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Clinical Efficacy and Safety of Rezafungin (CD101): Results from STRIVE, a Randomized, Double-blind, Multicenter, Phase 2 Study in the Treatment of Candidemia and/or Invasive Candidiasis

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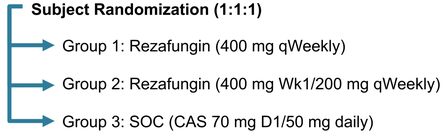
INTRODUCTION

- Rezafungin (previously CD101) is a novel echinocandin with a long half-life that allows for once-weekly dosing and high drug exposure early in therapy, when the rate and extent of drug effect can be maximized.[1,2]
- Rezafungin has demonstrated preclinical efficacy against *Candida*, *Aspergillus*, and *Pneumocystis* spp., including infections caused by resistant isolates.[3-5]
- Pharmacokinetic/pharmacodynamic analyses have demonstrated the pharmacometric rationale of rezafungin efficacy administered once weekly against invasive fungal infections.[6,7]
- In the Phase 2 STRIVE (NCT02734862) clinical trial, Part A was conducted using two dosing regimens of rezafungin to assess clinical safety and efficacy and to help determine dosing for Phase 3 study.

METHODS

- Adults (≥18 y) with attributable systemic signs and mycological confirmation of candidemia and/or invasive candidiasis (IC) were randomized to receive rezafungin or standard of care (SOC) with caspofungin (CAS) (Fig. 1).

Figure 1. STRIVE Treatment Groups



- The duration of therapy was ≥14 days, up to 4 weeks.
- Optional criteria-defined oral stepdown after ≥3 days of IV therapy was allowed in the SOC arm (Group 3).
- The microbiological Intent-to-treat population (mITT) comprised all subjects who received ≥1 dose of study drug and had documented *Candida* infection.

METHODS (cont'd)

Primary Objectives

- To evaluate the safety and tolerability of rezafungin
- To evaluate Overall Success (mycological eradication + resolution of signs of candidemia and/or IC) of rezafungin at day 14 in the mITT population

Key Endpoints

- Safety: adverse events (AEs) and overall mortality
- Efficacy: overall response, mycological response, and Principal Investigator (PI)–assessment of clinical response at day 14; All-Cause Mortality at day 30

RESULTS

- The study population was predominantly male (Table 1) and White, enrolled from 31 sites globally (not shown).
- Subjects in each treatment arm were generally comparable, however, the rezafungin groups had higher proportions of subjects with APACHE II scores of ≥20.

Table 1: Demographics and Baseline Characteristics (ITT[a])

Parameter	Group 1: RZF 400 mg qWk (N=35)	Group 2: RZF 400 mg/200 mg qWk (N=36)	Group 3: CAS 70 mg/50 mg QD (N=36)
	n (%), except where noted		
Age, mean ± SD years (range)	56.9 ± 15.9 (24–88)	57.0 ± 14.3 (26 –84)	60.7 ± 17.2 (24–93)
Male	21 (60)	22 (61.1)	17 (47.2)
Diagnosis			
Candidemia	32 (91.4)	31 (86.1)	33 (91.7)
IC	3 (8.6)	5 (13.9)	3 (8.3)
APACHE II score			
Mean ± SD	12.3 ± 7.2	13.9 ± 6.8	13.6 ± 6.9
0–9	12 (34.3)	9 (25.0)	9 (25.0)
10–19	16 (45.7)	18 (50.0)	21 (58.3)
≥20	6 (17.1)	8 (22.2)	3 (8.3)

APACHE=Acute Physiologic Assessment and Chronic Health Evaluation; CAS=caspofungin; IC=invasive candidiasis; RZF=rezafungin; SD=standard deviation.
[a]ITT (Intent-to-treat) population: all randomized subjects.

RESULTS (cont'd)

Safety

- No concerning trends in AEs were observed with rezafungin treatment (Table 2).

