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

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Candidemia and Invasive Candidiasis

"Fungal Diseases as Neglected Pathogens"[1]

- Global annual occurrence of invasive candidiasis: ~700,000[1,2]
- From the Emerging Infections Program: 56% of patients initially treated with fluconazole grew non-*albicans* species and 10.6% fluconazole-treated patients had a fluconazole-resistant isolate[3]
- Guidelines recommend empirical treatment with a first-generation echinocandin for patients with a high risk of invasive candidiasis or candidemia – is it enough?[4-6]
  - Patients classified as low-risk for Candida BSI and therefore left untreated had ~2x higher mortality (69% for untreated vs 35% for treated patients)[4]
  - Dosing of first-generation echinocandins, defined before modern PK/PD era, may be inadequate in the face of increasing echinocandin MICs (*FKS* mutations) and pharmacokinetics in critically ill, moderate-severe hepatic impairment, obesity, ECMO, and burn settings

1. Rodrigues and Nosanchuk. *PLOS Neglected Tropical Diseases* 2020; 14(2): e0007964. **2.** Bongomin et al. *J Fungi*. 2017;3:57. **3.** Gold, et al. *Clin Infect Dis*. 2021;73:1609-1616; **4.** Mazi et al. *Clin Infect Dis*. 2021; ciac004. **5.** Pea and Lewis. J Antimicrob Chemother 2018;73. **6.** Andes et al. *Antimicrob Agents Chemother* 2010;54.

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About Rezafungin

- Next-generation, once-weekly IV echinocandin
- Analog of anidulafungin, designed for increased stability and improved PK[1]
- Long-acting PK enables once-weekly dosing and front-loaded plasma exposure

	PHASE 3 TREATMENT TRIAL	PHASE 3 PROPHYLAXIS TRIAL
	ReSTORE	ReSPECT
Potential Indication	Treatment of candidemia & invasive candidiasis[2]	Prophylaxis against IFD caused by *Aspergillus*, *Candida* & *Pneumocystis* in allogeneic blood and marrow transplant patients[3]
Trial Size	187 patients in primary evaluable population (mITT)[2]	462 patients[3]
Trial Status	Complete[a]	Ongoing

Topline Results @ECCMID 2022
Latebreaker Poster LB0244

IFD=invasive fungal disease; PK=pharmacokinetics.

[a]Study sites in China are still recruiting patients for submission of rezafungin to the Center for Drug Evaluation in China.

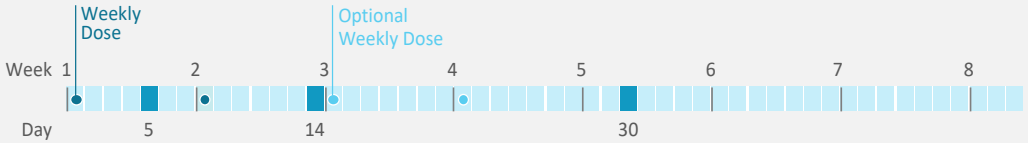
1. James et al *Antimicrob Agents Chemother* 2017;61:e01541-16. **2.** Thompson GR III, et al. 2022 ECCMID LB0244. **3.** Clinicaltrials.gov NCT04368559 accessed 20 April 2022.

Integrated Analysis of Phase 2 and Phase 3 Data of Rezafungin for the Treatment of Candidemia and/or IC

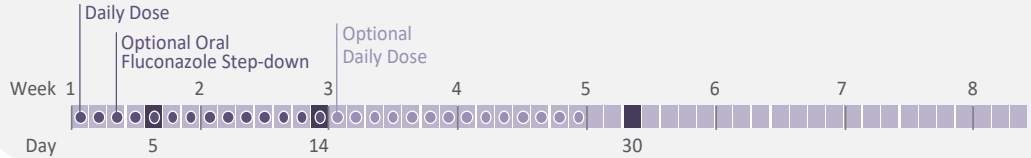
STRIVE and ReSTORE were Similarly Designed

Aligned Phase 2 and 3 Dosing and Design

REZAFUNGIN 400 mg/200 mg[a] once weekly (QWk). (N=139 combined)[b]



CASPOFUNGIN 70 mg/50 mg **once daily (QD).** (N=155 combined)[b]
with optional oral step-down[a] to fluconazole 6 mg/kg to nearest 200 mg QD



Pooled endpoints

- Primary[c]: All-cause mortality at Day 30
- Adverse events
- Secondary/exploratory
  - Mycological response at Day 5
  - Time to first negative blood culture

IC=invasive candidiasis; mITT=modified intent to treat.

