Treatment outcomes in candidaemia and/or invasive candidiasis among patients receiving rezafungin or caspofungin while the fungal culture was still positive

P2063

OA Cornely[1], GR Thompson III[2], A Soriano[3], B J Kullberg[4], M Kollef[5], J Vazquez[6], PM Honore[7], M Bassetti[8], J Pullman[9], C Dignani[10], AF Das[11], T Sandison[11], PG Pappas[12] on behalf of the ReSTORE trial investigators

[1]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Internal Medicine, Excellence Center for Medical Mycology (ECMM), Cologne, Germany; University of Cologne, Faculty of Medicine and University Hospital Cologne, Chair Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany; University of Cologne, Faculty of Medicine and University Hospital Cologne, Clinical Trials Centre Cologne (ZKS Köln), Cologne, Germany; German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany; [2]University of California Davis Medical Center, Davis, CA, USA; [3]Hospital Clínic de Barcelona, IDIBAPS, University of Barcelona, Spain; [4]Radboud University Medical Center, Nijmegen, The Netherlands; [5]Washington University, St. Louis, MO, USA; [6]Augusta University, Augusta, GA, USA; [7]Brugman University Hospital, Brussels, Belgium; [8]University of Genoa, Genoa, Italy; [9]Mercury Street Medical, Butte, MT, USA; [10]PSI-CRO, Durham, NC, USA; [11]Cidara Therapeutics, Inc., San Diego, CA, USA; [12]University of Alabama at Birmingham, Birmingham, AL, USA.

INTRODUCTION AND OBJECTIVES

- Despite wide-spread availability of antifungal medicines, candidemia and invasive candidiasis infections remain significant causes of morbidity and mortality in hospitals.[1,2]
- The Phase 3 ReSTORE trial (NCT03667690) demonstrated non-inferiority of the novel once-weekly echinocandin, rezafungin, against caspofungin for Day 30 all-cause mortality (ACM) and Day 14 global cure in subjects with candidaemia/invasive candidiasis.[3]
- The current analysis examined ReSTORE data for those subjects with a positive culture close to the randomisation time point to understand the potential impact on efficacy outcomes.

METHODS

- ReSTORE comprised a global, randomised, double-blind, double-dummy, Phase 3 non-inferiority trial. Adults ≥18 years with candidaemia/invasive candidiasis received rezafungin once-weekly intravenous infusion (Week 1: 400 mg; Weeks 2–4: 200 mg) or once daily caspofungin (Day 1: 70 mg; Days 2–28: 50 mg) for ≥14 days and ≤4 weeks.
- The current post hoc analysis examined data for a subgroup the modified intention-to -treat (mITT) population that had positive blood culture ≤12 hours prior to or ≤72 hours following randomisation, or positive culture from another normally sterile site ≤48 hours prior to or ≤72 hours after randomisation.
- Efficacy endpoints included Day 30 ACM, global cure (assessed by an independent data review committee [DRC]) and mycological response on Days 5 and 14. Safety endpoints included reporting of treatment-emergent adverse events (TEAEs) and treatment-related TEAEs.

RESULTS

Study population

- The analysis included 38 participants treated with rezafungin and 46 subjects receiving caspofungin. Table 1 shows the baseline demographics and characteristics for the population included in the analysis. The treatment arms were generally well-balanced concerning patient demographics and *Candida* species at baseline.

Table 1. Baseline demographics and characteristics for subjects included in the analysis.

	Rezafungin (400/200 mg) (N=38)	Caspofungin (70/50 mg) (N=46)
Age, mean ± SD (range), years	58.9 ± 14.11 (27, 87)	62.9 ± 14.55 (20, 87)
<65 years, n (%)	24 (63.2)	25 (54.3)
≥65 years, n (%)	14 (36.8)	21 (45.7)
Gender, n (%)		
Male	26 (68.4)	27 (58.7)
Female	12 (31.6)	19 (41.3)
Race, n (%)		
Black or African American	2 (5.4)	1 (2.2)
Asian	9 (24.3)	16 (35.6)
White	26 (70.3)	27 (60.0)
Other/not reported	1 (2.6)	2 (4.4)
Final diagnosis, n (%)		
Candidaemia	29 (76.3)	33 (71.7)
Invasive candidiasis[a]	9 (23.7)	13 (28.3)
Modified APACHE II score[b]		
≥20, n (%)	5 (13.5)	11 (23.9)
<20, n (%)	32 (86.5)	35 (76.1)
ANC <500/µL, n (%)	4 (10.8)	4 (8.7)
Mechanically ventilated at baseline, n (%)	29 (76.3)	31 (67.4)
Candida species		
Candida albicans	17 (44.7)	21 (45.7)
Candida dubliniensis	2 (5.3)	0
Candida glabrata	8 (21.1)	13 (28.3)
Candida krusei	2 (5.3)	2 (4.3)
Candida metapsilosis	1 (2.6)	0
Candida parapsilosis complex	4 (10.5)	7 (15.2)
Candida tropicalis	7 (18.4)	10 (21.7)