Table 2: Summary of Adverse Events (Safety[a])

Parameter	Group 1: RZF 400 mg qWk (N=35)	Group 2: RZF 400 mg/200 mg qWk (N=36)	Group 3: CAS 70 mg/50 mg QD (N=33)
	n (%), except where noted		
At least 1 TEAE	31 (88.6)	34 (94.4)	27 (81.8)
Severe	13 (37.1)	10 (27.8)	13 (39.4)
Study drug–related TEAE	4 (11.4)	6 (16.7)	4 (12.1)
TEAE leading to study drug D/C	4 (11.4)	1 (2.8)	1 (3.0)
Study drug–related	1 (2.9)	0	1 (3.0)
Serious AE	13 (37.1)	18 (50.0)	13 (39.4)
Study drug–related	0	1 (2.8)	1 (3.0)

AE=adverse event; CAS=caspofungin; D/C=discontinuation; RZF=rezafungin; TEAE=treatment-emergent AE (occurring after first dose of study drug is administered).
[a]Safety population: all subjects who received any amount of study drug.

- Overall, the safety and tolerability of rezafungin was similar to that of caspofungin.
- Most patients experienced at least one treatment-emergent AE (TEAE).
- The rate of severe AEs was slightly lower with the rezafungin 400 mg/200 mg regimen (Group 2) compared with Groups 1 and 3.
- The incidence of TEAEs leading to study drug discontinuation was relatively higher in Group 1 and similar in Groups 2 and 3; however, only two (n=1 each in Groups 1 and 3) were considered possibly related to study drug (Table 2).
- No concerning trends in System Organ Class groups or specific AEs were observed.
- The overall mortality rate was 15.2% in Group 1, 9.7% in Group 2, and 17.9% in Group 3.

RESULTS (cont'd)

Efficacy

- Rezafungin demonstrated efficacy in patients with candidemia and/or IC (Table 3), with the highest rates of Overall Success and Clinical Cure observed in Group 2 (rezafungin 400 mg/200 mg dose regimen).
- Indeterminate responses due to missing data point(s), particularly in Group 1, limited evaluation of outcomes and led to analyses excluding Indeterminates (Table 3).
  - The most common reasons for Indeterminate assessments in Overall Success were inadequate number of cultures (n=4) and assessment of systemic signs not completed (n=3).

Table 3: Overall Response and PI Assessment of Clinical Response at Day 14 and All-Cause Mortality at Day 30 (mITT[a])

Outcome	Group 1: RZF 400 mg qWk (N=33)	Group 2: RZF 400 mg/200 mg qWk (N=31)	Group 3: CAS 70 mg/50 mg QD (N=28)
	n (%)		
Overall Success (D14)	19 (57.6)	22 (71.0)	18 (64.3)
Failure	7 (21.2)	6 (19.4)	8 (28.6)
Indeterminate	7 (21.2)	3 (9.7)	2 (7.1)
Overall Success (D14), excluding Indeterminate[b]	19/26 (73.1)	22/28 (78.6)	18/26 (69.2)
Failure	7/26 (26.9)	6/28 (21.4)	8/26 (30.8)
Clinical Cure[c] (D14)	25 (75.8)	24 (77.4)	20 (71.4)
Failure	7 (21.2)	4 (12.9)	8 (28.6)
Indeterminate	1 (3.0)	3 (9.7)	0
Clinical Cure[c] (D14), excluding Indeterminate[b]	25/32 (78.1)	24/28 (85.7)	20/28 (71.4)
Failure	7 (21.9)	4 (14.3)	8 (28.6)
Mortality (D30)	5 (15.2)	1 (3.2)	3 (10.7)

CAS=caspofungin; PI=principal investigator; RZF=rezafungin.
[a]mITT (Microbiological Intent-to-treat) population: all subjects who received ≥1 dose of study drug and had documented *Candida* infection.
[b]Indeterminate response indicates inability to assess outcome due to missing data point(s).
[c]As assessed by the PI; most closely approximates primary outcome in prior candidemia/IC clinical trials

CONCLUSIONS

- Rezafungin IV demonstrated clinical safety and efficacy in the treatment of candidemia/IC.
- Rezafungin was safe and well-tolerated at both dose regimens.
- High numbers of Indeterminate responses in Group 1 accounted for an apparent difference in the rates of Overall Success and Clinical Cure.
- The rezafungin 400 mg/200 mg once-weekly dosing regimen had the highest efficacy in all assessments.
- These results support the use of rezafungin for further clinical study in Phase 3.

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