Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

George R Thompson III, Alex Soriano, Oliver A Cornely, Bart Jan Kullberg, Marin Kollef, Jose Vazquez, Patrick M Honore, Matteo Bassetti, John Pullman, Methee Chayakulkeeree, Ivan Poromanski, Cecilia Dignani, Anita F Das, Taylor Sandison, Peter G Pappas, on behalf of the ReSTORE trial investigators

Summary

Background Rezafungin is a next-generation, once-a-week echinocandin in development for the treatment of candidaemia and invasive candidiasis and for the prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp after blood and marrow transplantation. We aimed to compare the efficacy and safety of intravenous rezafungin versus intravenous caspofungin in patients with candidaemia and invasive candidiasis.

Methods ReSTORE was a multicentre, double-blind, double-dummy, randomised phase 3 trial done at 66 tertiary care centres in 15 countries. Adults (≥18 years) with systemic signs and mycological confirmation of candidaemia or invasive candidiasis were eligible for inclusion and randomly assigned (1:1) to receive intravenous rezafungin once a week (400 mg in week 1, followed by 200 mg weekly, for a total of two to four doses) or intravenous caspofungin (70 mg loading dose on day 1, followed by 50 mg daily) for no more than 4 weeks. The primary endpoints were global cure (consisting of clinical cure, radiological cure, and mycological eradication) at day 14 for the European Medical Agency (EMA) and 30-day all-cause mortality for the US Food and Drug Administration (FDA), both with a target non-inferiority margin of 20%, assessed in the modified intention-to-treat population (all patients who received one or more doses of study drug and had documented *Candida* infection based on a culture from blood or another normally sterile site obtained within 96 h before randomisation). Safety was evaluated by the incidence and type of adverse events and deaths in the safety population, defined as all patients who received any amount of study drug. The trial is registered with ClinicalTrials.gov, NCT03667690, and is complete.

Findings Between Oct 12, 2018, and Aug 29, 2021, 222 patients were screened for inclusion, and 199 patients (118 [59%] men; 81 [41%] women; mean age 61 years [SD 15·2]) were randomly assigned (100 [50%] patients to the rezafungin group and 99 [50%] patients to the caspofungin group). 55 (59%) of 93 patients in the rezafungin group and 57 (61%) of 94 patients in the caspofungin group had a global cure at day 14 (weighted treatment difference –1·1% [95% CI –14·9 to 12·7]; EMA primary endpoint). 22 (24%) of 93 patients in the rezafungin group and 20 (21%) of 94 patients in the caspofungin group died or had an unknown survival status at day 30 (treatment difference 2·4% [95% CI –9·7 to 14·4]; FDA primary endpoint). In the safety analysis, 89 (91%) of 98 patients in the rezafungin group and 83 (85%) of 98 patients in the caspofungin group had at least one treatment-emergent adverse event. The most common treatment-emergent adverse events that occurred in at least 5% of patients in either group were pyrexia, hypokalaemia, pneumonia, septic shock, and anaemia. 55 (56%) patients in the rezafungin group and 52 (53%) patients in the caspofungin group had serious adverse events.

Interpretation Our data show that rezafungin was non-inferior to caspofungin for the primary endpoints of day-14 global cure (EMA) and 30-day all-cause mortality (FDA). Efficacy in the initial days of treatment warrants evaluation. There were no concerning trends in treatment-emergent or serious adverse events. These phase 3 results show the efficacy and safety of rezafungin and support its ongoing development.

Funding Cidara Therapeutics and Mundipharma.

Division of Infectious Diseases, Department of Internal Medicine, and Department of Medical Microbiology and Immunology, University of California Davis Medical Center, Sacramento, CA, USA (Prof G R Thompson III MD); **Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Centro de Investigación Biomédica en Red Infecciosas, Barcelona, Spain** (Prof A Soriano PhD); **Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf and Excellence Center for Medical Mycology, and Clinical Trials Centre Cologne, Faculty of Medicine, University of Cologne and University Hospital Cologne, Cologne, Germany** (Prof O A Cornely MD); **German Centre for Infection Research, Partner Site Bonn-Cologne, Cologne, Germany** (Prof O A Cornely); **Radboudumc Center of Infectious Diseases and Department of Medicine, Radboud University Medical Center, Nijmegen, Netherlands** (Prof B J Kullberg MD); **Division of Pulmonary and Critical Care Medicine, Washington University, St Louis, MO, USA** (Prof M Kollef MD); **Division of Infectious Disease, Department of Medicine, Medical College of Georgia, Augusta University, Augusta, GA, USA** (Prof J Vazquez MD); **Intensive**

Introduction

Invasive candidiasis remains a significant cause of patient morbidity and death.[1] The attributable mortality of candidiasis has been estimated to be 15% to 20%, and associated hospitalisation costs exceed US$38 000 per episode.[2,3] Echinocandins are recommended as first-line drugs in the treatment of most types of invasive candidiasis on the basis of studies that have shown improved survival or reduced toxicity in comparison with other antifungal classes.[2,4] However, the changing epidemiology towards non-*albicans* *Candida* spp,[5] potential unpredictable dose–exposure relationships of

Care Department, Brugman University Hospital, Université Libre de Bruxelles, University Brussels, Belgium (Prof P M Honore PhD); **Intensive Care Unit, Centre Hospitalier Universitaire Université Catholique de Louvain Godinne, Université Catholique de Louvain, Belgium** (Prof P M Honore); **Department of Health Sciences, University of Genoa and Policlinico San Martino Istituto di Ricovero e Cura a Carattere Scientific Hospital, Genoa, Italy** (Prof M Bassetti MD); **Clinical Research, Mercury Street Medical, Butte, MT, USA** (J Pullman MD); **Division of Infectious Disease and Tropical Medicine, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand** (Prof M Chayakulkeeree MD); **University Multiprofile Hospital Active Treatment and Emergency Medicine NI Pirogov EAD, Medical University, Sofia, Bulgaria** (Prof I Poromanski PhD); **Medical Affairs, Pharma Support America-Clinical Research Organization, Durham, NC, USA** (C Dignani MD); **Cidara Therapeutics, San Diego, CA, USA** (A F Das PhD); **Clinical Development, Cidara Therapeutics, San Diego, CA, USA** (T Sandison MD); **Division of Infectious Diseases, Department of Internal Medicine, University of Alabama at Birmingham, Birmingham, AL, USA** (Prof P G Pappas MD)

Correspondence to Prof George R Thompson III, Division of Infectious Diseases, Department of Internal Medicine, and Department of Medical Microbiology and Immunology, University of California Davis Medical Center, Sacramento, CA 95817, USA
grthompson@ucdavis.edu

Research in context

Evidence before this study

Echinocandins are recommended in multiple national guidelines, including those of the Infectious Diseases Society of America, as first-line drugs for the treatment of candidaemia and invasive candidiasis. Since their introduction more than 20 years ago, echinocandins have become recognised for their favourable safety profiles and fungicidal antifungal efficacy. Caspofungin (approved in 2001), micafungin (2005), and anidulafungin (2006) are the first generation of echinocandins, each approved for once-a-day intravenous administration. Rezafungin is a novel echinocandin, designed to achieve improved chemical stability and pharmacokinetics that allow for front-loaded plasma exposure and once-a-week intravenous administration.

