Therapeutic indication:

*▼REZZAYO*® (rezafungin) is indicated for the treatment of invasive candidiasis in adults. Consideration should be given to official guidance on the appropriate use of antifungal agents.

**Prescribing Information**

Prescribing information can be found at the end of this document.

**Reporting adverse events**

Adverse events should be reported. Reporting forms and information can be found at <https://yellowcard.mhra.gov.uk/>. Adverse events should also be reported to Napp Pharmaceuticals Limited on 01223 424444.

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**Hospital Formulary Submission Pack for ▼ *REZZAYO®*** **(rezafungin acetate)**

# Summary

**Burden of invasive candidiasis**

* Invasive candidiasis (IC) is a severe, life-threatening systemic fungal infection characterised by bloodstream infection with *Candida* spp*.* (candidaemia [C]) and/or deep-seated infection in the organs and tissues1
* *Candida* is responsible for 70% to 90% of all invasive fungal infections2
* Invasive candidiasis imposes a significant healthcare burden3–5
  + Despite current antifungal treatments, mortality rates for invasive candidiasis range from 20% to 50% globally3
  + Patients with *Candida* infections spend a median of 4 to 33 days in the intensive care unit (ICU),6–9 and 14 to 51 days in the hospital overall10–16
  + In a European observational study in 20 countries, 16% of 621 patients with invasive candidiasis had their hospital stay extended specifically to finish their course of IV antifungal infusions17
* Treatment of invasive candidiasis faces increasing challenges:
  + Antifungals are often associated with drug–drug interactions (this issue is further increased due to the emergence of targeted therapies for haematological malignancies)18,19
  + Fluconazole resistance is on the rise20,21
  + Non-*albicans* species are increasingly common and now account for more than 50% of invasive candidiasis cases22,23

**The benefits of *REZZAYO®*** **– the first once-weekly echinocandin24**

* Rezafungin is different from other echinocandins because of the combination of its front-loaded dosing and distinct structural features that confer greater stability, leading to a prolonged half-life (5–6 days) that allows for once-weekly dosing24–28
* Rezafungindemonstrated non-inferiority to the caspofungin group in the treatment of invasive candidiasis in the ReSTORE phase 3 trial, including the primary efficacy outcome of global response rate at day 14.29 Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more. *REZZAYO*®’s efficacy was further supported by a pre-planned pooled analysis of phase 2 and 3 data.30
* In a pre-planned pooled analysis of ReSTORE (phase 3 trial) and STRIVE (phase 2 trial):
  + Primary endpoint:rezafunginwas non-inferior to the caspofungin group (optional step-down to oral fluconazole after 3 days or more\*1) in all-cause mortality at day 30 (mITT population): all-cause mortality was 19% (26/139) for rezafungincompared with 19% (30/155) for caspofungin (difference [95% CI]: -1.5 [-10.7 to 7.7]), (not powered to infer efficacy to a wider population)30
  + Secondary endpoint:Mycological eradication at day 5 in the mITT population was 73% (102/139 patients) for rezafunginand 65% (100/155) in the caspofungin group (weighted treatment difference 10.0% (95% CI −0.3–20.4)). Mycological eradication at day 14 was 72% (100/139) for rezafunginand 68% (106/155) in the caspofungin group (optional step-down to oral fluconazole after 3 days or more\*[[1]](#footnote-2)) (weighted treatment difference 4.3% (95% CI−6.2–14.7))30
  + In patients with candidaemia only, the rezafungin group had mycological eradication at day 5 of 80/100 patients and the caspofungin group (optional step-down to oral fluconazole after 3 days or more\*) of 78/115 patients (weighted treatment difference 12.9% [[95% CI 1.5–24.3]).29,30,31 [This analysis was not powered to detect significant differences]. In a pre-planned pooled analysis of ReSTORE and STRIVE, rezafunginwas non-inferior to the caspofungin group (optional step-down to oral fluconazole after 3 days or more) in all-cause mortality at day 30 (mITT population). Mycological eradication at day 5 was 73% (102/139 patients) for rezafunginand 65% (100/155) in the caspofungin group (weighted treatment difference 10.0% (95% CI −0.3–20.4)]30
* Rezafungin hasdemonstrated activity across a broad range of *Candida* species
  + Mycological eradication was demonstrated for a range of clinically important *Candida* species, including *C. albicans, C. glabrata, C. parapsilosis,* *C. tropicalis, C. krusei* and *C. dubliniensis30*
  + In the pre-planned pooled analysis, rezafungin showed mycological eradication in patients with *C. glabrata* infection at day 14 (*REZZAYO*®: 32/38 patients [84%]). The caspofungin group, which optionally switched to oral fluconazole after 3 days or more, had rates of (22/35 patients [63%]).30 [This analysis was not powered to detect significant differences]. In a pre-planned pooled analysis of ReSTORE and STRIVE, rezafunginwas non-inferior to the caspofungin group (optional step-down to oral fluconazole after 3 days or more†[[2]](#footnote-3)). Not powered to infer differences to a wider population. Mycological eradication at day 14 was 72% (100/139) for rezafunginand 68% (106/155) in the caspofungin group (optional step-down to oral fluconazole after 3 days or more) (weighted treatment difference 4.3% (95% CI −6.2-14.7))30
* Rezafunginwas generally well tolerated in the clinical trial programmes29,30
  + The once-weekly dosing of rezafungin did not have any additional safety outcomes compared to once-daily caspofungin group29
  + Serious adverse events (SAEs) were reported in 56% of patients (of which 2% were study-drug-related) in the rezafungin group and 53% of patients (of which 3% were study-drug-related) in the caspofungin group29
  + The most common treatment-emergent adverse events (TEAEs), occurring in at least 5% of patients in the rezafungin group, were pyrexia, hypokalaemia, pneumonia, anaemia and septic shock29
* The drug–drug interaction potential of REZZAYO® has also been assessed clinically. The need for dose adjustments is considered unlikely for: tacrolimus, cyclosporine, ibrutinib, mycophenolatemofetil and venetoclax, and no dose adjustments are required for special populations.\*[[3]](#footnote-4),19,24
  + These include patients with hepatic or renal impairment, elderly (≥65 years) or obese (BMI ≥30) patients. Rezafungincan be administered independently of the timing of haemodialysis24
* No requirement for therapeutic drug monitoring (monitoring of medication levels in the blood during treatment)24

Benefits specific to different healthcare settings are outlined below:

In a *post hoc* adjustment for mechanical ventilation of the pooled analysis (exploratory endpoint), the mean ICU length of stay was 17.3 days with rezafunginand 21.4 days with caspofungin33 (stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more\*29).

* Of the 294 patients included in the pooled analysis, 126 (43%) required ICU admission; 55 were treated with rezafungin and 71 received caspofungin therapy. Overall, 35 patients in the rezafungin arm and 53 patients in the caspofungin group were discharged from the ICU33,72
* Other potential benefits specific to the ICU with rezafunginmay include its:
  + Front-loaded dosing, which leads to high plasma drug concentration early in therapy, with AUC/MIC values maintained throughout the dosing interval†[[4]](#footnote-5),35–37
  + Broad activity across a range of *Candida* species, including some harder-to-treat species, such as *C. glabrata* and *C. parapsilosis*30,38,39
  + Non-clinical data, which support extensive tissue distribution40

# Invasive candidiasis and candidaemia

## Clinical presentation

Invasive candidiasis (IC) is a severe, life-threatening systemic fungal infection.1 The term refers to bloodstream infection with *Candida* spp*.* (candidaemia), deep-seated infection in the organs and tissues, or candidaemia with deep-seated/visceral infection.1 Manifestations include (but are not limited to) intra-abdominal abscesses, peritonitis, osteomyelitis and ocular involvement.1 Approximately half of candidaemia cases occur in the Intensive Care Unit (ICU) setting.1 Risk factors include the presence of indwelling central venous catheters, transplantation (stem cell or solid organ), chemotherapy, neutropenia, major surgery and prolonged hospital stay.1

## Epidemiology of Candida spp.

Although historically, many infections were caused by *C. albicans*, other species are becoming more common.23 Five species of *Candida* currently cause more than 90% of invasive candidiasis cases: *Candida albicans (C. albicans*)*, Candida glabrata (C. glabrata*)*,* *Candida parapsilosis (C. parapsilosis*)*,* *Candida tropicalis* (*C. tropicalis*) and *Candida krusei* (*C. krusei).42,43,44* Globally, non-*albicans* species are on the rise and responsible for more than 50% of invasive candidiasis cases.22,23 *C. glabrata* is the second most common invasive *Candida* infection after *C. albicans*.21

One reason for the increase in non-albicans infections is an increase in resistance to commonly used antifungal drugs such as fluconazole.21 Widespread use of fluconazole has been correlated with an increase in fluconazole-resistant strains, both for *C. albicans* and other *Candida* spp.20,21 Analysis of 20,788 invasive *Candida* isolates from the global SENTRY programme between 1997 and 2016 showed an increase in resistance to fluconazole among multiple strains of *Candida*.21

The species *C. auris,* first identified in 2009, has been increasing rapidly*.*45 Up to 40% of *C. auris* strains show multi-drug resistance, and mortality is 30% to 70% in affected patients.45 A worldwide alert has been raised to warn about the risks of *C. auris* infection.45 *C. albicans* and *C. auris* have been identified as critical priority pathogens in the World Health Organization fungal priority pathogens list (FPPL), with *C. glabrata, C. tropicalis* and *C. parapsilosis* ranked in the high- and *C. krusei* in the medium-priority groups.3

(Efficacy of rezafungin in treating infections caused by *C. Auris* has not been established in clinical trials. *In vitro* data does not imply clinical efficacy.)

## Burden of invasive candidiasis/candidaemia (IC/C)

*Candida* is the most common cause oflife-threatening fungal infection in people with weakened immunity and causes 70% to 90% of all invasive fungal infections.2 The number of cases of serious invasive fungal disease has increased steadily in recent years, mainly due to more people becoming high-risk.46 30-day mortality in ICU patients with invasive candidiasis in Europe in a 2019 meta-analysis was 37%.47

Invasive candidiasis imposes a considerable economic burden on hospitals and healthcare systems, predominantly due to prolonged ICU and hospital stays.4,5 Patients with *Candida* infections spend a median of 4 to 33 days in the intensive care unit (ICU),6–9 and 14 to 51 days in the hospital overall.10–16

# Characteristics of *REZZAYO®* rezafungin acetate

Rezafunginis a new addition to the echinocandin class of antifungal agents. It is administered by IV infusion once-weekly,24 whereas current echinocandins require daily infusion.26–28

