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## RESEARCH

# Length of hospital and intensive care unit stay in patients with invasive candidiasis and/or candidemia treated with rezafungin: a pooled analysis of two randomised controlled trials

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## Abstract

**Background** Invasive candidiasis/candidemia (IC/C) is associated with a substantial health economic burden driven primarily by prolonged hospital stay. The once-weekly IV echinocandin, rezafungin acetate, has demonstrated non-inferiority to caspofungin in the treatment of IC/C. This paper reports a post hoc pooled exploratory analysis of length of stay (LoS) for hospital and intensive care unit (ICU) stays in two previously published clinical trials (ReSTORE [NCT03667690] and STRIVE [NCT02734862], that compared rezafungin with daily IV caspofungin (stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more).

**Methods** LoS outcomes were analysed descriptively in the pooled modified intention to treat (mITT) population (all patients who had a documented *Candida* infection in line with trial requirements and received at least one dose of study drug). In addition, to adjust for an imbalance between treatment groups in the proportion receiving mechanical ventilation at baseline, a generalised linear model with mechanical ventilation as a binary covariate was applied. Responses to an exploratory question in the phase 3 trial on possible earlier discharge with weekly rezafungin are also reported.

**Results** 294 patients were included (rezafungin 139, caspofungin 155), of whom 126 (43%) had ICU admission. Patients treated with rezafungin had a numerically shorter LoS than with caspofungin in all analyses. Mean total LoS was 25.2 days, vs 28.3 days with caspofungin, and mean ICU LoS was 16.1 vs 21.6 days for rezafungin and caspofungin, respectively. After adjustment for mechanical ventilation status the difference in ICU LoS was 4.1 days, a relative difference of 24% (95% CI -11%, 72%). Physicians would have considered earlier discharge for 16% of patients (30/187) with weekly rezafungin, an average of 5–6 days earlier.

**Conclusions** Rezafungin may enable shorter hospital and ICU LoS in IC/C compared with daily IV caspofungin, with accompanying savings in resource use. Further research is needed to confirm this in the real-world setting.

Trial registration.

NCT03667690 (ReSTORE; September 12, 2018); NCT02734862 (STRIVE; April 12, 2016).

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## Background

Invasive candidiasis (IC) is the most common fungal infection in hospitals in high-income countries [1]. The term includes both candidemia (bloodstream infection with *Candida*) and deep-seated tissue candidiasis [2, 3]. IC is a significant cause of morbidity and mortality in at-risk groups, which include (but are not limited to) patients with immunosuppression, major surgery, solid organ or stem cell transplant, mechanical ventilation, and indwelling catheter [3]. Approximately half of all cases occur in the intensive care unit (ICU) [3]. A survey in nine European countries reported a cumulative incidence of ICU-acquired IC of 7.07 episodes per 1000 ICU admissions, with crude 40-day mortality of 42% [4], while a meta-analysis of European population-based studies found an incidence of 5.5 episodes per 1000 ICU admissions and 30-day mortality of 37% [5]. Worldwide, there are an estimated 700,000 cases of IC each year [6].

IC is associated with a substantial economic burden [1, 5]. A 2020 systematic review reported a mean total direct cost per patient in developed Western countries ranging from $48,487 to $157,574 (2016 USD), with hospitalisation accounting for over half the cost [7]. In US hospital inpatients at high risk of invasive fungal infection, the mean cost of an inpatient hospital stay in 2018 was reported as $29,640 (length of stay 5.36 days), but this rose to $162,750 (length of stay 22.2 days) in patients diagnosed with IC [8]. An estimate from US insurance claims data put the average cost per hospitalisation for IC at $64,723–$153,090 (2017 USD) [9]. The total economic burden of IC in the US (including direct medical costs and productivity loss) was estimated at $1.8 bn for 2019 [10]. Recent data on the economic burden in Europe are lacking, but a review covering 2000 to 2011 also found that invasive fungal infections were associated with longer hospital stay, with healthcare resource use driven by hospitalisation, diagnostic testing, and medications [11].

