Prof. Alex Soriano
asoriano@clinic.cat

Patient-Level Meta-Analysis of Efficacy and Safety from STRIVE and ReSTORE: Randomized, Double-blinded, Multicenter Phase 2 and Phase 3 Trials of Rezafungin in the Treatment of Candidemia and/or Invasive Candidiasis

A. Soriano,[1] G.R. Thompson III,[2] O.A. Cornely,[3] B. J. Kullberg,[4] M. Kollef,[5] J. Vazquez,[6] P.M. Honore,[7] M. Bassetti,[8] J. Pullman,[9] C. Dignani,[10] A.F. Das,[11] T. Sandison,[11] P.G. Pappas[12] on behalf of the ReSTORE trial investigators

[1]Hospital Clínic de Barcelona, IDIBAPS, University of Barcelona, Spain; [2]University of California Davis Medical Center, Davis, CA, USA; [3]Univ of Cologne and Univ Hospital Cologne, Excellence Center for Medical Mycology (ECMM), Cologne, Germany; [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

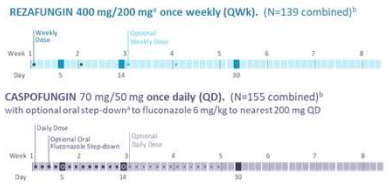
INTRODUCTION

Candidemia and invasive candidiasis (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. Herein are results of the INTEGRATED analysis of rezafungin – a patient-level meta-analysis of data from 294 subjects, from the Phase 2 trial (STRIVE; NCT02734862) and the recently completed pivotal Phase 3 non-inferiority (NI) ReSTORE trial (NCT03667690) of rezafungin once weekly (QWk) compared with caspofungin once daily (QD) for the treatment of candidemia and IC. ReSTORE showed rezafungin noninferiority to caspofungin for 30-day all-cause mortality (ACM) and global response at Day 14 with comparable safety.

METHODS

- Both trials were prospective, global, multicenter, double-blind, randomized, controlled trials to evaluate the efficacy and safety of rezafungin QWk versus caspofungin QD in adults (aged ≥18 years) with candidemia and/or IC documented by systemic signs and mycological confirmation (**Figure 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 population: all subjects (Ph2+Ph3) who received ≥1 dose of study drug and had documented *Candida* infection (candidemia and/or IC based on systemic signs and mycological confirmation). The Safety population included any subject who received any amount of study drug
- Pooled endpoints included the primary endpoint of all-cause mortality (ACM) at Day 30 and secondary/exploratory endpoints of Mycological response at Day 5 and time to first negative blood culture (TTNBC). Safety was assessed by adverse events (AEs) and serious AEs (SAEs)

Figure 1. Aligned STRIVE and ReSTORE Study dosing and design



[a]The rezafungin arm included optional oral step-down to placebo, to maintain the study blind.
[b]mITT population: as described in methods.

RESULTS

Subject Disposition and Baseline Characteristics

- There were 294 subjects in the mITT population
- Groups were well balanced at baseline (**Table 1**)

Table 1. Demographics at Baseline – mITT population

Characteristic	Rezafungin QWk (N=139)	Caspofungin QD (N=155)
Age, years, mean ± SD, (range)	59.8 ± 15.7 (19, 91)	60.8 ± 15.0 (20, 93)
≥65 years, n (%)	57 (41.0)	63 (40.6)
Female, n (%)	49 (35.3)	65 (41.9)
Race, n (%)		
Asian	24 (17.3)	34 (21.9)
Black or African American	11 (7.9)	8 (5.2)
White	95 (68.3)	106 (68.4)
Other[a]	9 (6.5)	7 (4.5)
BMI, kg/m², mean ±SD	25.78 ± 7.8	25.12 ± 6.02
ANC <500 µL[b,c], n (%)	7 (5.0)	5 (3.2)
Diagnosis, n (%)		
Candidemia only	100 (71.9)	115 (74.2)
Invasive candidiasis[d]	39 (28.1)	40 (25.8)
Modified APACHE II SCORE, n (%)[c]		
≥20	21 (15.1)	26 (16.8)
<20	116 (83.5)	126 (81.3)
Geographic region, n (%)		
United States	43 (30.9)	46 (29.7)
Europe/Israel/Turkey	67 (48.2)	76 (49.0)
Asia Pacific (ex China and Taiwan)	21 (15.1)	27 (17.4)
China/Taiwan	8 (5.8)	6 (3.9)

[a]Includes American Indian or Alaska native and not reported.
[b]At randomization.
[c]Reported for patients with data available.
[d]IC group includes some subjects with both deep tissue infection and candidemia.

Safety

- No concerning safety trends were observed in overall rates of AEs or SAEs (**Table 2**)

Table 2. Summary of Adverse Events

Adverse Event	Proportion of Patients with an AE, n (%)	
	Rezafungin QWk N=151	Caspofungin QD N=166
≥1 TEAE	138 (91.4)	138 (83.1)
Study drug–related[a]	22 (14.6)[a]	18 (10.8)
Serious AE	83 (55.0)	81 (48.8)
Study drug–related[a]	3 (2.0)[a]	5 (3.0)
AE leading to study drug discontinuation	14 (9.3)	15 (9.0)

TEAE=treatment-emergent adverse event.
[a]5 AEs assigned as study drug-related in the rezafungin group, including 2 serious AEs, were associated with placebo administration during blinded study drug administration.

