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Week 1 outcomes of rezafungin vs caspofungin treatment for candidemia and invasive candidiasis (CIC): Pooled analysis of two randomized trials exploring optimal echinocandin duration

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INTRODUCTION

- The second-generation echinocandin rezafungin (RZF) is approved for adult patients with CIC and is dosed once weekly, via a front-loaded regimen.[1,2]
- The Phase 2 STRIVE trial showed that RZF was safe and efficacious in CIC.[3]
- In the Phase 3 ReSTORE trial, RZF was non-inferior to caspofungin (CSF) at Day 14 (global cure) and Day 30 (all-cause mortality; ACM).[2]
- Pooled analysis of both trials confirmed this non-inferiority and suggested a potential early treatment benefit for RZF.[4]
- Subgroup analysis of these pooled data was performed, to assess Week 1 outcomes in relation to later time points and to explore optimal treatment duration.

METHODS

- Patients had systemic signs of candidemia, invasive candidiasis, or both, plus mycological evidence.
- Patients were randomized to receive[a]:
  - RZF 400 mg IV in Week 1, then 200 mg once weekly, for a total of two to four doses; or
  - CSF 70 mg IV loading dose, then 50 mg once daily for ≤4 weeks.
- Data were pooled from ReSTORE and STRIVE for subgroup analyses:[4]
  - Efficacy subgroup analysis: pooled mITT population at Days 7, 14 and 30.
  - Safety subgroup analysis: pooled safety population at Day 7.
- Outcomes assessed were safety, ACM, mycological response and time to first negative blood culture (TTNBC).

[a]Oral step-down therapy (fluconazole for CSF; placebo for RZF) was optional after ≥3 days IV treatment.

RESULTS

Table 1. Week 1 safety summary for RZF (safety population)

Patients with ≥1 event, n (%)	RZF n=151	CSF n=166
AE	109 (72)	101 (61)
TEAE	107 (71)	101 (61)
Most frequent TEAEs[a]		
Hypokalemia	10 (7)	10 (6)
Diarrhea	9 (6)	7 (4)
Anemia	9 (6)	5 (3)
Study drug-related TEAE	15 (10)	11 (7)
Severe / Grade ≥3[b] TEAE	31 (21)	33 (20)
SAE	23 (15)	23 (14)
Most frequent SAEs[c]		
Septic shock	4 (3)	6 (4)
Multiple organ dysfunction syndrome	2 (1)	2 (1)
Pneumonia	2 (1)	1 (<1)
Sepsis	0	2 (1)
Cardiac arrest	2 (1)	0
Study drug-related SAE	1 (<1)	2 (1)
Types of study drug-related SAEs		
Infusion-related reaction	1 (<1)	0
Ventricular tachycardia	0	1 (<1)
Anaphylactic shock	0	1 (<1)
SAE leading to death	12 (8)	12 (7)
Study drug-related SAE leading to death	0	0
TEAE leading to study drug discontinuation	10 (7)	9 (5)
TEAE leading to study discontinuation	13 (9)	13 (8)

[a]≥5% of patients in either group; [b]Severity was categorized as mild, moderate or severe in STRIVE, and graded in ReSTORE; [c]≥1% of patients in either group. AE, adverse event; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

Table 2. Outcomes at Days 7, 14 and 30 (mITT population)