A number of antifungal drugs are available for the treatment of IC, principally echinocandins, azoles and amphotericin B [12]. Echinocandins are the guideline-recommended choice for empiric and initial treatment in most circumstances, due to the greater renal toxicity of amphotericin B, the more limited spectrum of activity of fluconazole, and evidence that anidulafungin is superior to fluconazole in patients with candidemia, particularly *C. albicans*.[13–16] However, fluconazole (intravenous [IV] or oral) is recommended as an acceptable alternative to an echinocandin in selected patients [13]. Currently approved echinocandins require daily IV administration, which is burdensome for both patients and healthcare systems and can prolong hospital stay [17]. Stable patients with susceptible infection may be switched to oral fluconazole to simplify treatment and/or allow hospital discharge [14, 16].

Rezafungin is a novel echinocandin approved by the European Medicines Agency (EMA) for the treatment of invasive candidiasis in adults [18] and by the US Food and Drug Administration (FDA) for patients 18 years of age or older who have limited or no alternative options for the treatment of candidemia and invasive candidiasis [19]. It has an extended half-life compared with other echinocandins, and prolonged therapeutic drug concentrations in peripheral tissues [20]. This allows for once-weekly IV dosing consisting of a 400 mg loading dose on Day 1 followed by 200 mg on Day 8 and once weekly thereafter [21].

In the ReSTORE phase 3 trial in hospitalised adults with IC (NCT03667690), rezafungin was non-inferior to caspofungin on the two primary endpoints of global cure at day 14 (EMA endpoint) and 30-day all-cause mortality (FDA endpoint), with a comparable safety profile [22]. A pre-specified patient-level pooled analysis of ReSTORE and the phase 2 STRIVE study (NCT02734862) [23] confirmed non-inferior 30-day mortality for rezafungin (methodological differences meant that Day 14 global cure data were not suitable for pooling) [24]. The pooled analysis also found potential early treatment benefits with rezafungin: the proportion of patients with mycological eradication by Day 5 was 73.4% (102/139) and 64.5% (100/155) with rezafungin and caspofungin, respectively, and a weighted treatment difference (95% CI) of 10·0% (−0·3 to 20·4). Similarly, more patients in the rezafungin group had negative blood culture at 24 h (60.0% [63/105], compared with 49.1% [57/116] with caspofungin), suggesting that rezafungin may be associated with a shorter time to negative blood culture than caspofungin [24].

This paper presents an exploratory pooled analysis of length of ICU and hospital stay from the two trials, together with exploratory data on physician assessment of potential for early hospital discharge. This will be of interest to clinicians, hospital managers, and healthcare payers.

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## Methods

Clinical protocols and safety and efficacy results for the STRIVE and ReSTORE trials have been previously published [22, 23]. In brief, ReSTORE was a prospective, randomised, double-blind, double-dummy, non-inferiority phase 3 trial conducted in 66 tertiary care centres in 15 countries. A total of 199 patients (modified intention-to-treat [mITT] population) were randomised to receive either rezafungin (400 mg in week 1, followed by 200 mg weekly, for a total of 2–4 doses once every 7 days; n = 93), or caspofungin (70 mg on day 1 then 50 mg daily for up to 4 weeks; n = 94). Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more. Inclusion criteria included an established mycological diagnosis of candidemia and/or IC (IC/C) from a sample taken ≤ 96 h before randomisation, and presence of one or more systemic signs attributable to IC/C. Patients with candidemia and IC were defined as separate groups within the overall study population. STRIVE was conducted in 10 countries and had a similar design, except that patients (N = 183) were randomised to one of two weekly rezafungin doses (400/400 mg [n = 76], or 400/200 mg [n = 46]), or daily caspofungin (70/50 mg; n = 61) [23].