[a]The rezafungin arm included optional oral step-down to placebo, to maintain the study blind.

[b]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).

[c]Primary endpoints not pooled were Overall Response (Phase 2) and Global Response (Phase 3).

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Demographics and Characteristics at Baseline

mITT Population – Integrated Analysis of Phase 2 and Phase 3

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/m^2, 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)

Characteristic	Rezafungin QWk (N=139)	Caspofungin QD (N=155)
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)

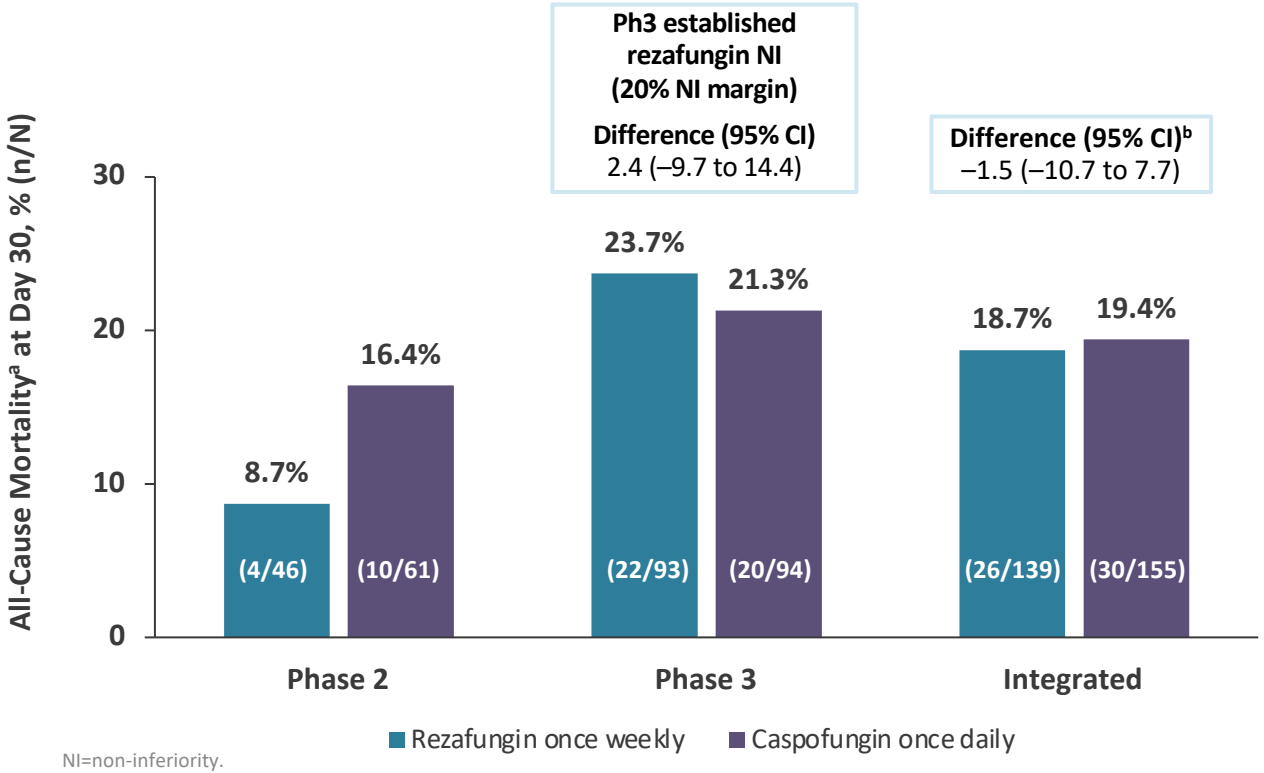
[a]Includes American Indian or Alaska native and not reported.
[b]At randomization.
[c]Reported for patients with data available.
[d]IC group includes some subjects with both deep tissue infection and candidemia.