Outcome	Day 7		Day 14		Day 30	
	RZF n=139	CSF n=132	RZF n=139	CSF n=132	RZF n=139	CSF n=132
ACM						
Deaths, n (%)	11 (7.9)	8 (6.1)	16 (11.5)	13 (9.8)	26 (18.7)	27 (20.5)
Difference (95% CI)	2.1 (−5.0, 9.2)		1.7 (−6.4, 9.7)		−2.3 (−12.0, 7.4)	
Mycological response						
Eradication, n (%)	99 (71.2)	84 (63.6)	100 (71.9)	88 (66.7)	92 (66.2)	77 (58.3)
Difference (95% CI)	7.6 (−3.5, 18.6)		5.3 (−5.7, 16.2)		7.7 (−3.6, 19.0)	
TTNBC,[a] n	109	103	109	103	109	103
Patients with an event, n (%)	94 (86.2)	77 (74.8)	99 (90.8)	85 (82.5)	99 (90.8)	85 (82.5)
TTNBC, median (IQR), hours	22.3 (14.3– 47.0)	24.3 (17.8– 111.3)	22.3 (14.3–47.0)	24.3 (17.8–111.3)	22.3 (14.3–47.0)	24.3 (17.8–111.3)

[a]Blood culture sampling was repeated daily (preferred) or every 2 days until first negative culture result. ACM, all-cause mortality; CSF, caspofungin; CI, confidence interval; IQR, interquartile range; mITT, modified intent-to-treat; RZF, rezafungin; TTNBC, time to first negative blood culture (patients with positive blood culture before randomization).

Figure 1. Day 7 difference in ACM rate (% [95% CI], RZF−CSF; mITT population)

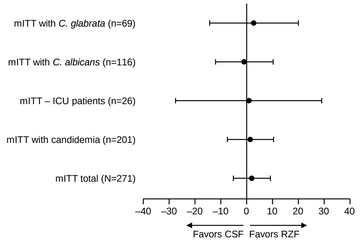
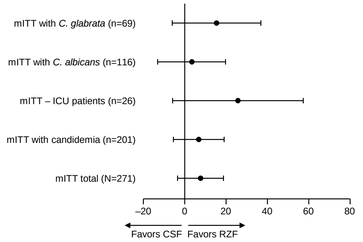
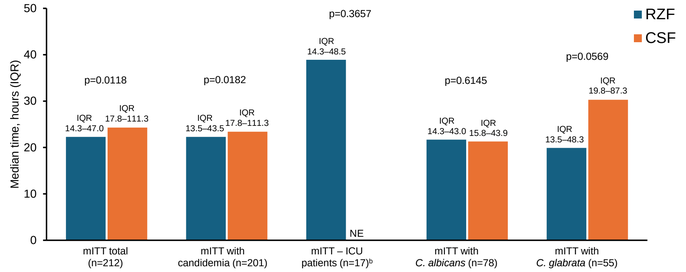


Figure 2. Day 7 difference in mycological response rate (% [95% CI], RZF−CSF; mITT population)



ACM, all-cause mortality; CI, confidence interval; CSF, caspofungin; ICU, intensive care unit; mITT, modified intent-to-treat; RZF, rezafungin.

Figure 3. Median (IQR) TTNBC (mITT population) at Day 7[a]



[a]Day 7 subanalyses were limited by small numbers. [b]Not estimable for ICU patients treated with caspofungin. CI, confidence interval; CSF, caspofungin; ICU, intensive care unit; IQR, interquartile range; mITT, modified intent-to-treat; NE, not estimable; RZF, rezafungin.

RESULTS SUMMARY

- RZF's Week 1 safety profile was comparable to its overall safety profile and to that of CSF.[2–4] The most frequent TEAEs were hypokalemia, diarrhea and anemia (**Table 1**).
- ACM was similar between the two groups as early as Day 7 and remained similar at later time points (**Table 2**, **Figure 1**).
- Mycological response was comparable between groups by Day 7 and at later time points (**Table 2**, **Figure 2**).
- Median TTNBC was significantly shorter (p=0.0118) for RZF vs CSF overall at Day 7 (**Figure 3**).

CONCLUSIONS

RZF demonstrated **good safety** and **efficacy**, which was **comparable to CSF**, in the **first week of treatment**.

Early treatment benefit of RZF might occur due to its front-loaded dosing regimen.[4]

RZF resulted in **shorter TTNBC** compared with **CSF**.

These data provide the **foundation** for **future investigation** of the **optimal duration** of **echinocandin therapy** for CIC.

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