Added value of this study

ReSTORE is a global, phase 3, non-inferiority trial that contributes pivotal clinical data on rezafungin for the treatment of patients with candidaemia and invasive candidiasis. The ReSTORE phase 3 study was similar to the previously published STRIVE phase 2 study, except for the use of two study groups instead of three, the calculated sample size to support the assessment of non-inferiority, and the use of a data review committee to assess outcomes. There is a small number of options for antifungal treatment, and, if approved, rezafungin would be the first new antifungal for the treatment of candidaemia and invasive candidiasis in more than 15 years and allow for a once-a-week regimen to be added to the antifungal armamentarium.

Implications of all the available evidence

The overall evidence for rezafungin shows a similar clinical safety and efficacy to caspofungin, as well as stability and pharmacokinetic properties that support high, front-loaded exposure and once-weekly dosing. Rezafungin is currently in development for treatment of candidaemia and invasive candidiasis and for prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp in blood and marrow transplantation. The availability of a safe and efficacious once-a-week echinocandin regimen with the attributes of rezafungin would have potential benefits on the frequency that catheter placement is required, along with the associated costs and risk of adverse outcomes associated with catheter placement and more frequent health-care interactions. Future research of rezafungin treatment might investigate the clinical implications of early efficacy (eg, outcomes in the initial days of therapy), improved tissue distribution, and real-world effect on health-care economics.

current echinocandins, such as in patients who are critically ill or obese,[6] and emerging resistance to antifungal drugs are of increasing concern and mandate the search for novel antifungals.[7]

Rezafungin is a novel echinocandin with a broad spectrum of activity and pharmacokinetic advantages over currently available echinocandins.[8] Echinocandin efficacy depends on concentration-dependent effects and drug concentrations within target tissue sites. Rezafungin has a prolonged half-life (around 133 h) that allows extended-interval dosing and provides high plasma drug concentrations early in therapy. These parameters might allow for more rapid clearance of *Candida* spp from blood or tissue and potentially prevent the development of resistance.[9–13] The safety of rezafungin in treating invasive candidiasis and the potential advantages of more rapid clearance of candidaemia were reported in the phase 2 STRIVE study.[14]

We aimed to compare the efficacy and safety of intravenous rezafungin (once weekly) versus intravenous caspofungin (once daily followed by optional oral fluconazole) for the treatment of candidaemia and invasive candidiasis.

Methods

Study design and participants

ReSTORE was a multicentre, prospective, randomised, double-blind, double-dummy, non-inferiority phase 3 study of intravenous rezafungin versus caspofungin, followed by optional oral step-down fluconazole therapy in patients who received caspofungin, for the treatment of candidaemia and invasive candidiasis. The study was done in 66 tertiary care centres in 15 countries (appendix p 2).

Eligible patients were adults aged 18 years or older who were willing and able to provide informed consent (or had a legally acceptable representative provide consent on their behalf), had systemic signs of infection attributable to candidaemia or invasive candidiasis (eg, fever, hypothermia, hypotension, tachycardia, or tachypnoea), mycological evidence of candidaemia or invasive candidiasis from a blood or normally sterile site (eg, intra-abdominal [including peritoneal space]) sample within 96 h before randomisation, were willing to initiate or continue medical treatment to cure infections, agreed to use birth control or sexual abstinence, if appropriate, and agreed to have blood cultures drawn within 12 h before randomisation (for patients with candidaemia). Patients with septic arthritis in a prosthetic joint, osteomyelitis, endocarditis, or myocarditis, meningitis, chorioretinitis, any CNS infection, chronic disseminated candidiasis, or urinary tract candidiasis were excluded. Other key exclusionary criteria were more than 48 h of previous antifungal therapy; alanine aminotransferase or aspartate aminotransferase concentrations more than ten times the upper limit of normal, or severe hepatic impairment with a history of chronic cirrhosis (Child–Pugh score >9); presence of an indwelling catheter or device that could not

be removed; or known hypersensitivity to echinocandins. Full exclusionary criteria are provided in the appendix (p 3).

The trial was done in accordance with current regulations, the International Conference on Harmonisation Good Clinical Practice, and the Declaration of Helsinki. Independent ethics committees or institutional review boards at participating sites approved the protocol and all amendments. All patients, or their legally authorised representative, provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) centrally using an interactive response technology to receive rezafungin (rezafungin group) or caspofungin (caspofungin group). The random allocation sequence was prepared by an independent, unmasked statistician. Randomisation was stratified based on diagnosis (candidaemia only or invasive candidiasis) and by modified Acute Physiology and Chronic Health Evaluation (APACHE) II score (appendix p 163), absolute neutrophil count (ANC; APACHE II score ≥20 or ANC <500 cells per µL *vs* APACHE II score <20 and ANC ≥500 cells per µL) at screening. Patients with both positive blood cultures and positive specimens from normally sterile sites were randomly assigned within the invasive candidiasis stratum. APACHE II score was calculated using vital signs and laboratory results from screening. Unmasked pharmacists at each study site obtained the study drug assignment via interactive response technology and were responsible for preparation and dispensing of the study drug to the masked study staff. Patients received intravenous study drug mixed in 250 mL of saline or 250 mL of saline as a placebo. Oral fluconazole and placebo were over-encapsulated and appeared identical to masked study staff and patients.

All study and site personnel who interacted with patients were masked to treatment assignment, including those providing informed consent, performing assessments, and making medical decisions. Patients were also masked to treatment assignment.

Procedures

Patients in the rezafungin group received 400 mg rezafungin intravenously on day 1 and 200 mg on day 8; patients who required more than 14 days of intravenous therapy received an optional third dose of rezafungin (200 mg) on day 15 and an optional fourth dose of rezafungin (200 mg) on day 22, at the discretion of the investigator. Patients received intravenous placebo on other study days to maintain masking.

Patients in the caspofungin group received a single 70 mg loading dose intravenously on day 1 followed by 50 mg intravenously once daily for a minimum duration of intravenous antifungal therapy of 3 days and up to a maximum of 28 days.

Patients in both groups could be switched to oral step-down therapy (caspofungin group received fluconazole and rezafungin group received placebo) after 3 days or more, if step-down criteria were met (eg, the *Candida* spp isolate was susceptible to fluconazole, all signs and symptoms of candidaemia or invasive candidiasis present at baseline were resolved, or recent blood culture was negative for *Candida* spp; appendix p 22). Patients in the rezafungin group who were switched to step-down therapy continued to receive intravenous rezafungin once a week and daily oral placebo to maintain the masking. Step-down therapy in the caspofungin group was oral fluconazole 200–800 mg daily (3 mg/kg or 6 mg/kg, based on creatinine clearance). To maintain masking, patients in the caspofungin group who were switched to oral step-down therapy received both oral fluconazole and an intravenous placebo on day 8, on day 15 for those who required more than 14 days of therapy, and on day 22 for patients who required more than 21 days of therapy.

