All-cause and attributable mortality in invasive candidiasis and/or candidaemia with rezafungin and caspofungin treatment: outcomes from the ReSTORE trial

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About Rezafungin

- Novel, once-weekly IV echinocandin
- Analogue 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 candidaemia & 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

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

References:
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.

Abbreviations:
IFD, invasive fungal disease; PK, pharmacokinetics.

Introduction/background

ReSTORE (NCT03667690) was a global, randomised, double-blind, double-dummy, Phase 3 non-inferiority trial, evaluating the efficacy and safety of rezafungin and caspofungin in the treatment of candidaemia and/or invasive candidiasis.[1]

References
1. Thompson GR, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2022 Nov 25:S0140-6736(22)02324-8.

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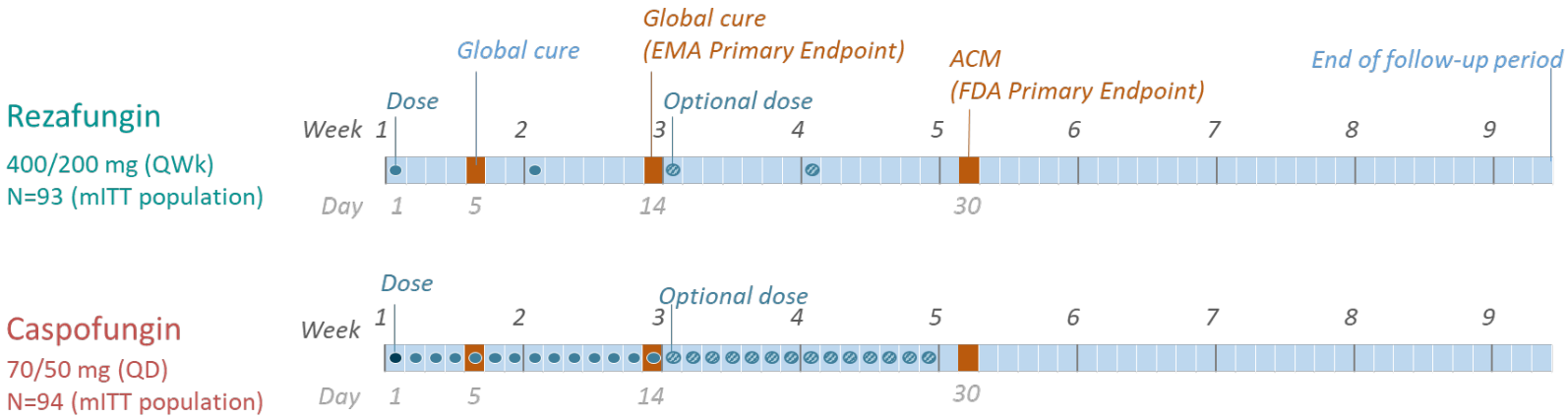
ReSTORE study design



- Adults diagnosed with candidaemia and/or invasive candidiasis (by systemic manifestations and mycological confirmation) were randomised to receive rezafungin once-weekly IV 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 (≤4 weeks)[1]
- Oral step-down treatment (caspofungin arm: fluconazole; rezafungin arm: placebo), was allowed from Day 4 for subjects with resolved/stable signs and symptoms of C/IC and negative blood cultures[1]

References
1. Thompson GR, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2022 Nov 25:S0140-6736(22)02324-8.

Abbreviations:
ACM, all-cause mortality; IV, intravenous; mITT, modified intention to treat.

ReSTORE analysis methodology

- The current analysis examined all-cause mortality (ACM) and therapeutic step-down data from the ReSTORE trial[1]
- Endpoints examined (mITT population):*
  - Day 30 (-2 days) ACM (20% non-inferiority margin)
  - Deaths attributable to candidaemia/invasive candidiasis through Day 59 (independent data review committee assessment)
  - Duration of treatment exposure
  - The proportion receiving step-down therapy

*All randomised subjects receiving ≥1 study drug dose

References
1. Thompson GR, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2022 Nov 25:S0140-6736(22)02324-8.

Abbreviations:
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Results: study population

The analysis included 93 subjects in the rezafungin arm and 94 in the caspofungin arm (mITT population).[1]

Baseline demographics and characteristics (mITT population)	Rezafungin (400/200 mg) (N=93)	Caspofungin (70/50 mg) (N=94)
Age, mean ± SD (range), years	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)
Sex, n (%)		
Male	62 (66.7)	56 (59.6)
Female	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	1 (1.1)	1 (1.1)
Final diagnosis		
Candidaemia-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
≥20, n (%)	12 (12.9)	17 (18.21)
<20, n (%)	80 (86.0)	77 (81.9)
Mean BMI, kg/m^2 ± SD	25.5 ± 7.19	24.3 ± 6.22
ANC <500/µL, n (%)	7 (7.5)	5 (5.3)
Mechanically ventilated at baseline, n (%)	16 (17.2)	28 (29.8)

mITT population: all subjects with documented *Candida* infection based on central laboratory evaluation (blood culture or a culture from a normally sterile site obtained ≤4 days [96 hours] before randomisation) receiving ≥1 dose of study drug.

