungin (400 mg Week 1/200 mg Week)
Caspofungin (70 mg loading/50 mg Q Day)

For this analysis, patients treated with RZF were stratified by baseline renal function and classified into the following categories: those with creatinine clearance (CrCl) <60 mL/min/1.73 m² (mild renal impairment to normal to augmented) and those with CrCl <60 mL/min/1.73 m² (moderate to severe renal impairment).

Data were evaluated for differences in safety, efficacy, or pharmacokinetics (PK) between renal categories.

METHODS (cont’d)
A RZF population pharmacokinetic model, derived using data from Phase 1 trials and the STRIVE trial,1 and Bayesian estimation were utilized to estimate RZF Week 1 area under the concentration-time curve (AUCCrCl) for each patient enrolled in Group 1 (IV RZF 400 mg Week 1 then 400 mg once weekly) or Group 2 (IV RZF 400 mg Week 1 then 200 mg once weekly).

Individual RZF AUCCrCl estimates from both groups combined (since first dose was 400 mg in all) were compared to Crl.

RESULTS
Demographics
Of the 65 patients stratified by baseline renal function, 23 had a CrCl of <60 mL/min/1.73 m² [median range: 34.5 [12.4–59.2] mL/min/1.73 m²] and 42 patients had a CrCl of ≥60 mL/min/1.73 m² [median range: 105.1 [60.0–294.7] mL/min/1.73 m²]. Other demographics were generally similar between the two groups, except age which was approximately 10 years older in the impaired group (median age: 63 versus 53.5 years).

Safety
Overall, rates of treatment-emergent adverse events (TEAEs) were lower among patients with CrCl ≥60 mL/min/1.73 m² (Table 1).

Table 1. Adverse event summary by baseline renal function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CrCl ≥60 mL/min/1.73 m² (N=23)</th>
<th>CrCl &lt;60 mL/min/1.73 m² (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>(N=23)</td>
<td>(N=42)</td>
</tr>
<tr>
<td>All adverse TEAEs</td>
<td>23 (100.0)</td>
<td>37 (88.1)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>8 (34.8)</td>
<td>13 (31.0)</td>
</tr>
<tr>
<td>TEAE leading to discontinuation</td>
<td>14 (60.9)</td>
<td>14 (33.3)</td>
</tr>
</tbody>
</table>

Pharmacokinetics
Mean (SD) RZF exposures and overall distribution of individual values (Figure 2) were similar between subjects with CrCl ≥60 mL/min/1.73 m² or <60 mL/min/1.73 m² (mean [SD] CrCl/AUCCrCl: 717.4 [253.9] µg·h/mL vs 717.4 [253.9] µg·h/mL). CrCl was not an important determinant of RZF exposure in the model, as illustrated by lack of correlation between CrCl and RZF Week 1 AUCCrCl (Figure 3).

Figure 2. Individual RZF Week 1 AUCCrCl in STRIVE patients with moderate and severe, or no worse than mild renal impairment

RESULTS (cont’d)

CONCLUSIONS
• Results from the Phase 2 STRIVE (Part A) clinical trial showed no meaningful trends in safety and efficacy outcomes based on baseline renal function
• A lack of correlation between CrCl and rezafungin exposure shows renal elimination is not an important route of rezafungin clearance
• Additional PK, safety, and efficacy evaluations of rezafungin in special patient populations will be obtained in planned Phase 1 studies and the ongoing Phase 3 development program

REFERENCES
1. Thompson GR, et al. Rezafungin Clinical Safety and Efficacy in Patients with Candidemia and/or Invasive Candidiasis in the Randomized, Double-blind, Multicenter, Phase 2 STRIVE Trial. IDWeek 2016.

ACKNOWLEDGMENTS
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