Groups were well balanced at baseline (mITT population = 294)

ANC=absolute neutrophil count; APACHE=Acute Physiology and Chronic Health Evaluation II; BMI=body mass index; QD=once daily; QWk=once weekly; SD=standard deviation.

Primary Endpoint: All-Cause Mortality at Day 30

mITT Population – Phase 2, Phase 3, and Integrated



Integrated analysis

All-Cause Mortality at Day 30 was comparable between once-weekly rezafungin and once-daily caspofungin

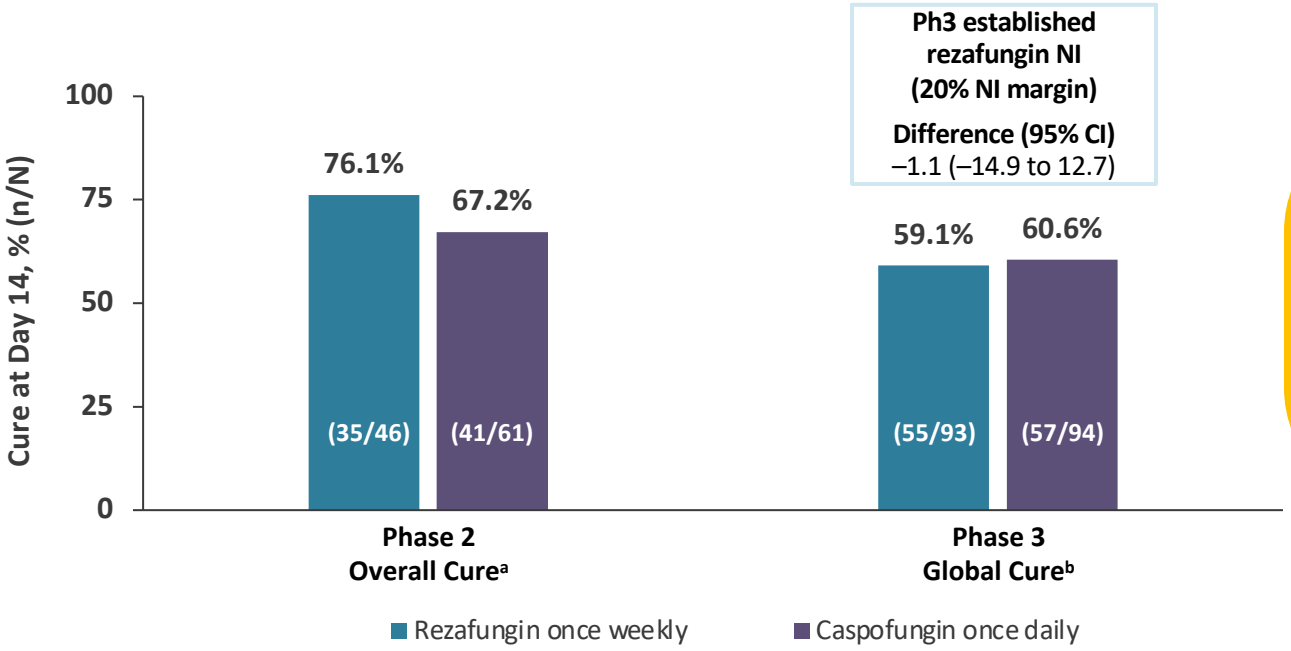
NI=non-inferiority.

[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.

Primary endpoint: Cure Rates at Day 14

mITT Population – Phase 2, Phase 3



Non-integrated analysis

Rates in each trial were comparable between treatments

NI=non-inferiority.

[a]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.

[b]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.

