Analysis of Outcomes By Baseline Renal Function from the Phase 2 STRIVE Clinical Trial of Rezafungin for the Treatment of Candidemia and/or Invasive Candidiasis

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INTRODUCTION

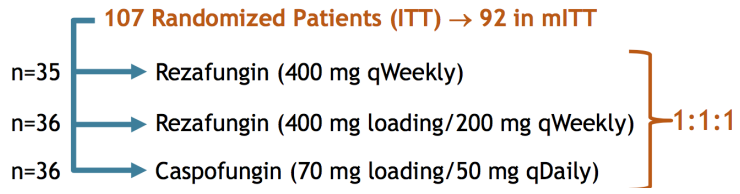
STRIVE (NCT02734862) is a global, randomized, double-blind, placebo-controlled, Phase 2 trial evaluating the safety and efficacy of IV rezafungin (RZF) in the treatment of candidemia and/or invasive candidiasis compared with standard-of-care (IV caspofungin with optional oral stepdown [fluconazole]).

Patient populations at risk of invasive fungal infections often have underlying disease or conditions or are receiving treatments associated with impaired 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 (or 28) days (**Fig 1**) as previously described.[1]

Figure 1. Treatment arms in the STRIVE trial.



For this analysis, patients treated with RZF were stratified by baseline renal function and classified into the following categories: those with creatinine clearance (CrCL) ≥50 mL/min and those with CrCL <50 mL/min, calculated using Cockcroft-Gault.

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

A RZF population pharmacokinetic model, derived using data from STRIVE and Phase 1 trials,[2] and Bayesian estimation were utilized to estimate RZF Week 1 area under the concentration-time curve ($AUC_{0\text{-}168}$) for each patient enrolled in Group 1 (IV RZF 400 mg once weekly) or Group 2 (IV RZF 400 mg Wk1 then 200 mg once weekly). Individual RZF $AUC_{0\text{-}168}$ estimates were compared to CrCL.

RESULTS

Of 71 RZF-treated patients in the ITT population, 65 had CrCL data available and were stratified by baseline renal function; 42 had a CrCL of <50 mL/min (range: 6.1–47.0 mL/min) and 23 had a CrCL of ≥50 mL/min (50.8–150.8 mL/min).

Safety

Rates of treatment-emergent adverse events (TEAEs) were generally similar between groups (**Table 1**).

Table 1. Adverse event summary by baseline renal function

Parameter	CrCL<50 mL/min (N=42)	CrCL ≥50 mL/min (N=23)
	n (%)	
At least 1 TEAE	40 (95.2)	20 (87.0)
Any severe TEAE	14 (33.3)	7 (30.4)
Any serious AE	20 (47.6)	9 (34.8)
TEAE leading to discontinuation	2 (4.8)	2 (8.7)

RESULTS (cont'd)

Efficacy

Small subgroup sizes notwithstanding, a total of 58 patients had CrCL and efficacy data evaluable for analysis (**Table 2**).

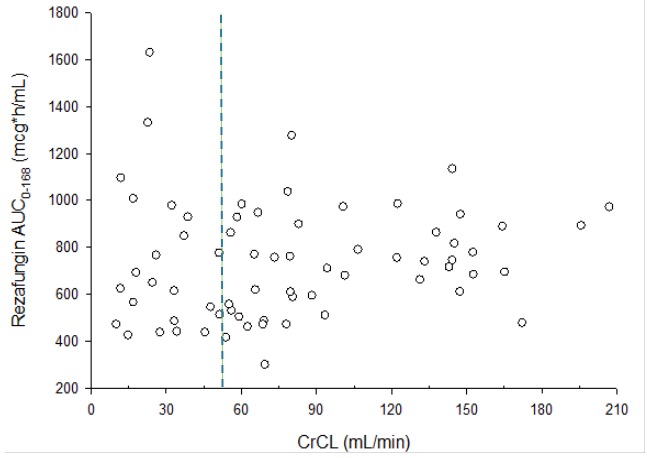
Table 2. Summary of efficacy by baseline renal function

Parameter	CrCL <50 mL/min (N=38)	CrCL ≥50 mL/min (N=20)
	n (%)	
Overall success at Day 14	25 (65.8)	12 (60.0)
Investigator-assessment of clinical response at Day 14	30 (78.9)	15 (75.0)

Population PK

CrCL was not an important determinate of RZF exposure, as illustrated by lack of correlation between CrCL and RZF Week 1 $AUC_{0\text{-}168}$ (**Fig 2**). Mean (%CV) RZF exposures were similar between subjects with CrCL <50 mL/min or ≥50 mL/min, although there was more variability among those with lower renal clearance (mean [%CV] $AUC_{0\text{-}168}$: 748.8 [44%] vs 731.9 [28%] mcg•h/mL).

Figure 2. Population PK–derived Bayesian estimates of RZF Week 1 $AUC_{0\text{-}168}$ versus CrCL in STRIVE patients



$AUC_{0\text{-}168}$= Area under the concentration time curve from time 0 to 168 hours; CrCL= creatinine clearance, calculated using Cockcroft-Gault formula; dotted line indicates CrCL of 50 mL/min.

CONCLUSIONS

- Results from the Phase 2 STRIVE (Part A) clinical trial showed no meaningful trends in outcomes based on baseline renal function.
- Lack of correlation between CrCL and RZF exposure shows renal elimination is not an important route of RZF clearance.
- These results support inclusion of patients with decreased renal function in Phase 3.
- Additional clinical evaluations are planned to further evaluate rezafungin in special populations.

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 2018.
2. Lakota E, et al. Pharmacokinetic-Pharmacodynamic Target Attainment Analyses to Support Rezafungin Dose Selection in the Treatment of *Candida* Infections. IDWeek 2018.

ACKNOWLEDGMENTS

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