Collection of health-economic endpoints focused on hospital and ICU length of stay (LoS). The health-economic endpoints of hospital and ICU length of stay were pre-defined endpoints in both the STRIVE and ReSTORE clinical studies and were conducted in the mITT population (all patients who had a documented *Candida* infection in line with trial requirements and received at least one dose of study drug). The total number of days in the hospital or ICU was defined as the total during the study period, including any re-admissions. For those patients who did not die before hospital/ICU discharge ('survivors'), the time to discharge for each admission to hospital and to ICU was generated and LoS was summarised. In addition, a post-hoc analysis of LoS was performed in all patients in the mITT population regardless of discharge status (i.e. including patients who died during the study period).

Additionally, physician-reported assessment of possible earlier discharge was captured during the ReSTORE Study. This was based on responses to a question on the case report form (CRF) for completion by the site Principal Investigator, which asked 'In your opinion, if you had the availability of once weekly IV rezafungin and did not need to administer daily placebo/caspofungin/fluconazole, would you have considered discharging this patient from hospital earlier than the actual discharge date (yes/no)? How many days earlier?'.

The methods of the pooled efficacy and safety analysis of STRIVE and ReSTORE have also been published [24]. The post-hoc pooled analysis reported here compared total hospital LoS and ICU LoS for patients receiving the 400/200 mg rezafungin dose with those in the caspofungin treatment arms (mITT populations). The rezafungin 400/400 mg arm from STRIVE was not included as this dose was not taken forward to phase 3. All outcomes were analysed using descriptive statistics. In addition, to adjust for an imbalance between treatment groups in the proportion of patients receiving mechanical ventilation at baseline, a generalised linear model (log-link, gamma distribution) with mechanical ventilation as a binary covariate was applied in the all-patients LoS analyses (i.e. including non-survivors).

## Results

### Baseline patient characteristics

The pooled analysis included 294 patients: 139 from rezafungin treatment arms and 155 from caspofungin arms. A total of 126 (43%) required ICU admission. Baseline patient characteristics are shown in Table 1. Treatment groups were well balanced at baseline, except for the proportion receiving mechanical ventilation (rezafungin: 12.2%; caspofungin: 21.9%). However, the distribution of APACHE II scores and absolute neutrophil counts were comparable between groups. Baseline characteristics for the ICU population are shown in Table 2, and were well balanced except for use of mechanical ventilation.

### ICU length of stay

Results for ICU LoS are shown in Tables 3 and 4. Overall, 35 patients in the rezafungin group and 53 in the caspofungin group were discharged from ICU (the ICU survivors population; Table 4). Mean length of ICU stay in survivors was 15.9 days for the rezafungin group and 23.0 days for the caspofungin group, a difference of 7.1 days. Adjustment for mechanical ventilation status in survivors resulted in a mean ICU LoS of 16.1 days for rezafungin and 21.6 days for caspofungin.

Similarly, in the population of all patients with an ICU stay (Table 3), patients in the rezafungin group spent less time in the ICU, with a difference in mean ICU stay of 5.5 days. Adjustment for mechanical ventilation status resulted in an increase of 1.2 days in the mean ICU LoS in the rezafungin group, whereas ICU LoS with caspofungin was changed very little. After adjustment for mechanical ventilation status, the difference in ICU LoS was 4.1 days, a relative difference of 24% (95% CI -11%, 72%). The difference remained present in sensitivity analysis run in patients with infections caused by albicans vs. non-albicans species (respectively, 5.2 days and 4.8 days difference of in favour of rezafungin when adjusted for mechanical ventilation). Reported differences were Total length of hospital stay.

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**Table 1** Baseline patient characteristics, pooled mITT population

