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Shawn Flanagan, PhD
Cidara Therapeutics, Inc.
San Diego, CA, USA
sflanagan@cidara.com

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

S. Flanagan,[1] E. Lakota,[2] C. Rubino,[2] T. Sandison,[1] P. Pappas,[3] L. Ostrosky-Zeichner[4]

[1]Cidara Therapeutics (San Diego, CA, USA); [2]ICPD (Schenectady, NY, USA); [3]University of Alabama at Birmingham (Birmingham, AL, USA); [4]University of Texas Health Center (Houston, TX, USA)

INTRODUCTION AND PURPOSE

Rezafungin is a novel once-weekly echinocandin antifungal in development for the treatment as well as prevention (prophylaxis) of invasive fungal infections.

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).

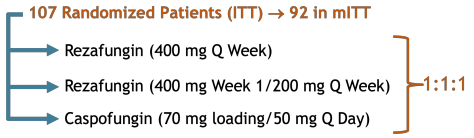
Following completion of the first part of STRIVE ("Part A"), enrollment was continued ("Part B") to achieve the target safety database, with Part B completion expected in 2019.

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]

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) ≥60 mL/min/1.73 m^2 (mild renal impairment to normal to augmented) and those with CrCl <60 mL/min/1.73 m^2 (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,[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 Wk1 then 400 mg once weekly) or Group 2 (IV RZF 400 mg Wk1 then 200 mg once weekly). Individual RZF $AUC_{0\text{-}168}$ estimates from both groups combined (since first dose was 400 mg in all) were compared to CrCl.

RESULTS

Demographics

Of the 65 patients stratified by baseline renal function, 23 had a CrCl of <60 mL/min/1.73 m^2 (median [range]: 34.5 [12.4–59.2] mL/min/1.73 m^2) and 42 patients had a CrCl of ≥60 mL/min/1.73 m^2 (median [range: 105.1 [60.0–294.7] mL/min/1.73 m^2). 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 m^2 (**Table 1**).

Table 1. Adverse event summary by baseline renal function

Parameter	CrCl <60 mL/min/1.73 m^2 (N=23)	CrCl ≥60 mL/min/1.73 m^2 (N=42)
	n (%), except where noted	
At least 1 TEAE	23 (100.0)	37 (88.1)
Any severe TEAE	8 (34.8)	13 (31.0)
Any serious AE	14 (60.9)	14 (33.3)
TEAE leading to discontinuation	2 (8.7)	2 (4.8)

RESULTS (cont'd)

Efficacy

Small subgroup sizes notwithstanding, a total of 58 patients had efficacy data evaluable for analysis (**Table 2**). Efficacy was similar in the two groups.

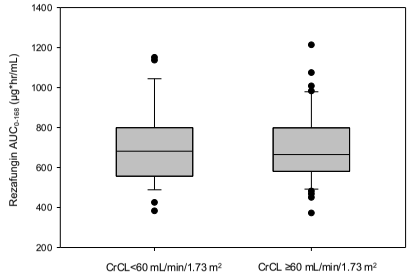
Table 2. Summary of efficacy by baseline renal function

Parameter	CrCl <60 mL/min/1.73 m^2 (N=21)	CrCl ≥60 mL/min/1.73 m^2 (N=37)
	n (%), except where noted	
Overall success at Day 14	14 (66.7)	23 (62.2)
Investigator-assessment of clinical response at Day 14	17 (81.0)	28 (75.7)

Pharmacokinetics

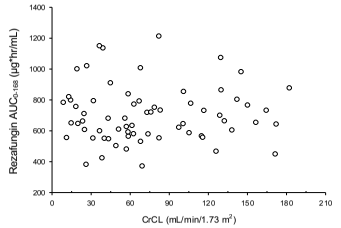
Mean (%CV) RZF exposures and overall distribution of individual values (**Figure 2**) were similar between subjects with CrCL <60 mL/min/1.73 m^2 or ≥60 mL/min/1.73 m^2, (mean [%CV] $AUC_{0\text{-}168}$: 700.6 [27%] µg•hr/mL vs 717.4 [25%] µg•hr/mL). CrCL was not an important determinate of RZF exposure in the model, as illustrated by lack of correlation between CrCl and RZF Week 1 $AUC_{0\text{-}168}$ (**Figure 3**).

Figure 2. Individual RZF Week 1 $AUC_{0\text{-}168}$ in STRIVE patients with moderate and severe, or no worse than mild renal impairment



RESULTS (cont'd)

Figure 3. Population PK–derived Bayesian estimates of RZF Week 1 $AUC_{0\text{-}168}$ versus CrCl in STRIVE patients



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 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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