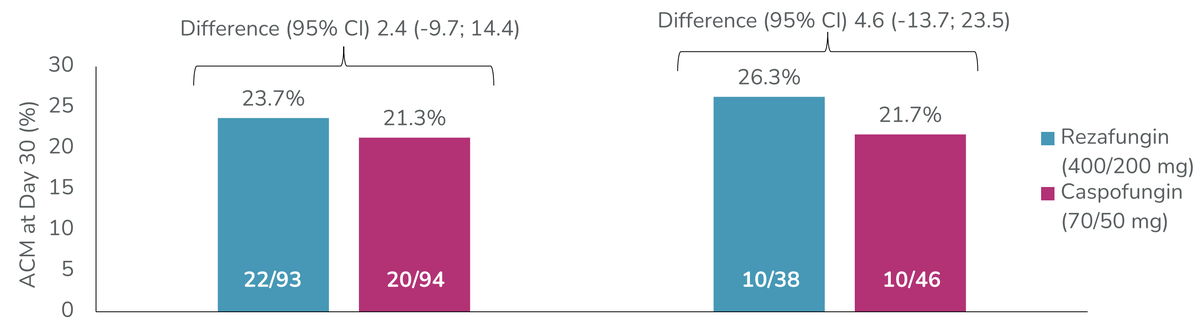
[a]Patients who progressed from candidaemia to invasive candidiasis based on radiological and/or tissue/fluid culture assessment through Day 14.
[b]Reported for patients with APACHE II score data available.
Analysis based on a subgroup of subjects diagnosed with candidaemia and/or invasive candidiasis by blood culture ≤12 hours prior to or ≤72 hours following randomisation, or via culture from another normally sterile site ≤48 hours prior to or ≤72 hours after randomisation. Subjects received either intravenous injection of rezafungin once-weekly (Week 1: 400 mg; Weeks 2–4: 200 mg) or caspofungin once daily (Day 1: 70 mg; Days 2–28: 50 mg) for ≥14 days (≤4 weeks).
Abbreviations: ANC, absolute neutrophil count; APACHE, acute physiology and chronic health evaluation; SD, standard deviation.

Day 30 ACM, global response and mycological response

- Figure 1 shows the Day 30 ACM rate for the full mITT population and the subgroup included in the post hoc analysis. Among patients with a positive culture close to randomisation, ACM at Day 30 was 26.3% (rezafungin arm) and 21.7% (caspofungin arm), with a between-group difference in outcome (95% confidence interval [CI]) of 4.6 (-13.7; 23.5). Day 30 ACM was 23.7% (rezafungin arm) and 21.3% (caspofungin arm) in the mITT population (difference [95% CI] 2.4 [-9.7; 14.4]).
- Figure 2 shows outcomes from the post hoc analysis for global response and mycological response at Days 5 and 14.
- DRC-evaluated Day 5 global response was 55.3% (rezafungin arm) and 43.5% (caspofungin arm). The between-group difference (95% CI) was 11.8 (-9.7; 32.2). Global response at Day 14 was 55.3% (rezafungin arm) and 50.0% (caspofungin arm). The between-group difference (95% CI) was 5.3 (-16.1; 26.0).
- DRC-assessed Day 5 mycological response was 71.1% (rezafungin arm) and 50.0% (caspofungin arm). The between-group difference (95% CI) was 21.1 (-0.2; 40.2). Mycological response at Day 14 was 63.2% in the rezafungin treatment arm and 54.3% in the caspofungin arm. The between-group difference (95% CI) was 8.8 (-12.4; 29.0).

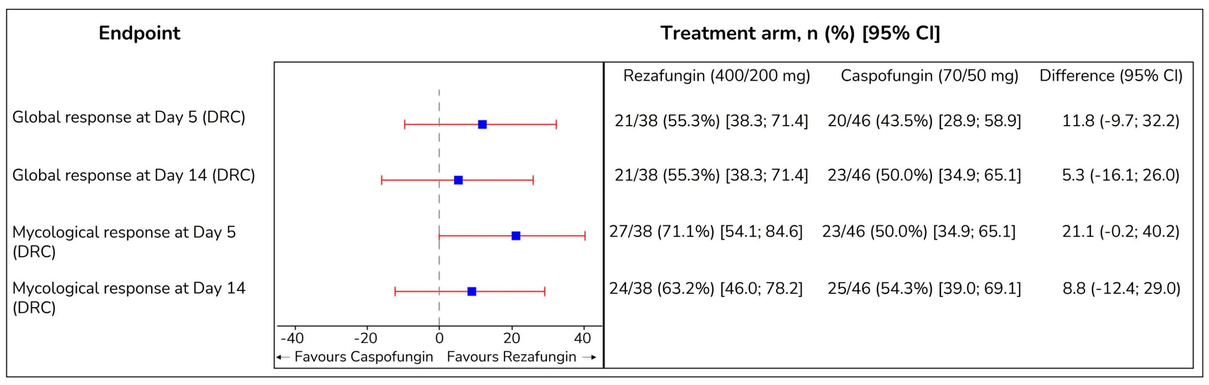
RESULTS (CONTINUED)