[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.

References
1. Thompson GR, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2022 Nov 25:S0140-6736(22)02324-8.

Abbreviations:
ANC, absolute neutrophil count; APACHE, acute physiology and chronic health evaluation; BMI, body mass index; mITT, modified intention-to-treat; SD, standard deviation.

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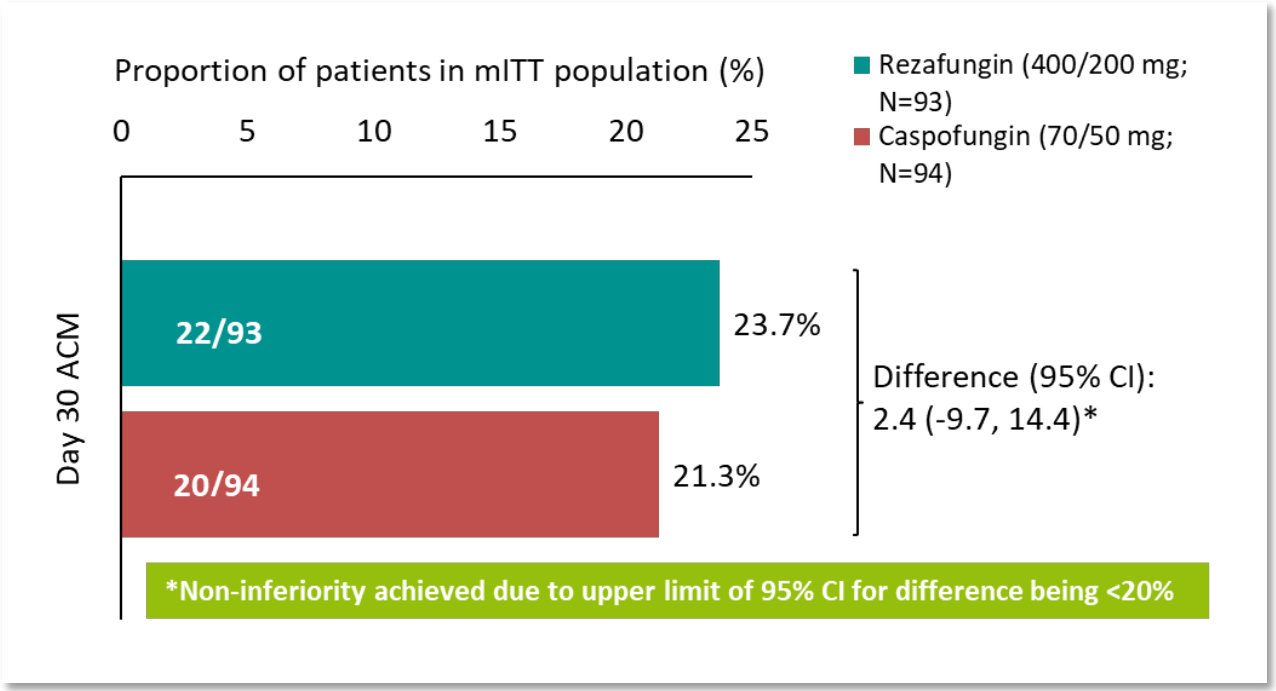
Results: Day 30 ACM rate

Day 30 ACM rate was **23.7%** (rezafungin arm) and **21.3%** (caspofungin arm).†



†US FDA primary endpoint[1]

References
1. Thompson GR, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2022 Nov 25:S0140-6736(22)02324-8.

Abbreviations:
ACM, all-cause mortality; CI, confidence interval; mITT, modified intention-to-treat; US FDA, United States Food and Drug Administration.