## Summary of product information

Table 1 *REZZAYO®* product characteristics

|  |  |
| --- | --- |
| **Generic name:** | Rezafungin acetate |
| **Brand name:** | *REZZAYO®* |
| **BNF Chapter: *(UK only)*** | Antifungals, systemic use |
| **ATC Code:** | J02AX0824 |
| **Manufacturer(s):** | Napp Pharmaceuticals Limited |
| **Therapeutic drug class:** | Antimycotics for systemic use, other antimycotics for systemic use.24  *REZZAYO®* belongs to the echinocandin class of antifungals. |
| **Pharmaceutical form and strength:** | 200 mg powder for concentrate for solution for infusion24 |
| **Active ingredient:** | Rezafungin acetate |
| **Mechanism of action:** | *REZZAYO®* selectively inhibits fungal 1,3-β-D-glucan synthase. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall that is not present in mammalian cells. Inhibition of 1,3-β-D-glucan synthesis results in rapid and concentration-dependent fungicidal activity in *Candida* species (spp.).24 |
| **License/Market authorisation status:** | *REZZAYO®* received a UK Marketing Authorisation on 29th January 2024.50  *REZZAYO®* was also granted orphan drug designation by the MHRA at the time of its approval in January 2024.51 |
| **Indication(s):** | *REZZAYO®* is indicated for the treatment of invasive candidiasis in adults.24  Consideration should be given to official guidance on the appropriate use of antifungal agents.24 |
| **Proposed indication(s):**  *If different from licensed indication(s),or any restrictions applied, please specify.* | As above |
| **Intended dose(s):** | Treatment with *REZZAYO®* should be initiated by a physician experienced in the management of invasive fungal infections.24  Posology: A single 400 mg loading dose on day 1, followed by 200 mg on day 8 and once weekly thereafter.24   * If a scheduled dose is missed (not given on the assigned day) the missed dose should be administered as soon as possible * If the missed dose is administered within 3 days of the assigned day, the next weekly dose may be given on schedule * If the missed dose is administered more than 3 days after the assigned day, the dosing schedule should be revised to ensure there are at least 4 days before the next dose24 * If administration is restarted after at least 2 weeks of missed dosing, the dosing should be started again at the 400 mg loading dose   No dose adjustment is required for elderly patients (age 65 years or more), patients with hepatic or renal impairment, or based on patient weight and BMI.24  The safety and efficacy of *REZZAYO®* in children below 18 years have not yet been established. No data are available.24 |
| **Administration/route:** | For intravenous use only.  *REZZAYO®* powder for concentrate for solution for infusion must be reconstituted with water for injections and diluted prior to administration, in accordance with the dosing table in the SmPC. It should be administered as a single agent via intravenous infusion in sodium chloride 9 mg/mL (0.9 %) solution for injection, sodium chloride 4.5 mg/mL (0.45 %) solution for injection, or 5 % glucose. Instructions for use are given in the Summary of Product Characteristics, Section 6.6.24  After reconstitution and dilution, the solution should be administered by slow intravenous infusion over approximately 1 hour. Infusion time may be increased up to 180 minutes to manage any evolving symptoms of infusion-related reaction.24 |
| **Expected treatment duration:** | For candidaemia without organ involvement, guidelines recommend IV antifungal treatment for 14 days after the end of candidaemia and resolution of candidiasis-related symptoms52,53 (or at least 14 days in neutropenic patients53,54 and individualised in critically ill patients55).  The duration of treatment with rezafunginshould be based on the patient's clinical and microbiological response. In general, antifungal therapy should continue for at least 14 days after the last positive culture. During clinical trials, patients were treated with rezafunginfor up to 28 days. The safety information on rezafungintreatment durations longer than 4 weeks is limited.24 |
| **Monitoring/testing requirements:** | The SmPC does not stipulate any requirements for therapeutic drug monitoring (monitoring of medication levels in the blood during treatment).  Patients who develop elevations in liver enzymes during rezafungintherapy should be monitored and the risk/benefit of continuing rezafungintherapy should be re-evaluated.24 |
| **Proposed formulary status (e.g., hospital only)/or expected prescription setting:** | *REZZAYO®* is indicated for the treatment of invasive candidiasis in adult patients. Treatment with *REZZAYO®* should be initiated by a physician experienced in the management of invasive fungal infections.24  Treatment is expected to be initiated in the hospital setting. |
| **Which products are currently in the formulary for similar indication(s)?** | The following products are currently in the formulary for the management of invasive candidiasis:  [Likely to be other echinocandins (caspofungin, anidulafungin, micafungin), fluconazole, amphotericin B (liposomal) and voriconazole. Check local formulary.] |
| **Will this product replace a product currently in the Formulary? (Y/N)**  *If not, why not?* | No. *REZZAYO®* will provide an additional treatment option to those already available. Specifically, it provides the option of once-weekly echinocandin administration, compared with the once-daily infusions required with other echinocandins.24  However, where used for the treatment of invasive candidiasis in adults, rezafungintreatment will be given instead of another product already listed on the formulary.24 |
| **Reason for request (if applicable):** | *REZZAYO®* is requested because it may offer the following benefits.   * The combination of its front-loaded dosing and distinct structural features, which confer greater stability, leads to a prolonged half-life (5–6 days) and allows for once-weekly dosing24 * It brings the benefits of once-weekly treatment without compromising efficacy (rezafungindemonstrated non-inferior efficacy to daily intravenous caspofungin\*[[5]](#footnote-6) [see Section 7.3] and the once-weekly dosing ofrezafungindid not have any additional safety outcomes compared to once-daily caspofungin)29 (see Table 11) * It has demonstrated mycological eradication for a range of clinically important *Candida* species,31 including some harder-to-treat species such as *C. glabrata* and *C. parapsilosis30,38,39* * In patients with candidaemia only, the rezafungin group had mycological eradication at day 5 of 80/100 patients and the caspofungin group (optional step-down to oral fluconazole after 3 days or more\*) of 78/115 patients (weighted treatment difference 12.9% [95% CI 1.5-24.3])\* 30,31 * In the pre-planned pooled analysis, patients in the rezafunginhad mycological eradication of 32/38 (84%), and the caspofungin group (optional stepdown to oral fluconazole after 3 days or more) was 22/35 (63%) in patients infected with *C.* *glabrata* at day 14; difference 21.4% [95% CI 1.9-40.8])\*30 * No dose adjustments are required for special populations (patients with hepatic or renal impairment, elderly [≥65 years] or obese [BMI ≥30]).24 The drug–drug interaction potential of rezafungin with a number of probe substrates of cytochrome P450 enzymes and/or transporter proteins has been assessed clinically. The need for dose adjustments is considered unlikely for medicinal products that are substrates for the CYP2C8, CYP3A4, CYP1A2, and CYP2B6 enzymes and P-gp, BCRP, OATP, OCT1, OCT2, MATE1, and MATE2 transporter proteins, when administered with rezafungin.19,24 |

## Pharmacology

### **Structure**

*Rezafungin* is a structural analogue of anidulafungin, a cyclic hexapeptide with a lipophilic tail with a choline moiety at the C5 ornithine position that differentiates it from anidulafungin.25

### **Pharmacodynamics**

In pooled clinical data,mycological eradication (at 5 and 14 days) with rezafungin was demonstrated for a range of *Candida* species, including *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. dubliniensis*, *C. krusei* and *C. parapsilosis30*

Activity *in vitro*

RezafunginMIC90 values (obtained using a modified EUCAST methodology) are generally ≤ 0.016 mg/L across non-*parapsilosis* *Candida* spp. (*Candida parapsilosis* MIC90 = 2 mg/L).24

When tested against a collection of clinical isolates of *Candida* spp. enriched for echinocandin-resistant and/or azole-resistant strains, rezafunginactivity was similar to that of anidulafungin.24

Rezafunginhas shown *in vitro* activity against a group of *C. auris* isolates.56 (Efficacy of rezafunginin treating infections caused by these isolates has not been established in clinical trials. *In vitro* data does not imply clinical efficacy.) With *REZZAYO®*, the area under curve (AUC) and minimum inhibitory concentration (MIC) targets are likely to be exceeded for >90% of *C. auris* isolates, including some isolates that have exhibited high MIC values with other echinocandins.37,56

Resistance

Reduced susceptibility to echinocandins, including rezafungin, arises from mutations in glucan synthase catalytic subunit-encoding *FKS* genes (*FKS1* for most *Candida* spp.; *FKS1* and *FKS2* for *C. glabrata*).24

Susceptibility testing interpretative criteria

MIC (minimum inhibitory concentration) interpretative criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for rezafungin; see SmPC for details.24

### **Pharmacokinetics**

The additional choline moiety on the central ring gives the rezafunginmolecule more stability and enhanced solubility compared with other echinocandins57 and increases its mean terminal half-life to 127–146 hours, substantially longer than with other echinocandins.24,26–28 This enables once-weekly administration,24 while other echinocandins have to be administered once daily.26–28 The pharmacokinetics of rezafunginhave been characterised in healthy subjects, special populations and patients. Plasma concentrations over the dosing interval are shown in Figure 1.

* Steady-state is achieved with the first loading dose (twice the weekly maintenance dose)24
* The first dose (400 mg) with rezafunginproduces high plasma concentration early in therapy, resulting in a high Cmax with elevated AUC/MIC values that are maintained throughout the dosing interval.36,37 Together with subsequent 200 mg doses, this provides fungicidal coverage throughout the treatment course35
* Rezafunginis rapidly distributed with a volume of distribution approximately equal to body water (~ 40 L).24 Non-clinical studies in rats have demonstrated that rezafunginhas extensive tissue distribution, providing concentrations within some major organs (e.g., kidney, lung, liver, spleen) approximately 4-fold higher than that in plasma (Figure 2).40 (Only non-clinical studies are available)
* Protein binding of rezafunginis high (> 97%)24

Figure 1 Plasma concentrations of *REZZAYO®* over the dosing interval

A graph of a number of times

Description automatically generated with medium confidence

Source: Data on file.35

A phase I, single centre, open-label, cross-over inpatient study of rezafungin in healthy adults. N=2419

Figure 2 Tissue and plasma AUC exposures for *REZZAYO®* (data from rats)

A graph of blue rectangular bars with numbers and symbols

Description automatically generated with medium confidence

Adapted from Ong et al., 201740

### **Drug–drug interactions**

Antifungals used to treat IC/C are often associated with drug–drug interactions (DDIs), including cytochrome P450 (CYP)-mediated interactions.19 The challenge of DDIs has further increased due to the emergence of multiple new targeted therapies for haematological malignancies.18

No known clinically relevant DDIs have been identified with *REZZAYO®*.19,24 In studies, rezafunginhad no or minimal effects on the exposure of probe drugs for the following substrates/ transporter proteins: CYP2B6 (efavirenz); CYP3A4 (midazolam and tacrolimus); CYP1A2 (caffeine); CYP2C8 (repaglinide); P-gp (digoxin and tacrolimus); OCT-1, OCT-2, MATE-1 and MATE-2 (metformin); OATP (pitavastatin, rosuvastatin and repaglinide); and BCRP (rosuvastatin).19,24

* The drug–drug interaction potential of rezafunginwith a number of co-administered medicinal products has also been assessed clinically.19 The need for dose adjustments is considered unlikely for tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax24
* The need for dose adjustments is considered unlikely for medicinal products that are substrates for the CYP2C8, CYP3A4, CYP1A2 and CYP2B6 enzymes and P-gp, BCRP, OATP, OCT1, OCT2, MATE1 and MATE2 transporter proteins, when administered with *REZZAYO®*24

*In vitro* rezafunginis metabolically stable and was found not to be a substrate for BCRP, P-gp, MRP2, OATP1B1, OATP1B3, OCT1, OCTN1 and OCTN2 transporter proteins. Therefore, the need for dose adjustments of rezafunginis considered unlikely when rezafunginis co-administered with other medicinal products.24

# Current treatment of IC/C and place of *REZZAYO®* rezafungin acetate in therapy

## Current treatment

### Targeted treatment

*REZZAYO®* is used for the treatment of invasive candidiasis in adults. Once invasive candidiasis is confirmed, targeted treatment is initiated. Echinocandins are recommended in clinical guidelines as the treatment class of choice (Class A recommendation in ESCMID guidelines); liposomal amphotericin B, voriconazole and fluconazole are also options.52–55 The currently available echinocandins are caspofungin, micafungin and anidulafungin.26–28

While on daily IV antifungal treatment, patients must either remain in hospital, return for daily outpatient infusions or receive daily home visits for administration. For candidaemia without organ involvement, guidelines recommend antifungal treatment for 14 days after the end of candidaemia and resolution of candidiasis-related symptoms52,53 (or at least 14 days in neutropenic patients53,54 and individualised in critically ill patients55).