Figure 1. Day 30 ACM with rezafungin (400 mg/200 mg) or caspofungin (70 mg/50 mg) in the mITT population and in subjects with a positive culture close to randomisation



The mITT population comprised all ReSTORE subjects with a mycological diagnosis of candidaemia and/or invasive candidiasis within 96 hours of randomisation who received ≥1 dose of study drug. Subjects with a positive culture close to randomisation comprised those in the mITT population who were diagnosed with candidaemia and/or invasive candidiasis by blood culture ≤12 hours prior to or ≤72 hours following randomisation, or via culture from another normally sterile site ≤48 hours prior to or ≤72 hours after randomisation. Subjects received either rezafungin once-weekly intravenous injection (Week 1: 400 mg; Weeks 2–4: 200 mg) or once daily caspofungin (Day 1: 70 mg; Days 2–28: 50 mg) for ≥14 days (≤4 weeks).
Abbreviations: ACM, all-cause mortality; CI, confidence interval; mITT, modified intention to treat. .

Figure 2. Treatment outcomes with rezafungin (400 mg/200 mg) or caspofungin (70 mg/50 mg) for subjects with a positive culture close to randomisation



Analysis based on a subgroup of subjects diagnosed with candidaemia and/or invasive candidiasis by blood culture ≤12 hours prior to or ≤72 hours following randomisation, or via culture from another normally sterile site ≤48 hours prior to or ≤72 hours after randomisation. Subjects received either intravenous injection of rezafungin once-weekly (Week 1: 400 mg; Weeks 2–4: 200 mg) or caspofungin once daily (Day 1: 70 mg; Days 2–28: 50 mg) for ≥14 days (≤4 weeks).
Abbreviations: CI, confidence interval; DRC, independent data review committee.

Time to negative blood culture

- For subjects with a positive culture close to randomisation, median time to negative blood culture was 23.9 hours (rezafungin arm) and 60.5 hours (caspofungin arm; *P*=0.094; Log Rank Test). At 24 hours, negative blood culture was observed in 55.2% (rezafungin arm) and 27.3% (caspofungin arm). At 48 hours, 58.6% (rezafungin arm) and 43.8% (caspofungin arm) had negative blood culture.

Safety data

- Among subjects included in the post hoc analysis, treatment-related TEAEs were reported by 5 (13.2%) in the rezafungin arm and 3 (6.5%) in the caspofungin arm (Table 2). One subject in the rezafungin arm had a serious adverse event (SAE) related to treatment (infusion-related reaction) and 2 drug-related SAEs were reported in the caspofungin arm (elevated transaminase levels and anaphylactic shock). The SAE reported for the rezafungin arm occurred during the Day 3 placebo infusion and was therefore considered unlikely to be related to rezafungin therapy.

Table 2. Safety data for subjects with a positive culture close to randomisation

	Rezafungin (400/200 mg) (N=38)	Caspofungin (70/50 mg) (N=46)
Subjects with ≥1 TEAE, n (%)	35 (92.1)	39 (84.8)
Subjects with ≥1 drug-related TEAE, n (%)	5 (13.2)	3 (6.5)
Subjects with ≥1 drug-related TEAEs (preferred term), n (%)		
Upper abdominal pain	1 (2.6)	0
Hyperphosphataemia	1 (2.6)	0
Hypomagnesaemia	1 (2.6)	0
Co-ordination abnormal	0	1 (2.2)
Nystagmus	0	1 (2.2)
Tremor	1 (2.6)	0
Erythema	1 (2.6)	0
Subjects with ≥1 SAE, n (%)	21 (55.3)	25 (54.3)
Subjects with ≥1 drug-related SAEs (preferred term), n (%)	1 (2.6)	2 (4.3)
Infusion-related reaction	1 (2.6)	0
Elevated transaminase levels	0	1 (2.2)
Anaphylactic shock	0	1 (2.2)

Safety outcomes reported for a subgroup of subjects diagnosed with candidaemia and/or invasive candidiasis by blood culture ≤12 hours prior to or ≤72 hours following randomisation, or via culture from another normally sterile site ≤48 hours prior to or ≤72 hours after randomisation. Subjects received either intravenous injection of rezafungin once-weekly (Week 1: 400 mg; Weeks 2–4: 200 mg) or caspofungin once daily (Day 1: 70 mg; Days 2–28: 50 mg) for ≥14 days (≤4 weeks).
Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event

CONCLUSION

- Day 30 ACM and Day 14 global response remained comparable between rezafungin and caspofungin treatment groups for ReSTORE trial subjects who had a positive culture close to randomisation.
- The median time to negative blood culture was significantly faster (*P*=0.094) in the rezafungin arm compared with the caspofungin arm. Improvements were also seen for other early outcomes, including Day 5 mycological response and the proportion of patients with a negative blood culture at 24 hours and 48 hours, suggesting a potential clinical effect associated with the front-loaded exposure of rezafungin.
- Safety outcomes were similar between the rezafungin and caspofungin treatment groups.

Disclosures

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