Poster #L0244

ReSTORE: Efficacy and Safety Results of the Phase 3, Noninferiority Trial of Rezafungin in the Treatment of Candidemia and/or Invasive Candidiasis (IC)

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INTRODUCTION

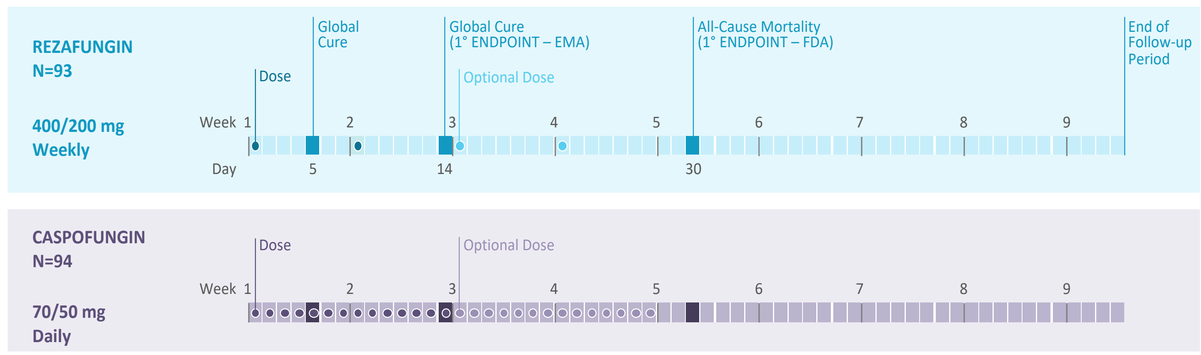
Candidemia and IC are life-threatening fungal infections, particularly for vulnerable patient populations such as the critically ill, elderly, post-transplantation, and other hospitalized patients with serious medical conditions.[1-4]

Rezafungin is a once-weekly, next-generation echinocandin in development for treatment of candidemia and IC and for prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp. in patients undergoing allogeneic blood and marrow transplantation. A Phase 2 treatment trial (STRIVE; NCT02734862) demonstrated the safety and efficacy of rezafungin in patients with candidemia and/or IC.[5] Herein are results of the recently completed ReSTORE trial (NCT03667690), the pivotal Phase 3 non-inferiority (NI) trial of rezafungin once weekly compared with caspofungin once daily for the treatment of candidemia and IC.

METHODS

- ReSTORE is a prospective, global, multicenter, double-blind, double-dummy, 1:1 randomized, controlled trial to evaluate the efficacy and safety of rezafungin once weekly (QWk) versus caspofungin once daily (QD) in adults (aged ≥18 years) with candidemia and/or IC documented by systemic signs and mycological confirmation (**Fig 1**).
- Patients were randomized to receive rezafungin QWk (400 mg on Week 1, then 200 mg QWk) or caspofungin QD (70 mg/50 mg) for ≥14 days (up to 4 weeks), with optional oral fluconazole step-down in the caspofungin arm.
- Efficacy was assessed in the modified intent-to-treat population (mITT; subjects having positive culture from blood or other normally sterile site ≤96h before randomization and ≥1 dose of study drug). The Safety population included any subject who received any amount of study drug.
- The primary endpoints were Global Cure at Day 14 (EMA) and all-cause mortality (ACM) at Day 30 (US FDA), respectively, with a 20% NI margin for both.

Figure 1. Study Design of ReSTORE (NCT03667690)

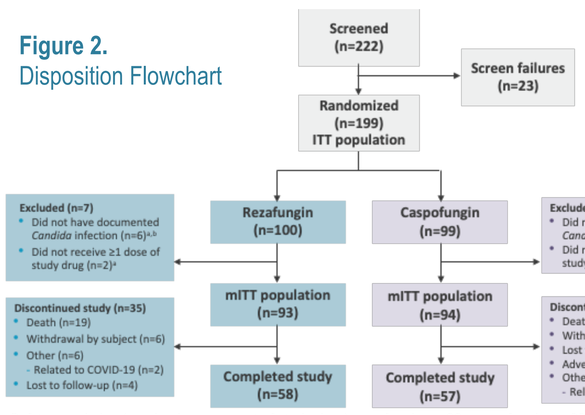


RESULTS

Subject Disposition and Baseline Characteristics

- There were 187 subjects in the mITT population and 196 subjects in the Safety population (**Fig 2**).
- Groups were well matched (**Table 1**). Enrollment was distributed across Europe/Israel/Turkey (39.7%); Asia-Pacific, excluding China/Taiwan (26.6%); US (25.6%), China/Taiwan (7.5%), and South America (0.5%).