Some guidelines recommend a transition from an echinocandin to fluconazole (usually within 5–7 days, route of administration not specified) for patients who are clinically stable, have isolates that are susceptible to fluconazole and have negative repeat blood cultures following initiation of antifungal therapy.52 Others state that step-down to oral treatment with fluconazole can be considered after 10 days if the species is susceptible to fluconazole and the patient is stable and able to tolerate oral treatment.52

## Place of REZZAYO® in therapy

Rezafunginprovides an alternative treatment option within the echinocandin class, providing the option of once-weekly rather than once-daily administration. International guidelines recommend echinocandins as the first-line treatment for IC.52–55

Rationale for use of *REZZAYO®*:

* Rezafunginfacilitates patients to receive guideline-recommended52–55 echinocandin treatment with weekly rather than daily infusions
* Rezafunginfacilitates continuity of care throughout antifungal treatment without the need to switch treatments
* In the ICU, the benefits of rezafungininclude no dose adjustment for special populations (patients with hepatic or renal impairment, elderly (≥65 years) or obese (BMI ≥30) patients);24 no known clinically relevant DDIs;\*10,19,24 front-loaded dosing leads to high plasma drug concentration early in therapy, with AUC/MIC values maintained throughout the dosing interval;\*11,35,36,37 no requirement for therapeutic drug monitoring during treatment (monitoring of medication levels in the blood during treatment); non-clinical data supporting extensive tissue distribution.40
* In a European observational study, 16% of 621 patients with invasive candidiasis had their hospital stay extended specifically to finish their course of IV antifungal infusions17
* Rezafunginmay reduce demand on health care resources compared with daily infusion and is cost-saving compared with current treatments (see Section IV)4

No therapeutic drug monitoring is required during rezafungintreatment (monitoring of medication levels in the blood during treatment).

See Table 2 (echinocandins) and Table 3 (azoles) for a comparison of rezafunginwith other commonly used treatments for invasive candidiasis.

Table 2 Comparison of product characteristics of *REZZAYO®* and other echinocandins [for indicative purposes only; refer to relevant summaries of product characteristics and guidelines when using these treatments clinically]

|  |  |  |  |
| --- | --- | --- | --- |
| **Approved and brand name** | | | |
| ***Rezafungin***  ***REZZAYO®*24** | **Caspofungin (CANCIDAS or generic)26** | **Micafungin (MYCAMINE or generic)27** | **Anidulafungin (ECALTA or generic)28** |
| **Licensed indication(s) in adults** | | | |
| Treatment of invasive candidiasis in adults. | Treatment of invasive candidiasis in adult or paediatric patients.  Treatment of invasive aspergillosis in adult or paediatric patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole. Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.  Empirical therapy for presumed fungal infections (such as *Candida*or *Aspergillus*) in febrile, neutropenic adult or paediatric patients. | Adults, adolescents ≥ 16 years of age and elderly:  Treatment of invasive candidiasis.  Treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate.  Prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/µl) for 10 or more days.  The decision to use micafungin should take into account a potential risk for the development of liver tumours. Micafungin should therefore only be used if other antifungals are not appropriate.  Children (including neonates) and adolescents < 16 years of age: indications as above, except for oesophageal candidiasis indication which does not apply to this age group. | Treatment of invasive candidiasis in adults and paediatric patients aged 1 month to < 18 years. |
| **Pharmaceutical form** | | | |
| Powder for concentrate for solution for infusion | Powder for concentrate for solution for infusion | Powder for concentrate for solution for infusion | Powder for concentrate for solution for infusion |
| **Mode and frequency of administration** | | | |
| IV infusion over approx. 1 hour  Once weekly | IV infusion over approx. 1 hour  Once daily | IV infusion over approx. 1 hour  Once daily | IV infusion. Rate of infusion that does not exceed 1.1 mg/min (equivalent to 1.4 mL/min when reconstituted and diluted per instructions)  Once daily |
| **Dose adjustments in special populations** | | | |
| No dose adjustments required for elderly patients, hepatic or renal impairment or patient weight. | Reduction recommended in moderate hepatic impairment (Child-Pugh 7–9) | Dosing depends on body weight.  Adjustment not necessary in mild or moderate hepatic impairment; micafungin is not recommended in severe hepatic impairment. | None required |
| **Monitoring requirements** | | | |
| Patients who develop elevations in liver enzymes duringrezafungintherapy should be monitored and the risk/benefit of continuingrezafungintherapy should be re-evaluated. | Patients who develop abnormal liver function tests during caspofungin therapy should be monitored for evidence of worsening hepatic function and the risk/benefit of continuing caspofungin therapy should be re-evaluated. | Liver function should be carefully monitored during micafungin treatment. To minimise the risk of adaptive regeneration and potentially subsequent liver tumour formation, early discontinuation in the presence of significant and persistent elevation of ALT/AST is recommended.  Patients should be closely monitored for worsening of renal function. | Patients with increased hepatic enzymes during anidulafungin therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing anidulafungin therapy. |
| **Storage** | | | |
| Does not require refrigeration before reconstitution and has a 3-year shelf life.  For storage conditions after reconstitution and dilution of the medicinal product, see SmPC for details. | Store in a refrigerator (2°C – 8°C).  For storage conditions after reconstitution and dilution of the medicinal product, see SmPC for details. | Does not require any special storage conditions.  For storage conditions after reconstitution and dilution of the medicinal product, see SmPC for details. | Store in a refrigerator (2°C – 8°C).  For storage conditions after reconstitution and dilution of the medicinal product, see SmPC for details. |
| **Susceptibility to *Candida* spp. (see respective SmPCs for full details)** | | | |
| RezafunginMIC90 values (obtained using a modified EUCAST methodology) are generally ≤ 0.016 mg/L across non-*parapsilosis* *Candida* spp. (*Candida parapsilosis* MIC90 = 2 mg/L).  When tested against a collection of clinical isolates of *Candida* spp. enriched for echinocandin-resistant and/or azole-resistant strains, rezafunginactivity was similar to that of anidulafungin. | Broad; see SmPC for details | SmPC states that micafungin exhibits fungicidal activity against most *Candida* species; breakpoints for *C. tropicalis, krusei, guilliermondii* and other *Candida spp*. are described as ‘insufficient evidence’ (See SmPC) | Anidulafungin exhibited *in vitro* activity against *C. albicans, C. glabrata, C. parapsilosis, C. krusei*and *C. tropicalis*. |
| **Drug–drug interactions** | | | |
| The need for dose adjustment when co-administered with other medicinal products is considered unlikely (see SmPC for details). | Dose increase should be considered when co-administered with inducers of metabolic enzymes, e.g., efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin or carbamazepine (see SmPC for details). | Patients receiving sirolimus, nifedipine or itraconazole in combination with micafungin should be monitored for sirolimus, nifedipine or itraconazole toxicity and the sirolimus, nifedipine or itraconazole dosage should be reduced if necessary. | Anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 isoenzymes.  No dose adjustments are recommended in relation to concomitant medications. |
| **Reimbursement status** | | | |
| **England:** Not subject of NICE Technology Appraisal  Block Contract Antifungal  **Scotland:** Accepted for Restricted use; **SMC No. SMC2659**  **Wales:** Not subject to AWMSG Review, local commissioning decision | **England:** Not subject of NICE Technology Appraisal  Block Contract Antifungal  **Scotland:** Accepted for Restricted use; **SMC No. 74/03**  **Wales:** Not subject to AWMSG Review, local commissioning decision | **England:** Not subject of NICE Technology Appraisal  Block Contract Antifungal  **Scotland:** Accepted for Restricted use; **SMC No. 497/08**  **Wales:** Recommended as an option for use within NHS Wales | **England:** Not subject of NICE Technology Appraisal  Block Contract Antifungal  **Scotland:** Accepted for Restricted use; **SMC No. 465/08**  **Wales:** Not recommended as an option for use within NHS Wales |
| **List price** | | | |
| Rezafungin 200mg vial: £1999.95 | Caspofungin 70mg: £416.6858  Caspofungin 50mg: £327.6758 | Micafungin 100mg: £341.0059 | Anidulafungin 100mg: £299.9960 |
| **Net price** | | | |
| For further information on the Net price of *REZZAYO*® please refer to the Alliance Healthcare Ordering System, your local procurement colleagues, or speak to a representative from Napp Pharmaceuticals. | Speak to local procurement | Speak to local procurement | Speak to local procurement |

Table 3 Comparison of product characteristics of *REZZAYO®* and azoles licensed for invasive candidiasis [for indicative purposes only; refer to relevant summaries of product characteristics and guidelines when using these treatments clinically]