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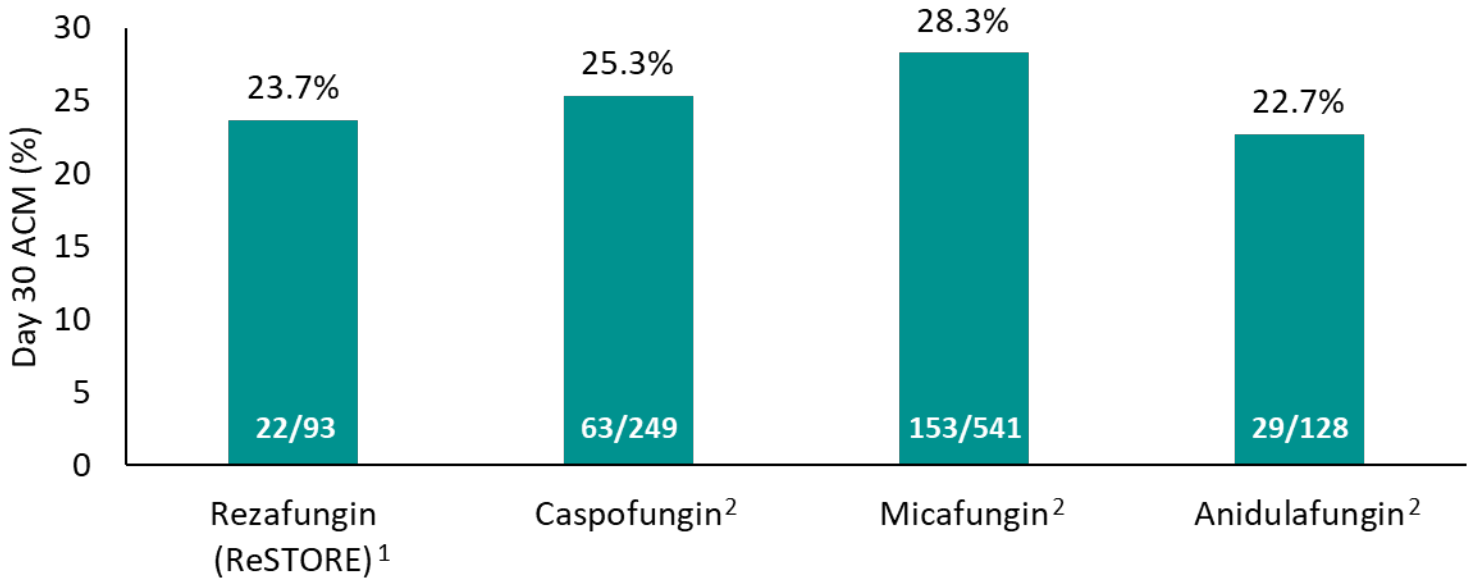
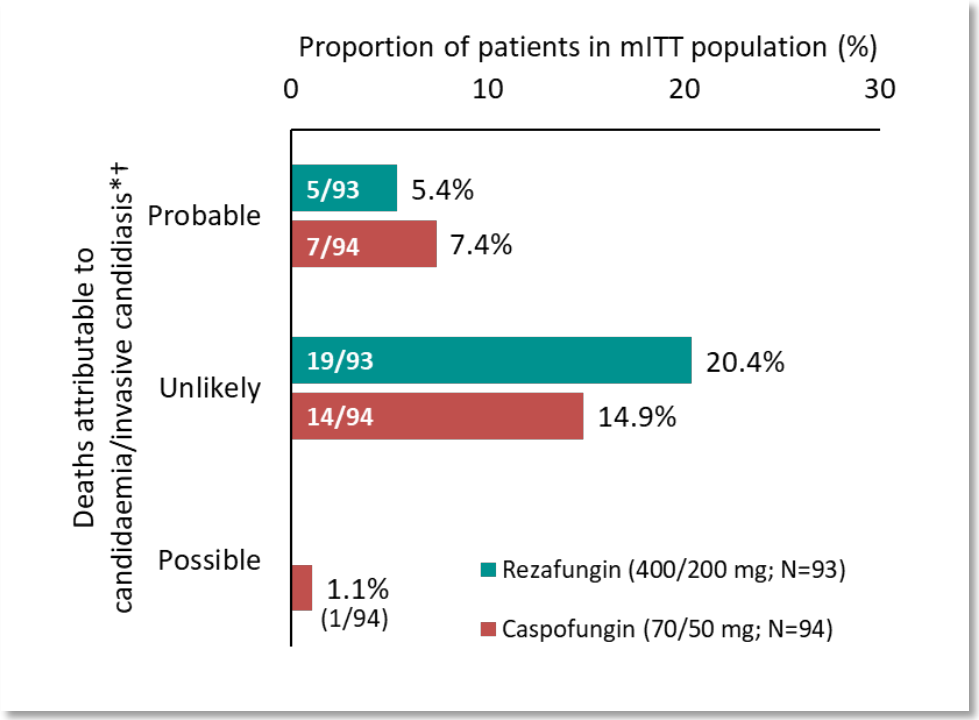
Results: Day 30 ACM versus other Phase 3 echinocandin data



References
1. Thompson GR, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2022 Nov 25:S0140-6736(22)02324-8; 2. Andes DR, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis. 2012 Apr;54(8):1110-22.

Abbreviations:
ACM, all-cause mortality.