For both treatment groups, the total intravenous plus oral treatment duration was a minimum of 14 days and a maximum of 28 days. An end-of-treatment visit was required within 2 days after the last dose of study drug. A follow-up visit occurred between days 52 and 59. The removal of central venous catheters was recommended for all patients with candidaemia.

Assessment of clinical symptoms and physical findings was done at screening, day 5, day 14 (assessment could be done on day 13, 14, or 15), day 28 to 30, at the end of treatment (within 2 days after the last dose of intravenous or oral study drug), and during follow-up (days 52–59). Radiological test type with findings and interpretation were recorded if the test provided initial evidence of invasive candidiasis or evidence of progression, stabilisation, improvement, or resolution of invasive candidiasis compared with previous radiographs.

Mycological diagnosis of candidaemia and invasive candidiasis was established by at least one blood culture positive for yeast or *Candida*, a positive Gram stain (or other method of direct microscopy) for yeast, or positive culture for *Candida* spp from a specimen obtained from a normally sterile site (eg, intra-abdominal [including peritoneal space]) collected no more than 4 days (96 h) before randomisation. Blood cultures were repeated daily or every other day until the first negative blood culture result for *Candida* spp with no subsequent positive culture. All fungal isolates cultured from blood and normally sterile tissue or fluid were sent to the central laboratory (located in North Liberty, IO, USA, for all sites except for those in China, which used a central laboratory in Shanghai, China) for species identification and antifungal susceptibility testing. All isolates were identified to species level via matrix-assisted laser desorption ionisation–time of flight using the MALDI Biotyper (Bruker Daltonics, Billerica, MA, USA) or with the VITEK2 COMPACT system (bioMérieux, Marcy-l'Étoile, France; Chinese trial site isolates only). Subsequently, susceptibility testing for rezafungin and

comparator antifungals was done following Clinical and Laboratory Standards Institute broth microdilution (M27 Ed4) methods, in accordance with quality control guidelines (M27M44S Ed3).

Outcomes

The trial was designed with two primary efficacy endpoints: one mandated by the European Medicines Agency (EMA; global cure at the day 14 visit) and one mandated by the US Food and Drug Administration (FDA; all-cause mortality up to the day-30 visit [30-day all-cause mortality]).

The EMA outcome of global cure was based on clinical cure as assessed by the investigator, radiological cure (for patients with invasive candidiasis documented by radiological or imaging evidence at baseline), and mycological eradication, as confirmed for all three by an independent blinded data review committee. For patients with positive blood cultures at screening, mycological eradication was determined by a negative blood culture after the first dose of study drug with no subsequent positive culture. For patients with a positive culture from a normally sterile site other than blood, mycological eradication was either documented (as determined by a negative culture on the day of assessment [eg, day 5 or day 14]) or presumed (as determined by clinical and radiological cure [for those with evidence of disease on imaging at baseline] if a specimen from the infected site was not available). Mycological failure was defined by documented or presumed fungal persistence, a change of antifungal therapy to treat candidaemia or invasive candidiasis, or if the patient died of any cause before or on the day of assessment. Indeterminate mycological response was defined by missing study data for evaluation of efficacy for any reason (eg, culture specimen or result not available or patient lost to follow-up). The estimand attributes for 30-day all-cause mortality and global response at the day-14 visit are provided in the appendix (p 4).

A secondary efficacy outcome was global cure (as defined previously and confirmed by the data review committee) at the day-5, day-30, end-of-treatment, and follow-up visits. Additional secondary efficacy outcomes were mycological eradication, clinical cure as assessed by an investigator, and radiological cure for invasive candidiasis at the day-5, day-30, end-of-treatment, and follow-up visits.

Investigators evaluated safety by monitoring adverse events and findings from physical examinations, vital signs, laboratory tests, and electrocardiograms. Treatment-emergent adverse events were defined as adverse events that occurred during or after study drug administration until the follow-up visit. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA; version 23.0).

Prespecified exploratory outcomes were time to the first negative blood culture (for patients enrolled with a positive blood culture), which was determined as the time (in hours) from the first dose of study drug to the first negative blood culture without subsequent positive culture, and the percentage of negative blood cultures at 24 and 48 h after the first dose of study drug.

Statistical analysis

Our sample size calculation was based on having sufficient power for both the US FDA and EMA primary efficacy endpoints, both of which were assessed in the modified intention-to-treat (mITT) population. For the EMA endpoint of global cure, using a 20% non-inferiority margin, one-sided alpha of 0·025, 80% power, a global cure of 70% in both the rezafungin and caspofungin groups, and a sample size methodology based on a continuity corrected Z-statistic, a total of 184 patients (92 in each treatment group) were required in the mITT population. Assuming 85% of patients would be evaluable for the mITT population, about 218 patients were required in total. For the FDA primary efficacy endpoint of 30-day all-cause mortality, using a 20% non-inferiority margin, one-sided alpha of 0·025, a 30-day all-cause mortality rate of 20% in both treatment groups, and the sample size methodology based on a continuity corrected Z-statistic, a total of 184 patients in the mITT population provided 89·7% power to show non-inferiority. The non-inferiority margin of 20% for both the US FDA and EMA primary efficacy endpoints was based on an analysis of studies in which patients received no treatment or inadequate treatment, and the high unmet medical need in patients with candidaemia or invasive candidiasis.