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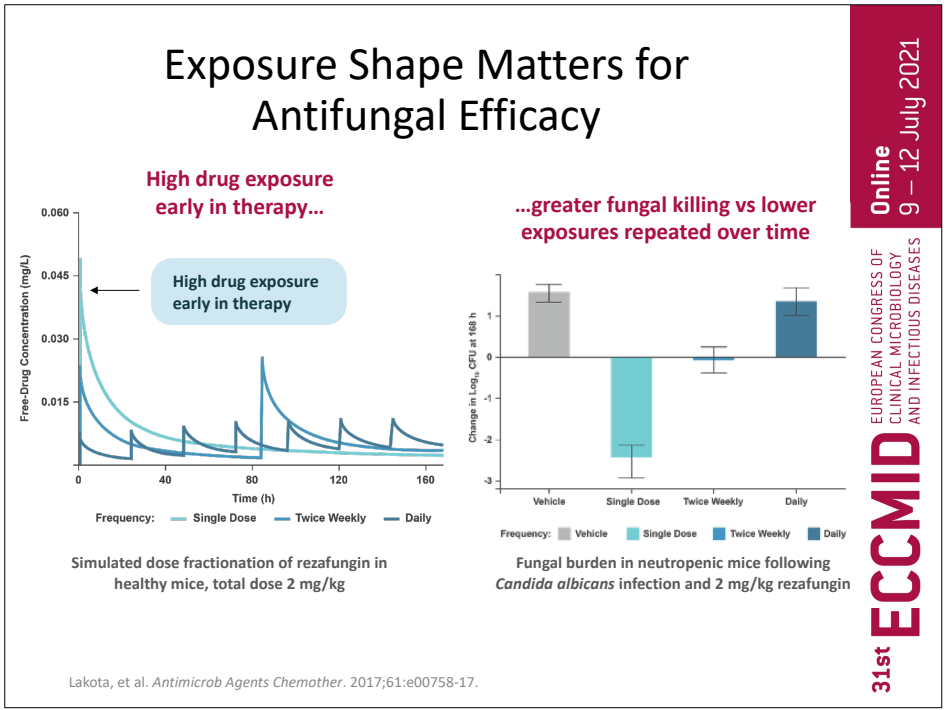
Early Efficacy Outcomes Assessed in Phase 2 and Phase 3 Suggest Potential Benefit of High, Front-Loaded Drug Exposure