Results: deaths attributable to candidaemia/invasive candidiasis



Through Day 59, **5 (5.4%)** deaths were attributable to candidaemia/invasive candidiasis in the rezafungin arm and **7 (7.4%)** in the caspofungin arm.*

	Attributable deaths*†	
Patient classification, n(%)	Rezafungin (400/200 mg) (N=93)	Caspofungin (70/50mg) (N=94)
Cancer	1 (1.1)	0
Cardiorespiratory failure	1 (1.1)	1 (1.1)
Cardiovascular disease	0	0
Infection	1 (1.1)	5 (5..3)
Multiorgan failure	1 (1.1)	0
Other	0	1 (1.1)
Unknown	1 (1.1)	0

*Independent data review committee assessment.

†Data were missing for 1 death in the rezafungin group, which the treating investigator considered not attributable to candidaemia/invasive candidiasis.

References
1. Thompson GR, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2022 Nov 25:S0140-6736(22)02324-8.

Abbreviations:
mITT, modified intention to treat.

Results: duration of IV therapy and step-down data

- Median duration of IV therapy exposure was 14 days in both arms.
- A switch to oral therapy was implemented for **25.8%** (24/93) of the rezafungin arm and **36.2%** (34/94) of the caspofungin arm.
- Overall, **83.4%** (20/24; rezafungin arm) and **61.8%** (21/34; caspofungin arm) of patients receiving oral step-down treatment met the criteria for step down by Day 7–9.

References
1. Thompson GR, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2022 Nov 25:S0140-6736(22)02324-8.

Abbreviations:
IV, intravenous.

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Conclusions

- Rezafungin for injection demonstrated non-inferiority, versus caspofungin, concerning Day 30 ACM.
- Mortality due to candidaemia/invasive candidiasis was low in both treatment groups during the study period.
- Median duration of IV therapy was similar in both arms, with >25% of patients meeting oral step-down criteria in each treatment group.

References
1. Thompson GR, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2022 Nov 25:S0140-6736(22)02324-8.

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Disclosures and funding

Disclosures

GR Thompson: grants and consulting fees from Amplyx, Astellas, Cidara, F2G, and Manye; grants from Merck; and data safety monitoring board membership for Pfizer, outside of the submitted work. **OA Cornely:** reports grants or contracts from Amplyx, Basilea, Bundesministerium für Bildung und Forschung, Cidara, German Center for Infection Research, European Union Directorate-General for Research and Innovation (101037867), F2G, Gilead, Matinas, MedPace, MSD, Mundipharma, Octapharma, Pfizer, and Scynexis; consulting fees from AbbVie, Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, IQVIA, Janssen, Matinas, MedPace, Menarini, Molecular Partners, Noxxon, Octapharma, Pardes, Pfizer, Pharma Support America, Scynexis, and Seres; honoraria from Abbott, AbbVie, Al-Jazeera Pharmaceuticals, Astellas, Gilead, Grupo Biotoscana/ United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, Noscendo, Pfizer, and Shionogi; payment for expert testimony from Cidara; data safety monitoring board or advisory board membership for Actelion, Allecra, Cidara, Entasis, IQVIA, Janssen, MedPace, Paratek, Pharma Support America, Pulmocide, Shionogi, and The Prime Meridian Group; a patent at the German Patent and Trade Mark Office (DE 10 2021 113 007.7); stocks from CoRe Consulting; and is a board member of German Society for Haematology and Medical Oncology, Deutsche Gesellschaft für Information und Wissen, ECMM European Confederation of Medical Mycology, International Society for Human & Animal Mycology, Mycoses Study Group–Education and Research Consortium, and Wiley, outside of the submitted work. **A Soriano:** grant from Gilead Sciences; consulting fees and honoraria from Angelini, Gilead, Menarini, MSD, and Shionogi, outside of the submitted work; and grants, consulting fees, honoraria, and support attending meetings from Pfizer, outside of the submitted work. **BJ Kullberg:** independent data review committee membership for Cidara. GRT reports grants and consulting fees from Amplyx, Astellas, Cidara, F2G, and Manye; grants from Merck; and data safety monitoring board membership for Pfizer, outside of the submitted work. **M Kollef:** grants from Barnes-Jewish Hospital Foundation and consulting fees from Merck, Pfizer, and Shionogi, outside of the submitted work. **J Vazquez:** consulting fees from and membership of data safety monitoring board or advisory board for F2G and consulting fees from Cidara and Scynexis, outside of the submitted work. **M Bassetti:** honoraria from and membership of data safety monitoring board or advisory board for Angelini, Cidara, Gilead, Menarini, MSD, Pfizer, and Shionogi, outside of the submitted work. **AF Das:** consulting fees from Cidara. **PG Pappas:** grants from and data review committee membership for Cidara; grants from Astellas, Scynexis, and Merck; and advisory board membership for F2G, outside of the submitted work. **T Sandison:** employee of and stocks in Cidara. All other authors declare no competing interests.

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