| Characteristic | Rezafungin (N = 139) | Caspofungin (N = 155) |
|---|---|---|
| Age (years)<br>Mean ± SD, years (range)<br>≥ 65 years, n (%) | 59.8 ± 15.7 (19, 91)<br>57 (41.0) | 60.8 ± 15.0 (20, 93)<br>63 (40.6) |
| Female, n (%) | 49 (35.3) | 65 (41.9) |
| BMI, kg/m$^2$, mean ± SD | 25.78 ± 7.8 | 25.12 ± 6.02 |
| Race, n (%)<br>Asian<br>Black or African American<br>White<br>Other | 24 (17.3)<br>11 (7.9)<br>95 (68.3)<br>9 (6.5) | 34 (21.9)<br>8 (5.2)<br>106 (68.4)<br>7 (4.5) |
| Final diagnosis, n (%)<br>Candidemia only<br>Invasive candidiasis | 100 (71.9)<br>39 (28.1) | 115 (74.2)<br>40 (25.8) |
| In ICU, n (%)<br>At randomisation<br>At any time | 46 (33.1)<br>55 (39.6) | 67 (43.2)<br>71 (45.8) |
| Mechanically ventilated, n (%)<br>No<br>Yes | 122 (87.8)<br>17 (12.2) | 121 (78.1)<br>34 (21.9) |
| Modified APACHE II Score<br>≥ 20, n (%)<br>< 20, n (%) | 21 (15.1)<br>116 (83.5) | 26 (16.8)<br>126 (81.3) |
| Absolute neutrophil count at randomisation<br>< 500 cells per μl, n (%)<br>≥ 500 cells per μl | 7 (5.2)<br>128 (94.8) | 5 (3.3)<br>146 (96.7) |
| Geographic region, n (%)<br>United States<br>Europe/Israel<br>Asia Pacific (excl. China & Taiwan)<br>China/Taiwan | 43 (30.9)<br>67 (48.2)<br>21 (15.1)<br>8 (5.8) | 46 (29.7)<br>76 (49.0)<br>27 (17.4)<br>6 (3.9) |

*APACHE*, Acute Physiology and Chronic Health Evaluation; *BMI*, body mass index; *ICU*, intensive care unit; *mITT*, modified intention to treat; *SD*, standard deviation

**Table 2** Characteristics of ICU population (from pooled mITT population)

| | In ICU at randomisation | | In ICU at any time | |
|---|---|---|---|---|
| | Rezafungin | Caspofungin | Rezafungin | Caspofungin |
| N (%) in ICU | 46 (33.1) | 67 (43.2) | 55 (39.6) | 71 (45.8) |
| Age, years<br>Mean (SD)<br>< 65, n (%) | 61.6 (11.55)<br>25 (54.3) | 61.5 (14.11)<br>37 (55.2) | 61.4 (11.70)<br>30 (54.5) | 62.2 (14.09) 38 (53.5) |
| Female, n (%) | 11 (23.9) | 23 (34.3) | 12 (21.8) | 24 (33.8) |
| Final diagnosis, n (%) | | | | |
| Candidemia only | 33 (71.7) | 50 (74.6) | 40 (72.7) | 51 (71.8) |
| Invasive candidiasis | 13 (28.3) | 17 (25.4) | 15 (27.3) | 20 (28.2) |
| Mechanically ventilated, n (%) | | | | |
| Yes | 16 (34.8) | 33 (49.3) | 16 (29.1) | 33 (46.5) |
| No | 30 (65.2) | 34 (50.7) | 39 (70.9) | 38 (53.5) |
| Baseline Modified APACHE II Score | | | | |
| Mean | 17.3* (7.47) | 16.0 (8.23) | 16.5* (7.53) | 15.9 (8.18) |
| < 20 | 28* (63.6) | 47 (70.1) | 36* (67.9) | 50 (70.4) |
| ≥ 20 | 16* (36.4) | 20 (29.9) | 17* (32.1) | 21 (29.6) |

* data missing for 2 patients

*APACHE*, Acute Physiology and Chronic Health Evaluation; *BMI*, body mass index; *ICU*, intensive care unit; *mITT*, modified intention to treat; *SD*, standard deviation

not found to be statistically significant

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**Table 3** Length of ICU stay in pooled analysis (patients with an ICU stay, mITT population)

| | Rezafungin (N = 55) | Caspofungin (N = 71) | Absolute difference | Relative difference |
|---|---|---|---|---|
| Unadjusted mean (SD)[a], days | 16.1 (15.2) | 21.6 (18.0) | 5.5 | 1.34 (95% CI 0.96,1.86) |
| ICU LoS Adjusted mean (95% CI)[a] LoS, days | 17.3 (13.4,20.6) | 21.4 (17.3,26.8) | 4.1 | 1.24 (0.89,1.72) |