Secondary and Exploratory Endpoints

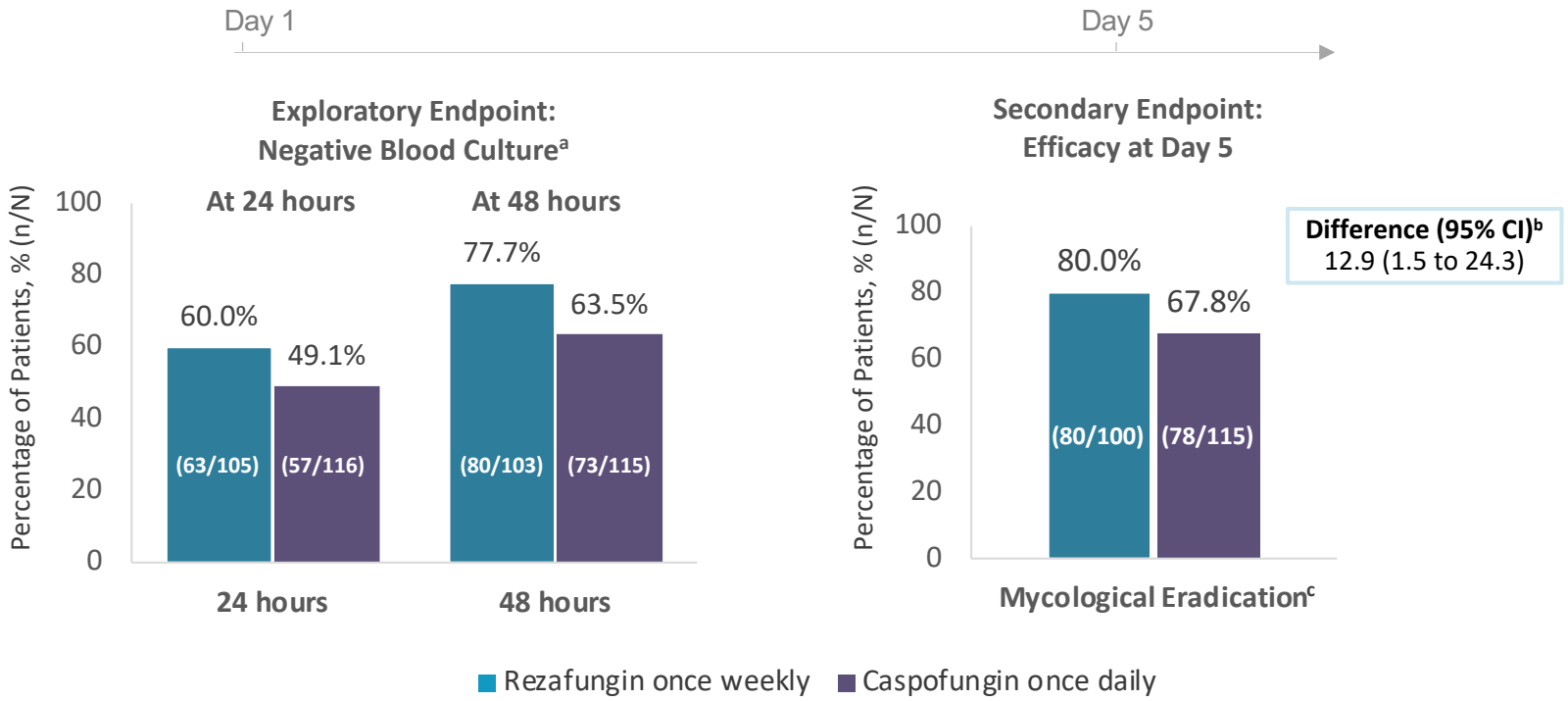
- Negative blood culture at 24 h and 48 h
- Mycological cure at Day 5
- Time to first negative blood culture

Patient Subgroups

- Positive blood culture proximal to randomization (within 12 hours before or 72 hours after randomization)
- Candidemia-only as final diagnosis (including all with a positive blood culture)

Outcomes in the Initial Days of Treatment

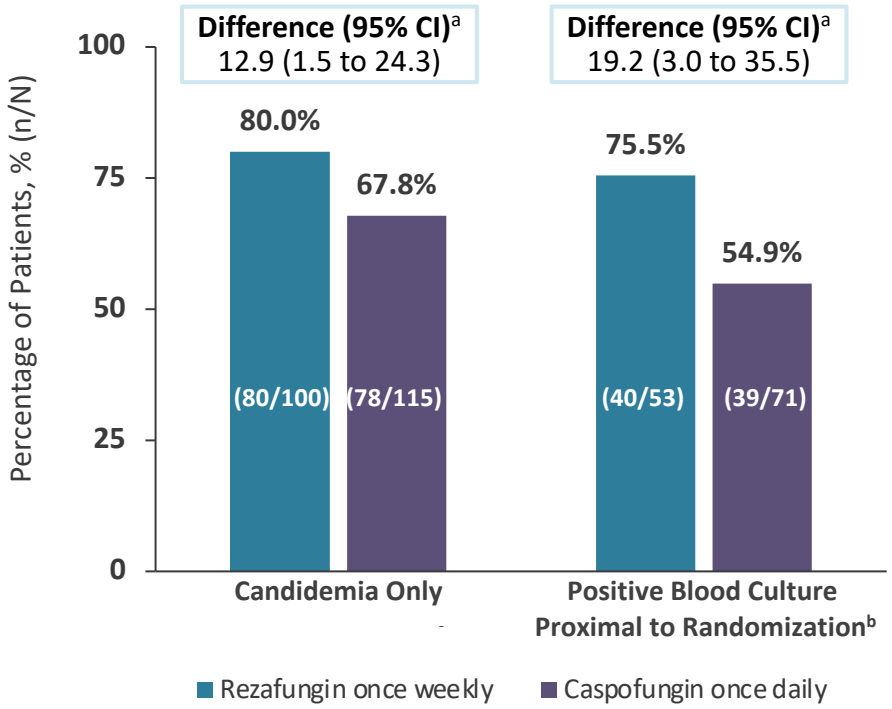
mITT Population – Integrated – Secondary and Exploratory Endpoints