|  |  |  |
| --- | --- | --- |
| **Approved and brand name** | | |
| ***Rezafungin (REZZAYO)®*24** | **Fluconazole (DIFLUCAN or generic)61** | **Voriconazole (VFEND or generic)62** |
| **Licensed indication(s) in adults** | | |
| Treatment of invasive candidiasis in adults | Treatment of invasive candidiasis in adults.  Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving hematopoietic stem cell transplantation).  Fluconazole is also indicated for the treatment and prophylaxis of a range of other fungal infections, including local infections (See SmPC for details). | Treatment of fluconazole-resistant serious invasive Candida infections (including *C. krusei*) in adults and children aged 2 years and above.  Treatment of candidaemia in non-neutropenic patients.  Voriconazole is also indicated for the treatment and prophylaxis of a range of other fungal infections, including invasive aspergillosis, serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. (See SmPC for details). |
| **Pharmaceutical form** | | |
| Powder for concentrate for solution for infusion | Capsules, hard | Film-coated tablets |
| **Mode and frequency of administration** | | |
| IV infusion over approx. 1 hour  Once weekly | Fluconazole may be administered either orally (Capsules and powder for oral suspension) or by intravenous infusion (Solution for infusion), the route being dependent on the clinical state of the patient.  Administration is once daily. | Loading dose regimen (IV or oral) is every 12 hours; maintenance dose regimen (IV or oral) is twice daily. |
| **Dose adjustments in special populations** | | |
| No dose adjustments required for elderly patients, hepatic or renal impairment or patient weight. | Dose reduction is required in patients with impaired renal function (see SmPC).  Fluconazole should be administered with caution to patients with liver dysfunction. | Maintenance dose can be increased if patient response to treatment is inadequate. Oral dose can be reduced if patient is unable to tolerate treatment at a higher dose.  Detailed information on dose adjustments for hepatic impairment and for use as prophylaxis for adults, children (2 to < 12 years) and young adolescents with low body weight (12 to 14 years and < 50 kg) is provided in the SmPC. |
| **Monitoring requirements** | | |
| Patients who develop elevations in liver enzymes during rezafungintherapy should be monitored and the risk/benefit of continuing rezafungintherapy should be re-evaluated. | Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury. | Patients receiving voriconazole must be carefully monitored for hepatic toxicity; monitoring of hepatic function should be carried out in both children and adults.  Additional monitoring (e.g., renal function, pancreatic function, ECG) may be recommended for patients with given risk factors. Detailed information on special warnings and precautions for use is provided in the SmPC. |
| **Storage** | | |
| This medicinal product does not require refrigeration before reconstitution and has a 3-year shelf life.  For storage conditions after reconstitution and dilution of the medicinal product, see SmPC for details. | This medicinal product does not require any special storage condition. | This medicinal product does not require any special storage conditions. |
| **Susceptibility to *Candida* spp. (see respective SmPCs for full details)** | | |
| RezafunginMIC90 values (obtained using a modified EUCAST methodology) are generally ≤ 0.016 mg/L across non-*parapsilosis* *Candida* spp. (*Candida parapsilosis* MIC90 = 2 mg/L).  When tested against a collection of clinical isolates of *Candida* spp. Enriched for echinocandin-resistant and/or azole-resistant strains, rezafunginactivity was similar to that of anidulafungin. | *In vitro,* fluconazole displays antifungal activity across clinically common Candida species (*including C. albicans, C. parapsilosis, C. tropicalis*). *C. glabrata* shows reduced susceptibility to fluconazole while *C. krusei* and *C. auris* are resistant to fluconazole. | *In vitro*, voriconazole displays broad-spectrum antifungal activity with antifungal potency against *Candida*species (including fluconazole-resistant *C. krusei*and resistant strains of *C. glabrata* and *C. albicans*).  Clinical efficacy defined as partial or complete response, has been demonstrated for *Candida*spp.Including*C. albicans, C. glabrata, C. krusei, C. parapsilosis and C. tropicalis;*and limited numbers of*C. dubliniensis, C. inconspicua and C. guilliermondii.* |
| **Drug-drug interactions** | | |
| The need for dose adjustment when co-administered with other medicinal products is considered unlikely (see SmPC for details). | Co-administration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide, quinidine and erythromycin are contra-indicated in patients receiving fluconazole.  Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor and a strong inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored. | Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.  Refer to SmPC for table of interactions between voriconazole and other medicinal products; table lists contraindications, dose adjustment and careful clinical and/or biological monitoring, and products that have no significant pharmacokinetic interaction but may be of clinical interest in this therapeutic field. |
| **Reimbursement status** | | |
| **England:** Not subject of NICE Technology Appraisal  Block Contract Antifungal  **Scotland:** Accepted for Restricted use; **SMC No. SMC2659**  **Wales:** Not subject to AWMSG Review, local commissioning decision | **England:** Not reimbursed**63** | **England:** Not reimbursed64  **Scotland:** Reimbursed with restriction65  **Wales:** Not endorsed66 |
| **List price** | | |
| Rezafungin 200mg vial: £1999.95 | Fluconazole 200mg Capsules: £3.92-£3.94 | £551.37 per 75ml of 200mg/5ml oral suspension67 |
| **Net price** | | |
| For further information on the Net price of *REZZAYO*® please refer to the Alliance Healthcare Ordering System, your local procurement colleagues, or speak to a representative from Napp Pharmaceuticals | Speak to local procurement | Speak to local procurement |

# Benefits of *REZZAYO®* rezafungin acetate for health systems and patients

Rezafunginhas a 7-day duration of action and once-weekly dosing,24 with efficacy non-inferior to caspofungin.29 As such, there are clear benefits compared with other echinocandins, which all require daily infusion.26-28

## Benefits for health systems

**No requirement for therapeutic drug monitoring or dose adjustment** for special populations,24 potentially saving on staff time.

**Potential to reduce the number of patients requiring a peripherally inserted central catheter**, compared with daily echinocandin treatment29 (a fixed catheter is not required for administration of *REZZAYO®)*.

Excessive **infusion fluid volume** can be associated with worse outcomes in ICU patients.32

**Potential to discharge appropriate patients early**

* A study conducted at 64 centres in Europe found that 16% of 621 patients with invasive candidiasis had their hospital stay extended specifically to finish their course of IV antifungal infusions17
* Where Outpatient Parenteral Antimicrobial Therapy (OPAT) services are used.

**Continuity** **of care:** once-weekly treatment with *REZZAYO®*24 facilitates continuity of echinocandin therapy throughout the antifungal care pathway – from ICU to ward, and ward to outpatient.

**Mean length of ICU stay**: In a *post hoc* pooled analysis of the length of ICU stay in phase 268 and phase 329 clinical trials33 (interpret with caution. Further investigation is required to confirm the *post hoc* results from the analysis):

* Mean ICU length of stay (LoS) was 15.9 days in the rezafungingroup and 23.0 days in the caspofungin group33
* Mean LoS in the ICU after adjustment for mechanical ventilation status was 17.3 (rezafungin) and 21.4 (caspofungin) days.33 (Details are provided in Section 7.4.2 of the SmPC)

## Benefits for patients

Treatment with rezafunginhas the potential to provide important benefits to patients:

* Effective antifungal treatment with an echinocandin, without the need for daily infusions. Having fewer infusion procedures reduces the treatment burden on the patient, reducing typical infusion time from 14+ hours to 2+ hours over a 14-day treatment period
* A fixed catheter is not required for administration of *REZZAYO®*
* A study conducted at 64 centres in Europe found that 16% of 621 patients with invasive candidiasis had their hospital stay extended specifically to finish their course of IV antifungal infusions17
* Once-weekly infusion24 with 7-day antifungal coverage with rezafunginmeans that suitable patients can be discharged from hospital without having to return for daily infusions or accommodate daily home infusions, or treated in the outpatient setting

# Prescribing, reimbursement and supply

## Setting

Rezafungin requires a prescription and initiation of treatment by a healthcare professional experienced in managing invasive fungal infections. It is administered in hospital weekly through intravenous infusion lasting at least 1 hour. The treatment duration varies based on patient response but should extend at least 2 weeks beyond the last detection of Candida in the blood. Adherence to national antifungal agent guidelines is recommended for proper use of REZZAYO®.49

Treatment with rezafunginacetate should be initiated by a physician experienced in the management of invasive fungal infections.24

Rezafunginwill be prescribed in the hospital setting. Initial administration will take place in the hospital. Patients who are suitable for discharge can receive subsequent infusions (every 7 days) as outpatients or via treatment at home (OPAT) services.

## Reimbursement status

Rezafungin was not topic-selected for a technology appraisal by NICE in England or AWMSG in Wales, and decisions on its use will be subject of local formulary and guidelines decisions.

Rezafungin has been reviewed by the SMC in October 2024, with full information available at: <https://scottishmedicines.org.uk/medicines-advice/rezafungin-acetate-rezzayo-full-smc2659/>

## Supply

REZZAYO® is available from Napp’s Wholesaler Partner, Alliance Healthcare. REZZAYO® can be ordered from Alliance under the PIP code 426-6128.

Stock of REZZAYO® to be available to order from Alliance from 13th March 2024.

# Clinical evidence for *REZZAYO®*: efficacy

The clinical efficacy of rezafunginin invasive candidiasis and candidaemia has been assessed in a phase 2 and a phase 3 trial, and in a pre-planned pooled analysis of the two trials.29,30,68,69 Details of each trial and the pooled analysis are given below.

**Key points**

* Therezafungingroup was non-inferior to the caspofungin group in the treatment of invasive candidiasis and candidaemia in the ReSTORE phase 3 trial, on the global response at day 14 (primary endpoint)29
* Rezafunginachieved mycological eradication for a range of clinically important *Candida* species, including *C. albicans, C. glabrata, C. parapsilosis,* *C. tropicalis, C. krusei* and *C. dubliniensis30*
* Rezafunginprovides high plasma concentration early in therapy36

Overview of trial methodology

Table 4 Overview of the STRIVE and ReSTORE trials

| **Study** | **STRIVE68** | **ReSTORE29** |
| --- | --- | --- |
| **Study design** | Phase 2, double blind, two-part multinational RCT:  Part A 107 subjects randomised 1:1:1 to rezafungingroup 1 (35 subjects) vs rezafunginGroup 2 (36 subjects) vs caspofungin\* (36 subjects).  Part B 100 subjects randomised 2:1 to rezafunginGroup 1 (46 subjects) then rezafungingroup 2 (21 subjects) vs caspofungin (33 subjects). | Phase 3, double blind, multicentre, multinational RCT:  Patients randomised 1:1 torezafungin(100 subjects) vs caspofungin\* (99 subjects). |
| **Population** | Adults ≥18 years of age, seeking treatment for candidaemia and/or invasive candidiasis confirmed by a recent (≤96 hours before randomisation) sample positive for yeast or *Candida*.  Exclusion criteria: Invasive candidiasis causing septic arthritis in prosthetic joint, osteomyelitis, endocarditis, myocarditis, *Candida* infections of the eye (e.g., endophthalmitis) or central nervous system; neutropenia; hepatic impairment. | Adults ≥18 years of age, with established mycological diagnosis of candidaemia and/or invasive candidiasis (≤96 hours before randomisation) and ≥1 systemic signs attributable to candidaemia and/or invasive candidiasis, willing to undergo treatment for infection.  Exclusion criteria: invasive candidiasis causing septic arthritis in prosthetic joint, osteomyelitis, endocarditis, myocarditis, meningitis, endophthalmitis, chorioretinitis or central nervous system infection, chronic disseminated candidiasis, urinary tract candidiasis; prior systemic antifungal for >48 hours; alanine aminotransferase or aspartate aminotransferase concentrations more than 10 times upper limit of normal, or severe hepatic impairment with a history of chronic cirrhosis (Child–Pugh score >9); pregnancy/lactating; indwelling vascular catheter or device that cannot be removed and is likely source of infection; hypersensitivity to study drug. |
| **Intervention** | Group 1: rezafungin400 mg day 1 and day 8; optional for all subjects 400 mg on day 15; optional for subjects with invasive candidiasis only 400 mg on day 22; normal saline placebo on other days; optional step-down to oral placebo after 3 infusion days.  Group 2: *REZZAYO®*: 400 mg day 1, 200 mg day 8; optional for all subjects 200 mg on day 15; optional for subjects with invasive candidiasis only 200 mg on day 22; normal saline placebo on other days; optional step-down to oral placebo after 3 infusion days. | Rezafungininfusion 400 mg dose in week 1, followed by 200 mg once weekly, for a total of 2 to 4 doses (3rd and 4th doses were optional, at the discretion of the investigator).  Patients received intravenous placebo on other study days to maintain masking. |
| **Comparator** | Caspofungin IV: 70 mg day 1, 50 mg/day for 14 days, optional 50 mg/day days 15–21; optional for subjects with invasive candidiasis only 50 mg/day days 22–28; optional step-down to oral fluconazole 800 mg on the first day followed by 400 mg/day thereafter after 3 infusion days | Caspofungin infusion 70 mg loading dose on day 1, followed by 50 mg once daily with the option to continue treatment ≤28 days, with optional stepdown after ≥3 days of treatment to oral fluconazole, 200–800 mg daily (3 mg/kg or 6 mg/kg, based on creatinine clearance). |
| **Primary outcome** | Overall response at day 14 (clinical and mycological resolution) in microbiological intent-to-treat population. | Global cure at day 14 (clinical cure as assessed  by the investigator) in the microbiological intent-to-treat population |
| **All other reported outcomes** | Overall response at day 5, day 14, day 28, follow-up (day 45 to 52 (candidaemia) or day 52 to 59 (invasive candidiasis)).  Mycological response (negative blood or tissue cultures) at days 5, 14, 28 (IC only) and follow-up.  Investigator assessment of clinical response (alive with no signs or symptoms of candidaemia/invasive candidiasis) on days 14, 28 (invasive candidiasis only) and follow-up.  All-cause mortality at day 30.  Time to first of 2 sequential negative blood cultures.  Safety: adverse events, vital signs, ECGs, radiologic tests, clinical evaluation, laboratory data. | All-cause mortality at day 30 and global response (Investigator assessment of clinical response + confirmed mycological eradication) at day 14 in modified intent-to-treat population.  Global response at day 5, day 30, end of treatment (EOT) and follow up (days 52–59) in mITT population.  Mycological eradication at day 5, day 14, day 30, EOT and follow up in mITT population.  Investigator assessment of clinical response at day 5, day 14, day 30, EOT and follow up in mITT population.  Radiological response at day 5, day 14, day 30, EOT and follow up in mITT population.  Safety and tolerability in safety population.  Pharmacokinetics of *REZZAYO®*.  Exploratory: time from first dose of study drug to first negative blood culture with no following positive culture; percentage of negative blood cultures 24hr and 48hr after first dose of study drug; resolution of systemic signs attributable to candidaemia and/or invasive candidiasis at day 5, day 14, day 30, EOT and follow up in mITT population. |
|  |  |  |

EOT: end of treatment, IC: invasive candidiasis, IV: intravenously, mITT: modified intention-to-treat, RCT: randomised controlled trial.

\* Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

## Phase 2 trial (STRIVE)68

### **Methods**

STRIVE was a phase 2 multicentre, prospective, randomised, double blind, two-part study of rezafunginand caspofungin for the treatment of adults with candidaemia and/or IC. Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more. The trial aimed to evaluate the safety and tolerability of IV rezafunginand the overall success of treatment at days 5, 14 and 28 (defined by mycological eradication and resolution of systemic signs attributable to candidaemia and/or invasive candidiasis), mycological success at days 5, 14 and 28, clinical response as assessed by the investigator at days 14 and 28, and the pharmacokinetics of rezafungin(Table 4).68

### **Baseline patient characteristics**

A total of 219 patients were screened and 207 were randomised (ITT population); 202 (97.6%) received at least 1 dose of study drug (safety population). A total of 183 patients (88.4%) in the safety population had documented *Candida* infection and comprised the mITT population.

Table 5 STRIVE clinical trial baseline characteristics: ITT population, Part A + Part B

| **Baseline characteristic** | **Rezafunginonce weekly**  **400 mg/200 mg (n = 57)** | **Caspofungin\* once daily**  **70 mg/50 mg (n = 69)** |
| --- | --- | --- |
| **Age in years** | Mean ± SD: 60 ± 16  Range: 24 - 91  <65 years, n (%): 32 (56.1)  ≥65 years, n (%): 25 (43.9) | Mean ± SD: 59 ± 16  Range: 24 - 93  <65 years, n (%): 40 (58.0)  ≥65 years, n (%): 29 (42.0) |
| **Sex, n (%)** | Male: 36 (63.2) | Male: 38 (55.1) |
| **Race, n (%)** | Asian: 1 (1.8)  Black or African American: 7 (12.3)  White: 44 (77.2)  Other: 2 (3.5)  Not reported: 3 (5.3) | Asian: 3 (4.3)  Black or African American: 4 (5.8)  White: 59 (85.5)  Other: 0  Not reported: 3 (4.3) |
| **Ethnicity, n (%)** | Hispanic/Latino: 9 (15.8)  Not Hispanic/Latino: 46 (80.7)  Not reported: 2 (3.5) | Hispanic/Latino: 7 (10.1)  Not Hispanic/Latino: 59 (85.5)  Not reported: 3 (4.3) |
| **Final diagnosis, n (%)** | Candidaemia only: 46 (80.7)  IC\*: 11 (19.3) | Candidaemia only: 56 (81.2)  IC\*: 13 (18.8) |
| **BMI†, mean ± SD kg/m²** | 26.8 ± 8.57 | 26.6 ± 5.63 |
| **APACHE II Category,**  **n (%)** | 0-9: 15 (26.3)  10-19: 26 (45.6)  ≥20: 14 (24.6)  Not available: 2 (3.5) | 0-9: 17 (24.6)  10-19: 37 (53.6)  ≥20: 9 (13.0)  Not available: 6 (8.7) |
| **APACHE II score** | N = 55  Mean ± SD: 14.1 ± 6.72  Range: 2.0 – 28.0 | N = 63  Mean ± SD: 14.0 ± 7.39  Range: 1.0 – 35.0 |

APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; SD, standard deviation.

\*Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more; †BMI calculated by dividing weight (kg) by height (m2) based on patients with available data.

Data from Thompson et al. 2021.68

### Results

Overall, rezafunginwas found to be efficacious in treating patients with candidaemia and/or invasive candidiasis. Outcomes, including overall success at day 5 and 14, survival through to day 30, mycological success on day 5 and 14, and investigators’ assessment of clinical response at day 14, were numerically higher for rezafunginthan caspofungin, but statistical significance was not analysed. Results are summarised in Table 6.

Table 6 Key outcomes in mITT population, STRIVE Part A + Part B

| **Treatment group** | | **Rezafunginonce weekly 400 mg/200 mg**  **(Group 2)** | **Caspofungin\*once daily 70 mg/50 mg** |
| --- | --- | --- | --- |
| **Number randomised** | | **46** | **61** |
| **Primary efficacy endpoint: Overall response at day 14, n (%) [95%CI]** | Overall response | 35 (76.1%) [61.2, 87.4] | 41 (67.2%) [54.0, 78.7] |
| Failure | 8 (17.4%) | 17 (27.9%) |
| Indeterminate | 3 (6.5%) | 3 (4.9%) |
| **Mycological response at day 5, n (%) [95%CI]** | Mycological success | 35 (76.1%) | 38 (62.3%) |
| **Investigator assessment of clinical response at day 14, n (%)** | Clinical response | 37 (80.4%) | 43 (70.5%) |
| **All-cause mortality at day 30, n (%)** | | 4.4% | 13.1% |
| **Overall response at day 5** | | 34 (73.9%) | 34 (55.7%) |
| **Mycological success at day 5** | | 35 (76.1%) | 38 (62.3%) |

\*Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

Data from Thompson et al. 2021.68

## Phase 3 trial (ReSTORE)29

### **Methods**

ReSTORE was a Phase 3, double-blind, randomised, global trial that evaluated the efficacy and safety of once-weekly rezafungincompared with once-daily caspofungin in the treatment of candidemia and/or invasive candidiasis. Patients were randomised (1:1) to receive rezafungin(400 mg on day 1 and 200 mg on day 8; n=100) or caspofungin (70 mg loading dose on day 1 and 50 mg once-daily thereafter; n=99). Stable patients in the caspofungin group who met relevant criteria could step down to oral fluconazole after 3 days or more (optional). Randomisation was stratified based on diagnosis (candidemia only and invasive candidiasis) and by modified APACHE II score and/or ANC at screening.29

Patients were adults aged ≥18 years who had systemic signs of infection attributable to invasive candidiasis and mycological evidence of candidemia and/or invasive candidiasis from a sample taken within 96 hours before randomisation.29

The primary endpoint was global response at day 14 (investigator assessment of clinical response + mycological eradication) and a secondary endpoint was 30-day all-cause mortality.29

### **Baseline patient characteristics**

A total of 222 patients were screened for inclusion, and 199 were randomised and included in the ITT population (Table 7).

Table 7 Baseline characteristics for patients in the ReSTORE trial, ITT population

| **Baseline characteristic** | **Rezafunginonce weekly**  **400 mg/200 mg** | **Caspofungin\* once daily**  **70 mg/50 mg** |
| --- | --- | --- |
| **Number randomised** | 100 | 99 |
| **Age group,**  **n (%)** | <65 years: 60 (60%)  ≥ 65 years: 40 (40%) | <65 years: 58 (59%)  ≥ 65 years: 41 (41%) |
| **Mean age in years (SD)** | 59.5 (15.8) | 62.0 (14.6) |
| **Sex, n (%), male** | 67 (67%) | 56 (57%) |
| **Race, n (%)** | Asian: 27 (27%)  Black or African American: 5 (5%)  White: 61 (61%)  Other or not reported: 7 (7%) | Asian: 31 (31%)  Black or African American: 4 (4%)  White: 60 (61%)  Other or not reported: 4 (4%) |
| **Mean BMI in kg/m² (SD)** | 25.43 (7.0) | 24.47 (6.5) |
| **Final diagnosis, n (%)** | Candidaemia only: 70 (70%)  IC:† 30 (30%) | Candidaemia only: 68 (69%)  IC: 31 (31%) |
| **Modified APACHE II score, n (%)** | ≥20: 15 (15%)  <20: 84 (84%) | ≥20: 18 (18%)  <20: 81 (83%) |
| **Mean modified APACHE II score (SD)** | 12.5 (8.0) | 13.1 (7.1) |
| **Absolute neutrophil count (ANC) (µL) at baseline, n (%)**‡ | <500µL: 9 (9%) | <500µL: 6 (6%) |
| ***Candida* pathogens from blood and sterile site cultures, mITT**  **n, (%)** | N=93  *C. albicans*: 39 (42%)  *C. glabrata*: 24 (26%)  *C. krusei*: 2 (2%)  *C. parapsilosis*: 8 (9%)  *C. tropicalis*: 20 (22%)  *C. dubliniensis*: 3 (3%)  Other:§ 4 (4%) | N=94  *C. albicans*: 40 (43%)  *C. glabrata*: 25 (27%)  *C. krusei*: 2 (2%)  *C. parapsilosis*: 17 (18%)  *C. tropicalis*: 17 (18%)  *C. dubliniensis*: 1 (1%)  Other: 2 (2%) |

APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; mITT, modified intention to treat; SD, standard deviation.

\*Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more; †Includes patients who progressed from C to IC based on radiological or tissue or fluid culture assessment up to day 14; ‡Reported for patients with data available; §Other: C. guilliermondii, C. lusitaniae, C. metapsilosis, C. nivariensis.

Data from Thompson et al. 2023.29

### **Results**

#### **Primary endpoints: All-cause mortality at day 30 and global response at day 14**

ReSTORE met its primary endpoint, demonstrating non-inferiority of once-weekly rezafunginvs once-daily caspofungin on the primary endpoint in the treatment of patients with candidemia and/or invasive candidiasis (Table 8).29

* Primary endpoint was global response at day 14 was 59.1% (55/93) for rezafungincompared with 60.6% (57/94) for caspofungin (difference [95% CI]: -1.1 [-14.9 to 12.7]) in the mITT population29
* Day 30 all-cause mortality was 23.7% (22/93) for rezafungincompared with 21.3% (20/94) for caspofungin (difference [95% CI]: 2.4 [-9.7 to 14.4]) in the mITT population.29 Not controlled for multiplicity

Table 8 All-cause mortality at day 30 and global response at day 14 in the modified intention-to-treat population

|  | **Rezafungingroup (n = 93)** | **Caspofungin group (n = 94)\*** | **Treatment difference (95%CI)** |
| --- | --- | --- | --- |
| **Global response at day 14 as assessed by DRC (primary outcome)** | | | |
| Response n (%) | 55 (59%) | 57 (61%) | -1.1 (-14.9, 12.7)† |
| Failure n (%) | 28 (30%) | 29 (31%) |  |
| Indeterminate n (%) | 10 (11%) | 8 (9%) |  |
| **All-cause mortality at day 30** | | | |
| Died n (%) | 22 (24%) | 20 (21%) | 2.4 (-9.7, 14.4)‡ |
| Known deceased n (%) | 19 (20%) | 17 (18%) |  |
| Unknown status n (%) | 3 (3%) | 3 (3%) |  |
| **Global response at day 14 as assessed by DRC by diagnosis** | | | |
| Candidaemia only |  |  |  |
| Response n/N (%) | 39/64 (61%) | 43/67 (64%) | −3·2 (−19·6, 13·3)‡ |
| Failure n/N (%) | 21/64 (33%) | 19/67 (28%) |  |
| Indeterminate n/N (%) | 4/64 (6%) | 5/67 (7%) |  |
| IC |  |  |  |
| Response n/N (%) | 16/29 (55%) | 14/27 (52%) | 3·3 (−22·4, 28·6)‡ |
| Failure n/N (%) | 7/29 (24%) | 10/27 (37%) |  |
| Indeterminate n/N (%) | 6/29 (21%) | 3/27 (11%) |  |
| **All-cause mortality at day 30 by diagnosis** | | | |
| Candidaemia only n/N (%) | 18/64 (28%) | 17/67 (25%) | 2·8 (−12·5, 18·0)‡ |
| IC n/N (%) | 4/29 (14%) | 3/27 (11%) | 2·7 (−16·7, 21·7)‡ |

DRC, Data Review Committee; IC, invasive candidiasis.