*CI*, confidence interval; *ICU*, intensive care unit; *LoS*, length of stay; *mITT*, modified intention to treat; *SD*, standard deviation

[a] Generalised linear model, unadjusted or adjusted for mechanical ventilation status; [c](C-R)/(C/R), where C is caspofungin and R is rezafungin. The data were log-transformed because of skewing. The estimate is the ratio of geometric means, with values > 1 indicating more time in the ICU in the caspofungin arm

**Table 4** Length of ICU stay in pooled analysis in survivors (patients discharged from ICU, mITT population)

| | Rezafungin (N = 35) | Caspofungin (N = 53) | Absolute difference |
|---|---|---|---|
| Mean (SD), days | 15.9 (16.4) | 23.0 (19.6) | 7.1 |

*SD*, standard deviation

Patients treated with rezafungin had a numerically shorter LoS than the caspofungin group in both survivor and all-patient analyses, with and without adjustment for mechanical ventilation (Table 5). The difference in mean total LoS between treatments was similar in the all-patients and survivor-only populations, at 3.1 and 3.0 days, respectively. In the all-patients population, patients treated with rezafungin spent a mean of 25.2 days in the hospital, compared with 28.3 days in patients treated with caspofungin. After adjusting for mechanical ventilation status, mean LoS was 25.9 and 28.8 days in the rezafungin and caspofungin groups, respectively. This equates to a relative difference of 12% (95% CI -6%, 33%) in favour of rezafungin-treated patients having the shorter stay.

Further post-hoc subgroup analysis of length of stay data found that patients with an ICU stay (at any time during the trial) in the rezafungin group had significantly shorter total hospital stay (26.1 days vs. 33.7 days in caspofungin group, $p = 0.047$), comprised of the numerically shorter ICU component as previously discussed, and the numerically shorter non-ICU component

(17.4 days in the rezafungin group vs. 20.2 days in the caspofungin group). For patients without an ICU stay during the trial, total duration of hospital stay was similar between arms (24.0 days in rezafungin group vs. 23.4 days in caspofungin group).

### Earlier discharge from the hospital

The Principal Investigators in ReSTORE reported that, if they had the availability of once-weekly IV rezafungin and did not need to administer daily echinocandin, they would have considered earlier discharge than the actual discharge date for 30 (16%) of the 187 patients for whom a response was available. The mean number of days earlier was 5.9 (median 5, range 1–14). The characteristics of the patients for whom early discharge would have been considered are shown in Table 6. The proportion who had had an ICU stay was lower than in the overall trial population.

### Discussion

Rezafungin was associated with numerically shorter hospital and ICU stays than caspofungin in this pooled analysis of two clinical trials, and this effect was found in two independent randomised controlled trials (RCTs). The point estimates for relative difference indicate a trend for shorter stays for patients treated with rezafungin; however, the confidence intervals were wide. Numerical differences in ICU LoS between treatment arms remained even after adjusting for differences in mechanical ventilation status. There was no difference in total hospital

**Table 5** Total length of hospital stay in the pooled analysis (mITT population)

| | Rezafungin (N = 139) | Caspofungin (N = 155) | Absolute difference | Relative difference [c] |
|---|---|---|---|---|
| All patients | | | | |
| Hospital LoS unadjusted mean (SD)[a], days | 25.2 (19.26) | 28.3 (20.16) | 3.1 | 1.12 (95% CI 0.94,1.33) |
| Hospital LoS adjusted mean (95% CI)[a], days | 25.9 (22.2,28.6) | 28.8 (25.2,31.9) | 2.9 | 1.11 (0.94,1.33) |
| Survivors only[b] | | | | |
| n (%) | 112 (80.6) | 125 (80.6) | – | – |
| Hospital LoS unadjusted mean (SD), days | 25.7 (18.4) | 28.7 (17.9) | 3.0 | – |