Primary Efficacy Endpoints

- ACM at Day 30 was comparable between once-weekly rezafungin and once-daily caspofungin (**Figure 2**) and cure rates were comparable at day 14 (**Figure 3**)

Figure 2. All-cause mortality at Day 30

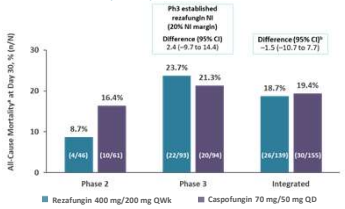
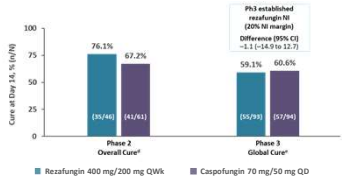


Figure 3. Cure rates at Day 14[c]

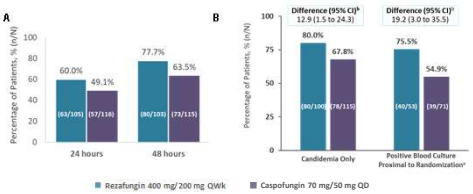


NI=non-inferiority.
[a]Subjects who died on or before Day 30, or with unknown survival status.
[b]Calculated using stratified analysis by study and by part A and B of STRIVE
[c]A difference in endpoint definitions precluded pooling of data on Cure (defined as "overall cure" in phase 2 and "global cure" in phase 3)
[d]Overall Cure (Phase 2): resolution of systemic signs attributable to candidemia or invasive candidiasis AND mycological eradication as demonstrated by a single tissue/fluid culture or 2 negative blood cultures at least 12 hours apart.
[e]Global Cure (Phase 3): investigator assessment of clinical cure AND mycological eradication as demonstrated by a single negative blood or tissue/fluid culture AND (if pertinent) improvement or resolution of evidence of invasive candidiasis on radiographic imaging.

Secondary / Exploratory Efficacy Endpoints

- Early efficacy was assessed by the percentage of patients with negative blood culture at 24 and 48 hours (**Figure 6A**), rates of mycological response at Day 5 (**Figure 6B**), and TTNBC (**Figure 7**)
- More pronounced difference in patients with a positive blood culture proximal to randomization suggests benefit from the potential clinical effect of front-loaded exposure

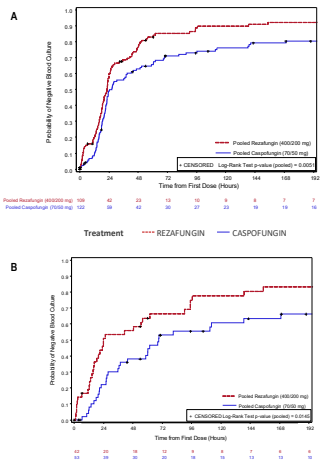
Figure 6. (A) negative blood culture at 24, 48 hours and (B) Mycological Eradication at day 5



[a]Positive culture from blood drawn within 12 hours prior to randomization or within 72 hours after randomization
[b]Calculated using stratified analysis by study and by part A and B of STRIVE.

- TTNBC was evaluated in subjects who had a positive blood culture at Screening (**Figure 7A**) and a subgroup whose positive blood culture was proximal to randomization (within 12 h prior to or 72 h after randomization) (**Figure 7B**)

Figure 7. TTNBC for (A) subjects with positive blood culture at Screening and (B) subjects with positive blood culture proximal to randomization.



CONCLUSIONS

- Rezafungin is a next-generation once-weekly echinocandin in development for treatment of candidemia and IC and for prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp. in blood and marrow transplantation
- 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) in the Phase 3 trial
- Rates of AEs and SAEs were similar between study arms
- In an exploratory analysis, rezafungin had a faster time to negative blood culture, suggesting the potential clinical effect of front-loaded exposure
- Integrated analysis of the Phase 2 and Phase 3 trials for rezafungin supports the conclusion that rezafungin is efficacious for the treatment of candidemia and IC

REFERENCES

1. Wisplinghoff H, et al. Clin Infect Dis. 2004;39:309-317. 2. Magill SS, et al. N Engl J Med. 2018;379:1732-1744. 3. Tsay SV, et al. Clin Infect Dis. 2020;71:e449-e453. 4. Thompson GR, et al, 2020;73:e3647-e3655.

DISCLOSURES AND ACKNOWLEDGEMENTS

We gratefully acknowledge the patients, investigators, and site personnel who participated in STRIVE and ReSTORE.
This presentation reports data from 2 clinical trials, the Phase 2 STRIVE trial (NCT02734862; funded by Cidara Therapeutics) and the Phase 3 ReSTORE trial (NCT03667690; funded by Cidara Therapeutics and Mundipharma).
This is an encore presentation of latebreaker oral abstract #04673 that was presented at the 32nd ECCMID (April 23-26, 2022; Lisbon, Portugal). Editorial support for this encore (poster reproduction) was provided by N. Andrews
Presenting on behalf of the Authors: V. Mehra (Kings College Hospital, London). Disclosures: Faculty speaker (Novartis, Celgene, Pfizer, Incyte, Cidara, Mundipharma, Jazz Pharma), advisory board member (Gilead, Pfizer, Sanofi), and research grants (Gilead, MSD, Pfizer).