\*Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

†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.

‡Two-sided 95% CI for the observed difference (%), rezafungin group minus caspofungin group. Not controlled for multiplicity.

Data from Thompson et al. 2023.29

#### **Secondary and exploratory endpoints**

ReSTORE met its secondary endpoint of global response at day 5, day 30, end of treatment (EOT) and follow up (days 52–59) in mITT population with weekly rezafunginvs once-daily caspofungin in the treatment of patients with candidemia and/or invasive candidiasis (Table 8).29

* Day 30 all-cause mortality was 23.7% (22/93) for rezafungincompared with 21.3% (20/94) for caspofungin (difference [95% CI]: 2.4 [-9.7 to 14.4]) in the mITT population.29 Not controlled for multiplicity

Secondary and exploratory endpoints at days 5 and 14 are summarised in Table 9, together with the proportion of patients with a negative blood culture at 24 and 48 h. Time to negative blood culture (an exploratory analysis) is shown in Figure 3: median time to negative culture was 23.9 hours in the rezafungingroup and 27.0 hours in the caspofungin group.29

Table 9 Secondary and exploratory endpoints, ReSTORE

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

CI, confidence interval; DRC, Data Review Committee.

\*Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

**†**Two-sided 95% CI for the observed difference (%), rezafungin group minus caspofungin group. Study not powered to infer differences between groups for secondary and exploratory endpoints.

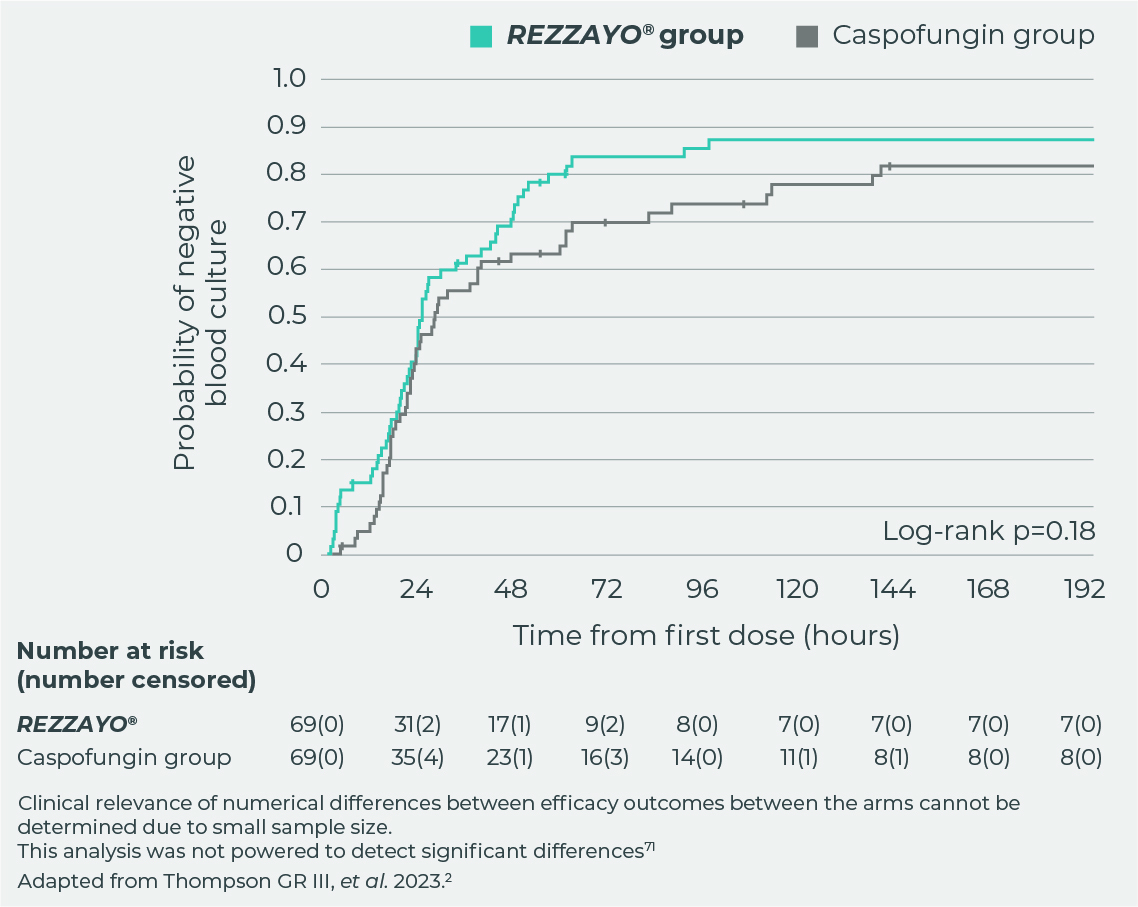
‡Programmatically derived from the outcome definition described in the methods.

§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.

Data from Thompson et al. 2023.29

Figure 3 Time to negative blood culture, mITT population (exploratory endpoint)

Blood cultures for efficacy following the first dose of study drug were performed until the first negative blood culture result for *Candida* spp. With no subsequent positive culture. Blood samples for cultures were drawn daily when possible although may have been drawn every other day.



Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

Clinical relevance of numerical differences between efficacy outcomes between the arms cannot be determined due to small sample size. This analysis was not powered to detect significant differences.71

Adapted from Thompson et al. 2023.29

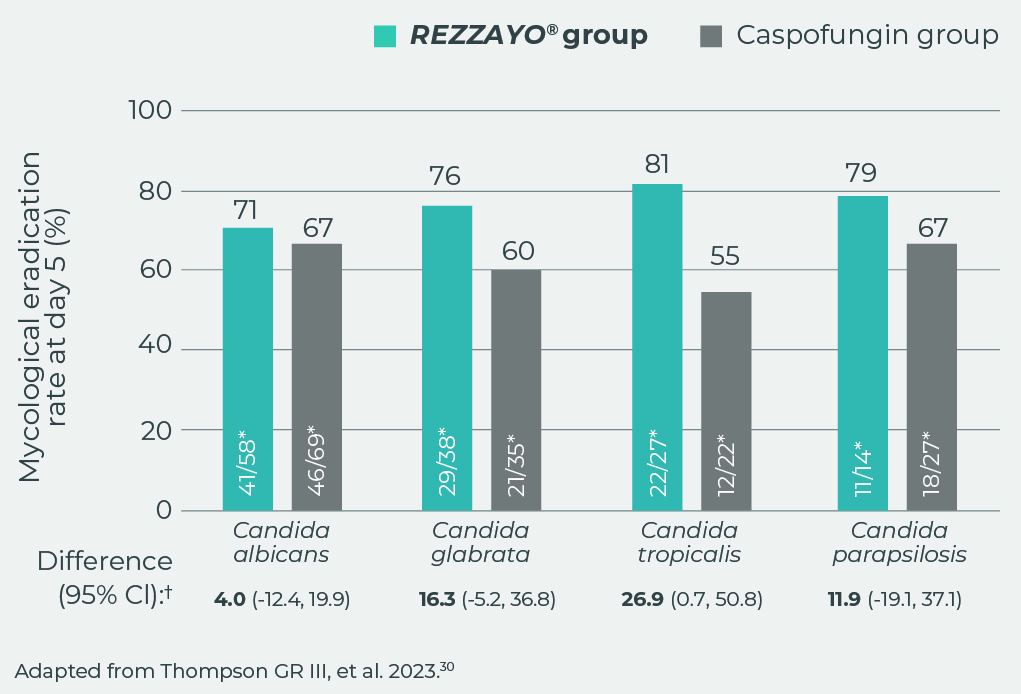
## Pooled analysis of STRIVE and ReSTORE trials

### **Clinical endpoints**

A pre-planned patient-level meta-analysis of the STRIVE (phase 2) and ReSTORE (phase 3) studies confirmed the efficacy of rezafungincompared with caspofungin7\* for the treatment of invasive candidiasis and candidemia (mITT population).30 Efficacy endpoints from this analysis are summarised in Table 10.

* Rezafunginwas non-inferior to the primary endpoint of global response at day 14: failure was 19% (26/139) in the rezafungingroup compared with 19% (30/155) in the caspofungin group (difference [95% CI]: -1.5 [-10.7 to 7.7])
  + Integrated analysis of the Global Response endpoint was not possible due to differences in the definitions of Global Response between the two trials
* Secondary endpoint: Mycological eradication at day 5 in the mITT population was 73% for rezafunginand 65% in the caspofungin arm (difference [95% CI], 10.0% [-0.3 to 20.4]). Mycological eradication at 5 days by *Candida* spp. is shown in Figure 4
* Exploratory endpoint: The proportion of patients with negative blood culture at 24 hours was 60% (63/105) for rezafunginand 49% (57/116) for caspofungin. At 48 hours, the proportion was 78% for rezafunginvs 64% for caspofungin
* In a pre-planned pooled analysis in patients with candidaemia only, mycological eradication at day 5 with rezafunginwas 80% (80/100 patients).30,31 Mycological eradication at day 5 in the caspofungin group: (optional step-down to oral fluconazole after 3 days or more\*) was 67% (78/115 patients). 30,31 [Note: This analysis was not powered to detect significant differences.]
* The pre-planned pooled analyses ReSTORE and STRIVE, observed rezafunginand caspofungin (optional step-down to oral fluconazole after 3 days or more) in the mITT population. Mycological eradication at day 5 was 73% (102/139 patients) for rezafunginand 65% (100/155) in the caspofungin group (weighted treatment difference 10.0% (95% CI −0·3-20.4)]30 [Note: This analysis was not powered to detect significant differences.]
* The pre-planned pooled analysis observed rezafunginand caspofungin, investigating mycological eradication (optional stepdown to oral fluconazole after 3 days or more) in patients infected with *C.* *glabrata* at day 14 (*REZZAYO*®: 32/38 (84%); caspofungin: 22/35 (63%); difference 21.4% (95% CI 1.9-40.8)(Figure 5).30 [Note: This analysis was not powered to detect significant differences.] In a pre-planned pooled analysis of ReSTORE and STRIVE, rezafunginwas non-inferior to the caspofungin group (optional step-down to oral fluconazole after 3 days or more\*[[6]](#footnote-7)) in all-cause mortality at day 30 (mITT population). Mycological eradication at day 14 was 72% (100/139) for rezafunginand 68% (106/155) in the caspofungin group (optional step-down to oral fluconazole after 3 days or more) (weighted treatment difference 4.3% (95% CI −6.2-14.7)).30