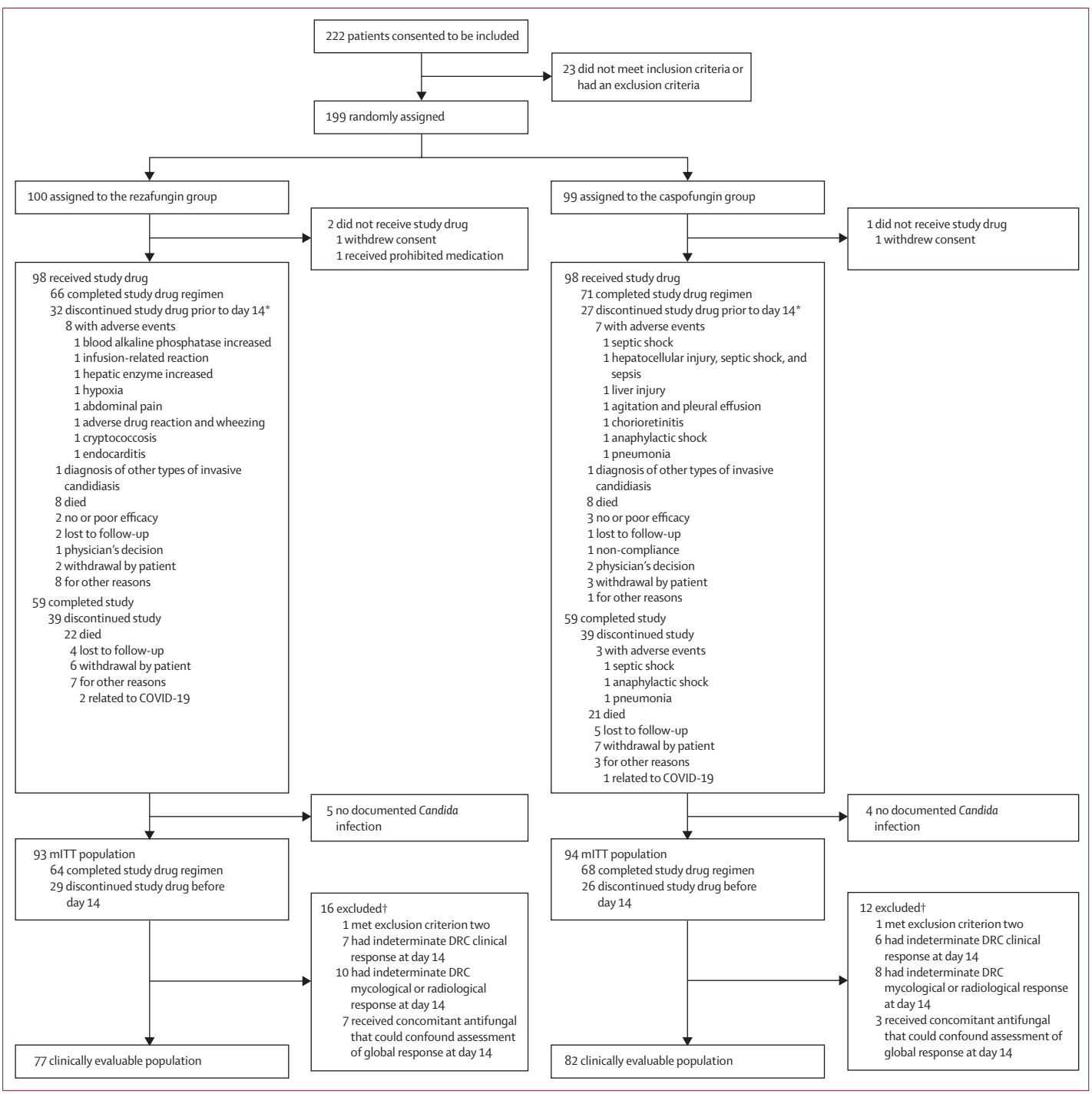
For all-cause mortality (FDA primary endpoint), the number of patients in each treatment group who were alive or dead (patients with unknown survival status [ie, missing data] were included as deceased) up until the day-30 visit was determined. A two-sided 95% CI for the observed difference (rezafungin minus caspofungin) in rates of 30-day all-cause mortality was calculated in the mITT population using an unweighted Miettinen–Nurminen methodology. Rezafungin was considered non-inferior to caspofungin for all-cause mortality if the upper bound of the CI was below 20%. Predefined sensitivity analyses excluded patients with unknown survival status and calculated a weighted (for the randomisation

Figure 1: **Trial profile**

The mITT population included all patients in the safety population with documented *Candida* infection. The clinically evaluable population included all patients in the mITT population who also met inclusion criterion four, did not meet exclusion criterion one, criterion two, criterion five (appendix p 3), had an assessment of both mycological and clinical response following assessment at day 13–15 (patients with invasive candidiasis documented by radiological or imaging evidence also must have had an assessment of radiological response), and did not have any other factor that could confound the assessment of the global response at day 14. DRC=data review committee. mITT=modified intent-to-treat. *Patients who discontinued study drug prior to day 14 did not have to discontinue the study, they may have continued in the study for safety analysis. †Some patients met multiple reasons for exclusion and are included with each exclusion reason met.

stratification factors) 95% CI using Miettinen–Nurminen method with Cochran–Mantel–Haenszel weights used for the stratum weights, and a multiple imputation for missing survival status. All-cause mortality was also stratified by diagnosis (candidaemia and invasive candidiasis).

For global response (EMA primary endpoint), the number and percentage of patients in each treatment group who had a global response of cure, failure, and indeterminate at the day-14 visit was assessed. Patients with an indeterminate response were included in the denominator and were considered to not have global cure. A two-sided 95% CI for the observed difference in global cure rates was calculated using the weighted (for the two randomisation strata) Miettinen–Nurminen methodology. Rezafungin was considered non-inferior to caspofungin



for global response if the lower bound of the CI was above –20%. Predefined sensitivity analyses defined an indeterminate response as a global cure, calculating an unweighted 95% CI, and completing the analysis in the clinically evaluable population. Global response was also stratified by diagnosis (candidaemia and invasive candidiasis).

No adjustment for multiplicity was required for the analyses of 30-day all-cause mortality and global response because these were separate primary endpoints for each of the regulatory authorities.

All randomly assigned patients were included in the intent-to-treat (ITT) population. All patients in the ITT population who had documented *Candida* infection confirmed by central laboratory evaluation of a culture from blood or another normally sterile site obtained within 96 h of randomisation and had received at least one dose of study drug were included in the mITT population. The clinically evaluable population included all patients in the mITT population who also met the inclusion criteria, did not meet exclusion criteria, had a response (other than an indeterminate response), and did not receive a concomitant antifungal that could confound the assessment of global response. The safety population included all patients who had received any amount of the study drug. Demographics and baseline characteristics were summarised in the ITT population. Catheter placement and efficacy outcomes were assessed in the mITT population. Treatment duration and safety outcomes were assessed in the safety population.

Post-hoc analyses were all-cause mortality at day 30 in patients with a positive blood culture at screening and for whom the catheter was retained, and all-cause mortality at day 30 in the mITT population, excluding patients who discontinued study treatment early for reasons other than death.

For patients enrolled with a positive blood culture, the prespecified exploratory outcome of the time to the first negative blood culture was analysed with the Kaplan-Meier method. Patients were censored if they received an alternative antifungal for the treatment of candidaemia or invasive candidiasis, died, or were lost to follow-up before a negative blood culture was reported. A log-rank test was done to test for differences in Kaplan-Meier curves between treatment groups. The number of patients in each treatment group who had a mycological response of eradication, failure, and indeterminate at day 5 and day 14 was assessed. A two-sided 95% CI for the observed difference in mycological eradication was calculated with the unweighted Miettinen–Nurminen method.

All data analyses were done using SAS software, version 9.4 or higher. The trial is complete and is registered with ClinicalTrials.gov, NCT03667690.

