Efficacy and Safety By Renal Function in the Phase 2 STRIVE Trial of Rezafungin in Treatment of Candidemia and Invasive Candidiasis (IC)

Shawn Flanagan[1], Patrick M. Honore[2], Alex Soriano[3], Jose Vazquez[4], Taylor Sandison[1]

[1]Cidara Therapeutics, Inc. San Diego, CA, USA; [2]Brugmann University Hospital, Brussels, Belgium; [3]Hospital Clínic de Barcelona, IDIBAPS, University of Barcelona, Spain; [4]Augusta University, Augusta, Georgia, USA

Shawn Flanagan, PhD
Cidara Therapeutics, Inc.
6310 Nancy Ridge Drive, Suite 101
San Diego, CA, USA
sflanagan@cidara.com

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INTRODUCTION

- Renal dysfunction is a common cause of mortality and increased comorbidity in patients who develop candidemia or IC[1]
- Certain patient populations, such as renal transplant patients, are at increased risk of nephrotoxicity[2]
- The STRIVE trial (NCT02734862) is a randomized, controlled, Phase 2 trial of rezafungin (RZF) in patients with candidemia and/or IC
- Previously, pharmacokinetic (PK) analysis of STRIVE demonstrated that drug exposures of RZF were not affected by renal function[3]
- The present analysis was conducted to evaluate safety and efficacy outcomes in the STRIVE trial based on renal function

METHODS

- Adults (≥18 y) with systemic signs of infection and mycological confirmation of candidemia and/or IC were randomized to either RZF (Group 1: 400 mg once weekly; Group 2: 400 mg on Week 1, 200 mg once weekly thereafter [Phase 3 dosing]) or caspofungin (CAS; 70 mg on Day 1, 50 mg once daily thereafter with optional step-down to oral fluconazole)
- In this analysis, patients were stratified by baseline renal function based on creatinine clearance (CrCl) normalized for body surface area: **CrCL ≥60 mL/min/1.73 m²** | **CrCL <60 mL/min/1.73 m²**
- A RZF population PK model[3] and Bayesian estimation were utilized to estimate RZF Week 1 area under the concentration-time curve ($AUC_{0\text{-}168}$) for patients with available data. Safety and efficacy outcomes were evaluated for differences between renal categories or treatments. RZF outcomes are reported for the pooled arms (RZF Group 1 and RZF Group 2)

RESULTS

Table 1. Demographics by Baseline Renal Function (ITT Population[a])

Characteristic	CrCL ≥60 mL/min/1.73 m²		CrCL <60 mL/min/1.73 m²	
	RZF (N=83)	CAS (N=39)	RZF (N=46)	CAS (N=25)
Mean age, y (range)	55 (24–83)	55 (24–81)	67 (24–91)	67 (30–93)
Aged ≥65 y, n (%)	25 (30.1%)	12 (30.8%)	27 (58.7%)	15 (60.0%)

[a]All randomized.

Table 2. Safety Outcomes by Baseline Renal Function (Safety Population[a])

Safety Endpoint, n (%)	CrCL ≥60 mL/min/1.73 m²		CrCL <60 mL/min/1.73 m²	
	RZF (N=81)	CAS (N=41)	RZF (N=46)	CAS (N=25)
≥1 TEAE	69 (85.2%)	29 (70.7%)	45 (97.8%)	24 (96.0%)
Severe	27 (33.3%)	11 (26.8%)	16 (34.8%)	15 (60.0%)
Serious AE	33 (40.7%)	11 (26.8%)	26 (56.5%)	17 (68.0%)
TEAE leading to study D/C	3 (3.7%)	2 (4.9%)	3 (6.5%)	2 (8.0%)

AE=adverse event; D/C=discontinuation; TEAE=treatment-emergent adverse event.
[a]All patients who received any amount of study drug.

Table 3. Efficacy Outcomes by Baseline Renal Function (mITT Population[a])

Endpoint at Day 14, n (%)	CrCL ≥60 mL/min/1.73 m²		CrCL <60 mL/min/1.73 m²	
	RZF (N=74)	CAS (N=36)	RZF (N=41)	CAS (N=23)
Overall success	46 (62.2%)	24 (66.7%)	30 (73.2%)	15 (65.2%)
Investigator assessment of clinical cure	52 (70.3%)	26 (72.2%)	33 (80.5%)	15 (65.2%)
Mycological Response	48 (64.9%)	25 (69.4%)	32 (78.0%)	15 (65.2%)

[a]All patients who received any amount of study drug and with documented *Candida* infection.