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**Table 6** Demographics and baseline characteristics of 'earlier discharge' population

|  | Rezafungin N = 15/93 (16%) | Caspofungin N = 15/94 (16%) | All patients N = 30/187 (16%) |
|---|---|---|---|
| Mean age (Years, SD) | 52.3 (16.58) | 60.6 (12.88) | 56.5 (15.18) |
| Age > =18– <65 | 10 (66.7%) | 9 (60%) | 19 (63%) |
| Male gender | 8 (53.3%) | 9 (60%) | 17 (57%) |
| Initial diagnosis |  |  |  |
| Candidemia only | 13 (86.7%) | 12 (80%) | 83% |
| Invasive candidiasis | 2 (13.3%) | 3 (20%) | 17% |
| Top 3 represented risk factors |  |  |  |
| Broad-spectrum antibiotic therapy | 11 (73.3%) | 8 (53.3%) | 19 (63.3%) |
| Central venous catheter | 8 (53.3%) | 9 (60%) | 17 (56.7%) |
| Major surgery | 8 (53.3%) | 6 (40%) | 14 (46.7%) |
| ICU involvement |  |  |  |
| ICU at any time | 3 (20%) | 5 (33.3%) | 8 (26.7%) |
| ICU at randomisation | 2 (13.3%) | 5 (33.3%) | 7 (23.3%) |
| Baseline Modified Apache II Score |  |  |  |
| < 20 | 13 (86.7%) | 12 (80%) | 83% |
| > =20 | 2 (13.3%) | 3 (20%) | 17% |

*ICU*, intensive care unit; *SD*, standard deviation

LoS in patients who were not admitted to ICU, and a difference was not expected due to the double-dummy study design in which patients in the rezafungin arm still required daily placebo infusions, which affected any potential discharge date.

Both the STRIVE and ReSTORE trials were double-blind and double-dummy, meaning that patients randomised to rezafungin received placebo infusions on days when rezafungin was not administered [22, 23]. Thus, the differences in length of hospital and ICU stay in the trial setting are not likely to be attributed to the once-weekly administration. However, rezafungin may facilitate early hospital discharge for medically stable patients in the real-world setting. As reported here, 16% of patients in the ReSTORE trial would have been considered for earlier hospital discharge (median 5 days earlier) if rezafungin had been available without the need for daily echinocandin (or placebo infusion), according to the investigating physicians.

As described in the introduction, the pooled efficacy analysis of STRIVE and ReSTORE found a potential early treatment benefit with rezafungin, which the authors noted might reflect its front-loaded dosing regimen [24]. As noted by Thompson et al. in the primary publication from the ReSTORE study [22], the efficacy of echinocandins is dependent on drug concentrations within the target tissues, as the echinocandin class exhibits concentration-dependent fungal killing [20]. It is possible that the shorter lengths of ICU and hospital stay seen in the trials may also be due to front-loaded antifungal efficacy with rezafungin and/or the faster clearance of the pathogen (as evidenced by time to first negative blood culture).

There is a recognised unmet need for new antifungals with similar activity to the currently available echinocandins, but with longer half-lives and/or oral administration. [17] In a study of the relationship between adherence to guideline recommendations and outcomes at 64 centres in Europe, Hoenigl et al. found that treatment with echinocandins was associated with improved survival (90-day mortality) compared with other antifungals. However, they also described longer hospital stays, with 1 in 7 patients with candidemia having their hospitalisation extended solely to allow completion of IV echinocandin treatment. [17].

Hospitalisation costs are a major driver of the economic burden of IC. [7, 8, 11] Any reduction in overall or ICU LoS would be associated with significant cost savings, and would help to free up hospital beds and reduce overflow in many institutions across the world. In addition, rezafungin could also facilitate echinocandin treatment in the outpatient parenteral antimicrobial therapy (OPAT) setting, which is challenging with currently available echinocandins which require once daily IV administration. [25] The availability of a once-weekly IV option could facilitate more optimal use of OPAT pathways for antifungal treatment as well as reducing demand for the placement of central lines.