	Rezafungin group (n=100)	Caspofungin group (n=99)
Age	59·5 (15·8)	62·0 (14·6)
<65 years	60 (60%)	58 (59%)
≥65 years	40 (40%)	41 (41%)
Sex		
Male	67 (67%)	56 (57%)
Female	33 (33%)	43 (43%)
Race		
Asian	27 (27%)	31 (31%)
Black or African American	5 (5%)	4 (4%)
White	61 (61%)	60 (61%)
Other or not reported	7 (7%)	4 (4%)
Diagnosis		
Candidaemia only	70 (70%)	68 (69%)
Invasive candidiasis*	30 (30%)	31 (31%)
Mean modified APACHE II score†	12·5 (8·0)	13·1 (7·1)
≥20	15 (15%)	18 (18%)
<20	84 (84%)	81 (83%)
Body-mass index mean, kg/m²	25·4 (7·0)	24·5 (6·5)
Absolute neutrophil count, <500 cells per µL†	9 (9%)	6 (6%)

Data are n (%) or mean (SD). APACHE=Acute Physiology and Chronic Health Evaluation. *Includes patients who progressed from candidaemia to invasive candidiasis based on radiological or tissue or fluid culture assessment up to day 14. †Reported for patients with data available.

Table 1: **Demographics and baseline characteristics in the intention-to-treat population**

Role of the funding source

This study was cofunded by Cidara Therapeutics and Mundipharma. Cidara Therapeutics was involved in the study design, study conduct, data collection, data analysis, and reporting of the trial. Mundipharma was involved in the data analysis and reporting of the trial.

Results

Between Oct 12, 2018, and Aug 29, 2021, 222 patients were screened for inclusion, and 199 patients (118 [59%] men; 81 [41%] women; mean age 61 years [SD 15·2]) were randomly assigned (100 [50%] patients to the rezafungin group and 99 [50%] patients to the caspofungin group) and included in the ITT population (figure 1).

Patient baseline characteristics are reported in table 1 and the appendix (p 5). Distribution of *Candida* species was similar in the two treatment groups; the most common species isolated was *Candida albicans* (appendix p 6). 192 (>99%) of the 193 isolates were susceptible to caspofungin and 193 (>99%) of the 194 isolates were susceptible to rezafungin based on available caspofungin and provisional rezafungin Clinical and Laboratory Standards Institute breakpoint values (M27M44S).[15,16]

The median duration of intravenous and oral treatment combined in the safety population was 14 days (IQR 7–14)

in the rezafungin group and 14 days (13–15) in the caspofungin group. The median duration of intravenous treatment was 14 days (6–14) in the rezafungin group versus 14 days (8–15) in the caspofungin group. A longer duration of intravenous treatment (15–28 days) was seen in 17 (17%) patients in the rezafungin group and 27 (28%) patients in the caspofungin group. In the rezafungin group, 25 (25%) patients switched to oral step-down for a median duration of 10 days (7–11), whereas in the caspofungin group 35 (36%) patients switched to oral therapy for a median duration of 10 days (5–12). 16 (64%) of the 25 patients who were switched to oral step-down in the rezafungin group and 18 (51%) of the 35 patients who switched in the caspofungin group switched between day 4 and day 6. Seven (13%) of 56 patients in the rezafungin group and 14 (28%) of 51 patients in the caspofungin group with candidaemia and a catheter present at screening had catheter removal within 48 h of diagnosis. The median duration of catheter placement since first positive blood culture was 76·0 h (54·7–169·2) in the rezafungin group and 72·4 h (36·3–127·5) in the caspofungin group.

Results for the US FDA primary efficacy endpoint of all-cause mortality at day 30 in the mITT population are reported in table 2. 22 (24%) of 93 patients in the rezafungin and 20 (21%) of 94 patients in the caspofungin group were either known to be dead or had an unknown survival status (treatment difference 2·4% [95% CI –9·7 to 14·4]; table 2). Non-inferiority of rezafungin was shown because the upper limit of the 95% CI for the treatment difference (14·4%) was lower than the prespecified upper bound of the CI of 20%, corresponding to a non-inferiority margin of 20%. Non-inferiority of rezafungin was shown in all sensitivity analyses (appendix p 8). A post-hoc analysis excluding patients who discontinued study treatment for reasons other than death also showed similar all-cause mortality in the rezafungin group (13 [18%] of 72 patients) and caspofungin group (16 [21%] of 76 patients; treatment difference –3·0% [–15·8 to 9·8]; appendix p 9). Similar rates of all-cause mortality at day 30 were also found in a post-hoc analysis of patients for whom catheters were retained (14 [26%] of 53 patients in the rezafungin group *vs* 13 [34%] of 38 patients in the caspofungin group; treatment difference –6·8% [–26·2 to 12·7]; appendix p 10). 30-day all-cause mortality rates by diagnosis are reported in table 2. 30-day all-cause mortality rates were similar between treatment groups when evaluated in subgroups defined by patient age, sex, race, geographical region, or modified APACHE II score or ANC at randomisation (appendix p 18).

The EMA global cure rates at day 14 are reported in table 2. In the mITT population, 55 (59%) of 93 patients in the rezafungin group and 57 (61%) of 94 patients in the caspofungin group had a global cure at day 14 (weighted treatment difference –1·1%; 95% CI –14·9 to 12·7; table 2). The lower limit of the 95% CI for the treatment difference (–14·9%) was above the

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)
All-cause mortality at day 30 (US FDA primary outcome)			
Died	22 (24%)	20 (21%)	2·4 (–9·7 to 14·4)*
Known to have died	19 (20%)	17 (18%)	..
Unknown survival	3 (3%)	3 (3%)	..
All-cause mortality at day 30 by diagnosis			
Candidaemia only	18/64 (28%)	17/67 (25%)	2·8 (–12·5 to 18·0)*
Invasive candidiasis	4/29 (14%)	3/27 (11%)	2·7 (–16·7 to 21·7)*
Global response at day 14 as assessed by DRC (EMA primary outcome)			
Cure	55 (59%)	57 (61%)	–1·1 (–14·9 to 12·7)†
Failure	28 (30%)	29 (31%)	..
Indeterminate	10 (11%)	8 (9%)	..
Global response at day 14 as assessed by DRC by diagnosis			
Candidaemia only			
Cure	39/64 (61%)	43/67 (64%)	–3·2 (–19·6 to 13·3)*
Failure	21/64 (33%)	19/67 (28%)	..
Indeterminate	4/64 (6%)	5/67 (7%	..
Invasive candidiasis			
Cure	16/29 (55%)	14/27 (52%)	3·3 (–22·4 to 28·6)*
Failure	7/29 (24%)	10/27 (37%)	..
Indeterminate	6/29 (21%)	3/27 (11%)	..

Data are n (%) or n/N (%). ANC=absolute neutrophil count. APACHE II=Acute Physiology and Chronic Health Evaluation II score. DRC=data review committee. EMA=European Medical Agency. FDA=Food and Drug Administration. *Two-sided 95% CI for the observed difference (%), rezafungin group minus caspofungin group. †Two-sided 95% CI for the weighted difference (%), rezafungin group minus caspofungin group adjusted for the two randomisation strata of diagnosis (candidaemia *vs* invasive candidiasis) and high risk (APACHE II score ≥20 or ANC <500 cells per μL) versus low risk (APACHE II score <20 and ANC ≥500 cells per μL).