[a]Subjects with positive blood culture at Screening.
[b]Calculated using stratified analysis by study and by part A and B of STRIVE.
[c]Mycological eradication rates for subjects with candidemia only.

Mycological Eradication at Day 5

mITT Population – Integrated – Secondary Endpoint



Integrated analysis

More pronounced effect in patients with a positive blood culture proximal to randomization

Suggests benefit from the potential clinical effect of front-loaded exposure

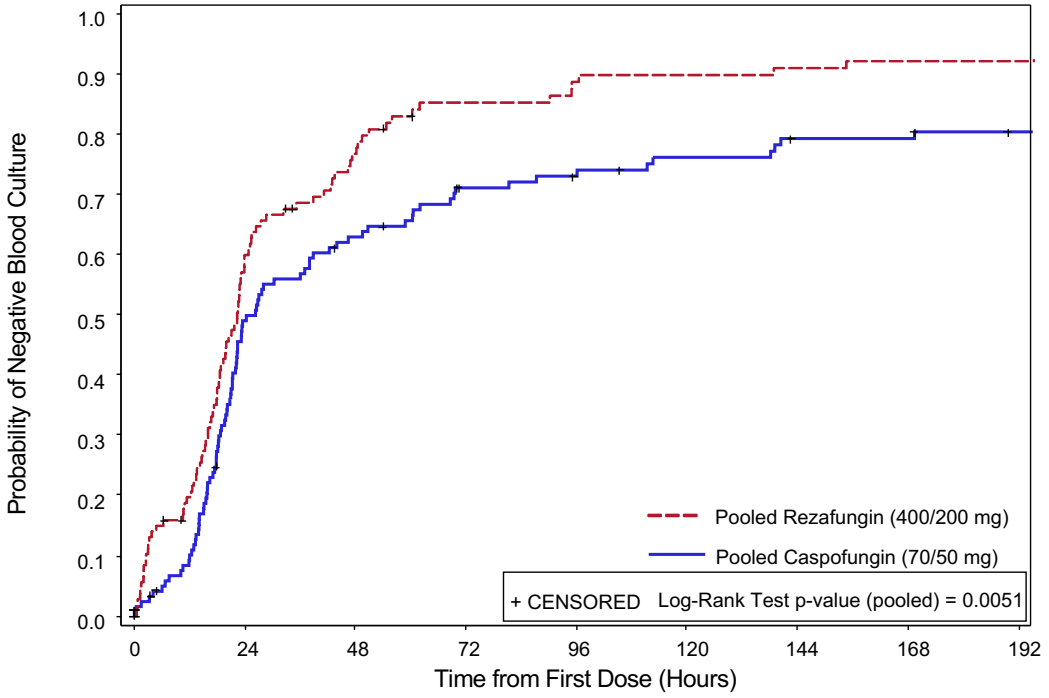
[a]Calculated using stratified analysis by study and by part A and B of STRIVE.
[b]Positive culture from blood drawn within 12 hours prior to randomization or within 72 hours after randomization.