Other aspects of healthcare resource utilisation are associated with IV administration, such as nursing time, pharmacy time, and infusion-related consumables,

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would also be substantially reduced by a factor of 7, with weekly rather than daily echinocandin infusions. In a given week, weekly infusion would release up to 3 h of pharmacist (or pharmacy technician) time spent on drug reconstitution, which can take up to 30 min for IV drugs supplied as powders [26], and additionally reduce the nurse time spent on setting up and monitoring IV infusions by a factor of sevenfold. The actual size of potential gains requires appropriate further research.

Daily IV infusions are burdensome for patients, both in the hospital and outpatient settings, as they contribute to the health risks associated with long-term indwelling catheters (in patients who do not need them for other reasons, including upon discharge) as well as the burden of the costs of the peripherally inserted central catheter (PICC line) itself. [22] Weekly infusion would reduce the burden of treatment associated with current echinocandin treatment for IC. For some patients it may avoid the need for placement of a central venous catheter, sparing the patient from the procedure and the associated infection risk. [22] Daily infusions also increase the fluid volume that patients receive compared with weekly infusion. Fluid volumes must be carefully managed, particularly in critically ill patients, as volume overload is associated with increased mortality. [27] Finally, drug-drug interactions and side effects are important considerations and potential barriers to transitioning patients to an oral triazole antifungal agent. A once weekly echinocandin provides an opportunity to discharge patients from hospital without the need for oral step-down and to continue treatment in the outpatient setting.

Our analyses have several limitations. The design of both trials meant that all patients in the rezafungin group received IV therapy during the whole treatment period, but in the caspofungin group most were switched to fluconazole before the end of therapy. This could be considered a bias in favour of rezafungin given that the benefit of an echinocandin vs. fluconazole has been demonstrated. [16] There was high heterogeneity in the data and the confidence intervals for differences between treatment arms were wide. The analyses are based on exploratory endpoints from trials primarily designed to assess efficacy and safety. The trials did not collect health-related quality of life (HRQoL) data, so it was not possible to ascertain whether shorter LoS resulted in improved quality of life for patients. This is being explored in a health economic analysis using HRQoL from a clinically-validated proxy from another condition, to be published separately. There is no standard definition of what constitutes an ICU: the nature of units, the severity of the patients admitted, and the criteria for their discharge will vary between centres, particularly depending on whether or not intermediate care units are available. Provision of intermediate care units varies widely between centres and regions, and it was not possible to adjust for their use as data were not available. There was also considerable heterogeneity among the types of patients in the analysis.

The severity of patients arriving in ICU is an important predictor of length of ICU stay. The STRIVE and ReSTORE trials aimed to balance severity by stratifying randomisation by diagnosis (candidemia only or IC), modified APACHE II score (ReSTORE only), and absolute neutrophil count. [22] APACHE scores were well-balanced between treatment groups in the pooled analysis. The use of vasopressors in the pooled ICU population was also broadly comparable between the two groups (analysis to be published separately). However, there was an observed imbalance in the proportion of patients receiving mechanical ventilation, which has been identified as one of the factors associated with longer length of ICU stay. [28] Due to the complexity of ICU patients, and the inability to control for confounding factors such as APACHE II/SOFA scores, and/or mechanical ventilation status, data on ICU length of stay required further adjustments. Adjustment for mechanical ventilation status resulted in a reduction in the difference in ICU LoS between the rezafungin and caspofungin treatment arms from 5.5 days (unadjusted) to 4.1 days, a relatively small difference that supports the finding of a treatment-related difference. However, an influence from differences in patient severity cannot be ruled out.

In candidemia, removal of indwelling catheters is strongly recommended in guidelines [14]. Accordingly, the study protocol recommended that central venous catheters (CVC) should be removed within 48 h after diagnosis with candidemia. However, this only occurred in a minority of patients. [22] The impact of this on length of stay is difficult to assess. Given that rates of removal were low in both arms it is not expected to significantly impact any differences between arms, and could overestimate the LoS in the rezafungin arm as fewer patients in this arm had their CVC removed within 48 h.