Table 2: **All-cause mortality at day 30 and global response at day 14 in the modified intention-to-treat population**

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)*
Patients with negative blood culture†			
24 h	36/67 (54%)	30/65 (46%)	..
48 h	49/66 (74%)	41/64 (64%)	..
Outcomes at the day 5 visit			
Global cure as assessed by DRC	52 (56%)	49 (52%)	3·8 (–10·5 to 17·9)
Mycological eradication‡	64 (69%)	58 (62%)	7·1 (–6·6 to 20·6)
Patients with candidaemia only	50/64 (78%)	46/67 (69%)	9·5 (–5·8 to 24·4)
Investigator assessment of clinical cure	59 (63%)	70 (74%)	–11·0 (–24·0 to 2·3)
Outcomes at the day 14 visit			
Global cure as assessed by DRC§	55 (59%)	57 (61%)	–1·1 (–14·9 to 12·7)¶
Mycological eradication	63 (68%)	62 (66%)	1·8 (–11·7 to 15·2)
Patients with candidaemia only	46/64 (72%)	47/67 (70%)	1·7 (–13·9 to 17·2)
Investigator assessment of clinical cure	62 (67%)	63 (67%)	–0·4 (–13·8 to 13·1)

Data are n (%) or n/N (%). ANC=absolute neutrophil count. APACHE=Acute Physiology and Chronic Health Evaluation. DRC=data review committee. *Two-sided 95% CI for the observed difference (%), rezafungin group minus caspofungin group. †Exploratory endpoint. ‡Programmatically derived from the outcome definition described in the methods. §Primary endpoint for the European Medicines Agency (secondary endpoint for the US Food and Drug Administration). ¶Two-sided 95% CI for the weighted difference (%), rezafungin group minus caspofungin group adjusted for the two randomisation strata of diagnosis and APACHE II score and ANC.

Table 3: **Secondary and exploratory endpoints of efficacy in the modified intention-to-treat population**

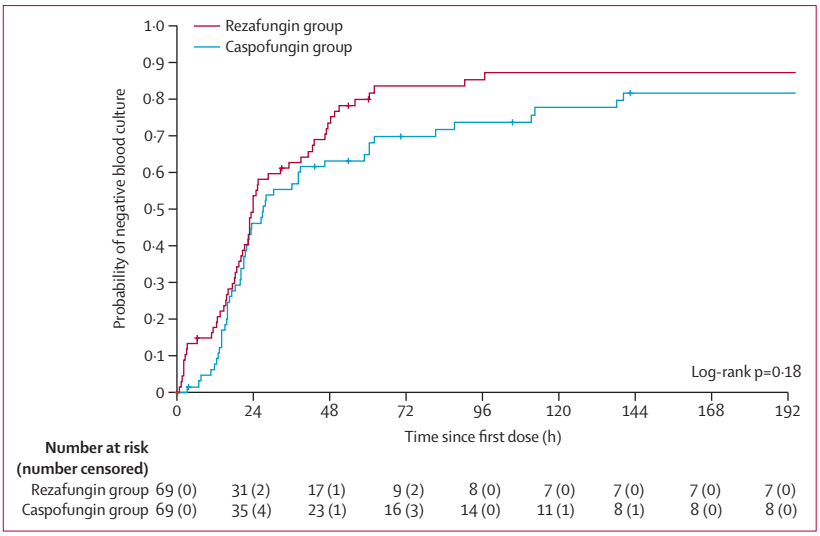


Figure 2: **Time to negative blood culture after treatment with rezafungin versus caspofungin in the modified intention-to-treat population**

prespecified lower bound of the CI of –20%, corresponding to a non-inferiority margin of 20%. Therefore, the study shows the non-inferiority of rezafungin compared with caspofungin for global cure. Clinical and mycological reasons for failure were similar between the two groups, but were imbalanced for radiological reasons with more patients not showing improvement or resolution of imaging findings by day 14 in the caspofungin group compared with the rezafungin group (appendix p 11).

Non-inferiority of rezafungin was shown in all sensitivity analyses, including the clinically evaluable population (appendix p 8). Outcomes by diagnosis (candidaemia *vs* invasive candidiasis) are also summarised in table 2.

Early differences were observed in rates of global response, mycological eradication, and investigators' assessment of clinical response at the day-5 visit (table 3). By the day-14 visit (tables 2, 3) and later secondary endpoint visits (day-30, end-of-treatment, and follow-up visits; appendix p 12), efficacy endpoints were similar between treatment groups. Of the exploratory endpoints, the proportions of patients with negative blood culture at 24 h and 48 h are reported in table 3. The time between the blood culture used for diagnosis being taken and the first treatment dose are reported in the appendix (p 13). For patients recruited with a positive blood culture, the median time to a negative blood culture was 23·9 h (IQR 15·4–48·3) for the rezafungin group and 27·0 h (16·4–111·3) for the caspofungin group (p=0·18; figure 2).

Nearly all patients in the safety population had at least one treatment-emergent adverse event (89 [91%] of 98 patients in the rezafungin group and 83 [85%] of 98 patients in the caspofungin group; table 4). The most common treatment-emergent adverse events were

	Rezafungin group (n=98)	Caspofungin group (n=98)
Patients with ≥1 treatment-emergent adverse event	89 (91%)	83 (85%)
Treatment-emergent adverse events with incidence ≥5% in either treatment group		
Pyrexia	14 (14%)	5 (5%)
Hypokalaemia	13 (13%)	9 (9%)
Pneumonia	10 (10%)	3 (3%)
Septic shock	10 (10%)	9 (9%)
Anaemia	9 (9%)	9 (9%)
Hypomagnesaemia	7 (7%)	3 (3%)
Diarrhoea	6 (6%)	7 (7%)
Sepsis	6 (6%)	4 (4%)
Vomiting	6 (6%)	2 (2%)
Abdominal pain	5 (5%)	4 (4%)
Bacteraemia	5 (5%)	3 (3%)
Constipation	5 (5%)	3 (3%)
Hypophosphataemia	5 (5%)	4 (4%)
Hypotension	5 (5%)	6 (6%)
Multiple organ dysfunction syndrome	5 (5%)	2 (2%)
Nausea	5 (5%)	2 (2%)
Urinary tract infection	4 (4%)	6 (6%)
Acute kidney injury	3 (3%)	8 (8%)
Hyperkalaemia	2 (2%)	6 (6%)

Table 4: **Treatment-emergent adverse events in the safety population**

pyrexia (14 [14%] patients), hypokalaemia (13 [13%] patients), pneumonia (ten [10%] patients), septic shock (ten [10%] patients), and anaemia (nine [9%] patients) in the rezafungin group and hypokalaemia, septic shock and anaemia (each occurring in nine [9%] patients), diarrhoea (seven [7%] patients), and hypotension, urinary tract infection, and hyperkalaemia (each occurring in six [6%] patients) in the caspofungin group. Serious adverse events occurred in 55 (56%) in the rezafungin group and 52 (53%) patients in the caspofungin group. Study-drug-related adverse events were reported in 16 (16%) patients in the rezafungin group and nine (9%) patients in the caspofungin group. Five serious adverse events related to study drug were reported: two in the rezafungin group (one infusion-related reaction on day-3 infusion of saline placebo that resolved the same day, and one urticaria during oral [placebo] dosing period) and three in the caspofungin group that were all related to active study drug (hypertransaminasaemia, liver injury, and anaphylactic shock).