Figure 4 Mycological eradication at day 5, according to baseline *Candida* species in the pooled analysis (mITT population)†, \*[[7]](#footnote-8)



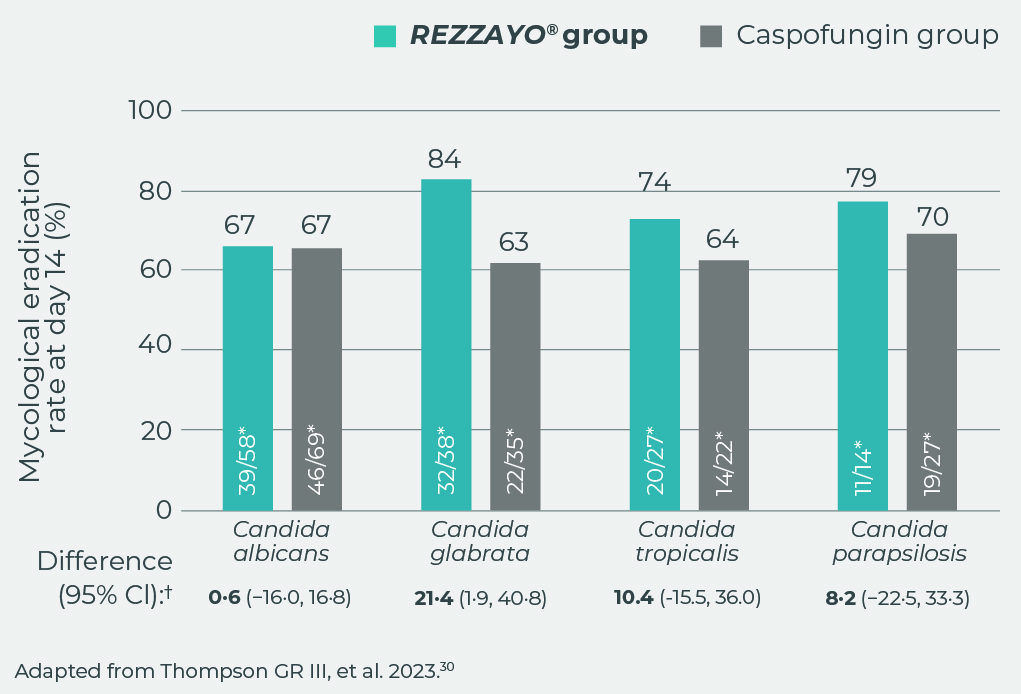
\*n/N = number of subjects with Candida species demonstrating mycological eradication/total number of subjects with the corresponding species at baseline.

†Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more. Blood cultures for efficacy following the first dose of study drug were performed until the first negative blood culture result for Candida spp. with no subsequent positive culture. Blood samples for cultures were drawn daily when possible although may have been drawn every other day.

95% CIs were calculated using unstratified Miettinen and Nurminen methodology and only completed for species observed in >10 patients; descriptive statistics.

Adapted from Thompson et al. 2023.30

Figure 5 Mycological eradication at day 14, according to baseline *Candida* species in the pooled analysis (mITT population)†, \*[[8]](#footnote-9)



\*n/N = number of subjects with Candida species demonstrating mycological eradication/total number of subjects with the corresponding species at baseline.

†Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more. Blood cultures for efficacy following the first dose of study drug were performed until the first negative blood culture result for Candida spp. with no subsequent positive culture. Blood samples for cultures were drawn daily when possible although may have been drawn every other day.

95% CIs were calculated using unstratified Miettinen and Nurminen methodology and only completed for species observed in >10 patients; descriptive statistics.

Table 10 Efficacy endpoints in the pooled analysis, mITT population

|  | **Rezafungingroup (n = 139)** | **Caspofungin group (n = 155)** | **Treatment difference (95%CI\*)** |
| --- | --- | --- | --- |
| **Primary pooled efficacy endpoint: all-cause mortality at day 30, n (%)** | | | |
| Deceased or unknown survival status | 26 (19) | 30 (19) | - |
| Known deceased | 21 (15) | 25 (16) | - |
| Unknown status | 5 (4) | 5 (3) | - |
| Alive | 113 (81) | 125 (81) | - |
| Treatment difference in death rate (95% CI) | - | - | -1.5 (-10.7 to 7.7) |
| **Secondary efficacy endpoint: mycological eradication, n (%)** | | | |
| ***Day 5*** | | | |
| Eradication | 102 (73) | 100 (65) | - |
| Failure or indeterminate | 37 (27) | 55 (35) | - |
| Treatment difference in eradication rate (95% CI) | - | - | 10.0 (-0.3 to 20.4) |
| ***Day 14*** | | | |
| Eradication | 100 (72) | 106 (68) | - |
| Failure or indeterminate | 39 (28) | 49 (32) | - |
| Treatment difference in eradication rate | - | - | 4.3 (-6.2 to 14.7) |
| **Exploratory efficacy endpoints** | | | |
| ***Day 14 global response, n(%)†*** | | | |
| Response | 90 (65) | 97 (63) | - |
| Failure | 36 (26) | 48 (31) | - |
| Indeterminate | 13 (9) | 10 (6) | - |
| Treatment difference in response (95% CI) | - | - | 2.3 (−8.2 to 13.9) |
| ***Patients with negative blood culture, n (%)‡*** | | | |
| N | 109 | 122 | - |
| At 24 hours | 63/105 (60) | 57/116 (49) | - |
| At 48 hours | 80/103 (78) | 73/115 (64) | - |

Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

\*95% confidence interval (CI) calculated using stratified (by study and, where applicable, study part) Miettinen and Nurminen methodology, study not powered to infer differences in groups; †In STRIVE, global response was determined based on investigator assessment of clinical response and mycological response; in ReSTORE, it was determined based on clinical response, mycological response and radiological response, and confirmed by an independent data review committee.

‡Denominator is patients in the mITT population with a positive blood culture at baseline. Patients who received an alternative antifungal, died, or were lost to follow-up prior to 24 and 48 hours were censored and excluded from the denominator.

Data from Thompson 2023.30

**ICU subgroup**

*Post hoc* analysis outcomes for the subgroup of patients treated in the ICU (pooled analysis; n=55 for *REZZAYO®*, n= 71 for caspofungin) were also analysed:72

* All-cause mortality at day 30 was 36.4% with rezafungin(20/55) with 4 (7.3%) deaths attributable to invasive candidiasis and candidaemia,\*[[9]](#footnote-10) and 26.8% (19/71) with caspofungin (interpret with caution, this analysis was not powered to detect significant differences and further investigation is required to confirm the *post hoc* results)
* Median time to negative blood culture was 18 h with rezafunginversus 38 h with caspofungin (stratified log-rank P = 0.003; not adjusted for multiplicity)

### **Length of ICU stay**

A *post hoc* analysis of length of ICU stay was carried out in the pooled population.33 The Statistical Analysis Plan (SAP) for the STRIVE and ReSTORE trials stipulated that ICU LoS outcomes should be reported for survivors only (i.e., patients who did not die in the ICU). Of the 294 patients included in the pooled analysis, 126 (43%) required ICU admission, of whom 55 were treated with rezafunginand 71 received caspofungin33 (stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more).

In total, 35 patients in the rezafungingroup and 53 in the caspofungin group were discharged from the ICU. The characteristics of the treatment groups were well balanced at baseline, with the exception of the proportion receiving mechanical ventilation (MV; rezafungin12.2%, caspofungin: 21.9%). However, the distribution of APACHE II scores and absolute neutrophil counts were comparable between the groups.33

* Mean ICU LoS was 15.9 days in the rezafungingroup and 23.0 days in the caspofungin group
* Mean ICU after *post hoc* adjustment for mechanical ventilation status was 17.3 and 21.4 days in the rezafunginand caspofungin groups, respectively33

Figure 6 Mean length of ICU stay, *post hoc* results from pooled analysis of STRIVE and ReSTORE.

A graph of numbers and a number of patients

Description automatically generated

Interpret with caution. Further investigation is required to confirm the post hoc results from the analysis. Of the 294 patients in the pooled analysis, the ICU population (patients treated in the ICU at any time) was n=126 (n=55, REZZAYO®; n=71, caspofungin). n=37/126 of patients had impaired renal function (baseline creatine clearance <50 mL/min: n=18, REZZAYO®; n=19, caspofungin). Baseline patient characteristics were similar between the arms, except for the proportion of patients undergoing mechanical ventilation: 29.1% (16/55) with rezafungin and 46.5% (33/71) with caspofungin. Proportion of patients with APACHE II score ≥20 was 32.1% (17/53) with rezafungin and 29.6% (21/71) with caspofungin.

Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

Source: Mundipharma data on file73 and Bielicka et al. 2022.33

# Safety and tolerability of *REZZAYO®* rezafungin acetate

## Phase 3 trial (ReSTORE)

In the phase 3 ReSTORE trial, rezafunginwas generally well tolerated and had comparable rates of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) to caspofungin.29

* In the safety population (n=98 in both groups), 90.8% of patients treated with rezafunginand 84.7% of patients treated with caspofungin reported TEAEs. Study-drug–related TEAEs were reported in 16.3% and 9.2% of patients receiving rezafunginand caspofungin, respectively29
* Serious adverse events occurred in 56.1% and 53.1% of patients in the rezafunginand caspofungin groups, respectively. Five events were related to the study drug: 2 in the rezafunginand 3 in the caspofungin group29
* No patients in the rezafungingroup discontinued the study due to adverse events, compared with 3 (3.0%) in the caspofungin group29

Table 11 Breakdown of treatment-emergent adverse events (TEAEs) in ReSTORE reported in 5% or more of the safety population

|  |  |  |
| --- | --- | --- |
| **TEAE** | **Rezafungingroup (N=98), n (%)** | **Caspofungin\* group (N=98), n(%)** |
| 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) |

\*Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

Data from Thompson et al. 2023.29

## Overall summary of safety

Based on clinical trial experience, the most frequently reported adverse reactions for rezafunginwere hypokalaemia, pyrexia, diarrhoea and anaemia (very common adverse reactions). Transient infusion-related reactions have occurred with *REZZAYO®*, characterised by flushing, sensation of warmth, nausea and chest tightness.24 Prescribers should refer to the SmPC for special warnings and precautions for use.

The following table includes adverse reactions from 151 subjects who received rezafungin400/200 mg listed by system organ class (SOC) and MedDRA preferred terms with frequency corresponding to very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and from spontaneous reports with frequency not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 12 Table of adverse reactions with rezafungin400/200 mg

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **System organ class** | **Very common**  **≥ 1/10** | **Common**  **≥ 1/100 to < 1/10** | **Uncommon**  **≥ 1/1 000 to < 1/100** | **Not known** |
| Blood and lymphatic system disorders | Anaemia |  |  |  |
| Metabolism and nutrition disorders | Hypokalaemia | Hypomagnesaemia, hypophosphataemia | Hyperphosphataemia, hyponatraemia |  |
| Vascular disorders |  | Hypotension |  |  |
| Respiratory, thoracic and mediastinal disorders |  | Wheezing |  |  |
| Gastrointestinal disorders | Diarrhoea | Vomiting, nausea, abdominal pain, constipation |  |  |
| Skin and subcutaneous tissue disorders |  | Erythema, rash | Phototoxicity | Urticaria |
| Musculoskeletal and connective tissue disorders |  |  | Tremor |  |
| General disorders and administration site conditions | Pyrexia |  |  |  |
| Investigations |  | Blood alkaline phosphatase increased, hepatic enzymes increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased | Eosinophil count increased |  |
| Injury, poisoning and procedural complications |  | Infusion-related reactions |  |  |

Source: SmPC25

## Pooled analysis (STRIVE and ReSTORE)

In the pooled analysis of the phase III (ReSTORE) and phase II (STRIVE) trials, a difference was noted between rezafunginand caspofungin (optional-step down to oral fluconazole after 3 days or more)\*[[10]](#footnote-11) for the category of ≥1 AEs (*REZZAYO®*: 92%; caspofungin: 83%; P=0.018) (not controlled for multiplicity) and ≥1 TEAEs (rezafungin: 91%; caspofungin: 83%; P=0.0304). Not controlled for multiplicity. No significant differences were identified for study-drug–related TEAEs, severe or grade ≥3 TEAEs, SAEs, study-drug–related SAEs or any TEAEs leading to interruption or discontinuation of study drug or study.30 TEAEs reported in ≥ 5% of adults in either pooled treatment in safety population are shown in Table 13.