Furthermore, the ReSTORE study was partially conducted during the COVID-19 pandemic [22], which may have affected the overall management of patients, including time to CVC removal. Patients enrolled during the peri-COVID period had a higher baseline incidence of some poor prognostic factors than patients enrolled pre-COVID, including use of invasive interventions, antibiotics, and active cancer. However, the distribution of these factors was similar between trial arms. [29].

Further studies are needed to confirm the effect of rezafungin treatment on length of ICU and hospital stay in the real-world setting and to understand how rezafungin could facilitate discharge in patients who are unable to step down to oral options due to resistance,

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tolerability or requirement for an IV route. A full cost-effectiveness analysis will be required to confirm and quantify the overall health economic effects of introducing rezafungin to the treatment pathway for IC/C. This is currently being undertaken and will be published separately.

## Conclusions

Pooled data from two RCTs found that weekly IV rezafungin for the treatment of IC or candidemia was associated with numerically shorter hospital and ICU stays than daily IV caspofungin. In addition, 16% of patients in the phase 3 trial would have been considered for earlier hospital discharge if a once-weekly echinocandin had been available. Further studies are needed to confirm these findings in the real-world setting. Given its previously demonstrated non-inferiority to caspofungin, rezafungin has the potential to lower the healthcare resource and cost burden associated with current standard of care options, including daily IV echinocandin treatment, and transform the treatment of invasive candidiasis and candidemia.

### Abbreviations

| | |
|---|---|
| APACHE | Acute physiology and chronic health evaluation |
| BMI | Body mass index |
| CI | Confidence interval |
| CRF | Case report form |
| EMA | European medicines agency |
| FDA | Food and drug administration |
| HRQoL | Health-related quality of life |
| IC/C | Invasive candidiasis/candidemia |
| ICU | Intensive care unit |
| IV | Intravenous |
| LoS | Length of stay |
| mITT | Modified intention-to-treat |
| MV | Mechanical ventilation |
| OPAT | Outpatient parenteral antimicrobial therapy |
| PICC | Peripherally inserted central catheter |
| RCT | Randomised controlled trial |
| SD | Standard deviation |
| SOFA | Sequential organ failure assessment |
| US | United States |

### Author contributions
JFA, MB, OAC, HD, PMH, MHK, JP, PP, GRT and JV were investigators on the STRIVE and/or ReSTORE trials. MB, OAC, TS, GRT and JV contributed to the design of one or both trials. IB, DS and NM designed and analysed the pooled analysis. All authors reviewed the design of the pooled analysis and interpreted the data. IB wrote the draft manuscript. All authors critically reviewed and revised the draft and approved the final manuscript for publication.

## Declarations

### Data and availability of materials
Data supporting the findings of this study are available on request from Sara Dickerson, Sara.Dickerson@mundipharma.com.

### Ethics approval and consent to participate
Both the STRIVE and ReSTORE trials were in conducted in accordance with current country and local regulations, the International Conference on Harmonisation Good Clinical Practice, and the Declaration of Helsinki. Ethics committees or institutional review boards at participating sites approved the protocols and all amendments. All patients, or their legally authorised representative, provided written informed consent.

### Consent for publication
Not applicable.

### Competing interests
PMH reports grants or contracts from Baxter, Cytosorbents, and Pfizer; consulting fees from Baxter, Cytosorbents, and Pfizer; honoraria from Baxter, and Cytosorbents; and support for attending meetings from Mundipharma, and Pfizer, outside of the submitted work. 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. 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; outside of the submitted work. HD reports consulting fees from Pfizer, Gilead, MSD, Mundipharma, Shionogi, Viatris, outside of the submitted work. JF was an advisor/consultant and received grant support and honoraria for talks on behalf of Astellas Pharma, Gilead Sciences, Merck Sharp & Dohme and Pfizer, 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. PP reports grants from Astellas, Gilead, Scynexis, and Cidara; fees for scientific advisory board from F2G, Matinas, TFF, Basilea outside of the submitted work. JP Reports no conflict of interest. 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. IB and NM report being employees of Mundipharma. TS reports being an employee of and holding stocks in Cidara Therapeutics. 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.

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