Discussion

In this double-blind, randomised, multicentre trial, we compared the efficacy and safety of rezafungin once-a-week versus caspofungin once a day, with optional oral step-down therapy with fluconazole in the caspofungin group, for the treatment of candidaemia and invasive

candidiasis. Our findings show that rezafungin is non-inferior to caspofungin for the prespecified primary endpoints of all-cause mortality at 30 days and global cure at day 14.

The pharmacokinetic profile and once-a-week dosing of rezafungin[8] could provide advantages beyond mere convenience for patients with candidaemia and invasive candidiasis. Because every medical procedure or health-care interaction introduces the potential for opportunistic infection, less frequent dosing might reduce the requirement for peripherally inserted central catheter placement, and associated costs, and reduce the risk of catheter-related adverse outcomes. We report that 17% of patients in the rezafungin group and 28% of patients in the caspofungin group received 15–28 days of intravenous therapy, representing one or two additional doses of rezafungin (optional third dose on day 15 and an optional fourth dose on day 22) compared with up to 28 days of once-daily administration of caspofungin. These reductions in the need for daily intravenous therapy might also reduce the duration of hospitalisation in some patients.

Early efficacy outcomes, such as those at day 5 or earlier, were of interest because of the reported benefit of early targeted treatment;[17,18] previous phase 2 study findings[14] in patients who receive rezafungin; the front-loaded, high plasma drug concentrations of rezafungin that were theorised to result in more rapid clearance of fungaemia; and understanding of when the effect of antifungal treatment might be greatest.[11,13,19,20] The analysis of time to negative blood culture showed a favourable, although not statistically significant, difference between the rezafungin and caspofungin groups, consistent with previous studies.[13,14] These outcomes suggest a potential clinical benefit of front-loaded high plasma rezafungin concentrations. Additionally, the observed treatment difference in mycological eradication at day 5 in patients with candidaemia was 78% in the rezafungin group and 69% in the caspofungin group (table 3). Other key secondary efficacy outcomes, including global cure at day 30, end of treatment, and follow-up, were also similar between treatment groups.

C albicans and *Candida glabrata* were the most common isolated pathogens at baseline, similar to the baseline epidemiology of previous invasive candidiasis studies.[7,22–24] As expected, the number of patients with less common *Candida* species (eg, *Candida dubliniensis*, *Candida krusei*, and *Candida guilliermondii*) were low.

Approximately 70% of the patients in the ReSTORE study had candidaemia only. As might be expected, outcomes differed by diagnosis; however, between-treatment differences were similar for both diagnoses. All-cause mortality at day 30 by diagnosis was consistent with the overall results, and no differences were found between patients with candidaemia only and those with invasive candidiasis with or without candidaemia, an important group to include in randomised trials because of the difficulty in obtaining source control and adequate drug concentrations at some tissue sites.[21] Treatment differences by diagnosis for global cure at day 14 were −3·2% in patients with candidaemia only and 3·3% in patients with invasive candidiasis.

Safety and tolerability were similar between the two groups and were consistent with the reported safety profile of echinocandin class drugs.[22–26] Our data add to the safety profile of rezafungin observed in the STRIVE trial,[14] in which drug-related serious adverse events were seen in less than 3% of patients in both the rezafungin and caspofungin treatment groups.[14]

Limitations of this study are the exclusion of paediatric patients and those with certain forms of candidiasis. The excluded forms of invasive candidiasis typically require long courses of antifungal treatment (lasting months or indefinitely; eg, biofilm-related invasive candidiasis) or occur at sites in which echinocandin penetration is poor (eg, urinary tract and the CNS); therefore, inclusion of patients with these forms of invasive candidiasis was not feasible in a randomised clinical trial. However, forms of invasive candidiasis for which long-term treatment are necessary might be areas in which the long half-life of rezafungin can be leveraged for patient and health system convenience during treatment or to decrease hospital length of stay. In future studies of refractory candidiasis or non-candidaemic forms of invasive candidiasis requiring prolonged therapy (eg, osteomyelitis or endocarditis), the favourable pharmacokinetic and pharmacodynamic characteristics of rezafungin might prove advantageous.

Pharmacokinetic modelling based on phase 2 data showed only small differences, with no dose adjustments recommended in special patient populations.[27] Due to the contraindication of caspofungin, safety has not been studied in patients with severe hepatic impairment, a patient population at risk of invasive candidiasis. However, pharmacokinetic data and results of a phase 1 trial of rezafungin in hepatic impairment support no rezafungin dose adjustment.[28] Nevertheless, additional studies of rezafungin in patient populations excluded in this trial are needed. Although clinical trial data might be scarce, real-world experience from the rezafungin expanded access programme might provide additional insights into rezafungin treatment in these specific patient populations.[29,30]

In conclusion, this large multicentre study shows the non-inferiority of once-a-week rezafungin compared with daily caspofungin for the treatment of candidaemia and invasive candidiasis. The rates of all-cause mortality at day 30 and global cure at day 14 were similar in the rezafungin and caspofungin groups, and the rate of drug-related serious adverse events was low.

Contributors

AFD, BJK, GRT, JV, MB, OAC, PGP, and TS designed the study. AS, CD, GRT, IP, JP, JV, MC, and PMH collected the data. AFD, GRT, and TS analysed the data. AFD, AS, BJK, CD, GRT, JP, JV, IP, TS, MC, MK, OAC, PGP, and PMH interpreted the data. AFD, GRT, and TS wrote the manuscript. AS, BJK, CD, GRT, IP, JP, JV, MB, MC, MK, OAC, PGP, and PMH critically reviewed the manuscript. GRT and AFD verified the

data reported in the manuscript. All authors had full access to all the data in the study, approved the final manuscript for submission, and agreed to take responsibility for the decision to submit for publication.

Declaration of interests

AFD reports consulting fees from Cidara. AS reports a 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. BJK reports 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. JV reports 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. TS reports being an employee of and stocks in Cidara. MC reports grants and study materials from Cidara; grants from Siam Pharmaceuticals; honoraria from Gilead and MSD; and consulting fees, honoraria, and support to attend meetings from Pfizer. MB reports 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. MK reports grants from Barnes-Jewish Hospital Foundation and consulting fees from Merck, Pfizer, and Shionogi, outside of the submitted work. PGP reports 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. OAC 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. All other authors declare no competing interests.