Table 13 Most commonly occurring TEAEs reported in ≥ 5% of adults in either pooled treatment in safety population

|  |  |  |
| --- | --- | --- |
| **TEAE** | **Rezafungingroup (n = 151)** | **Caspofungin\* group (n = 166)** |
| Pneumonia | 12 (8%) | 7 (4%) |
| Septic shock | 11 (7%) | 12 (7%) |
| Sepsis | 10 (7%) | 8 (5%) |
| Urinary tract infection | 5 (3%) | 9 (5%) |
| Diarrhoea | 17 (11%) | 17 (10%) |
| Vomiting | 14 (9%) | 7 (4%) |
| Nausea | 13 (9%) | 8 (5%) |
| Abdominal pain | 11 (7%) | 9 (5%) |
| Constipation | 8 (5%) | 8 (5%) |
| Hypokalaemia | 22 (15%) | 17 (10%) |
| Hypomagnesaemia | 12 (8%) | 5 (3%) |
| Hypophosphataemia | 8 (5%) | 5 (3%) |
| Hyperkalaemia | 3 (2%) | 9 (5%) |
| Pyrexia | 18 (12%) | 11 (7%) |
| Pleural effusion | 3 (2%) | 10 (6%) |
| Anaemia | 15 (10%) | 13 (8%) |
| Hypotension | 7 (5%) | 10 (6%) |
| Acute kidney injury | 6 (4%) | 11 (7%) |

TEAE: treatment-emergent adverse event.

\*Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

†A statistical analysis using Fisher’s exact test was performed evaluating differences between the rezafungin and caspofungin groups.

Data from Thompson et al. 2023.30

## Special populations

No dose adjustments are required in elderly patients (aged 65 years or older), patients with hepatic impairment or patients with renal impairment. Rezafungincan be given without regard to the timing of haemodialysis. No dose adjustment is required based on patient weight.24

## Warnings and precautions for use

Special warnings and precautions for use are listed in the SmPC as follows:

The efficacy of rezafunginhas only been evaluated in a limited number of neutropenic patients.24

Hepatic effects

In clinical trials, elevations in liver enzymes have been seen in some patients treated with *REZZAYO®*. In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with *REZZAYO®*, clinically significant hepatic dysfunction has occurred; a causal relationship to rezafunginhas not been established. Patients who develop elevations in liver enzymes during rezafungintherapy should be monitored, and the risk/benefit of continuing rezafungintherapy should be re-evaluated.24

Infusion-related reactions

Transient infusion-related reactions have occurred with *REZZAYO®*, characterised by flushing, sensation of warmth, nausea and chest tightness.

In clinical trials, infusion reactions resolved within minutes, some without interruption or discontinuation of the infusion. Patients should be monitored during the infusion. If the infusion is stopped due to a reaction, consideration may be given to restarting the infusion at a slower rate after the symptoms have resolved.24

Phototoxicity

Rezafunginmay cause increased risk of phototoxicity. Patients should be advised to avoid sun exposure and other sources of UV radiation without adequate protection during treatment and for 7 days after the last administration of *REZZAYO®*.24

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose; that is to say, essentially ‘sodium-free’.24

## Additional safety considerations

No additional safety concerns have been identified in relation to storage, preparation, use and disposal. Instructions for reconstitution, dilution and administration are provided in the SmPC. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.24

# Cost and budget impact of *REZZAYO®* rezafungin acetate

## Eligible patient population

The rates of bloodstream infections due to yeast have steadily increased since 2013, peaking in 2022 at 4.0 per 100,000 population in England.70 In 2022, 91% of the 2,265 reported cases of yeast bloodstream infections in England were identified to the species level, consistent with previous years.70 Candida albicans was the most frequently identified species, accounting for 39% of reports (881 cases), a slight decrease from 2021 (912 cases, 42%).70 The second most commonly reported yeast species in England in 2022 was Nakaseomyces glabratus (previously Candida glabrata) (28%), followed by Candida parapsilosis (12%).70

Rates of yeast bloodstream infections vary across regions. In 2022, all Office for National Statistics regions except the North East experienced higher rates of fungaemia compared to 2018.70 Similarly, rates increased in all ONS regions except London and the Midlands and East of England from 2021 to 2022.70 The most significant increase occurred in the North West and South West regions, rising from 3.7 and 3.4 per 100,000 population in 2021 to 4.8 and 4.5 per 100,000 population in 2022, respectively.70 Based on this information, the North West and South West regions would be primary targets for treatment with rezafungin due to the notable increase in rates of yeast bloodstream infection.70

## Cost of REZZAYO®

## Impact on existing formulary and services

Initially, rezafunginwill offer an additional treatment option, potentially replacing one of the standard-of-care treatments. Any costs associated with rezafungin will be incremental. Furthermore, there will be no additional laboratory work with rezafunginbeyond the culture testing already required for existing antifungal treatments.

Once-weekly treatment with rezafunginhas the potential to reduce the pharmacy and nursing time required for issue, preparation and administration, compared with once-daily alternatives (see Section 5.1).

## Budget impact analysis

In addition to drug acquisition costs, the following aspects should be accounted for when assessing the overall cost and budget impact of antifungal treatments:

* Treatment-specific drug reconstitution time and associated pharmacist costs
* Nursing time required to administer infusion and record
* Infusion-related consumables (e.g., IV giving sets)
* Any unit costs for daily/regular laboratory testing
* Hospital setting costs, e.g., daily costs for ICU and general ward stay

Examples of some of these costs in the UK are shown in Table 14.

Table 14 Costs for disease management and drug administration

|  |  |
| --- | --- |
| Items | Cost (£ [GBP]) |
| Laboratory test costs (per test) | 10.1874 |
| Hospital-based nurse cost (per hour\*) | 56.5075 |
| Pharmacist cost (per hour†) | 52.0075 |
| ICU cost (per day) | 2,979.0076 |
| General ward cost (per day) | 412.0076 |

\*Average of bands 6 and 7.

†Based on the cost of band 6, hospital-based physiotherapists.

## Budget impact calculator tool

A hospital trust specific budget impact assessment can be provided by Napp Pharmaceuticals Limited using the REZZAYO® Budget Impact Model.

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* **REZZAYO (rezafungin) 200 mg powder for concentrate for solution for infusion**

**PRESCRIBING INFORMATION**

For Prescribing information for REZZAYO (rezafungin) 200 mg powder for concentrate for solution for infusion please click here:

<https://www.emcpi.com/pi/44417>

Or, scan the QR Code below:

A qr code on a white background

AI-generated content may be incorrect.

**Adverse event reporting: Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/**[**.**](http://www.mhra.gov.uk/yellowcard)**Adverse events should also be reported to Napp Pharmaceuticals Limited on 01223 424444**

1. \* Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more29 [↑](#footnote-ref-2)
2. † Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more29 [↑](#footnote-ref-3)
3. \* *REZZAYO®* had no or minimal effects on the exposure of probe drugs for the following enzymes/ transporter proteins: CYP2B6 (efavirenz); CYP3A4 (midazolam and tacrolimus); CYP1A2 (caffeine); CYP2C8 (repaglinide); P-gp (digoxin and tacrolimus); OCT-1, OCT-2, MATE-1 and MATE-2 (metformin); OATP (pitavastatin, rosuvastatin and repaglinide); and BCRP (rosuvastatin). The drug–drug interaction potential of *REZZAYO®* with a number of co-administered medicinal products has also been assessed clinically. The need for dose adjustments is considered unlikely for tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax. [↑](#footnote-ref-4)
4. \*29 Interpret with caution. Further investigation is required to confirm the *post hoc* results from the analysis.

   † Assessed in healthy adults. [↑](#footnote-ref-5)
5. \* Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more29 [↑](#footnote-ref-6)
6. \* Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more29 [↑](#footnote-ref-7)
7. \* Efficacy of rezafungin in treating infections caused by these isolates has not been established in clinical trials. For species with low n number, descriptive statistics were provided. For Candida krusei, 2/5 patients in the rezafungin group and 2/3 in the caspofungin group achieved mycological eradication at day 5. At day 14, 2/5 patients in the rezafungin group and 3/3 patients in the caspofungin group achieved mycological eradication. For Candida metapsilosis, 3/3 patients in the rezafungin group achieved mycological eradication at day 5 and day 14. No patients in the caspofungin group were infected with Candida metapsilosis. For Candida dubliniensis, 3/3 patients in the rezafungin group and 2/2 patients in the caspofungin group achieved mycological eradication at day 5 and day 14. For Candida guilliermondii, 1/2 patients in the rezafungin group achieved mycological eradication at day 5 and day 14. No patients in the caspofungin group were infected with Candida guilliermondii. For Candida kefyr, 1/1 patients in the caspofungin group achieved mycological eradication at day 5 and day 14. No patients in the rezafungin group were infected with Candida kefyr. For Candida nivariensis, 1/1 patients in the caspofungin group achieved mycological eradication at day 5 and day 14. No patients in the rezafungingroup were infected with Candida niviariensis. For Candida lusitaniae, 1/1 patients in the rezafungin group and 1/1 patients in the caspofungin group achieved mycological eradication at day 5 and day 14.30 [↑](#footnote-ref-8)
8. \* Efficacy of rezafungin in treating infections caused by these isolates has not been established in clinical trials. For species with low n number, descriptive statistics were provided. For Candida krusei, 2/5 patients in the rezafungin group and 2/3 in the caspofungin group achieved mycological eradication at day 5. At day 14, 2/5 patients in the rezafungin group and 3/3 patients in the caspofungin group achieved mycological eradication. For Candida metapsilosis, 3/3 patients in the rezafungin group achieved mycological eradication at day 5 and day 14. No patients in the caspofungin group were infected with Candida metapsilosis. For Candida dubliniensis, 3/3 patients in the rezafungin group and 2/2 patients in the caspofungin group achieved mycological eradication at day 5 and day 14. For Candida guilliermondii, 1/2 patients in the rezafungin group achieved mycological eradication at day 5 and day 14. No patients in the caspofungin group were infected with Candida guilliermondii. For Candida kefyr, 1/1 patients in the caspofungin group achieved mycological eradication at day 5 and day 14. No patients in the rezafungin group were infected with Candida kefyr. For Candida nivariensis, 1/1 patients in the caspofungin group achieved mycological eradication at day 5 and day 14. No patients in the rezafungin group were infected with Candida niviariensis. For Candida lusitaniae, 1/1 patients in the rezafungin group and 1/1 patients in the caspofungin group achieved mycological eradication at day 5 and day 14.30 [↑](#footnote-ref-9)
9. \* Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.29  [↑](#footnote-ref-10)
10. \* Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.29 [↑](#footnote-ref-11)