Demographics

- Groups with CrCl of <60 mL/min/1.73 m² had a higher percentage of patients aged ≥65 y (Table 1)

Safety

- Rates of AEs were generally higher for patients with CrCl of <60 mL/min/1.73 m²; differences by renal function were observed for both RZF and CAS (Table 2)

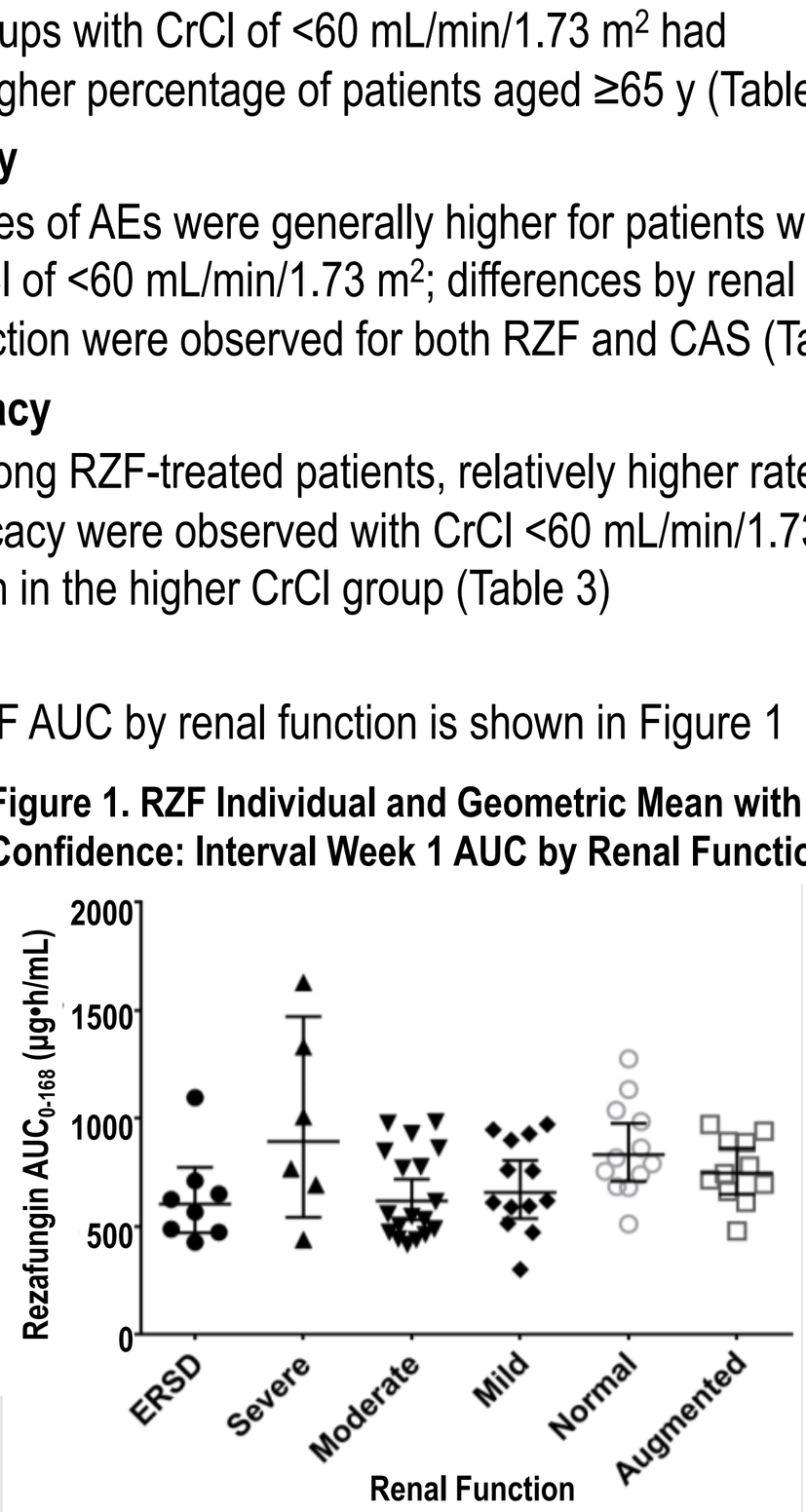
Efficacy

- Among RZF-treated patients, relatively higher rates of efficacy were observed with CrCl <60 mL/min/1.73 m² than in the higher CrCl group (Table 3)

PK

- RZF AUC by renal function is shown in Figure 1

Figure 1. RZF Individual and Geometric Mean with 95% Confidence: Interval Week 1 AUC by Renal Function



Renal Function Categories by CrCL (mL/min/1.73m²): ERSD (End stage renal disease)=CrCL of <15 or history of dialysis; Severe=CrCL of 15–29; Moderate=CrCL of 30–59; Mild=CrCL of 60–89; Normal=CrCL of 90–129; Augmented≥130.

CONCLUSIONS

- In the Phase 2 STRIVE trial, renal impairment did not appear to affect safety or efficacy of antifungal treatment with RZF
- Consistent RZF exposures were observed over a wide range of renal function
- The ongoing Phase 3 treatment trial of RZF (ReSTORE; NCT03667690) will provide additional data for evaluation
- The clinical relevance of these findings is underscored by the comorbidities and polypharmacy in patients with candidemia or IC, including hospitalized patients with acute renal failure or kidney transplant recipients, for whom antifungal-related dose adjustments and nephrotoxicity, are important considerations when choosing an antifungal

REFERENCES

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