Data sharing

The study protocol is provided in the appendix (pp 19–174). Access to anonymised data can be requested by contacting info@cidara.com. Requests for data can be made beginning 9 months and ending 36 months following Article publication. Each request will be reviewed by the sponsor for scientific merit.

Acknowledgments

The ReSTORE trial was cofunded by Cidara Therapeutics (San Diego, CA, USA) and Mundipharma (Cambridge, UK). The authors thank the investigators, trial personnel, and patients who made the ReSTORE trial possible. A list of contributing ReSTORE Trial Investigators is provided in the appendix (pp 14–17). The authors also thank Thierry Calandra, Carol Kauffman, and Luis Ostrosky-Zeichner for their contributions as members of the independent data and safety monitoring board, and Malathi Shivaprakash for DSMB coordination. Special thanks to Luis Ostrosky-Zeichner for his contributions to the trial design and to Laura Navalta, Karen Mena, Gordana Schnider, and Lorena Kanu. Thanks also go to Kevin Garey, Russel Lewis, Johan Maertens, Kieran Marr, Andrej Spec, George R Thompson, Matteo Bassetti, Oliver Corney, Patrick M Honore, Marin Kollef, Bart Jan Kullberg, Alex Soriano, Peter G Pappas, and Jose A Vazquez for their valuable advice and insights as members of the ReSTORE scientific publications steering committee. Writing and editorial assistance was provided by Merry H Saba (Cidara Therapeutics) on outline development; by Thomas Owens, PhD, (Aspire Scientific) on submission preparation and author and contributor coordination with funding by Cidara Therapeutics; and by Tressa Chung (Cidara Therapeutics [at the time work was completed]).

References

1 Tsay SV, Mu Y, Williams S, et al. Burden of candidemia in the United States, 2017. *Clin Infect Dis* 2020; **71:** e449–e53.

2 Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; **62:** e1–50.

3 Benedict K, Jackson BR, Chiller T, Beer KD. Estimation of direct healthcare costs of fungal diseases in the United States. *Clin Infect Dis* 2019; **68:** 1791–97.

4 Cornely OA, Bassetti M, Calandra T, et al. ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect* 2012; **18** (suppl 7)**:** 19–37.

5 Ricotta EE, Lai YL, Babiker A, et al. Invasive candidiasis species distribution and trends, United States, 2009-2017. *J Infect Dis* 2021; **223:** 1295–302.

6 Sinnollareddy MG, Roberts JA, Lipman J, et al. Pharmacokinetic variability and exposures of fluconazole, anidulafungin, and caspofungin in intensive care unit patients: data from multinational Defining Antibiotic Levels in Intensive care unit (DALI) patients study. *Crit Care* 2015; **19:** 33.

7 Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. *Nat Rev Dis Primers* 2018; **4:** 18026.

8 Ham YY, Lewis JS 2nd, Thompson GR 3rd. Rezafungin: a novel antifungal for the treatment of invasive candidiasis. *Future Microbiol* 2021; **16:** 27–36.

9 Zhao Y, Prideaux B, Nagasaki Y, et al. Unraveling drug penetration of echinocandin antifungals at the site of infection in an intra-abdominal abscess model. *Antimicrob Agents Chemother* 2017; **61:** e01009–17.

10 Howard SJ, Livermore J, Sharp A, et al. Pharmacodynamics of echinocandins against *Candida glabrata*: requirement for dosage escalation to achieve maximal antifungal activity in neutropenic hosts. *Antimicrob Agents Chemother* 2011; **55:** 4880–87.

11 Bader JC, Bhavnani SM, Andes DR, Ambrose PG. We can do better: a fresh look at echinocandin dosing. *J Antimicrob Chemother* 2018; **73:** i44–50.

12 Shields RK, Nguyen MH, Press EG, Clancy CJ. Abdominal candidiasis is a hidden reservoir of echinocandin resistance. *Antimicrob Agents Chemother* 2014; **58:** 7601–05.

13 Lakota EA, Bader JC, Ong V, et al. Pharmacological basis of CD101 efficacy: exposure shape matters. *Antimicrob Agents Chemother* 2017; **61:** e00758–17.

14 Thompson GR, Soriano A, Skoutelis A, et al. Rezafungin versus caspofungin in a phase 2, randomized, double-blind study for the treatment of candidemia and invasive candidiasis: the STRIVE Trial. *Clin Infect Dis* 2021; **73:** e3647–55.

15 Clinical and Laboratory Standards Institute. Epidemiological cutoff values for antifungal susceptibility testing [M57S]. 4th edn. Pittsburgh, PA: Clinical and Laboratory Standards Institute; 2022.

16 Clinical and Laboratory Standards Institute. Performance standards for antifungal susceptibility testing of yeasts [M27M44S]. 3rd edn. Pittsburgh, PA: Clinical and Laboratory Standards Institute; 2022.

17 Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis* 2006; **43:** 25–31.

18 Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to *Candida* infection: importance of empiric therapy and source control. *Clin Infect Dis* 2012; **54:** 1739–46.

19 Sandison T, Ong V, Lee J, Thye D. Safety and pharmacokinetics of CD101 IV, a novel echinocandin, in healthy adults. *Antimicrob Agents Chemother* 2017; **61:** e01627–16.

20 Zhao Y, Perez WB, Jimenez-Ortigosa C, et al. CD101: a novel long-acting echinocandin. *Cell Microbiol* 2016; **18:** 1308–16.

21 Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. *Clin Microbiol Rev* 2014; **27:** 68–88.

22 Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis* 2007; **45:** 883–93.

23 Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med* 2002; **347:** 2020–29.

24 Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med* 2007; **356:** 2472–82.

25 Ostrosky-Zeichner L, Kontoyiannis D, Raffalli J, et al. International, open-label, noncomparative, clinical trial of micafungin alone and in combination for treatment of newly diagnosed and refractory candidemia. *Eur J Clin Microbiol Infect Dis* 2005; **24:** 654–61.

26 Kuse E-R, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *Lancet* 2007; **369:** 1519–27.

27 Rubino CM, Flanagan S. Population pharmacokinetics of rezafungin in patients with fungal infections. *Antimicrob Agents Chemother* 2021; **65:** e0084221.

28 Huguet J, Ong V, Sandison T, et al. 982. Effect of hepatic impairment on the safety and pharmacokinetics of rezafungin. *Open Forum Infect Dis* 2021; **8** (suppl 1)**:** S582–83.

29 Adeel A, Qu MD, Siddiqui E, Levitz SM, Ellison RT III. Expanded access use of rezafungin for salvage therapy of invasive *Candida glabrata* infection: a case report. *Open Forum Infect Dis* 2021; **8:** ofab431.

30 Pechacek J, Yakubu I, Vissichelli NC, Bruno D, Morales MK. Successful expanded access use of rezafungin, a novel echinocandin, to eradicate refractory invasive candidiasis in a liver transplant recipient. *J Antimicrob Chemother* 2022**: 77:** 2571–73.