Figure 2. Disposition Flowchart



Safety population (received any amount of study drug): rezafungin, n=98; caspofungin, n=98.
[a]Reasons are not mutually exclusive; [b]Based on Central Laboratory evaluation of a blood culture or a culture from a normally sterile site obtained ≤4 days (96 hours) before randomization.

Table 1. Demographics at Baseline – mITT population

Characteristic	Rezafungin QWk (N=93)	Caspofungin QD (N=94)
Age, mean ± SD, years (range)	59.5 ± 15.8 (19, 89)	61.9 ± 14.6 (20, 91)
Age <65 years, n (%)	55 (59.1)	56 (59.6)
Age ≥65 years, n (%)	38 (40.9)	38 (40.4)
Female, n (%)	31 (33.3)	38 (40.4)
Race, n (%)		
Asian	23 (24.7)	31 (33.0)
Black or African American	5 (5.4)	4 (4.3)
White	59 (63.4)	55 (58.5)
Other/Not reported	6 (6.4)	4 (4.3)
Final Diagnosis[a]		
Candidemia only, n (%)	64 (68.8)	67 (71.3)
Invasive candidiasis, n (%)[a]	29 (31.2)	27 (28.7)
Modified APACHE II score[b]		
Mean (SD)	12.3 (7.54)	13.0 (7.18)
Median (range)	12 (0–40)	11.5 (0–37)
≥20, n (%)	12 (12.9)	17 (18.1)
<20, n (%)	80 (86.0)	77 (81.9)
Mean BMI[b], kg/m^2 ± SD	25.5 ± 7.19	24.5 ± 6.22
ANC <500/μL[b], n (%)	7 (7.5)	5 (5.3)

[a]Subjects who were randomized as having candidemia only and progressed to IC based on radiologic and/or tissue/fluid culture assessment through Day 14 are considered to have a final diagnosis of IC. IC group includes some subjects with deep tissue infection and candidemia.
[b]Reported for patients with data available for the given characteristic.

Primary Efficacy Endpoints

- Non-inferiority was achieved on ACM at Day 30 (**Table 2**) and Global Cure at Day 14 (**Table 3**).

Table 2. All-cause mortality at Day 30 (–2 days)

Endpoint	Proportion of Patients, % (n)	
	Rezafungin QWk N=93	Caspofungin QD N=94
ACM at Day 30	23.7 (22)	21.3 (20)
Difference (95% CI)	2.4 (–9.7, 14.4)	
Known deceased	20.4 (19)	18.1 (17)
Unknown survival	3.2 (3)	3.2 (3)
Alive	76.3 (71)	78.7 (74)

Table 3. Global response at Day 14 (±1 day)

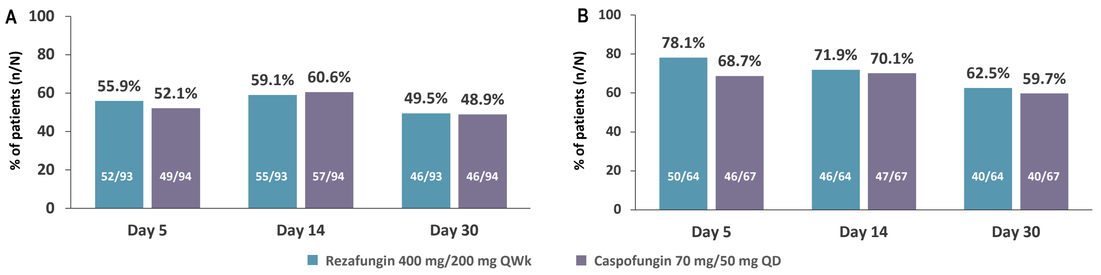
Endpoint	Proportion of Patients, % (n)	
	Rezafungin QWk N=93	Caspofungin QD N=94
Global Cure[a] at Day 14	59.1 (55)	60.6 (57)
Difference (95% CI)[b]	–1.1 (–14.9 to 12.7)	
Failure	30.1 (28)	30.9 (29)
Indeterminate	10.8 (10)	8.5 (8)

[a]Defined as 1) clinical cure as assessed by the investigator; 2) radiological cure for those patients with IC documented by radiologic/imaging evidence at baseline; and 3) mycological eradication, as confirmed by an independent DRC.
[b]Adjusted for the two randomization strata and APACHE II score/ANC at screening.

Secondary / Exploratory Efficacy Endpoints

- Global Cure and Mycological Eradication at multiple timepoints (Days 5, 14, and 30) demonstrate overall comparable outcomes between treatment arms over time, with relatively greater numerical differences observed at Day 5 (**Figs 3A, 3B**).