Exploratory Endpoint: Faster Time to First Negative Blood Culture

mITT Population – Integrated

Integrated analysis

Rezafungin once weekly eradicated fungi faster than caspofungin once daily



Pooled Rezafungin (400/200 mg)	109	42	23	13	10	9	8	7	7
Pooled Caspofungin (70/50 mg)	122	59	42	30	27	23	19	19	16

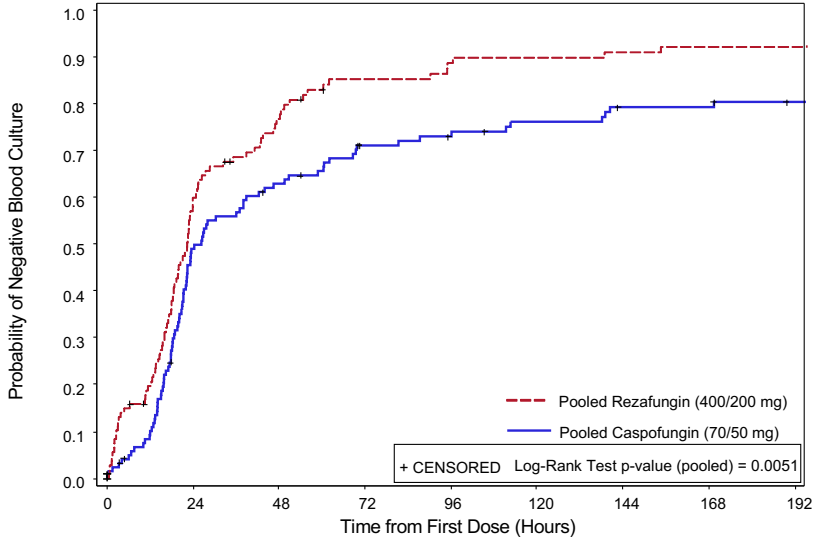
p-value for the pooled groups is from a stratified log-rank test with Study ID and part as a stratum.

Exploratory Endpoint: Faster Time to First Negative Blood Culture

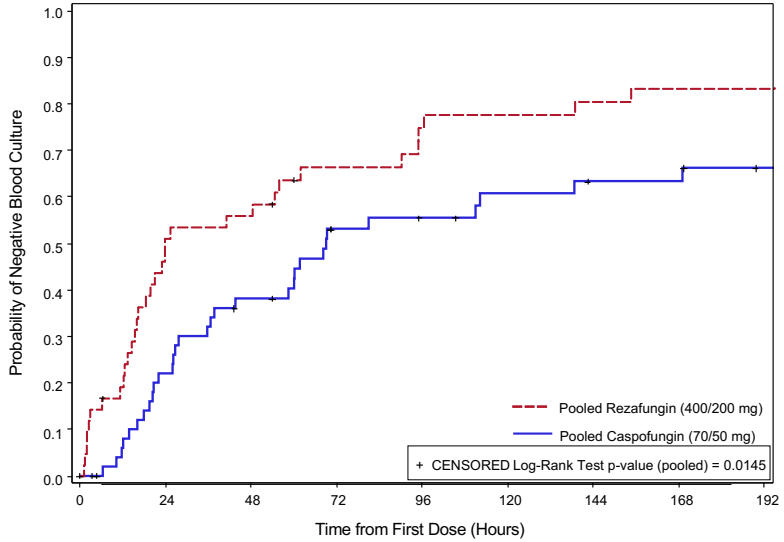
mITT Population – Integrated

Integrated analysis: a more pronounced effect for rezafungin seen in patients with positive blood culture proximal to randomization

Patients with positive blood culture at Screening



Patients with positive blood culture proximal to randomization[a]



Pooled Rezafungin (400/200 mg)	109	42	23	13	10	9	8	7	7
Pooled Caspofungin (70/50 mg)	122	59	42	30	27	23	19	19	16

42	20	18	12	9	8	7	6	6
53	39	30	20	18	15	13	13	10

p-values for the pooled groups is from a stratified log-rank test with Study ID and part as a stratum.

[a]Positive culture from blood drawn within 12 hours prior to randomization or within 72 hours after randomization.

Summary of Adverse Events

Safety Population – Integrated

Rezafungin was generally well tolerated and had a similar safety profile to caspofungin

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

AE: adverse event; TEAE: treatment-emergent AE.

[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.

Summary

- 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) – Latebreaker Poster #L0244
- Rezafungin had a similar safety profile to that of caspofungin
- 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

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