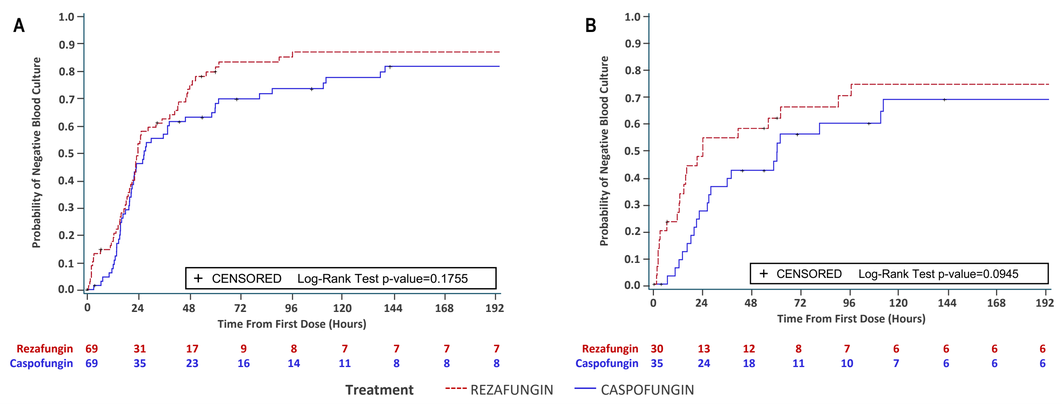
Figure 3. Efficacy outcomes at Days 5, 14, and 30 on (A) Global Cure[a] and (B) Mycological Eradication[b]



[a]Confirmed by an independent DRC based on 1) clinical cure as assessed by the investigator; 2) radiological cure for those patients with IC documented by radiologic/imaging evidence at baseline; and 3) mycological eradication.
[b]Subjects with candidemia only.

- Time to negative blood culture (TTNBC) was evaluated in subjects who had a positive blood culture at Screening (**Fig 4A**) and a subgroup whose positive blood culture was proximal to randomization (within 12 h prior to or 72 h after randomization) (**Fig 4B**).

Figure 4. TTNBC for (A) subjects with positive blood culture at Screening and (B) subjects with positive blood culture proximal to randomization.



Safety

- No concerning safety trends were observed in overall rates of adverse events (AEs) (**Table 4**) or serious AEs (SAEs) (**Table 5**).
- Of treatment-emergent AEs (TEAEs) occurring in >5% of subjects, the most common in each treatment arm were:
  - Rezafungin group: Pyrexia (n=14, 14.3%), hypokalaemia (n=13, 13.3%), pneumonia (n=10, 10.2%), septic shock (n=10, 10.2%), and anaemia (n=9, 9.2%).
  - Caspofungin group: Hypokalaemia (n=9, 9.2%), septic shock (n=9, 9.2%), anaemia (n=9, 9.2%), acute kidney injury (n=8, 8.2%), and diarrhoea (n=7, 7.1%).

Table 4. Summary of Adverse Events

Adverse Event	Proportion of Patients with an AE, n (%)	
	Rezafungin QWk N=98	Caspofungin QD N=98
≥1 TEAE	89 (90.8)	83 (84.7)
Study drug–related[a]	16 (16.3)	9 (9.2)
Serious AE	55 (56.1)	52 (53.1)
Study drug–related[a]	2 (2.0)	3 (3.1)
AE leading to study drug discontinuation	13 (13.3)	11 (11.2)

TEAE=treatment-emergent adverse event.
[a]May be considered related to study drug or placebo due to investigator blinding. 5 AEs in the rezafungin arm and 0 AEs in the caspofungin arm were considered related to placebo administration.

Table 5. Summary of Serious Adverse Events (>5% in Either Arm)

System Organ Class (Preferred Term)	No. of Subjects, n (%)	
	Rezafungin QWk N=98	Caspofungin QD N=98
Cardiac disorders	7 (7.1)	4 (4.1)
Gastrointestinal disorders	7 (7.1)	9 (9.2)
General disorders and administration site conditions	8 (8.2)	4 (4.1)
(Multiple organ dysfunction syndrome)	5 (5.1)	2 (2.0)
Infections and infestations	24 (24.5)	29 (29.6)
(Septic shock)	8 (8.2)	8 (8.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (5.1)	2 (2.0)
Respiratory, thoracic and mediastinal disorders	7 (7.1)	9 (9.2)
Vascular disorders	6 (6.1)	0 (0.0)

CONCLUSIONS

- Rezafungin was found to be non-inferior to caspofungin for both of its primary endpoints (all-cause mortality at Day 30, US FDA; global cure at Day 14, EMA).
- Rates of AEs and SAEs were similar between study arms.
- Exploratory endpoints of early efficacy (mycological eradication and global cure at Day 5, TTNBC) support the conclusion that rezafungin is efficacious for the treatment of candidemia and IC
- Further analyses of this pivotal, phase 3, NI trial are underway.

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